THE 59TH ANNUAL MEETING OF
THE JAPANESE TERATOLOGY SOCIETY
THE 13TH WORLD CONGRESS OF
THE INTERNATIONAL CLEFT LIP AND PALATE FOUNDATION
- CLEFT 2019 -

MEIJO KOEN CAMPUS

AICHI GAKUIN UNIVERSITY

3-11 MEIJO, KITA-KU, NAGOYA, 462-8739, JAPAN

"Golden Dolphins" locating on the top of Nagoya Castle, a symbol of Nagoya, were made from real gold equivalent to 1,940 pieces of big oval gold coins/ 17,975 pieces of oval gold coins (280 kg) in 1612 and are a symbol of this conference.

Opening Address

I would like to deliver the opening message as the president of Japanese Cleft Palate Foundation (JCPF) which is host organization of this joint meeting. JCPF was established by Mr Kohei Abe who was the chairman of Chubu Electric Power Co., Inc. in 1992. Mr Kohei Abe acted the first president of JCPF and Mr Fumio Kawaguchi who was also the chairman of Chubu Electric Power Co., Inc. acted the president of JCPF from 2005. In this year, the first year of Reiwa, new era changing from Heisei, I assumed the third president of JCPF and Professor Nagato Natsume is in charge of daily operations as the executive director.

JCPF has supported the handicapped persons and their parents with not only medical community but also political and business communities.

JCPF organized International Cleft Lip and Palate Foundation (ICPF) in 1997 and has been in charge of the staff office for ICPF. JCPF also has made presentations with our activities in the annual meeting of the Japanese Teratology Society consistently.

It is our great honor and gratitude to host the joint meeting for the international congress and the subcommittee of the Japanese Association of Medical Sciences, recognized for our achievements.

We sincerely hope that joint meeting will be meaningful for all of you.

Akihisa Mizuno

Honorary Congress President of the Joint Meeting, the 59th Annual Meeting of the Japanese Teratology Society and the 13th World Congress of the International Cleft Lip and Palate Foundation -CLEFT 2019-
President of Japanese Cleft Palate Foundation
Chairman of the Board of Directors, Chubu Electric Power Co., Inc

Welcome Remarks from ICPF President

On behalf of the Board of Trustees of the International Cleft Lip and Palate Foundation, it's my great pleasure to extend to each of you a warm welcome to our thirteenth World Congress, held jointly for the first time with the fifty-ninth Congress of the Japanese Teratology Society. The theme of our joint meeting is "For the Future of Our Children."

The joint Congress will be held from July 26 until July 29, 2019. Over Seven-hundred participants from Japan and forty additional countries will attend. We will present an outstanding scientific program, one that includes international experts lecturing on their specific areas of expertise. We have always been committed to the belief that multidisciplinary teams in modern-day global conditions are the best way to deliver excellence of treatment, and we particularly welcome our teratology colleagues and friends. They provide a special opportunity for vital cooperation and improvement in the care of our children with better understanding of basic science and teratology. Emphasizing important elements from teratology, we will offer lectures, workshops, and important discussions of the latest scientific information for improvement of diagnosis and treatment of children with cleft lip and palate and all craniofacial disorders.

We are delighted to be meeting in the beautiful, modern, clean, and centrally located city of Nagoya, which offers numerous exciting possibilities for exploration during your free time. The meeting's Social Event Committee has planned a wide variety of fascinating excursions, and without doubt, you will experience legendary Japanese hospitality throughout your stay.

A very important aspect of every meeting such as this one is the opportunity to see old and new friends and engage informally as well as formally about science, medicine, and our shared service to children. You are about to experience four days of unparalleled scientific, medical, and cultural stimulation in a setting that is extraordinary.

My wife Luci and I look forward to greeting you in person during the Congress, and on behalf of the Board of Trustees of the ICPF, I wish you a wonderful and very memorable experience here in Nagoya.

Kenneth E. Salyer, M.D. FACS, FAAP

President, ICPF
Founder & Chairman of the Board
World Craniofacial Foundation

Welcome Remarks from JTS President

It is our great pleasure that the 59th Annual Meeting of the Japanese Teratology Society (JTS) is held in conjunction with the 13th World Congress of International Cleft Lip and Palate Foundation (ICPF), CLEFT2019, by the prominent arrangement of Co-President of the two meetings Prof. Nagato Natsume, and generous support from JTS Emeritus President Mr. Akihisa Mizuno, in Nagoya, Aichi, which is the geographical center as well as one of the industrial and academic centers of Japan. On behalf of JTS, I would like to deeply thank President Prof. Natsume and his colleagues for their enormous effort in the arrangement and preparation and to express my cordial welcome to all the participants from all over Japan and the globe including ICPF members.

Based on the idea that multidisciplinary approach is necessary to confront birth defect-related problems, JTS, since its establishment in 1961, has been continuing its activity as an interdisciplinary society where doctors, researchers, practitioners of various clinical and basic biomedical fields get together and propagate the achievements toward the world including publishing Congenital Anomalies, the JTS official journal with an Impact Factor. Birth defects in the head, neck and maxillofacial region have been one of the main topics and actively discussed in JTS. This joint meeting is therefore an ideal opportunity for all the participants from JTS and ICPF to interact and exchange information crossing over each expertise.

Toward realization of the main theme of this joint meeting “For the Future of Children: Disseminating a philosophy of “Medicine is Jinjustsu” (a benevolent art) from Japan to the world” advocated by President Prof. Natsume, I wish all the participants take an active part in this joint meeting in Japan, and learn history and share the state-of-the-art accomplishments in the related broad and various fields to integrate them for the further progress in each activity.
COI: None

Hiroki Otani

Chief Director, the Japanese Teratology Society
Department of Developmental Biology, Faculty of Medicine, Shimane University

Greetings from the Congress President

I am honored to be the Congress President of this joint meeting of *The 59th Annual Meeting of the Japanese Teratology Society and The 13th World Congress of the International Cleft Lip and Palate Foundation -CLEFT 2019-*.

The International Cleft Lip and Palate Foundation (ICPF) was led to be established by me together with Prof. David S. Precious. We held the inaugural meeting in Kyoto in 1997 and the first academic meeting in Zurich in 2000. ICPF consists of 89 countries, communicates with more than 5,200 individuals and holds the academic meetings every year at various sites in the world.

The Japanese Teratology Society (JTS) is an academic society which I joined when I was a graduate student and whose annual meetings I have attended every year since then.

I hope this joint meeting will bring the benefit both JTS and ICPF, through an interaction between ICPF and JTS, and through encouraging ICPF members to submit articles to the official journal of JTS, Congenital Anomalies.

I set the theme of this joint meeting to be 'For the Future of Children -*Disseminating a philosophy of "Medicine is Jinjutsu" from Japan to the world* -.'

As the topics, I picked up the following subjects: '*Protecting the lives of fetuses*,' '*Treatment and research for congenital anomalies* - Introduce the delicate skills and techniques and the latest research from Japan -,' '*Current status and outlook for international medical assistance in congenital anomalies* - Disseminating the philosophy of "Medicine is Jinjutsu -a benevolent art-,' '*The role of monitoring of congenital anomalies in Japan* - Including the data of 'Fukushima' after the 2011 nuclear accident,' and '*Possible roles of the folic acid for prevention of congenital anomalies*.'

I hope this joint meeting held in Aichi prefecture in Japan is fruitful for everyone.

Nagato NATSUME
Congress President

Secretary Treasurer, International Cleft Lip and Palate Foundation
Executive Director, Japanese Cleft Palate Foundation

Director, Cleft Lip and Palate Center, Aichi Gakuin University Dental Hospital
Professor, Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University

ICPF Board of Trustees

President:

Professor Kenneth E. Salyer:

Founding Chairman and Director, World Craniofacial Foundation, USA

Secretary Treasurer:

Professor Nagato Natsume:

Cleft lip and palate Center, Aichi-Gakuin University, Japan

Members

Professor Marie M. Tolarova:

Executive Director, Pacific Craniofacial Team and Cleft Prevention Program, Dugoni School of Dentistry, University of the Pacific, USA, Founder and President, Cleft Prevention International Foundation, Inc.

Professor S. M. Balaji:

Director and Senior Consultant, Balaji Dental, Craniofacial Hospital & Research Institute, Chennai, India

Dr. A. F. Markus:

Consultant Maxillofacial Surgeon, Poole Hospital, UK

Professor Ma Lian:

Peking University School and Hospital of Stomatology, China

Professor Yoshihide Mori:

Section of Oral and Maxillofacial Surgery, Faculty of Dental Science, Kyushu University, Japan

Dr. Ida A. Astuti:

Spesialis Bedah Multut Kantor, R. S. HasanSadkin, Indonesia

Professor Jong-Ryoul Kim:

Director, Jaw & Face Surgery Center, On General Hospital, Republic of Korea

Professor Jean-Charles Doucet:

Dept. of Oral and Maxillofacial Sciences, Faculty of Dentistry, Dalhousie University, Canada

Professor Robert Alexander Sader:

Director of the Department of Oral, Cranio-Maxillofacial and Facial Plastic Surgery, University Hospital Frankfurt am Main/Germany

Dean for Student Affairs, Medical Faculty of the Johann Wolfgang Goethe-University Frankfurt am Main, Germany

Professor Jin-Young Choi:

Dept. of Oral & Maxillofacial Surgery, Seoul National University Dental Hospital, Republic of Korea

Professor Adil Mamedov:

Dept. of Pediatric Dentistry and Orthodontics, I.M. Sechenov Moscow State Medical University, Russian Federation

Professor Alexander Hemprich:

Prof. & Chairman, Dept. of Maxillofacial and Plastic Surgery of University of Leipzig, Germany

Professor Ariuntuul Garidkhuu:

Lecturer, Global Health Department, School of Medicine, International University of Health and Welfare, Japan; For mer Dean., School of Dentistry, Mongolian National University of Medical Sciences, Mongolia.

Professor Adi Rachmiel, DMD, PhD:

Head department of oral and maxillofacial surgery, Rambam Medical Center, Technion Faculty of Medicine, Haifa, Israel

The Japanese Teratology Society Board of Directors

Chief Director (2016-2019)

Hiroki Otani:
Shimane University

Congress President (2019)

Nagato Natsume:
Aichi Gakuin University, School of Dentistry

Directors (2016-2019)

Hiroaki Aoyama:
The Institute of Environmental Toxicology

Sachiko Iseki:
Tokyo Medical and Dental University

Kenji Kurosawa:
Kanagawa Children's Medical Center

Kenjiro Kosaki:
Center for Medical Genetics, Keio University School of Medicine

Yuji Nakashima:
Osaka City University

Nagato Natsume:
Aichi Gakuin University Dental Hospital

Toshihisa Hatta:
Kanazawa Medical University Department of Anatomy

Fumiki Hirahara:
National Hospital Organization Medical Center

Michio Fujiwara:
Astellas Pharma Inc.

Kiyoshi Matsumoto:
Takeda Pharmaceutical Company Ltd.

Shigehito Yamada:
Congenital Anomaly Research Center, Kyoto University Graduate School of Medicine

Michiko Yamanaka:
St. Luke's International Hospital

Atsushi Yoshiki:
RIKEN BioResource Research Center

Auditors (2016-2019)

Hirotomo Saitsu:
Hamamatsu University School of Medicine

Hitoshi Funabashi:
Sumika Chemical Analysis Service, Ltd.

Humanitarian Award

ICPF was established for the purpose of exchanging knowledge and information among NGOs for the patient with cleft lip and palate. In the 2nd business meeting in 1999, this award was decided to introduce for the people who has dedicated his/her life to such patient as charitable operations as voluntary work.

In recognition of outstanding contributions in supporting patients with cleft lip and palate and advancing the medical skills in developing countries with deep gratitude and thankfulness presents this testament of appreciation.

2000: Professor Byong-II MIN, D.D.S., ph.D,. F.l.C.D, Korea

2008: Samuel NOORDOFF, Professor M.D. FACS, USA
Hans-Dieter PAPE, Professor Dr. med, Dr. med. Dent, Germany
Hideo TASHIRO, M.D., PhD, Professor Emeritus, Doctor, Japan

2010: Kenneth E. SALYER, Professor Doctor, USA
Takeshi KATSUKI, Professor Emeritus, Japan

2012: HERMANN F. SAILER, Prof. Dr. Dr. Dr.h.c.mult, Switzerland

2013: David S. PRECIOUS, Professor CM, DDS, MSc, FRCDC, FRCS, Dr hc, LLD, Canada
Geniku KOHAMA, Professor Emeritus, Japan
TRAN VAN TRUONG, Professor, Vietnam

2015: Shigetaka YANAGISAWA, Professor Emeritus, Doctor, Japan

2016: Ko Ko MAUNG, Professor, Myanmar
Adil MAMEDOV, Professor, Russian Federation
Karimpat Mathangi RAMAKRISHNAN, Professor, India

2017: Guomin WANG, Professor D.D.S., PhD, China

2018: Thomas KREUSCH, Professor Dr. Dr., Germany

2019: Marie M. TOLAROVA, M.D., Ph.D., D.Sc., Professor and Executive Director, USA

Precious Award

The first chairman of the ICPF, Prof. David S. Precious has passed on Feb. 3, 2015 with his glorious achievement. In honor of Prof. D.S. Precious, the Precious Award was established in 2015 at the board of trustee meeting in CLEFT2015 in Moscow, Russia.

It is presented annually to the best presenter of academic research or clinical experience before the ICPF Congress. Each ICPF council member has one vote to select the best presentation to nominate.

Those multi-nominates are ultimately selected by the board of trustee members. The presentation type should not be limited to free paper and/or only research.

The winner receives and be presented the Precious Award at the next congress.

The award is limited to be given to ONE researcher/clinician, and he/she receives the testimonial, 1,000 USD and free registration fee for the next ICPF congress

Short description on the certification: In honor of Prof. David S. Precious, first chairman of the ICPF, the Precious Award is given annually to the best presenter of academic research or clinical experience before the Congress of the ICPF.

2017: Dr. Kazuto Hoshi, M.D., PhD, The University of Tokyo, Japan, for his presentation of "Three-dimensional tissue-engineered cartilage using biodegradable polymers" (lectured on October 26, 2016, during 10th ICPF World Cleft Congress in Chennai)

2018: Prof. Dr. S. M. BALAJI, MDS, PhD, DSc (Hons), Balaji Dental and Craniofacial Hospital, Chennai, India, for his presentation of "Management of Craniofacial Clefts" (lectured on November 12, 2017, during 11th ICPF World Cleft Congress in Wuhan)

2019: Professor Kurt-Wilhelm Butow, BSc, BChD, MChD(in MFOSurg), Dr Med Dent, PhD, DSc(Odont), FCMFOS, FIBCSOMS, University of Pretoria & The Wilgers Hospital, South Africa, for his presentation of "280 Pierre Robin sequence patients, what is new?" (lectured on April 20, 2018, during 12th ICPF World Cleft Congress in Leipzig)

Awards

1. ICPF & JTS The Best Authors for Oral and Poster Presentation

All participants are asked to vote for the best authors for oral and poster presentations. Eleven oral presentations and 10 best posters will be selected and awarded in the closing ceremony. The Precious Award is given to the best oral presentation author. The Precious Award winner will be awarded with 1,000 USD in ICPF2020 in St. Petersburg, Russia!

Vote boxes are placed at the reception desk. The deadline of voting is 3:00 p.m. on 28th.

Your voting papers are in the congress bag. Please make sure to fill in the voting papers with the first author, the number of presentation and the brief title of presentation.

2. Excellent poster presentation awards in JTS

Excellent poster presentation awards are selected from the general poster presentations of young researchers. The oral presentation for winners will be given at the Selected Poster Session (13:00-14:00 on July 28 (Sun)) in this congress. Winners of the Excellent poster presentation awards in JTS will receive the awards in the Selected Poster Session.

P234

Dlx5-augmentation in neural crest cells induces ectopic calvarial cartilages

Tri Vu Hoang[1)], Masaki Takechi[1)], Miki Shimizu[2)], Taro Kitazawa[2)], Hiroki Higashiyama[2)], Akiyasu Iwase[2)], Hiroki Kurihara[2)], Sachiko Iseki[1)].
[1)]Section of Molecular Craniofacial Embryology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU)
[2)]Department of Physiological Chemistry and Metabolism, Graduate School of Medicine, The University of Tokyo (Japan)

【Background】 Although the cranial vault is formed by intramembranous ossification, cartilaginous structures are also observed in this area, suggesting a potential of both osteoblast and chondrocyte differentiation in cranial vault formation. Distal-less homeobox 5 (Dlx5) is a homeobox transcription factor that induces osteoblastic and chondrogenic differentiations. Endogenous Dlx5 is not expressed in the forming calvaria, but we have found that the augmentation of Dlx5 in the mouse NCC (Wnt1-Cre;Rosa26Dlx5/+, called thereafter NCC-Dlx5) induces conspicuous ectopic cartilages in the apical region of the cranium. This is an important implication for understanding molecular mechanisms of the calvaria formation.

【Purpose】 To elucidate developmental basis of calvaria formation by disrupting gene expression involved in bone and cartilage formation.

【Methods】 In this study, in situ hybridization, immunohistochemistry, alizarin red & alcian blue skeletal staining, hematoxylin & eosin staining, toluidine blue staining, transmission electron microscopy, and micro-CT analyses were performed.

【Results】 Newborn NCC-Dlx5 mice showed the ectopic cartilage formed under developing frontal bone, which expanded to the posterior and displayed patchy bone defects. Histological analysis demonstrated the ectopic cartilage seemed to be formed in the dura mater derived from NCC-derived head mesenchyme. To reveal developmental process leading to the phenotype, gene expression patterns of Dlx5, osteoblast (Runx2) and chondrocyte (Sox9) markers were examined in earlier fetal stages of the NCC-Dlx5. At E10.5, Dlx5 was transcribed in the maxillary processes, supraorbital regions, where Dlx5 is not normally detected, but no difference was found in the histological structure. To E11.5, in the NCC-derived head mesenchyme of NCC-Dlx5, Dlx5 is expressed ubiquitously, Runx2 is expressed in both osteoblasts and chondrocytes, Sox9 was found in the chondrocytes. Those expressions were not found in the counterparts of the control. The head mesenchyme was thickened, accompanied by increased number of PHH3-positive cells in the NCC-Dlx5. The mesenchymal condensation started at E12.5 near the apical cranium. Dlx5 expression mainly remained in the differentiating chondrocytes and osteoblasts, and Runx2 expression level in chondrocytes became faint. By E13.5, Runx2 expression diminished in the cartilaginous structure.

【Discussion】 The augmentation of Dlx5 in NCC developed ectopic cartilage in the dura mater layer, and enlarged the frontal bone. It is suggested that Dlx5 overexpression stimulates proliferation, subsequently, differentiation of chondrocytes and osteoblasts in NCC-derived head mesenchyme. However, the calvarial phenotype, together with temporal changes of Runx2 and Sox9 expression during development suggest that Dlx5-induced osteogenesis and chondrogenesis compete each other at the apical cranium.

P428

Upper incisors are most susceptible to phenytoin-induced hypoxic stress during mouse tooth development

Kotono Kibe[1, 2)], Mitsushiro Nakatomi[1)], Shinji Kataoka[1)], Takashi Toyono[1)], Yuji Seta[1)]
[1)]Division of Anatomy, Department of Health Improvement, Kyushu Dental University
[2)]Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University (Japan)

【Background】Congenital anomalies are caused by gene-environmental interactions during embryonic development. Among environmental factors, hypoxic stress can be induced by smoking, arrhythmia, sleep apnea syndrome, living at high altitudes, and uptake of medicine. Compared with other organs, it has not been fully understood how hypoxic stress affects tooth development.

【Purpose】This study aimed to address the effect of hypoxic stress during odontogenesis using mouse embryos.

【Method】Pregnant wild-type mice were intraperitoneally injected with phenytoin, an anti-epileptic drug and a known arrhythmia inducer, at various stages from embryonic day (E) 13 to E16. Dissected embryonic tooth germs were histologically analyzed by H&E staining and immunohistochemistry detecting hypoxic markers Hif1a, VEGFa, and Hydroxyprobe. Quantitative RT-PCR analysis was carried out using cDNA derived from phenytoin-treated and non-treated upper and lower incisor germs and Hif1a, VEGFa, and GAPDH primers. In addition, pregnant mice were kept in a chamber in which oxygen concentration was maintained at 10% from E14 to E17 and fetal tooth germs were histologically analyzed.

【Results】Phenytoin injection induced vascular dilation of 100 μm or more in diameter in the dental pulp in 21 of upper incisors and 2 of lower incisors but not in molars among 110 right and left jaws (55 individuals). No such phenotype was observed in tooth germs obtained from the hypoxic chamber group. Upper incisors of the group of phenytoin injection at E15-16 and dissected at E17 exhibited the highest incidence rate of vasodilation. Hif1a, VEGFa, and Hypoxyprove were immunopositive in phenytoin-treated odontoblasts. Quantitative RT-PCR analysis revealed that the expression of Hif1a and VEGFa was significantly up-regulated in phenytoin-treated group than in non-treated.

【Discussion】Our data indicated that upper incisors were most susceptible to phenytoin-induced hypoxic stress than other tooth types. One reason why incisors are more susceptible than molars would be that the size of molar germs is bigger than that of incisors due to being multi-rooted and therefore vascularization could easily occur in molars. However, it remains unclear why upper incisors are more susceptible than lower incisors. One possible explanation to no phenotype of hypoxic chamber group is that phenytoin can pass through the placenta and affect the embryos directly, whereas lower oxygen concentration influences the embryos indirectly via mothers. In conclusion, our results suggest that hypoxic stress caused by medication during pregnancy would increase the risk of dental malformation especially in single-rooted teeth.

【COI】The authors declare no conflicts of interest.

【Grant】This work was supported by the Japan Society for the Promotion of Science KAKENHI (Grant Number 15K11019 to M.N.).

P235

Statin and Other Lipid-Lowering Therapy During First Trimester, Lipoprotein Apheresis Between the Second Trimester, and Lactation Period and Pregnancy Outcome in Heterozygous Familial Hypercholesterolemia: A Case Report

Ayami Miyai[1)], Naotake Maruyama[1)], Hiromi Sekimoto[1)], Mitsuo Kinugasa[2)], Kyosuke Takeuti[3)]
[1)]Department of pharmacy, Kobe medical center
[2)]Department of Cardiovascular medicine
[3)]Department of Obstetrics and Gynecology (Japan)

【Background and Purpose】Pregnancy in heterozygous familial hypercholesterolemia (HeFH) is related to further elevation of already markedly elevated low-density lipoprotein cholesterol (LDL-C) levels, especially if lipid-lowering therapy is discontinued. This increases the cardiovascular risk of the mother and fetus. Lipoprotein apheresis is the current recommended treatment for HeFH patients; however, this is costly and time consuming. Furthermore, HeFH women who are taking statins may become pregnant in future. In Europe and many other countries, statins are considered as contraindicated drugs, signifying that they have potential fetal risks. If HeFH women under statin therapy become pregnant, they may become anxious on the detrimental effects of statins on the fetus, and proper counseling is necessary.

【Case Presentation】We present the case of a 31-year-old Japanese woman who was diagnosed with effort angina pectoris (EAP). Her total cholesterol level was 433 mg/dl, which was quite high, and FH was suspected before admission. She had also previously taken conjugated estrogen and synthetic progesterone for infertility treatment. She underwent coronary angiography (CAG) and percutaneous coronary intervention (PCI) for EAP. Her chief complaint was anterior chest wall pain. She started to take low-dose aspirin, ezetimibe, rosuvastatin, prasugrel, and esomeprazole. Subsequently, prasugrel was switched to clopidogrel. After PCI, she was diagnosed with HeFH and discerned PCSK9 gene negative. We advised her that she needs to consider a planned pregnancy and continue to take her medications; however, one year later, she got naturally pregnant and got anxious about the effects of her medications on her baby. We counseled her and explained how the medications could affect the fetus, such as that described in case studies and prospective cohort studies, and recommended apheresis during pregnancy. Then she decided to continue the pregnancy. She continued to take her medications until she was 16 weeks and 6 days pregnant. In her 17th week of pregnancy, she was referred to the National Cardiovascular Center to undergo LDL apheresis. Successful childbirth was achieved as well as management of LDL, without any adverse events. When she was 38 weeks and 4 days pregnant, she gave birth to a 3270 g baby boy via normal spontaneous vaginal delivery under epidural anesthesia.

【Conclusion】HeFH is a severe health condition and has an influence on life expectancy. Although numerous women with HeFH have a high cardiovascular risk, pregnancy is not rare.

For women of childbearing age anticipating LDL-C reduction, proper counseling must be considered.

Brief History of ICPF

Preliminary Period
The year 1993
The organization was named International Cleft Lip and Palate Foundation (ICPF), after the discussions with many overseas volunteers who have got acquainted with Japanese Cleft Palate Foundation (JCPF) through their international activities.

JCPF initiated preparing a meeting for establishing ICPF that was simultaneously to be held in the Kyoto Meeting of IAOMS in 1997. During the preliminary period, JCPF was able to get supports and advices from many people. Prof. David Precious, the representative of Canadian NGO and Prof. Nagato Natsume, also the representative of JCPF, have led the preparation works.

- Guidelines in international medical assistance with initiatives to provide better international medical assistance to developing countries established in ICPF meeting in Zurich,2000 (under the patronage of the World Health Organization)

1st Business Meeting
1997. Oct 24: Kyoto Takaragaike Prince Hotel in Kyoto, Japan
Establishing International Cleft Lip and Palate Foundation with 20 countries joined. It was decided that next meeting will be held in Washington USA in 1999 and also decided that ICPF meeting will be held biennially.
The 1st congress will be held by Prof. Herman Sailer in Switzerland in the year of 2000, the 2nd will be held 2002 in Munich by Prof. Hans Henning Horch and the 3rd will be 2004 in Canada by Prof. David Precious.

2nd Business Meeting
1999. April 24: Hilton & Towers Hotel in Washington, USA
For preparing the first congress of ICPF in Zurich, we decided the outline of the congress. The guidelines of charitable operations were discussed. Also Humanitarian Award was introduced at the first congress.

CLEFT 2000
July 1-5 Zurich Switzerland
1st World Cleft Congress of the International Cleft Lip & Palate Foundation
Under the Patronage of the World Health Organization (WHO)
Participants; 526
Adoption of Zurich declaration
・Guideline for Medical Humanitarian Aid
・Charity Operation Information Network
・The World Cleft Gene Bank

3rd business meeting
2000, Nov.4-5, NOGA Hilton Geneva, Switzerland
ICPF hold the meeting with medical professionals, Patients, representatives of Patient's groups and overseas NGO'S, obtaining a subsidy of "Appropriate technology transferring" from the Japanese Foreign Ministry.
Medical professionals: Switzerland, USA, Estonia, China, Germany, Israel, Japan and Canada as well as reports from Indonesia, Mongolia and Korea.
NGO, Operation Smile and Smile Train. They exchanged opinions frankly and confirmed ICPF's roles, charity operation and being on neutral ground in favor of developing countries and patients. Among those, they especially focused on avoiding safari surgery with exchanging information between doctors from developing countries, NGO's and recipients,

4th Business Meeting
2001, June 26 : Hotel Gothia in Gothenburg, Germany
Cleft 2002 in Munich, The ICPF Workshop, publication of a book about Cleft Lip & Palate, Medical Guidelines, World Cleft Gene Bank and ICPF Website. Collaboration with Smile Train, Operation Smile were discussed

CLEFT 2002
Sep. 15-19 Technische Universitat Munchen
2nd World Cleft Congress of International Cleft Lip and Palate Foundation
Under the Patronage of the Bavarian Prime Minister Dr. Edmund Stoiber
Participants: 513 from 54 countries

The Cleft 2002 made a historic congress that first embraces collaboration among patients and medical experts in its main themes as "get together", under the presidency of Prof. Horch and devoted effort of Dr. Sader.

5th Business Meeting
April 12-13 during ACPA in North Carolina Meeting
During ACPA meeting, evaluation of 2nd ICPF congress was discussed.

CLEFT 2004
June 22-26, Halifax, Canada
3rd Biennial World Cleft Congress of the International Cleft Lip and Palate Foundation: main theme "The Patient comes first: Defining Direction"
Organized by Prof. D. Precious, chairman of ICPF.
Under the Honorary Patron of Her Honour Myra Freeman Lieutenant Governor of Nova Scotia .
Participants: 200
For considering the convenience for the participants, First & Second Choice of Hotel.

Workshop 2005
Dec.3-6, 2005, Chennai (Madras), India
1st International Workshop of the ICPF
Organized by Prof. S. M. Balaji
Participants 150 (abroad 80, Indian 70)
First attempt to conduct a workshop with Live Surgery. Appreciated with enthusiasm by participants were tried.
For the future congress and workshop candidate showed their advantage and Beijing, China has been decided to be the host country (by Prof. Ma)

CLEFT 2006
June 25-27, Eastbourne, Sussex, United Kingdom
4th Biennial World Congress of International Cleft Lip & Palate Foundation: congress theme: "Facing the challenges"
Participannts:180
It was stimulating meeting tackling some of the many controversies in Cleft management. The problems of all the Cleft "Team" were addressed. President of the congress was keen to attract our young trainees, and s Symposium on Sunday afternoon was about working in the Developing World. The final report on the expense of the 4th Congress in Eastbourne said slightly excess over the expected budget. The congress was held successfully and the organization committee promoted the congress ideally. The chairman, Prof. Ward Booth, took a great role on that congress. Our chairman (Late Prof. D. S. Precious) appreciated his efforts.

Workshop 2007
Nov. 25-29, 2007 Beijing, China
2nd International Cleft Lip & Palate Foundation Workshop
Organized by Prof. Lian Ma
Participants 64
This workshop was an opportunity for an international forum of interrelated experts on this field. It was a platform for enhancement of skills of the surgeons in management patients with cleft lip and palate too.

CLEFT 2008
September 22-26, Dallas-Fort Worth, Texas, USA
5th Biennial World Cleft Congress of the International Cleft Lip and Palate Foundation: "The Passion for Excellence in Cleft and Craniofacial Care"
organized by Prof. Kenneth E. Salyer, WCF (President of ICPF)
In response to the main concept of this congress, participants reached to 315 from 55 countries
(More than 140 residents and doctors from developing countries financially supported by The Smile Train participated in the educational session including 5 live surgeries.) The faculty was represented by over 50 surgeons from 18 different countries. The goal of this congress is to publish the recorded craniofacial surgery document. Full papers from faculty members and poster presentations have been published an appropriate scientific journal.

- Charity Operation Information Network (COIN) is currently under construction within ICPF website and, information regarding a charity operation exchange program is distributed frequently. This serves communication both from recipient countries and developed countries.

- Distribution of Fellowship announcement of postdoctoral position in the USA, mainly to developing countries based on the requests of our members in USA. There were several candidates, whom ICPF recommended with their career evaluation. One of them from Africa was accepted for a position in USA, and now is happy to work in academics. The professor is also satisfied with his work.

6th Business Meeting
Sept. 2009, in Brazil
The nominating future world congress (2017) on International Association of Oral Maxillofacial Surgeons was prepared. The vote went to India.

CLEFT 2010
June 9-12, Seoul, Korea
6th Biennial World Cleft Congress of the International Cleft Lip and Palate Foundation: "Happy Smiles to the People with Cleft"
organized by Prof. Emeritus Min with Prof. M-J Kim(congress president)
Participants: 350 from 27 countries
The main concept of the congress is "Happy Smiles to the People with Cleft". CLEFT2010ICPF served as an important platform for the discussion and exchange with a world-wide perspective, of current issues in the field of Cleft Lip and Palate.
- The congress was held in conjunction with the 4th National Congress of Korean Cleft Lip and Palate Association.

Workshop 2011
June 9-12, 2011, San Francisco, USA
3rd International Cleft Lip & Palate Foundation Workshop
(organized by Prof. Marie Toralova)
"May Every Child Sing and Smile"
Number of attendees; 206 from 27 countries
Scholarship; Total amount $34,800(22 scholarships ranging from $500 to $2000)
Sponsors; University of the Pacific Arthur A. Dugoni School of Dentistry, Smile Train, Rotaplast Intl.Inc. Azul Vista, ACPA-CPF, Green Box Hosting, Berkeley Dental Society

7th Business meeting
Oct. 28, 2011, New York, USA
Prof. Precious (late), Prof. Salyer and Prof. Natsume visited to Dr. Charles B. Wang president of Smile Train. They discussed on the collaboration on charitable operations.

CLEFT 2012
May 7-11 Mahe in Seychelle
7th Biennial World Cleft Congress of the International Cleft Lip and Palate Foundation: "Gateway to Africa"
Organized by Prof. S. M. Balaji
The total support from Seychelles Island, except for the budget, the conference ends with full of success, particularly many attendants from Africa.
Participant: ca. 160
Doctors from Africa were attending including Dr. Adekeye and Dr. Butow.
Cleft 2012 gave an award for every free paper session. Best poster award and Best free paper award were given at the closing ceremony.

CLEFT 2013
Nov. 23-25, Hanoi, Vietnam
8th World Cleft Congress of the International Cleft Lip and Palate Foundation:
Organized by prof. Nguyen Duc Hinh, Hanoi Medical University
This was the first congress, the president of congress was not ICPF trustee board member but distinguished in some other academic field. We could make our activities to the related field taking care of cleft patients
Participant: 529 from 28 countries
The opening ceremony was held in Opera House (half day). Scientific program was held in Hanoi Medical University, in conjunction with annual meeting of domestic society. Especially the participants from Asian Countries, the number of overseas participants reached 115
The specific announcement "Hanoi-declarations" was introduced. This is aiming at stopping abortion particularly with expected baby (or fetuses) with cleft.

Workshop 2014
Sept. 9-12, 2014, Ulaanbaatar Mongolia
4th International Cleft Lip & Palate Foundation Workshop
Organized by Prof. G. Ariuntuul
Participant: 250 Mongolian participants and 60 participants from 17 countries.
As the productive outcome, Mongolian Speech and Hearing Association was established after the workshop. A proposal for collaboration with WHO was discussed.

CLEFT 2015
Sept.2-4, 2015, Moscow, Russian Federation
9th World Congress of the International Cleft Lip and Palate Foundation
Organized by Prof. A. Mamedov
Participants: 331 from 26 countries including of 194 Russian participants.
The international conference on medical field has been seldom carried out under the various conditions. This is the first conference held in Russian Federation. Many European delegates and domestic participants were interested in uniquely developed treatment for the patient with cleft lip and palate. The special excursion at the Third Medical University was held.

CLEFT 2016

Oct.24-28, Chennai, India

10th World Congress of the International Cleft Lip and Palate Foundation

Organized by Prof. S. M. Balaji:

Participants: 420 from 34

A total of 128 delegates participated in the two days preconference live surgical workshop that was held at Balaji Dental & Craniofacial Hospital, Chennai. Nine live surgeries were performed and a total of 9 patients with varying degrees of cleft and craniofacial deformities benefitted from these surgeries. Ten international and national faculties conducted the program. The entire cost of these surgeries was borne by the hospital as it was for a noble cause.

In order to sensitize the public on the burden posed by orofacial clefting and also highlight the availability of resources to treat such clefting, the organizing team invited Hon. Minister for Health, Govt. of Mauritius, His Excellency Mr. Anil Gayan to inaugurate the conference.

To document the deliberations, the conference proceedings and transactions was published in the form of a book. In all, there were 7 keynote lectures, 14 scientific sessions, 20 plenary sessions, and 3 symposiums.

There were 86 free papers, 23 delegate posters and 42 students' posters. The scientific content of this meeting was appreciated by all the delegates.

CLEFT 2017

Nov. 10-17, Wuhan, China

11th World Congress of the International Cleft Lip and Palate Foundation:

Organized by Prof. Lian Ma

Participants: ca. 400 (80 from abroad)

To treat and prevent cleft lip and palate and related deformities are mutual concern of patients, doctors in the whole globe. The target of the congress is PERSISTENCE, HIGHER and STRONGER. The conference in conjunction with Shino-cleft annual meeting will become the platform to allow all of you to share your advanced diagnostic technology, precious surgical skill, sweet nursing care and pioneer genetic research with the friends and colleague over the world. The happy and cherry life to cleft lip and palate kids will be returned by our heart and hands.: from president message

CLEFT 2018

April 19-21, Leipzig, Germany

12th World Congress of the International Cleft Lip and Palate Foundation

Organized by Prof. Alexander Hemprich

Participants: 303 from 40 countries

Leipzig Consensus was proposed by trustee board members and now discussed on various aspect.

Outline of Leipzig consensus is based on the concept of Hanoi Declaration, which was approved in 2013 in Hanoi and has been widely supported by many medical professionals. The human rights of fetuses with curable anomalies should be respected. Turning back of ICPF establishment, ICPF is aiming at supporting the healthy growth of the patient children and supporting the patents as well, in cooperation with the obstetricians and the midwives to make an appropriate decision to protect the human rights of the fetus. We expect the medical professionals will provide sufficient information to the parents to protect the fetus.

Past Congress Presidents of International Cleft Lip and Palate Foundation

Cleft 2018
4/19-21, 2018
The 12th World Congredd of International Cleft Lip and Palate Foundation
Leipzig, Germany
Prof. Alexander Hemprich
Prof. & Chairman, Dept. of Maxillofacial and Plastic Surgery of University of Leipzig

Cleft 2017
11/11-13, 2017
The 11th World Congredd of International Cleft Lip and Palate Foundation
Wuhan, China
Prof. Lian Ma
Professor of the Oral Institute, The University of Medical Sciences, Peking University School of Dentistry

Cleft 2016
10/24-28, 2016.
The 10th World Congredd of International Cleft Lip and Palate Foundation
Chennai, India
Prof. S. M. Balaji
Balaji Dental, Craniofacial, Hospital & Research Institute

Cleft 2015
8/31-9/4, 2015
The 9th Biennial World Congress of International Cleft Lip and Palate Foundation
Moscow, Russia
Prof. Adil Mamedov
Department of Pediatric Dentistry and Orthodontics, I.M. Sechenov Moscow State Medical University

Cleft 2014
9/9-12, 2014
4th International Cleft Lip & Palate Foundation Workshop
Ulanbaataar, Mongolia
Prof. Ariuntuul Garidkhuu School of Dentistry, Mongolian National University of Medical Sciences

Cleft 2013
Nov. 25-28, 2013
The 8th Biennial World Cleft Lip & Palate Congress of International Cleft Palate Foundation
Hanoi, Vietnam
Madam Truong My Hoa, Ex-Vice President of the Socialist Republic of Vietnam
Prof. Nguyen Duc Hinh
President, Hanoi Medical University

Cleft 2012
5/7-11, 2012
The 7th Biennial World Cleft Lip & Palate Congress of International Cleft Palate Foundation
Mahe, Seychelles
Prof. S. M. Balaji
Balaji Dental, Craniofacial, Hospital & Research Institute

Cleft 2011
6/9-12, 2011
3rd International Cleft Lip & Palate Foundation Workshop
San Francisco, USA
Prof. Marie Toralova Executive Director, Dugoni School of Dentistry,University of the Pacific

Cleft 2010
6/9-12, 2010
The 6th Congress of the International Cleft Palate Foundation
Seoul, S. Korea
Hon. President: Professor Emeritus Byong Il Min (South Korea)
Professor Myung-Jin Kim
Department of Oral & Maxillofacial Surgery, Seoul National University, Dental Hospital

Cleft 2008
9/22-26, 2008
The 5th World Congress of International Cleft Palate Foundation
Dallas, USA
Prof. Eenneth E. Salyer
Founding Chairman and Director, World Craniofacial Foundation

Cleft2007
11/25-27, 2007
2nd International Cleft Lip & Palate Foundation Worksho
Beijing, China
Prof. Lian Ma Professor of the Oral Institute, The University of Medical Sciences, Peking University School of Dentistry

Cleft 2006
6/25-27, 2006
The 4th World Congress of International Cleft Palate Foundation
EastBorn, UK
Prof. Peter Ward Booth
Consultant Oral and Maxillofacial Surgeon, The Queen Victoria Hospital

Cleft 2005
12/3-5, 2005
1st International Workshop of the ICPF
Chennnai, India
Prof. S. M. Balaji Balaji Dental, Craniofacial, Hospital & Research Institute

Cleft 2004
6/22-26, 2004
The 3rd World Congress of International Cleft Palate Foundation
Halifax, Canada
Prof. David S. Precious
Department of Oral & Maxillofacial Sciences, Dalhousie University

Cleft 2002
9/15-19, 2002
The 2rd World Congress of International Cleft Palate Foundation
Munich, Germany Technische Universitat Munchen
Prof. Dr Dr Dr Hans Henning Horch
Klinik und Poliklinik fur Mund Kiefer Gesichtschiurgie, der Technischen Universitat

Cleft 2000
7/1-5, 2000
The 1st World Congress of International Cleft Palate Foundation
Professor Herman F. Sailer
Dept. of Oral and Cranio-Maxillofacial Surgery, University Hospital Zurich

Past Presidents of the Annual Meeting of Japanese Teratorogy Society

The 1st Shigeru Mitani August 1961 Tokyo

The 2nd Tameyoshi Baba August 1962 Osaka

The 3rd Ujihiro Muramami July 1963 Nagoya City Aichi Prefecture

The 4th Yutaka Moriyama July 1964 Tokyo

The 5th Hideo Nishimura July 1965 Kyoto

The 6th Yoshiki Mikami July 1966 Tsu City Mie Prefecture

The 7th Ichiro Hayashi July 1967 Nagasami

The 8th Tadao Takatsu April 1968 Tokyo

The 9th Tetsuo Ito June 1969 Kyoto

The 10th Shudo Takai August 1970 Yokohama City Kanagawa Prefecture

The 11th Yukio Hukuyama April 1971 Tokyo

The 12th Genichi Watanabe July 1972 Niigata

The 13th Naomasa Okamoto July 1973 Hiroshima

The 14th Masakuni Suzuki July 1974 Sendai City, Iwate Prefecture

The 15th Kazuo Baba November 1975 Tokyo

The 16th Yoshio Kameyama September 1976 Nagoya City Aichi Prefecture

The 17th Takayoshi Ikeda July 1977 Nagasaki

The 18th Yutaka Sugawa July 1978 Yokohama City Kanagawa Prefecture

The 19th Toru Nakao July 1979 Sapporo City Hokkaido

The 20th Toshiaki Oura July 1980 Osaka

The 21st Toshiaki Fujimoto July 1981 Kumamoto

The 22nd Hiroshi Furutani July 1982 Tokyo

The 23rd Mineo Yasuda July 1983 Hiroshima

The 24th Eiji Marumo July 19834Tokyo

The 25th Koh Tanimura July 1985 Kyoto

The 26th Shinji Murachi July 1986 Nagoya City Aichi Prefecture

The 27th Masataka Arima July 1987 Tokyo

The 28th Morimi Shimada July 1988 Kyoto

The 29th Akira Endo July 1989 Ymagata

The 30th Kunio Hayakawa July 1990 Miyazaki

The 31st Osamu Tanaka July 1991 Izumo City Shimane Prefecture

The 32nd Teruo Kitakawa July 1992 Tokyo

The 33rd Takayuki Miura July 1993 Nagoya City Aichi Prefecture

The 34th Hiromu Hara July 1994 Kochi

The 35th Tadao Kojima July 1995 Tokyo

The 36th Seiichiro Fujimoto July 1996 Sapporo City Hokkaido

The 37th Kouhei Shiota July 1997 Kyoto

The 38th kaoru Suzumori July 1998 Nagoya City Aichi Prefecture

The 39th Koichiro Miyata July 1999 Kagoshima

The 40th Hiroki Otani July 2000 Matsue City Shimane Prefecture

The 41st Yoshikazu Kuroki July 2001 Yokohama City Kanagawa Prefecture

The 42nd Yoshihiro Tsutsui July 2002 Hamamatsu City Mie Prefecture

The 43rd Hiroshi Kamiishi July 2003 Toyonaka City Osaka Prefecture

The 44th Shinichi Miyahara July 2004 Saga

The 45th Kazuhiro Eto July 2005 Tokyo

The 46th Toshihiko Ogino July 2006 Yamagata

The 47th Reiji Senba July 2007 Nagoya City Aichi Prefecture

The 48th Takamichi Satoh June 2008 Tokyo

The 49th Yojiro Oshima June 2009 Kagoshima

The 50th Yoshihiro Fukui July 2010 Awaji City Hyogo Prefecture

The 51st Fumiki Hirahara July 2011 Tokyo

The 52nd Makiko Osawa July 2012 Tokyo

The 53rd Yuji Nakamura July 2013 Toyonaka City Osaka Prefecture

The 54th Kazuyoshi Arishima July 2014 Sagamihara City Kanagawa Prefecture

The 55th Kenji Kurosawa July 2015 Yokohama City Kanagawa Prefecture

The 56th Toshiaki Watanabe July 2016 Himeji City Hyogo Prefecture

The 57th Hiroaki Aoyama August 2017 Tokyo

The 58th Hironao Numabe July 2018 Tokyo

The 59th Nagato Natsume July 2019 Nagoya City Aichi Prefecture

Japanese Cleft Palate Foundation

– Specified Non Profit Organization –

A specified non profit organization, Japanese Cleft Palate Foundation (JCPF) was established by Professor Nagato Natume, aiming for supporting domestic and overseas patients born with congenital oral and maxillofacial malformations and their families, under the patronage of Mr. Kohei Abe, Chairman of Chubu Electric Power Co., Inc. at that time who acted as the president of JCPF. Businesses and politicians in Chubu (central Japan) area including Toyota Motor Corporation also supported JCPF, acting as directors and counselors of the foundation. The late Dr. Tsuyoshi Kawai, Professor Emeritus of Aichi Gakuin University and the former and beloved teacher of Professor Natsume, also helped the establishment of JCPF.

Professor Natsume became fully aware of the importance of a non-profit organization for oral and maxillofacial malformations through his experience of volunteer activities at a doctorless village as a member of the Study Group of Public Health in Aichi Gakuin University at age 18, and with his experience of participating in American Cleft Palate - Craniofacial Association (ACPA) when he was a graduate school student.

JCPF has been supporting children who were born with congenital oral and maxillofacial malformations in Japan and developing Asian countries since January 1992, when JCPF was established.

Particularly in overseas, JCPF has dispatched medical teams to mainly Asian countries such as Vietnam, Myanmar, Indonesia, Bangladesh, Mongolia and Laos. The overseas destination countries are now expanded to Africa including Tunisia and Ethiopia. JCPF has been providing free-of-charge surgeries for children who have cleft lip and/or palate.

JCPF was recognized the specified non-profit organization in June 2002 and then was qualified to be registered as a UN Roster in April 2003. JCPF was the first organization that acquired UN Roster membership in Chubu area in Japan, evaluated well for the medical support activities in Asian countries. JCPF has also been recognized by the regional taxation bureau as the organization who can accept the tax-deductible donation.

Mr. Fumio kawaguchi (Former Chairman of Chubu Electric Power Co., Inc.) acted as the 2nd President of JCPF from 2005 to May 2019 and Mr. Akihisa Mizuno (Chairman of the Board of Directors of Chubu Electric Power Co., Inc.) is acting as the current President of JCPF.

Mr. Shoichiro Toyoda (Honorary Chairman of Toyota Motor Corporation) is acting as the Honorary Advisor of JCPF and Professor Nagato Natsume is in charge of the staff office as the Executive Director of JCPF.

Representatives of the notable companies in Chubu area and experts assumed directors of JCPF. JCPF has over 100 corporate members and many individual members.
Social service activities in Japan and medical cooperation overseas by JCPF have been funded with donations from individuals and corporate members. Some of the overseas operations of JCPF are supported by funds from Japanese government such as the Ministry of Foreign Affairs.

JCPF donated an endowed course “Genetics for Oral and Maxillofacial Congenital Anomalies and Linguistics” to Aichi Gakuin University in April, 2006.

About Aichi Prefecture

Aichi Prefecture has the fifth largest city of Nagoya and is located in the geographical center of Japan. It's population is approximately 7.5 million, while the population of 3 surrounded region -called Tokai 3 prefectures (Aichi, Gifu, Mie)- reaches to 11.2 million. From time to time, this rich farmland provided enough food for the residents and produced the governmental individuals such as Ieyasu Tokugawa and Hideyoshi Toyotomi, the former is the founder of Tokyo, and the latter is the originator of Osaka, respectively.

Taking advantage of the Nagoya's geographical location, more than 60 globally leading companies like Toyota Motor Corporation and twenty thousand of midsize mainly industrial companies carry on their businesses in the Aichi prefecture. They have stayed on the top of industrial production in the whole Japan for half a century. They produce 40% of the total exported industrial product in Japan. The economical value, approximately JPY48 trillion, reaches to more than 1% of the world GDP. Among this, the trade surplus is approximately JPY 7.6 trillion and supports the Japanese economy. If we look at the area within 100 km radius from the VENUE of this congress: Meijo campus of Aichi-Gakuin University, the economical product of this area reaches to about 2% of the world GDP

The local companies have prioritized environmental improvement of this area since the World Environmental Conference that was held in Nagoya in 2010. Now, it seems to be the most environmentally friendly industrial area in the world. The economic progress and development have provided for various city functions, such as huge underground shopping towns, famous department stores, where a wide variety of shops and restaurants supply international goods and fantastic tastes to customers. The majority of the shops are open all days in a year to satisfy their guests.

Nagoya offers a number of corporate museums like the Toyota Commemorative Museum of Industry and Technology, Noritake Garden (Ceramics Museum and Shop). The City of Nagoya operates the Science Museum with Planetarium, Aquarium, Zoo and Botanical Garden (Higashiyama Park). There is also a private Samurai museum (Tokugawa Museum) exhibiting swords, costumes and articles of daily use, once owned by Tokugawa families during the 17th-19th centuries.

About the Aichi Gakuin University

Aichi Gakuin University (AGU) has 142 years history since its establishment in 1876, when it started as a College of Monks. Now AGU School Corporation is one of the biggest private general universities in the area with a junior high school, a senior high school, technical college, undergraduate schools with 16 departments of 9 faculties and 9 graduate schools. It has three major campus in Nagoya area, the congress venue of Meijo Koen Campus is the newest one with ecological facilities. Among the presidents of company in Aichi Prefecture, the ratio of AGU graduates is the top. They lead the business community in this region. In addition, many prefectural councilors, city councilors are produced by AGU.

Registration Information

Welcome to the 59th Annual Meeting of the Japanese Teratology Society & the 13th World Congress of The International Cleft Lip and Palate Foundation!

Your registration and information desk are located on the 10 floor of the Agals Tower 26 July and first floor of the Castle Hall 27, 28 July.

Your JTS and ICPF full registration includes:

· Access to all academic program including the Workshop.

· Access to Hands-on Seminar (reservation in advance only)

· Access to the Opening Ceremony and Closing Ceremony.

· Participation in social programs, such as the Welcome Reception and Wine & Discussion.

· Participation in the Japanese Culture Experience Classes such as Tea Ceremony (Sado), Japanese Calligraphy (Shodo) and Zen. (Please make a reservation at the information desk)

Your JTS full registration includes

· Three Meal Coupons (lunch in Kinshachi Dining and Saru Café)

Your ICPF full registration includes

· Six Meal or Drink Coupons (lunch in Kinshachi Dining and Saru Café, breakfast/drink/bar in Saru Café)

· Shuttle Pass between Hotel Nagoya Castle and The Congress Venue, the Downtown (Departing from the Nagoya Tokyu Hotel) and the KKR Nagoya Hotel and the Conference Hall.

Additional Fee Ticket

· A ticket purchased in advance is required for Gala Dinner.

· Gala Dinner tickets are SOLD OUT.

· No on-site Gala Dinner Tickets are available.

General Information

Cloak Room –Luggage and Coat Check–

Cloak Room locates on the 10 floors of the Agals Tower 26 July and first floor of the Castle Hall. You may store your jacket and luggage while you are attending to the academic program 27, 28 July. It opens from 9:00 a.m. to 7:00 p.m.

Food and snacks:

The Congress Venue operates Kinshachi Dining and Saru Café, both offer a variety of food. Especially Kinshachi Dining offers you a variety of food, including some Don (rice bowl), Ramen, Pizza, Vegan Pizza as well as Gluten-Free Choice. Saru Café offers you breakfast from 8:00 a.m., lunch from 11:00 a.m., bar from 3:00 p.m. and coffee/ tea and other drinks all day.
Also the counter locating on the first floor of the Castle Hall offers you Grab-and-Go (pastries, onigiri and salad), snacks and coffee/tea/juice.

You can order what you feel like to eat and drink with your Meal or Drink Coupons at Kinshachi Dining and Saru Café.

Internet and Wi-Fi:

Free wireless internet service is offered by the Congress Venue. You find the internet ID and password at the registration desk.

Lounge:

The designated space for participants to gather and rest in between sessions is located on the first floor of the Castle Hall.

Poster Presentation

Poster presenters are not required to check in at the Speaker-Check-In Desk. Poster presenters are required to hang their poster material on their assigned poster boards. Posters must remain in place until the Wine and Discussion (July. 28).

All poster boards must be cleared after the closing ceremony, so presenters must remove their posters before/after the closing ceremony.

Restrooms:

Restroom facilities for men and women are conveniently located on each floor of the Castle Hall and the Agals Tower.

Smoking:

Smoking is not allowed inside/outside the Congress Venue except for the designated smoking area.

Speaker-Check-In

The Speaker-Check-In Desk locates on the 10th Floor of the Agals Tower on July 26 and by the registration desk on the first floor of the Castle Hall on July 27 and 28. Oral presentation speakers must provide their final presentation file to the stuff at the desk. USB is ONLY ACCPETABLE. All oral presentation speakers must check in at the Speaker-Check-In Desk at least 2 hours in advance of their respective sessions. (Presenters in sessions between 9:00-10:00 must check in at least 30 minutes in advance of their respective sessions)

Presenters are not allowed to use their own laptop/computer equipment in session rooms.

NOTE: The closing of the Speaker-Check-In on Sunday, July 28, will be 1:00 p.m.

Schedule at a Glance

Thursday, July 25

15:00 — 17:00	ICPF Board Meeting

Friday, July 26

8:30 — 17:00	Registration and Material Pickup
8:45 — 17:00	Speaker Check-In Open
9:00 — 10:15	CLEFT Sessions
10:15 — 10:30	Coffee Break
10:30 — 11:45	CLEFT Sessions
11:45 — 13:00	Lunch in the Saru Café/Kinshachi Dining
13:00 — 17:00	CLEFT Sessions
17:00 — 18:00	Welcome Reception

Saturday, July 27

8:30 — 17:00	Registration and Material Pickup
8:30 — 17:00	Speaker Check-In Open
9:00 — 9:45	Poster Check-In and Poster Lounge Open
10:00 — 12:00	Opening Ceremony Opening Remarks Humanitarian Award Ceremony/ Precious Award Ceremony Presidential Speech
12:00 — 13:00	Lunch in the Saru Café/Kinshachi Dining/ Grab-and-Go
13:00 — 19:00	Education Sessions/ General Sessions/ Posters
19:45 — 22:00	Gala Dinner

Sunday, July 28

8:30 — 13:00	Registration and Material Pickup
8:30 — 13:00	Speaker Check-In Open
9:00 — 18:30	Education Sessions/ General Sessions/ Posters
12:00 — 13:00	Lunch in the Saru Café/Kinshachi Dining
15:00	Vote Closing
17:30 — 18:30	Wine and Discussion/ Poster Presentations
18:30 — 18:50	Closing Ceremony (Award Ceremony)

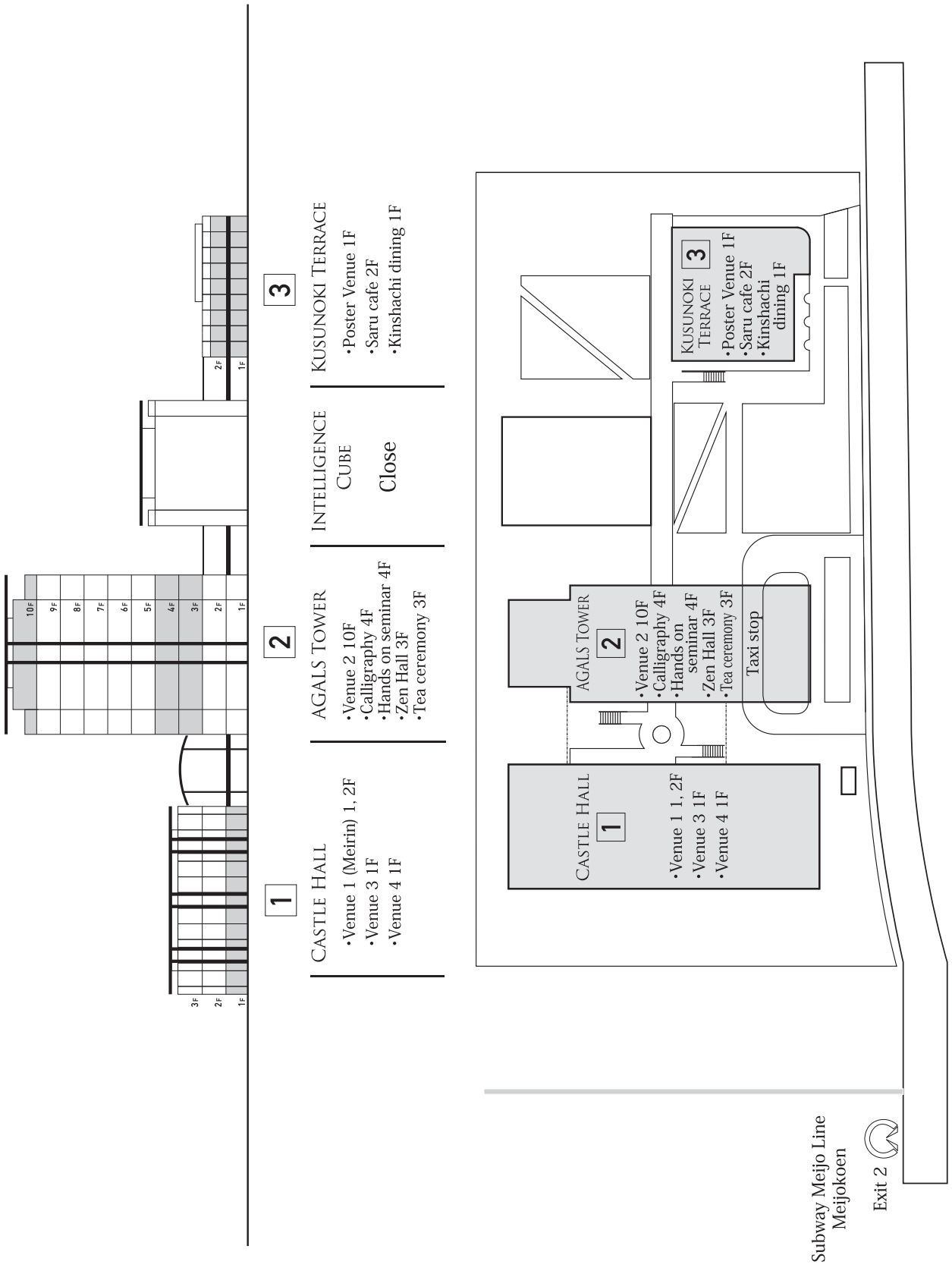
Monday, July 29

Excursion/ The Hamaoka Nuclear Power Station
9:00 — 19:00

The Japanese Teratology Society
Guidance of the board / Committee

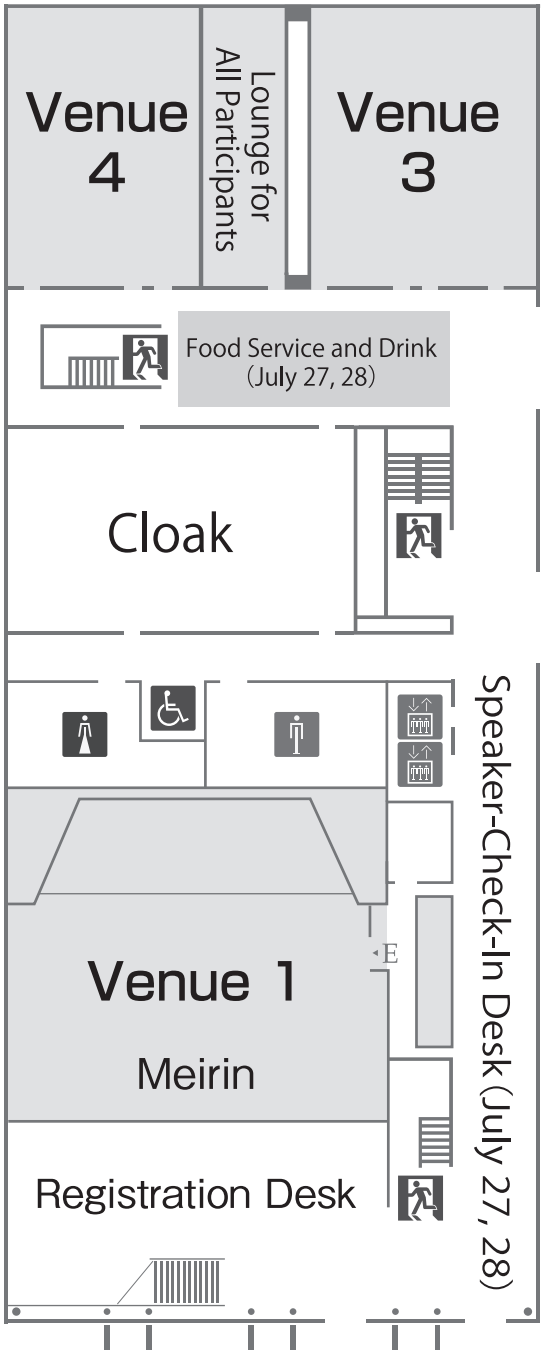
Board / Committee	Date	Time	Place
Board of Councilors General Meeting	July 27 (Sat.)	13:00 － 14:00	Venue 3
Governing Board	July 26 (Fri.)	09:30 － 12:00	Conference Room 2
Editorial Committee	July 26 (Fri.)	13:00 － 14:00	Conference Room 1
Developmental Neuro Toxicology (DNT) Committee	July 26 (Fri.)	14:00 － 15:00	Conference Room 1
Educational Committee	July 26 (Fri.)	14:00 － 15:00	Conference Room 2
Term Committee	July 26 (Fri.)	15:00 － 15:30	Conference Room 2
Future Plan Review Committee	July 26 (Fri.)	15:30 － 16:00	Conference Room 1
Academic Program Committee	July 26 (Fri.)	16:00 － 17:00	Conference Room 2

Floor Plan


1
CASTLE HALL
・Venue 1 (Meirin) 1, 2F
・Venue 3 1F
・Venue 4 1F
2
AGALS TOWER
・Venue 2 10F
・Calligraphy 4F
・Hands on seminar 4F
・Zen Hall 3F
・Tea ceremony 3F
INTELLIGENCE CUBE
Close
3
KUSUNOKI TERRACE
・Poster Venue 1F
・Saru cafe 2F
・Kinshachi dining 1F
CASTLE HALL 1
・Venue 1 1, 2F
・Venue 3 1F
・Venue 4 1F
AGALS TOWER 2
・Venue 2 10F
・Calligraphy 4F
・Hands on seminar 4F
・Zen Hall 3F
・Tea ceremony 3F
Taxi stop
KUSUNOKI TERRACE 3
・Poster Venue 1F
・Saru cafe 2F
・Kinshachi dining 1F
Subway Meijo Line
Meijokoen
Exit 2

Castle Hall

1F

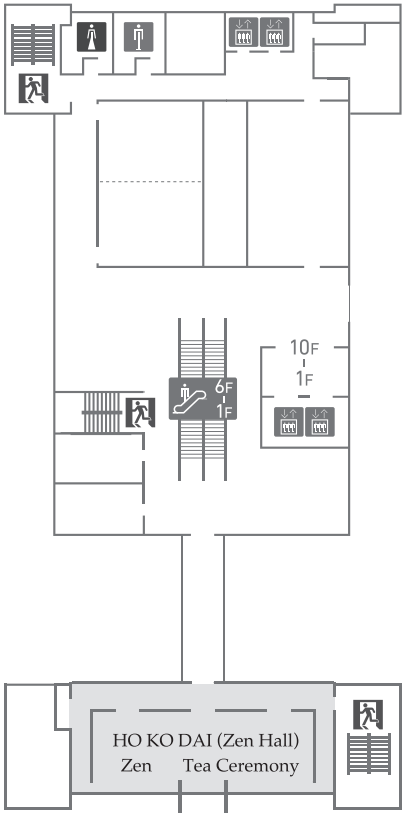


1F:
Concierge service

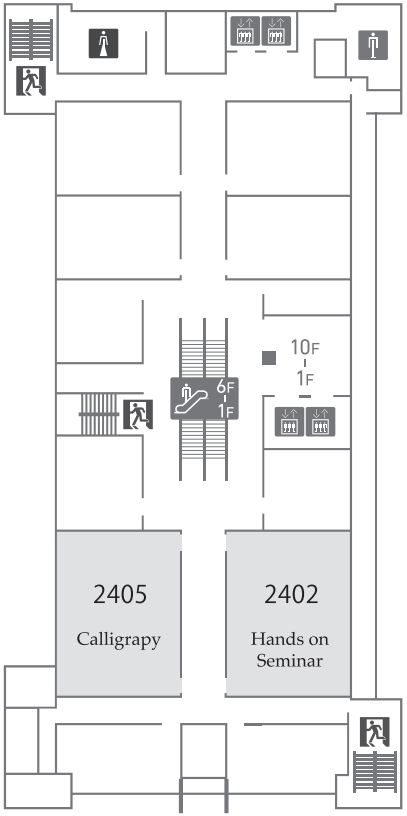
2F:
Book Store
Display of books

AGALS Tower

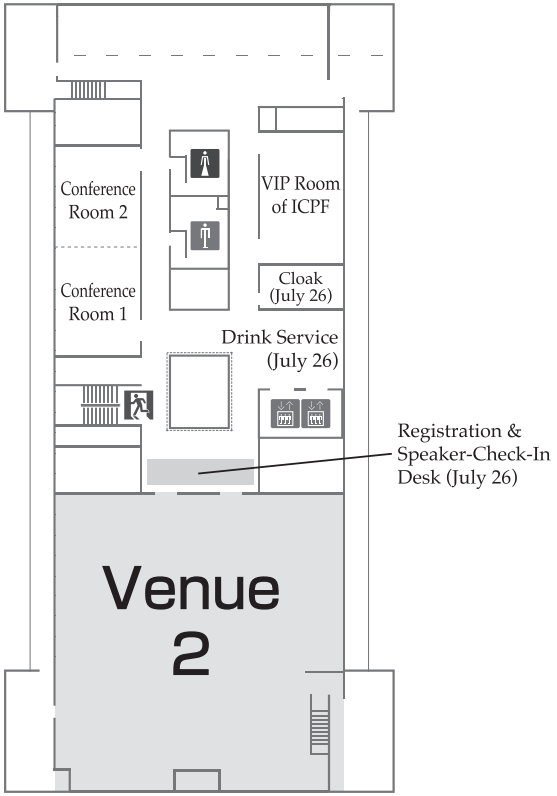
3F



4F

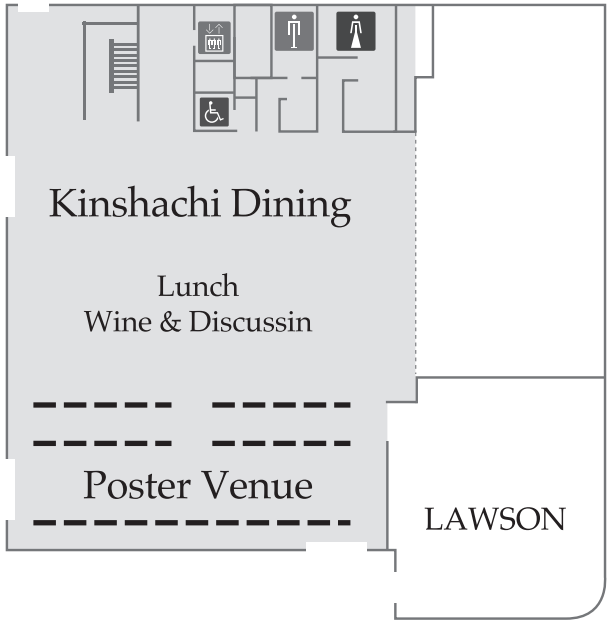


10F

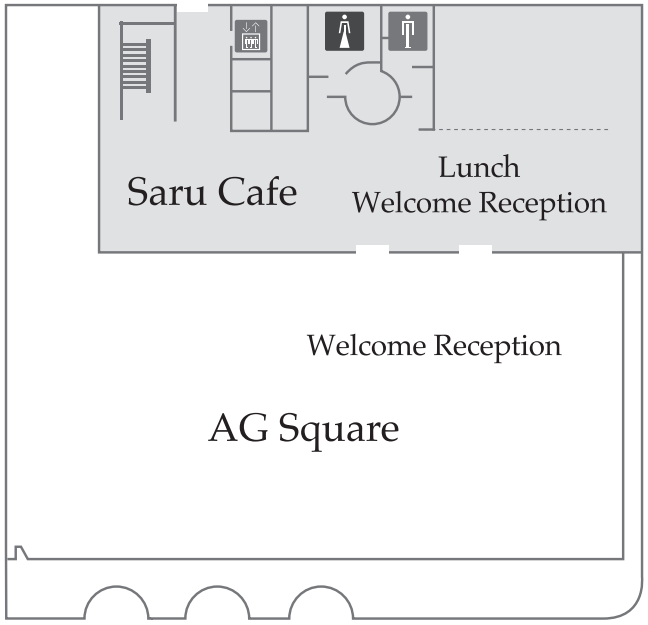


Kusunoki Terrace

1F



2F



July 26, 2019 VENUE 2

	VENUE 2			
		Affiliation	Lecturer	Chairperson
9:00	Primary surgery for unilateral cleft lip	Straight line repair for unilateral cleft lip	Makoto Noguchi ***P83***	Yoshihide Mori
9:15		Surgical correction of the mal-positioned nasal cartilages and the lining defect at the time of primary lip repair to treat unilateral cleft lip nasal deformity	Shunsuke Yuzuriha ***P84***	
9:30	Primary surgery for bilateral cleft lip	primary management and cheiloplasty for bilateral cleft lip and/ or palate patients	Kazuhide Nishihara ***P85***	
9:45	Primary surgery for cleft palate	Modified two-flap palatoplasty for primary cleft palate	Yasuyoshi Tosa ***P86***	
10:00		Palatoplasty	Hideto Saijo ***P87***	
10:15	Coffee Break			
10:30	Secondary surgery for cleft lip	Secondary Repair of Cleft Lip and Nose	Koichi Ueda ***P88***	Koichi Ueda
10:45		The strategy of secondary repair for unilateral and bilateral cleft lip	Yoshihide Mori ***P89***	
11:00	Alveolar bone graft surgery	Reliability of our simple evaluation system for alveolar bone grafting using CT images	Yoshimichi Imai ***P90***	
11:15		Monocortical mandibular bone grafting for reconstruction of alveolar cleft	Tadashi Mikoya ***P91***	
11:30	Secondary surgery for cleft palate (Speech Surgery)	Effects of intravelar veloplasty in repushback palatoplasty	Masaaki Sasaguri ***P92***	
11:45	Lunch Break（11:45-13:00）			

13:00 13:15 13:30 13:45	Cleft Lip Operation	Unilateral Cleft Lip/Nose Repair	Kenneth E Salyer ***P68***	SM Balaji
14:00	Speech aid	Speech assistant device	Teruyuki Niimi ***P93***	Yoichiro Kameyama
14:15	Prosthetic device	A transition of prosthodontic treatment for CLP patients	Shogo Ozawa ***P94***	
14:30	Fiberscope	Nasoendoscopic assessment of velopharyngeal function of cleft palate	Naoki Saito, Toko Hayakawa, Nagato Natsume ***P96***	
14:45	Coffee Break			
15:00	Orthodontic treatment	Early alveolar cleft closure using human umbilical cord mesenchymal stem cells in experimental model	Naoto Suda ***P95***	Yuri Fujiwara
15:15		Current approaches to orthodontic management of cleft lip and palate and future perspective	Noriaki Yoshida ***P98***	
15:30	Speech therapy for cleft palate	Dental appliances employed in treatment of cleft palate speech -for improvement of velopharyngeal insufficiency and articulation disorders-	Ichiro Yamamoto ***P99***	
15:45		Bulb type palatal lift prosthesis (bulb-PLP) therapy for velopharyngeal dysfunction in cleft palate	Yuko Ogata ***P100***	
16:00		Electropalatography observation of cleft palate speech to supplement perceptual assessment	Yuri Fujiwara ***P101***	
16:15	Osteotomy	Treatment of sever jaw deformities due to cleft lip and palate using distraction osteogenesis	Nobuyuki Mitsukawa ***P102***	
16:30		Orthognarthic surgery in the consistent treatment protocol of cleft lip and palate.	Tomohiro Yamada ***P103***	
17:00	Welcome Reception at SARU Café			

July 27, 2019 VENUE 1 & 2

Poster Venue: Kusunoki Terrace 1F Kinshachi Dining
Exhibition 12:00 p.m.～7:00 p.m.

	VENUE 1 (English)		VENUE 2 (English)	
		Chairperson		Chairperson
10:00	Opening ceremony			
	Presidential Speech Nagato Natsume ***P67***	Kenneth E Salyer (USA)		
12:00	Lunch Break			
13:00	Keynote Lecture; Craniofacial Surgery: Past, Present, Future Kenneth E Salyer (USA) ***P69***	Nagato Natsume (Japan)	Comprehensive Team Care for Children with 22q11.2 Deletion Syndrome Richard E.Kirschner Adriane L.Baylis Canice Ellen Crerand Courtney E.Hall (USA) ***P78***	Robert A. Sader (Germany)
13:15				

13:30 13:45 14:00 14:15	Keynote Lecture; Folic Acid, Prevention of birth defects, and epigenetics: Marie M Tolarova (USA) ***P70***	Anastasia Maclennan (Russian Federation)	Comprehensive Team Care for Children with 22q11.2 Deletion Syndrome Richard E.Kirschner Adriane L.Baylis Canice Ellen Crerand Courtney E.Hall (USA) ***P78***	Robet A. Sader (Germany)
14:30	Long-term outcomes of 41 nonsyndromic sagittal craniosynostosis patients as adults: Gyorgy K Sandor (Finland) ***P122***	Mzubanzi Mabongo (South Africa)	Evaluation of velopharyngeal complex in children after veloplasty: Oleg Shafeta (Ukraine) ***P193*** Vomer morphometric parameters in norm and children with bilateral complete cleft lip and palate: Oleg Shafeta (Ukraine) ***P193***	Lian Ma (China)
14:45	Functional and aesthetic outcome in cleft nose repair: Siegmar Wilfried Reinert (Germany) ***P192***		Bony Syngnathia - a rare congenital anomaly: Myra Elliott (Singapore) ***P131***	
15:00	Towards establishment of 'Embryatrics'; revisited and to be continued: Hiroki Otani (Japan) ***P73***	Hiroaki Aoyama (Japan)	Coffee Break	
15:15			Orthodontic treatment in Hemifacial Microsomia Martin Romero (Spain) ***P133***	Naoto Suda (Japan)
15:30 15:45	Where do we come from? What are we? Where are we going? - A teratologist's personal perspective: Kohei Shiota (Japan) ***P76***	Hiroshi Otani (Japan)		
16:00 16:15	My Experience as a Member of the Japanese Teratology Society for 56 Years: Mineo Yasuda (Japan) ***P77***	Kenji Kurosawa (Japan)	Cleft missions of Korean Association of Maxillofacial Plastic and Reconstructive Surgeons with a case of bilateral Tessier No. 3 cleft: Youngwook Park (Korea) ***P134*** Global Evaluation of Surgical Techniques and Results of bilateral Cleft Lip Repairs: Angela S. Volk (USA) ***P194*** A Model Demonstrating an Internationa Cleft Charity's Work in Eliminating the Backlog of Unrepaired Cleft Lip Cases: Angela S. Volk (USA) ***P194***	Myra Eliott (Singapore) Youngwook Park (Korea)

16:30	Identification of new syndromes and its implications: Kenjiro Kosaki (Japan) ***P75***	Sachiko Iseki (Japan)	Utilization of Cleft Lip and Palate Post-Operative Care Guidebook for Caregivers Based on Local Wisdom for Rural Area Communities: Anindita Zahratur Rasyida (Indonesia) ***P210***	Youngwook Park (Korea)
			Result of organization in-country mission for last 15 years in Uzbekistan: M.M.Jafarov (Uzbekistan) ***P195***	
16:45			Overseas medical support activities for patients with Cleft Lip and Palate in Laos : Hajime Sunakawa (Japan) ***P104***	
17:00	SURVEY SHEETS IMPLEMENTATION IN PRENATAL DIAGNOSIS AND CONSULTATION AMONGST COULPS EXPECTIONG CHILDREN WITH CLEFT LIP AND PALATE: Maclennan A.B. (Russian Federationn) ***P125***	Noriaki Yoshida (Japan)	Experiences of cleft lip and palate volunteers in the Republic of Tunisia since 2007: Takehiro Fujimoto (Japan) ***P105***	
17:15	Challenge for treatment of congenital maxillofacial anomalies using tissue engineering: Kazuto Hoshi (Japan) ***P163***		Associated genetic anomalies and clinical manifestations ; are etiological factors for prenatal and postnatal growth retardation among patients with cleft palate in Sri-Lanka ? Lahiru Prabodha Lande Bandarage（Sri Lanka） ***P136***	Miroslav Tolar (USA)
17:30	Secondary Alveolar Bone Grafting, My Clinical Perspective: Aysegul M.Tuzuner: (Turkey) ***P126***	Ana Tache (Belgium)	Coffee Break	
17:45	Piloting the Use of ICHOM in Children with Clefts: Speech and Communication: Selena Ee-Li Young (Singapore) ***P127***		THE APPLICATION OF 3D IMPRESSION IN THE PRESURGICAL ORTHOPEDICS IN BILATERAL CLEFT LIP: Nagore SOLAECHE (Spain) ***P192***	Geoff Williams (USA)
			Orthodontic Management of a Pre-pubertal Patient with Schwartz-Jampel Syndrome (SJS) to Alleviate Severe Obstructive Sleep Apnea (OSA): Thanate Assawakawintip (Thailand) ***P195***	
18:00	Cytomegalovirus Initiates Infection Selectively from High-Level β1 Integrin-Expressing Cells in the Brain: Hideya Kawasaki (Japan) ***P156***	Rika Kosaki (Japan)	Surgical Correction of Velopharyngeal Insufficiency with functional reconstruction of soft palate: Hongping Zhu (China) ***P196***	Rizk Girgis (Egypt)
18:15	Mesenchymal-derived actomyosin contractility is required for the tissue fusion during tubular urethral formation in mice: Kentaro Suzuki (Japan) ***P155***		Folded Pharyngeal Flap Methed: 40 years expelience: Masaki Sawada (Japan) ***P145***	
18:30	Critical Growth Processes for Morphogenesis of the Midfacial Skeleton in the Early Prenatal Period: Motoki Katsube (Japan) ***P144***		A palatal pushback operation combined with musclo-mucosal flap from the posterior pharyngeal wall: Yoshio Yamawaki (Japan) ***P146***	
18:45	Sulcal infolding abnormality induced by exposure to valproic acid at the late stage of cortical neurogenesis in ferrets: Kazuhiko Sawada (Japan) ***P154***		International medical assistance for cleft lip and palate in Indonesia: Muhammad Ruslin (Indonesia) ***P137***	
			OUTCOMES OF SECONDARY ALVEOLAR BONE GRAFTS IN CLEFT PATIENTS: Mzubanzi Mabongo (South Africa) ***P205***	
19:00				
19:45	Gala Dinner (Reseravation in advance only) at Tenshunoma (Kings Room) Hotel Nagoya Castle 2F			

July 27, 2019 VENUE 3 & 4

Poster Venue: Kusunoki Terrace 1F Kinshachi Dining
Exhibition 12:00 p.m.～7:00 p.m.

	VENUE 3 (Japanese)		VENUE 4 (English)	
		Chairperson		Chairperson
10:00			Opening ceremony broadcast VENUE 1	
11:30				
12:00	Lunch Break			
13:00	JTS General Assembly / Council of Councilors (JTS Member Only)			
13:15				

13:30 13:45	13:40 ～ Letter of thanks presented (JTS Member Only)			
14:00	A molecular mechanism of hyperactivity in animal model of congenital hyperbilirubinemia: Arata Oh-Nishi (Japan) ***P168***	Tadashi Kaname (Japan)	Craniosynositosis diagnosed during fetal and neonatal periods: Aya Harada (Japan) ***P157***	Kenneth E Salyer (USA)
14:15	Dietary folate intake in young women: Comparison between university students in the Department of Nutrition and other departments: Mami Hiraoka (Japan) ***P184***		Craniosynostosis: diagnosis and current surgical treatment: Northwestern University Feinberg School of Medicine Akira Yamada (USA) ***P138***	
14:30	The mechanism of the L-arginine effect on culture rat embryos: Atsushi Yokoyama (Japan) ***P169***		Kenote Lecture: 20 Years of Empowering Medical Professionals in LMICs to Provide Safe, High-Quality Cleft Care Agrawal Karoon (India) Smile Train ***P72***	
14:45	Maxillary growth and speech outcomes of 10-year-old children after simultaneous lip and palate repair using presurgical orthodontics:Ushio Hanai (Japan) ***P170***			
15:00	International standardization of reproductive and developmental toxicity tests 1 The current actions for development of pediatric medicines and future perspective: Kikuko Ikeda Pharmaceutical and Medical Devices Agency ***P106***	Kiyoshi Matsumoto (Japan) Hiroshi Mineshima (Japan)	Demystifying assessment of speech in individuals with cleft lip and palate: Savitha Vadakkanthara Hariharan (India) ***P139***	
15:15			Diagnosis and treatment of VPD: A Global Survey Angie C Morillas（USA） ***P140***	Selena Ee-Li Young (Singapore)
15:30	2 Development of evaluation systems for brain development using mouse models of developmental disorders: Shigeo Uchino, Hitomi Shimizu, Chikako Waga Graduate School of Science and Engineering, Teikyo University ***P107***		Unpredictable speech outcome on Submucous Cleft Palate: Lian MA (China) ***P142***	
15:45			Nature of oral-glottal double articulation in patients with velopharyngeal insufficiency— Consideration of laryngeal involvement in consonant production —: Naohiro Kido (Japan) ***P147***	
16:00	3 Acoustic Startle Response and Prepulse Inhibition :Mikio Sasaki Ina Research, Inc. ***P108*** 4 Allocation method of juvenile rat toxicity study :Ayumi Inoue Drug Safety Research Laboratories, Shin Nippon Biomedical Laboratories, Ltd. (SNBL DSR) ***P109***		Articulation therapy for the clients with glottal stops accompanying velopharyngeal insufficiency -Prevention of oral-glottal double articulation-:Jin Kawamura (Japan) ***P210***	
16:15			Preliminary study of Electroglottography application on glottal stop in Mandarin cleft palate patients: Zhen Ren (China) ***P206*** Longitudinal study of vocal development and language environments in Korean-learning children with and without cleft palate: Seunghee Ha (Korea) ***P207***	

16:30			Long-term outcomes of primary palate surgery -one surgeon's experience: Ana Tache (Belgium) ***P193***	Selena Ee-Li Young (Singapore)
16:45			Secondary correction of cleft lip nasal deformity: Jin-Young Choi (Korea) ***P119***	Adil Mamedov (Anastasia Maclennan) (Russian Federation)
17:00	Role of orthodontics in the team approach to cleft lip and palate care: assessing the effectiveness of the NAM appliance: Momotoshi Shiga (Japan) ***P171***	Shigetaka Yanagisawa (Japan)	CAD-CAM construction of a pilot guide for a bone-anchored epithesis to replace an absent pinna: Ana Tache (Belgium) ***P209***	
17:15	Long term assessment of the effects of occlusal management and oral myofunctional therapy in cleft lip and palate patients: Junko Nagata (Japan) ***P172***		The Triangular Skin-white Roll Flaps Technique for Creation of Cupid's Bow in Bilateral Cheiloplasty: Geoff Williams (USA) ***P209*** Our 15-years experience for chelioplasty: Murod M. Jafarov (Uzbekistan) ***P208*** Prevention of postoperative deformities in treatment of children with congenital cleft lip: Yuliya Stepanova (Russian Federation) ***P208***	
17:30	Genome sequence for diagnosis and successive research of genetic disorders.: Koh-ichiro Yoshiura (Japan) ***P173***	Nobuhiro Suzumori (Japan)	The Challenge of Operating Clefts in Mozanbique: Antonio Alberto (Mozanbique) ***P143***	
17:45			Cut Back: a new technique of repair of wide bilaleral cleft lip: Mohammad Mughese Amin (Pakistan) ***P128***	Akira Yamada (USA)
18:00	Pioneer's message: A senior sending a message to junior: Ryozo Hashimoto (Japan) ***P186***		EXPERIENCE OF ISLANDED GREATER PALATINE ARTERY FLAP FOR ANTERIOR ORONASAL FISTULA REPAIR : Mohammad Mughese Amin (Pakistan) ***P129***	
18:15	Role of formin-mediated actin assembly in mouse cranial neurulation: Ryu Takeya (Japan) ***P174***		Adult cleft lip and palate : a last chance: Mohammad Mughese Amin (Pakistan) ***P130***	
18:30	Diagnosis and treatment of craniosynostosis - Current status and problems -: Takuya Akai (Japan) ***P185***	Hajime Sunagawa (Japan)		
18:45	Problems and measures of complicated cleft lip and palate treatment: Azusa Watanabe (Japan) ***P175***			
19:00				
19:45	Gala Dinner (Reseravation in advance only) at Tenshunoma (Kings Room) Hotel Nagoya Castle 2F			

July 28, 2019 VENUE 1 & 2

Poster Venue: Kusunoki Terrace 1F Kinshachi Dining
Exhibition 9:00 a.m.～5:30 p.m.
Wine & Discussion（Free）（Poster presentation）
at Kinshachi Dining 5:30 p.m.～

14:00 -17:00 Microtia Hands-on Workshop: Creating 3D Framework with Rib Cartilage Model
Kenneth E Salyer（World Craniofacial Foundation/International Cleft Lip and Palate Founation)
Akira Yamada (Northwestern University Feinberg School of Medicine)
Room 2402 (AGALS Tower 4F)

<table>
<tr><th></th><th colspan="2">VENUE 1 (English)</th><th colspan="2">VENUE 2 (English)</th></tr>
<tr><td></td><td></td><td>Chairperson</td><td></td><td>Chairperson</td></tr>
<tr><td>9:00</td><td rowspan="4">Symposium: Congenital anomaly monitoring in Japan

Population-based case-control study: Kanagawa Birth Defects Monitoring Program (KAMP):
Kenji Kurosawa (Japan) P79

Epidemiological study on patients with cleft lip and palate in Tokai area, Japan:
Hideto Imura (Japan) P80

Survey of pregnant women in Fukushima prefecture:
Hyou Kyozuka (Japan) P81

Congenital Anomaly Monitoring in Japan:
Kentaro Kurasawa (Japan) P82</td><td rowspan="4">Fumiki Hirahara
(Japan)</td><td>Assessment of orthodontic treatment outcome using Peer Assessment Rating (PAR) index among patients with unilateral cleft lip and palate:
Satineder Pal Singh (India) P196</td><td rowspan="3">Martin Romero
(Spain)</td></tr>
<tr><td>9:15</td><td>Algorithm of complex surgical and orthodontic treatment of children with congenital bilateral cleft lip and palate in deciduous dentition:
Irina Fomenko (Russian Federation) P197</td></tr>
<tr><td></td><td>Orthodontic treatment in the management of patients with cleft lip and palate:
Yilin JIA (China) P198</td></tr>
<tr><td>9:30</td><td>How is the created alveolar space finally restored after Maxillary Anterior Segmental Distraction Osteogenesis?:
Jung Yul Cha (Korea) P197</td><td rowspan="3">Kazuto Hoshi
(Japan)</td></tr>
<tr><td></td><td>Repair of huge anterior palatal fistula in bilateral cleft lip and palate patient using double anterior pedicel dorsal tongue flaps:
Xia ZHOU (China) P198</td></tr>
<tr><td>9:45</td><td>Comparison of West China SF palatoplasty and Sommerlad intravelar palatoplasty : 1128 Cases included: Yang LI (China) P198</td></tr>
<tr><td></td><td></td><td></td><td>Skeletal Stability of Le Fort I osteotomy in patients with Cleft Lip and Plate:
Sang Hun Park (Korea) P198</td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="2">Coffee break</td></tr>
<tr><td>10:00</td><td rowspan="2">Human Embryology and Kyoto CIlection:
Shigehito Yamada (Japan)
P74</td><td rowspan="2">Yuji Nakajima
(Japan)</td><td rowspan="2">Management of Orbital dystopia in Craniofacial Clefts: SM Balaji (India)
P135</td><td rowspan="4">Aysegul M.Tuzuner
(Turkey)</td></tr>
<tr><td>10:15</td></tr>
<tr><td>10:30</td><td rowspan="2">Tissue engineering using mesenchymal stem cells in dental science:
Masaki Honda (Japan)
P148</td><td rowspan="2">Jun Takebe
(Japan)</td><td>Sonic hedgehog is required for patterning of the intrinsic tongue musculature:
Sachiko Iseki (Japan)
P167</td></tr>
<tr><td>10:45</td><td>Intestinal loop formation: herniation into the extraembryonic coelom and return to the abdominal coelom: Tetsuya Takakuwa (Japan) P166</td></tr>
</table>

11:00	Workshop; Proven Techniques for Cleft Lip and Palate and Microtia : Kenneth E Salyer (USA) (World Craniofacial Foundation) Akira Yamada (USA) (Northwestern University Feinberg School of Medicine) ** Discussion time until 13:00 at Room 2402 in Agals Tower (4F) ***P117***	Gyorgy Sandor (Finland)	Costello syndrome phenotype with a de novo MRAS mutation: Hisato Suzuki (Japan) ***P211***	Ariuntuul Garidkhuu (Mongolia)
11:15			Application of teeth and bone co-supported interdental distraction osteogenesis in the treatment of extensive alveolar cleft: Jiaqiang Liu (China) ***P199***	
11:30			Application of CGF in patient of poor wound healing after alveolar cleft bone grafting: case report: Dandan Wu (China) ***P200***	
11:45			What can we do for facial cleft Patients?: Dandan Wu (China) ***P200***	
			Speech Outcomes in the patients with Asymmetric Cleft Palate after Double-Opposing Z-Palatoplasty: Hyeonwoo Kim (Korea) ***P199***	
			Preliminary Study on Classification of Cleft Palate Bone Defect: Feifei SHANG (China) ***P199***	
			Boosting fetal medicine in Japan: Nobuhiko Hayashi (Japan) ***P152***	
12:00	Lunch Break			
13:00	22q11.2 deletion syndrome: clinical phenotypes to pathogenesis of mental disorders associated with this variant.: Genome Medical Center, Nagoya University Hoslital Norio Ozaki (Japan) ***P158***	Michiko Yamanaka (Japan)	The development of a 3D printing trans-sinus maxillary distraction device on cleft patient: Ming Cai (China) ***P209***	Siegmar Wilfried Reinert (Germany)
13:15			Prevalence of supernumerary teeth in children with cleft lip and/or palate: A CBCT study: Ravi Kumar Gudipaneni (India) ***P202***	
13:30			Cleft Lip Palate Profile and Influence of Distance from Hospital and Nutritional Status in Surabaya, Indonesia: Rosalyn Devina Santoso (Indonesia) ***P201***	
13:45			Post Operative seizure following Cleft Lip Surgery: Rosalyn Devina Santoso (Indonesia) ***P201***	
			Improving orthognathic surgery in patients with bilateral cleft lip and palate: Maria Ivanovna Shuba (Russian Federation) ***P201***	
			Unilateral Microform Cleft Lip Repair Through Intraoral and Intranasal Mucosal Incisions in adult patients: Yongqian Wang (China) ***P202***	
			Evaluation of lip symmetry after nasoalveolar molding in patients with unilateral cleft lip and palate - A four year follow up study: Abdulaziz Othman Alyahyawi (Kuwait) ***P202***	
			Patients with cleft lip and/or palate at orthodontic depatment of Kyungpook National University in Republic of Korea from 2007 to 2016: Mihee Hong (Korea) ***P200***	
14:00	Management of Obstructive sleep apnea in craniofacial deformities: Adi Rachmiel (Israel) ***P120***	Alexander Ivanov (Russian Federation)	Speech and neurologic development in cleft palate with and without Pierre Robin Sequence: Michael Krimmel (Germany) ***P203***	Marie Tolarova (USA)
14:15	Management of Maxillary Cleft Deficiency -- Distraction Osteogenesis Vs conventional orthognathic surgery: Adi Rachmiel (Israel) ***P121***		The mortality and morbidity of very low birth weight (VLBW) infants with trisomies in Japan.: Hidenori Kawasaki (Japan) ***P211***	
14:30	The outcomes of monocortical mandibular bone grafting of alveolar cleft: Soichi Tanaka (Japan) ***P149***		Effectiveness of integrated interpretation of exome and corresponding transcriptome data in detecting splicing variants: Population and clinical studies: Mamiko Yamada (Japan) ***P212***	
			Mouse resource infrastructure for studies of genome functions and disease mechanisms: Atsushi Yoshiki (Japan) ***P212***	
			Reduction of CDK8 kinase activity induces human congenital defects through inhibition of WNT pathway: Tomoko Uehara (Japan) ***P213***	
			Rogdi plays an important role during enamel mineralization: Silvia Naomi Mitsui (Japan) ***P214***	

14:45	The role of retinoic acid signaling for developing the face: Hiroshi Kurosaka (Japan) ***P150***	Alexander Ivanov (Russian Federation)	Coffee Break	
15:00	Primary Microcephaly and D40: Masato Takimoto(Japan) ***P159***	Orest Zinovievitch Topolniatsky (Russian Federation)	Challenges in cleft patients rehabilitation and the ways to overcome it: Alexander Ivanov (Russian Federation) ***P132***	Adi Rachmiel (Israel)
15:15			New strategies to prevent Neural Tube Defects by folic acid supplementation with public-private partnership in Japan: Seika Kamohara (Japan) ***P214***	
			Anthropometric measurements analysis in patients age 4-6 and patients age 9-11 with unilateral aveolar cleft prior to and after bone grafting: Artem Vitalievich Makeev (Russian Federation) ***P203***	
15:30	Essential Roles of Mesenchymal Stem Cells in wound healing: Miroslav Tolar (USA) ***P123***	Anastasia Maclennan (Russian Federation)	Premaxillary osteotemy in treatment of bilateral cleft lip and palate: Yang LI (China) ***P204***	
			A Three-Center Study of Dental Arch Relationships Outcomes Following Two-Stage Palatoplasty: Junya Kato (Japan) ***P213***	
15:45	Keynote: An Update from the Teratology Society (North America) : Elise Madison Lewis (USA) ***P71***		Continuing research to provide coordinated care for patients with 22q11.2 deletion syndrome: Chiaki Kitamura (Japan) ***P160***	
16:00			Factors affecting the post-operative velopharyngeal function in adult patients: Yang Chen (China) ***P205***	Lahiru Prabodha Lande Bandarage (Sri Lanka)
			Multiple distraction osteogenesis in upper arch for maxillary three-dimensional hypoplasia on patients with cleft palate: Zhu Min (China) ***P205***	
16:15	In utero gene therapy for cleft palate: Masayuki Endo (Japan) ***P161***	Yuhei Nishimura (Japan)	Evaluation of The Airway Spaces in Patients With and Without Cleft Lip and Palate Using Cone Beam Computed Tomograph: Kevser Tutunculer Sancak (Turkey) ***P204***	
			Rhinoplasty with combination of diced costal cartilage and caved framework for treatment of secondary nasal deformity of unilateral cleft lip: Bin Zhang (China) ***P206***	
16:30	Genetic counseling for prenatal diagnosis: Nobuhiro Suzumori (Japan) ***P153***		A prospective cohort study of patients with 22q11.2 deletion syndrome aiming at early detection and treatment of psychiatric disorders: Shu Kushima (Japan) ***P162***	
16:45	Boosting prenatal support in Japan: Nobuhiko Hayashi (Japan) ***P152***		Current Status of Cleft Lip and Palate Care in Iraq Ali Mohammed saeed Alkhayat (Iraq) ***P164***	Mario Esquillo (Philipine)
17:00	MULTIDICIPLINARY APPROACH TO CLEFT LIP AND PALATE TREATMENT OF CHILDREN IN A NEWBORN PERIOD: Mamedov Ad.A. (Russian Federation) ***P124***		Prediction of Cleft Lip and Palate with the application of genetic markers of folic acid and genes of detoxication of xenobiotics in regions with ecotoxicants: Sergei V Chuykin (Russian Federationn) ***P165***	
17:30	Wine and Deiscussion / Poster Presentations　POSTER VENUE			
18:30	Closing Remarks at POSTER VENUE			

July 28, 2019 VENUE 3 & 4

Poster Venue: Kusunoki Terrace 1F Kinshachi Dining
Exhibition 9:00 a.m.～5:30 p.m.
Wine & Discussion（Free）（Poster presentation）
at Kinshachi Dining 5:30 p.m.～

14:00 -17:00 Microtia Hands-on Workshop: Creating 3D Framework with Rib Cartilage Model
Kenneth E Salyer（World Craniofacial Foundation/International Cleft Lip and Palate Founation)
Akira Yamada (Northwestern University Feinberg School of Medicine)
Room 2402 (AGALS Tower 4F)

	VENUE 3 (Japanese)		VENUE 4 (Japanese)	
		Chairperson		Chairperson
9:00	General purpose drug teratogenicity seminar >> Cleft palate observed in developmental and reproductive study: Hanako Yamasaki (Japan), Kazuhiro Shimomura (Japan) ***P113*** >> Corticosteroids during pregnancy and cleft lip and palate: Ai Ohno(Japan) ***P115*** >> Consideration of cleft lip and palate caused by antiepileptic drug: Masayuki Maeda (Japan) ***P114*** >> Clinical evaluation of antipsychotic drugs: Yuri Fushimi (Japan) ***P116*** >> Discussion	Kazuhiro Shimomura (Japan), Masahiro Hayashi (Japan)	Influences of biotin on fetal development in mice.: Hiromi Sawamura (Japan) ***P188***	Akimune Fukushima (Japan)
9:15			Two patients with Au-kline syndrome : Nobuhiko Okamoto (Japan) ***P189***	
9:30			Perinatal diagnosis and management of skeletal dysplasias: Jun Murotsuki (Japan) ***P181***	Tomohiro Yamada (Japan)
9:45			Sleep pattern of before and after surgery in infants with cleft lip and palate: Ryo Murasugi (Japan) ***P182***	
10:00			Effect of L-proline on cultured rat embryos: Masaharu Akita (Japan) ***P183***	
10:15			Role of clinical genetics in a medical healthcare facility for children with disabilities: Seiji Mizuno (Japan) ***P190***	Nobuhiko Okamoto (Japan)
10:30				
10:45			Prenatal exposure to thalidomide cause abnormalities of inhibitory neuron in rat olfactory nervous system: Ida Eto M (Japan) ***P215*** A novel de novo variant in the MAP3K7 gene causes Cardiospondylocarpofacial syndrome by dominant-negative effect.: Tadashi Kaname (Japan) ***P216***	

11:00			Effects of alveolar bone grafts on the quality of life (QoL) of patients with alveolar bone defects: Takao Minamidate (Japan) ***P216***	Nobuhiko Okamoto (Japan)
			Immunohistological study for the connection between the testis and epididymis: Takuya Omotehara (Japan) ***P217***	
11:15			3D computer-assisted two-layer and three-layer facial models of the congenital anomaly and AR technology: Misato Katayama (Japan) ***P215***	
11:30			Heparanase during palate formation in mice: Azumi Hirata (Japan) ***P191***	
11:45				
12:00	Lunch Break			
13:00	Reproductive developmental development education seminar 1. 13:00 - 13:55 From fertilization to implantation Masako Yamamoto (Professor Emeritus of Azabu University) ***P110***	Yoshinori Kawamura (Japan), Kenichi Noritake (Japan)		
13:15				
13:30				
13:45	2. 13:55 - 14:50 Genetic variants and congenital anomalies Hirotomo Saitsu (Professor ofBiochemistry Department, Hamamatsu University School of Medicine) ***P111***			
14:00	14:50 – 15:05 Coffee Break 3. 15:05 - 16:00 The current situation and future of prescription drug package inserts in Japan Hiromi Hamada (Professor of Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tsukuba) ***P112***		14:00 -17:00 Microtia Hands-on Workshop: Creating 3D Framework with Rib Cartilage Model Kenneth E Salyer（World Craniofacial Foundation/International Cleft Lip and Palate Founation) Akira Yamada (Northwestern University Feinberg School of Medicine) Room 2402 (AGALS Tower 4F)	
14:15				
14:30				

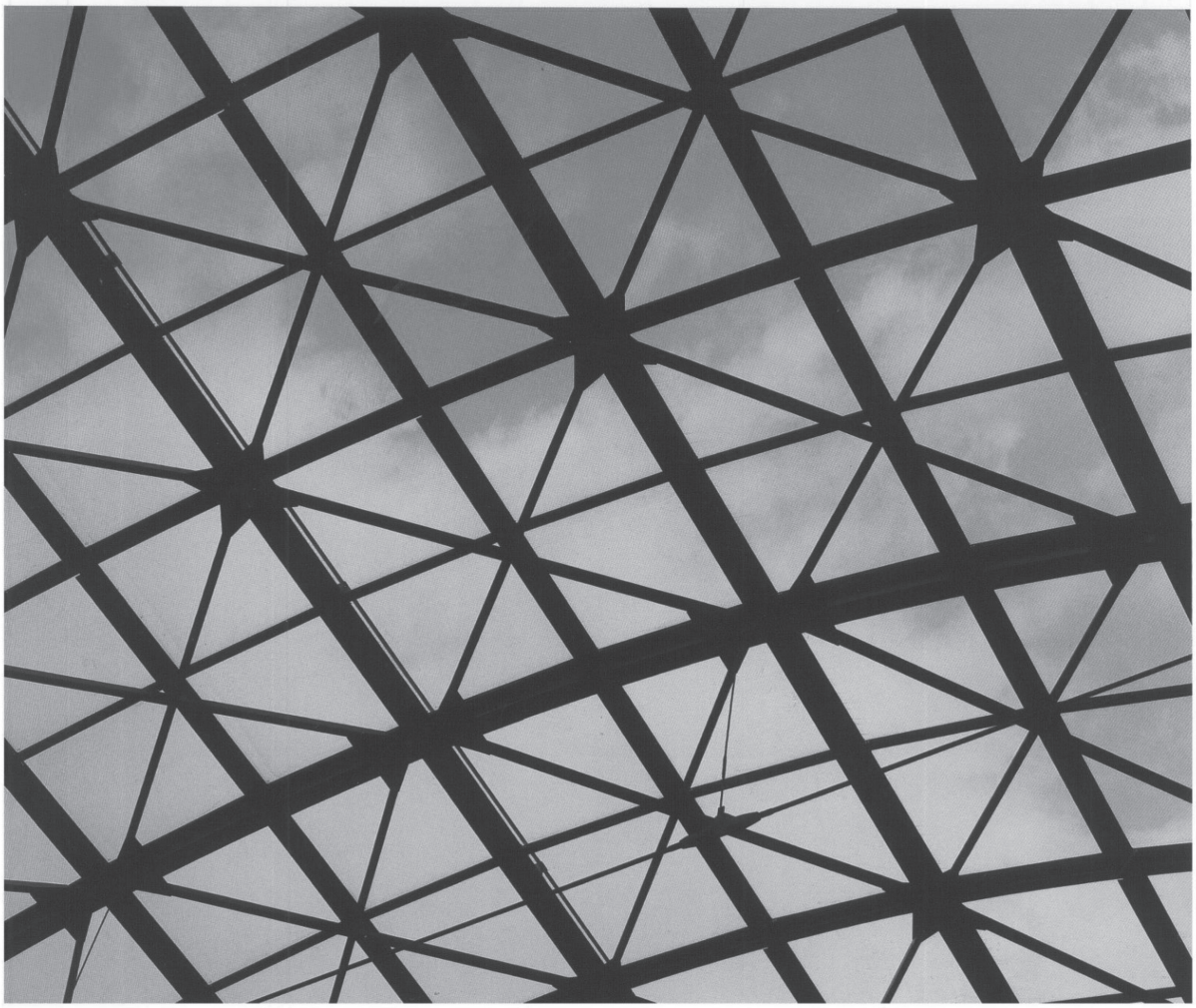
14:45		
15:00		
15:15		
15:30		
15:45		
16:00	How to use the latest genetic information and technology in clinical practice?: Haruka Hamanoue (Japan) ***P176***	Seiji Mizuno (Japan)
16:15	Evaluation of Face2Gene using facial images of patients with congenital dysmorphic syndromes recruited in Japan: Hiroyuki Mishima (Japan) ***P177***	
16:30	IGF2 overexpression due to IGF2-DMR0 hypomethylation in Sotos syndrome.: Ken Higashimoto (Japan) ***P178***	
16:45	A survey to primary maternity clinics for editing a manual to study prenatal genetic testing.: Takahiro Yamada (Japan) ***P179***	
17:00	A novel in vivo role of the schizophrenia-related gene, FILIP: Hideshi Yagi (Japan) ***P180***	
17:15	Neural Tube Defects are folic acid preventable: How many of such pregnancies have been terminated?: Atsuo Kondo (Japan) ***P187***	
17:30	Wine and Deiscussion / Poster Presentations　POSTER VENUE	
18:30	Closing Remarks at POSTER VENUE	

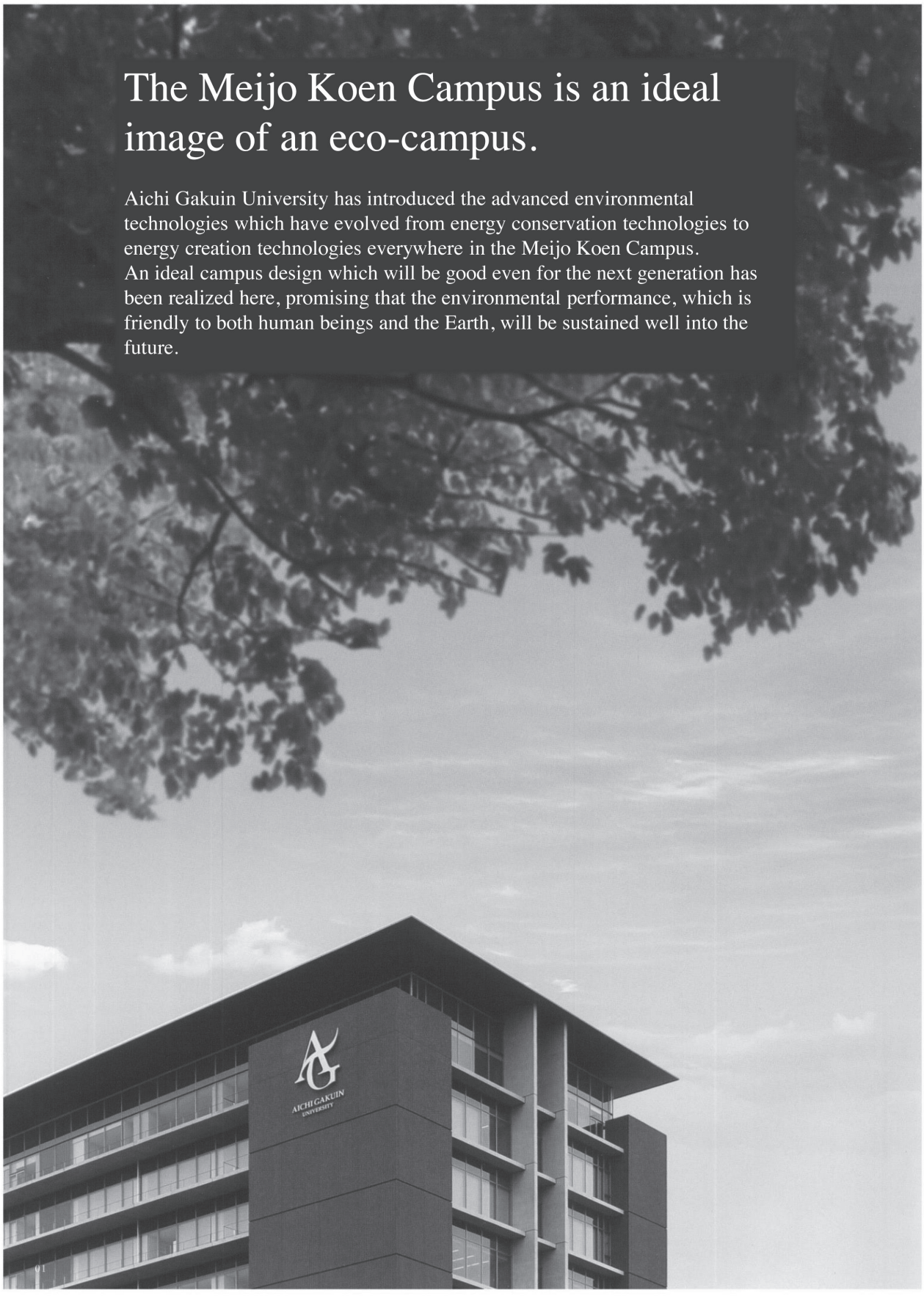
14:00 -17:00 Microtia Hands-on Workshop: Creating 3D Framework with Rib Cartilage Model
Kenneth E Salyer（World Craniofacial Foundation/International Cleft Lip and Palate Founation)
Akira Yamada (Northwestern University Feinberg School of Medicine)
Room 2402 (AGALS Tower 4F)

FACILITY GUIDE
MEIJO KOEN CAMPUS
AICHI GAKUIN UNIVERSITY

AICHI GAKUIN
UNIVERSITY

VENUE

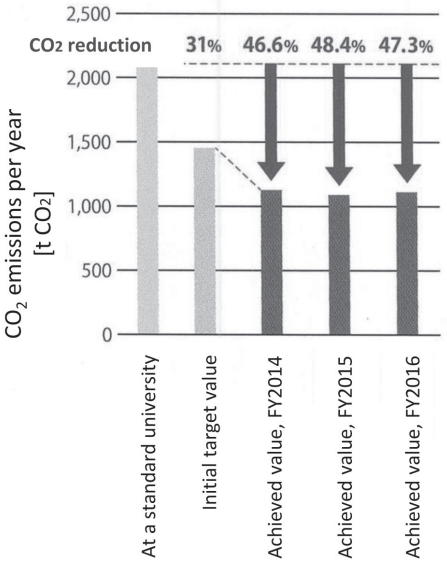



The Meijo Koen Campus is an ideal image of an eco-campus.
Aichi Gakuin University has introduced the advanced environmental technologies which have evolved from energy conservation technologies to energy creation technologies everywhere in the Meijo Koen Campus.
An ideal campus design which will be good even for the next generation has been realized here, promising that the environmental performance, which is friendly to both human beings and the Earth, will be sustained well into the future.
AICHI GAKUIN UNIVERSITY

01

The Meijo Koen Campus achieved a reduction of CO_2 emissions per year by 46.6%.

The Meijo Koen Campus has introduced cutting-edge CO_2-reduction technologies and equipment, aiming to realize a low-carbon society. It employs the commissioning and tuning to ensure appropriate operations. The campus seeks a reduction of CO_2 emissions per year by 643t or 31%, comparing to standard collages and universities. The most appropriate operations achieved the reduction of 46.6%, 48.4%, and 47.3% respectively in three consecutive years, meaning that the reduced CO_2 amounts were far more than the initial target value.

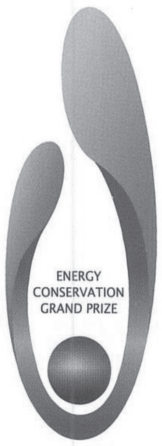


We received the Minister of the Environment's 2016 Commendation for Global Warming Prevention Activity.

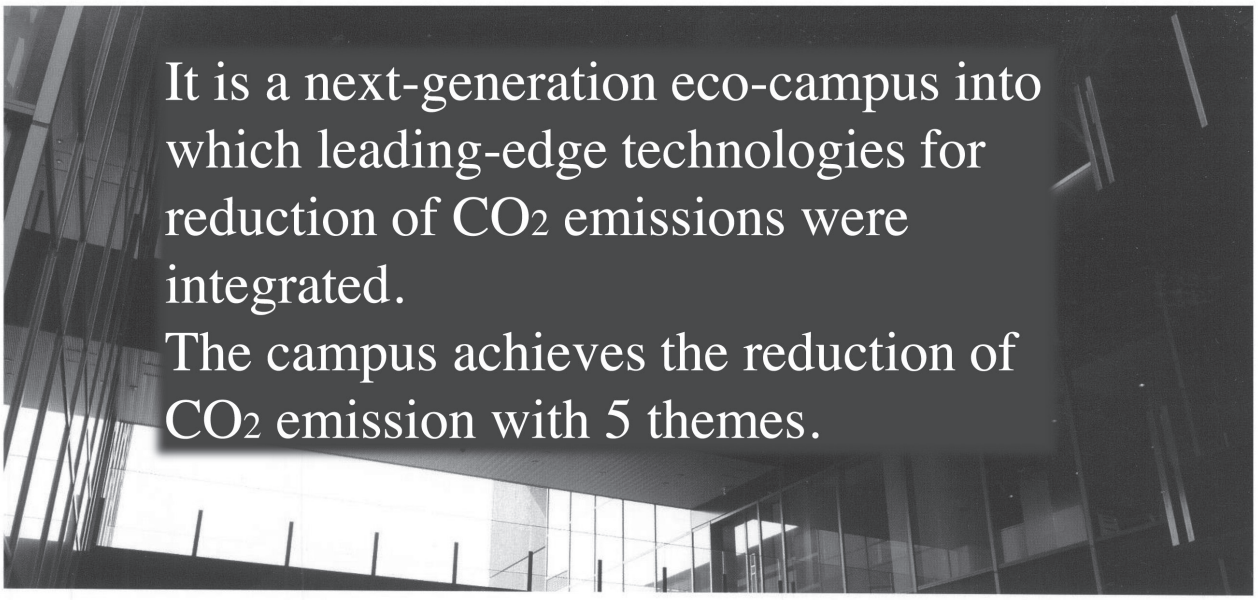
We received the Minister of the Environment's 2016 Commendation for Global Warming Prevention Activity for the Introduction of Advanced Warming Prevention Technologies, since the government acknowledged our efforts for low-carbon campus. We have received three other well-recognized awards.

We received the Energy Conservation Grand Prize for the Applications of Energy Conservation Measures.

We received the Energy Conservation Grand Prize for the Application of Energy Conservation Measures which is sponsored by the Energy Conservation Center, Japan. Our various efforts to establish an ideal next-generation eco-campus had been recognized and awarded.



FY2016
Energy Conservation Grand Prize
for Application of Energy Conservation Measures
Sponsored by Energy Conservation Center, Japan



1. Environmentally friendly architecture utilizing the regional characteristics

We achieve an energy-saving effect and create a pleasant environment with the environmentally friendly architecture and the self-generation technologies, utilizing the regional characteristics.

2. System composition with consideration of electric power supply and demand

We take power-saving measures against surges of power demand in summer, combining various power generation systems and accumulators.

3. Realization of both reduction of CO_2 emission and self-supporting functions in the event of disasters

The campus is prepared for unexpected power failures and other disasters with emergency back-up power supplier.

4. Effective utilization of natural energy and untapped resources

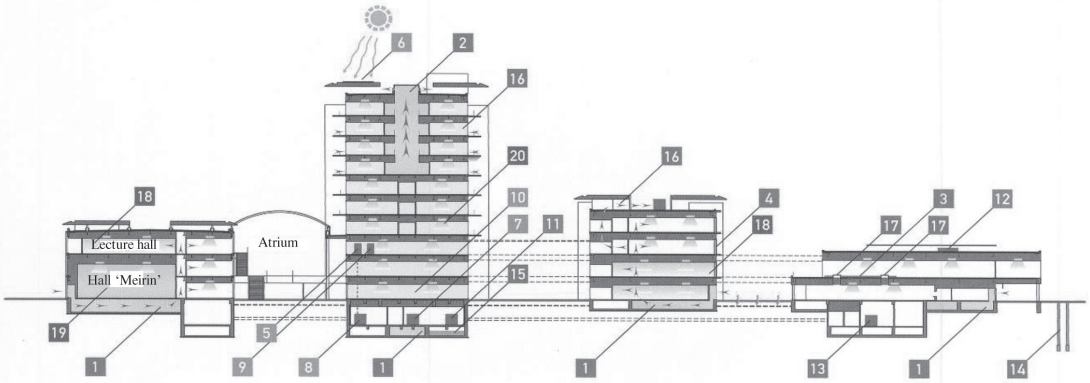
The campus realizes sustainable energy utilization through effective utilization of natural energy and untapped resources.

5. Accomplishing both a high-quality study environment and reduction of CO_2 emission

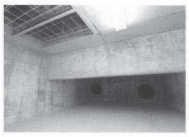
We pursue to make the study environment comfortable for students and scholars, offering the friendly-to-the-environment air-conditioning system and the comfortable-for-reading lightings.

The Advanced Environmental Technologies

CASTLE HALL | AGALS TOWER | INTELLIGENCE CUBE | KUSUNOKI TERRACE

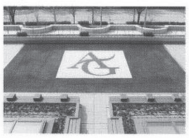


1 Cool and heat pit for the ventilation system

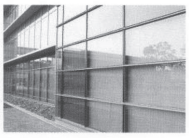


2 Enhanced natural ventilation system

3 Rooftop greening



4 Low-E double glazing

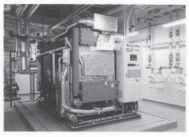


5 Gas cogeneration system with the capabilities of responding to power outages

6 Solar-power generation system

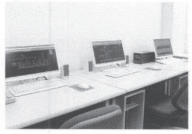
7 Lithium-ion batteries

8 Gas absorption chiller heater with auxiliary waste heat recovery



9 High-efficiency air-cooled heat pump module chiller

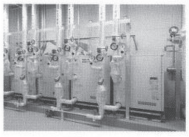
10 Building energy management system (BEMS)



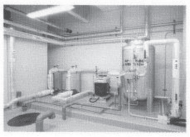
11 Emergency power generator

12 Gas engine driven heat-pump air conditioner

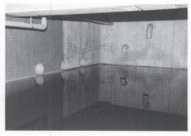
13 Geothermal heat pump air conditioner



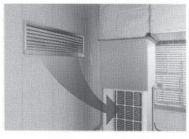
14 Cascade use of well water



15 Rainwater storage tank



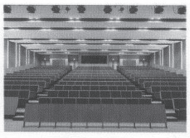
16 Cascade use of air-conditioned room air



17 Usage of skylight

18 All-air supplied induction radiant air-conditioning system

19 Air conditioning restricted to the occupied zone



20 Dimmer- and time-controlled lighting system with LED lights

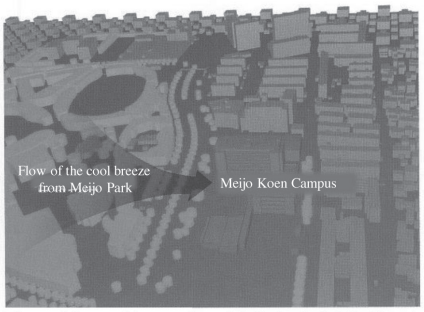
1. Environmentally friendly architecture utilizing the regional characteristics

Meijo Koen Campus is an environmentally friendly architecture with advanced environmental technologies everywhere, utilizing the regional characteristics. The air-conditioning system which offers preferable air flows and uses self-generation technologies contributes to the comfortable, human-friendly environment.

Active utilization of the cool breeze from Meijo Park (Meijo Koen)

We utilize the cooling effects of greenery in the Meijo Park and in our Meijo Koen Campus to the fullest extent, realizing active outside-air cooling. The buildings in the Meijo Koen Campus are positioned so as to be suitable for ventilation and reduction of solar load, intended to reduce the heat load to the surrounding buildings and also to reduce the energy consumption in the campus for the long future.

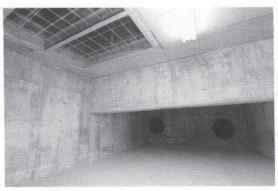
Mijo Park (Meijo Koen)

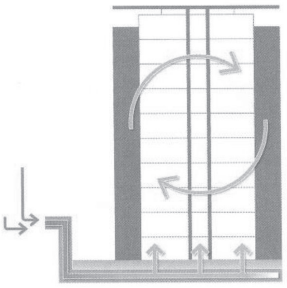


Flow of the cool breeze from Meijo Park (Meijo Koen)

Cool and heat pit for the ventilation

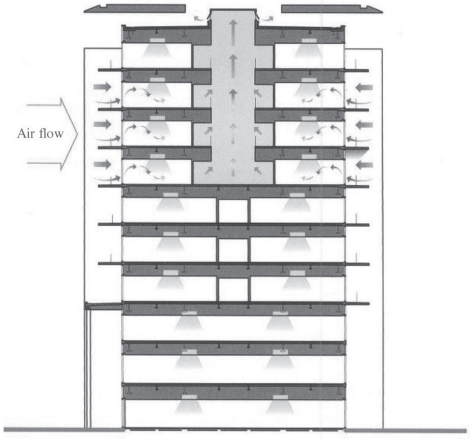
The cool and heat pit for the ventilation system is a kind of air conditioning system which utilizes the underground characteristics, 'cool in summer, warm in winter.' The system takes in outside air from outdoor and use the pre-cooled or pre-warmed air for the air conditioning, reducing consumption of energy required for air conditioning.

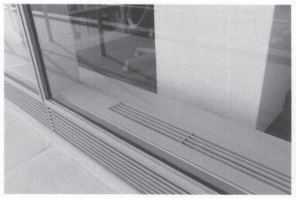


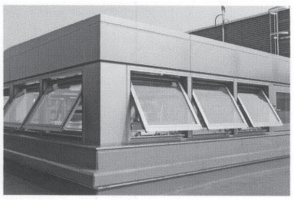


Enhanced natural ventilation system

Agals Tower employs natural ventilation system which utilizes the law of nature, 'warm air rises without consuming external energy,' during intermediate seasons. Laboratories have fresh-air inlets at the feet of windows, and the fresh air cooled by greenery in Meijo Park comes in through the inlets, runs through the rooms, gets out of the rooms through gaps above the doors into the corridors, rises through the open ceiling space, and goes out through the ventilation windows on the roof.

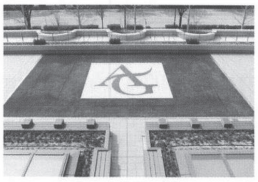



Fresh-air inlets


Ventilation windows on the roof

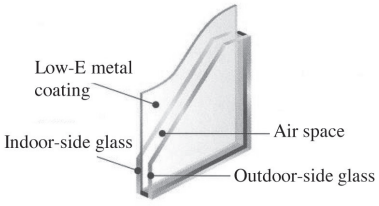
Rooftop greening system

Rooftop greening suppresses rising of temperature in summers via thermal insulation effects and heat absorption associated with water vaporization. It also suppresses losing heat in winters via heat insulation effects. That will lead to energy saving by saving energy for air-conditioning.



Low-E double glazing

The campus buildings employ double-glazing thermal-insulated windows in which low-emissivity (Low-E) glass with a special metal coating is used. Low E glass reflects outdoor heat in summer and retains indoor heat in winter. It works to suppress heating and cooling load according to seasons, reducing the energy requirements for air-conditioning.



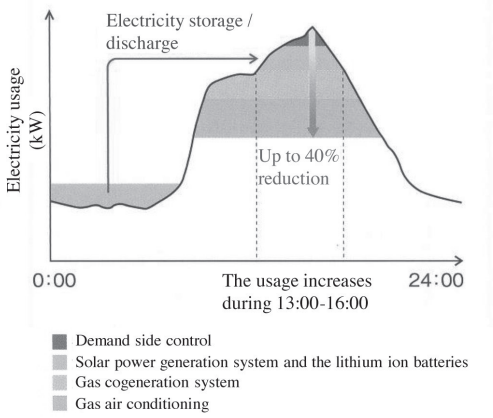
2.

System composition with consideration of electric power supply and demand

In summer, electric power demand increases radically. We take reasonably practicable power-saving measures. The combination of a solar power generation system and two gas cogeneration systems with lithium ion batteries enables us to reduce the peak-time power demand. It also enables us to handle risk management in power outages.

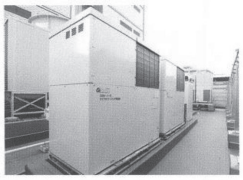
Combination of various power generation systems with lithium ion batteries helps to ease electricity peaks.

In general, electricity load increases in the daytime of summer. We employ an energy system that takes account of electric power supply and demand. The system enables us to reduce the electricity usage at the peak demand hours up to 40%. It employs a distributed power supply, which consists of a solar power generation system (30kW), two gas cogeneration systems (35kW each) and lithium ion batteries (60kWh), an advanced air-conditioning system, and a demand-side control.



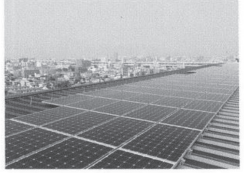
Gas cogeneration system with the capabilities of responding to power outages

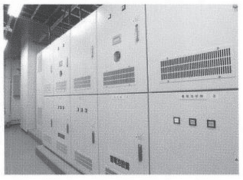
A gas cogeneration system produces power with a gas engine. It is an energy saving system that utilizes conventionally-discarded exothermic heat generated during power generation for hot-water supply and air-conditioning. Meijo Koen Campus utilizes the exothermic heat generated during the gas cogeneration to operate air-conditioning, realizing peak-shaving and energy-saving. The system can be operated without commercial power, making it possible to deal with power outages.



Combination of the solar power generation system and the lithium ion batteries

The solar power generation system and electrical storage system based on the lithium ion batteries on Meijo Koen Campus contribute to realization of a low-carbon society to prevent global warming. We store the electricity generated by solar power generation system with the lithium ion batteries, and realize peak shaving via discharging stored electricity at peak power demands.





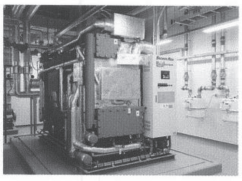
VENUE 2

Combination of advanced energy sources of electricity and gas

Meijo Koen Campus employ 'gas cogeneration system with the capabilities of responding to power outages,' 'gas absorption chiller heater with auxiliary waste heat recovery,' and 'high-efficiency air-cooled heat pump module chiller,' as a combined energy source of electricity and gas. They realize optimized usage of gas and electricity via effective use of exhaust heat and BEMS (Building Energy Management System) for an energy controlling method.

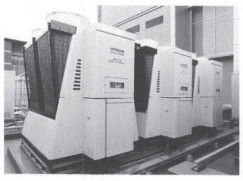
Gas absorption chiller heater with auxiliary waste heat recovery

We provide cool and hot water from gas absorption chiller heater which is driven by adopting city gas as fuel. The chiller heater makes it possible to reduce the consumption of fuel gas by utilizing exhaust heat generated from the gas cogeneration system. It can be operated by exhaust heat only, in cases when the cooling load or the power consumption is low.



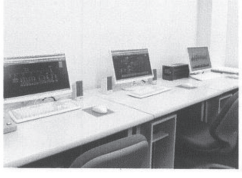
High-efficiency air-cooled heat pump module chiller

The high-efficiency air-cooled heat pump module chiller can achieve high energy-saving effect by extracting heat energy from the outside air via a heat pump. One unit of input energy can produce 3 or more units of air-conditioning capacity. It has an excellent part load performance by using an inverter-controlled compressor, resulting in substantial reduction of annual power consumption.



Building Energy Management System (BEMS)

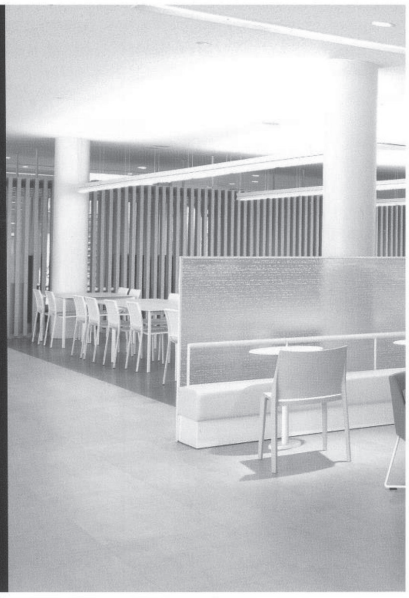
BEMS (Building Energy Management System) is a computer-mediated central-control system which controls the state of energy use on the campus. It realizes energy- and CO_2-savings without losing human comfort in the buildings. We realize optimization of energy consumption of the buildings through controlling power demands.



3.

Realization of both reduction of CO_2 emission and self-supporting functions in the event of disasters

Self-supporting functions in the event of disasters are regarded as important, requiring securing the life-line within the campus in the time of disaster. Mijo Koen Campus makes preparations for self-supporting of water, gas, and electricity on the campus for a few days. We realize a high level of security while taking CO_2-saving into consideration.



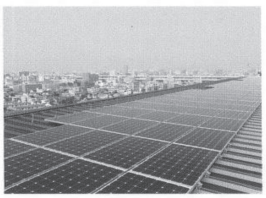
POSTER VENUE

Preparation for disasters via combination of CO_2-saving facilities

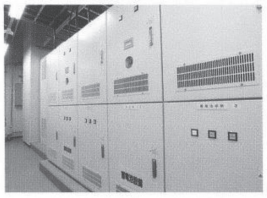
We realize self-supporting functions in the event of disasters as well as daily CO_2-savings. The major examples are the multiplication of power supply with 'an emergency power generator,' and 'a solar power generation system combined with lithium ion batteries,' and the combination of air-conditioning systems of 'the gas engine driven heat-pump air conditioner with the capabilities of responding to power outages, equipped with emergency liquid propane gas (LPG) cylinders,' and 'a geothermal heat pump air conditioner (see p.11).'

Solar power generation system combined with lithium ion batteries

The high-efficiency air-cooled heat pump module chiller can achieve high energy-saving effect by extracting heat energy from the outside air via a heat pump. One unit of input energy can produce 3 or more units of air-conditioning capacity. It has an excellent part load performance by using an inverter-controlled compressor, resulting in substantial reduction of annual power consumption.



Solar power generation system

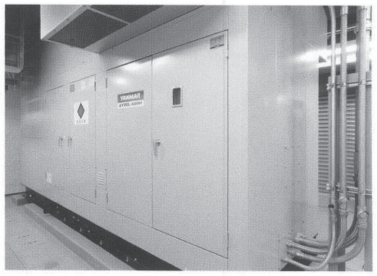


Lithium ion batteries

POSTER VENUE

Emergency power generator

The campus is equipped with an emergency power generator in case we have a power outage or a natural disaster. In such cases, electricity will be sent to Kusunoki Terrace, the designated evacuation site on the campus, securing power supply to the site.

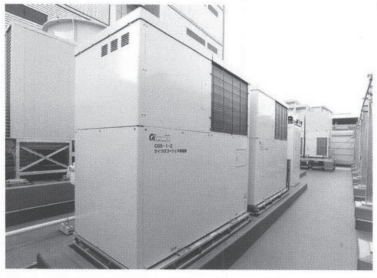


Gas engine driven heat-pump air conditioner with the capabilities of responding to power outages

The gas engine driven heat-pump air conditioner located at Kusunoki Terrace will work as an emergency power supplier in case of disasters. The heat pump air conditioner not only can operate autonomously but also will supply electricity to designated outlets in case of power failures. In case of power outages, it will continue to operate for a few days with stored LPG as the energy source instead of usual natural gas.

Gas cogeneration system with the capabilities of responding to power outages

The gas cogeneration system has the capability to send power to electrical-type air conditioners located on the first- and second-floor of Agals Tower in case of power outages. We are equipped with multiple power generators, which makes it possible to supply electricity in case of power outages and other disasters.

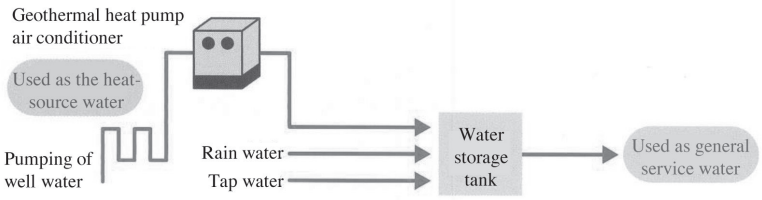


4. Effective utilization of natural energy and untapped resources

We have natural energy and untapped resources all around us. We utilize those energy sources effectively, making it possible to use sustainable energy sources.

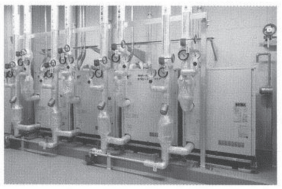
The cascade use of well water

The well water is first used as the heat-source water for the geothermal heat pump air conditioner, then recycled for use in flushing toilets and watering plants, reducing water usage on the campus. In combination with the usage of super water-saving type toilets, we are trying to reduce the water usage on the campus by 30%.



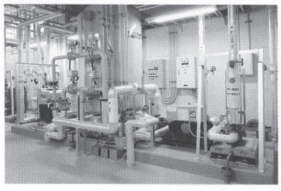
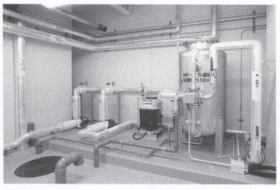
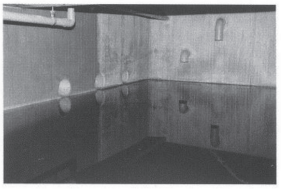
■ Geothermal heat pump air conditioner

The geothermal heat pump air conditioner pumps out the underground water from the geothermal heat exchange well and uses the water as the heat source for air conditioning. The unique, highly efficient hybrid system realizes a low emission of exhaust heat to the atmosphere and contributes to the society by offering a countermeasure against the heat island phenomenon.



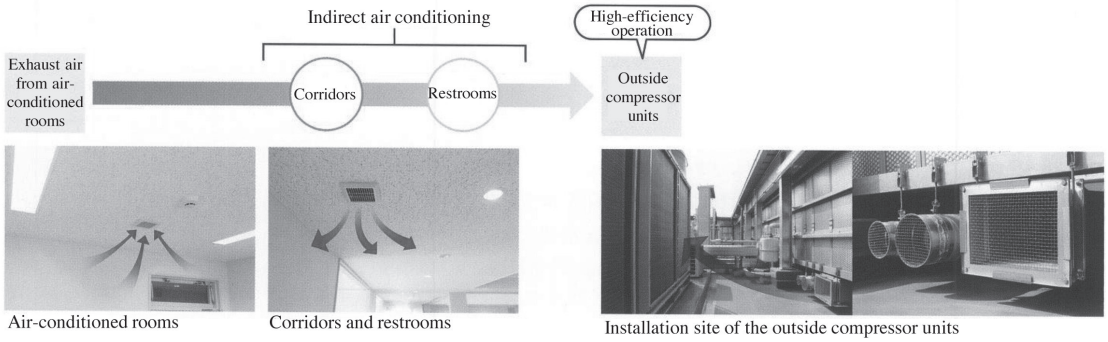
■ Geothermal heat pump air conditioner

The geothermal heat pump air conditioner pumps out the underground water from the geothermal heat exchange well and uses the water as the heat source for air conditioning. The unique, highly efficient hybrid system realizes a low emission of exhaust heat to the atmosphere and contributes to the society by offering a countermeasure against the heat island phenomenon.

The cascade use of air-conditioned room air

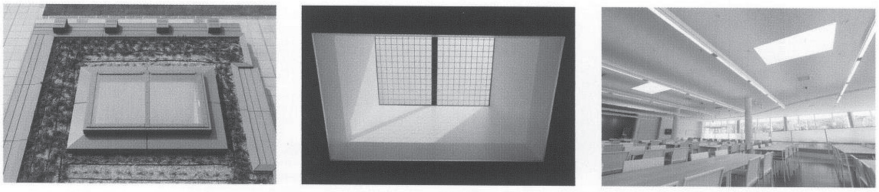
We utilize the air of air-conditioned rooms for indirect air-conditioning of shared spaces. The air used for indirect air-conditioning is released into the outside air around the compressor units, making the next air-conditioning cycle efficient.



Various applications of sunlight

■ The usage of skylight

We reduce the lighting usage by utilizing natural light through the roof skylight. The soft light from the roof skylight provides comforting effects which contribute to make the study environment comfortable.



■ Solar power generation system combined with lithium ion batteries

The campus is equipped with a stationary power storage system based on the solar power generation system combined with lithium ion batteries. That will contribute to the realization of a low-carbon society.

5.

Accomplishing both a high-quality study environment and reduction of CO_2 emission

Comfortableness such as appropriate brightness and pleasant air conditioning is an important factor for a positive classroom environment. We pursue a comfortable classroom environment for students who study there. That includes lightings with an appropriate brightness for reading and writing and the air-conditioning system friendly to humans and environments.

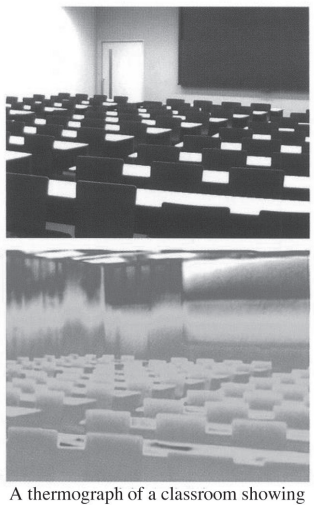
A comfortable study environment without unevenness of temperature

VENUE 3, 4

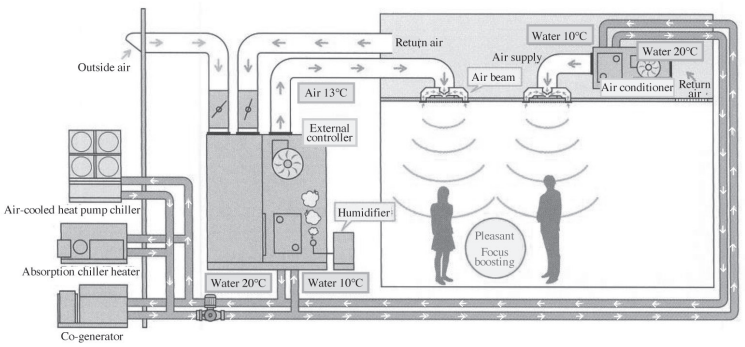
We introduce the air-conditioning system which does not let people inside feel an air flow or unevenness of temperature, creating a comfortable environment for both students and staff. It also contributes to reduction of CO_2 emissions.

■ All-air supplied induction radiant air-conditioning system

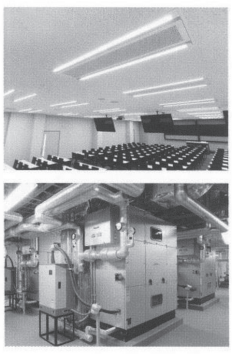
We employed the all-air supplied induction radiant air-conditioning system which is characterized by such refreshing feeling as to be in a forest and by such comfortable warmth as to be basking in the sun on a warm autumn day. It provides heat radiation (electromagnetic wave) and radiant air (slight air flow) to every corner of the room without unevenness of temperature or recognizable air flow, realizing a high-quality study environment. The system employs a warm air blowing system with low air-flow to implement a CO_2-saving air conditioning system without sacrificing comfortability.



A thermograph of a classroom showing the thermal environment of the room



Energy Conservation Grand Prize



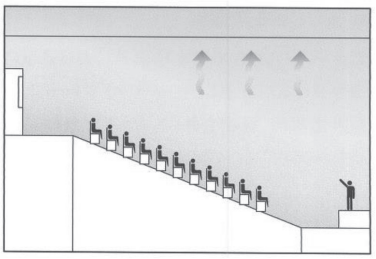
The Castle Hall employs the "Mizu-Excel," a high-efficiency, cool-and-hot-water based air-conditioning system which won a FY2013 Energy Conservation Grand Prize.

Air conditioning restricted to the occupied zone

In the high-ceiling Meirin Hall, only the occupied zone, or the lower part of the hall space, is air-conditioned for energy saving without sacrificing comfortableness.

■ The displacement-ventilation temperature-stratification (restricted to the occupied zone) air-conditioning system

This system air-conditions only the occupied lower spaces, with a small airflow rate without disturbing the air in the room. It supplies just-a-little-lower-temperature fresh air via the air supply outlets placed just above the floor, pushing the foul air in the room up toward the unoccupied upper space of the room, air-conditioning up to 2 meters high from the floor efficiently.



The air conditioning restricted to the occupied zone in the Meirin Hall : VENUE 1

■ Control of the amount of outside air to be introduced into the rooms coordinating with CO_2 sensors.

The sensor detected the concentration of CO_2 in the rooms to adjust the amount of air introduced into the rooms. That prevents the excess amount of summer heat and winter chill to flow into the rooms, reducing the air-conditioning load.

Meirin Hall: VENUE 1

Controlling LEDs with various sensors and regulators

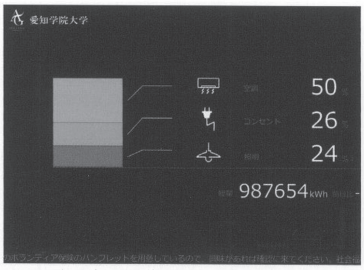
We employ low energy LEDs throughout the campus buildings, reducing the lighting energy consumption. We endeavor to reduce energy consumption on the campus even more, by introducing various sensors and a task ambient lighting system into the campus buildings.

■ The dimmer- and time-controlled lighting system with LED lights

Many LED tube lights have been installed in the classrooms on the campus, reducing power usage and CO_2 emission by 26%, compared to the conventional inverter-controlled fluorescent light tubes. Lifetime of those LED lamps is approximately 40,000 hours, that is, about 3.3 times longer than conventional ones. That also means we can reduce the amount of waste of used lamps. The lightings are time-controlled. They are also controlled via the sensors that detect the presence or absence of people and via the sensors that detect the brightness of the surroundings. That again contributes to reduce the electricity consumption without sacrificing human comfort.

■ Energy management and people enlightenment activities: VENUE 3, 4

We install monitors to show the energy consumption and CO_2 emission on the campus, aiming to raise awareness of facility users. We provide the opportunities for students to learn the efforts for reducing CO_2 emissions on the campus, holding eco-learning events regularly.



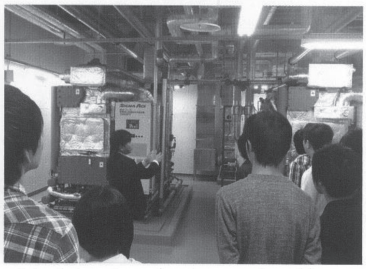
A monitor for public awareness

In the car of an elevator in Agars Tower


A lecture regarding the CO2-saving project

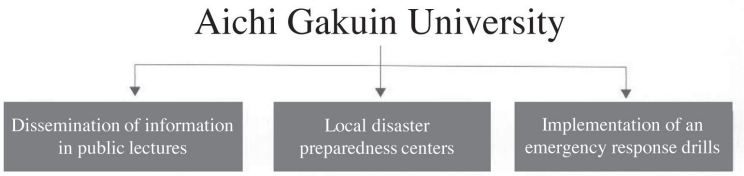

The first floor entrance hall of Agars Tower


'Eco-Senryu (short humorous poem)' event on the Star Festival


A backstage tour of underground machinery room

■ Control of the amount of outside air to be introduced into the rooms coordinating with CO_2 sensors.

The sensor detected the concentration of CO_2 in the rooms to adjust the amount of air introduced into the rooms. That prevents the excess amount of summer heat and winter chill to flow into the rooms, reducing the air-conditioning load.




Nagoya Open University of the Environment

External electrically powered louvers

The external louvers suppress the temperature increase near the windows by reflecting solar radiation heat. Because external louvers block off the sunlight outside the windows, they do not increase the room temperature as indoor blinds would do. The heat insulation properties of outside louvers are more prominent than those of indoor blinds.

Outside-air cooling

During intermediate seasons when outside air is cool, we can reduce the energy consumption by utilizing the outside-air cooling without operating a heat source machine.

Highly reflective roller blind

It reduces air-conditioning load by reflecting intense solar radiation of summer.

Free cooling

Cold water is produced only by the cooling effect of the cooling tower, without operating a heat source machine during the seasons when the temperature of outside air is low. Free cooling offers excellent energy saving effect.

Thermal barrier coating

The thermal barrier coating on the window glass in the western wall of the Castle Hall reduces the temperature rising caused by exposure to the afternoon sun.

Water conveyance with large temperature differences

Making the temperature differences between the coming and the going water 10°C instead of 5°C, the consumption energy of the water pump is reduced due to the reduced amount of pumped water. We employ small diameter-size pipes for the cold and hot water circulation, for further reduction of pumping energy.

Super water-saving type toilets

We introduced super water-saving type toilets which use as little as 4.8L of water per flush instead of 6-13L of water per flush* required by conventional type toilets.
*Cited from the *Handbook of Air-conditioning and Sanitary Engineering*.

Variable water volume control of cold and hot water

We employ inverter pumps which optimize the amount of water flow of cold and hot water according the load, resulting in saving the energy consumption of the pump.

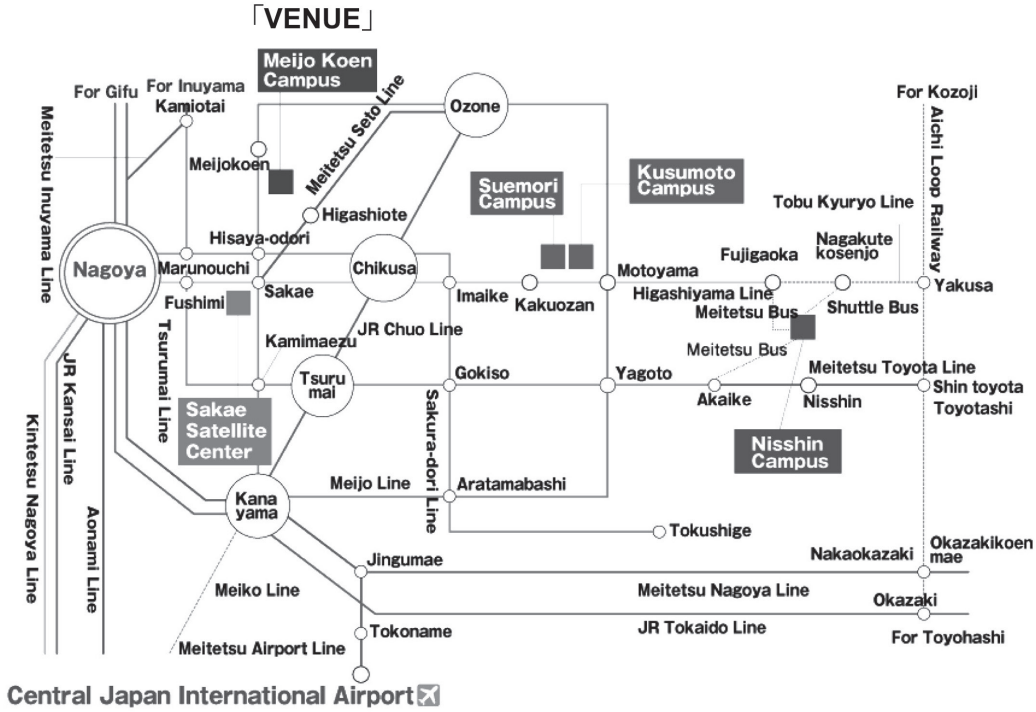
Automatic faucets with power generation function

The electricity for the sensor for detecting hands in position is generated by self-equipped power generator which uses the water flow as the energy source. It requires no power supply, contributing to energy saving.

Piping resistance reducing agent

The piping resistance is reduced by adding a piping resistance reducing agent to the circulating cold and hot water. That reduces the power usage of the pump.

Aichi Gakuin University campus access map



Nagoya Information

Access to Aichi Gakuin University Meijo Koen Campus

Meitetsu Railroad

From Central Japan International Airport Station to Kanayama Station

At Kanayama Station you can transfer to the **Meijo Line (subway-Purple line).**

Rapid Limited Express Train (All First Class Cars)

Central Japan International Airport ＞ Kanayama Station

Required travel time:24mins

Fare:1,170yen

Limited Express Train

Central Japan International Airport ＞ Kanayama Station

Required travel time:32mins

Fare:810yen (You need to purchase an additional 360 yen ticket)

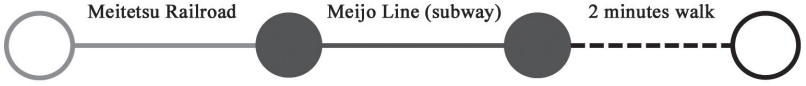
Nagoya City Subway

From Kanayama Station to Meijyo Koen Station

Take Meijo line subway-purple line clockwise from Kanayama Station, and get off Meijyo Koen Station.

Required travel time:11mins Fare:240yen

Subway Line Map



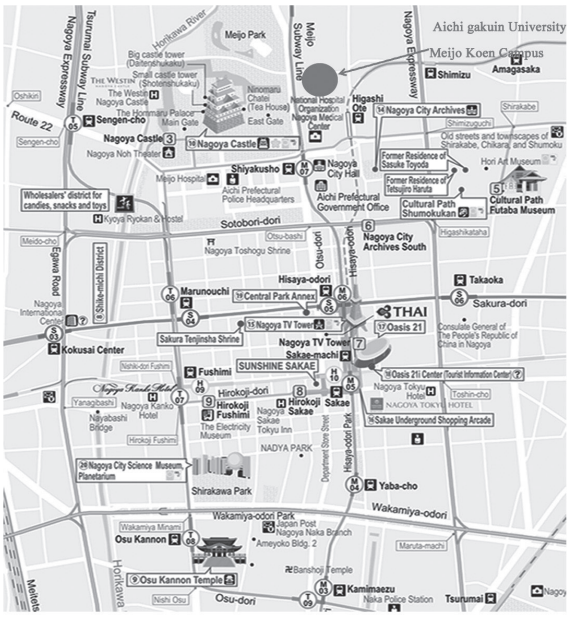
Central Japan International Airport

Kanayama Station

Meijo Koen Station Exit Gate 2

Aichi Gakuin University Meijo Koen Campus

Meijo Koen Campus Area Map



Sightseeing spots around Meijo Campus

Nagoya Castle

In 1610, Ieyasu Tokugawa began construction of Nagoya Castle as a castle residence for his son Yoshinao. It was lost to flames during WWII, but the large donjon (approx. 48 m) with golden "shachi" ornaments adorning its roof and the small donjon (approx. 24 m) were rebuilt in 1959. You can see a full-scale replica of a golden shachi ornament, experience the pulling of stones used in the castle's construction as well as riding in a palanquin, and come to know the sights and sounds of life within the castle and the castle town. Anyone can enjoy themselves as they learn the history of Nagoya Castle and the city it resides in.

Oasas 21

This park opened in 2002 in Sakae.

This is complex multi-level park with the theme of “Space ship Aqua" that is the symbol of the park and abundant throughout.The “Field of Green" is on the ground level where flowers and trees are planted.

The “Galaxy Platform" is basement level where many events are held. Also on the ground level, there are various shops and restaurants.

Social Program

Japanese Culture Experience Classes
Shodo (Japanese Calligraphy), Sado (Tea Ceremony), Zen,

	July 27		July 28			
Shodo	1:00 PM	2:00 PM	10:00 AM	11:00 AM	1:00 PM	2:00 PM
Sado	1:00 PM	2:00 PM	10:00 AM	11:00 AM	1:00 PM	2:00 PM
Zen	1:00 PM	3:00 PM	9:00 AM			3:00 PM

Location:
Shodo: Agals Tower 4F (Room 2405)
Sado: Agals Tower 3F (Room HOKODAI)
Zen: Agals Tower 3F (Room HOKODAI)

NOTE:
1. All Groups are limited to ten participants per class.
2. Sessions last about one hour.
3. All reservation requests will be processed in the order received!




Welcome Reception:
Welcome Reception will be held at Saru Café (2nd Floor) on 26th. It is a casual buffet style party. There is no dress code. A variety of appetizers, beverages and alcohols is served. No tickets required.

Gala Dinner:
Gala Dinner will be held at the Tenshu-no-Ma (King's Room) on 2nd floor, at Nagoya Castle Hotel on 27th. This all-seated dinner serves you a full French course and a variety of beverage including wine, domestic beer, Sake and else. The dress code is semi casual. The Gala Dinner tickets required.

Wine and Discussion:
Wine and Discussion will be held at the Kinshachi Dining (1st Floor) on 28th. It serves a casual buffet. The purpose of this time is to let poster presenters interact with participants to talk about the research. There is no dress code. A variety of side dish, beverage and alcohol is served. No tickets required.

Donors

Donors

AICHI ELECTRIC CO.,LTD.
AICHI KINZOKU KOGYO Co., Ltd.
Aida Chemical Industries Co., Ltd.
Akiko Furukawa
Asahi Pretec Corp.
CENTRAL JAPAN INTERNATIONAL AIRPORT COMPANY , LIMITED
Chubu Doboku Co., Ltd.
CHUBU Electric Power Co.,Inc.
Chubu Plant Service Co.,Ltd.
CHUBUSEIKI Co.,Ltd
Chuden Auto Lease Co.,Ltd.
Chuden CTI Co.,Ltd.
Chuden Haiden Support Co., Ltd.
Chuden Prevention of Disaster Co., Ltd.
Chuden Real Estate Co.,Inc.
Chuden Transportation Service Co., Ltd.
CHUDENKOGYO Co.,Ltd.
CHUO DENKI KOJI Co., LTD.
Coca-Cola Bottlers Japan Inc.
Daimaru Matsuzakaya Department Stores Co.Ltd.
DyDo DRINCO, INC.
Electric Power Development Co.,Ltd.
Himeno Co., Ltd.
Hitachi, Ltd.
Japan Medical Technology Co., Ltd.
Kajima Corporation
MUFG Bank, Ltd.
Nagoya Railroad Co.,Ltd.
NGK INSULATORS, LTD
Shinichi Nakahara
Shinki Corporation Co.,Ltd.
TAISEI CORPORATION
Techno Chubu Company,Ltd.
TOENEC CORPORATION
TOHO GAS Co., Ltd.
Tokio Marine & Nichido Fire Insurance Co., Ltd
Toshiba Energy Systems & Solutions Corporation
TOYOTA MOTOR CORPORATION

Supporters

ASO International, Inc.
Cenergy Co.
Coca-Cola Bottlers Japan Inc.
C-TECH CORPORATION.
Otsuka wellness vending Co., Ltd.
TOYOBO Co., Ltd.

Exhibition

CHARLES RIVER LABORATORIES JAPAN, INC.
Japan Medicalnext Co., Ltd.
KINOKUNIYA COMPANY LTD.
Koshin Kagaku K.K.
Okada Medical Supply Co.,Ltd.
OSADA ELECTRIC CO., LTD.
Smile Train
TAGUCHI MEDICAL Co.,Ltd.
Yamato Co.,Ltd

Advertisement

ASO International, Inc.
Coca-Cola Bottlers Japan Inc.
GC CORPORATION
J. MORITA CORP.
Japan Medical Technology Co., Ltd.
Nobelpharma Co., Ltd.
TEIJIN MEDICAL TECHNOLOGIES CO., LTD

Drink

Coca-Cola Bottlers Japan Inc.
ASAHI SOFT DRINKS CO., LTD.
DyDo DRINCO, INC.
ITO EN, LTD.
Kirin Beverage Company,Limited
Otsuka wellness vending Co., Ltd.

Donors & Supporters

International Cleft Lip and Palate Foundation

The Japanese Teratology Society

Dentistry Alumni Association

AICHI GAKUIN UNIVERSITY

Aichi Gakuin University

20 SmileTrain YEARS OF SMILES

NAGOYA CONVENTION & VISITORS BUREAU

Suzuken Memorial Foundation

DAIKO FOUNDATION

Organizing Committee

Organizers:

Japanese Teratology Society
International Cleft Lip and Palate Fonadtion

Honorary Congress President:

Akihisa Mizuno
President, Japanese Cleft Palate Foundation
Chairman of the Board of Directors, Chubu Electric Power Co., Inc

Congress President and Organizing Chair:

Nagato Natsume
Professor, Aichi Gakuin University, School of Dentistry
Executive Director, Japanese Cleft Palate Foundation

Congress Vice Presidents:

Koichi Ueda
Professor, Department of Plastic and Reconstructive Surgery, Osaka Medical College
Yuri Fujiwara
Visiting Professor, Osaka Health Science University
Noriaki Yoshida
Professor, Department of Orthodontics and Dentofacial Orthopedics, School of Dentistry, Nagasaki University
Jun Takebe
Professor, Department of Removable Prosthodontics, School of Dentistry, Aichi Gakuin University

ICPF Local Committee Chair:

Toko Hayakawa

JTS Local Committee Chair:

Hideto Imura

JTS Local Committee Vice Chair:

Masaaki Ito

Local Organizing Committee:

Hiroo Furukawa
Teruyuki Niimi
Katsuhiro Minami
Akira Arasaki
Akihiro Mori
Chisato Sakuma
Arisa Suzuki
Davaasuren Amgalanbaatar
Ichinnorov Chimedtseren
Maya Yoshida
Kayo Hayami
Rie Osakabe
Hideo Ohira
Yoshitaka Toyama
Akiko Yoshida
Anar-Erdene Gantugs
Chisako Inoue
Haruka Mochizuki
Junko Akashi
Mika Murota
Nguyen Minh Duc
Satoru Takumi
Shinichi Nakahara
Tran Le Duy
Tsutomu Eda
Yoshio Akiyama
Tomoko Mori
Yumiko Ikegami
Nguyen Thu Tra
Satoshi Suzuki
Tran Duc Thong
Yasunori Akiyama
Yoshiko Aihara
Yuki Akiyama
Yusuke Ichihashi

Japanese Culture Experience:

Hiroko Suzuki
Mayumi Imai
Yoko Goto
Mayuko Goto
Miwako Izaki
Yoriko Tane

Technologist and Interpreter:

Kenji Kinoshita(Chair)
Osamu Miyata
Yuji Iwasaki
Yasuhiro Okada
Tomoe Shimada
Kaori Esaki
Shinichi Endo
Carter D. Witt
Rangi McCall

Volunteers:

Akiko Miwa
Ayane Endo
Emina Hashimoto
Hikaru Ito
Koki Kawasaki
Nagana Natsume
Rumi Ito
Ryotaro Hashiba
Tomoka Yoshida
Yurina Saito
Akina Minamikawa
Ayami Nomura
Harumi Ejiri
Keito Hayami
Masako Doi
Naoki Saito
Ryohei Matsukawa
Takatsugu Onishi
Tyler Witt Hayakawa
Nagoya convention & visitors bureau volunteers

Self Care Parent Support Group

22HEART CLUB

Association of Parents and Children with Congental Limb Disabilities(Fubonokai)

Japan Down Syndrome Society

Marfan Network Japan

NPO for Family and Baby Wellness

Self help group for Cleft Lip and Palate "Tanpopo"

Tsukushi of Meeting(Nationwide Achondroplasia patient・family of Meeting)

Presidential Speech

Dedicating my life to treat cleft lip and palate with deep appreciation to ICPF and JTS

Nagato NATSUME
Congress President

Secretary Treasurer, International Cleft Lip and Palate Foundation
Executive Director, Japanese Cleft Palate Foundation

Director, Cleft Lip and Palate Center, Aichi Gakuin University Dental Hospital
Professor, Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University

I was born in a family of doctors that has continued for generations. My father dedicated his life to medical care in a remote area. He always said that medical care was not business but love for humanity. I grew up looking at the back of my father. I have been engaged in many volunteer activities since I was young.

Since when I became an oral and maxillofacial surgeon, I started supporting patients and their families suffering from cleft lip and/or palate in Japan and also in overseas countries. Also, I believed that research was necessary to overcome cleft lips and palates, and was actively engaged in the research.

I established Japanese Cleft Palate Foundation (JCPF) in 1992 after six years of preparation. Since then, JCPF has been supported by many people. Then, Dr. David S. Precious and I established the International Cleft Lip and Palate Foundation (ICPF) in 1997. Since when the ICPF held its first international congress in 2000, ICPF has been active as an international academic society for 20 years.

This year, I am the Congress President of the Japanese Teratology Society (JTS). I joined JTS when I was a graduate student, and I learned and experienced a lot of things at the annual meetings of this society.

This time, I decided to hold the annual meetings of the two societies together to hold an international joint meeting, with understanding from members of both JTS and ICPF. That is because I have great hopes and a plan for the future of JTS and ICPF for the next ten or twenty years.

ICPF originally held an international congress every other year, but now it has been managed successfully enough to hold a congress every year. Unfortunately, International Federation of Teratology Societies (IFTS), to which JST is a member, has not held an international meeting since 2006. I hope that researchers in as many fields of congenital anomalies as possible interact with each other in this joint academic meeting. I hope that interaction will lead to academic development and a better future. I believe ICPF members could learn a lot from fellow researchers who are the members of IFTS. I am hoping I can talk to fellow researchers of IFTS members for more joint meetings like this one to be held in USA and in Europe, and would like to learn a lot from them.

While ICPF does not have an official journal, ICPF currently forms a network with 5,200 members in 89 countries. I intend to encourage the members of ICPF to submit articles to Congenital Anomalies, the official journal of JTS. Congenital Anomalies has a journal impact factor. The journal does not take manuscript submission fee. I believe it is a great journal.

I hope that the joint meeting of the 59th annual meeting of JTS and the 13th International Congress of ICPF - CLEFT 2019 - will be a catalyst for mutual cooperation between JTS and ICPF.

At present, the development of prenatal diagnosis has revealed birth defects of the fetus before birth, and there is a possibility that the fetus may be aborted even if the birth defects can be treated. The human rights of the fetus are in crisis. I would like to work actively on this issue as well.

Now I would like to thank the many people for their help.
I would like to devote the rest of my life to the children with cleft lip and/or palate and their parents.

Thank you for your participation.

Keynote Addresses

K 001
Surgical Technique in Unilateral Primary Lip/Nose Complex Repair

Kenneth E. Salyer
International Cleft Palate F., President
WorldC.F., Chairman of the Board (USA)

Unilateral Primary Lip/Nose Repair is an important technique which this author began pioneering 50 years ago with modifications through the years has become the standard of care along with many techniques practiced today. The purpose of this presentation is to emphasize the importance of looking at the "primary lip" repair as an integrated lip/nose procedure that frees and places all the displaced anatomic structures of the lip and nose together in a normal anatomic relationship. This technique used for repair of the cleft lip-nose deformity has been extensively reported in the literature by the author and utilized by many centers and surgeons. The evolution of the original technique has improved, with certain modifications to provide better symmetry and balance with less scarring.

【METHODS】The closed pre-periosteal surgical technique used today will be presented. The abnormal skeletal base is ignored when reconstructing the lip and nose. Placement of the intranasal incision should be at the level of the inferior turbinate, extending into the lining of the nose just far enough in each case to achieve complete mobility of all the nasal elements without distortion when repositioned. Complete freeing of all the elements of the lip and nose at the time of primary repair is necessary to achieve optimal normal growth and good long-term outcomes. This is where many surgeons fail to achieve an optimal result. After freeing the displaced muscles of the lip, placement of the key suture in the orbicularis oris muscle sets up the foundation for a symmetric anatomic nose and lip. Accurate positioning and symmetry of the alar base and sill is aided by limiting the transverse incision in the rotation-advancement lip repair. This incision is not made until after the key muscle suture is placed. The technique for floor-of-the-nose reconstruction avoids a small nostril, with no discarded tissue, and provides adequate nasal lining. This experience is based on the performance in the U.S. of over 1000 consecutive primary lip/nose repairs in the same center by the same surgeon using this technique. Twenty consecutive outcomes from patients 20 years old or older will be presented. This procedure eliminates major deformity, but most patients require aesthetic refinements after growth is complete.

【MAIN OBJECTIVES OF PRESENTATION】To emphasize the importance of repairing the lip/nose complex together at the primary operation and demonstrate the technique one surgeon has use to obtain consistently good results in a large experience over 50 years.

【CONCLUSION】Fifty year experience with a closed primary lip/nose procedure has led to refinements, which contribute to consistent, predictable, and achievable outcomes for all unilateral cleft lip/nose patients, where normal appearance and function in each and every case remains a challenge for all surgeons.

K 002
Craniofacial Surgery: Past, Present, Future

Kenneth E. Salyer, MD, FACS, FAAP
International Cleft Palate F., President
WorldC.F., Chairman of the Board (USA)

【PAST】Paul Tessier provided a major advance in medicine which lead to the creation of a new subspecialty, craniofacial surgery presented 1967.
Thus a new exciting era was initiated. He excited and inspired the then current generation of plastic surgeon's including maxillofacial and neurosurgeons. A group of diverse international surgeons first met in Paris at Tessier's invitation May 1972 which gave rise to the "Band of Brothers." They pioneered infant craniofacial surgery and popularized craniofacial surgery internationally giving rise to the International Society of Craniofacial Surgeons.
【PRESENT】Major advances have been made in craniofacial surgery. This has occurred in centers with multidisciplinary teams headed by leading surgeons (ISCFS) concentrating on this work. The majority of craniofacial teams are in developed countries. There is a lack of knowledge, leadership, and support of craniofacial teams in developing countries. Most countries in the developing world do not have organized training programs let alone independent organizations maintaining standards of training and care. If China and other Asian countries are going to compete in the global arena of medicine and dentistry such programs must be insisted upon by its own leaders in order to develop true training programs in craniofacial academic achievement, with an organized graduated experience in clinical care, examinations, additional proof of team care with personal records of intracranial surgery independently performed and submitted for approval. This must be done in all of medicine and surgery, craniofacial surgery is just one example.

The World Craniofacial Foundation (WCF), a 501C3 (USA) tax exempt foundation, with a Board of Directors consisting of leaders from business, industry, economics, law, medicine, and dentistry. The Medical Advisory Board is comprised of leading specialists relating to craniofacial surgery. Their vision is to produce and make available excellence of multi-specialty craniofacial care in developed and developing countries. The WCF approach was drafted by the leaders of ISCFS in their strategic plan. This was used as a guide for the WCF plan of action.

- Provide expansion and knowledge in craniofacial surgery through teaching, educational programs, scholarships, research studies, and a worldwide patient information database and triage of patients to closest team of excellence.
- Support and facilitate recognized leading craniofacial centers to increase their care of indigent patients.
- Create, facilitate, and provide financial support, as seed money for the development of sustainable integrated craniofacial teams within existing hospitals, universities, and other medical centers.
- Create sustainable craniofacial teams in private hospitals in developing countries.
- Motivate, stimulate, and provide opportunities for careers in craniofacial and cleft surgery.
- Provide and facilitate public as well as medical education about reconstructive plastic surgery.
- Establish teaching centers for craniofacial and cleft care in developing countries.

The World Craniofacial Foundation has initiated programs which will be presented in detail. These include fellowships, visiting professorships, equipment and financial support for established centers, and publicity about the needs of children worldwide. The goal is expansion of existing centers, creation of new centers, teaching conferences, negotiations with governments, and partnering with other foundations such as ICPF to provide and educate excellence in ongoing multidisciplinary integrated care as the model.
【FUTURE】Together with support from foundations like ICPF, WorldCF, and other like minded organizations Future Multidisciplinary Dedicated Teams in strategic locations in the developing world can be developed in existing centers and new ones created adopting established standards of care for achieving excellence.

K 003
FOLIC ACID, PREVENTION OF BIRTH DEFECTS, AND EPIGENETICS

Marie M. Tolarova and Miroslav Tolar
University of the Pacific, Dugoni School of Dentistry (USA)

【BACKGROUND】Folate (vitamin B9) is a critical cofactor in cellular one-carbon metabolism. In order to function normally, folate needs to be ingested, absorbed in the intestine and by individual cells, and methylation of DNA, proteins and lipids should proceed normally. Alterations on any level may lead to consequences of folate deficiency. It has been found associated with increased risk for neural tube defects (NTD), cleft lip and palate (CLP), conotruncal heart defects, cardiovascular and neurodegenerative diseases and cancer. Supplementation and fortification of staple foods with folic acid (FA) led to remarkably decreased prevalence of NTDs, less of CLP. Thus, other levels of folate actions also need to be explored.

Orofacial structures are the most complex – and most vulnerable - structures that are formed during embryonic period of prenatal development. Starting at the 4th week of gestation, a complex choreography of mesenchymal and epithelial tissues is orchestrated by five groups of important genes – polarizing signals, growth factors and receptors, transcription factors, cell adhesion molecules, extracellular matrix modifying factors. About 64 genes are upregulated in the 4th week, 26 genes in the 5th week (frontonasal prominence), in the 6th week - 45 genes in lateral prominences and 36 genes in medial prominence.

【METHODS】Numerous descriptive, retrospective, prospective, randomized studies - including ours - focused on periconceptional supplementation with FA and on folate-metabolism related genes showed promising results in relation to prevention of CLP. An overview will be given in our presentation.

【RESULTS AND DISCUSSION】Epigenetic mechanisms obviously have an important role in prevention of CLP. Lifestyle and dietary factors, including folate, may help to rescue cells from endoplasmic reticulum stress leading to cell death, may mitigate harmful effects of smoking, toxic chemicals and some drugs.

On molecular level, methylated DNA and modified histone proteins control switching on/off of expression of specific genes. Harmful factors, including folate deficiency, may lead to alterations in gene networks that may run in a family and that we call “genetic susceptibility”. Therefore, folic acid periconceptional supplementation may decrease recurrences and occurrences of CLP.

【CONCLUSION】Epigenetics with possibilities of epigenetic modifications opened our eyes to new opportunities and powerful strategies for prevention of CLP and other congenital anomalies. It allows us to implement precision and customized medicine approach in prevention protocols.

K 004
An Update from the Teratology Society (North America)

Elise M. Lewis, PhD, Vice President,
Teratology Society (USA)

The Teratology Society was established as a multidisciplinary scientific society in 1960. Today, this international nonprofit consists of nearly 700 members specializing in a variety of disciplines, including developmental biology and toxicology, reproduction and endocrinology, epidemiology, cell and molecular biology, nutritional biochemistry, and genetics as well as the clinical disciplines of prenatal medicine, pediatrics, obstetrics, neonatology, medical genetics, and teratogen risk counseling. Our mission is to promote research, communicate information, and provide education and training on the causes, mechanisms, treatment, and prevention of birth defects and developmental disorders. The Teratology Society and its members work closely with various organizations on critical areas related to birth defects prevention including public advocacy for issues including, but not limited to folic acid fortification in cereal grains, neural tube surveillance, and raising awareness about the Zika virus effects on the fetus. Engaging and educating scientists is a key activity of the Society. In addition to the Society's journal, Birth Defects Research, influential position papers, and social media communiques, we have a newly updated resource titled the Teratology Primer. The Primer is a free online birth defects research introductory textbook for basic scientists, clinical scientists, healthcare professionals, trainees, policy makers, and anyone who has an interest in the field of teratology. In addition to promoting our science through publications and advocacy, we highlight cutting edge research during our annual meetings where we encourage our membership to network and expand their breadth of our multidisciplinary science. By working together in a multidisciplinary way, from students to world-renowned experts, we are dedicated to advancing the science, eliminating or ameliorating birth defects, and ensuring the impact of our science on the health of future generations. Our Society recently updated our 5-year strategic plan, with a focus on advancing emerging and fundamental science, building value for our members, strengthening external awareness of the Society's value, and advocating for resources for the field of birth defects research and prevention. In addition, the membership recently elected to transition the Society name from the Teratology Society to the Society for Birth Defects Research and Prevention to further strengthen the impact and relevance of the Society. This scientific exchange between the Japanese Teratology Society and the North American Teratology Society also aligns with our strategic plan to expand our communication with other like-minded societies to increase our global impact through collaboration to address international issues.

K 005
20 Years of Empowering Medical Professionals in LMICs to Provide Safe, High-Quality Cleft Care

Karoon Agrawal,
Smile Train (India)

There is a startling gap between accessibility of surgical services and need in the developing countries. An estimated 170,000 children are born in the developing world each year with cleft lip and palate, a surgically treatable facial deformity that impairs a child's health, well-being and survival. The lack of trained local surgical teams and expense of surgical care pose major obstacles to these children accessing high-quality reconstructive surgery and essential ancillary treatment services.

Smile Train started its journey 20 years back. Since beginning Smile Train has mandated to empowering and training local medical professionals to provide safe, high-quality, comprehensive cleft treatment for poor children suffering from cleft lip and palate. Since inception, we have invested in hospital partnerships by providing education and training in areas where there is limited local capacity, enabling partners to build sustainable infrastructures for year-round patient care. Some models of treating surgical disease, such as the mission model, are costly and difficult to scale, often disempower local medical professionals and disrupt health systems, and cause patients to wait lengthy periods of time for treatment or be unable to access follow-up care. Smile Train's model was designed to provide sustainable essential services by educating and empowering the local workforce and health systems.

Smile Train's partner network of nearly 1,100+ partner hospitals and 2,100+ empowered medical professionals fully embrace the "teach a man to fish" model, and train others healthcare providers in their countries. The focus of our Quality Improvement Training Programs is not to send international doctors to the developing world, but instead to utilize local and regional trainers whenever possible. This model keeps costs down, eliminates challenges around potential cultural and language barriers, and empowers both the trainer and the trainee.

Partner medical professionals excelling in their respective areas of cleft treatment regularly lead Smile Train's quality improvement training. In our training programs we work with MDs, specialists, non-physician clinicians and others, depending on who is performing clinical care within the country. With 2,000+ formal, active partner surgeons and thousands of anesthesia and nursing providers who have worked alongside us since 1999, Smile Train has reached a significant number of medical professionals across the developing world and equipped them with essential training information and best practices.

Smile Train moved from primary surgery to secondary surgery and now we are striving towards comprehensive cleft care including orthodontia, speech support and nutritional support. The impact over 20 years has been immense -- with over 1.5 million surgeries and thousands of comprehensive cleft care treatments provided to children in more than 90 countries around the world.

Smile Train is working towards greater cooperation with various government and non-government agencies in the respective countries, towards putting smiles to every child with cleft lip and palate. This is high time for cooperation rather than competition.

Special Lectures

T 001
Towards establishment of 'Embryatrics'; revisited and to be continued

Hiroki Otani
Department of Developmental Biology, Faculty of Medicine,
Shimane University, Shimane (Japan)

We have been observing multiple organ systems in human embryos/fetuses of the Kyoto Collection of Human Embryos and Fetuses (Congenital Anomaly Research Center of Kyoto University), a part of which had been transferred to Shimane University, at macroscopic, light-, and electron-microscopic levels. Based on the observation, we made hypotheses regarding mechanisms regulating organogenesis and histogenesis of human organs, and have been experimentally proving these hypotheses using mainly mouse embryos.

We reported wide variations in the sizes of fetal organs, such as kidney and pancreas, which develop by branching mechanism in fetuses of Kyoto Collection. Since the organ size after the completion of histogenesis is basically proportional to its total function including the reserve, it is critical to understand the mechanism to generate variations in organ size.

In recent years, we have been working on interkinetic nuclear migration (INM) in the pseudostratified epithelia as a mechanism which may connect organogenesis with histogenesis of organs. INM accompanies stem/progenitor cell expansion in the neural and other ectoderm-derived epithelia, and has been suggested to regulate not only stem/progenitor cell proliferation/differentiation but also organ/tissue overall/localized size and shape. We have so far demonstrated INM in the developing esophagus/gut, trachea, and ureter epithelia of endoderm/mesoderm origin. Whereas this suggests that INM is a general strategy for the stem/progenitor cell expansion in the developing epithelia, the mode of INM appears to differ depending on the organ, region, and developmental stage and may regulate total/regional number of stem cells and the resulting daughter cells, and thus the size/shape and total function of each organ including reserve, which would be closely related with the individual patient's onset and course of non-communicable diseases. Organogenesis and histogenesis may therefore be closely connected via INM and both are therefore important periods for the developmental origins of health and disease/ predictive adaptive response (DOHaD/PAR).

The late Prof. Hideo Nishimura, the founder of Kyoto Collection, published a review article: "Towards Establishment of Embryatrics" (Okajimas Folia Anat. Jpn., 58:1187-1197, 1982). He described Embryatrics as a prospective new branch of medicine, which deals with embryos from the standpoint of prevention and management of congenital malformations, i.e. abnormal organogenesis. While the importance regarding disturbed organogenesis is even increasing due to advancement in the genetic/epigenetic research and imaging technology, events during histogenetic period has to be included as another important aspect of Embryatrics based on the possible relation between organ histogenesis and DOHaD/PAR.

This work was supported by KAKENHI (JSPS 15209034, 17790740, 19659414, 22659289; MEXT 23112006). COI: None

T 002
Human Embryology and Kyoto Collection

Shigehito Yamada
Congenital Anomaly Research Center,
Kyoto University Graduate School of Medicine (Japan)

The Kyoto Collection of Human Embryos is renowned as the largest collection of human embryos worldwide. It has started in the 1960s, and the Congenital Anomaly Research Center, Kyoto University Faculty of Medicine was established in 1975 to preserve the collection and to promote the human embryonic researches. The Kyoto Collection is known as following unique characteristics: (1) the collection is considered to represent the total population in Japan; (2) it comprises a large number of specimens with a variety of external abnormalities; (3) for most specimens there are clinical and epidemiological data from the mothers and the pregnancies concerned. Therefore, the specimens have been used for morphological studies and could potentially be used for epidemiological analysis. Recently, several new imaging modalities in non-destructive way have been used for human embryos such as magnetic resonance microscopy and phase-contrast X-ray computed tomography. Using obtained images with high-resolution, geometric morphometrics are adopted for the quantitative morphological analyses and it shows a new aspect of embryology. The Kyoto collection, as well as of other human embryo collections worldwide, is still valuable and it will continue to contribute to human embryological studies in the future.

T 003
Identification of new syndromes and its implications

Kenjiro Kosaki
Center for Medical Genetics,
Keio University School of Medicne (Japan)

Recent global effort in terms of studies on “patients without syndromic diagnosis” through exome analysis or whole genome analysis is uncovering new genetic causes of birth defects. Since 2015, our laboratory has been recruiting >1000 “patients without syndromic diagnosis” nationwide through Japan’s Initiative on Rare and Undiagnosed Diseases and exome analysis of the cohort has delineated several new syndromes, including Kosaki overgrowth syndrome, Takenouchi-Kosaki syndrome, and CDK8-related disorder.

Kosaki overgrowth syndrome [KOGS] is characterized by overgrowth, a prominent forehead, proptosis, downslanting palpebral fissures, a wide nasal bridge, a thin upper lip, a pointed chin, hyperelastic and fragile skin, and progressive neurologic deterioration, with white matter lesions on brain imaging. Through genotype-driven global case-matching, more than 10 patients have been identified. The molecular pathology in KOGS is a gain-of-function mutation of the PDGFRB gene, and the condition is potentially treatable by inhibition of the downstream tyrosine kinases. Treatment with Imatinib is now underway in two patients internationally.

Takenouchi-Kosaki syndrome [TKS] is characterized by variable intellectual disability, dysmorphic facial features, macrothrombocytopenia, hearing loss, and lymphedema. The molecular pathology in TKS is gain-of-function mutation of CDC42. Theoretically, treatment with CDC42 inhibitors would be effective. Some FDA-approved drugs have been shown to have inhibitory activity against CDC42 and are promising candidates. Mice carrying human CDC42 mutations are being developed by gene editing for animal preclinical studies. Studies on these two new disorders illustrate the upcoming paradigm shift in birth defect research: from diagnosis to treatment.

As exemplified by these two new syndromes, delineation of the pathogenetic mechanism is critical for designing treatment strategies. Studies using animal models are often instrumental in useful for unraveling such mechanisms. We recently identified that missense mutations in the CDK8 gene can cause a novel neurodevelopmental disorder. Overexpression of missense mutations in zebrafish showed that these mutations represent hypomorphic alleles.

In view of the aforementioned three new disorders, upcoming trends in research on congenital malformations can be summarized as follows: 1) Global collaboration, beyond national borders, is indispensable; 2) Clinical observation of undiagnosed patients can contribute to advancement in basic research in morphogenesis; 3) Gene editing technology allows generation and evaluation of animal models of human mutations derived from patients; 4) At least some of the congenital malformation syndromes are indeed treatable.

Educational Lectures

E 001
Where do we come from? What are we? Where are we going? - A teratologist's personal perspective

Kohei Shiota
Shiga University of Medical Science, Otsu, Shiga (Japan)

Birth defects are the major cause of mortality and disabilities in children. Past teratologists have identified various teratogenic causes in humans and have provided preventive measures for some specific birth defects such as rubella embryopathy, fetal alcohol effects and part of neural tube defects by preconception health strategies, counseling for young families and improving environmental conditions. Developmental toxicology, dysmorphology and clinical genetics have contributed to identifying various environmental and genetic factors that cause human birth defects. In addition, the advances in molecular biology and developmental biology during the latter half of the 20th century promoted our understanding of the pathogenetic mechanisms of developmental abnormalities. However, some 3% of babies are born with structural and/or functional disturbances and the etiology is unknown or difficult to identify in many of the cases. Further, recent studies have revealed that the teratogenic mechanisms are not that simple and there are many unsolved problems such as the epigenetic modification of developmental genes (gene-gene and gene-environmental interactions). Hopefully new technologies such as next-generation sequencing (NGS) and big data analyses would provide us with new insight into the etiology and prevention of human birth defects that are now untreatable. For example, the Initiative on Rare and Undiagnosed Diseases (IRUD) launched by the Japan Agency for Medical Research and Development (AMED) in 2015 seems to be a promising project and would help lead to diagnostic and therapeutic innovations for rare diseases including various birth defects.

Research on birth defects requires multidisciplinary collaboration among basic scientists, toxicologists, clinicians, epidemiologists and health organizations. In this regard, the Japanese Teratology Society has a nice mixture of members with diverse disciplines. In addition to the scientific research on birth defects, we should be more active for education of the public and mass media to make them properly understand human birth defects so as not to leave the people with birth defects and their families behind.

E 002
My Experience as a Member of the Japanese Teratology Society for 56 Years

Mineo Yasuda
Hiroshima University (Japan)

I have been one of members of the Japanese Teratology Society (JTS) for 56 years since 1963. I first attended the third Annual Meeting held in Nagoya in July, 1963 under the presidency of Professor Ujihiro Murakami, who was one of the founding fathers of JTS. Since then, Nagoya has hosted seven annual meetings of JTS, including the 59th Meeting. Seven is second to 15 meetings held in Tokyo, and this number indicates that Nagoya has been one of academic centers of teratology in Japan.

I began my scientific career under the guidance of Professor Hideo Nishimura at the Department of Anatomy, Kyoto University in April, 1963. At that time Professor Nishimura eagerly collected human embryos and fetuses, and the collection is now utilized internationally by many scientists. If you are not familiar with this collection, please visit the following web site (http://www.cac.med.kyoto-u.ac.jp). There are many specimens with craniofacial anomalies including cleft lip and/or palate in this collection.

Professor Nishimura asked me to help him for publication of "Proceedings of the Congenital Anomalies Research Association of Japan", collection of English abstracts of papers presented at annual meetings of the Association (present JTS). This experience was invaluable for me to understand the wide range of research activities of teratologists. From 1990 to 1999 I served as the Editor in Chief of our official journal, Congenital Anomalies, and my early experience helped me tremendously for this job.

My experience as one of members of the Terminology Committees of JTS and the International Federation of Teratology Societies (IFTS) was also memorable. Lively discussions in national and international committee meetings resulted in publication of "Terminology of Developmental Abnormalities in Common Laboratory Mammals", version 1 (1998) and version 2 (2009), now indispensable tools for experimental teratologists and developmental toxicologists.

Today scientific information is available quickly via the electronic network, but direct personal contact at scientific meetings is still very important to improve your scientific sense. I heartily wish you to expand your acquaintance in teratology through this meeting.

Symposiums 1

S 101
Comprehensive Team Care for Children with 22q11.2 Deletion Syndrome

Richard Kirschner, MD
Canice Crerand, PhD
Courtney Hall, MS, CNP
Adriane Baylis, PhD
Nationwide Children's Hospital (USA)

22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion syndrome and is commonly associated with craniofacial anomalies, developmental disorders, psychiatric disorders, cardiac defects, speech-language disorders and velopharyngeal dysfunction (VPD). Children with 22q11.2DS have unique medical, surgical, psychosocial, developmental, and educational needs. Establishment of an interdisciplinary 22q11.2DS center can improve care coordination, facilitate ease of scheduling, increase support opportunities for families, enhance standardization of care, and improve outcomes and family satisfaction. Additional benefits of an interdisciplinary 22q11.2DS team include identifying and facilitating access to syndrome-specific care, such as those evaluations and procedures recommended by international 22q11.2DS care guidelines (Bassett et al., 2011).

The purpose of this panel presentation is to describe the components and care delivery model for an established 22q11.2DS team at a large, pediatric academic medical center in the US that has provided care to over 400 patients with 22q11.2DS and related 22q conditions. Panelists will include a nurse practitioner (who serves as the primary care coordinator for the team), a plastic surgeon (who specializes in management of VPD in 22q11.2DS), a speech-language pathologist and a pediatric psychologist with expertise in 22q11.2 DS. Team composition and provider roles will be discussed. Data from an ongoing quality-improvement project will demonstrate that children receiving coordinated interdisciplinary team care have significantly greater adherence to key international care guidelines (Bassett et al., 2011) compared to children who do not receive team care. A syndrome-specific team approach to speech-language assessment and intervention will be presented, as well as guidelines for therapy planning and implementation. Pre-operative VPD surgical planning, including the role of imaging studies, and strategies to customize surgical management, will be discussed. Developmental, educational, and psychosocial assessment and management strategies for 22q11.2DS will also be discussed. Lastly, panelists will review 22q11.2DS parent support, networking and family education initiatives.

Symposiums 2

S 201
Population-based case-control study: Kanagawa Birth Defects Monitoring Program (KAMP)

Kenji Kurosawa,
Yoshikazu Kuroki (Japan)

【Background】Kanagawa Birth Defects Monitoring Program (KAMP) has been in operation since October 1981 as the first population-based monitoring system in Japan [Kuroki et al., 1982; Kuroki and Konishi, 1984]. KAMP covers one-half of the total births (40,000 births annually) in Kanagawa Prefecture.

【Methods】All live births and stillbirths are screened for 44-48 marker malformations (only surface anomalies), arranged in 10-11 groups, and they are examined by general obstetricians or occasionally by general pediatricians within 7 days after birth. During the study period between 1981 and 2008, the KAMP was divided into four stages according to a minor modification in marker anomalies and registration systems. The first two stages, for 1981-1983 and 1984-1988, had total birth registration systems including all the malformed infants, normal infants and all multiple births. However, in the last two stages, 1989-2000 and 2001-2008, all malformed infants as well as all multiple births were registered with two consecutive normal infants.

【Results and Discussion】Evaluation of multiple congenital abnormality patterns may offer a clue for better understanding of causes, pathogenesis, and phenotypic manifestations of the birth defects. Although we had not detected birth defects caused by the teratogenic agents such as thalidomide, our study revealed valuable implications on child health and assisted reproductive technology from the data from KAMP. In this report, we present epidemiological studies of the KAMP during the 25 years.

S 202
Epidemiological study on patients with cleft lip and palate in Tokai area, Japan

Hideto Imura, Nagato Natsume,
Toko Hayakawa, Chisato Sakuma,
Satoshi Suzuki, Teruyuki Niimi,
Katsuhiro Minami, Hiroo Furukawa
School of Dentistry Division of Research and Treatment for
Oral and Maxillofacial Congenital anomalies
Aichi-Gakuin University,
Aichi-gakuin University Hospital,
Cleft lip and palate center (Japan)

【Purpose】 We started to investigate the incidence of cleft lip and palate in Aichi Prefecture located since 1981 with the aim of monitoring the real incidence rate of cleft lip and palate, andin addition, Gifu prefecture since 1986, Mie Prefecture since 1988. So far, 1,846,346 new born babies have been monitored. We report the incidence of cleft lip and palate in 2017 and the birth status.

【Mehods】 This study was conducted at all obstetrics medical facilities in Tokai three prefectures (Aichi, Gifu, Mie having the total population of 11.34 million). It was conducted with a questionnaire survey and questionnaires were mailed to all obstetric medical facilities in these areas. The survey period is one year from January 1 to December 31, 2017. Survey items included the total birth rate, survey coverage rate, incidence of cleft lip and palate, and cleft type classification, etc.

【Results】

1. The number of responses in this survey was 128 out of 273 and the response rate was 46.9%.
2. The number of births of cleft lip and palate in three prefectures of Tokai area was 63, and the incidence of cleft lip and palate was 0.13% (1/745).
3. The total number of births for the year is 946,065 in Japan, and the number of new born babies with cleft lip and palate in Japan in 2017 estimated from the incidence rate of cleft lip and palate in three prefectures was between 956.43 and 1583.11 (on the other hand, the number of newborn babies with CLP in three prefectures of Tokai area between 90.11 and 149.16) (95% CI).

【Discussion】 It is important to know the real number of babies with birth defects. We have been continuously monitoring not only hospitals but also all midwifery institutes in three prefectures of Tokai area.

The incidence of cleft lip and palate in Japan is said to be about 1/500 (0.20%). According to the results of a statistical survey of external malformations by the Japan Society of Gynecologists in 2016, the incidence of cleft lip and palate was approximately 1/430 (0.23%) at 12 representative hospitals in three prefectures of Tokai area. The incidence of cleft lip and palate in 2017 by our survey was about 1/745 (0.13%).

In recent years, fetal diagnosis by ultrasound has been becoming common. If fetal abnormalities are defected, mothers are transferred to a general perinatal maternal and child medical center or a regional perinatal maternal and child medical center, etc., deliver babies. As the difference in incidence rate of cleft lip and palate was recognized by the surveyed facilities, it can be said that monitoring for all obstetrics facilities is essential to understand the real incidence of cleft lip and palate.

S 203
Survey of pregnant women in Fukushima prefecture

Hyo Kyozuka, Tsuyoshi Murata,
Toma Fukuda, Syun Yasuda,
Akiko Yamaguchi, Yasuhisa Nomura,
Keiya Fujimori
Fukushima Medical University (Japan)

The Great East Japan Earthquake of March 11, 2011, followed by a tsunami, and the subsequent nuclear accident at Fukushima Daiichi Nuclear Power Plant have been the most catastrophic events in recent Japanese history. After the power plant accidents, many people including pregnant women were forced to evacuate suddenly by government order. The effects of the radiation disaster on pregnant women, in addition to a natural disaster, have never been experienced before in the history of humankind. At this time, we would like to introduce three epidemiological studies about pregnant women in Fukushima prefecture launched after the disaster.

Fukushima Health Management Survey (FHMS) and Maternal Survey: FHMS is a population-based study conducted by Fukushima prefecture government. The maternal survey was part of the FHMS and assessed the health conditions of pregnant women and newborns affected by the Fukushima Daiichi nuclear disaster. The research used a self-report questionnaire which addressed antenatal health, delivery method, and maternal mental health questions, as well as the results of the first-month child health checkup.

Japan Environment and Children's Study (JECS): JECS is a nationwide and government-funded birth cohort study that started in January 2011 investigating the effects of environmental factors on children's health. JECS is comprised of 15 regional centers and a national center. In Fukushima, the regional center for JECS was established in Fukushima Medical University. At the beginning of JECS, pregnant women in Fukushima city, which is the capital of Fukushima prefecture, and Futaba County, which is part of the coastal area of Fukushima prefecture, were designated for the study. After the disaster, Fukushima regional center was relaunched on October 1, 2012, to cover all areas in Fukushima prefecture.

Fukushima Reproductive Study (FRS): FRS is an all-facility complete survey of pregnancy, abortion, and miscarriage in Fukushima prefecture conducted by our department. In this obstetric institution survey of pregnancy within the prefecture, the rate of spontaneous and induced abortions were 10-11% and 15-18%, respectively. Although some seasonal fluctuations may exist, no major changes in the rates of spontaneous and induced abortions were observed before and after the disaster.

S 204
Congenital Anomaly Monitoring in Japan

Kurasawa K[1, 2)], Fujimori K[3)], Yamanaka T[4)],
Hmanaoue H[1, 2)], Sugo Y[1)], Kinoshita K[2)],
Miyagi E[1)], Hirahara F[1, 2)]
[1)]International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)
Japan CenterYokohama City University, Yokohama
[2)]Japan Association of Obstetrics and Gynecologists (JAOG), Tokyo
[3)]Fukushima Medical University Department of Obstetrics, Fukushima
[4)]Yokohama City University Department of Clinical Biostatistics, Yokohama (Japan)

The incidence of congenital anomalies has been reported to be 3%–5%, and they are not rare conditions. The surrounding environment is complex, and it is essential to avoid preventable congenital anomalies. In Japan, thalidomide, which was marketed between 1958 and 1962, affected >300 individuals, and the need for an information network on congenital anomalies emerged. Thereafter, congenital anomalies were locally monitored, including in the Tottori Prefecture, Kanagawa Prefecture, Ishikawa Prefecture, and Tokyo. The Japan Association of Obstetricians and Gynecologists (JAOG) started a statistical survey on congenital malformations on a nationwide basis in 1972. Subsequently, the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) was established as an organization of the WHO, and the first meeting was held at Helsinki in 1974.

The survey by the JAOG on congenital malformations is the only nationwide survey in Japan, and approximately 12.1% of births from around 330 hospitals nationwide are being monitored. At the commencement of the survey, children born at ≥8 months of pregnancy were targeted; however, currently, children born at ≥22 weeks of pregnancy and diagnosed within 1 month after birth are being targeted. The incidence of congenital anomalies in Japan is gradually increasing owing to the increase in the rate of intrauterine diagnosis attributable to the spread of ultrasonic diagnostic devices, the concentration of cases because of the consolidation of facilities handling childbirth, and the increase in the incidence of pregnancy and delivery at higher ages. The major congenital anomalies include ventricular septal defect (VSD), patent ductus arteriosus (PDA), Down syndrome, cleft lip/palate, atrial septal defect (ASD), ear fistula, trisomy 18 syndrome, duodenal and small intestinal atresia, hypospadias, and cleft lip.

According to the survey results in 2017, there were no abnormal variations, such as the more frequent occurrence of a specific congenital anomaly in a specific region. The survey on congenital malformations responds to requests from the Ministry of Health, Labour and Welfare, and it is reported as the only relevant data in Japan. Concurrently, it is supported by the JAOG Ogyaa Donation Foundation and the Japan Agency for Medical Research and Development. It is essential to continuously monitor the safety of mothers and children with the dedicated cooperation of medical institutions nationwide that participate in this program.

Cleft Treatment
-Benevolent Art from Japan to the World-

J 001
Straight line repair for unilateral cleft lip

Makoto NOGUCHI
Department of Oral & Maxillofacial Surgery,
Graduate School of Medicine and Pharmaceutical Sciences for Research,
University of Toyama (Japan)

Cleft lip repair is challenging to surgeons involved in its treatment. There are several goals in the surgical correction that addresses roughly to two parts: the lip and the nose. In terms of the lip, it is hoped to achieve a balance and symmetric lip scars that are hidden in natural anatomical scars. There is a myriad of surgical techniques or incision lines, and they can be roughly divided into three types: Millard type repair, Randall type repair, and straight line repair. Straight line repair was first described by Rose and Thompson. This has been considered to be suitable for incomplete cleft lip or cases where the discrepancy in philtral column heights was not too much. Thereafter several surgeons have revised the straight line repair to achieve adequate lip length. There has been resurgence in use of straight line repair.

Straight line repair mimics the philtral column on the normal side. Superior cosmetic results could be achieved by secondary surgery to perfect the initial surgery in most patients with complete unilateral cleft lip. From this point of view, simple scar could be advantageous to do it. I would like to share my experience with you.

J 002
Surgical correction of the mal-positioned nasal cartilages and the lining defect at the time of primary lip repair to treat unilateral cleft lip nasal deformity

Shunsuke Yuzuriha
Department of Plastic and Reconstructive Surgery,
Shinshu University School of Medicine,
Matsumoto, Nagano prefecture (Japan)

【Background】Primary correction of cleft lip nasal deformity synchronous with lip repair has become commonplace during the past 30 years on the basis of some reports on long terms follow-up results. However, a deep rooted myth that early nasal surgery affects cartilage growth is still believed by some cleft surgeons.

【Purpose】The purpose of this paper is to introduce our approach to unilateral cleft lip nasal deformity at the time of primary nasolabial repair and to show the long terms follow-up results.

【Method】Integrants of the procedure are as follows: First, the deformity and malposition of both the septo-lateral cartilaginous complex and the lower lateral cartilage are certainly corrected and firmly fixed by transposing the lateral crus into a space resulting from cutting the upper lateral cartilage. Second, the bony platform is conserved without surgical contact. Third, the abundant extranasal tissue originated from bilateral cleft margins is transposed into the nasal vestibule and nasal floor to dispose the lack of nasal lining.

【Result】One hundred and eighty-three cases of unilateral complete cleft lip and palate were repaired under our surgical concept. Primary repairs were performed between 1 and 4 months old. Sixty-four cases of all who were followed up over 18 years were evaluated retrospectively. Revisions were required in 80% of the cases and needed twice in 58%. Final nasal shapes were a little wider comparing to the normal Japanese nose in anthropometrical evaluation. Other measuring values of the nose were normal.

【Discussion】The patients themselves and parents hope to have the natural nose in every growing period. Follow-up surgical corrections were usually needed with the growth change of the patient face. The natural and normal shape of the nose was obtained in all patients without any growth disturbance after our primary nasal repair. While we take potential undesirable progress of the nasal deformity as a result of keeping the deformed cartilages and the psychological trauma of the patients and their parents into account, the deformity and malposition of the nasal cartilages should be corrected early in the life with plastic cartilages and their psychological agony should be eliminated early.

J 003
Primary management and cheiloplasty for bilateral cleft lip and/or palate patients

Kazuhide NISHIHARA
Department of Oral and Maxillofacial Functional Rehabilitation, Graduate School of Medicine, University of the Ryukyus (Japan)

【Introduction】Many patients with bilateral cleft lip and/or palate (BCL/P) have a short columella, depressed nasal tip, dislocated nasal alar, and when the premaxilla is extremely protruded, correction of the lip and nose become more difficult.

After birth, we manage the baby's feeding by applying a Hotz plate and perform presurgical orthopedics using nasoalveolar molding plate (NAM) and taping. The stent fixed at the anterior part of the Hotz plate approaches the top of the medial crura of the lower lateral cartilage. NAM provides elongation of the columella length and push-back the premaxillar bone by elastic power.

Primary cheiloplasty of cleft lip and/or palate patients is carried out 3 months after birth, and palatoplasty is performed at 1 and half years. Autogenous bone grafting in the alveolar cleft is performed at around 9 years old. For BCL/P, I performed primary lip repair by one-stage surgery or two-stage surgery depending on the volume of the upper lip. When the length of the upper lip is greater than 10 mm, one-stage surgery is carried out, but when the upper lip is smaller, or the premaxilla is severely protruded, two-stage surgery is adopted.

The surgical procedure of one-stage cheiloplasty is carried out by Manchester's straight-line method, and two-stage is achieved using cronin's triangle flap method. Two-stage surgery is performed at 3 months and 6 or 7 months after birth.

On the surgery, vestibular incision and wide dissection around the piriform margin is very important for correction of the laterally deviated nasal alar base. Especially, in cases with protruded premaxilla, vestibular incision is thought to be the key for good results. These procedures allow 3D movement of the deviated alar base point in BCL/P. If these procedures are not adequate, tension between the lips become very tight resulting in a wide scar and wide nasal form. The results following primary correction are not always satisfactory since the bilateral cleft has more or less inherent tissue defects.

【Conclusions】Preoperative orthopedics by NAM followed by simultaneous advancement of nasolabial components will provide good nasal forms with minimum invasion in patients with ceft lip and/or palate. Long-term follow-up will be necessary to clarify effects on the growth of nasal tissues reconstructed in infancy.

J 004
Modified two-flap palatoplasty for primary cleft palate

Yasuyoshi Tosa, MD, Ph.D.,
Koichi Kadomatsu, MD, Ph.D.
Department of Plastic and Reconstructive Surgery,
Showa University School of Medicine (Japan)

【Background】Cleft lip and palate are the most frequent anomalies amomg congenital malformations of the face. There is racial difference in the frequency of occurrence,, with about 1 case in 500 births of Asians. The inicidence of cleft palate is about 1 case in 600-700 births. The surgical goals of palatoplasty are complete closure, veloparyngeal competence and normal maxillary growth.

Several palatoplasty techniques for cleft palate have been reported to achieve these goals. In cases with soft cleft palate alone, we choose the Furlow technique. For hard and soft cleft palate, we use a modified two-flap technique.

Here, we focus on the modified two-flap method, which has a low incidence of palatal fistula after palatoplasty, even for cleft palate with a relatively wide width.

【Subjects, Methods and Results】We used the modified two-flap palatoplasty for palatal closure. Our modified two-flap method is based on a Bardach-type two-flap technique and combines a Z-plasty of the soft cleft palate on the nasal side with a intravelar veloplasty.

In the unilateral cleft lip and palate patient group who underwent this method between 1 year and 1 year and 6 months, the number of cases that were evaluated for language continuously until age 5 years was 22 cases. The evaluation by speech pathologists showed that the velopharyngeal competence and the frequency of speech of dysarthria were generally good.

Regarding the maxillary growth, in a patient that has reached 5 years and 10 months of age, cephalogram showed a favorable course relating to the maxilla and occlusion.

The incidence of postoperative fistula complication was 0% with 0 cases.

【Discussion】The two-flap technique is a method of palatoplasty that was first reported in 1967 by Barcach in Polish, and spread through the West after being reported in English in 1984. Its advantage is that low formation in maxillary growth is unlikely to occur, since no raw surface remains at the anterior region of the hard palate. The disadvantage is that in cases of a wide cleft, there is a wide dead space between the oral cavity side and the nasal cavity side emmidiately after suturing.

We report on the modifid two-flap palatoplasty, presenting representative cases as well as reviewing the literature.

J 005
Palatoplasty

Hideto SAIJO
Department of Oral-Maxillofacial Surgery,
Dentistry and Orthodontics,
University of Tokyo Hospital (Japan)

There are several purposes of palatoplasty. The first purpose is to intercept between the oral cavity and the nasal cavity in the palatal part. The second purpose is to reconstruct the divided muscle tissue, such as the levator veli palatini muscles, in the soft palate. And the final purpose is to obtain normal velopharyngeal closure function.

Velopharyngeal closer is a requirement for an ordinary speech function. Palatoplasty is often performed on infants at 1 to 2 years of age in order to allow their speech development from 2 years of age. This is because the development of the correct articulation is expected by closing the cleft palate and obtaining velopharyngeal function earlier than that. On the other hand, it has been reported that the formation of scar tissue in the hard palate as a result of the hard palate closure at an early age causes maxillary growth suppression. Although various methods have been reported to solve such a contradicting problems of speech and maxillofacial growth so far, no evidence has been reached on the most effective technique for these reports.

In palatoplasty, our department chooses either the pushback method which accompanies posterior shifting of palatal flap or the method of the Furlow's double-opposing Z-palatoplasty, taking the width of the palatial cleft, the state of the soft palate, and the depth of the oropharyngeal posterior wall. In other words, we choose the Furlow method for cleft lip and palate or cleft palate cases when the tissue of the soft palate is developed enough and the width of the palatal cleft is relatively small as well as the tension of the muscles is weak.

In recent years, the method of Velar adhesion and the first cheiloplasty are performed together if a patient has a the cleft wider than 10 mm in the soft palate. In this session, I would like to discuss the methods used in palatoplasty which is performed in our department.

J 006
Secondary Repair of Cleft Lip and Nose

Koichi Ueda
Department of Plastic and Reconstructive Surgery,
Osaka Medical College (Japan)

【Background】Reverse-U incision technique was reported by Tajima,S (Plast Reconstr Surg 60:256,1977). We performed simultaneous nasal correction by reverse-U incision in the primary cleft lip repairs previously and reported that about 30% of them required secondary correction of reverse-U incision again (Jpn J Plast Surg, 50:293,2007).

Now we perform nasal corrections by reverse-U incision before entering primary school.
Deficiency of the free border of the lip is encountered in secondary cleft lip deformities.

We reported Deepithelialized oral vestibular flap (boot flap) for treatment of free border deformity in unilateral cleft lip (Plast Reconstr Surg, 130: 913e, 2012) and Whistling lip deformity in bilateral cleft lip (Plast Reconstr Surg, 132: 881e, 2013).

【Purpose】For postoperative evaluation, scoring evaluation method was designed. By using this method, evaluations were performed in the cleft lip nose by secondary repair.

And we evaluated results of boot flap in unilateral cleft lip and in whistling lip deformity in bilateral cleft lip.

【Method】Thirty-three patients were operated on January 2000 to May 2010. We divided the patients into three groups (cleft lip patients, cleft lip and alveolar cleft patients, and cleft lip and palate patients).The outcomes of the secondary repair by reverse-U incision were evaluated by the scoring method.

The boot flap was used from July 2005 to August 2010 to correct deficiencies of the free border of the lip in 20 patients with unilateral cleft lip and was used August 2007 to July 2012 to correct whistling lip deformity in 11 patients with bilateral cleft lip.

【Results】Manifest improvement of the scores in all three groups was obtained after the secondary nasal repairs and then the scores remains stable.

Eighteen patients who undertook boot flap could be followed postoperatively for 12 to 80 months (average, 24.5 months). Mild atrophy of the flap was noted in one patient. In the other 17 patients, good results were obtained. A little swelling caused by overcorrection was noted for a few months. After that, good contours were seen. Softness of the flap continued postoperatively, with no firmness.

【Discussion】The secondary repair by reverse-U incision gives us stable operative results. The direct sutures for correcting notching of the vermillion border may cause deformities again because of scar contracture. To prevent the recurrence, it is important to interrupt the contracture plain by incorporating the flap there and augmenting the volume.

J 007
The strategy of secondary repair for unilateral and bilateral cleft lip

Yoshihide Mori, Tomohiro Yamada
Section of Oral and Maxillofacial Surgery,
Faculty of Dental Science,
Kyushu University (Japan)

Cleft lip (CL) cases that need secondary repair have not only conspicuous scar, but also various morphological problems. In case of unilateral (U) CL, deviation of alar base in minor segment occurs caused by contracted nasal vestibular fold. Deviation of median line and asymmetry is remained on the lip and nose. Insufficient making of orbicular muscle, short or excess in volume of red lip is often observed. On the other hand, bilateral (B) CL is deficient in vertical length of the prolabium and columella absolutely. It is important to solve this problem.

For UCL, we usually use the Onitsuka's formula to repair lip. It is essential to elongate contracted nasal vestibular fold. We incise the base of nasal vestibular fold and elongate to upper side, and transplant incised scared epithelium to arisen tissue defect. Incision and elongation on the center of nasal vestibular fold often causes defect of nasal hairs and/or distortion of external nose. We use reverse U incision for closed rhinoplasty.

We sometimes use the Millard's forked flap to elongate columella in preschool period for BCL. Open rhinoplasty is adopted by this method. However, another surgery is required to repair defect of red lip.

J 008
Reliability of our simple evaluation system for alveolar bone grafting using CT images

Yoshimichi Imai[1)],
Kazuaki Nishimura[2)],
Kaoru Igarashi[2)]
[1)] Department of Plastic and Reconstructive Surgery,
Tohoku University Hospital
[2)] Clinics for Maxillo-Oral Disorders, Dental Center,
Tohoku University Hospital (Japan)

【Objective】 Although secondary alveolar bone grafting (SABG) is a relatively simple procedure, it plays an important role in comprehensive cleft care. SABG can provide nicely arranged permanent dental arch by ordinary orthodontic works without any prosthesis, however multidisciplinary approach is essential to achieve expected goals. In our presentation, we are going to introduce our approach to SABG including our evaluation system, results, and surgical techniques.

【Participants】 We reviewed 591 consecutive SABG procedures using medical and dental records. All these cases were treated in our clinic from January 1996 to December 2017.

【Surgical Procedures】 The timing of SABG was generally decided with the patient's dental condition such as just before eruption of the lateral incisor on the cleft side. The incision was put on the alveolar cleft border and continued to the gingival pocket, then raised towards the buccal sulcus. We divided the mucoperiosteum on each side of the wall of the alveolar cleft into nasal and palatal side. And we made a recipient space of alveolar cleft with suturing the bilateral mucoperiosteal flaps at both of nasal and palatal sides. The recipient space should have the same height as the bony nasal floor on the contralateral side, and should also have the depth close to the incisal foramen.

【Main outcome measures】 We evaluated the early outcomes of SABG by standard computed tomographic (CT) images taken 6 months after the procedure. We set a range to be filled by the bone graft (RFB) for each slice of the CT image. RFB was set as a space of the alveolar cleft between the anterior and posterior lines connecting the borders of the alveolus on each side. The early outcome was evaluated as "successful", if RFBs were filled by bone graft in consecutive 4 slices of the CT images of 2 mm intervals. On the other hand, we evaluated the final outcomes of SABG by dental X-rays taken at the age of permanent dentition using Kochi's score.

【Results】 Our SABG was evaluated as "successful" in 92% of cases postoperatively. And the 97% of those cases were score 4 or 3 in the permanent dentition. And 67% of non "successful" cases were evaluated as score 1 or 2 in the permanent dentition.

【Conclusions】 Our early evaluations of SABG could be reliable to predict final outcomes. And overall outcome revealed our approach to SABG to be quite reasonable.

J 009
Monocortical mandibular bone grafting for reconstruction of alveolar cleft

Tadashi Mikoya[1)], Yusuke Matsuzawa[2)], Soichi Tanaka[3)],
Izumi Sogabe[3)], Yumi Ito[2)], Junya Kato[3)],
Makoto Matsuoka[3)], Tetsuya Seikai[3)]
[1)] Center for Advanced Oral Medicine, Hokkaido University Hospital
[2)] Oral and Maxillofacial Surgery, Keiyukai Sapporo Hospital
[3)] Oral and Maxillofacial Surgery, Graduate School of Dentistry,
Hokkaido University (Japan)

【Background and Purpose】We have contrived a monocortical mandibular bone grafting procedure that takes full advantage of the conventional mandibular bone grafting, and can be possibly applied for larger alveolar clefts (Mikoya,T.,et.al: Cleft Palate Craniofac J 47, 2010). This study aims to prospectively evaluate the effectiveness of our procedure.

【Mterials and Methods】Bone grafting was performed by harvesting lateral cortical bone plates from the symphysis and/or body and then placing them on the labial and palatal openings of the alveolar process defect. No particulate bone grafts were packed into the bony cavity. Subjects comprised 88 alveolar clefts of 75 consecutive Japanese patients. Mean age at bone grafting was 7 years 1 month. Mean follow-up after bone grafting was more than 4 years. Bone bridge formation were evaluated qualitatively on axial computed tomography (CT) 6 months postoperatively. Marginal bone quality around cleft-adjacent teeth was assessed using the Chelsea scale on the most recent periapical radiographs. Periapical radiographs were scored independently by 3 observers, and intra- and inter-observer agreement measured using unweighted kappa statistics were good. The cleft defect sizes were correlated with the grades of bone bridge formation and marginal bone quality using Spearman's rank correlation coefficients.

【Results】Sufficient bone bridge formation in 83.0% of clefts was shown. More than 75% of the root surfaces of cleft-adjacent teeth were covered with spanning bone in 93.2% of clefts. In 86.4% of clefts the canines erupted spontaneously. There was not a statistically significant correlation between the cleft defect sizes and both the grades of bone bridge formation and marginal bone quality in all cases.

【Conclusions】This procedure appears extremely effective for sufficient bone bridge formation and facilitation of cleft-adjacent teeth eruption. The procedure is advantageous in that the quantity of bone required per unit volume of cleft defect is relatively reduced, and larger clefts can thus be treated.

J 010
Effects of intravelar veloplasty in repushback palatoplasty

Masaaki Sasaguri[1)], Takeshi Mitsuyasu[2)],
Shinsaku Arai[2)], Norifumi Nakamura[3)],
Manabu Habu[1)], Seiji Nakamura[2)],
Kazuhiro Tominaga[1)]
[1)]Department of Science of Physical Functions,
Division of Oral and Maxillofacial Surgery,
Kyushu Dental University
[2)]Section of Oral and Maxillofacial Oncology Division of
Maxillofacial Diagnostic and Surgical Sciences Faculty of
Dental Science Kyushu University
[3)]Department of Oral and Maxillofacial Surgery,
Field of Maxillofacial Rehabilitation,
Kagoshima University Graduate School of
Medical and Dental Sciences (Japan)

【Background and purpose】Speech impairment is a serious problem faced by patients with cleft palate in their early lives. When this speech problem is related to velopharyngeal incompetence (VPI), surgical correction will usually be required eventually. For surgical correction of VPI in the cleft palate, the pharyngeal flap operation is thought to be the most reliable treatment method for achieving successful velopharyngeal closure function (VPF), even though it produces an abnormal pharyngeal anatomy. On the other hand repushback palatoplasty is thought to be a more biological procedure without disturbance of the normal velopharyngeal anatomical structures. In the patients with mild VPI, repushback palatoplsty is successful velophryngeal closure function, but not always successful in the patients with severe VPI and may result in persistent VPI. Intravelar velopasty (IVVP) with muscle superposition in repushback palatoplasty is thought to increase the achievement of velopharyngeal competence in patients undergoing repushback palatoplasty. The purpose of this study is to evaluate effects of IVVP in repushback palatoplasty.

【Methods】Twenty two patients with severe PVI who had been treated by repushback surgery and followed up for more than 2 years for 14 years. These patients were divided into two groups. Group A of 11 petients undergoing two layers repushback palatoplasty without IVVP or with small IVVP were compared the group B of 11 patients undergoing three layers repushback palatoplasty with IVVP with muscle superposition. VPF was evaluated before and after the repushback palatoplasty by speech therapist. Lateral cephalometric radiographs were taken at rest and during phonetion of /i/ before and after the repushback palatoplasty. V-P distance which is the distance from velar to pharyngeal wall during phonetion of /i/ and velar length were evaluated.

【Result and conclusion】Complete disappearance of VPI was observed 18.2% of patients of group A and 54.5% of patients of group B. Decrement of V-P distance of patients of group B was significantly larger than that of patients of group A. IVVP with muscle superposition was effective in improving velophryngeal structure and function.

J 011
Speech assistant device

Teruyuki Niimi
Division of Research and Treatment for Oral and
Maxillofacial Congenital Anomalies,
School of Dentistry, Aichi-Gakuin University,
Nagoya (Japan)

【Introduction】One of the problems that occur after surgery for cleft palate patients is velopharyngeal insufficiency. The causes of velopharyngeal insufficiency are movement disorder of the soft palate and wide velopharyngeal (short palate).

The treatment of velopharyngeal insufficiency is speech therapy, but sometimes surgery and/or the use of speech assistant devices are combined. Usually, the speech assistant device uses paratal lift for movement disorders of the soft palate and speech aid for wide velopharyngeal (short palate).

Here I present these fabrication methods and effects.

How to make device

【Palatal lift】An impression is taken using an alginate impression material. Make a palatal plate with clasps. I usually use Adams clasps for posterior teeth and single arm clasps for anterior teeth. Single arm clasps design the tip on the distal side to resist lift reaction. After wearing the palatal plate, extend it backward with resin. Then lift up soft palate after extending palatal plate to a predetermined position. A clear color resin is used so that the color of the palatal lift area mucosa can be observed.

【Speech aid】An impression is taken using an alginate impression material. Make a palatal plate with clasps. Bend the wire reaching to the velopharyngeal cavity. The wire is recommended thickness of 0.8 - 1.0mm. The wire in the velopharyngeal area is covered with resin to form a core of bulb. Check the position of the core on the lateral cephalogram radiograph. The bulb is made of temporary lining material for dentures (SOFT-LINER®, GC Corporation, Tokyo JAPAN). The bulb should be placed over the area where the soft palate rises most.

【Effect of devices】Both devices narrow velopharynx physically, but the effect is not only this. By stimulating surrounding muscles, it activates the muscles and promotes movement.

I will present the case and explain the effects of the device.

J 012
A transition of prosthodontic treatment for CLP patients

Shogo Ozawa
Department for Removable Prosthodontics,
Aichi Gakuin University (Japan)

Prosthodontic treatment for cleft and palate patients require not only esthetic restoration for missing anterior teeth, but also stabilization of maxillary dental arch against relatively strong mandibular arch. Recently number of the prosthetic therapy decreased since technique developments for early intervention such as NAM and secondary bone graft in systematic multidisciplinary approach. The patients who have large discrepancy in skeletal relation and multiple missing teeth are indication for prosthodontic option.

In our department we have treated more than three hundred CLP patients since 1980s. Professional oral care and meticulous maintenance of occlusion are essential after the prosthodontic treatment. Long spanned fixed restoration provides favorable cross arch stabilization, but also yields difficulties in hygiene and adaptation for aging. Removable restoration with double crown abutments have been applied to the CLP patients and given promising outcomes based on over 20 years' experience. Advantages of this treatment called Konus Bridge are esthetic restoration, ease for cleaning, stable in function, and accommodate for denture repair. There are no visible abutments such as metal clasp, and friction retention provides appropriate stability. Once remove the prosthesis, normal oral care is enough for hygiene and maintenance and repair are easy. Needs for multiple teeth preparation and relatively high cost and technique for fabrication are drawback of this option. Long term clinical results of the Konus Bridge are going to be introduced.

Another prosthetic option is application of magnetic attachment. This attachment is applicable for complex defect such as obturation of fistula and compromised abutment teeth. Removable prosthesis with the magnetic attachment also results in esthetic restoration, functional stability and easy to handle.

CLP patients who need prosthodontic care should be final treatment before social life begin. It is essential to select best applicable treatment plan for each individual from various options including dental implant therapy, based on his/her original background with medically, psychologically and social considerations.

J 013
Early alveolar cleft closure using human umbilical cord mesenchymal stem cells in experimental model

Naoto Suda
Division of Orthodontics,
Department of Human Development and Fostering,
Meikai University School of Dentistry (Japan)

【Background】The alveolar cleft causes the morphological and functional abnormality. Regenerative medicine using the mesenchymal stem cells (MSCs) is expected to be useful to form bone bridge between alveolar clefts.

【Purpose】In this study, we examined the bone formation of the human umbilical cord derived MSCs using the rat alveolar cleft model.

【Method】Human umbilical cord were digested by enzymatic procedure and isolated cells (UC-EZ) were collected. Using magnetic activated cell sorting, CD146-positive cells (UC-MACS) were isolated from UC-EZ. To evaluate bone formation in vivo, UC-MACS were transplanted with hydroxyapatite and collagen (HA+Col) into alveolar cleft model.

【Result】Both type of cells showed MSC gene/protein expression and multipotency, in vitro. Observation of micro computed tomography and histological staining showed that UC-MACS induced more abundant bone formation than HA+Col implantation solely. Cells immunopositive for osteopontin were accumulated and embedded in newly formed bone. Cells immunopositive for human-specific mitochondria were seen in both mineralized and non-mineralized tissues.

【Discussion】These findings indicate that UC-MACS are responsible for new bone formation. It is shown that UC-MACS can be expected as an useful bioresource for alveolar cleft regeneratio

J 014
Nasoendoscopic assessment of velopharyngeal function of cleft palate

Naoki Saito, Toko Hayakawa, Nagato Natsume
Cleft Lip and Palate Center,
Aichi Gakuin University Dental Hospital (Japan)

We perfome a nasoendoscopic assessment of velopharyngeal function on all the patient children, who were born with cleft palate and treated at Aichi Gakuin University Dental Hospital, at age 6 to 8 years. Here we report details of the procedure and points to be noted.

1. We employ Olympus ENF-V3 video rhinolaryngoscope for the assessment. ENF-V3 has a slim 2.6 mm diameter at the tip of the endoscope. We insert the endoscope through the nostril into the velopharynmgeal cavity, and observe movement of velum and pharyngeal wall, and size, location and shape of gaps during speaking sample sentences and sylables. We set the two monitors so that the patient child can see the same endoscopic images as the practitioner.

Because the children who experienced cheiloplasty and/or palatoplasty often have extremely narrow nasal cavity, the practitioner should perform a pre-treatment of the nasal cavity before inserting the endoscope.

First, the practitioner should mesure 2 mL of Xylocaine Jelly 2% and 0.5 mL of Bosmin in a dish and mixes them. The practitioner should then take the mixture onto a cotton swab and apply it to the nasal cavity. The application with a cotton swab is better than spray application because the drug solution would not flow onto the tongue or into the larynx and, even better than that, the patient child would not feel scared with the swab application.

When the practitioner feels registance with the swab, the practitioner should pause the application and insert the endoscope to check the condition of the inside of the nasal cavity. The practitioner should figure out the insertion route with the endoscope observation and further apply the pre-treatment drugs onto the surface of the route.

The pre-treatment would be completed when the swab goes into the velopharynx smoothly.

Note: It is important to apply antifog to the endoscope before insertion.

2. The practitioner should study the monitor to let the endoscope move forward, with rotating and bending the endoscope towards the destination.

The areas the practitioner should be careful are Kiesselbach's area and Woodruff's plexus, because both of which easily cause nasal bleeding.

（Kiesselbach's area、Woodruff's plexus）（epistaxis ／ nasal bleeding）

The first choice of the route will be the lower end of middle concha route because the condition of the velopharyngeal closure is usually more appearant. The second choice may be the lower end of inferior concha route when the first choice is not applicable.

（the condition/pattern of velopharyngeal closure）

Discussion

In 1968, McWilliams et al. reported that the extended head position caused less sufficient velopharyngeal closure in the cases with borderline velopharyngeal insufficiency after cleft palate treatment.

Momentary bubbling often does not affect much on speech sounds. In such cases, the endoscopic findings will be consistent with the cephalometric radiograph findings, imaged as the velum contact to the posterior pharyngeal wall.
Continuous bubbling from the median position will affect speech sounds. Cases accompanied by bubbling may sometimes show the velum contact to the posterior pharyngeal wall in the cephalograms.

There is a case in which the velum is elevated but no contact to the posterior pharyngeal wall in the cephalogram image.

Passavant's ridge on the posterior pharyngeal wall can also be observed in the cephalogram image.

Pharyngeal stop is a maladaptive compensatory error produced by making contact between the base of tongue and posterior pharyngeal wall in a stop manner.

(While pharyngeal fricative is a maladaptive compensatory error produced by constriction of the vocal tract or constriction between the retracted base of tongue and pharynx to create frication.)

In a sagittal closure, a massive protrusion from the pharyngeal lateral wall occurs, resulting in an image of lateral cephalometry as if there is a wide protrusion of posterior pharyngeal wall.

Conclusion

Although nasoendoscopic assessment and diagnoses are useful, making correct diagnoses will require a substantial experiences.

A nasoendoscopic diagnosis can be differenct from diagnosis derived from other tests such as audiological test. A nasoendoscopic diagnosis is inevitably a subjective assessment because the nasoendoscopic images are distorted at the periphery of the lens, making quantitative measurement impossible. There is a blind area because the field of view of the endoscope is limited. And it is possible that the fear and foreign body sensation accompanied with insertion of the endoscope can make the patient child different from the normal state.

Because of the above reasons, we should try to make accurate assenssment and diagnoses by applying appropriate pre-treatments on appropriate areas, employing endoscopes with high-performance and high-resolution, taking the head position into account, and making the patient relaxed.

We would be happy if our experiences are helpful for many practitioners.

J 015
Current approaches to orthodontic management of cleft lip and palate and future perspective

Noriaki Yoshida
Department of Orthodontics and
Dentofacial Orthopedics,
Nagasaki University Graduate School of
Biomedical Sciences (Japan)

Cleft lip and palate (CLP) is the most frequent congenital facial abnormality accompanied with malocclusion. Prevalence of reversed occlusion is extremely high due to the effect of scar produced after cleft lip and palate reconstruction. Sine plastic surgery operations on cleft lip and palate have been improved considerably in recent years, more and more patients could be treated without orthognathic surgery. Depending on the cases, tooth extraction in the phase two orthodontic treatment would facilitate such treatments if only there is no severe skeletal discrepancy. Treatment that does not rely on orthognathic surgery would contribute to the reduction of patient's burden, and also an establishment of stable occlusion.

Some patients need prosthetic treatment after completion of the phase two orthodontic treatment. However, the patients are not necessarily satisfied with the treatment outcome from an aesthetic point of view. Treatment that does not rely on dental implant or bridge will be introduced as one of treatment options.

Lastly, future perspectives on optimizing treatment mechanics using numerical methods or artificial intelligence (AI) will be discussed.

J 016
Dental appliances employed in treatment of cleft palate speech -for improvement of velopharyngeal insufficiency and articulation disorders-

Ichiro Yamamoto
Yamamoto Dental Clinic, Orthodontic Practice (Japan)

【Introduction】In Kobe area, joint cleft palate conference has been continued for 24 years. Specialists on cleft palate treatment (plastic surgeons, orthodontists, audiologists, speech therapists, etc.) get together and see the clients together. While there are various reasons and types of problems for client visiting, speech disorder is the major issue. This presentation will provide the decision-making process for the timing of an intervention; surgery, prosthetics, and speech therapy from our long-term experience.

【Method】From the records of the conference, two types of intervention were selected. One was palatal lift prosthesis (PLP) to improve velopharyngeal function and the other was electropalatography (EPG) for visual feedback articulation training. The treatment procedures and the outcome with these interventions will be presented on 4 cases.

【Result】The factors of velopharyngeal inadequacy (VPI) include ① structural abnormalities, ② physiological disorders, ③ articulation errors, and ④ fistulae. In case of ① and ② , PLP or Bulb-PLP were introduced and speech therapy was carried out. After reevaluation, the necessity of surgical intervention was discussed. In case of ③, visual feedback training using electropalatography (EPG) was carried out. In case of ④ , palatal obturator was applied.

Case A with submucous cleft palate: After speech training with PLP, pharyngeal flap operation was performed.

Case B with occult submucous cleft palate: After speech training with PLP, VP function and speech became normal without surgery.

Case C with cleft palate: Backing misarticulation was persistent in spite of adequate VP function. Visual feedback training with EPG produced a good result in a short period.

Case D with unilateral cleft lip and palate, post pharyngeal flap operation: Speech training with PLP and EPG solved the problem without another surgery.

【Conclusion】Dental appliances, like PLP or bulb-PLP, and EPG were shown effective in the treatment of cleft palate speech.

J 017
Bulb type palatal lift prosthesis (bulb-PLP) therapy for velopharyngeal dysfunction in cleft palate

Yuko Ogata[1, 2)], Masahiro Tezuka[3)], Norifumi Nakamura[3)], Masaaki Sasaguri[4)],
Takeshi Mitsuyasu[2)], Sachiyo Hasegawa[2)], Seiji Nakamura[2)]
[1)]Kurashige Pediatric Clinic
[2)]Section of Oral and Maxillofacial Oncology Division of Maxillofacial Diagnostic and Surgical Sciences Faculty of Dental Science Kyushu University
[3)]Department of Oral and Maxillofacial Surgery, Field of Maxillofacial Rehabilitation, Kagoshima University Graduate School of Medical and Dental Sciences
[4)]Department of Science of Physical Functions, Division of Oral and Maxillofacial Surgery, Kyushu Dental University (Japan)

【Background】Velopharyngeal dysfunction (VPD) following primary palatoplasty causes serious speech problems with resultant communication disorders in patients with cleft palate. This consequently decreases the quality of the patient's life. Postoperative VPD is caused by several factors, including oro-nasal fistula, insufficient palatal length and movement of the soft palate. The treatment of VPD cannot be treated by a single's specialist owing to the presence of complex problems. When these speech problems are recognized as being related to postoperative VPD, velopharyngeal closure function (VPF) should be recovered through a multidisciplinary approach involving many specialties of medicine, dentistry, and speech. Prosthetic therapy is the one of the treatment approaches for VPD. A prosthetic speech bulb is widely used for the treatment of persistent VPD to facilitate speech generation by separating the nasopharynx from the oropharynx, thereby impounding oral air pressure that is required for avoidance of nasal speech sounds. In this presentation, we review two of our earlier prosthetic studies regarding the effects of bulb-type palatal left prosthesis therapy on VPD.

【Study1】This study included 18 patients (3-52 years old) who underwent bulb-PLP therapy for persistent VPD following palatoplasty. All patients achieved adequate VPF with bulb-PLP. After treatment, 10 patients (55.6%) achieved successful activation of VPF without bulb-PLP (the effective group), whereas VPD was persistent VPI remained in 8 patients (the ineffective group).

【Study 2】This study included 24 patients (3-49 years old) who underwent bulb-PLP therapy for persistent VPD following palatoplasty or congenital velopharyngeal insufficiency. In the effective group, i.e., the group that could withdraw the bulb-PLP, the effect of wearing the prosthesis was noted in 9/18(50%) patients and improvement in articulation was noted after wearing the prosthesis. However, in the ineffective group, i.e., the group that could not withdraw the bulb-PLP, the prosthesis was not worn well in many cases, and there was no improvement in articulation; thus, half the patients in this group had to undergo surgery.

【Conclusion】The results of both above-mentioned studies indicate the usefulness of bulb-PLP therapy in facilitating speech and consequently reducing the need for secondary surgery in patients with persistent VPD following palatoplasty. The possible signs of a subsequent effective activation of VPF are as follows: 1) preexisting adequate VPF under blowing condition, 2) smaller V-P distance, and 3) synchronized palatopharyngeal movement.

J 018
Electropalatography observation of cleft palate speech to supplement perceptual assessment

Yuri Fujiwara[1)], Ichiro Yamamoto[2)]
[1)]Osaka Health Science University
[2)]Yamamoto Dental Clinic (Japan)

【Purpose】Perceptual assessment is a primary tool for SLTs to judge articulatory skills of clients with cleft palate. In Japan, the development of standardized perceptual assessment system is under way on the basis of Cleft Audit Protocol for Speech-Augmented (CAPS-A)1). However, there exist covert atypical gestures which cannot be deduced from perceptual judgement. This presentation will provide the dynamic articulatory electropalatography (EPG) data to supplement perceptual assessment.

【Method】Perceptually judged as Japanese palatalized misarticulation and nasopharyngeal misarticulation were extracted from the charts of the clients who underwent EPG visual feedback training. These EPG data were analyzed using the Articulate Assistant Software (Articulate Instruments Ltd., Musselburgh, UK).

【Result】Japanese palatalized misarticulation used to be defined as distorted alveolar sounds which are produced at the posterior border of the hard palate and the anterior of the soft palate. However, a variety of tongue-palate contact patterns were observed; i.e. wide range of contact from alveolar to hard palate, contact from middle to posterior hard palate, and limited contact to posterior hard palate (Fujiwara, 2010)2). Japanese nasopharyngeal misarticulation is defined as distorted consonant-vowel syllables, often contain high vowels, which are produced at velopharyngeal area. The EPG data revealed that complete closure at the middle or posterior region of the hard palate and no releasing of tongue-palate contact during production of consonant and vowel.

【Discussion】The concept of Japanese palatalized misarticulation did not stand up to the variation of tongue-palate contact patterns observed with EPG. It is suggested to classify into two categories; palatalization/palatal and backed to velar/uvula, following the classification of CAPS-A. The EPG data of Japanese nasopharyngeal misarticulation coincided with the previous study (Yamashita, 1989) 3). This atypical production is similar to “active nasal fricative” in CAPS-A, however, it differs in involvement not only consonants but also vowels.

【Conclusion】As a supplement of perceptual assessment, electropalatography data is helpful to review the categorization and terminology of cleft type characteristics.

1) John, A., Sell, D., Sweeney, T. et al. The cleft audit protocol for speech-augmented: a validated and reliable measure for auditing cleft speech. Cleft Palate J. 2006;43:272-88.
2) Fujiwara, Y. and Yamamoto, I. Electropalatographic analysis of Japanese alveolar sounds produced by patients with cleft palate. The Japan J. of Logopedics and Phoniatrics. 2010;51:26-31.
3) Yamashita, Y. and Michi, K. Misarticulation caused by abnormal lingual-palatal contact in patients with cleft palate with adequate velopharyngeal function. Cleft Palate J. 1991;28:360-66.

J 019
Treatment of sever jaw deformities due to cleft lip and palate using distraction osteogenesis

Nobuyuki Mitsukawa[1)],
Tadashi Morishita[2)],
Atsuomi Saiga[3)]
[1)]Department of Plastic and Reconstructive Surgery,
Chiba University
[2)]Department of Orthodontics,
St. Mary's Hospital
[3)]Department of Plastic and Reconstructive Surgery,
St. Mary's Hospital (Japan)

【Purpose】The jaw deformity by cleft lip and palate presents a unique idiosyncratic facial configuration, which causes the affected patient to bear a great burden and suffering not only in function but also mentally. Acquiring a good occlusion and making a significant change in the patient's facial configuration is the given fate and goal of maxillofacial surgeon. Here, we report our treatment strategy for patients with severe cleft jaw deformity after cleft surgery, and actual cases of surgical treatment using various distraction osteogenesis.

【Methods】Our subjects comprised 10 patients who presented with severe and complicated jaw deformities due to maxillary hypoplasia or mandibular hyperplasia due to cleft lip and palate. Ages ranged from 12 to 37 years (mean 21.6 years) with 4 males and 6 females. Preoperative orthodontics were indispensable, and by diagnostic imaging and three-dimensional solid model, we prepared careful surgical plan. The treatment was performed with skeletal treatment while making full use of various distraction technique. Orthodontic correction after surgery is essential and as a rule, soft tissue procedures such as rhinocheiloplasty are performed after hard tissue correction is completed.

【Results】A normal occlusion, the objective, was successfully achieved in all cases, with marked improvements in appearance and no major complications were observed.

【Discussion】Regarding the treatment of skeletal anomaly, especially cleft lip and palate with severe jaw deformities, we should give priority to reconstruction of hard tissue, and selection of optimal timing and operational method is important. Distraction osteogenesis can start treatment from the child stage and has the great advantage of not limiting bone extending as well as extending soft tissue. We believe distraction osteogenesis is one of the very useful means for severe and complicated cleft jaw deformities.syoroku

J 020
Orthognarthic surgery in the consistent treatment protocol of cleft lip and palate.

Yamada T, Sugiyama G, Mori Y
Section of Oral and Maxillofacial Surgery, Faculty of Dental Science,
Kyushu UniversityDepartment of Bioresource Sciences,
Graduate School of Bioresource and Bioenvironmental Sciences,
Kyushu University (Japan)

Cleft lip and palate is treated in the consistent treatment protocol, and consideration for growth of the jaw is generally taken. Therefore, jaw deformity due to the maxillary undergrowth tends to decrease in recent years. However, malocclusion and patient-specific jaw deformities sometimes occur due to sagittal, vertical and horizontal undergrowth of maxilla. In addition, constriction of maxillary dentition, lingual inclination of the maxillary incisor, inner and posterior displacement of the minor maxillary segment are noted, and displacement of the mandible can be associated with asymmetry of the maxillary dentition. As a result, open bite and/or facial asymmetry as well as mandibular prognathism are often recognized. In the choice of technique, care must be taken. For example, despite maxillary anterior positioning is essential, the posterior movement of the mandible alone may cause a shortage of oral cavity volume for containing the tongue or a constriction of the airway, which may lead to post-operative dysfunction. If the maxilla is moved forward, the soft palate may also be pulled forward, resulting in nasopharyngeal insufficiency. Furthermore, it is necessary to keep in mind the tension in the relapsed direction due to scarring and the lack of blood flow.

Therefore, in our hospital, in the case of mild prognathism or asymmetry of the mandible, which does not require forward movement of the upper jaw, posterior movement of the mandible alone, and two-jaw osteotomy if the amount of forward movement of the maxilla is within 5 mm. And distraction osteogenesis (DO) of the maxilla is often performed when maxillary movement of more than 5 mm is required. In DO, internal fixation device are sometimes used, but due to the degree of freedom of movement direction and the stability of the result, we mainly use the external fixation device, RED system. In order to minimize the influence on nasopharyngeal function, maxillary anterior segment distraction osteogenesis (MASDO) is considered useful.

With these treatment strategies, aimed correction for jaw deformities can be generally achieved, and by correcting the facial skeleton to appropriate position, not only masticatory function but also aesthetic improvement is obtained. Furthermore, definitive lip repair usually becomes easy after orthognathic treatment of the maxilla for cleft lip patients.

International Activity

I 001
Overseas medical support activities for patients with Cleft Lip and Palate in Laos.

Hajime Sunakawa[1)],
Nagato Natsume[2)],
Kazuhide Nishihara[1)],
Keiichi Arakaki[3)],
Akira Arasaki[1)]
[1)]University of the Ryukyus
[2)]Aichi-Gakuin University
[3)]Okinawa Prefectural Chubu Hospital (Japan)

Laos,located in the center of the Indochina peninsula,is one of the economically disadvantaged developing countries with focusing on agriculture, and it's medical environment is not sufficient.

Due to the fact that infectious diseases prevention and hospital Quality have been improved by the JICA project etc. since 1992, the project called "medical support activities and technology transfer for patients with cleft lip and palate" have been implemented since 2001.

This activity was carried out by a team consisting of Anesthesiologists and Nurses, mainly Oral Surgery staff at the University of the Ryukyus Hospital, in cooperation with the Japan Cleft Lip and Palate Foundation(JCPF).

347 cases with cleft lip and palate were operated at the Sethathirath Hospital from 2001 to 2018.

There were many patients, from 3 month old infants to adults in their 60s, came from all over the country.

And elder patients from distant places were preferentially operated .

We have been engaged in 17 times activities for years. Continuously, we are eager to steadily carry out medical assistance activities and technology tranfer to Laos on the premise of "reliability and security".

I 002
Experiences of cleft lip and palate volunteers in the Republic of Tunisia since 2007

Takehiro Fujimoto[1)], Yoshiro Koma[1, 2)],
Kazutoshi Kamei[3)], Kenji Nakazawa[4)]
[1)]Department of Oral and Maxillofacial Surgery, Iwata City Hospital
[2)] Nagoya University Graduate School of Medicine
[3)] Department of Oral and Maxillofacial Surgery,
Division of Oral and Maxillofacial Reconstructive Surgery,
Yokohama Rosai Hospital
[4)] Anes-Care (Japan)

【Purpose】The Republic of Tunisia, located at the northern end of the African continent and slightly south of Italy, has a population of about 11 million and an area of about 2/3 that of Japan, and its GDP per capita is about 1/10. Until now, there are not enough medical personnel who can perform cleft lip and palate treatment and from 2000, support activity of cleft lip and palate medical care has been started from Japan with the Tunis Rotary Club as the counterpart. The author has been participating in this aid activity since 2007 and will give an overview of it and the changes I felt over 12 years.

【Method】We have provided free medical assistance for cleft lip and palate patients almost every year from 2000 to 2019. Initially, the operation was not sufficiently performed by a Tunisian doctor, so the Japanese oral surgeon, the Canadian oral surgeon and the Italian plastic surgeons have conducted a medical examination and surgery in a stay of about 9 days.

【Result】Only four operations were performed in 2000 and there were only a limited number of hospitals that can use the operating room, and we have been operating at different hospitals every year. Hoever, since 2009, surgery can be performed at the same hospital, and the medical participation of Tunisian doctors have become active.

【Discussion】The Jasmine Revolution broke out in Tunisia in January 2011 and the mission that was scheduled for February of that year was discontinued. Due to the killing of foreign travelers including Japanese by terrorism in Tunisia and large-scale demonstrations by assassination of politicians in 2011, 2013, 2015, and 2016, there is a request from the Ministry of Foreign Affairs of Japan for travel restrictions, and the Japanese team could not participate. However, the political situation has been stable in recent years, and medical assistance activities have been continued for three years from 2017 and will continue in the future.

Workshops

in Japanese

N 101
The current actions for development of pediatric medicines and future perspective

Kikuko Ikeda
Pharmaceuticals and Medical Devices Agency (Japan)

Drug development for pediatric population is very tough due to limited number of patients, requirement of appropriate formulation, differences of pharmacokinetic profile according to age and so on. As a result, many medicines have not been approved for pediatric use and many pediatricians prescribe such medicines for infants and children out of high medical needs. Not only Japan but also foreign countries also face the same situation. To solve this problem, regulations which require to develop pediatric medicines simultaneously with development for adults were enforced in the United States and Europe.

In 2000, The guideline on Clinical Investigation of Medicinal Products in The Paediatric Population (ICH E11) was adopted in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH E11 provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population. In 2017, addendum of ICH E11 (ICH E11 (R1)) whose objectives to complement and provide clarification and current regulatory perspective also reached consensus. In this addendum the concept of 'Pediatric Extrapolation' is defined. A new guideline (ICH E11A) for Pediatric Extrapolation is currently under discussion. It is expected that the concept of Pediatric Extrapolation helps to enhance pediatric drug development.

In Japan, although there is no regulation mandating development of pediatric medicines, several frameworks including extension of re-evaluation period, pediatrics premium addition to drug price and council for unapproved drugs/indications have been implemented so far. These actions have attained some progress in pediatric drug development. In addition, the Ministry of Health, Labor and Welfare (MHLW) have recently implemented a new approach "Medical Pediatric Breakthrough Program". The Medical Pediatric Breakthrough Program is a system to encourage pharmaceutical companies to develop pediatric medicines in Japan as early as the EU and the US. In this system, the Japan Pediatric Society fully supports pharmaceutical companies and the company has the option to take out a funding loan from the AMED.

Pharmaceutical and Medical devices agency (PMDA) has established a pediatric drug working group. Its tasks are encouraging industries and investigators to develop medicinal products for children, strengthening collaboration with foreign regulatory agencies for development of pediatric medicines, studying and organizing past reviews and cases of consultations and exchanging views with domestic stakeholders such as medical institutions and industry groups.

In this workshop, I would like to share current actions for development of pediatric drugs and discuss future perspective in Japan.

in Japanese

N 102
Development of evaluation systems for brain development using mouse models of developmental disorders

Shigeo Uchino,
Hitomi Shimizu,
Chikako Waga,
Graduate School of Science and Engineering,
Teikyo University (Japan)

Evaluation systems of brain development for various external environmental factors (foods, chemicals, relaxation, exercise, stress, etc.) in modern society have not been fully developed. We have analyzed the effects of external environmental factors on brain development in neonatal and juvenile mice using various techniques such as molecular biology, biochemistry, brain histology and behavioral sciences. In recent years, there has been concern that chemicals including pesticides cause developmental disorders, but the biological basis is unclear. In this presentation, I introduce the results of the following three research subjects and discuss the evaluation system of brain development.

1) Effects of pesticide compounds (neonicotinoids) on gene expression in the brain
2) Gene expression and behavior analysis using mouse model of developmental disorders due to exposure to developmental neurotoxin (valproic acid) during the fetal period
3) Behavioral analysis of neonatal and young mice using a disease model mouse of autism spectrum disorder (ASD)

As for the evaluation systems of brain development, it is considered important that both in vitro evaluation systems using molecular and cellular analysis and in vivo evaluation systems using behavioral analysis are correlated. However, behavioral analysis methods for neonatal and young mice have not been established. In this presentation, in addition to behavioral analysis methods to evaluate the sociability of young mice, I will also show the latest findings regarding ultrasonic vocalization by neonatal mice.

in Japanese

N 103
Acoustic Startle Response and Prepulse Inhibition

Mikio Sasaki
Ina Research, Inc. (Japan)

Acoustic startle responses (ASR) are generalized muscle contractions, elicited by a sudden and intense acoustic stimulus, commonly observed in all mammals. Although ASR is a reflex, it can be modulated by different kinds of stimuli. A weak pre-stimulus (prepulse) inhibits ASR. This neurological phenomenon is called prepulse inhibition (PPI). ASR, including PPI, is known to be different in patients with psychiatric and neurological disorders such as schizophrenia and autism, and is recommended as a parameter for evaluating developmental neurotoxicity in various nonclinical guidelines for the development of chemicals. In drug development, ASR is not mentioned as a parameter for evaluating effects on the central nervous system (CNS) in the currently effective guidelines for reproductive and developmental toxicity studies (ICH S5 (R2)) or for nonclinical toxicity studies in juvenile animals issued by the FDA, EMEA, and MHLW. However, ICH S5 (R3) and the nonclinical safety testing guideline for the development of pediatric medicines (ICH S11) were released for public comment last year, in which ASR (habituation or PPI) is specified as an indicator in behavioral testing. In this presentation, the basic mechanism and factors influencing the results of ASR and PPI (e.g. sex, estrous cycle, age, strain, stress, lighting, circadian rhythm, etc.) are reviewed based on existing knowledge. In addition, what data, and how that data are generated and evaluated, is explained using actual experiment data in rats obtained at Ina Research. Furthermore, the necessity and usefulness of this line of testing will be discussed.

in Japanese

N 104
Allocation methods for juvenile rat toxicity studies

A Inoue
Drug Safety Research Laboratories,
Shin Nippon Biomedical Laboratories,
Ltd. (SNBL DSR) (Japan)

For allocations of animals for juvenile rat toxicity studies, investigators need to be aware of genetic bias, maternal nursing ability, and littermate bias. Therefore, it is necessary to consider the study objective (dose range-finding study or definitive study), age at administration start, dosing period, recovery period, dosage level, dosing route, possible target organs of test agent, end points, number of juvenile animals, blood collection volume and method for toxicokinetics, 3Rs, and etc. Investigators also need to consider the number of maternal animals and their allocation methods. The draft ICH S11 Step 2 guidelines published in December 2018 describe more specific allocation methods, and several publications introduce other methods for animal allocation. However, each allocation method has both advantages and disadvantages. In our laboratories, 35 juvenile rat toxicity studies have ever been conducted since 2008 using various study designs and several allocation methods. In this presentation, the allocation methods for juvenile rats, including their advantages and disadvantages will be introduced, and their proper use depending on study design will be proposed.
COI: None

in Japanese

N 201
From Fertilization to Implantation

Masako Yamamoto
Azabu University (Japan)

Spermatogenesis takes place in the seminiferous tubules of the testis and does not occur until puberty. In contrast, in the females, oogenesis starts during fetal life. But primary oocytes enter a state of meiotic arrest that persists until puberty. The oocyte complete meiosis only if a spermatozoon fertilized it. Fertilization takes place in the oviduct. After oocyte finishes meiosis, the paternal and maternal chromosomes come together, resulting in the formation of a zygote containing a single diploid nucleus. Embryonic development starts at this point. The embryo undergoes a series of cell division, cleavage, it rolls towards the uterus in the oviduct. The zygote first into two cells, then into four, then into eight, and so on. Starting at the 8-cell stage of development, the originally round and loosely adherent blastomeres begin to flatten, developing an inside-outside polarity that maximizes cell-to-cell contact among adjacent blastomeres. This reorganization called compaction. At this time, the cleaving embryo, or morula, differentiates into two groups of cells: a peripheral outer cell layer and a central inner cell mass. The outer cell layer, called the trophoblast, forms the fetal component of the placenta and associated extraembryonic membranes, whereas the inner cell mass, also called the embryoblast, gives rise to the embryo proper and associated extraembryonic membranes. By the 30-cell stage, the embryo begins to form a fluid-filled central cavity, the blastocyst cavity. By the 5th to 6th day of development, the embryo is a hollow ball of about 100 cells called a blastocyst. At this point, it enters the uterine cavity and begins to implant into the endometrial lining of the uterine wall. Proteolytic enzymes, including several metalloproteinases, are secreted by the cytotrophoblast to break down the extracellular matrix between the endometrial cells. Between days 6 and 9, the embryo becomes fully implanted in the endometrium. The embryo and the fetus receive nutrients and eliminate their metabolic wastes via the placenta, an organ that has both maternal and fetal components. Exchange of nutrients is not the only function of the placenta; the organ also secretes many hormones, including the sex steroids that maintain pregnancy. Maternal antibodies cross the placenta to enter the fetus, where they provide protection against fetal and neonatal infections. Unfortunately, teratogenic compounds and some microorganisms also cross the placenta.

in Japanese

N 202
Genetic variants and congenital anomalies

Hirotomo Saitsu
Department of Biochemistry,
Hamamatsu University School of Medicine (Japan)

Genetic variants can be underlying causes of human disorders. There are several kind of genetic variants including single nucleotide variant, small insertion/deletions, and copy number variant (CNV). In genetic analysis, therefore, we should examine these types of variants. Recent advances in next-generation sequencing (NGS) technology caused paradigm shift in genetic analysis of mendelian disorders including congenital anomalies. Whole exome sequencing (WES), which employs the targeted capture of protein encoding exons, has enabled the comprehensive examination of variants in more than 95% of human coding exons, and can detect both rare and common variants. In addition, recent bioinformatics advances enable us to use WES data for CNV analysis, making WES an extremely useful tool for molecular diagnosis in human disorders, especially in both clinically and genetically heterogeneous disorders. Furthermore, WES of patients' and their parental samples (trio analysis) can systemically detect de novo variants in the patients. If a de novo variant occurred in gamete and the affected gamete takes part in fertilization, this de novo variant will be a germline de novo variant, resulting that all cells of the affected individual have the variant. Importantly, the number of germline de novo variants is highly correlated with paternal age and, to a lesser extent, with maternal age. On the other hand, if a de novo variant occurred during the mitotic cell divisions, only a subset of cells have the variant. This de novo variant is more specifically termed "somatic variants". In this presentation, I will introduce usefulness of WES in genetic analysis of mendelian disorders and show several examples of genetics variants related to congenital anomalies including germline de novo variants and somatic variants.

in Japanese

N 203
The current situation and future of prescription drug package inserts in Japan

Hiromi Hamada
Department of Obstetrics and Gynecology,
Faculty of Medicine,
University of Tsukuba (Japan)

Japanese package inserts for drugs are documents made by the marketing authorization holder of the drug to provide information required by medical professionals, such as doctors, dentists, and pharmacists, to ensure proper drug use and secure the safety of the patients administered the drug. There are two types of drugs in Japan: prescription drugs, which are prescribed by doctors and dentists in medical institutions, and over-the-counter drugs, which are sold in pharmacies. Results of reproductive and developmental toxicity studies of drugs are written on the prescription drug package inserts to enable medical professionals to use the information on this document.

There are established instructions for package inserts of prescription drugs. The instructions for package inserts were revised in June 2017 and the new instructions have been enforced since this April. All descriptions in package inserts must now comply with the new instructions, and this also applies to information regarding reproductive and developmental toxicity studies.

In today's presentation, I would now like to discuss the current and future situation of prescription drug package inserts in Japan as an obstetrician from the standpoints of "usage of information on reproductive and developmental toxicity studies" and "administration of drugs to pregnant women" based on these revisions to the instructions. I would also like to touch on the topic of interview forms, which are documents made by pharmaceutical companies to supplement the information on package inserts.

in Japanese

N 301
Cleft palate observed in developmental and reproductive study

H Yamasaki[1)],
K Shimomura[2)]
[1)]Toxicology Laboratory,
Taiho Pharmaceutical Co., Ltd., Tokushima
[2)]Vaccine Research Laboratories,
Daiichi Sankyo Co., Ltd.,
Tokyo (Japan)

Data from the cohort studies and clinical case studies are mainly used for a consultation with pregnant women. However, it takes long time for an accumulation of these data, and few data exist for new drugs. On the other hand, a lot of non-clinical animal data exists even for new drugs, because the data are required for new drug application. Human fetal risk is evaluated using both human and animal data in the labeling of drugs. The animal data become more important when human data is not enough, and it could be obtained from the “Interview Form” on the website of the pharmaceutical companies. Education seminar “Teratogenicity of common drugs” has been held in the annual meeting of the Japanese teratology society for 12 years. We selected adrenal corticosteroid, antiepileptic drug and antipsychotic drug for this year’s meeting. Prednisolone, Dexamethasone and Betamethasone are including in adrenal corticosteroids. We pick up Phenytoin, Sodium Valproate, Topiramate and Lamotrigine from antiepileptic drugs. Fluphenazine, Perphenazine, and Haloperidol are known as antipsychotic drugs. We will introduce the results of developmental and reproductive studies of these drugs. Cleft palates have been observed in some of these drugs. Then, we would like to discuss the meaning of cleft palate in animal data for evaluation of human fetal risk.

COI: None

in Japanese

N 302
Consideration of cleft lip and palate caused by antiepileptic drug

Masayuki Maeda
Nara Medical University Hospital (Japan)

Epilepsy seizure during pregnancy may cause fetal dysfunction, fetal brain damage, and fetal death due to maternal hypoxemia. Thus, it is important to choose antiepileptic drug during pregnancy with the consideration of risks and benefits.

In addition, the importance of continued dose for antiepileptic drug even during pregnancy is clearly described in “2018 Guideline for Treatment of Epilepsy”. However, the evaluation for Japanese prescription trend indicates that the prescription rate of antiepileptic drug decreases during early/mid pregnancy. This is because it may be related to prescription with hesitation due to the package insert describing antiepileptic drug during pregnancy as possible beneficial effects. In addition, because anyone can easily search for information via the Internet, pregnant women themselves are excessively concerned about safety of drug and effects on fetus, then eventually consider discontinuation of drug or abortion on their own judgment.

Many articles reported that birth defect rate by antiepileptic drug could increase several times compared to a general birth defect rate. For physical deformity, the possibility for cleft lip and palate or heart malformation could be high while a relation with valproic acid, carbamazepine, and neural tube defect has been clinically gaining attention. For cleft lip and palate as a research theme, there are some drugs denying any risk by the subsequent studies even though the description of increased incidence rate in the package insert. If a patient with epilepsy desires to be pregnant, the patient needs pre-pregnancy education such as a seizure control by low-risk drugs and prohibition to discontinue medication even after pregnancy.

It is important for health-care professionals to extensively gather new information and select the best way of treatment each time.

in Japanese

N 303
Corticosteroids during pregnancy and cleft lip and palate

Ai Ohno
Anjo Kosei Hospital (Japan)

Corticosteroids are classified to two main classes, glucocorticoids and mineralocorticoids. Glucocorticoids such as cortisol have anti-inflammatory and immunosuppressive effects. Synthetic corticosteroids (prednisolone, methylprednisolone, dexamethasone, betamethasone) were developed as pharmaceutical drugs. These drugs are used in a variety of conditions in women of childbearing potential. Prednisolone is generally considered safe in pregnancy because of its low fetal transfer.

In animal reproduction studies of corticosteroids, cleft palate of the fetus was observed. The incidence of cleft palate showed increased tendency in the high dose level.

In a prospective controlled study of 311 pregnancies who exposed to corticosteroids in the first trimester, the rate of major anomalies did not significantly differ between the groups [12/262=4.6%(glucocorticoids),19/728=2.6%(control)]. In another prospective cohort study and meta-analysis of epidemiological studies, although prednisolone does not represent a major teratogenic risk in humans at therapeutic doses, it does increase by an order of 3.4-fold the risk of cleft lip and palate. In the meta-analysis reported in 2017, the overall findings showed a certain association between maternal corticosteroid use and occurrence of cleft lip and palate, compared with non-users (OR=1.16 [95% CI: 1.01-1.33]). When study type was considered this association was significant only for case-control studies (OR=1.22 [95% CI: 1.02-1.47]), and not for cohort studies (OR=1.09 [95% CI: 0.88-1.34]).

I would like to introduce these data and discuss the clinical evaluation of the fetal risk of corticosteroids.

in Japanese

N 304
Clinical evaluation of antipsychotic drugs

Y Fushimi
Department of PharmacyAiiku Hospital Imperial Gift Foundation
Boshi-Aiiku-kai Maternal & Child Health Center,
Tokyo (Japan)

Many psychiatric disorders such as schizophrenia develop at the females of childbearing age and need to be continuously treated with antipsychotic drugs. It is not uncommon for pregnancy to be discovered during treatment for internal use. The problem is that the women decide to have abortions because these drugs are contraindicated for pregnancy, and that the patient may discontinue their oral administration due to concerns about the effects on the fetus, which may lead to the deterioration of the psychiatric condition. Among the antipsychotic drugs, there are drugs that contraindicate the use for pregnant women in the package insert because of teratogenicity including cleft lip and palate.

There are some first-generation antipsychotic drugs for which cleft lip and palate have been observed in animal studies, but for which epidemiological studies on the taking of pregnant women have not found any significant effects. Since the development of second-generation antipsychotics drugs, the proportion of second-generation antipsychotic drugs prescriptions has increased but first-generation antipsychotic drugs are still sometimes necessary.

In recent years, more attention has been paid to perinatal mental health, and interventions with multiple types of medical staff have begun to be conducted from the early pregnancy. At the same time, it is also important to provide medication counseling so that the pregnant woman can have the correct awareness of the drug.

Based on the epidemiological studies on haloperidol and perphenazine, we will introduce and discuss the clinical evaluation of the fetal risk of the antipsychotic drugs in this symposium.

N 401
Proven Technique of Microtia construction: autogenous approach - Spiral Curve is the Key

Akira Yamada[1)],
Kenneth E Salyer[2, 3)]
[1)] Northwestern University Feinberg School of Medicine
[2)] World Craniofacial Foundation
[3)] International Cleft Lip and Palate Founation(USA)

Microtia Construction with autogenous rib cartilage was established by Radford Tanzer of New Hampshire in 1950's. Since then, rib cartilage framework construct has been the gold standard of Microtia construction. I witnessed that his patient, after 50 years, still maintained external ear shape well. Based on this and my personal 20 years experiences, autogenous rib cartilage framework construct is still the best option for long term benefit for the Microtia patients.

In order to achieve excellent outcomes in total auricular construction, surgeons must four keys in your mind: 1) skin envelope 2) 3D framework 3) proper anatomical location 4) spiral curve. Both inner ear and external ear have spiral curves in it. One of the important key of external ear reconstruction is how to create or restore the spiral curves of the auricle.

Primary surgery, means no previous surgery, is the best opportunity for optimal outcome. Original skin flap is the best skin envelope to cover the framework with sensation. Skin graft plus temporoparietal fascia flap is the second best option, useful for secondary construction. Skin graft plus occipital fascial flap would be the alternative when superficial temporal artery is severed, but with donor site skin numbness.

Available amount of vestige skin envelope determine the complexity of 3D framework. Complex Nagata Type 3D framework alone would not work without lobule split technique for lobule type microtia. Concha type microtia has more available skin envelope, with better chance of definition of the auricle. Difficulty of concha type microtia is the discrepancy between existing lobule and new framework.

Proper anatomical location of the new auricle is practically not easy to identify and often is underestimated the importance of it. The first step of total auricular construction is to identify ' auricular rectangle' where the new auricle will be placed. This will determine the skin incision design of anterior lobule flap, posterior W-flap, and anterior lobule flap for lobule type microtia. Normally auricle has 15-20 degree posterior inclination. Upright auricle, or anterior inclined auricle often occur, because surgeon try to avoid posterior hair line.

N 402
Microtia Hands-on Workshop: Creating 3D Framework with Rib Cartilage Model

Akira Yamada MD.PhD. (Japan)

The key to achieve excellent outcomes in microtia construction are 1) well vascularized thin skin envelope, 2) identify proper location of the new ear, 3) creating spiral curves in ear, and 4) 3D framework. All four key must be perfect to obtain optimal outcomes. The purpose of microtia workshop is to experience the difficulty and the joy to create 3D framework. There are many detail and tricks to create three dimensional spiral structure of the ear framework. Without step by step approach, this is almost impossible task to master the techniques. Nagata-type 3D framework is composed of five components: 1) Base frame, 2) Helix, 3) Antihelix, 4) Tragus, and 5) Concha. We will use Type A 54 mm template which is most commonly used in my clinical practice. Fine wire (36-38G), used in the workshop, is another crucial instrumentation in order to create delicate structures. We are trying to create complex shape in limited space, thus please remember that 1 mm difference influences a lot for the overall structure. For that reason, frequent checking with template is vital to create balanced three dimensional structure. Surgeon must check the framework progress by overlapping the template on the framework, so one can see the difference, then you can correct the shape. Free improvisation usually does not work well for 3D framework. Instead, preciseness, like industrial design, is more important for 3D ear framework process. Helix is indeed a spiral structure: it starts from the bottom, attached at the back of base frame, then spiral curve goes up on top of the base frame and ends at antitragus level. Creating nice smooth curve of helix is a challenge, but this must be achieved if you wish a nice auricular shape. Antihelix starts as bifurcation at the lowest height at the top, then goes up in height and becomes highest in the mid portion, then goes down slowly toward intertragal notch. Often creating antitragus is forgotten. Tragus is the anterior wall of relatively large space of conceal bowl. Many have hard time to understand the shape of tragus. Small piece of concha piece helps to prevent soft tissue obscure the definition of the framework.

Invited Oral Presentations

IE 001
Secondary correction of cleft lip nasal deformity

Jin-Young Choi DDS, MD
Dept of Oral and Maxillofacial Surgery, School of Dentistry,
Seoul National University (Korea)

One of the most challenging procedures in cleft lip and palate related surgery is the correction of the cleft lip nasal deformity. Cases differ widely in terms of whether they are associated with unilateral or bilateral cleft lips, depending on the severity of the clefting. It is very important to analyse where and how much deformity in nasal anatomical structure of the patients exist to correct nasal deformity. With that in mind, an individualized approach approapriate to the patients deformity should be adopted in each case. The basic techniques for the correction of cleft lip nasal deformities are as follows

1. Symmetrical positioning of alar cartilage and dome
2. Cartilage graft for
   - Increasing projection and symmetry
   - Comouflage residual asymmetry
3. Septoplasty, nasal osteotomy for
   - Correction of septal deviation
4. Cartilage, bone graft for
   - Profile deficiency, depression, irregularity,

Also the patients with cleft lip nasal deformities may have problems which patients without cleft lip nasal deformities have in Asian country such as dorsal augmentation or tip projection. Rhinoplasty should be done considering not only cleft lip nasal deformity but also nasal aesthetics. In this presentation, the anatomy of nose, basic rhinoplastic techniques, implant materials, its applications focusing on my favorite techniques will be introduced and discussed.

IE 003
Management of Obstructive sleep apnea in craniofacial deformities

Adi Rachmiel (Israel)

Obstructive sleep apnea (OSA) in paediatric population is often associated with congenital craniofacial malformations manifesting with a hypoplastic mandible and decreased pharyngeal airway. Part of the patients exhibit respiratory distress and the other part have already undergone permanent tracheostomy. Adult patients with OSA are usually non syndromatic, their symptoms develop with aging and are worse in obese.

【Methods】The paediatric patients were treated by mandibular distraction using external or internal distraction devices. The adult patients were treated by maxillomandibular advancement (MMA).

【Results】An increase in mandibular body length and pharyngeal airway was obtained in all pediatric patients resulting in clinical improvement of OSA symptoms. Decannulation was performed in all patients following the removal of the distraction devices. The advantages and disadvantages of each method will be presented. In adults, MMA gives satisfactory results in eliminating OSA symptoms.

【Conclusions】In children, mandibular distraction osteogenesis results in marked increased airway. The external device permits greater distraction length but the drawback of child discomfort and risk of pin loosening which may need replacement or shortening of the retention period, should be taken into account. The internal devices are more comfortable to the child, efficient, predictable and should be considered as the first choice. The external devices should be used when it is impossible to place the internal devices or when there is a need for greater distraction length. In adults, MMA is efficient in improving the symptoms of OSA.

IE 004
Management of Maxillary Cleft Deficiency -- Distraction Osteogenesis Vs conventional orthognathic surgery

Adi Rachmiel (Israel)

Correction of the hypoplastic maxilla secondary to cleft patients is a great challenge due to significant vertical and horizontal deficiency and difficulty in mobilizing the hypoplastic maxilla as a result of scarring from previous operations and a great tendency for relapse.

Objective: Present our experience using conventional orthognathic surgery and distraction osteogenesis in maxillary cleft deficiency.

【Methods】The operations includes Conventional method by Le Fort I and Maxillary distraction using Rigid External Distraction devices (RED) or Internal Distraction Devices (IDD). Long term follow up of 5 years will be presented.

【Results】For mild retrusion up to 9mm conventional Le Fort I was suitable. However, for growing patients or in deficiencies of 10 mm and more the method of distraction osteogenesis offer better results. The RED system offers greater distraction length, better control on the vector of lengthening and is easily removed. However, it is uncomfortable for the patients. When wearing for several months, the device is exposed to external trauma forces and there is a risk of parietal bone penetration. IDD are efficient in advancement of the deficient maxilla, are safer to wear for long periods of time, they do not create social discomfort and therefore permit longer retention periods which may contribute to better stability than external devices. Their major disadvantage is the need of a second operation for device removal.

【Conclusions】The hypoplastic maxilla in cleft patients is associated with moderate to severe retrusion, and in moderate to severe cases is better treated by distraction osteogenesis then by conventional orthognathic surgery. The internal devices should be considered first even when taking into account the major disadvantage of a second operation for device removal.

IE 005
Long-term outcomes of 41 nonsyndromic sagittal craniosynostosis patients as adults.

Gyorgy K Sandor (Finland)

This study evaluated the long-term outcome of adult patients treated for scaphocephaly during early childhood with a population consisting of patients operated for sagittal synostosis at Oulu University Hospital between 1978 and 1998. Exclusion criteria included patients with any associated disease. 41 patients fulfilled the inclusion criteria and participated in the follow up evaluation. An equal number of age and sex matched healthy persons were randomly selected as controls from the national civil register. Both patients and controls answered questions relating to their education, housing, marital status, employment and the presence of mental disturbances. The participants rated their own satisfaction with their appearance using a 10-point 100mm Visual Analogue Scale (VAS). Using the standardized photographs taken during the follow up visit, a panel consisting of dentists evaluated the cosmetic outcome also using the same VAS scale. The mean age at follow up of the patient group was 26.9 years. There were no differences in education, housing, marital status, employment, general health or the presence of mental health problems between the patient group and the controls. The average satisfaction with the one's own appearance was 7.4 in the patients and 7.7 in controls. Both groups have had orthodontic treatment due to malocclusions in 60 % of cases. The panel gave a lower score to patients than to controls (6.4 and 7.3 accordingly).

Patients treated for scaphocephaly did manage in life as well as controls in general. They were also equally satisfied with their appearance. However, the independent evaluators scored lower points for patients than controls.

IE 006
ESSENTIAL ROLES OF MESENCHYMAL STEM CELLS IN WOUND HEALING

Miroslav Tolar and
Marie M. Tolarova (USA)

【INTRODUCTION】Among main factors in pathogenesis of tissue and cell injury are mechanical injury and hypoxia. Mesenchymal stem cells (MSC) are essential drivers of tissue response to injury. MSC function in three important ways: 1. MSC proliferate and replace the dead cells, 2. MSC release mediators helping stressed differentiated cells to survive, 3. MSC modulate innate immune response by controlling transition of macrophages from pro-inflammatory to anti-inflammatory phenotype. Each surgery causes cell injury. The purpose of this presentation is to show cellular and molecular background of tissue reaction to injury and why cell injury needs to be minimized.

【MATERIALS AND METHODS】We have developed a cell culture model, in which we study response of human periodontal cells to mechanical stress and/or severe hypoxia. Human periodontal cells were isolated from the extracted teeth in the Dugoni School of Dentistry, UOP (IRB protocol Nr. 16-128).

【RESULTS】Human periodontal cells exposed to mechanical stress and/or hypoxia respond by unfolded protein response. They respond to severe hypoxia by activation of HIF1alpha pathway. Our results show a temporal sequence of very early subcellular and molecular changes in response to cell stress caused by de-stretch and/or severe hypoxia.

【CONCLUSIONS】Our findings show how rapidly cells react to stressors in their microenvironment and how quickly their damage may become irreversible and lead to cell death. It is very important to protect stem cells in order to achieve a successful healing of the surgical wound. The surgeons need to minimize cell damage by using minimally invasive techniques, by supporting early blood supply, and, potentially, by using biomimetics. Also, the patient needs to be advised that his/her health condition can affect healing after surgery. Patients can protect quantity and quality of their stem cell pool by healthy lifestyle and diet.

IE 008
MULTIDICIPLINARY APPROACH TO CLEFT LIP AND PALATE TREATMENT OF CHILDREN IN A NEWBORN PERIOD

Mamedov Ad.A.,
Maclennan A.B.,
Admakin O.I.,
Morozova N.S.,
Mazurina L.A.
I.M. Sechenov Moscow Medical State Unversity (Sechnov University);
Department of pediatric dentistry and orthodontics (Russia)

The timing of repair of a cleft lip continues to be debated. One of the reasons for delaying operation has been the belief that there is an increased risk of anaesthesia during the neonatal period. In our experience with neonate cheiloplasty all of the babies were diagnosed antenatally with an orofacial cleft. Antenatal diagnosis of cleft defects has now become a routine part of any antenatal screening programme and recent improvements in the diagnostic accuracy using three-dimensional ultrasonography has suggested that the current antenatal detection rate is likely to be much higher. All parents with an antenatal diagnosis were offered counselling by the cleft team

IE 009
SURVEY SHEETS IMPLEMENTATION IN PRENATAL DIAGNOSIS AND CONSULTATION AMONGST COULPS EXPECTIONG CHILDREN WITH CLEFT LIP AND PALATE

Maclennan A.B.,
Mamedov Ad.A.,
Admakin O.I.,
Morozova N.S.,
Mazurina L.A.
I.M. Sechenov Moscow Medical State Unversity (Sechnov University);
Department of pediatric dentistry and orthodontics (Russia)

Main objective for this multidisciplinary approach is to provide comprehensive rehabilitation for patients with oro-facial pathology in a specialised center. Quality of life of children with cleft lip and palate in different age periods, the impact of early rehabilitation programs and the terms of surgical rehabilitation on the quality of life of children with a pathology of the maxillofacial region and their families remains poorly understood. Quality of life assessment of children with CLP and their families determines their need for medical care. Survey sheets for families expecting children with cleft lip and palate help improve algorithms for providing comprehensive health care in the health care system. Care provided for patients and their families during the whole treatment period can also be assessed using specialised survey sheets.

IE 010
Secondary Alveolar Bone Grafting, My Clinical Perspective

Aysegul M. TUZUNER, DDS, PhD (Turkey)

Alveolar bone grafting is an important part of the reconstructive journey for many cleft lip and palate patients. The reconstruction of the alveolar cleft can provide both aesthetic and functional benefits to the patient.

Concern over the cleft in the region of the alveolar process is often recognized later. However most patients with an alveolar cleft that is un-repaired present with one or more number of problems associated with this deformity.

A new reliable method which alveolar bone grafting at the time of eruption of the maxillary central incisor at about 5.5 to 6 years of age performed by Precious in 2009.

In this presentation, the philosophy of reconstruction of a cleft alveolus is revealed with my clinical outcomes.

IE 011
Piloting the Use of ICHOM in Children with Clefts : Speech and Communication

Selena Ee-Li YOUNG
KK Women's and
Children's Hospital (Singapore)

【Background】In 2002, the World Health Organisation recognised the need for standardising and systematising outcome measurements in cleft care. International experts in cleft care were assembled by the International Consortium for Health Outcome Measures (ICHOM) to identify a standard set of outcome measures designed for the comprehensive appraisal of cleft care, using measures that reflect the complexity of management and which matter most to individuals with cleft lip and/or palate (Allori et al., 2017). The outcome domains included in ICHOM-Cleft were chosen to reflect essential components of the WHO ICF framework. Relevant to Speech Therapists are outcomes measuring speech intelligibility, and patient-reported psychosocial outcomes related to speech. The clinical utility of these outcome measures in cleft care will be explored to provide a better insight into outcomes that matter to patients with clefts in Singapore.

【Method】Referencing the suggested tools for Speech Therapists listed in the ICHOM Cleft Lip and Palate Data Collection Reference guide, we piloted the forms on children with clefts aged between 4 and 16 years of age in Singapore. We evaluated the following: (a) Speech severity operationalised as Percentage Consonants Correct (PCC) scores derived from the DEAP Articulation assessment (Dodd et al., 2002). (b) Speech intelligibility with a clinician rating of a conversational sample, and a parent rating on the Intelligibility-in-Context Scale (ICS; McLeod et al., 2012)., and (c) Child's perceptions using the CLEFT-Q Speech Function and Speech Distress scales (Klassen et al., 2018).

【Results】Children with cleft lip and palate had significantly poorer PCC scores than children with cleft palate only, but no significant differences were observed for parent- and clinician-reported speech intelligibility ratings. Overall, ICS and PCC were significantly associated with clinician-reported speech intelligibility. Listener familiarity influenced parents' judgement of their child's speech intelligibility on the ICS. Children who reported poorer speech function also reported experiencing greater speech distress. Children's perspectives of speech function and speech distress were significantly related to speech severity but not to speech intelligibility ratings.

【Discussion】Differences in speech outcomes between children of different cleft types may allow for more targeted intervention planning, by informing clinicians which group of children will likely require more intensive speech therapy. Functional parent- and clinician-reported speech intelligibility measures should be supplemented with objective and patient-reported outcomes to better guide intervention planning. In addition, the CLEFT-Q speech function and distress scales were found to be valuable clinical tools to understand psychosocial function related to speech.

IE 012
CUT BACK, A NEW TECHNIQUE OF REPAIR OF WIDE BILATERAL CLEFT LIP .

Mohammad Mughese Amin
Amin plastic and reconstructive
surgery clinic (Pakistan)

【Introduction】In Pakistan we have one of the highest incidence of clefts in the world . Due to lack of facilities the patients do not get proper pre-surgical treatment. Most of the patients which present with bilateral cleft lip and palate they are usually not properly managed and in bilateral cleft lip the PROLABIUM is protruding very high and usually it is very difficult to repair these clefts with high protruding prolabium .At Amin plastic surgery we have innovated a new technique of operating these wide bilateral cleft lip by a technique called the cutback method. In this cutback technique we can easily treat a very wide bilateral cleft without presurgical orthodontic. we make cutbacks at every level and in every segment of the lip that is we do a cut back in the mucosa ,we make a cutback in the muscle and we do cut back if required in the skin.

【Results】Results are very encouraging and we can get a very nice closure in a single stage . We dont have to go for any lip adhesion or fracturing to premaxilla. We get a nice collomellar length and perfect aesthetic results.

【Conclusion】we highly recommend this technique for very wide bilateral cleft lip and even in unilateral cleft lip. We also recommend this technique in the upper lip defects after trauma as well.

IE 013
EXPERIENCE OF ISLANDED GREATER PALATINE ARTERY FLAP FOR ANTERIOR ORONASAL FISTULA REPAIR

Mohammad Mughese Amin
Amin plastic and reconstructive
surgery clinic (Pakistan)

【Objective】Big problem easy solution.the usefulness of islanded greater palatine artery flap for repair of anterior Palatal Fistulae

【Study design】Descriptive case series study

Place and duration of study: Plastic and Reconstructive Surgery Department Bahawal Victoria Hospital, Bahawalpur from January 2013 to January 2017

【Methodology】twenty eight patients were selected for study with history of cleft palate repair and a residual anterior Palatal Fistulae of size between .5 cm to 1 cm. Selection was based on location and size of fistula and amount of residual palatal mucosa. Assessment was done for reliability of procedure, postoperative speech and swallowing, and donor site morbidity.

Results: All the patients underwent islanded greater palatine artery flap. Three patient were operated with bilateral islanded flaps. Post-operative liquid started between 1st to 3rd day (mean, 2 days). Patients were discharged on 3rd -5th (mean 4th day) postoperative day without any postoperative donor site or recipient site complications. Donor site re-epithelialized within 2 to 3 weeks in all patients.

【Conclusion】The islanded greater palatine artery flap offers a reliable method of primary reconstruction of anterior palatal defects.

【Key words】Islanded greater palatine artery flap, anterior palatal fistula, cleft palate repair

IE 014
Adult Cleft lip and palate: a last chance

Mohammad Mughese Amin
Amin plastic and reconstructive
surgery clinic (Pakistan)

【Introduction】Bahawalpur is the remotest part of Pakistan where people still live in primitive ages. Cleft lip and palate is still considered a gift of God and people don't wanna get them repaired.

Plastic surgery department was established in Bahawalpur in 2004. Before that there was no plastic surgery unit. Cleft surgeries were offered free of cost. It was difficult to convince patients to get their clefts operated. People live below poverty line and all adult patients who have come for surgery cannot come back again for a second or revision surgery, so we have to produce our best results and in a single surgery.

【Material and method】since 2004 we operated 450 adult patients of cleft lip and palate. 265 cases were fresh cases and rest were operated before. Basic protocol of the surgeries was the same but we have to do combo surgeries to limit the no of visits for the patients. Patients have to travel from far flung areas and some times they have to travel from nearly 400 km to get their surgery done.

We provide patients with accommodation food and boarding and lodging facilities free of cost.

【Results】We our these free surgery facilty ,excellent results , advertisement and free boarding and lodging the no of patients have significantly increased and their confidence has also increased.

【Conclusion】Still a lot of work has to be done to improve already existing cleft patients and a lot of help is required in research to prevent this disease in underdeveloped countries as well.

IE 015
Bony Syngnathia – a rare craniofacial anomaly

Dr. Myra Elliott
National University of
Singapore (Singapore)

This is a rare anomaly when the maxilla and mandible are fused together. Only about 60 of such cases have been reported in the literature. This condition is often associated with cleft palate, pits in lower lip and other deformities in the limbs. As a large proportion of the infants that are reported have died – the management of these children have proved to be difficult. With fused jaws, nutrition and speech are severely hampered.

We share the experience of surgically managing a child with bony syngnathia, fusion of tongue to hard palate, cleft soft palate, and bilateral coronoid hyperplasia.

IE 016
Challenges in cleft patients rehabilitation and the ways to overcome it

Ivanov A.L., Starikova N.V., Evtekhova N.I.,
Reshetnyak E.I., Gorbonosov V.A.,
Anashkina D.U., Novikov M.M.
The cleftsCentral Research Institute of Stomatology and
Maxillofacial Surgery (Russia)

The cleft treatment protocols are numerous. The clefts manifestations are various. Rehabilitation includes multistage multidisciplinary procedures on growing patients from infancy to adulthood. The overall rehabilitation process requires both correct technique choosing and execution. All these conditions make challenging the analysis of techniques and approaches. Up to now there is no accepted by most surgeons best therapeutic algorithm to achieve good result in all cases.

The results could be evaluated using both functional and esthetic outcomes and long-term effects. Primary surgery expectations of parents are mostly esthetic. But the long-term effects of non-funtional restoration of the lip are poor and contribute to facial deformity during growth. On the other hand the functional surgery is difficult and demanding for surgeon's experience. Sometimes the primary surgery in neonates leads to poor results when the initial satisfaction of parents and surgeon changes to disappointment and frustration. What to do if unsatisfactory result occurs after the primary lip reconstruction is the important question for those who have created this situation and those who can occasionally admit such a patient.

The cleft palate closure rationale is another point at issue – one or two stage, what age, technique, how to avoid and manage complications, how to help patients been operated elsewhere. We use an original palatoplasty technique which helps to achieve good functional result and normal palatal appearance compatible with actual intravelar veloplasty approach and eventual additional surgeries due to velopharingeal incompetence.

The alveolar bone grafting is a key surgery for successful rehabilitation but most contradictory. Both the technique and timing choice could benefit to good result. The technique has to be applicable in majority of cases and give consistent satisfactory results.

The final steps in cleft patients rehabilitation may include orthognathic surgery and open rhinoseptoplasty. The indications and possibilities of orthodontic compensation are still disputable point between different specialists even in the same team.

We conclude that the team functional approach is an appropriate conception for cleft lip and palate treatment. The best approach is to keep the patients treated by the same team of specialists from start to completion of rehabilitation. The most difficult situations may appear in case of unusual extreme clefts and deformation after unsatisfactory previous surgeries. The appropriate protocol helps to perform procedures and get such a patients back to standard protocol to successfully finish the rehabilitation. This remains still the craft in specialists' hands and requires to learn with every patient.

The specialists must be competent and maintain closed collaboration within the team. Accomplishment of these principles are sometimes challenging. It can lead to unsatisfactory results.

It seems that surgeon's experience and techniques used have more significant impact to final result comparing with other factors. It is still important to develop personal skills and choose appropriate techniques to improve own results. It is crucial to remain self critical and constantly work in team to improve proper results.

This work was supported by RFBI grant № 18-29-03238.

IE 017
Orthodontic treatment in Hemifacial Microsomia

Martin Romero Maroto (Spain)

Hemifacial microsomia is the second most common congenital anomaly of the face, second to cleft lip and palate. It occurs in aproximately one out of 5600 births and the main manifestation is asymmetric mandibular development.

Treatment options are functional appliances trying to estimulate growth on the affected side, distraction osteogenesis with different appliances depending on the patient age and orthognatic surgery, including sometimes the placement of a condyle prothesis.

IE 018
Cleft missions of Korean Association of Maxillofacial Plastic and Reconstructive Surgeons with a case of bilateral Tessier No. 3 cleft

Young-Wook Park
Department of Oral & Maxillofacial Surgery,
Gangneung-Wonju National University,
Gangneung (Korea)

Cleft lip and/or palate (CLP) is the most common oro-facial anomaly, and constitute a significant global disease burden. To overcome the burden, humanitarian global missions for CLP care in low-income countries are essential. Korean Association of Maxillofacial Plastic and Reconstructive Surgeons (KAMPRS) is an academic society which had founded in 1962 and made up of about 2,400 oral and maxillofacial surgeons. Since 1996, KAMPRS has performed the voluntary surgical missions for CLP in China, Kazakhstan, and Vietnam. In this presentation, I'd like to focus on the friendship operations in Vietnam, and to share our experiences of voluntary surgical missions for CLP.

In total, 477 CLP-related operations have been performed as a free-of-charge surgery from 2004 to 2018. Our voluntary activities took place once a year for a duration of a week. The Korean staffs performed all operations in collaboration with Vietnamese staff. Patients were selected as the priority of primary cases who were older, patients from far places. Our goal was delivering safe CLP care, which means maximizing patient and wound safty with minimal complications. Also, we have trained in-country doctors on cleft surgical techniques and concepts of CLP care. And, we tried to maintain good coordination and communication with the local collegues, sometimes through personal interchange.

Additionally, we invited some patients, who needs major operation. Now, I report a case of bilateral Tessier No. 3 facial cleft. We achieved acceptable results functionally and esthetically by midfacial advancement with facial muscle reposition instead of traditional interdigitating Z-plasties. In coclusion, although the ultimate goal for a global mission for CLP care is to eatablish an institute providing long-term cares, voluntary surgical missions still have an important role.

IE 019
Management of Orbital dystopia in Craniofacial Clefts

SM Balaji (India)

Few of the orofacial clefting processes only involves the orbit. Such defect may be unilateral or bilateral and very rarely found along the midline. In any situation, considerable sum of orbital bone mass may be missing or defective in size. Additional impairments such as those of ears, loss of adjacent structures or uncoordinated growth may impede the treatment goals. It is not uncommon to find associated disorders of nervous structures such as mengiocele or other neural defects. Very rarely associated cranial bones such as frontal bones may also be involved. Needless to say, if hypertelorism persists, that should be corrected. The final goal would be to correct any abnormal slants.

In any of the case, as in cleft lip and palate the goal would be to save the eyeball, if there is functional capacity. The next step would be to close the defects as much as possible to obliterate clefting. This would help to evolve proper feeding, swallowing, speech, prevent repeated nasal/sinus infections etc., Next stage would be reconstruction of the associated soft tissue defects. If involving nasal cavity, late rhinoplasty may be required to complete the nasal defect. The timing of the surgery needs to be extremely customized.

The presentation will take through the 25 years of experience in treating oro-facial clefts with special emphasis on orbital dystopia correction from simple clefts and missing orbital bones to complex, multiple Tessier's orofacial clefting. Appropriate example from the author's surgical experience will help to draw meaningful algorithm to plan and surgically treat the patients

IE 020
Associated Genetic anomalies and clinical manifestations; are etiological factors for prenatal and postnatal growth retardation among patients with cleft palate in Sri Lanka?

Prabodha LBL[1)], Dias DK[2)], Nanayakkara BG[3)], Ilayperuma I.[4)]
[1)]Senior Lecturer, Specialist Clinical Geneticist, Molecular Genetics Laboratory, Department of Anatomy, Faculty of Medicine, University of Ruhuna
[2)]Consultant OMF surgeonRegional Cleft Centre & Maxillo-Facial Department, Teaching Hospital, Karapitiya
[3)]Professor in Anatomy, Molecular Genetics Laboratory, Department of Anatomy, Faculty of Medicine, University of Ruhuna
[4)]Chair Professor of Anatomy, Molecular Genetics Laboratory, Department of Anatomy, Faculty of Medicine, University of Ruhuna (Sri Lanka)

【Background】Since in the ancient times man was ignorant of embryology and morphogenesis and his explanation for the existence of congenital deformities was based on a combination of religion, superstition, invention and charlatanism. Cleft lip and palate is one of the commonest craniofacial anomalies with the prevalence ranging from 1 in 750 live births in Asians to 1 in 2500 live birth in African Americans. Morphogenesis of cleft lip and palate is based on genetic and environmental factors in early stages of embryogenesis. It is associated with many more syndromes and clinical manifestations and exhibits prenatal and postnatal growth retardation among majority.

The objective of the study was to evaluate the genetic anomalies and syndromes, other clinical manifestations, prenatal and post natal growth parameters among cleft palate subjects in Sri Lanka.

【Methods】The subjects were identified among those who are currently under review in the Regional Cleft Centre & Maxillo-Facial Department, Teaching Hospital, Karapitiya, Galle. All the consented subjects with isolated cleft palate registered at the clinic from the 1st of January 2001 to 31st of December 2017 were included in the study. All the patients were examined by the researcher and relevant information were documented by interviewing the subjects and parents.

【Results and Discussion】There were 323 subjects with cleft palate of which majority (57.9%: $p<0.05$) were females. Out of all 56.7% had other associated clinical manifestations including 14 subjects with identified genetic syndromes. There were 38.8% ($p<0.0001$) subjects with low birth weight. According to the WHO recommendations, occipito-frontal circumference, height, weight and BMI for age of majority of subjects were below the 3rd centile. Most had developmental delay and altered psychological manifestations. There was a significant association with low birth weight and postnatal growth retardation among cleft palate subjects who had other associated clinical manifestations and genetic syndromes ($p<0.05$). Feeding difficulty was the most common nutritional complication seen among cleft palate subjects especially before cleft surgery. There were only 1% of mothers who had periconceptional folic acid supplementation among cleft palate subjects.

The results of this study indicated that there was a strong association of genetic syndromes and other clinical manifestations with prenatal and postnatal growth retardation among cleft palate subjects. Further it is recommended to modify the feeding techniques and indicated requirement of screening the genetic etiology in the management of cleft palate in Sri Lanka.

【Keywords】Cleft palate, Genetic Syndromes, Prenatal and postnatal growth retardation, Periconceptional folic acid, Sri Lanka.

IE 021
International medical assistance for cleft lip and palate in Indonesia

Muhammad Ruslin, DDS., MS., PhD
Department of Oral and Maxillofacial Surgery,
Faculty of Dentistry, Hasanuddin University,
Makassar (Indonesia)

We have been working on international medical assistance with University of Toyama for approximately ten years. The Hasanuddin University in Makassar, Sulawesi Island, is one of the famous Universities in eastern of Indonesia. Oral and maxillofacial surgeon in Hasanuddin University lead to a cleft lip and palate treatment in this area.

University of Toyama (Prof. Noguchi Makoto) and us carried out the charitable operation for cleft lip and palate patients. We visited many cities in the Island, for example Palu, Bantaeng, Toraja, Gorontalo and also Berau (Borneo), and operated a lot of patients at each local hospital. By our activity, both of Indonesian and Japanese side organized not only oral surgeons but also anesthesiologists, nurses and trainee doctors. The advantage of our activity is education and surgery technique transfer.

We give opinions by each other's teams and make an effort to provide a better operation.

In addition, in Makassar, Japanese doctors make the lectures for the dentist who worked at the dental hospital and students in Faculty of Dentistry, Hasanuddin University.

The education to a young dentist and dental student becomes the important part of this activity.

IE 022
Craniosynostosis

Akira Yamada MD PhD
Northwestern University Feinberg School of Medicine (USA)

It is known that the clinical diagnosis of craniosynostosi has over 90 % accuracy among established craniofacial surgeons. But for the rest 10%, imaging study is needed to differentiate between benign positional plagiocepahly and craniosynostosis. Plain X-ray is still the best initial screening modality for differential diagnosis, considering the minimum radiation exposure. Ultrasound frequently ends up as undetermined. We should use CT and/or MRI scan to investigate brain , confirmation of craniosysnostosi, or surgical planing as the next step.

Awareness of craniosynosstosis among pediatrician increased significantly over the last 10 years. It influence and change the pictures of treatment strategy dramatically in developed countries. Earlier diagnosis made pediatrician to refer the patients more to neurosurgical services, where neurosurgeons do ‘ endoscopic ‘ craniotomy at the age of 3-5 months. ‘Endoscopic’ appeals more to the family of craniosynostosis. Although long-term consequences, such as 10% chance of late raised ICP was reported after strip craniectomy, endoscopic approach becomes popular trend for earlier surgical intervention in the countries such as USA. The major role of Craniofacial surgeons has shifted toward the treatment for the children with late presentation of craniosynostosis for which endoscopic approach is not indicated, and cranial vault remodeling would be the best option.

Clinical practice of craniosynostis currently divides into two opposite directions: minimally invasive endoscopic strip craniectomy vs total cranial vault remodeling.

We need long term clinical study for neurocognitive development of children with craniosynostosis to determine which way would be the optimal answer for the children. We still do not have an answer what timing, and what surgical intervention would be most beneficial from neurocognitive perspectives.

IE 024
Demystifying assessment of speech in individuals with cleft lip and palate

Dr. V.H. Savitha, M.Sc. (Sp. & Hg.), Ph.D.
Professor in Audiology and Speech Language PathologySRM Medical
College Hospital & Research CentreChennai (India)

Assessment of speech in individuals with cleft lip and palate is a dynamic process involving multiple dimensions. Comprehensive assessment of speech encompasses assessment of domains including articulation, nasal air flow, resonance, voice, and global speech understandability. These are the universal elements to be assessed, irrespective of the culture and region where speech assessment is being carried out. In order to assess these elements, it is important to elicit appropriate speech stimuli from individuals with cleft lip and palate in the regional/primary language used for communication. Understanding the sound structure of the regional language is essential to design comprehensive speech stimuli (set of words and sentences) to be elicited during assessment. Eliciting appropriate stimuli based on the pressure consonants of the language increases the possibilities of eliciting cleft type characteristics, if any, exhibited by individuals with cleft. Designing the speech stimuli to be elicited in a language is a crucial step when speech assessments are being carried out in a particular region. This step involves working closely with those who have knowledge about the regional language. Specific guidelines are available for designing speech stimuli to be elicited for comprehensive speech assessment (Henningsson et al., 2008). Once the speech stimuli are designed, identifying the cleft speech characteristics can be performed by any trained speech language pathologist through perceptual assessment.

Perceptual assessment is the ‘gold standard’ for assessing speech in individuals with cleft lip and palate. A set of comprehensive speech stimuli and trained ears are the primary requisites to make the perceptual assessment clinically relevant and meaningful. This presentation will highlight the common elements of speech assessment and throw light on how speech services have been developed across centres in India and in Myanmar.

IE 025
Diagnosis and treatment of VPD: A Global Survey

Angie Morillas[1)], Meghan O'Brien[2)],
Richard Kirschner[2)], Adriane Baylis[2)]
[1)]Asociación Benéfica Morillas (Peru)
[2)]Nationwide Children's Hospital (USA)

【Background】There is lack of consensus to guide procedure selection for patients with Velopharyngeal dysfunction (VPD). Approaches to diagnosing and managing VPD may differ according to the country in which a patient is treated, the surgeon's experience and factors like language, culture, and resource availability. A survey-based study was undertaken to explore differences in the treatment and diagnosis of VPD in countries that are underrepresented in the English literature.

【Methods】A 16-item online survey was distributed to 226 surgeons practicing in 21 different countries outside the U.S. Respondents were asked to report on their training and experience as surgeons, their approach to diagnosing and treating VPD, and any barriers impeding their ability to address VPD. The survey was made available in Spanish, Portuguese, French, English and Mandarin. Descriptive statistics were computed to describe care practices for the entire sample and three subgroups (Asia, Africa, Latin America) assigned based on the respondent's country of practice. Additional analyses were performed to examine differences among the subgroups.

【Results and Discussion】A total of 108 surgeons contributed data to the study. The majority of surgeons operated in Latin America (n=39, 44.8%) or Africa (n=35, 40.2%), with 14.8% (n=13) practicing in Asia (primarily India).

Eighty one percent of respondents indicated that they worked as part of a multidisciplinary VPD/Cleft team; of these, 15.2% did not include a speech language pathologist (SLP). Approximately half of respondents reported conducting VPD assessments in partnership with an SLP. Twenty five percent of surgeons did not use a diagnostic tool for VPD, or used one not supported by evidence. Posterior pharyngeal flap was the most commonly reported VPD treatment (41.8%, n=33), followed by Furlow palatoplasty (n=29, 36.4%) and speech therapy to treat hypernasality.

Lack of instrumentation/imaging equipment and issues related to patient access/follow-up were reported by more than 50% of the sample. When asked about training opportunities, respondents expressed the greatest interest in improving (1) speech evaluation accuracy (n=45, 61.4%), and (2) their own technical skills as a surgeon (n=43 58.8%). Respondents from Africa were significantly more likely to select these as training needs than those in Latin America and Asia (p=.002, P<.001).

【Conclusions】Surgeons operating internationally vary in their approach to addressing VPD, although region-specific trends are apparent. Increasing access to (1) instrumentation/imaging tools and (2) training opportunities related to speech evaluation and surgical intervention may help international surgeons to better address VPD.

【References】

1. de Blacam C, Smith S, Orr D. Surgery for Velopharyngeal Dysfunction: A Systematic Review of Interventions and Outcomes. Dublin, Ireland Cleft Palate Craniofac J. 2018 Mar;55(3):405-422
2. Abyholm, F, D'Antonio, L, Davidson Ward, SL, Kjoll, L, Saeed, M, Shaw, W, Sloan, G, Whitby, D, Worhington, H, Wyatt, R. Pharyngeal flap and sphincterplasty for velopharyngeal insufficiency have equal outcome at 1 year postoperatively: results of a randomized trial. Cleft Palate Craniofac J. 2005;42:501–511 VPI surgical Trial group (UK-Norway-USA)
3. Ysunza, A, Pamplona, MC, Molina, F, Drucker, M, Felemovicius, J, Ramirez, E, Patino, C. Surgery for speech in cleft

palate patients. Int J Pediatr Otorhinolaryngol. 2004;68:1499–1505 Mexico D.F

4. Boneti, C, Ray, PD, Macklem, EB, Kohanzadeh, S, de la Torre, J, Grant, JH. Effectiveness and safety of autologous fat grafting to the soft palate alone. Ann Plast Surg. 2015;74(suppl 4):S190–S192.USA
5. Brandao, GR, de Souza Freitas, JA, Genaro, KF, Yamashita, RP, Fukushiro, AP, Lauris, JR. Speech outcomes and velopharyngeal function after surgical treatment of velopharyngeal insufficiency in individuals with signs of velocardiofacial syndrome. J Craniofac Surg. 2011;22:1736–1742, Brazil.
6. Chen, PKT, Wu, JTH, Chen, YR, Noordhoff, MS, Furlow, LT. Correction of secondary velopharyngeal insufficiency in cleft palate patients with the Furlow palatoplasty. Plast Reconstr Surg. 1994;94:933–943. Taiwan Taipei
7. Conley, SF, Gosain, AK, Marks, SM, Larson, DL. Identification and assessment of velopharyngeal inadequacy. Am J Otolaryngol. 1997;18:38–46 Milwaukee USA
8. D'Antonio, LL, Scherer, NJ. Communication disorders associated with cleft palate. In: Losee, JE, Kirschner, RE, eds. Comprehensive Cleft Care. New York: McGraw-Hill Medical; 2009:569–588 USA
9. Hynes, W. Pharyngoplasty by muscle transplantation. Br J Plast Surg. 1950;3:128–135 USA-Europe

IE 026
Unpredictable speech outcome on Submucous Cleft Palate

Lian MA, Xia ZHOU
Cleft Lip and Palate Treatment CenterSchool of
StomatologyPeking University (China)

Submucous cleft palate(SMCP) is a special type of cleft palate, where the intact palate is shown while the velopharyngeal function is effected in various degrees resulting in poor speech outcoming. Diagnosis, treatment and prognosis have become challenging due to the characteristics of SMCP. In this current report, we share our experience regarding the clinical significant, indication of operation and prognosis of SMCP

1 Anatomical characteristics and diagnosis criteria on SMCP

Typical criteria for diagnosis SMCP has been well known but the relationship between velopharyngeal closure functions which effect on the speech still is unclear. In author opinion, the diagnosis of SMCP should based on clinical symptom-hypernasality or unclear speech combining with clinical sign(bifid uvular, transparent zone on palate and touchable V shape on posterior border of hard palate), which so called “true submucous cleft palate” . The function of velopharyngeal closure was effected by the defect of hard palate on SMCP.

2 Maxillary growth and Velopharyngeal function of SMCP

As a phenotype, SMCP occurred in about at least 100 syndromes of head and neck, which also have hearing impairment and intelligent retardation. Speech rehabilitation in SMCP is more difficulty than rest type of cleft palate. Maxillary hypoplasia in SMCP is associated with the degree of attachment vomer and palate plate. Velopharyngeal incompetence related with bony defect in SMCP

3 Surgical intervention of SMCP

The operation indication on SMCP was discussed and Langenbeck procedure with or without release incision had been always the first choice. The author describe the operation procedure in detail for SMCP with lager bony defect.

IE 027
The Challenge of Operating Clefts in Mozanbique

António Alberto
Nampula Central Hospital Nampula (Mozambique)

1. The challenge of operating orofacial clefts with few human resources, scarce material and technical means, to satisfy a high population.
2. We have few trained mentors in the matter of labial , Palate clefts and craniofacial anomalies. And in all country has only six hospitals for this kind of surgery, but without modern technology for it.
3. We have served as the support of our partners in the area of health nations as Japan, China, Vietnam, Korea, Cuba, India, Germany, Spain, Brazil incluiding USA and also some non-governmental entities like Smile Trian and lately Operation Smile.

IE 028
Critical Growth Processes for Morphogenesis of the Midfacial Skeleton in the Early Prenatal Period

Motoki Katsube[1, 2], Shigehito Yamada[2, 3], Yutaka Yamaguchi[2],
Tetsuya Takakuwa[3], Akira Yamamoto[4], Hirohiko Imai[5],
Atsushi Saito[6], Akinobu Shimizu[6], Naoki Morimoto[1]
[1] Department of Plastic and Reconstructive Surgery,
Kyoto University Graduate School of Medicine
[2] Congenital Anomaly Research Center,
Kyoto University Graduate School of Medicine
[3] Human Health Sciences,
Kyoto University Graduate School of Medicine
[4] Department of Diagnostic Imaging and Nuclear Medicine,
Kyoto University Graduate School of Medicine
[5] Department of Systems Science,
Kyoto University Graduate School of Informatics
[6] Institute of Engineering,
Tokyo University of Agriculture and Technology (Japan)

【Background】Congenital midfacial hypoplasia is one of the most challenging malformations for craniofacial surgeons and is a typical condition for those with the Binder phenotype and syndromic craniosynostosis. To understand their pathogenesis, it is important to grasp the critical growth processes of the midface during the early fetal period; however, this has remained unclear because conventional measurements in 2–dimension applied in previous studies using late fetal specimens have not provided sufficient elucidation. The growth centers, such as the nasal septum and the synchondroses around the sphenoid, have known to relate closely with their pathogenesis; however, such relation in prenatal period has never been investigated.

【Purpose】To demonstrate the critical growth processes of midfacial skeleton in 3–dimension and investigate the developmental association between the growth centers and midface during the early fetal period.

【Method】Magnetic resonance images were obtained from 60 human fetuses during the early fetal period. Three–dimensional changes in the shape of the craniofacial skeleton caused by growth were quantified and visualized using geometric morphometrics (GM). The growth trajectory was estimated as allometric shape (AS) vector. The shape change along the vector was visualized. Subsequently, the degree of development was computed as AS score. Furthermore, the developmental association between the growth centers and the midfacial skeleton was statistically investigated and visualized.

【Result】The zygoma expanded drastically in the antero-lateral dimension, and the lateral part of the maxilla developed forward. The AS score indicated that the midfacial skeleton was matured approximately 13 weeks of gestation. The growth centers such as the nasal septum and anterior portion of the sphenoid were highly associated with forward growth of the midfacial skeleton ($RV = 0.589$; $p < 0.001$).

【Discussion】This study first demonstrated the growth trait of the midfacial skeleton in the early fetal period in 3-dimension. Growth disturbance of the zygoma and maxilla before 13 weeks of gestation could induce severe midfacial hypoplasia. Moreover, impairment in the growth centers could cause midfacial hypoplasia observed in the Binder phenotype or syndromic craniosynostosis. GM could be a great help not only to quantify the 3-dimensional structures, but also to grasp the complicated results with visual aids.

COI: none

This work was supported by JSPS KAKENHI Grant Numbers 17H05296, 17H05294, 26220004, and 26108002.

IE 029
Folded Pharyngeal Flap Method: 40 years experience

Masaki Sawada, MD[1)],
Yoshiro Yamawaki, MD[2)],
Ichiro Yamamoto, DDS[3)]
[1)]Sawada Plastic Surgery and ENT Clinic(Kobe City),
[2)]Plastic Surgery of Hyogo Prefectural Amagasaki General Hospital,
[3)]Yamamoto Dental Clinic (Nishinomiya City) (Japan)

【Background and Purpose】Treatment of cleft palate has been improved to the level that little disturbance of speech might be left. More than 90 % of the cases can acquire normal velopharyngeal competency after the first push-back surgeries for cleft palate cases and do not require secondary operations. The remaining cases of less than 10%, which are left with velopharyngeal incompetency after the first cleft palate surgeries. In such cases, we have mostly applied the folded pharyngeal flap techniques which Isshiki invented and applied to first cleft case, 1973, and published in the paper, 1975.

More than 40 years, we operated about 500 cases of this folded pharyngeal flap method. This time, we studied postoperative speech problem and nasal respiration problem after the folded pharyngeal flap surgery.

【Method】The velopharyngeal and nasal air way resistances have measured during the utterance of voiceless plosives, Pa/Pi/Pu, and nasal respiration, by means of active posterior rhinomanometry.

【Result and Discussion】The velopharyngeal resistances at the utterance of plosives, PA/PI/PU, have been high enough regardless of their ages at the time of operation. In fact, no hypernasality was recognized in any of these cases at the utterance of monosyllables as far as we examined. As to nasal respiration, most of all cases had no problem and complaint.

We concluded that velopharyngeal competence could be fully recovered by the folded pharyngeal flap operation on such cases which have no serious motility problems of velopharyngeal lateral walls. It was also confirmed that the pharyngeal flap has kept same state and efficacy for a long period of time after surgery. This long term stability is supposed to attribute to the softness and good blood circulation of the flap free from contraction due to the smaller scar exposure enabled by folding the flap. This signifies that we need not consider unpredictable postoperative flap contractions at the operation and facilitates operation designing.

IE 030
A palatal pushback operation combined with musclo-mucosal flap from the posterior pharyngeal wall

Yoshio Yamawaki[1)], Masaki Sawada[2)],
Ichiro Yamamoto[3)], Osamu Horio[1)],
Takesi Nomura[1)], Shota Matsuda[1)],
Mina Nagai[1)]
[1)]Department of Plastic and Reconstructive Surgery,
Hyogo prefecturalAmagasaki General Medical Center
[2)]Sawada Clinic
[3)]Yamamoto Dental Clinic (Japan)

A palatal pushback operation combined with musclo-mucosal flap from the posterior pharyngeal wall of the pharynx applied to patients with velopharyngeal insufficiency after primary closure of cleft palate. After long-term follow up, it was suggested that the surgical procedures not only normalized velopharyngeal function but also reconstructed physiological VP closure dynamics.

【Materials & Methods】Palatal pushback operation combined with musclo-mucosal flap from the posterior pharyngeal wall of the pharynx performed on 10 cases with VPI after primary closure of cleft palate. All cases had undergone primary surgery at another hospital. Two of ten cases were bilateral cleft lip and palate, six cases were unilateral, and two cases were cleft palate. The mean age of patients undergoing the procedure was 8.6 years old and the mean duration of follow-up was 7 years and 2 months (Table). All of them had abnormal insertion or disordered sling of the levator veli palatini muscle. Their muscle sling reconstructed further back beyond its normal anatomical position by this secondary velopharyngeal surgery.

【Result】Nine of the 10 patients acquired physiological nasopharyngeal closure function on phonation not depend on musclo-mucosal flap; the nasopharyngeal space was closed by soft palate elevation and lateral wall movement of the pharynx during phonation, and the musclo-mucosal flap was pushed up to a site cranial to the closed nasopharyngeal surface. The musculomucosal flap was not directly involved in closure. One case judged mild dysfunction of VP closure after surgery had severe scar formation at the soft palate due to primary surgery and could not be extended to pharynx side.

【Discussion】Pharyngeal flap surgery is effective method for velopharyngeal insufficiency (VPI) after primary closure of cleft palate, but post-operative velopharyngeal (VP) closure dynamics is not physiological.

On the other hands, a palatal pushback operation combined with musclo-mucosal flap from the posterior pharyngeal wall is capable of reconstructing physiological closure dynamics. We attached importance to reconstruct the muscle sling further back beyond its normal anatomic position in this surgery. We will detail this surgical procedure and present post-operative naso-pharyngoscopic findings.

IE 031
Nature of oral-glottal double articulation in patients with velopharyngeal insufficiency – Consideration of laryngeal involvement in consonant production –

Naohiro KIDO[1,3,4], Yuri FUJIWARA[2],
Jin KAWAMURA[1], Naritaka KIMURA[3,4]
[1] Hiroshima City Asa Citizens Hospital,
Dept. of Rehabilitation Medicine, Hiroshima, Japan
[2] Osaka Health Science University,
Dept. of Speech Therapy, Osaka, Japan
[3] Hiroshima City Hiroshima Citizens Hospital,
Dept. of Plastic and Reconstructive Surgery, Hiroshima, Japan
[4] Hiroshima City Hiroshima Citizens Hospital,
Cleft Lip and Palate Center, Hiroshima, Japan

【Purpose】In the improving process of glottal stops, there exist two types of clients; one shows normal vocal folds movement and another shows glottal stop movement along with acquiring production of oral pressure consonants. The latter atypical production is known as oral-glottal double articulation and affects prognosis of articulation disorders. This presentation will provide laryngo-fiberscopic observation of oral-glottal double articulation and interpret its nature in clients with velopharyngeal insufficiency.

【Method】The subjects were 56 clients whose voiceless consonants were perceptually judged as oral-glottal double articulation. All of them had moderate to severe velopharyngeal insufficiency due to cleft palate. The laryngo-fiberscopic observation was done during the production of Japanese voiceless stops and affricatives [p, t, k, ʧ (ʨ), ʦ] in single tone (C) or monosyllable (CV). The laryngeal movement was classified into normal pattern in which vocal folds were abducted during production of voiceless consonants and abnormal pattern in which pre-vocalic adduction was followed by abduction of vocal folds which corresponded to consonant production.

【Result】All of 56 clients showed abnormal pattern. Trial speech therapy was performed on 29 clients during laryngo-fiberscopic observation, but it did not work up normal laryngeal movement.

【Discussion】During production of normal voiceless consonants, the airflow passes through glottic opening, i.e. the vocal folds are abducted at rest and do not contribute consonant production. However, in oral-glottal double articulation, the vocal folds are adducted to create subglottic pressure which is necessary to produce consonants above glottis, subsequently causing “glottal stop”. In other words, the vocal folds adduction actively helps to build up oral pressure for consonant production. The laryngeal involvement in consonant production takes shape as adduction of vocal folds prier to consonant production. This laryngeal control is considered to be specific among subjects with velopharyngeal insufficiency. This time, abnormal laryngeal movement was observed in every consonant produced by 56 clients. It is suggested that the first mislearning of oral-glottal double articulation on one consonant was generalized into other consonants regardless of the place of articulation. As speech therapy under laryngo-fiberscopy was ineffective, this abnormal laryngeal movement seems to be highly repeatable automatic control. Laryngeal participation in consonant production is a big factor to make it difficult to obtain normal articulation for the clients with oral-glottal double articulation.

IE 032
Tissue engineering using mesenchymal stem cells in dental science

Masaki Honda DDS, Ph. D.
Aichi Gakuin University School of Dentistry,
Department of Oral Anatomy (Japan)

Tissue engineering is based on the interaction between cells, biomaterials and growth factors delivered in injured tissue or organ. To date, researchers are working on effective and efficient methods to ensure safe and predictable protocols to translate research into clinical research.

The orofacial region contains multiple type of mesenchymal stem cells (MSCs) that have shown a great plasticity towards the main lineages. Orofacial tissue-derived MSCs share properties with bone marrow-derived MSCs and there is a considerable potential for the cells to be used in different MSC-based therapies, such as nerve regeneration. The numerous populations of MSCs isolated from oral tissues (DPSCs, SHEDs, PDLSCs, and SCAPs) also retain proliferation ability and multipotency. In addition, as a source of MSCs, oral tissue-derived MSC has advantages. All these MSCs show elevated proliferation rate when compared to bone marrow-derived MSCs and it can be easily obtained from several oral tissues.

Dental pulp stem cells (DPSCs) are the most investigated MSCs from oral tissues. Dental pulp is a connective tissue and has functions that include initiative, formative, protective, nutritive, and reparative activities. DPSCs have also been reported to be a good alternative in high plasticity toward bone, vascular and neural phenotypes. In recent years, the challenge has been to finally use DPSCs together with biomaterials or scaffold-free techniques, to obtain strategic tools for regenerative dentistry and medicine. We presented here on the proper use of such MSCs within a biological characteristics and the proper way for future clinical use.

IE 033
The outcomes of monocortical mandibular bone grafting of alveolar cleft

Soichi Tanaka[1)], Tadashi Mikoya[2)], Yusuke Matsuzawa[3)],
Tetsuya Seikai[1)], Junya Kato[1)], Makoto Akasaka[1)],
Izumi Sogabe[1)], Yumi Itoh[1)], Kanchu Tei[1)]
[1)]Department of Oral and Maxillofacial Surgery,
Division of Oral Pathobiological Science,
Graduate School of Dental Medicine,
Hokkaido University
[2)]Stomatognathic Function Center for Advanced Oral Medicine,
Hokkaido University Hospital
[3)]Department of Oral and Maxillofacial Surgery,
Keiyukai Sapporo Hospital,
Social medical corporation (Japan)

【Background】Alveolar bone grafting is well-established procedure for the management of patients with alveolar cleft. The aim of this treatment is to create an osseous environment and then to facilitate of cleft-adjacent teeth eruption into the dental arch. Grafting of the alveolar cleft is usually accomplished with cancellous bone from the ilium or tibia or corticocancellous particulate material from the calvaria or the mandibular body. The choice of donor site is principally the iliac crest, which supplies large amount of osteogenic precursor cells, bone formation factors and is easily obtained. However, the harvesting from the ilium show several physical impediments, so that we usually harvest the bone grafts from the mandibular symphyseal region as mono-cortical bone grafts without particulate bone.

【Purpose】o assess and develop a mono-cortical mandibular bone grafting procedure for reconstruction of alveolar cleft.

【Method】135 clefts of 114 consecutive Japanese patients who have been treated according to a strict clinical protocol. Mean age at bone grafting was 7 years 1 month. In bilateral alveolar cleft cases, bone grafting was performed in a two-step procedure. Approximately 3 months after grafting was completed for alveolar clefts on one side, the other side was done. Bone grafting was performed by harvesting lateral cortical bone plates from the symphysis and/or body and then placing them on the labial and palatal openings of the alveolar process defect. No particulate bone grafts were packed into the bony cavity. Mean follow-up after bone grafting was more than 4 years. Status of the grafted area and eruption of cleft-adjacent teeth were assessed prospectively using computed tomography (CT) and periapical radiography.

【Result】At 6 months postoperatively, CT showed sufficient bone bridge formation at the cleft site in 87.4% of clefts. Periapical radiography showed ≥75% of the root surfaces of cleft-adjacent teeth were covered with spanning bone in 93.2% of clefts. In 86.4% of clefts in which the cleft-adjacent canine was uncovered with bone during follow-up, the canines erupted spontaneously.

【Discussion】Mono-cortical mandibular bone grafting appears extremely effective for sufficient bone bridge formation and facilitation of cleft-adjacent teeth eruption. The procedure is advantageous in that the quantity of bone required per unit volume of cleft defect is relatively reduced, and larger clefts can thus be treated.

IE 034
The role of retinoic acid signaling for developing the face

Hiroshi Kurosaka (Japan)

【Background】Cleft palate (CP) is one of the most common congenital craniofacial anomalies in humans and can be caused by either single or multiple genetic and environmental factor(s). With respect to environmental factors, excessive intake of vitamin A during early pregnancy is associated with increased incidence of cleft palate in offspring both in humans and in animal models. Vitamin A is metabolized to retinoic acid (RA), however, the pathogenetic mechanism of cleft palate caused by altered RA signaling during early embryogenesis is not fully understood.

【Purpose】To investigate the detailed cellular and molecular mechanism of retinoic-acid-induced cleft palate,

【Method】To investigate the detailed cellular and molecular mechanism of retinoic-acid-induced cleft palate, we administered all-trans RA to pregnant mice at embryonic day 8.5.

【Result】In the RA-treated group, we observed altered expression of Sox10, which marks cranial neural crest cells (CNCCs). Disruption of Sox10 expression was also observed at E10.5 in the maxillary component of the first branchial arch, which gives rise to secondary palatal shelves. Moreover, we found significant elevation of CNCC apoptosis in RA-treated embryos. RNA sequencing comparisons of RA-treated embryos compared to controls revealed alterations in Sonic hedgehog (Shh) signaling. More specifically, the expression of Shh and its downstream genes Ptch1 and Gli1 was spatiotemporally downregulated in the developing face of RA-treated embryos. Consistent with these findings, the incidence of cleft palate in association with excessive RA signaling was reduced by administration of the Shh signaling agonist, SAG.

【Discussion】Altogether, our results uncovered a novel mechanistic association between retinoic-acid-induced cleft palate with decreased Shh signaling and elevated CNCC apoptosis.

IE 035
Boosting prenatal support in Japan

Nobuhiko Hayashi[1, 2, 3)], Yoshihiro Sano[1)],
Ayaka Tsushima[1)], Chiaki Kitamura[1)],
Mayumi Mitogawa[1)], Noriko Nakamura[1)],
Kenjiro Ishida[1)], Makio Shozu[1, 3)]
[1)]NPO for Family and Baby Wellness
[2)]Chiba Aoba Municipal Hospital
[3)]Chiba University (Japan)

In Japan, aborting a fetus due to fetal abnormalities was made illegal in 1996. However, these kinds of abortions have continued to take place in spite of the law. Policy makers in Japan, therefore, decided not to provide prenatal testing as standard maternity care, because the test could potentially lead illegal terminations.

Despite the low, it is well known that many couples are choosing discontinuing pregnancy when they found fetal abnormalities without official approval nor social support. We, therefore, established a non-profit organisation to support families before/during/after prenatal diagnoses.

- Helping children who need special care

We visited several countries to learn how children are supported to go to school. Although the government encourages children to go to "ordinal" schools, it is still extremely challenging if you need medical care such as a ventilator in Japan. As a trial, we have been sending nurses to make it possible. We are now creating guidelines for the local government, schools, and medical professions about how to support children who need medical care.

- An app for finding families like you

We released an online peer-support system in 2016. Approximately 200 families have joined the network to share their experience. This network made peer-support possible without sharing your confidential information, regardless where you are, what is the condition you are facing.

- Creating booklets and helpline

We realized that many families have common questions and difficulties, such as "how to tell colleagues/children if I choose abortion." We are creating 8 booklets which help families who are struggling to face the results of prenatal diagnoses. The booklets tell tips to tell your results to your partner/friends/children/grandparents. To make the booklets, we visited a UK charity organisation "ARC;antenatal results and choices", and raised approximately 40,000 USD through crowd funding and selling charity T-shirts.

- Global connection for fetal therapy

There are still some conditions which we can not offer fetal therapy in Japan, for instance, open spina bifida, selective termination, embryo reduction. When the couple needs informationand/or treatment, we provide an international arrangement to reach the care.

We hope advancement of fetal medicine would be helpful for all women and babies. We will continue ask a question "What is prenatal diagnoses for ?" "How we can make prenatal diagnoses ethical and practical?"

IE 036
Boosting fetal medicine in Japan

Nobuhiko Hayashi[1, 2, 3], Ayaka Tsushima[1],
Hiroyuki Numata[1], Yoshihiro Sano[1]
[1]The Fetal Medicine Foundation Japan
[2]Chiba Aoba Municipal Hospital
[3]Chiba University (Japan)

【Background】Many of congenital diseases are now prenatally detectable. Some of them are treatable or curable if they are diagnosed by certain timing. In Japan, although there are several tertial hospitals which are offering fetal therapy, the idea of seeing and treating fetuses are still not widely spread.
Unfortunately, prenatal tests are still stated as "options only if the couple asked and requested", because aborting a fetus due to fetal abnormalities was made illegal in 1996. Medical professions are still not encouraged to give couples options of prenatal testing.
【Purpose】Build an infrastructure of fetal medicine, involving preventive medicine; rubella vaccination/folic acid, prenatal screening; ultrasound/genetic screening, prenatal diagnosis; ultrasound/CVS/amniocentesis/micro array, fetal therapies, fetal palliative cares.
【Method】Firstly, I organised several workshops to feel whether fetal medicine is acceptable in Japan. Secondly, I visited fetal medicine centre in 10 different countries to understand history and the whole system of fetal medicine. Finally, I started building a "fetal medicine network" involving international and domestic members.
【Result】To spread fetal therapy, it is inevitable to create a system to screen and diagnose congenital abnormalities. Governmental understanding and support are necessary to develop the system. Social understanding is also essential to support the autonomy of the couple. Cooperation between hospitals, family support organisations, government and schools is the key.
【Discussion】Prenatal testing can give the couple the option of medical abortion. I understand that the Japanese government is hesitating to create a system of prenatal testing. However, we need to build a high standard of prenatal testing, otherwise we can not help fetuses who are needing fetal therapies. To spread prenatal testing, we need not only to train medical professions, but also create an international and domestic network.

IE 037
Genetic counseling for prenatal diagnosis

Nobuhiro Suzumori, MD, PhD
Department of Obstetrics and Gynecology,
Nagoya City University Graduate School of Medical Sciences,
Nagoya (Japan)

【Background】Although many studies have focused on the development and quality of laboratory techniques for prenatal diagnosis, these techniques must be placed into a health services context after consideration of the clinical, ethical, social, legal and economic issues.

【Purpose】Genetic counseling for prenatal diagnosis is important, and we review prenatal testing, i.e. ultrasounds, MRI, CT, amniocentesis, chorionic villus sampling, non-invasive prenatal testing (NIPT) shown to be accurate for the detection of fetal anomalies.

【Method & Result】In Japan, NIPT was begun in April 2013 at the institutes approved by the Japan Society of Obstetrics and Gynecology (JSOG) and the Japanese Association of Medical Sciences (JAMS). Prenatal diagnosis includes maternal serum screening for aneuploidy, NIPT, fetal ultrasonography, screening for a history of a prior pregnancy with a trisomy, MRI, CT etc. The American College of Obstetrics and Gynecology has recommended that a maternal age of 35 years alone should no longer be used as a threshold to determine who is offered screening versus invasive testing. Individual choice for prenatal diagnosis meets individual needs and thereby could reduce anxiety and stress. However, posttraumatic stress, depression, and anxiety are common after prenatal diagnosis for congenital heart defects. Women undergoing prenatal diagnostic procedures experience more psychological distress, which may be currently underestimated.

【Discussion】As for prenatal diagnosis, the establishment of interdisciplinary treatment settings where access to psychological support is facilitated may be beneficial. While increasing patient autonomy and reassurance on the one hand, this expansion in fetal information may also increase patient anxiety or generate unjust outcomes surrounding fetal selection and elective abortion. Therefore, appropriate genetic counseling should be offered to pregnant women case by case before and after prenatal diagnosis.

IE 038
Sulcal infolding abnormality induced by exposure to valproic acid at the late stage of cortical neurogenesis in ferrets

Kazuhiko Sawada
Department of Nutrition, Faculty of Medical and Health Sciences,
Tsukuba International University (Japan)

【Background】There have been documented with regard to abnormities in cortical folding/sulcal infolding in human neurodevelopmental disorders such as autism and schizophrenia. Valproic acid (VPA) is known as an inhibitor of histone deacetylases. Developmental exposure of VPA caused reportedly autism-like abnormal social behaviors in ferrets. Here, I introduce our recent findings regarding the effect of VPA at the late stage of cortical neurogenesis on sulcal infolding using gyrencephalic animal model, ferrets, by MRI-based morphometric and quantitative histocytological approaches.

【Method】Ferret pups were given an injection of VPA intraperitoneally on postnatal days (PDs) 6 and 7, corresponding to the late stage of cortical neurogenesis, and they were also received BrdU 2 hours after the last injection of VPA for tracking newly-generated neurons.

【Results】Ex vivo MRI-based morphometry revealed a significantly smaller infolding in the rostral suprasylvian sulcus (rsss) and splenial sulcus (ss) with thickening their floor cortex, but an increased surface area of the lateral sulcus (ls) in VPA-treated ferrets on PD 20. By immunohistochemical analysis, BrdU-labeling appeared largely in parvalbumin transiently-expressing small-sized neurons throughout the ferret cortex on PD 20. Notably, a significantly higher density of those neurons was seen in the expanded cortical strata of particular sulcal floors in VPA-treated ferrets, i.e., the inner stratum of the rsss floors, the outer stratum of the ls floors, and either the outer or inner stratum of the ss floors.

【Discussion】Mechanical forces causing sulcal infolding were known to be reduced by an expansion of the inner stratum, but increased conversely by an expansion of the outer stratum of sulcal floor cortex. Since parvalbumin transiently-expressing small-sized neurons were originated from basal radial glia (bRG) in the inner and outer subventricular zones of premature cortex, our results suggest that increased bRG-derived neurons by VPA alter mechanical forces influencing sulcal infolding via modifying cortical laminar structures. The sulcal infolding abnormality in our VPA-treated ferret model was reminiscent to a type of gyrification abnormality in human autistic patients. HDACs may modulate sulcal infolding via regulations of proliferation and differentiation of bRG, as well as one of responsible factors for causing cerebral cortical abnormality in autism.

Grant: supported by grants from JSPS KAKENHI (15K08144).
COI: No.

IE 039
Mesenchymal-derived actomyosin contractility is required for the tissue fusion during tubular urethral formation in mice

Kentaro Suzuki, Gen Yamada
Institute of Advanced Medicine,
Wakayama Medical University (WMU) (Japan)

Tissue fusion is crucial for the correct formation of many organs, including palate, heart, neural tube closure, and tubular urethral formation. Defective fusion processes lead to the birth defects related with such developmental contexts. Despite the importance during organ development, the molecular and cellular mechanisms regulating tissue fusion are not fully understood.

The palate development is one of the good models to reveal the mechanisms of tissue fusion. The midline epithelial seam (MES), which develops transiently contact of the two palatal shelves, must be removed to provide mesenchymal continuity throughout the fused palate, and failure results in cleft palate. The developmental genes associated with palatal fusion have been identified, such as Wnt/b-catenin, TGFb3, and Snails. In addition to the molecular aspects, epithelial-to-mesenchymal transition (EMT), apoptosis, and epithelial cytoskeletal remodeling were identified as the essential cellular events for MES removal.

The development of mammalian external genitalia (ExG) gives rise to androgen-induced sexually dimorphic structures, such as tubular urethra. The tubular urethral formation shows morphological changes characteristic of tissue fusion, including removal of midline epithelial structure, urethral plate epithelium (UPE), and mesenchymal confluence. We show that mesenchymal-derived actomyosin contractility by the motor protein, non-muscle myosin II (MYH10), is essential for the fusion of UPE during tubular urethral formation. MYH10 was expressed prominently in the mesenchyme adjacent to the UPE of male eExG. Inhibition of actomyosin contractility through blebbistatin treatment and mesenchymal genetic deletion induced defective UPE fusion with reduced mesenchymal condensation. Furthermore, b-catenin expression was dramatically reduced by inhibition of actomyosin contractility. We also suggest that actomyosin contractility regulates androgen-dependent mesenchymal directional cell migration to form the condensation in the mesenchyme leading to the fusion of UPE. Thus, mesenchymal-derived actomyosin contractility is indispensable for androgen-driven tubular urethral formation. These findings further highlight the importance of mesenchymal dynamics for epithelial fusion during organ development.

【References】Acebedo AR, Suzuki K et al, Mesenchymal actomyosin contractility is required for androgen-driven urethral masculinization in mice.

Commun Biol., doi: 10.1038/s42003-019-0336-3, 2019.

Suzuki K. et al, Sexually dimorphic expression of Mafb regulates masculinization of the embryonic urethral formation.

Proc Natl Acad Sci U S A., 111(46):16407-16412, 2014.

IE 040
Cytomegalovirus Initiates Infection Selectively from High-Level β1 Integrin-Expressing Cells in the Brain

Hideya Kawasaki
Hamamatsu University School of Medicine,
Preeminent Medical Education & Research Center,
Institute for NanoSuit Research (Japan)

【Background】Cytomegalovirus (CMV) is a prevalent infectious pathogen of intrauterine infections causing congenital anomalies such as CMV encephalitis, which is characterized by the focal areas of reactive gliosis, reactive mononuclear cells, microglial nodules, and ventriculoencephalitis. The incidence rate of congenital CMV infection exceeds that of Down syndrome. At birth, fatally infected infants present microcephaly, periventricular calcification, and ocular abnormalities. Those with non-fatal, subclinical congenital infection subsequently develop mental retardation, hearing loss, and visual defects.

【Purpose】To elucidate the mechanisms underlying the susceptibility of CMV in the developing brain, cell tropism and the infectious dynamics of CMV infection have been investigated.

【Method】We have analyzed the distribution of cytomegalovirus (CMV) particles during the acute phase of infection, termed primary viremia, using a simple method of intracerebroventricular and intravascular injection of viral particles or fluorescent microbeads into the neonatal mouse brain. The localization pattern of the virus and nanoparticles could be detected by microscopic evaluation or by in situ hybridization.

【Results】Murine CMV (MCMV) immediate early 1-positive cells colocalized mainly with meninges and choroid plexus following intraventricular infection and colocalized with endothelial cells and pericytes following intravascular infection. Using green fluorescent protein-expressing recombinant MCMV particles and fluorescent microbeads (100–300 nm), we revealed that CMV particle size is the primary factor determining the initial CMV distribution. β1 integrin inhibition using a short hairpin RNA and functional blocking antibody significantly reduced MCMV infection. Immunohistochemical, flow cytometric, and brain slice analyses strongly support that high level β1 integrin-expressing cells, such as endothelial cells, pericytes, meninges, choroid plexus, and neural stem progenitor cells, are the first targets of MCMV.

【Conclusions】Our data demonstrates that the initial distributions of MCMV particles and β1 integrin determine the distinct pattern of infection in the brain in the acute infection phase.

IE 041
Craniosynositosis diagnosed during fetal and neonatal periods

Aya Harada[1, 2], Susumu Miyashita[3], Ryuhei Nagai[4],
Shintaro Makino[5], Jun Murotsuki[6]
[1] Center for iPS cell research and application,
Kyoto University
[2] JSPS fellow (DC1)
[3] Department of Maternal and Fetal Medicine,
Dokkyo Medical University
[4] Department of Obstetrics and Gynecology,
Kochi Health Sciences Center
[5] Department of Obstetrics and Gynecology,
Juntendo University
[6] Department of Maternak and Fetal Medicine,
Miyagi Children's Hospital (Japan)

【Background】Prenatal diagnosis of craniosynostosis is desired in clinical situation from several aspects. In most severe cases, the maintenance of upper airway, associated with midfacial hypoplasia, is difficult and careful planning of the delivery methods and prenatal care are essential. Other concerns include the multiple reconstruction surgeries needed after infancy periods or possible neurologic dysfunctions secondary to hydrocephalus, chiari malformations or other types of neurological pathophysiology. Prenatal course of craniosynostosis will also help to understand the nature of craniosynostosis before birth, which has not been often been discussed .

【Purpose】To explore the sonographic findings of fetuses with craniosynostosis and investigate their prognosis

【Method】We conducted a 5-year, multicentre retrospective study and collected data on patients with craniosynostosis diagnosed in the perinatal period.

【Result】Of 41 cases, 30 cases (73%) were syndromic craniosynostosis, 8 cases (20%) were non-syndromic craniosynostosis and the other 3 cases (7%) were secondary craniosynostosis of chromosomal deletion syndromes. The prenatal detection rate was 61%. Half of the cases of syndromic craniosynostosis detected during the perinatal period were Pfeiffer syndrome. Most frequently detected finding leading to prenatal diagnosis was abnormal head biometry, which was closely correlated with deformation of the cranial shape. Three cases presented with distorted ventriculomegaly and exophthalmos but normal cranial shape and size. The overall survival rate of infants with syndromic craniosynostosis was 79%, while all of the infants with non-syndromic craniosynostosis survived.

【Conclusion】Prenatal diagnosis of craniosynostosis is difficult, especially when dysmorphic change of the fetal cranium is not evident. Abnormal head biometry and distorted ventriculomegaly could potentially be additional markers of fetal craniosynostosis and consequently increase the prenatal detection rate.

IE 042
22q11.2 deletion syndrome: clinical phenotypes to pathogenesis of mental disorders associated with this variant.

Norio Ozaki
Department of Psychiatry,
Nagoya University Graduate School of Medicine (Japan)

22q11.2 deletion(22q11D) syndrome is the most common chromosomal microdeletion disorder. The first description of the constellation of findings now known to be due to this chromosomal difference was made in the 1960s in children with DiGeorge syndrome, who presented with the clinical triad of immunodeficiency, hypoparathyroidism and congenital heart disease. The syndrome is now known to have a heterogeneous presentation that includes multiple additional congenital anomalies and later-onset conditions, such as palatal abnormalities, and mental disorders. The psychiatric expression of 22q11D syndrome is characterized by high variability, both interindividual and intraindividual (different expressions over the lifespan). Besides varying levels of intellectual disability, the prevalence of autism spectrum disorder, attention deficit hyperkinetic disorder, anxiety disorder, and schizophrenia in individuals with 22q11D is significantly higher than in the general population. Our genome analysis in Japanese schizophrenia also confirmed significant association between 22q11D and this condition1). Management requires a multidisciplinary approach involving pediatrics, dental and oral surgery, psychiatry and genetic counselling. In addition to elucidate longitudinal trajectories of psychiatric diagnoses, we have recently started a prospective cohort study of children with 22q11.2 deletion in collaboration with Aichi Gakuin University.

Equally important, 22q11D syndrome has become a model for understanding mental disorders, and may provide a platform to better understand these conditions. Therefore, researchers including us are trying to clarify molecular pathogenesis of mental disorders such as autism spectrum disorder and schizophrenia based on this variant. Thus, we focused on reticulon 4 receptor gene (RTN4R) located within chromosome 22q11.2, a region and identified that one of the discovered rare mutations, R292H was significantly associated with schizophrenia and the R292H mutation affected the function of this molecule2). We also make model mice with 22q11D and establish induced pluripotent stem cell (iPSC) from patients with this variant and analyze the phenotype of mental disorder model mice and neuronal cells derived from iPSC to elucidate the molecular pathogenesis of these conditions.

The recent findings about the clinical phenotypes of 22q11D syndrome and pathogenesis of mental disorders associated with this variant will be discussed in this lecture.

【Ref】

1) Kushima I, Ozaki N et al. Comparative Analyses of Copy-Number Variation in Autism Spectrum Disorder and Schizophrenia Reveal Etiological Overlap and Biological Insights Cell Rep 24,11 p2838-2856,2018
2) Kimura H, Ozaki N et al. A novel rare variant R292H in RTN4R affects growth cone formation and possibly contributes to schizophrenia susceptibility Transl Psychiatry 7,8 pe1214,2017

IE 043
Primary Microcephaly and D40

Masato Takimoto
Institute for Genetic Medicine, Hokkaido University (Japan)

Primary Microcephaly (MCPH) is autosomal recessive hereditary disease(s) with small brain, not resulting from other disorders, and affects about 1/100,000 in newborns, with about 200 families worldwide. The patients with MCPH manifest small head of prenatal onset, with affected brain development and neurogenesis, with mild-to-moderate intellectual impairment and short stature, usually without additional neurological or somatic abnormalities. Some patients, however, show neurological abnormality, such as mild seizures, and dysmorphism, and some patients show more severe phenotypes, such as dwarfism with bird-headed appearance and mental retardation. ¬So far, 13 major MCPH loci and their causal genes have been reported. Interestingly, most of the MCPH causing genes encode the proteins that play essential roles in cell-division and cell cycle-regulation.

We had previously cloned a human gene D40 (alias: AF15q14, KNL1, CASC5) on chromosome 15, and characterized D40 as a member of cancer/testis gene family that is predominantly expressed in normal testis and widely expressed in various human cancers. D40 gene was identical to AF15q14, which mutually translocated with the MLL gene in acute myeloid leukemias. In testis, marked expression of D40 protein was observed in spermatocytes and pre-acrosomes of spermatids. In cancers, D40 expression was correlated with the clinic-pathological characteristics of primary lung tumors, such as patients' smoking habits.

Subsequent studies revealed that D40 was identical with a kinetochore protein in the mitotic machinery, KNL1, which binds not only to Mis12 and Ndc80, comprising the KMN network, but also to several other proteins including tubulin, the spindle assembly checkpoint proteins. By binding to those proteins, D40 plays critical roles in kinetochore formation, connecting chromosomes and spindles, and regulating SAC. RNA interference to D40 gene, with use of short inhibitory double-stranded RNA, D40 siRNA, induced apoptosis of human cancer cell lines and inhibited their growths in vitro and animal experiments.

While we had been studying on D40 gene and protein, this gene was reported to be the causing gene for one of Primary Microcephaly, MCPH4. There are about 15 patients in consanguineous families in developing countries and one sporadic case in America. In family cases, homozygous point mutations were observed in D40 gene, which caused not only single amino acid substitutions but also potential frame-shift of the sequence. All the point mutations were located at 3' side of the gene and close to carboxyl terminal of the protein.

In summary, D40 gene encodes a kinetochore protein and is the causing gene for MCPH4.

IE 044
Continuing research to provide coordinated care for patients with 22q11.2 deletion syndrome.

Chiaki Kitamura[1, 3)], Simon Elderton[2)],
Nobuhiko Hayashi[3)]
1) Seisen Jogakuin College
2) Niigata College of Nursing
3) NPO for Family and Baby Wellness (Japan)

We are in the process of establishing a coordinated care network for people with 22q11.2 deletion syndrome (22q11.2DS). In this session, we discuss our efforts to improve care guidance for patients and families.

22q11.2DS is the most common microdeletion syndrome in humans and is estimated to affect one in every 2,000 to 4,000 live births. 22q11.2DS has many possible features that can affect almost any part of the body, including cleft palate, heart defect, feeding problems, unique facial characteristics, hearing loss, developmental delay and learning disabilities. The severity of the condition can vary significantly between patients.

It has been suggested that patients with 22q11.2DS are more likely to find opportunities to participate in society if they are cared under the continuing medical support and have the opportunity to learn with individual support that has been modified appropriately for their cognitive and developmental features.

To develop appropriate long-term support systems for individuals and families affected by 22q11.2DS, we have investigated the situation regarding patient and family support. We developed a questionnaire and conducted an interview survey with approximately 50 patients with 22q11.2DS and their families.

33 responses were received. The average age of patients was 6.2 years (0-39 years); the average age at diagnosis was 2.68 years (24 of them were under one year old); and the percentage of patients with complications was 84.8% for heart diseases, 81.8% for non-cardiac diseases, 69.7% for developmental disorders and 48.5% for other problems.

Parents were anxious about the future because 22q11.2DS remains under-recognised. In particular, there were many cases where parents were feeling uncomfortable because they were not receiving adequate information about how their children's future would look. Parents' anxieties include complications in their child's child rearing, growth and development and the disease's influence on school attendance or work, children's siblings, and parents' employment.

We are currently developing three guides those can be put in place to answer the needs identified: a Child Rearing Guide, an Entering School Guide and a Transition to Adulthood Guide. Furthermore, we are currently developing a professional team which is dedicated to discussing the appropriate strategy of providing continuing support for the patient and of maximising the use of the local resources such as rehabilitation-centre, additional school, on-the-job training site, and medical professionals ready for the life-long follow-up of the patients with 22q11.2DS. Our future goal is to establish and roll out a comprehensive care support network nationally.

IE 045
In utero gene therapy for cleft palate

Masayuki Endo[1,2], Chadwick Wu[3,4],
Phillip W Zoltick[1], Alan W Flake[1],
Hyun-Duck Nah[3,4]
[1] The Children's Center for Fetal Research,
The Children's Hospital of Philadelphia,
Philadelphia, Pennsylvania (USA)
[2] Department of Children and Women's Health,
Graduate School of Medicine,
Osaka University (Japan)
[3] Division of Plastic and Reconstructive Surgery,
The Children's Hospital of Philadelphia,
Philadelphia, Pennsylvania
[4] Division of Plastic Surgery,
The University of Pennsylvania School of Medicine,
Philadelphia,
Pennsylvania (USA)

【Background】Intra-amniotic gene transfer (IAGT) has been used to target organs exposed to amniotic fluid, that is, the skin, amniotic membranes and the respiratory and digestive systems. However, the fetal milieu is constantly changing because of the exponential growth and development of the fetus and its investing compartments. Thus, the timing of gene transfer may be critically important in targeting a specific cell or cell population to achieve the desired therapeutic or biological effect.

【Purpose】In this study, our purpose is to prove whether intra-amniotic gene transfer (IAGT) approaches have therapeutic potential to prevent cleft palate in utero, especially those resulting from palatal midline epithelial dysfunction.

【Method】Using Tgf 3–/– mice, which display complete penetrance of the cleft palate phenotype, we tested the hypothesis that intra-amniotic gene transfer could be used to prevent cleft palate formation by restoring palatal midline epithelial function. An adenoviral vector encoding Tgf 3 was microinjected into the amniotic cavity of mouse embryos at successive developmental stages.

【Result】Transduced Tgf 3–/– fetuses showed efficient recovery of palatal fusion with mesenchymal confluence following injection at E12.5 (100%), E13.5 (100%), E14.5 (82%), and E15.5 (75%). Viral vectors injected into the amniotic sac transduced the most superficial and transient peridermal cell layer but not underlying basal epithelial cells.

【Discussion】TGF 3 transduction of the peridermal cell layer was sufficient to induce adhesion, fusion, and disappearance of the palatal shelf MEE in a cell nonautonomous manner. The timing of intervention was critically important to avoid cleft palate from becoming permanent. This study supports the potential for treatment of cleft palate by prenatal gene transfer.

IE 046
A prospective cohort study of patients with 22q11.2 deletion syndrome aiming at early detection and treatment of psychiatric disorders

Shu Kushima (Japan)

22q11.2 deletion syndrome, caused by microdeletion of chromosome 22, occurs in about 1 of every 2,000-4,000 live births, is associated with not only medical problems, but also a range of neurodevelopmental, psychiatric disorders. Specifically, autism spectrum disorder and attention deficit/hyperactivity disorder are observed in about 30% of children with 22q11.2 deletion. Schizophrenia and anxiety disorders are observed in about 30% of adult patients. Consistent with this, we previously performed the genomic analysis of schizophrenia in the Japanese population (2,500 cases and 2,100 healthy controls) and confirmed that 22q11.2 deletion is strongly associated with risk for schizophrenia (Kushima I, et al. Cell reports 2018). However, longitudinal trajectories of psychiatric diagnoses are still unclear at the level of individual patients.

To elucidate this point, we have recently started a prospective cohort study of children with 22q11.2 deletion in collaboration with Aichi Gakuin University. The purpose of this study is to longitudinally examine psychiatric symptoms and cognitive function of children with 22q11.2 deletion who are treated for cleft palate in Aichi Gakuin University. To data, we have recruited 14 children with 22q11.2 deletion (8 male/6 female, average age = 9 years, range: 4-16 years) and have done baseline assessments. All study participants were confirmed to have de novo 22q11.2 deletions (deletion size: 3 mega base pairs) by array CGH. The frequently observed physical comorbidities included cleft lip/palate or velopharyngeal insufficiency (N=11), congenital heart diseases (N=10), and chronic otitis media (N=4). Their cognitive abilities, as measured by WISC-IV and Vineland-II, were mainly in the range of mild to moderate intellectual disability. The assessment using the Autism Diagnostic Observation Schedule (ADOS-2) revealed that 11 of 14 (79%) met the criteria of “autism” or “autism spectrum”. Consistent with this, the results of Social Responsiveness Scale (SRS-2) also suggested high rates of social impairment in this cohort. Moreover, children with 22q11.2 deletion had a high prevalence of other psychiatric comorbidities including attention-deficit/hyperactivity disorder (ADHD) (N=2), enuresis (N=3), and separation anxiety disorder (N=2).

Although this prospective cohort study has just begun, it will provide longitudinal data on psychiatric phenotypes in children with 22q11.2 deletion. It is expected that the study findings will be useful for early detection and early treatment of psychiatric disorders and improving psychosocial function in those with 22q11.2 deletion.

IE 047
Challenge for treatment of congenital maxillofacial anomalies using tissue engineering

Kazuto HOSHI
Oral and Maxillofacial Surgery, Department of Sensory and
Motor System Medicine Graduate School of Medicine,
The University of Tokyo (Japan)

【Background】Secondary correction of cleft lip-nose deformity presents a formidable challenge in cleft lip and palate surgery. Numerous approaches including autologous bone graft, autologous cartilage graft and implantation of artificial materials have been proposed to address the cleft nose deformity. However, suitable graft materials that possess sufficient length and straightness with the mechanical strength equivalent to the native cartilage cannot be obtained from any part of body or artificial biomaterials.

【Purpose】The purpose of our study is to established the tissue-engineered cartilage with greater firmness and a 3D structure, which we term “implant-type”, in order to overcome limitation of the present graft materials.

【Methods】We developed 1) a proliferation medium for chondrocytes to realize a more than 1000-fold increase in number without using fetal bovine serum, and 2) a scaffold system that effectively preserves chondrocytes in the engineered tissue and provides the adequate 3D shape to the tissue. By these techniques, we could make the three-dimensional tissue-engineered cartilage. The safety and the effectiveness of the engineered tissues were confirmed in the in vitro experiments or by the autologous transplantation of the tissue-engineered cartilage in beagles. After the acquisition of institutional and governmental permission, we began the clinical trial of that tissue-engineered cartilage for treatment of a nasal deformity in patients with a cleft lip and palate.

【Results and discussion】Post-operatively, safety has been confirmed based on the incidence of adverse events including pain, infection or graft failure requiring the removal of tissue-engineered cartilage after transplantation. Effectiveness was also assessed based on exploratory evaluation indicators, such as satisfaction level of patients, activity of daily living, improvement of facial features, less-invasiveness at donor sites and formation of regenerated cartilage. Now, we carry out the multicenter clinical trial to confirm the safety and usefulness of this cartilage. In the presentation, we will show the research and development of the three-dimensional tissue-engineered cartilage and discuss future application of this construct.

IE 048
Current status of cleft lip and palate care in Iraq

Ali Mohammed Saeed Ahmed Alkhayat
Ninava directorate of health, ministry of health (Iraq)

Iraq is a country whose still in war for the last 40 years.The result was massive destruction of the cities and their infrastructures including the main hospitals.the prevalence of cleft lip and palate in Iraq was estimated to be lower than that reported in Asians and Europeans, and slightly higher than that reported in Africans.

Unfortunately there is no specialized centers for the treatment of cleft children , and the mission is usually taken as a heroic task of the surgeon alone … the cause behind this is the lack of modern training in the field of cleft lip and palate. also lack of patient education causes some patients to be reluctant to seek treatment for their cleft alveolus , nasal deformity or velopharyngeal incompetence.

There is frank increase in the prevalence of congenital deformities in general since gulf war and this was investigated by many researchers who found that the most common deformities were congenital heart defects, neural tube defects, and cleft lip/palate. The suspected causative factors are depleted Uranium and other pollutants.

IE 049
PREDICTION OF CLEFT LIP AND PALATE WITH THE APPLICATION OF GENETIC MARKERS OF FOLIC ACID AND GENES OF DETOXICATION OF XENOBIOTICS IN REGIONS WITH ECOTOXICANTS
To conduct a molecular genetic analysis of the polymorphism of xenobiotic detoxification genes in patients with congenital cleft lip and palate.

Sergey Vasilyevich Chuykin, Oleg Sergeevich Chuykin,
Tatyana Viktorovna Viktorova, Olga Sergeevna Tselousova,
Marsel Venerovich Gilmanov, Azamat Maratovich Muratov,
Olesya Ilfatovna Murzagaleeva,
Bashkir State Medical University (Russia)

【Background】 the problem of prenatal prediction is important in congenital maxillofacial pathology. We have developed a method for predicting congenital cleft lip and palate using molecular genetic analysis.

【Method】 To study the relationship between environmental and genetic risk factors, polymorphisms of CYP1A1, GSTM1, GSTP1 genes were studied, taking into account the place of residence of patients - in areas with the petrochemical industry (NHP) and in environmentally friendly areas.

【Result and discussions】 The frequency distribution of the alleles of the CYP1AI gene was characterized by a significant predominance of the Val allele in patients with VRGN compared with control (7.00% and 2.49%, respectively). The relative risk of developing VRGN in the presence of a mutant allele was 2.95 (CI = 1.20-7.30).

A comparative study of the frequency distribution of the genotypes of the GSTM1 gene in patients with congenital cleft lip and palate and in the control group found that among patients with carriers of the deletion of the GTPM1 gene were found somewhat more frequently, with a frequency of 49.00% versus 37.85% in the control group (49 and 76 children, respectively).

Glutathione S-transferase Pl (GSTPl) gene polymorphism analysis showed no statistically significant differences between the total sample of patients with congenital cleft lip and palate and the control group (x2 = 1.86; p = 0.39). In both groups, the Ile / Ile genotype prevailed in frequency (63.00% and 69.27%, respectively); Ile / Val heterozygotes were detected with a frequency of 33.00% and 28.78%, respectively.

At the next stage, we studied the frequency distribution of genotypes of xenobiotic detoxification genes in patients with congenital cleft lip and palate, taking into account the nosological forms of the disease. There was a tendency to an increase in the frequency of the Ile / Val genotype of the CYP1Al gene in patients with an isolated cleft of the palate to 15.80% compared with an isolated cleft of the upper lip and a combined cleft of the upper lip, alveolar process, soft and hard palate, where its frequency was 12.50 % and 8.70% respectively. In patients with isolated cleft palate, individuals with a deletion of the GSTM1 gene were more common (21 individuals — 55.27%). Among patients with an isolated cleft of the upper lip and a combined cleft of the upper lip, alveolar process, soft and hard palate, carriers of the normal genotype GSTM1 (+) were more common (62.50% and 52.17%, respectively). Patients with an isolated cleft of the upper lip showed a tendency to increase the proportion of heterozygous genotype lle / Val of the GSTP1 gene to 43.75% and homozygous for the Val / Val genotype to 6.25% compared to other clinical forms.

IE 050
Intestinal loop formation: herniation into the extraembryonic coelom and return to the abdominal coelom

Tetsuya Takakuwa
Human Health Science, Graduate School of Medicine,
Kyoto University (Japan)

【Background】Drastic changes occur during the development of the intestinal loop (IL), including physiological umbilical herniation (PUH) and its return. The present study was designed to analyze such developments three-dimensionally during human embryonic and early fetal period.

【Materials and Methods】The software AMIRA was used to analyze the 3D digitalized data (high-resolution MRI, phase-contrast X-ray CT) obtained from the Kyoto Collection.

【Results and Discussion】Based on the results of our analysis, the following time line and main features of IL formation were revealed:

Herniate phase (Carnegie stage (CS)14-CS23, Crown-rump length (CRL) < 35 mm): IL rotation was initially observed as a slight deviation of the duodenum and colorectum from the median plane up to CS16. The PUH was noticeable after CS16. The IL displayed a hairpin-like structure, with the superior mesenteric artery (SMA) running parallel to the straight part and the cecum located to the left at CS18. The IL rotated around the SMA only during the early stages (until CS19). The IL gradually moved away, running transversely after CS19. Embryos with liver malformation showed PUH, which indicated that PUH occurred independent of liver volume.

【Transition phase (CRL = 37, 41, and 43 mm)】Intestinal return began from proximal to distal part in samples with CRL of 37 mm. The cecum returned before the distal end of the small intestine (ileum) in samples with CRLs of 41 and 43 mm.

【Return phase】The cecum immediately reached its final position in the right lower quadrant of the abdomen (the adult position). The anti-clockwise “en-bloc rotation” described by descent and fixation of the cecum in the abdominal cavity may not exist. A rapid increase in the space available for the intestine in the abdominal coelom that exceeded the intestinal volume in the extraembryonic coelom was observed. The height of the umbilical ring increased in a stepwise manner between the transition and return phases and its height in the return phase was comparable to or higher than that of the hernia tip during the herniation phase. We speculated that the space is generated to accommodate the herniated portion of the intestine, similar to the intestine wrapping into the abdominal coelom as the height of the umbilical ring increases.

【Conclusion】The data obtained in the present study demonstrate the precise timeline of IL formations, which indicate several points of discrepancy in the results of previous studies.

IE 051
Sonic hedgehog is required for patterning of the intrinsic tongue musculature

Sachiko Iseki
Dept. of Molecular Craniofacial Embryology,
Graduate School of Medical and Dental Sciences,
Tokyo Medical and Dental University (Japan)

The secreted signaling molecule sonic hedgehog (SHH) functions in many diverse biological events extending from early development through to post-natal tissue homeostasis. Loss of SHH function results in holoprosencephaly in which cleft palate is one of the characteristic phenotypes. During oropharyngeal development, Shh is expressed in the epithelium of tongue primordium and palatal shelves, which is partly regulated by MFCS4, a Shh cis-enhancer, activated from embryonic day (E)11.0.

The compound heterozygous deletion mouse of Shh coding region and MFCS4 (MFCS4+/-;Shh-/+) results in full penetrance of cleft palate by failure in palate shelf elevation, which is thought to require cooperation between intrinsic factors within palatal shelves and extrinsic factors for creating space in oral cavity including tongue descendant.

The maxillary organ culture showed that palatal shelves seemed to be able to elevate. Histological analyses of the tongue revealed that Shh expression levels in the tongue epithelium was severely reduced and Ptch1, Shh receptor, was down-regulated in cranial neural crest (CNC)-derived lingual mesenchyme that forms lingual tendons in the MFCS4+/-;Shh-/+. In the mutant, arrangement of intrinsic lingual myotubes was disorganised but myotube differentiation did not seem to be affected. We therefore investigated lingual tendon formation and found that lingual tendons in the dorsum of the tongue including the septum are hypoplastic or aplastic, which was confirmed by decreased expression of Sox9 and scleraxis, tendon formation markers. CNCC-specific deletion of the Orofaciodigital syndrome 1 (Ofd1)-encoding ciliary protein in Wnt1-Cre; Ofdfl/Y mice produced complete loss of normal myotube arrangement and hypoglossia. In addition, temporally specific deletion of Shh expression in CreERTM;Shhflox/flox mice revealed that differentiation of the mesenchyme into the lingual tendon begins after E10.5.

These results suggest that Shh expressed in the lingual epithelium affects the differentiation of CNC-derived mesenchyme into tendon structures that regulate intrinsic myotube patterning. Thus we propose a novel function for SHH signaling in mouse tongue development.

in Japanese

IJ 001
A molecular mechanism of hyperactivity in animal model of congenital hyperbilirubinemia.

Arata Oh-Nishi[1, 3], Shoko Miura[2],
Keiko Tuchie[2], Ryosuke Arauchi[2],
Tsuyoshi Miyaoka[2], Masatoshi Inagaki[2],
[1]Department of Immune-Neuropsychiatry, Faculty of Medicine,
Shimane University
[2]Department of Psychiatry, Faculty of Medicine,
Shimane University
[3]RESVO Inc. (Japan)

【Background】It has been reported that Jaundice or neonatal hyperbilirubinemia increase the risk of Attention Deficit Hyperactivity Disorder (ADHD) (Wei 2015), although the molecular mechanisms are not yet well unclear.

【Purpose】We previously reported that the Gunn rat, which is a animal model of congenital Jaundice, has hyperactivity similar to ADHD (Hayashida 2009, Tuchie 2013). The study further sought to the molecular mechanism of neonatal hyeprbilirubinaemia associated ADHD using the Gunn rats.

【Methods】The amounts of monoamine and its metabolites in the brain of the Gunn rats were measured by high performance liquid chromatograph, furthermore, the ADHD associated behaviors in the Gunn rats were measured by rodent behavioral tests.

【Results】We found that there were significantly higher serotonin and its metabolite at the frontal cortex in the Gunn rats compared to the control rats. It is well known that the serotonin in frontal cortex associates several cognitive functions. We investigated whether intervention with serotonergic transmission improve behavioral abnormality in Gunn rats. A serotonin receptor agent improved the ADHD like behaviors in the Gunn rats.

【Discussion】The serotonergic dysfunction in the frontal cortex seems to play an important role in neonatal hyeprbilirubinaemia associated ADHD. Our study suggests that intervention with abnormal serotonergic transmission may improve symptom of neonatal hyeprbilirubinaemia associated ADHD.

【Conflict interest】Funding came from the Shimane University Faculty of Medicine Lab Sciences Research Grants. A. O-N is CSO in RESVO Inc. and has more than 5% RESVO Inc shares, but had no role in the study design data collection and analysis, decision. Other authors have no Competing Interests to declare.

in Japanese

IJ 002
The mechanism of the L-arginine effect on culture rat embryos

Atsushi Yokoyama[1)],
Masaharu Akita[2)],
Hitoshi Yokoyama[3)]
[1)]Life Science Laboratory of Kanagawa
[2)] Kamakura Women's University
[3)]Laboratory of Hyogo Clinical Medicine (Japan)

【Purpose】The mechanism of the L-arginine effect on cultured rat embryos is important to understand gut development of rat embryo. We were reported to the effect of L-citruline on cultured rat embryos in the 58th annual meeting of the Japanese teratology society. In this meeting, the advantages of whole embryo culture are to examine the direct effects of the L-arginine of L-citruline metabolite on rat cultured embryo.

【Method】Rat embryos on day 11.5 of gestation were cultured for 48 hours with L-arginine. In this whole embryo culture system, rat embryos were explanted on day 11.5 gestation and cultured of rat serum with 95 % O2 and 5 % CO2 using improved rotator for 48 hours.

【Result and Discussion】The group of treated embryos of L-arginine were not exchanged in the heart beats (153 ± 2), the crown-rump length (8.6 ± 0.2 mm), the embryonic protein contents (4,670 ± 41μg) and the embryonic total number of somites (56 ± 0.3). The malformation was not observed in the cultured embryos with L-arginine. On the other hand, the group of treated embryos of L-arginine significantly increased in blood flow on the tail of cultured rat embryos.

in Japanese

IJ 003
Maxillary growth and speech outcomes of 10-year-old children after simultaneous lip and palate repair using presurgical orthodontics

Ushio Hanai[1)], Tadashi Akamatsu[1)],
Noriaki Sakata[2)], Ryoichi Niikura[2)],
Hiroyuki Muramatsu[3)], Tomoe Okawa[1)],
Yuko Sakuma[1)]
1) Department of Plastic and Reconstructive Surgery,
Tokai University School of Medicine
2) Department of Oral Surgery,
Tokai University School of Medicine
3) Ichikawa Orthodontic Practice (Japan)

【Background】Previous studies have reported normal speech outcomes after early palatoplasty. However, early palatoplasty had not been standardized because surgery of the immature palate of infants causes severe disturbances in maxillary growth. Therefore, we performed a less-invasive palatoplasty at an early age of 6 months after narrowing the cleft palate using presurgical orthodontics in children with unilateral cleft lip and palate.

【Purpose】In this study, we aimed to assess whether pediatric patients who underwent palate closure at 6 months of age have normal maxillary growth and speech. For this purpose, we monitored and evaluated maxillary growth and speech outcomes of our patients for 10 years.

【Method】19 patients with complete unilateral cleft lip and palate were enrolled in this study. At 6 months of age, we performed simultaneous lip, maxilla, and palate repair after using presurgical orthodontics. Speech development was assessed by evaluating velopharyngeal function (VPF) and development of articulation for 10 years. Maxillary growth was assessed using the Goslon Yardstick and a cephalometric analysis at the age of 4 and 10 years.

【Result】No articulation disorders were observed after 4 years of age. Although palatalized articulation was evidently temporary in 3 cases before 4 years of age, all patients recovered without any speech training. Normal VPF rates were as follows: at 4 and 7 years of age 78.9% (n = 15), 10 years of age 73.7% (n = 14). The mean values of Goslon score were 3.20 at 4 years of age, and 2.67 at 10 years of age. Significant difference was observed between two periods. ($p < 0.05$). At the age of 4, the mean SNA value was 78.0 and the mean ANB value was 3.1. At the age of 10 years, the mean SNA value was 77.6 and the mean ANB value was 2.7. There was no significant difference between two periods.

【Discussion】In our patients, no articulation disorders were observed after 4 years of age. It is suggested that early palatoplasty is beneficial for development of articulation. However, early repair will never be accepted unless maxillary growth is considered. Using an orthodontic appliance allowed the use of less-invasive palatoplasty because of minimal lateral tension during palatoplasty and postoperative contracture. In this way we could accelerate timing of palate repair. This protocol may circumvent maxillary growth disturbances and result in both normal speech and maxillary growth.

in Japanese

IJ 004
Role of orthodontics in the team approach to cleft lip and palate care: assessing the effectiveness of the NAM appliance

Momotoshi Shiga[1, 5], Masaaki Sasaguri[2], Hiromi Sawada[5],
Manabu Habu[2], Koji Watanabe[3], Yuko Fujita[3], Mana Hayakawa[2],
Masahiro Mizuhar[1], Hideo Tanaka[6], Hirohito Takeuchi[6], Wataru Fujii[4],
Kenshi Maki[3], Kazuhiro Tominaga[2], Noriyoshi Sumiya[7], Tatsuo Kawamoto[1]
[1] Division of Orofacial Functions and Orthodontics,
Kyushu Dental University
[2] Division of Maxillofacial Surgery,
Kyushu Dental University
[3] Division of Developmental Stomatognathic Function Science,
Kyushu Dental University
[4] Unit of Education on Healthcare Team School of Oral Health Siences,
Kyushu Dental University
[5] Department of Orthodontics Seirei Hamamatsu General Hospital
[6] Department of Oral Surgery Seirei Hamamatsu General Hospital
[7] Department of Plastic Surgery Seirei Hamamatsu General Hospital (Japan)

【Background】 In the team approach to cleft lip and palate care in newborn infants, the dentist's role is to improve feeding by providing a palatal plate and altering the nasal shape with Nasoalveolar molding (NAM) appliance. In our team, the orthodontist is responsible for providing the infant with the NAM appliance. The effectiveness of this intervention has not yet been documented in Japan.

【Purpose】 In this study we measured four items related to changes in the nasal and lip shape in newborn children with unilateral cleft lip and palate who underwent NAM appliance intervention. We investigated whether the NAM appliance was effective in improving nasal morphology and cleft lip.

【Method】 Ten children with unilateral cleft lip and palate (5 boys and 5 girls) who underwent orthodontic treatment at Kyushu Dental University Hospital Orthodontic Clinic and Seirei Hamamatsu Hospital from April 2013 to April 2017 were surveyed. Using photographs taken before insertion of the NAM appliance and immediately before cheiloplasty, the following items were measured ① The nose tip / wings of the nose ratio ② The degree of displacement of columella ③ The affected side / unaffected side ratio ④ The inter-lip separation space. The NAM appliance used was loaded with a retention shaft and a nasal bulb stent attached to the palatal plate, and was retained by well-positioned elastic and tapes from the cheek. The appliance was adjusted every two weeks so that the nasal cavity was pulled upward from the inside, and was used until just before cheiloplasty,.

【Result】① The nose tip / wings of the nose ratio showed improvement from before insertion of NAM appliance until immediately before lip closure surgery in nine cases, and one case showed almost no change. ② The degree of displacement of columella showed improvement in all cases. ③ The affected side / unaffected side ratio of the nose wing showed a tendency to improve in eight cases, with one case almost unchanged and one case getting worse. ④ The inter-lip separation space improved in eight cases but worsened in two cases.

【Discussion】 Our findings suggest that the NAM appliance could be effective in improving nasal morphology based on examination of the symmetry of the nose and other parameters. However, future research including long-term controlled designs is required to confirm these results.

in Japanese

IJ 005
Long term assessment of the effects of occlusal management and oral myofunctional therapy in cleft lip and palate patients.

Junko Nagata
Division of Oral and Maxillofacial Surgery,
Department of Sensory and Motor Organs,
Faculty of Medicine, Miyazaki University
The Advanced Cleft Lip and Cleft Palate Center,
University of Miyazaki Hospital (Japan)

Sometime the determination of the optimal timing and procedure of orthodontic treatment for children with cleft lip and palate is controversial. In our Cleft Lip and Cleft Palate Center, active occlusal treatment is provided for patients with cleft lip and/or palate from primary dentition.

The initial orthodontic treatment to newborn baby is presurgical nasoalveolar molding treatment (PNAM). In our hospital most of the PNAM treatment are started within 1-2 weeks after birth, for patients with cleft lip and palate（CLP）and cleft lip and alveolar（CLA）. The aim of PNAM are to align and approximate the intraoral alveolar segments and to correct the deformed cleft lower lateral cartilage. In addition, we aim to reduce of the alveolar cleft width, and extend of the alveolar crest. After cheiloplasty, the prevention of the tongue intrusion is continued by wearing simple palatal plate made with thermo-plasticity material. This palatal plate support to reduce articulation disorder which is the subsequent serious obstruct in CLP patients. During this time, language hearing therapy in the rehabilitation department, and otolaryngology and pediatric management are continued.

It is reported that 60-80% of CLP patients have crossbite malocclusion, at initial orthodontic visit. It is known that the crossbite malocclusion inhibit the normal maxillary growth and oral functional development. The effects of maxillary protractor are also known to be high at younger age. Therefore, especially in patients with crossbite, we start the orthodontic treatment as fast as possible. In some cases, oral appliance for myofunctional therapy or palatal lift prosthesis (PLP) may be used before or simultaneously with the orthodontic treatment. The most CLP patients have the normal growth of maxilla according to the early improvement of crossbite. In the almost CLP patients have the tendency to retrusive positions of the maxilla and mandible, clockwise rotation of the mandibular plane, and flat soft tissue profile were recognized in our treatment data. In the literature, by the CLP patients of 10-25%, it is necessary to be taken the orthognathic surgery. However, in our treatment results are within less than 2%.

In conclusion, it is suggested that the early stage of active occlusal treatment is caused to more effective normal jaws growth in CLP cases. We also experienced some CLP cases with severe generall complications. Several oral surgeries were accomplished in collaboration with specialists such as pediatrics, pediatric surgery, plastic surgery and anesthesiology. (397words)

in Japanese

IJ 006
Genome Sequence for diagnosis and successive research of genetic disorders.

Koh-ichiro Yoshiura,
Hiroyuki Mishima,
Akira Kinoshita
Department of Human Genetics, Nagasaki University (Japan)

【Background】Technologies of genome sequencing have been progressed recently at a rapid speed. Clinically significant genomic variant(s), especially in single gene defects, could be pointed out even if those disorders are ultra-rare disorders. Of course, it is needless to say that clinical assessment is the most important part for diagnosis.

【Purpose】Our interest is to reveal the genetic variants causing genetic disorder for drug discovery or for revealing the pathogenesis, because the clinical symptoms in genetic disorders give us the significant clues to new concept for the disease-causing gene(s), even if it is an ultra-rare disorder.

【Method】We applied short read sequencing and also are trying to apply long read sequencing to identify disease-causing gene.

【Result】Variant is identified in about one third of cases that skillful clinical expert did not diagnosed. Variants are not found, vice versa, in two thirds of cases with putative single gene disorders. This does not mean that two thirds of cases are not single gene disorders. Variants in gene with unknown function may be overlooked, or complex structural genomic variations may be involved. I will present various our experience in clinical diagnosis process and following research after sequencing.

【Discussion】It is relatively easy to diagnose when the relationship between the gene and special syndrome already, but it is difficult to identify “the” variant that cause the special phenotype, or to obtain full evidence that the variant caused special phenotype. It is important issue what we can do in the undiagnosed cases. I will discuss the matters rising in this genomic medicine era showing our experiences.

in Japanese

IJ 007
Role of formin-mediated actin assembly in mouse cranial neurulation

Hikmawan Wahyu Sulistomo,
Takayuki Nemoto,
and Ryu Takeya
University of Miyazaki (Japan)

【Background】Neurulation requires dynamic reorganization of the actin cytoskeleton. However, how F-actin assembly is regulated in mammalian neurulation remains largely unknown.

【Purpose】We examined the role of formin homology 2 domain–containing 3 (Fhod3), a formin protein that mediates F-actin assembly by regulating actin nucleation and elongation, in cranial neural tube closure in mouse embryos.

【Method】The Fhod3 knockout mice were generated by replacing exon 1 with the β-galactosidase (lacZ) reporter gene; the resultant Fhod3-null embryos (Fhod3lacZ/lacZ) showed defects in neural tube closure. Immunohistochemical and ultrastructural analysis of homozygous Fhod3-null (Fhod3lacZ/lacZ) and control heterozygous Fhod3+/lacZ embryos was performed to clarify the role of Fhod3 during neural development.

【Result】The Fhod3 expression was observed only at the lateral plate of the neural tube and restricted segmentally to rhombomeres 1 to 6 of the hindbrain. Fhod3-mediated actin assembly contributed to lateral plate–specific apical constriction, since the apical accumulation of F-actin and constriction were impaired specifically at the lateral plates in Fhod3-null embryos. In addition, Fhod3-mediated apical constriction at the lateral plate contributed not only to mediolateral bending, to advance tube closure, but also to the anteroposterior bending associated with rhombomere bulging.

【Discussion】The present findings provide direct evidence that a mammalian formin participates in epithelial morphogenesis during the embryonic developmental stage.

in Japanese

IJ 008
Problems and measures of complicated cleft lip and palate treatment

Azusa Watanabe
Saitama Children's Medical Center (Japan)

【Background】The treatment method and timing of repair for cleft lip and palate are often determined by a protocol established to some extent by each institution. However, patients with complications often can't be treated according to the protocol, and it is necessary to decide on a treatment policy for each patient. Many malformations and genetic disorders are known to be combined with cleft lip and palate, and there are several cases in our facility that suffer from treatment. Treatment of cleft palate is performed for the purpose of functional recovery such as feeding and speech. However, depending on the underlying disease, there are cases where their recovery is not able be expected even after be repaired.

In addition, patients with complications often require special intensive care after surgery, and an environment capable of intensive care is essential.

I would like to present the actual cases being treated at Saitama Children's Medical Center and examine the problems.

in Japanese

IJ 009
How to use the latest genetic information and technology in clinical practice?

Haruka Hamanoue
Department of clinical genetics,
Yokohama city University Hospital (Japan)

The knowledge of congenital anomalies has developed remarkably, such as embryology, pharmacology, cytogenetics, molecular genetics, epigenetics and genetic epidemiology.

However, many people do not know the potential, limitations or problems of the technology. Moreover, the genetic information is difficult for the people. It is necessary to support the patient and the family to be able to use those information correctly.

We have performed all kinds of genetic counseling. I'll introduce the contents.

in Japanese

IJ 010
Evaluation of Face2Gene using facial images of patients with congenital dysmorphic syndromes recruited in Japan

Hiroyuki Mishima
Department of Human Genetics,
Nagasaki University Graduate School of Biomedical Sciences,
Nagasaki (Japan)

An increasing number of genetic syndromes present a challenge to clinical geneticists. A deep learning-based diagnosis assistance system, Face2Gene, utilizes the aggregation of "gestalt," comprising data summarizing features of patients' facial images, to suggest candidate syndromes. Because Face2Gene's results may be affected by ethnicity and age at which training facial images were taken, the system performance for patients in Japan is still unclear. Here, we present an evaluation of Face2Gene using the following two patient groups recruited in Japan: Group 1 consisting of 74 patients with 47 congenital dysmorphic syndromes, and Group 2 consisting of 34 patients with Down syndrome. In Group 1, facial recognition failed for 4 of 74 patients, while 13–21 of 70 patients had a diagnosis for which Face2Gene had not been trained. Omitting these 21 patients, for 85.7% (42/49) of the remainder, the correct syndrome was identified within the top 10 suggested list. In Group 2, for the youngest facial images taken for each of the 34 patients, Down syndrome was successfully identified (100%, 34/34) as the highest-ranking condition using images taken from newborns to those aged 25 years. For the oldest facial images taken at ≥20 years in each of 17 applicable patients, Down syndrome was successfully identified as the highest- and second-highest-ranking condition in 82.2% (14/17) and 100% (17/17) of the patients using images taken from 20 to 40 years. These results suggest that Face2Gene in its current format is already useful in suggesting candidate syndromes to clinical geneticists, using patients with congenital dysmorphic syndromes in Japan. Additional cases from Japan, however, should be submitted to Face2Gene to improve its performance.

in Japanese

IJ 011
IGF2 overexpression due to IGF2-DMR0 hypomethylation in Sotos syndrome.

Ken Higashimoto[1)], Hidetaka Watanabe[1)], Noriko Miyake[2)],
Sumiyo Morita[3)], Takuro Horii[3)], Toshiyuki Maeda[4)], Hidenori Hidaka[1)],
Saori Aoki[1)], Hitomi Yatsuki[1)], Nobuhiko Okamoto[5)], Izuho Hatada[3)],
Naomichi Matsumoto[2)], Hidenobu Soejima[1)]
[1)] Division of Molecular Genetics and Epigenetics, Department of Biomolecular Sciences, Faculty of Medicine, Saga University, Saga
[2)] Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama
[3)] Laboratory of Genome Science, Biosignal Genome Resource Center, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi
[4)] Department of Pediatrics, Faculty of Medicine, Saga University, Saga
[5)] Department of Medical Genetics, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi (Japan)

【Background】 Sotos syndrome (SoS) is characterized by overgrowth, distinctive facial features, and various degrees of mental retardation. It is caused by haploinsufficiency of NSD1 gene, located at 5q35, encoding a histone H3 lysine 36 (H3K36) methyltransferase. Beckwith-Wiedemann syndrome (BWS), an another overgrowth syndrome, shares some clinical features with SoS, and caused by dysregulation of imprinting at 11p15. The major cause of imprinting dysregulation is DNA methylation defects at imprinting control regions (ICRs), which are differentially methylated between two parental alleles (differentially methylated regions: DMRs). In addition, the interaction between H3K36 methylation (H3K36me) and DNA methylation are previously reported. These suggest that NSD1 may be implicated in the formation of imprinted DMRs.

【Purpose】 The purpose of this study is to elucidate the molecular mechanism of the relationship between NSD1 and DNA methylation of DMRs, which interprets similar features between SoS and BWS.

【Method】 Methylation analysis with MALDI-TOF MS and bisulfite pyrosequencing, was conducted on 28 imprinted DMRs in 31 SoS patients with NSD1 defects. The function of IGF2-DMR0 for IGF2 promoters was investigated by luciferase assay, ChIP assay for histone modifications, and CRISPR-Cas9 mediated epigenome editing in three cell lines. Impact of transient NSD1 knockdown on epigenetic modifications at IGF2-DMR0 and IGF2 expression was analyzed by bisulfite pyrosequencing, quantitative RT-PCR, and ChIP assay.

【Result】 Six of 28 DMRs were aberrantly hypomethylated in SoS patients. The hypomethylation concentrated on IGF2-DMR0 and IG-DMR. The function of IGF2-DMR0 was an enhancer for IGF2-P0 promoter. In addition, demethylation of IGF2-DMR0 induced by the epigenome editing increased the enhancer activity. NSD1 depletion did not affect IGF2-DMR0 methylation status and IGF2 expression level. However, H3K36me2 at IGF2-DMR0 decreased significantly in all cell lines, while H3K36me3 decreased moderately in cell-type specific manner.

【Discussion】 IGF2 overexpression due to H19-DMR hypermethylation in IGF2/H19 imprinting domain contributes to the overgrowth of BWS. IGF2-DMR0, an another DMRs in the domain, was hypomethylated in a substantial proportion of SoS. Since IGF2-DMR0 functioned as an enhancer for IGF2-P0 promoter and its DNA methylation was essential for IGF2 expression, IGF2-DMR0 hypomethylation in SoS patients may interpret their occasional phenotypic similarity between SoS and BWS. In addition, no effect of NSD1 depletion on both DNA methylation and IGF2 expression suggested a role of NSD1 in IGF2-DMR0 methylation establishment through H3K36me during post-implantation stage.

This work was supported by Grants-in-Aid for Scientific Research.

in Japanese

IJ 012
A survey to primary maternity clinics for editing a manual to study prenatal genetic testing.

Takahiro Yamada[1, 10)], Akihiko Sekizawa[2, 10)], Makoto Kanai[3, 10)],
Kayoko Saito[4, 10)], Osamu Samura[5, 10)], Hideaki Sawai[6, 10)],
Fumio Takada[7, 10)], Mari Urano[4, 10)], Satoko Nakagomi[3, 10)],
Hiroshi Yoshihashi[8, 10)], Shingo Io[1, 10)], Hidehiko Miyake[9, 10)],
Shigehito Yamada[1, 10)], Ikuo Konishi[1, 10)]

[1)] Kyoto University
[2)] Showa University
[3)] Shinshu University
[4)] Tokyo Women's Medical University
[5)] The Jikei University
[6)] Hyogo College of Medicine
[7)] Kitasato University
[8)] Tokyo Metropolitan Children's Medical Center
[9)] Ochanomizu University
[10)] The Project of Health Research on Children, Youth and Families by Ministry of Health, Labour and Welfare (2017-2019) (Japan)

【Background】In an attempt to standardize genetic medicine in primary maternity clinics in Japan, we previously reported the importance of balanced information and genetic counseling (GC) without pressuring them into prenatal diagnosis (PD). To make it possible, the cooperation system of primary clinics and tertiary facilities is indispensable. For the establishment of it, we planned to publish a study manual for primary clinics. As an initial study to know the problems to be solved for providing the information of prenatal genetic testing in primary maternity clinics, we performed questionnaire survey to primary maternity clinics and extracted 8 problems in 2017. Based on the results of the survey, we made a manual of preliminary version in 2018.
【Purpose】The objective of this study was to evaluate the preliminary manual and extract the problems to improve and establish it.
【Methods】A questionnaire was administered to 282 medical professionals at 141 institutions throughout Japan. This study was approved by the institutional review board of Showa University.
【Results】A total of 37.9% (107/282) responded to the questionnaire. 85.0% (91/107) of respondents was medical doctor. 82.2% (88/107) could not spend more than 20 min for the clients of PD. The manual contains 15 questions and answers including guidance for 8 problems (guidelines, ethics, knowledge of clinical genetics, genetic disorders, genetic testing, experience and knowledge of GC, time for GC, referral institution) to be solved for providing the information of prenatal genetic testing in primary maternity clinics. They could solve the problems by the manual respectively (85.2%, 87.3%, 78.3, 85.5%, 93.4%, 77.9%, 65.6%, 86.2%). As free additional comments, some helpful suggestions were obtained, including graphical presentation, simple explanation, organizing seminars etc.
【Discussion】The problems in the management of PD in primary clinics might be highly solved by this manual. However, the response rate was relatively low. Based on these results, the contents of study manual could be improved. Our study group is preparing a combined seminar program of role-play and the lecture series using this manual. The cooperation system of primary clinics and tertiary facilities could be possible by this strategy.

COI: None
Funding: Health and Labour Sciences Research Grants (sukoyaka-ippann-002, 2017)

in Japanese

IJ 013
A novel in vivo role of the schizophrenia-related gene, FILIP

Hideshi Yagi[1)],
Makoto Sato[2, 3)]
[1)] Anatomy and Cell Biology,
Hyogo College of Medicine
[2)] Department of Anatomy and Neuroscience,
Graduate School of Medicine,
Osaka University
[3)] Department of Child Development,
United Graduate School of
Child Development (Japan)

【Background】The pathogenesis of schizophrenia is attracted much attention and have been intensively studied, especially from the point of view of development. We have investigated the in vivo function of the molecule, FILIP that we identified and is reported of which transcript is mutated in schizophrenic patients.

【Purpose】The purpose of this study is to reveal the in vivo role of FILIP.

【Methods】All experiments involving animals were conducted according to the guidelines for animal experiments and approved by the appropriate the animal research committee. We used a conventional gene targeting method to generate a knockout mouse. Phenotypes of the knockout mice were investigated using conventional histological methods including Golgi staining. Further, we used in utero electroporation to analyze the migration of neurons in the developing cortex. We also performed primary culture of neurons derived from the knockout mice.

【Results】We first studied the gross neuroanatomy of the FILIP knockout mice and found no apparent abnormalities. We found broadly distributed excitatory neurons, compared with the control, in the cortex labeled by in utero electroporation at E14.5. We identified a subset of callosal neurons was dislocated in the knockout mice. Further, we found that FILIP was involved in neuronal spine morphology.

【Discussion】Our results indicated that the molecule played a role in brain development and morphological control of neurons. As spine morphology is related to the efficiency of excitatory synaptic transmission, it is possible that the molecule played a role in the pathogenesis of psychiatric diseases including schizophrenia.

【Conflicts of Interest】We declare no conflicts of interest associated with this presentation.

This work was supported in part by the Grant-in-Aid for Scientific Research “JSPS KAKENHI” from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

in Japanese

IJ 014
Perinatal diagnosis and management of skeletal dysplasias

Jun Murotsuki
Department of Maternal and Fetal Medicine,
Tohoku University Graduate School of Medicine,
Miyagi Children's Hospital (Japan)

【Background】Skeletal dysplasias are heterogenous group of genetic disorders characterized by abnormal growth and development of bone and cartilage. Precise prenatal diagnosis skeletal dysplasias using ultrasonography could be very difficult, but differentiation between a lethal and a nonlethal variety is very important in terms of antenatal care and the prediction of fetal outcome. Among these skeletal dysplasias, perinatal form of hypophosphatasia (HPP) is a rare, potentially life-threatening, and systemic metabolic bone disease that can be difficult to recognize in utero and even postnatally.

【Purpose】The objectives of this study are to to review focuses on the role of fetal and neonatal imaging modalities including ultrasound and fetal CT in the differential diagnosis of perinatal HPP from other skeletal dysplasias, and to exam the effect of Asfotase alpha as enzyme replacement therapy on mortality in these type of HPP patients and to reveal the characteristics of the group that can be saved by this enzyme replacement.

【Material and Methods】A total of 328 cases fetal skeletal dysplasias were consulted or registered to the Japan Forum of Fetal Skeletal Dysplasias (JFFSD) from 2007 until 2017, and extract the typical prenatal ultrasonographic and pathologic findings. We analyzed 27 cases of perinatal HPP. The diagnosis of HPP was based on postnatal bone radiographs, and the blood ALP values and the results of the genetic test were also referred.

【Results】Fetal diagnosis included thanatophoric dysplasia (48 cases), achondroplasia (25), osteogenesis imperfect (48), hypophosphatasia (27), spondyloepiphyseal dysplasia congenital (13), short rib dysplasia (8), achondrogenesis (5), and dyssegmental dysplasia (3). In 27 cases of HPP, 20 case were perinatal lethal form and 7 cases were perinatal "benign" form (perinatal mild type) in the conventional classification. We had 10 cases of enzyme replacement therapy with Asfotase alpha after birth, 8 cases of survived and 2 cases died.

【Discussion】The majority cases of skeletal dysplasias are unsuspected and sporadic, usually found on the sign of a shortened femur. The most common skeletal dysplasias have the most accurate diagnosis by ultrasound, and the less common dysplasias are likely to have a specific diagnosis. However, ultrasound interpretation and counseling sometimes focus on outcome as lethal versus non lethal. As a feature of the group which could not survive even by Asfotase alpha, it was confirmed by the bone radiograph that the ossification of the skull was absent and long tubular bones and vertebrae were not substantially ossified. Recent development of enzyme replacement therapy dramatically changes the prognosis of these patients. The group that was considered perinatally lethal was newly divided into two categories, a survival group with Asfotase alpha and a still lethal group. We proposed to call these groups as perinatal moderate type and perinatal severe type, respectively.

in Japanese

IJ 015
Sleep pattern of before and after surgery in infants with cleft lip and palate.

Ryo Murasugi[1)], Hisashi Hosoya[2)], Hitoshi Kawanabe[2)],
Eiko Kuroda[2)], Hiroyuki Kurabeishi[2)], Yasuhiko Hukuya[2)],
Nariyuki Mitachi[4)], Ken Satou[5)], Kazunori Hukui[2)]
[1)]Department of Dentofacial Orthopedics, Ohu University School of Dentistry, Graduate School of Dentistry
[2)]Division of Orthodontics and Dentofacial Orthopedics, Department of Oral Growth and Development, Ohu University School of Dentistry
[3)]Department of plastic and reconstrauctive surgery, Ohtanishinouchi Hospital, Ohta General Hospital Foundation
[4)]Department of Medical Pharmacy, Ohu University School of Dentistry
[5)]School of Computer Science, Tokyo University of Technology (Japan)

【Background】Sleep-disordered breathing (SDB) has been reported as a cause of growth disorder, attention deficit hyperactivity disorder (ADHD), and many other disorders. Early detection of SDB is key to prevent having these type of disorders later on.

【Purpose】It is difficult to perform polysomnography (PSG) in infants. Because infants have difficulty attach the device. We investigated sleep disorders in cleft lips and palate, as well as investigate sleep respiratory state change before and after surgery.

【Method】The subjects were 2 boys and 2 girls with 6 months old with cleft lip and palate, a girl and boy with 1 year old with soft cleft palate, 2 girls with 6 months old without cleft lip and palate as control group.

Using the F-SAS sensor, we compared the sleep states before and after surgery by a simple sleep test. Measurement is immediately before surgery and one month after surgery.

【Result】In 2 control infants without cleft lip and palate, Pre-AHI averaged 0 times / h. On the other hand, in 2 infants with unilateral cleft lip and palate, Pre-AHI averaged 10.5 ± 6.5 times / h, and in 2 infants with soft cleft palate, Pre-AHI averaged 1.9 ± 0.5 times / h. After surgery, in the cleft lip and palate group, Pre-AHI decreased to an average of 4.22 ± 0.22 times / h. In the soft palate cleft group, Pre-AHI in which only 1 case was operated this time decreased slightly from 2.26 times / h to 2.18 times / h.

【Discussion】Pre - AHI is considered by improving nasal cavity / oral mucosa thickening after surgery and lowering resistance of upper respiratory tract. Horibe et al. reported that it may cause sleep disordered breathing after soft palate repair. However , in this study soft cleft palate is thought that nasopharyngeal closure function improved after soft palate repair.

in Japanese

IJ 016
Effect of L-proline on cultured rat embryos

Masaharu Akita[1)],
Atsushi Yokoyama[2)],
Hiroshi Yokoyama[3)]
and Roberto Los[3)]
[1)]Kamakura Women's University
[2)]Life Science Laboratory of Kanagawa
[3)]University of Baltimore (Japan)

【Purpose】We have developed the teratogen test for drug and chemical compound of food by the use of rat whole embryo culture. The advantages of whole embryo culture are to examine the direct effects of the L-proline on rat cultured embryo.

【Method】Rat embryos on day 11.5 of gestation (plug day = 0) were cultured for 48 hours with L-proline. In this whole embryo culture system, rat embryos were explanted on day 11.5 gestation and cultured of rat serum with complex gas (95 % O2 and 5 % CO2) using improved rotator for 48 hours.

【Results and Discussion】The group of treated embryos of L-proline were not exchanged in the heart beats (157 ± 3), the crown-rump length (8.9 ± 0.1 mm), the embryonic protein contents (4,700 ± 44μg) and the embryonic total number of somites (56 ± 0.9). The malformation was not observed in the cultured embryos with L-proline. On the other hand, L-proline (the metabolite of L-arginine) treatment group was not changed in blood flow on the tail of cultured rat embryos.

in Japanese

IJ 017
Dietary folate intake in young women: Comparison between university students in the Department of Nutrition and other departments

Mami Hiraoka[1)], Chiharu Nishijima[2)],
Kaori Sakamoto[3)], Mitsuyo Kageyama[4)],
Yoshiko Kontai[5)], Mayumi Yurimoto[3)],
and Yasuo Kagawa[3)]
[1)] Shukutoku University
[2)] National Institute of Health and Nutrition
[3)] Kagawa Nutrition University
[4)] Yamanashi Gakuin University
[5)] University of Niigata Prefecture (Japan)

【Background】Consuming adequate amounts of folate and folic acid can reduce the risk of neural tube defects. Hence, in Japan, the Ministry of Health, Labour and Welfare has recommended that women of childbearing age and those planning a pregnancy or capable of pregnancy should consume a healthy diet plus 400 μg/day of folic acid from supplements or folic acid-fortified foods up to 3 months before conception until the end of the first trimester of pregnancy (3 months). However, the average folate intake of Japanese childbearing-aged women (15–39 years old) was 228 μg/day, below the Japanese recommended dietary allowance of folate (i.e., 240 μg/day), according to the National Health and Nutrition Survey in Japan in 2017.

【Purpose】To examine the folate intake of young female students and to determine the differences in their knowledge of nutrition.

【Methods】The participants comprised women who were university students, including those in the Department of Nutrition (n=235, 20.1±0.7 years) and in other departments (n=107, 19.6±0.8 years). Of these, the latter had insufficient knowledge of nutrition and folate. Dietary analysis based on a brief-type self-administered diet history questionnaire was completed in 2015–2018. The data show intakes after energy adjustments.

【Results】The dietary intakes of folate (median, range) were 354 (108–1129) μg/day and 325 (114–649) μg/day in the nutrition students and others, respectively. There was a significant difference between these students ($p<0.05$). The intake of "green leafy vegetables," which are rich in folate, was higher in nutrition students (121 g) than in other students (93 g). The percentages of supplement users who took supplements at least once a week were 15.0% in the nutrition students and 20.6% in the other students.

【Conclusion】Our results suggest that nutritional knowledge including that of folate is required to increase folate intake. It is necessary to consider how to provide accurate information about folic acid.

This work was supported by AMED under Grant Number 18gk0110023h0003.

in Japanese

IJ 018
Diagnosis and treatment of craniosynostosis - Current status and problems -

Takuya Akai[1)],
Masanobu Yamashita[2)],
Satoshi Kuroda[1)]
[1)]Department of Neurosurgery, Toyama University
[2)]Department of Plastic and Reconstructive surgery,
Kanazawa Medcal Unievrsity (Japan)

【Background】Craniosynostosis with early closure of skull sutures is categorized either as simple or as syndromic if present with congenital anomalies such as syndactyly, midface hypoplasia, syndactyly, joint contracture and big toes. Some children have a single affected suture, and some have multiple affected sutures. Skull shape varies depending on the affected sutures, and the treatment needs to be done in the period of skull growth, which depends on age and skull shape. New less invasive treatment methods such as distraction osteogenesis and endoscopic suturectomy combined with molding helmets has been developed, but unsolved problems continue to be present.

【Purpose】In this study, we discuss chronological changes in treatment methods, current status and problems, treatment algorithms, and genetic study, with personal experience and literature review.

【Results】1) Chronological changes in treatment methods: Affected suturectomy and bandage is a basic procedure for infant with scaphocephaly. Recently, molding helmet is indicated instead of bandage. Conventional cranioplasty has been done for the skull expansion, but recently distraction osteogenesis has been introduced because of less invasiveness, easiness, little chance of back tracking and wound trouble. Distraction method has been done for fronto-orbital advancement and lateral expansion. Recently this method has been done for the occipital expansion to get larger expansion for syndromic patients. 2) Problems: 1. Mental prognosis: We can resolve the elevated intracranial pressure (ICP) condition by the operation, but it is not obscure whether the operations can save the patients mental condition. 2. Timing of operation: To do the suturectomy, the operation should be performed for infant. But, in Japan, the timing of diagnosis is still late. Early operation can support normal brain growth, on the other hand, it increase chance of re-operation. 3. Frontal ridge: The indication of cranioplasty for frontal ridge is not clear. 3) Genetic study: We studied 48 children and found 15 mutations. In syndromic group, all children had mutation in FGFR or TWIST gene, on the other hand, no child showed mutation in non-syndromic group. In some children, same genotype resulted in different phenotype.

【Discussion】1) We have to choose the best treatment method depend on age, skull shape and association of ICP elevation. 2) Genotype is the important factor to decide the phenotype, but it cannot explain everything. 3) If we can find out why some specific sutures will be affected, we might be prevent this disease.

【Key words】craniosynostosis, operation, genetic mutation

391 < 400 words

in Japanese

IJ 019
Pioneer's message: A senior sending a message to junior.

Ryozo Hashimoto
Kariya Toyota General Hospital Takahama
Branch Medical Checkup Center (Japan)

In autumn 2018, I received a mail informing the death of Professor Kameyama. It is possible, I believe, such words that would be difficult for some people who knew him for a long time. Therefore, I would like to convey some words I heard from Professor Kameyama to young researchers attending this meeting who encountered difficulties in their works.

I first met Professor Kameyama at the Research Institute of Environmental Medicine at Nagoya University when I entered the university's Graduate School of Medicine. I had studied congenital anomalies especially in the field of digestive systems (,e.g., Ryozo Hashimoto, Sen-ichi Oda, Minoru Inouye, Hideki Yamamura. "The pathogenesis oh anorectal malformation induced by all-trans retinoic acid in mice". Congenit Anom., 32: 132-142, 1993).

After that I was away from research for a while. In those difficult times for me to continue studying; whether or not I should quit studying had soon become something that I quite obviously should have thought about. During that time, Professor Kameyama sometimes told me his opinion, it was a deeply kind aphorism for me. His advice was: Principally you should choose a theme that nobody studies, continue to work hard until you make it as your original paper; then you will find that you don't mind being alone, and moreover, to dare to tread a thorny path. There will be people somewhere in the world who will read your paper and understand your work correctly, and so on, which seemed to be like a maxim generally but for me was a kategorischer Imperativ ("categorical imperative" in English) in those days.

These words consequently brought me "serendipity".

I fortunately happened to observe the developing paramesonephric duct when I studied the development of the human anorectum at the Congenital Anomaly Research Center Kyoto University Graduate School of Medicine through the kindness the kindness of Professor Shiota. The citation of the article at that time is RYOZO Hashimoto. "Development of the human Müllerian duct in the sexually undifferentiated stage". Anat Rec A Discov Mol Cell Evol Biol., 272A:514-519, 2003), which can be viewed online through Wikipedia.

in Japanese

IJ 020
Neural Tube Defects are folic acid preventable: How many of such pregnancies have been terminated?

Atsuo Kondo[1)], Takuya Matsuo[2)], Nobuhito Morota[3)],
Katsuhiko Tada[4)], Akito Miyauchi[5)], Shunsuke Ichi[6)]
[1)]Department of Urology, Atsuta Rehabilitation Hospital, Nagoya,
[2)]Department of Anatomy, Kindai University Hospital, Osaka Sayama
[3)]Department of Neurosurgery, Kitasato University School of Medicine, Sagamihara
[4)]Department of Obstetricians and Gynecologists, Okayama Medical Center, Okayama
[5)]Department of Obstetricians and Gynecologists, Japanese Red Cross Medical Center, Tokyo
[6)]Department of Neurosurgery, Japanese Red Cross Medical Center, Tokyo (Japan)

【Background and Aims】The Japan Association of Obstetricians and Gynecologists (JAOG) has reported the prevalence of neural tube defects (myelomeningocele, anencephaly) without showing the number of those terminated over the past 40 years. Aims of our study were to evaluate a total number of neural tube defects including those delivered or terminated, to clarify a proportion of those terminated, and to internationally compare the prevalence among 7 developed countries, i.e., Canada, USA, Italy, Germany, France, UK, and Japan,.

【Methods】A questionnaire was sent to more than 1,000 hospitals asking to report live births (LB), stillbirths (SB), live births and still births with myelomeningocele or anencephaly, and termination of pregnancy (ToP) due to myelomeningocele or anencephaly prior to 22 weeks of the gestation which took place in 2014 and 2015. Two hundred sixty-two replies were collected and analyzed.

【Results】Based on >156,000 deliveries per year obtained from 262 hospitals, we identified that a rate of total neural tube defects (ToP +LB +SB) was 8.29 per 10,000 deliveries for the year 2014 and was 8.72 for 2015, which were 1.5 and 1.6 times higher than the respective values (LB + SB) reported by JAOG. It is also observed that a ratio of the total number of myelomeningocele to that of anencephaly was approximately 1.0: 1.2, that a half of pregnancies afflicted with neural tube defects were terminated, and that a proportion of ToP due to myelomeningocele and due to anencephaly was 20 % and 80 %, respectively. Internationally, the real prevalence of neural tube defects in Japan was comparatively high, ranking 5th among 7 developed countries, and the proportion of ToP ranged between the North American countries and the European countries.

【Discussion】Our study has identified the real prevalence of total neural tube defects for the first time which was approximately 1.5 times higher than that (LB + SB) reported by JAOG. Furthermore, a half of pregnancies afflicted with the anomalies have been terminated, where 80 % of them suffered from anencephaly and 20 % myelomeningocele. In conclusion, the real prevalence of NTDs was 1.5 times higher than that currently reported by JAOG.

in Japanese

IJ 021
Influences of biotin on fetal development in mice.

Hiromi Sawamura[1, 2],
Toshiaki Watanabe[2, 3]
[1] School of Human Science and Environment,
University of Hyogo
[2] Research Institute for Food and Nutrition Sciences,
University of Hyogo
[3] Department of Health and Nutrition, Faculty of Health Science,
Osaka Aoyama University (Japan)

【Background】Vitamins are essential for growth and development. Biotin is a water-soluble vitamin that is classified as a B-group vitamin. Numerous studies have demonstrated that biotin is essential for reproduction and embryonic development in mammals. Additionally, it has recently been reported that decreased urinary excretion of biotin in the late stage of gestation is observed even in normal pregnancy, suggesting that pregnant women develop mild biotin deficiency. However, the relationship between biotin and fetal development is not well known.

【Purpose】To clarify the role of biotin in palatal formation, we investigated the effects of biotin deficiency on the development of palatal processes in fetuses.

【Method】Nulliparous female ICR mice were mated with healthy males for a short mating period in the morning. Pregnant females were randomly divided into two groups: a biotin-deficient group fed a biotin-deficient diet and a control group fed a biotin-supplemented diet (biotin-deficient diet supplemented with 5 mg of biotin/kg). These mice had ad libitum access to the diets and distilled water for 15 days in early pregnancy.

【Result】The incidence of cleft palate among fetuses in the biotin-deficient group was 97.4%. In biotin-deficient mice, the total biotin concentration was significantly reduced in the maternal serum (22% of control), liver (59%), placenta (16%), fetal liver (3%) and palatal process (10%) as compared with the control group.

【Discussion】We confirmed that maternal biotin deficiency in mice induced a high incidence of cleft palate in fetuses at midgestation. Analyses of epigenetic regulation, including histone biotinylation, in fetuses of biotin deficient mice are currently under way.

I have no financial relationships to disclose. This work was supported by JSPS KAKENHI Grant Number JP17K12906.

in Japanese

IJ 022
Two patients with Au-Kline syndrome

Nobuhiko Okamoto
Department of Medical Genetics,
Osaka Women's and Children's Hospital (Japan)

【Background】Au-Kline Syndrome (AKS: OMIM#616580) is a new syndrome due to loss-of-function variants in the heterogeneous nuclear ribonucleoprotein K gene (HNRNPK). HNRNPK belongs to the subfamily of ubiquitously expressed heterogeneous nuclear ribonucleoproteins (hnRNPs). The hnRNPs bind RNAs and complex with hnRNA. The hnRNPs are associeiated with pre-mRNAs in the nucleus and seem to influence pre-mRNA processing. AKS is characterized by intellectual disability (ID), distinctive facial dysmorphism and multiple anomalies. Abnormal pre-mRNA processing it the basic nature of AKS. Differential diagnosis of AKS include Kabuki syndrome (KS).

【Purpose】We will present two patients with AKS.

(Patient 1) The 4-year-old male was the first child of healthy and non-consanguineous Japanese parents. He had a cleft palate, an omphalocele, bilateral hydronephrosis, right congenital hip dislocation, and bilateral clubfeet. Physical examination revealed dysmorphic features including a flat occipital bone, metopic suture ridging, arched eyebrows, epicanthal folds, long simple ears, a flat nasal bridge, a long philtrum, a longitudinal groove in the tongue, and open mouth He showed severe ID. Brain MRI showed cerebral atrophy.

(Patient 2) The 7-year-old female had a congenital cardiac anomaly. Her development was mildly delayed. Physical examination revealed dysmorphic features indluding a scaphocephaly, metopic suture ridging, arched eyebrows, epicanthal folds, long simple ears, a flat nasal bridge, a longitudinal groove in the tongue, and open mouth. Saggital craniosynostosis was revealed by CT scan.

【Methods】After obtaining informed consents based on a permission approved by the institution's ethical committee, peripheral blood samples were obtained. We sequenced all coding exons and exon-intron boundaries of HNRNPK

【Result】A novel splicing variant (c.1361+1G>A) of HNRNPK was found in patient 1. Patient 2 had a novel missense variant p. (Lys219Arg).

【Discussion】Patients win AKS have characteristic facial features, skeletal and connective tissue anomalies, craniosynostosis, congenital heart malformations, and renal anomalies. The inital diagnosis of the patient 1 was Okamoto syndrome (OS). OS is also characterized by severe ID, generalized hypotonia, stenosis, of the ureteropelvic junction with hydronephrosis, cardiac anomalies and characrteristic facial features. We noticed that he had features overlapping with AKS. We suggeat that OS is identical to AKS. There is considerable overlap between AKS and Kabuki syndrome (KS), our patients demonstrate that AKS does have a distinct facial gestalt and phenotype that can be differentiated from KS. Further studies are necessary to establish better management protocol for AKS patients.

in Japanese

IJ 023
Role of clinical genetics in a medical healthcare facility for children with disabilities

Seiji Mizuno
Dept of Pediatrics / Clinical Genetics,
Aichi Developmental Disability Center Central Hospita (Japan)

"Ryoiku" is a unique term in Japanese with a meaning including rehabilitation, education, medical care, and mutual support among patients. In Japan, there are approximately 100 such medical Ryoiku out-patient facilities. Most patients are children with intellectual disabilities, motor dysfunction, autism spectrum disorder, and so on. Moreover, many of these are diseases or disorders with a genetic background.

The clinical application of comprehensive gene analysis by next generation sequencing has revealed nearly half of the genetic pathogeneses of intellectual developmental disorders and epileptic encephalopathy in the recent years. In 2015, a nationwide comprehensive gene analysis project to identify rare and undiagnosed diseases was launched. Since then the number of children attending the Ryoiku hospital and clinics who registered for the project are increasing. At present, the genetic cause of these disorders has been identified in 40% of registered patients.

Clarifying the genetic cause of the intellectual disability and autism g confers a direct benefit to the patients. For example, it enables individual medical management such as early diagnosis of complications, planned health management, drug selection, accurate prediction of morbidity, development of therapeutic agents by elucidation of the pathological mechanism, and peer support among patients with the same disease. In order to obtain these benefits, mutual matching and information sharing among groups of patients, doctors, and researchers is necessary. Furthermore, it is desirable to create an online database for the same. Human resource development related to genetic medicine is also desirable.

In this presentation, the speaker will introduce the practice of genetic medicine in medical facilities for children with disabilities.

in Japanese

IJ 024
Heparanase during palate formation in mice

Azumi Hirata and Yoichi Kondo
Department of Anatomy and Cell Biology,
Osaka Medical College, Takatsuki (Japan)

【Background and Purpose】Palatogenesis is directed by epithelial-mesenchymal interactions, in which many factors may work in concert spatially and temporally. After adhesion of the bilateral palatal shelves in the midline, complete palatal fusion requires the formation and subsequent disappearance of the medial epithelial seam (MES), as a result of the extracellular matrix (ECM) remodeling. Here, we assessed the distribution of the ECM components within the basement membrane of the MES and heparanase, which cleaves the heparan sulfate (HS) chains in perlecan, in developing mouse palate to determine whether heparanase might function in palate formation.

【Materials and Methods】Embryos recovered from timed pregnant C57BL/6By mice were used. We examined the immunolocalization of heparanase during secondary palate formation in mice. We also examined immunohistochemically the distribution of the ECM components, perlecan, laminin, type IV collagen, and HS, within the basement membrane of the MES in fusing palatal shelves.

【Results】In the palatal shelves in the vertical position, heparanase was not observed in the palatal shelves. When the palatal shelves were oriented horizontally, heparanase localized to the epithelial cells of these shelves. When the palatal bilateral shelves first made contact, the heparanase localized to epithelial cells at the nasal side of shelves. In contrast, HS immunoreactivity was faint in the basement membrane located nearby the tip of shelves. Later in fusing palatal shelves, the cells of the MES were labeled with intense heparanase immunoreactivity. In contrast, the basement membrane was scarcely observed in the palatal shelves, perlecan labeling was sparse in the basement membrane of the MES, on which laminin and type IV collagen were observed. As palatogenesis was complete, heparanase localization was observed in the basal cells of oral and nasal epithelium of the palate. Osteoblasts on the palatal and maxillary bone surface also had heparanase immunoreactivity.

【Summary】Our findings indicated that heparanase is involved in development of palate because it mediated degradation of the ECM of palatal shelves. Heparanase may participate in the regression of MES during palate formation. (328/400 words)

COI: No potential conflict of interest is disclosed.

This work was supported in part by Grants-in-Aid for Scientific Research (Nos. 24592996, 16K11772, and 16K11773).

General Oral Presentations

O 001

Functional and aesthetic outcome in cleft nose repair

Siegmar Reinert, Michael Krimmel
University Hospital Tubingen (Germany)

【Background】 The repair of nasal deformities in cleft patients remains most challenging. The complexity of nasal deformities is caused in part by the inborn deformity and in part by prior surgical corrections. Nasal deformities in unilateral and bilateral CLP patients are typical.

【Method】 From 2002 to 2018 more than 450 cleft nose repairs were performed, 390 complete septorhinoplasties in the age of skeletal maturity, more than 60 corrections in childhood and adolescence due to severe functional or aesthetic problems and columella lengthening procedures.

For final correction open approach is the standard procedure. The septum is addressed through an interdomal approach. Septal cartilage is resected as necessary, spreader grafts are often used to preserve septal straightening, the severely deformed septum can be completely removed with ex vivo creation and replacement of an L-strut. Next the dorsum is addressed by rasping or osteotomy. Four years ago we changed the regime from internal to external osteotomies. If needed radix augmentation is achieved with cartilage (diced cartilage or diced cartilage in fascia). The correction of the nasal tip includes creating a sufficient projection using septal extension grafts with septal or rib cartilage, creation of a symmetrical platform using existing lower lateral cartilages and augmenting with cartilage grafts.

For outcome rating a morphometric analyses and a rating by a neutral jury was performed.

【Result and Discussions】 All patients with compromised nasal ventilation reported about improvement of nasal ventilation after surgery. In a follow up investigation 88 % of the patients were satisfied with the aesthetic outcome. A neutral jury rated the preoperative situation as aesthetic good, in 9%, in 91 % as aesthetic bad, the postoperative result was rate das good in 85 % and in 15 % as bad.

Morphometric measurements demonstrated a significant improvement in all parameters, however remaining asymmetries were still seen depending on the degree of the initial deformity.

Complete analysis of the nasal functional and aesthetic deformity as well as analysis of the facial pathology (position of the maxilla and alar base, lip length and symmetry) are the key to for successful management of the cleft nasal deformity.
A number of techniques have been suggested for cleft nose repair, which indicates that there is no ideal procedure. New techniques e.g. diced cartilage in fascia improve results and can be advocated. The patient should be informed that in severe cases a secondary surgical procdure can be mandatory to achieve a good result.

【References】

[1] Bull T R (2001) Percutaneous osteotomy in rhinoplasty. Plast Reconstr Surg 107: 1624-1625
[2] Daniel R K (2008) Diced Cartilage Grafts in Rhinoplasty Surgery: Current Techniques and Applications. Past Reconstr Surg 122: 1883-1891
[3] Hoehne J, Gubisch W, Kreutzer C, Haack S (2016) Refining the Nasal Dorsum with Free Diced Cartilage. Fac Plast Surg 32: 345-350
[4] Rohrich R J, Ahmad J (2017) Secondary Rhinoplasty by the Global Masters. Vol I and II CRC Press, Boca Raton

O **002**

THE APPLICATION OF 3D IMPRESSION IN THE PRESURGICAL ORTHOPEDICS IN BILATERAL CLEFT LIP

Solaetxe Prieto N., Tuduri Limousin I.,
García Fernandez R., Valdivieso Castro M.,
Cardenal Alonso-Allende T,
Álvarez Martínez L. Pediatric Plastic Surgery
Cruces University Hospital.Bilbao (Spain)

【Objective】 to show an innovative and effective way of improving the results in bilateral cleft lip utilizing the newest 3D impression tools

【Material and Methods】 A nasal elevator model for presurgical orthopedics in bilateral cleft lips have been created using high-accuracy 3D printing technology.

The used tools have been the followings:

- Stereolithography (SLA)
- System: Formlabs 2
- Material: Dental SG resin, a special material with extended use in Maxillofacial area, as it creates biocompatible surgical models.

We apply it along with lip taping (Dynacleft) and an ortorthodontic plate.
Iconography will be provided.

【Results】 comparing with the traditional method, greater accuracy is reached as the exerted traction force is more uniform and constant. It adapts better to the child´s physiognomy with the possibility of being modified as the patient grows.

Otherwise, it is more comfortable as parents and professionals does not have to lose time in realigning the device.

In the spare of economic cost, we have seen that the new device is cheaper than the conventional one.

Conclusions: it is a more precise, cheaper and comfortable way of managing bilateral celft lip presurgical orthopedics.

O 003

Evaluation of velopharyngeal complex in children after veloplasty.

Iakovenko Ludmila, Shafeta Oleg
Bogomolets National Medical University (Ukraine)

【Background】 The velopharyngeal complex (VPC) is a multifunctional system whose indicators are important for the determination of surgical tactics and its evaluation in children with cleft palate (CP).

【Method】 MRI of 93 children without CP, 15 - with CP, after veloplasty in age from 5 to 18 years.

【Result and Discussions】 The most significant indicators of the VPC and their correlation with soft palatal muscles are determined (tab.1). In children with CP after veloplasty (the clinic technique) VPC indicators up to 6 years are in line with the norm, from 7 to 18 years a decrease in the length of soft palate (6.9 ± 4.2 mm), increase of the width (5.3 ± 2.4 mm) and a depth of mesopharyngs (4.3 ± 1.9 mm), the distance to the posterior wall of the pharynx (3.6 ± 0.9 mm) are observed. For the planning of veloplasty, it's required to determine the length of the soft palate (VL), width (PhW), depth (PhD), height (PhH), distance to the posterior wall of the pharynx (VPR) and the size of soft palatal muscles (LVP, VID, TVP) for their reconstruction. Changing the indicators of the VPC may indicate development of velopharyngeal insufficiency and need for active loading of soft palate muscles.

O 004

Vomer morphometric parameters in norm and in children with bilateral complete cleft lip and palate.

L. Iakovenko[1)], O. Shafeta[1)],
S. Rebenkov[2)], N. Kiselyova[1)]
[1)]Oral and Maxillofacial Surgery of Childhood Department, Bogomolets National Medical University
[2)]Children Hospital №7 (Ukraine)

【Background】 Premaxillary and vomer morphometric parameters of the length, thickness and density are determined with age-related changes in normal and bilateral cleft lip and palate (BCLP).

【Method】 A retrospective analysis of premaxillary and vomer morphometric parameters was performed according to CT data in 20 children with BCLP aged from 6 days to 8 years and 114 children from 6 days to 14 years are normal.

【Results】 Vomer growth occurs in length up to 1 year by 24% in the norm most actively. Growth spurt were noted at 5 and 7 years, accordingly to 13% and 20%. Growth activity falls by age 8 to 8% per year and slow down by age 14. Vomer thickens most actively up to 2 years. Vomer density has increased along its entire length in 2 from 1 month to 3 years, wherein from birth to 6 months - by 6%, up to 1 year - by 19%. The density jump occurs from 1 to 2 years by 56%. Density peak is observed at 3 years with slow induration by age 8 ($p<0,05$). Vomer density holds steady along its entire length from 8 to 14 years. Vomer middle part is the most dense HU2= 742±120 mg/cm3 ($p<0,05$) in all age groups in normal. Correlations were founded between density and vomer length, more in its caudal part (0,888, $p<0,01$).

The child with BCLP was born with protrusion, where vomer and premaxillary total length is 1,6 as large than normal ($p<0,001$). Vomer growth is slow, premaxillary process manifests itself more actively up to 1 year, increasing by 33%. Vomer growth stabilization is noted from 1 to 4 years, after 4 to 8 years regrowth. Vomer thickness in children with BCLP is in1,6 as large by age 1 and after a year in 2,3 as large compared to normal ($p<0,001$). Vomer density is 3 as large in children with BCLP than normal, at every of the age groups and at each points of definition ($p\leq0,001$). Indicator values rising was identified from the point HU1= 952±120 mg/cm3 to point HU3= 1168±187 mg/cm3 ($p<0,001$).

【Discussion】 The tendency of the order of vomer growth and increase its density is determined as a result of vomer morphometric parameters research normally. This tendency was not observed in children with BCLP. Vomer density is increases in the proximal-distal direction in children with BCLP, the caudal part is densest.

O 005

Long-term outcomes of primary palate surgery-one surgeon's experience

Ana Tache, MD, DMD,
Prof. Maurice Y. Mommaerts, MD, DMD, PhD,
European Face Centre,
Brussels University Hospital (Belgium)

【Background】 The treatment of children born with a cleft lip, alveolus and/or palate requires long-term dedication and involvement of both parents and surgeon. The success of primary cleft is measured by the achievement of intelligible and socially acceptable speech. Speech outcomes have improved significantly with the evolution of the palatoplasty techniques, emphasis on a proper muscle repair and speech therapy. Over the years has been great debate about the protocol and technique used: one-stage or two stage and need for secondary surgery to correct the VPI. The literature review that we conducted shows an overall rate of secondary pharyngeal surgery between 2.1%-63.4% with a mean of 12.7%. The highest velopharyngeal surgery rate was registered after modified Von Langenbeck/ Wardill closing of the palate (35.9% -63.4%) and the lowest surgery rate after Furlow palatoplasty (0%-20%).

【Method】 All patients who underwent primary cleft repair between 1990-2018 by the same surgeon were identified using our computerized data system. The setting was represented by two university centers in Belgium: AZ Sint Jan, Bruges and UZ Brussels. All potential cases were screened through a review of medical records to ensure that the information of each patient was accurate. The following parameters were collected: age, gender, timing of the primary cleft surgery, procedures performed, need of secondary surgery to correct the velopharyngeal incompetence.

【Results】 Out of 168 patients included in the study, 5 (2.9%) required a second surgery in order to correct the velopharyngeal insufficiency. Two of the patients were Veau II and three were Veau III.

【Discussion】 In the literature timing and technique of the primary cleft surgery have been a debated subject. We managed to achieve more than satisfactory results (2.9%) regarding frequency of velopharyngeal insufficiency using a standardized protocol and a two-stage protocol of the palate.

1. Yuan N, Dorafshar AH, Follmar KE, Pendleton C, Ferguson K. Effects of Cleft Width and Veau Type on Incidence of Palatal Fistula and Velopharyngeal Insufficiency After Cleft Palate Repair Annals of Plastic Surgery. 2016.76(4):406-410
2. Jackson O, Stransky C et al. he Children's Hospital of Philadelphia modification of the Furlow double-opposing Z-palatoplasty: 30-year experience and long-term speech outcomes. Plastic and Reconstructive Surgery J. 2013.132(3):613-622
3. Tang JA, Salapatas AM, Bonzelaar LB, Friedman M. Long-Term Incidence of Velopharyngeal Insufficiency and Other Sequelae following uvulopalatopharyngoplasty. Otolaryngol Head Neck Surg. 2017 Apr;156(4):606-610
4. Ruda JM, Krakovitz P, Rose AS. A review of the evaluation and management of velopharyngeal insufficiency in children. Otolaryngol Clin North Am. 2012 Jun;45(3):653-69

O 006

Global Evaluation of Surgical Techniques and Results of Bilateral Cleft Lip Repairs

Angela S. Volk, MD[1)],
Robert F. Dempsey, MD[1)],
Mohamad Masoumy, MD[1)],
Larry H. Hollier, Jr., MD[1, 2)],
Edward P. Buchanan, MD[1)]
[1)]Division of Plastic Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX
[2)]Smile Train, Houston, TX (USA)

【Background】 Smile Train, an international cleft charity, supports comprehensive cleft treatment in 85+ countries around the world by empowering local medical professionals to treat patients in their own communities. As there is no universally accepted cleft lip repair technique or system to evaluate outcomes, Smile Train has developed lip grading criteria to ensure that optimal results are achieved following cleft surgery. The aim of this study is to evaluate aesthetic outcomes of bilateral cleft lip repair operations based on the surgical technique used implementing Smile Train's lip grading criteria.
【Methods】 Experienced plastic and reconstructive surgeon reviewers perform lip grading from pre- and post-operative frontal photographs. A score is assigned based on the severity of the pre-operative defect (grade 1-5) and the final post-operative result (grade 1-5), where 5 is the highest severity and optimal outcome, respectively. Values are multiplied, producing a composite grade. Acceptable results include a composite grade of ≥ "3" for a pre-operative grade of "1" and composite grade of ≥ "6" for pre-operative grades "2-5".

A retrospective review identified bilateral cleft lip repair cases performed by Smile Train's partnering surgeons in Africa, the Americas, Asia Pacific, Europe, and the Middle East, between 2014 and 2018. Cleft symmetry and involvement of the alveolus and/or palate were recorded. Surgical techniques included the straight-line repair, forked flap, Mulliken, and 2-stage repair. Using the lip grading criteria, acceptable outcomes were identified and compared with the surgical technique used.
【Results and Discussions】 1,536 cases were reviewed: straight-line (775 cases), forked flap (507 cases), Mulliken (184 cases), and 2-stage repair (70 cases). Overall, the forked flap produced the most acceptable outcomes (92.5%), followed by the Mulliken (89.1%), straight-line (88.8%), and the 2-stage repair (74.3%) ($p < 0.001$). The forked flap again produced the most acceptable outcomes for symmetric complete clefts (93.8%), and asymmetric complete cleft cases (100%) ($p < 0.05$). The Mulliken repair produced the most acceptable outcomes for symmetric incomplete clefts (87%), however, results were not statistically significant ($p > 0.05$).

Smile Train surgeons maintain high rates of successful surgical outcomes, regardless of the technique used. The forked flap was commonly performed and produced a high rate of acceptable outcomes, especially for the more common symmetric complete clefts. Results of our study will help to better inform Smile Train training programs for partner surgeons around the world.

O 007

A Model Demonstrating an International Cleft Charity's Work in Eliminating the Backlog of Unrepaired Cleft Lip Cases

Angela S. Volk, MD[1)],
Nguyễn Trí Dũng, MBA[2)],
Larry H. Hollier Jr, MD[1, 3)]
[1)]Division of Plastic Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX
[2)]Smile Train, Ho Chi Minh City, Vietnam
[3)]Smile Train, Houston, TX (USA)

【Background】 Cleft lip (CL) is a common congenital anomaly with a high incidence within low- and middle-income countries (LMIC). Unrepaired clefts may cause psychosocial distress and a risk of lifelong neglect and poverty with surgical repair recommended within the first year of life. Various barriers prevent children in LMICs from receiving treatment contributing to the backlog of unrepaired CL cases. Smile Train, an international children's charity, provides safe, high-quality cleft care throughout the world by partnering with local healthcare systems. The aim of this study was to create a model demonstrating the backlog of unrepaired CL cases in Myanmar to enhance Smile Train's work in eradicating this surgical disease.
【Methods】 A model was created using data from Smile Train's program in Myanmar since its establishment in 2013 through 2018. Data regarding all cleft lip repair operations performed by Smile Train was retrieved. Patients were classified by presentation as "early", ≤ 1 year of age, or "late", > 1 year of age, and the percentages of early surgical repairs

within our sample were calculated. Using statistical inferences, this ratio was extrapolated to represent the entire population allowing further calculations to estimate surgeries performed by other organizations, the incidence of new cleft cases, and the surgical backlog.

【Results and Discussion】 The model was created from a total of 4,161 CL repair operations performed by Smile Train partnering surgeons in Myanmar. In 2013, nearly 80% of unrepaired CL cases were in patients older than 1 year of age. By 2018, Smile Train performed 970 CL surgeries (487 in children ≤ 1 year of age; 483 in those > 1 year of age) correlating to 68% coverage of the unmet need. The model estimates that by 2021, over 74% of CL cases will be attributed to new births. Thus, there will be significant elimination of the backlog in those > 1 year of age, and over 75% of all CL cases will be surgically corrected.

This novel model estimates the backlog of unrepaired CL cases in Myanmar using real surgical data from the largest international cleft charity. By predicting the number of new CL cases and the surgical backlog, real surgical repair data allows us to predict the future unmet need. These estimates will help Smile Train develop strategies to further support cleft care in eradication of the surgical backlog.

O 008

Result of organization in-country mission for last 15 years in Uzbekistan.

Murod M. Jafarov, MD, PhD,
Mirjamol M. Jafarov, MD,
Timur Radjamatov MD,
Aziz Boykuvvatov, MD
Clinic of Tashkent pediatric medical
Institute (Uzbekistan)

【Background】 From 2003 to the present, 52 missions have been organized in Uzbekistan to treat the cleft lip and palate. If in the period 2003 - 2012 the majority of the action was carried out jointly with foreign medical teams, then since 2012 the number of participation of local doctors in this action has increased. Uzbek doctors began to independently carry out missions in the regions on the basis of the acquired experience of joint work with foreign surgeons.

【Method】 During the period 2003 - 2018, 52 shares were held, on average, it was 3-4 shares per year. This period can be divided into two phases, the first one, jointly with foreign specialists (Korea, Turkey, Singapore, Malaysia, the Philippines) and the second, more local doctors. The experiences of surgeons were from 3 to 20 years, most were young.

【Result】 Over the past period, more than 6,000 children with various congenital disorders of the face and limbs were examined. The first day was the examination and selection of patients for surgery, a pediatrician and an intensivist examined the selected patients, tests were checked and then the sick child was hospitalized. 3 hours before the operation, the patient stopped taking any food; all operations were performed under general anesthesia using sevoflurane. All surgical interventions were without complications. During the chelioplasty operation, the Millard method and its modification were used; in the case of palatoplasty, the two or three-patch method was used, as well as the Furlov method.

【Discussion】 What are the positive points that were obtained when conducting the mission data?

Firstly, the quality of previous operations in the regions required their significant improvement, for example, palatoplasty in children was carried out in late periods, at 7–8 years old, and the wound was sutured with non-absorbable suture materials, which were removed for 10–14 days. The field operations conducted a master class helped to change the approach to these operations, after many years of training today, the operation of palatoplasty is carried out in 2–3 years.
Secondly, local doctors learned the tactics of the operation according to Millard and the postoperative management of patients. Most doctors refused the old methods of surgery, such as closing with buttons.

Thirdly, low-income families did not need to go to the capital to undergo chelioplasty or palatoplasty; the doctors would periodically go to the places where the patients live.
After many years of participation in the work together with foreign specialists, local Uzbek doctors began to widely carry out actions like foreign missions. One of the problems with these promotions was the lack or absence of consumables and mobile anesthetic devices.

O 009

Orthodontic Management of a Pre-pubertal Patient with Schwartz-Jampel Syndrome (SJS) to Alleviate Severe Obstructive Sleep Apnea (OSA)

Thanate Assawakawintip, Siew Peng Neoh,
Supatchai Boonpratham, Rochaya Chintavalakorn,
Nuntinee Nanthavanich, Yodhathai Satravaha,
Supakit Peanchitlertkajorn
Orthodontic Department, Faculty of Dentistry,
Mahidol University (Thailand)

【Background】 Schwartz-Jampel syndrome (SJS) is an extremely rare autosomal recessive genetic disorder characterized by multiple skeletal deformity, short stature, and generalized myotonia. The prevalence is less than 1:1,000,000 and only 150 cases have been reported in the literature. The etiology is mutation of heparinsulfate proteoglycan 2(HSPG2) gene which encodes Perlecan, a proteoglycan protein found in muscle and cartilage. Perlecan dysfunction or deficiency can cause: 1) disruption of acetylcholinesterase synthesis causing acetylcholine abundance in the neuromuscular junction that triggers prolonged muscle contraction; 2) pericellular matrix deficiency around the chondrocytes in long bone during osteogenesis causing bone shortening. Craniofacial features include blepharophimosis, microstomia, and bimaxillary hypoplasia that could cause obstructive sleep apnea (OSA).

【Method】 An 8-year-9-month-old male patient diagnosed with SJS was referred for orthodontic treatment of OSA. The patient presented with multiple skeletal deformities, short stature, and generalized myotonia. Notable facial characteristics included blepharophimosis, blepharospasm, microstomia, limited mouth opening, and severe bimaxillary hypoplasia. Intraorally, he

was in mixed dentition with very severe dental crowding and two congenitally missing lower lateral incisors. Both upper and lower arches were extremely constricted as a result of intense and continuous contraction of the orofacial musculature. Large palatine tonsils were seen in retropharyngeal area. Cephalometric analysis demonstrates retrognathic maxilla and mandible, retroclined and retruded upper incisors. Additionally, the patient presented with OSA symptoms that included loud snoring, choking or gasping for air, nocturnal enuresis, morning drowsiness, nausea, and headache. He was diagnosed with severe OSA (AHI = 29) at the age of 7. Despite of an AHI decrease to 8.1 (moderate OSA) following the use continuous positive airway pressure (CPAP), the patient continued to suffer the aforementioned OSA symptoms.

【Result】Rapid maxillary expansion (RME) was planned to expand the nasomaxillary complex to reduce nasal airway resistance and improve his sleep breathing. Following RME, his AHI decreased to 3.4 (mild OSA) along with significant improvement of OSA symptoms. The parents reported less snoring, no choking & gasping, no morning headache & nausea, and no daytime sleepiness. The patient also received Botulinum toxin injections to reduce orofacial muscle contractions and blepharospasm.

【Discussion】Improvement in OSA symptoms resulted from expansion of nasomaxillary complex with RME. Tonsillectomy is not considered as patients with SJS were reported to have a greater risk of experiencing malignant hyperthermia during surgery.

【Conclusion】An interdisciplinary approach is recommended for treatment of craniofacial anomalies and OSA in children.

O 010

Surgical Correction of Velopharyngeal Insufficiency with functional reconstruction of soft palate

Hongping Zhu
Peking University School of Stomatology (China)

【Backgrounds】The primary goal of cleft repair is to provide for the development of normal speech. It has been estimated that between 10~35% of patients will suffer from persistent velopharyngeal insufficiency (VPI) following primary cleft palate repair, who need secondary surgical correction to achieve the successful establishment of the function of the velopharynx closure. Although the procedures of posterior pharyngeal flap and sphincter pharyngoplasty are very common and effective to correct VPI, both are unphysiological substitute for the velopharyngeal mechanism, which frequently resulted in airway obstruction, even sleep apnea. Radical intravelar veloplasties is playing more role in primary cleft palate repair. The experience of correction of secondary VPI with radical IVVs was summarized.

【Subjects & Methods】242 cases with various cleft palate were speech evaluated and diagnosed as mild to severe VPI, which ages at 3~45 years (mean age =7.5 years). All cases have been performed primary cleft repair except for 6 cases with submucous cleft palate. These cases were divided into 3 groups to undergo 3 surgical procedures, according to the length and soft tissue condition of soft palate. Group I (184 cases) were performed modified Hogan Posterior pharyngeal flap (PPF) surgery. Group II (36 cases) were performed surgery in the way of extending Furlow double-opposing Z-plasty. Group III (22 cases) were performed surgery in the way of Sommerald radical IVV. All cases were followed up at 6 months to 1 year after surgery, accepted speech evaluation and objective examination of nasendoscopy and fixed position lateral X ray. The X-ray images of lateral view of velum was read through PACS image system. The total length and effective work length of soft palate, and the pharyngeal gap when the velum at rest and function were measured directly through PACS system. And the data of each case before and after surgery were compared by paired T test through SPSS 19.0 software.

【Results】180 of 184 cases (97.8%) in PPF group, 34 of 36 cases（94.50%）in Extending- Furlow group and 21 of 22 cases（95.5%）in Sommerald group finally recovered complete velopharyngeal closure. Comparison between before and post operation, the effective work length of soft palate increase by 13.65±3.45mm in group I, 9.50±2.35mm in group II, 7.50±3.32mm in group III. The differences are statistically significant by paired T test ($P < 0.001$).

【Conclusions】The leveator palatii muscle were radical dissected in different way but getting the same result, the soft palate could be functionally reconstructed resulting in lengthening velar and improving mobility of velar. All three procedures are highly effective to be recommended for surgical correction of VPI. Strictly selection of operation indications and excellent surgical skill are necessary for good treatment outcomes.

O 011

Assessment of orthodontic treatment outcome using Peer Assessment Rating (PAR) index among patients with unilateral cleft lip and palate

Satineder Pal Singh
Unit of Orthodontics,
Oral Health Sciences Centre,
Postgraduate Institute of Medical Education & Research (India)

【INTRODUCTION】Cleft lip and/ or palate is one of the commonest craniofacial anomaly. According to the World Health Organization (WHO), Cleft lip and/ or palate is a dental public health problem because of the oral conditions of the individuals and their aesthetic, functional and psychological impairments

This retrospective study was conducted to evaluate the orthodontic treatment outcome using PAR index among unilateral cleft lip and palate patients (UCLP) treated with various treatment modalities.

【AIM & OBJECTIVES】

- To evaluate orthodontic treatment outcome in patients with unilateral cleft lip and palate using PAR index
- To assess and compare the changes in score of PAR index before and after the comprehensive orthodontic and/or orthognathic treatment in patients with unilateral cleft lip and palate.

【METHODS】The pre- and post-treatment study models of 73 patients (32 male and 41 female) with UCLP who met the inclusion and exclusion criteria were selected for the study. Sample was divided into four groups according to treatment modalities viz. Group 1 (N = 44); Comprehensive Orthodontics alone, Group 2 (N = 9); Functional Jaw Orthopaedics followed by Orthodontics, Group 3 (N = 6); Orthodontics with Conventional Orthognathic Surgery, Group 4 (N = 14); Orthodontics with Distraction Osteogenesis.
【RESULTS】The mean pre-treatment unweighted and weighted PAR score was 18.73 ± 8.34 and 30.03 ± 13.07 respectively. The mean post-treatment unweighted and weighted PAR score was 4.07 ± 2.77 and 6.51 ± 5.01 respectively. The mean percentage change of 75.94 ± 17.76 and 76.58 ± 17.87 with unweighted and weighted PAR index respectively. Out of all treatment modality groups, pre-treatment PAR score was more in group 4 and lowest in group 1, but reduction in PAR score in all groups were satisfactory and more than 70 % of cases in each group were 'greatly improved'. Out of total 73 cases; 56 (76.7 %) cases were 'Greatly improved', 15 (20.5 %) cases were 'Improved' and 2 (2.7 %) showed 'Worse/no improvement'.
【CONCLUSIONS】The results of the PAR index revealed a high standard of orthodontic treatment rendered by the department in all treatment modalities groups.

O 012

How is the created alveolar space finally restored after Maxillary Anterior Segmental Distraction Osteogenesis?

Cha J.Y., Kim D.S.M., Choi E.H. , Sha Ha-Na
College of dentistry, Yonsei University,
Orthodontic department (Korea)

【Background】Maxillary anterior segmental distraction osteogenesis (MASDO) for cleft and palate patients has been the alternative treatment option to correct malocclusion with maxillary arch deficiency and severe crowding. After MASDO, prosthetic considerations are crucial for patients with cleft lip and palate because it is related to facial esthetics and occlusal function. The objectives of this study were to investigate the final restoration type for created alveolar space by maxillary anterior segmental DO.
【Method】Thirteen patients with cleft lip and palate who underwent MASDO and orthodontic treatment from the years 2000 to 2010 in Yonsei university were examined. Final restorations are classified as dental implants, conventional prosthesis, orthodontic space closure and investigate correlation between the distracted area. We evaluated lateral cephalograms obtained at predistraction osteogenesis (pre-DO; T1), postdistraction osteogenesis (post-DO; T2), and debond (T3), and measured changes from T1 to T2 and from T2 to T3
Result and Discussions: An average of 9.5 mm alveolar bone was created for 24 created alveolar spaces. For final restoration, implants were implanted in eight spaces (33%), and bone grafting was performed in four of them. Seven spaces (29%) were restored with a bridge and the remaining nine spaces (38%) were closed by orthodontic tooth movement.

There was no significant difference of final restoration percentage of dental implants, conventional prosthesis, and space closure with orthodontic treatment. However, dental implants and conventional prostheses were applied more frequently in the posterior area and in the anterior area, respectively.

The MASDO site should be decided, based on final restoration goal. Retention strategies are needed to prevent relapse. Among the created alveolar spaces, implants were applied mainly to the posterior site and the conventional prostheses were mostly restored to the anterior site.
【Acknowledgement】The material is based upon work supported the Ministry of Trade, Industry & Energy (MOTIE, Korea) under Advanced Technology Center Program. No.10077361, 'Integrated System for Dental Diagnosis, Treatment Simulation & PSI(Patient Specific Instrument) Design'.

O 013

Algorithm of complex surgical and orthodontic treatment of children with congenital bilateral cleft lip and palate in deciduous dentition

Irina Fomenko
Volgograd State Medical
University (Russia)

【Objectives】One of the severe forms of congenital face malformations is a bilateral cleft lip and palate, which frequency is from 12 to 25% of all children with cleft. The most complex group of patients is children with protrusive premaxilla. Evaluation of the result of multidisciplinary treatment is important for the planning of subsequent therapy. The aim of the study was to evaluate the results of the algorithm for complex surgical and orthodontic treatment bilateral cleft lip and palate with protrusive premaxilla in deciduous dentition.
【Methods】Analyses were based on 44 patients with bilateral cleft lip and palate in deciduous dentition. Primary cheiloplasty was performed with the main elements of the Millard technique at the age of 1-11 months, two stage soft and hard palate repair was performed before 3 y.o. Efficacy of surgical treatment was assessed in children aged 3-4 years before orthodontic treatment. Than the children were divided into 2 groups, depending on the method of orthodontic treatment. Analyses of orthodontic treatment was performed in one year after starting. Used clinical, anthropometric, photometric, biometric methods
【Results】After a primary bilateral cleft lip complete repair in with protrusive premaxilla, a good and satisfactory aesthetic and functional outcome of the operation (97.6%) was achieved without early orthopedic treatment with intraoral fixation devices. Higher efficacy of orthodontic treatment in patients protrusive premaxilla (stage II) was obtained using a modified removable apparatus, which was confirmed by the formation of functional occlusion in 72.2% of patients in group 2, compared to 4.5% of children in group1.
【Conclusions】The results showed that in the complex rehabilitation algorithm - primary bilateral cleft lip repair, soft palate. hard palate repair for children with bilateral complete cleft lip and palate should be performed before the age of 3 years.

O 014

Orthodontic treatment in the management of patients with cleft lip and palate

Yilin Jia, Lian Ma
Department of Orthodontics and Department of Maxillofacial Surgery
Peking University School of Stomatology (China)

Cleft lip and palate is a common congenital deformity and various defects are associated with patients with cleft lip and palate. In order to achieve optimal results, multidisciplinary approach is usually needed. Surgeons commonly face difficulties in doing surgical procedures including alveolar bone grafting and orthognathic surgery. In some situation, the surgical procedures can't be performed without orthodontic intervention. The presentation will discuss the collaboration between orthodontist and surgeons in order to obtain the multidisciplinary treatment goal for patients with cleft lip and palate.

【Keywords】Cleft lip and palate, orthodontics, multidisciplinary treatment

O 015

Skeletal Stability of Le Fort I osteotomy in patients with Cleft Lip and Palate

Sang Hun Park, Jin Young Choi
Department of Oral and Maxillofacial Surgery,
Seoul National University Dental Hospital (Korea)

【Background】Cleft lip and palate (CLP) is the most common congenital birth defect of oral and maxillofacial region with incidence of about 1 in 700 births. Multitude of treatment modalities and principles have been studied and reported, and most management strategies include primary lip and palate repair performed during infancy and childhood. Although the primary repair of soft tissue helps in developing normal speech, occlusion, facial appearance, and self-esteem during childhood, early surgical intervention often times induce maxillary growth restriction. The purpose of this study was to evaluate skeletal stability of cleft orthognathic surgery by comparing horizontal and vertical location of a reference point at late (>9 months) post-operative lateral cephalograph to that of immediate (<1 week) post-operative period.

【Methods】20 patients who underwent cleft-orthognathic surgery at Seoul National University Dental Hospital between 2007 and 2013 were selected. Pre-op (T0), immediate post-op (T1), and 9~12 months post-op (T3) lateral cephalographs were traced, juxtaposed and the horizontal and vertical movement of reference point (A-point) were measured.

【Results and Discussion】Average amount of maxillary advancement was 3.43(□ }1.21)mm with average horizontal relapse of 073(□ }1.13)mm. On vertical dimension, average impaction of 0.75(□ }1.71)mm with average relapse of 1.4(□ }1.05)mm. Compared to similar previous studies such as Posnick (1993) and Ayliffe (1995), the amount of maxillary horizontal relapse was much smaller. This may be so because the patients included in this study went through Le Fort I osteotomies with smaller amount of advancement. In a fundamental level, patients included in this study were originally planned for small amount of maxillary advancement because no further advancement was necessary for esthetic results. Asians, especially East Asian population, have relatively protruded maxilla and mandible. Therefore there was no strong need for excessive maxillary advancement even in cleft-orthognathic patients. On the contrary,

O 016

Repair of huge anterior palatal fistula in bilateral cleft lip and palate patient using double anterior pedicel dorsal tongue flaps

Xia Zhou, Lian Ma
Cleft Lip and Palate Treatment Center
Oral and Maxillofacial Department
School of Stomatology
Peking University (China)

【Background】Even it is wildly accepted that the tongue flap is an effective and feasible for repairment of huge palatal fistula, there still exacts a few failed cases due to severe or complicated situation. The aim of this paper is to report the validity and feasibility of using double tongue dorsal flaps to repair a huge anterior fistula.

【Methods】A 10-year-old boy diagnosed with Van de Woude syndrome with repaired bilateral cleft lip and palate represented a huge anterior fistula divided by septum. A double tongue dorsal flaps was designed to cover the fistula.

【Results】The huge unusual anterior palatal fistula was repaired successfully by usage of double pedicel tongue flaps with a follow-up period of one month.

【Conclusions】The double tongue flaps is an alternative choice to handle a large residual fistula in anterior part of palate which was divided into two fistulas by septum.

O 017

Comparison of West China SF palatoplasty and Sommerlad intravelar palatoplasty: 1128 Cases included

Li Yang PhD. DDS., Zhu zhibing MDS.,
Guo chunli BN., Shi Bing PhD. DDS.
State key laboratory of oral diseases;
National clinical research center for oral diseases;
Department of cleft lip and palate,
West china hospital of stomatology,
Sichuan university (China)

【Aim】To compare the outcomes of West China SF palatoplasty (SF) and Sommerlad (S) intravelar palatoplasty.

【Method】Totally 1128 cases were included in this 10-year retrospective study, 562 case in SF group and 566 cases in S group. Velopharyngeal function, need of releasing incision and fistula were evaluated respectively after 12 months postoperation.

【Result】Ratio of complete velopharyngeal closure (VPC) after surgery in SF group was 92.68% when patients accepted primary palate repair within first 1 year after birth. Ratio of VPC was higher in SF group that in S group among all ages. The ration of fistula was lower in SF group (3.9%) than S group (6%), although the need of releasing incision was much higher in S group (61.1% if vomer flap applied with primary

cheiloplasty and 85.19% if no vomer flap applied).
【Conclusion】Considering the farthest velopharyngeal function recovery and the limited maxillary growth interruption, West China SF technique was a valuable technique in primary palate repair.

O 018

Speech Outcomes in the patients with Asymmetric Cleft Palate after Double-Opposing Z-Palatoplasty

Hyeonwoo Kim[1)], Guang Lin[2)], Sukwha Kim[2)]
[1)]Department of Plastic and Reconstructive Surgery, Seoul National University Boramae Hospital
[2)]Division of Pediatric Plastic Surgery, Seoul National University Children's Hospital (Korea)

【Introduction】Asymmetry is a rare presentation in the patients with cleft palate and there have been only a few case reports to date. The relationship of asymmetry with poor speech outcome has not been fully evaluated yet. In this study, we present the series of asymmetric cleft palate (ACP) undergone double opposing Z-palatoplasty and compare the speech outcome between ACP and symmetric cleft palate.
【Materials and methods】537 patients undergone palatoplasty between 2010 and 2015 were analyzed retrospectively. Among 537 cases, 415 cases were diagnosed as isolated cleft palates. Syndromic patients, patients with other comorbidities, and patients lost to follow-up were excluded. We defined three criteria for ACP – 1) Palatal length discrepancy, 2) Asymmetry in faucial pillar, 3) Unilateral hypoplastic uvula. The cases which met these criteria were classified as ACP. Among 216 cases which met the inclusion criteria, 26 ACP were identified and their speech outcomes were compared with the other 190 cases.
【Results】The mean age at palatoplasty of the patients with ACP was 14.2 ± 2.6 (10.7–20.2) months. The mean difference of palatal lengths of ACP was 4.49 ± 1.96 mm. There were only one patients suspected with hemifacial microsomia in the patients of ACP. All the cases of ACP were operated with double-opposing Z palatoplasty and there was no case with postoperative fistula or secondary operation for velopharyngeal insufficiency. There were no significant differences in the speech results between the patients with ACP and the others.
【Conclusion】The asymmetry in the cleft palate patients who undergone double-opposing Z-palatoplasty was not a significant risk factor for the poor speech outcomes.

O 019

Preliminary Study on Classification of Cleft Palate Bone Defect

Feifei SHANG, Xia Zho, Lian Ma
Peking University, School and Hospital of Stomatology (China)

【Background】With the popularization of computer tomography(CT) examination and other imaging techniques, clinical studies have found that the degree between soft tissue defect and bony defect are not completely consistent, and different bony defects may result in different degree of deformity of cleft palate patients, choice of treatment methods, the prognosis of speech outcomes and in identifying the genes expression involved. However, studies on the description of the shape of the bony defect and the classification criteria are still limited.
【Objective】To classify the shape of palatal bony defect in patients with cleft palate.
【Methods】161 patients with incomplete cleft palate (Veau Classification I & II) who were admitted in Peking University School and Hospital of Stomatology from January 2018 to December 2018 were recruited into this study. 152 patients were included in the study envetually. According to the shape of the bony defect, it was divided into " 丿乚 " shape, inverted "V" shape , inverted "U" shape, atypical shape and five assessor perform the assessment twice individually.Statistical analysis: 1. Consistency analysis between different assessors. 2. The chi-square test was used to analyze the difference in the proportion of bony defect classification among different number of assessors; 3. On the basis of the number of cases with consistent judgment of three or more than three people, the classification composition ratio of four types of bony defects was calculated.
【Results】1. The bony defect of cleft palate can be divided into four types: " 丿乚 " shape, inverted "V" shape, inverted "U" shape, and atypical shape, which ratios of each were 17.10%（26/152）、28.95%（44/152）、48.03%（73/152）and 5.92%（9/152）in order. 2.The agreement rates among the five judgers were 67.70%, 76.40%, 62.11%, 60.87%, and 77.02%, and the average agreement rate was 68.82%. The lowest value of the consistency rate between the two was 59.01% and the highest value was 78.88% .
【Conclusions】1. The shape of palatal bone defect is different between patients with cleft palate.2. The defects of cleft palate can be divided into four types: " 丿乚 ", "inverted V", "inverted U" and "atypical".The different shapes of cleft palate bone defects are of great significance for the selection of surgical methods, the effect of cleft palate speech rehabilitation and the basic research of teratogenic genes.
KEY WORDS: Cleft palate, Bony defect, Classification

O 020

Application of teeth and bone co-supported interdental distraction osteogenesis in the treatment of extensive alveolar cleft

Jiaqiang Liu, Jun Shi, Yiting Sun, Yu Chen, Tiange Wang
Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University (China)

【Objective】To evaluate the application of teeth and bone co-supported interdental distraction osteogenesis in the treatment of extensive alveolar cleft.
【Methods】Two patients who underwent treatment in Center of Craniofacial Orthodontics,9th People's Hospital, School of Medicine, Shanghai Jiaotong University were involved in this study. A teeth and bone co-supported device for interdental distraction osteogenesis was used for the patients with

extensive alveolar cleft. We placed micro implants, titanium plate or mini screw expander on the alveolar bone mesial and distal to the gap, combining them with power chain, making it possible to move the teeth and the alveolar bone bodily and close the gap. The teeth movement, width of the cleft and the bone repair effect were investigated.
【Results】 Both of the alveolar clefts were completed closed by the teeth and bone co-supported interdental distraction osteogenesis without obvious teeth incline. It creates good conditions for bone grafting and post-surgical orthodontic treatment.
【Conclusions】 Teeth and bone co-supported interdental distraction osteogenesis was effective to bodily move the teeth and the alveolar bone, closing the extensive alveolar cleft and achieving the ideal bone tissue repair.

O 021

What can we do for facial cleft Patients?

Guomin Wang, Dandan Wu, Ming Cai,
Teng Wan, Kenneth E. Salyer
Therapy and Research Center of Cleft Lip and Palate,
Department of Oral and Cranio-Maxillofacial Surgery,
Ninth People's Hospital, College of Stomatology,
Shanghai Jiao Tong University School of Medicine;
National Clinical Research Center of Oral Diseases;
Shanghai Key Laboratory of Stomatology &
Shanghai Research Institute of Stomatology (China)

Translated into time, a baby with a cleft will be born somewhere in the world every two minutes, 648 per day, and 236,400 per year. The etiology of this congenital deformity basically attributes to environmental and genetic factors. Genetic factors contributing to cleft lip and cleft palate formation have been identified for some syndromic cases, but knowledge about genetic factors that contribute to the more common isolated cases of cleft lip/palate is unclear. Thus, how to improve the therapeutic outcome has attracted more attention from physicists. The conception of combined and sequential therapy for cleft patients has reached a consensus. However, timing of some interventions is still controversial. Some surgical results of traditional treatment are not satisfying, especially for more complicated case such like 22q deletion syndrome. A modification of current surgical skill and application of new technology might benefit the final outcomes.
Key Words: facial cleft, surgery, team aproach

O 022

Application of CGF in patient of poor wound healing after alveolar cleft bone grafting: case report

Dandan Wu, Xudong Wang, Guomin Wang,
Ming Cai, Teng Wan
Therapy and Research Center of Cleft Lip and Palate,
Department of Oral and Cranio-Maxillofacial Surgery,
Ninth People's Hospital, College of Stomatology,
Shanghai Jiao Tong University School of Medicine;
National Clinical Research Center of Oral Diseases;
Shanghai Key Laboratory of Stomatology &
Shanghai Research Institute of Stomatology (China)

In some patients, the wound healing is poor after alveolar bone grafting, and exposure of the implanted bone can lead to poor bone healing. CGF can be extracted from venous blood and is a platelet-derived product. CGF contains various growth factors and fibrin, which has the unique property of improving and enhancing tissue regeneration. We report a patient with poor soft tissue healing after alveolar cleft bone grafting, and using CGF in wound. Two weeks later, the wound healed well and only a small amount of bone resorption. Therefore, we suggested that CGF can be used to promote wound healing in such cases.
【Key words】 CGF, alveolar cleft, wound healing, regeneration

O 023

Patients with cleft lip and/or palate at orthodontic depatment of Kyungpook National University in Korea from 2007 to 2016

Sang-Yun Lee[1)], Mihee Hong[2)]
[1)]Graduate Student, Department of
Orthodontics, School of Dentistry,
Kyungpook National University
[2)]Assistant Professor, Department of
Orthodontics, School of Dentistry,
Kyungpook National University (Korea)

【Key Words】 cleft lip and/or palate, dental anomaly, orthodontic treatment
【Introduction】 In Korea, orthodontic treatment for cleft lip and/or palate patients has been supported by National Health Insurance System from the March in this year, followed by their primacy surgical treatment since 1989. Reviewing the past longitudinal data is expected to provide baseline data for the future orthodontic care for patients the cleft lip and/or palate.
Objectives: The purpose of the study was to provide basic clinical information regarding orthodontic diagnosis and treatment of the cleft lip and/or palatal patients by analyzing data from a national dental hospital as a cleft center of the province over the last decade.
【Methods】 Examination was fulfilled for dental records, diagnostic models and panoramic X-ray films belonged to 110 patients with cleft lip and/or palate visited the department of orthodontics of Kyungpook National University Dental Hospital from 2007 to 2016, were examined. Age, sex, types of cleft including bilateral cleft lip and palate (BCLP), unilateral cleft lip and palate (UCLP-Left and UCLP-Right), and anomaly such as missing and peg shaped morphology were investigated.
【Results】 In the case of initial examination, 5-year-old, 2-month-old female was the youngest patient, while the oldest was 41-years-old 1-month-old female. The mean age was 15-years old and 2-months. The number of male and female was 81 (73.6%) and 29 (26.4%), respectively. The number of BCLP, UCLP-Left, and UCLP-Right was 24(21.8%), 50(45.5%), and 36(32.7%), respectively. In BCLP, the mean age at initial examination was 13 years-old and 2-months and the number of male was double number of female (18-male vs. 6-female). UCLP-Left patients were composed of 19-females and 31-males. UCLP-Right patients were composed of 4-females and 32-males. Missing was examined in 73 patients

(66.4%): 18 out of 24 in BCLP (75%), 31 out of 50 in UCLP-Left (62%) and 24 out of 36 UCLP-Right (66.7%). The number of patients with Peg lateralis was 62 (56.4%): 16 out of 24 in BCLP (66.7%), 26 out of 50 in UCLP-Left (52%), and 20 out of 36 in UCLP-Left (55.6%).

【Conclusion】 Male patients were dominant for the last decade. UCLP-Left was the half of the patients. More than 60 % patients presented missing or peg shaped anomaly in their dentition.

O 024

POST OPERATIVE SEIZURE FOLLOWING CLEFT LIP SURGERY

Santoso RD[1)], Saputro ID[2)], Hardiono[3)]
[1)]Resident Medical Officer
[2)]Division of Plastics Reconstructive Surgery
[3)]Division of Anesthesiology and Reanimation,
Consultant of Intensive Care and
Cardiovascular Premier Surabaya
Hospital (Indonesia)

【Background】 Cleft lip surgery is regarded as a minor procedure that usually goes uneventful. In this study, we report a postoperative seizure as a serious complication following cleft lip surgery. This case report serves to increase awareness about this previously rarely reported complication

【Method】 This case report is using data from electronic based medical record and direct observation of the registered patient. A 4-month old boy with congenital left unilateral complete cleft lip palate without associated congenital anomaly, allergy and medical history underwent primary cleft lip repair and tip rhinoplasty. He was categorized as PS ASA 1. The procedure and perioperative were uneventful. Six hours after surgery, he vomitted and developed generalized tonic clonic seizure, leading to cardiac arrest. ROSC was aechieved, seizure was managed, patient was intubated and put under controlled ventilation, followed by transfer to Intensive Care Unit. Initial blood gas analysis and serum electrolyte showed respiratory acidosis (PH 7.187 PCO2 63.8) and severe hyponatremia (Sodium 117 meq/L). Head CT and chest xray results were unremarkable. Hypoglycemia was found (38mg/dl).

【Result and Discussions】 Seizure was controlled with Midazolam and Propofol, while airway and breathing was managed under assisted ventilation. Sodium level of 117 was corrected with Saline to the point of 134. Blood glucose was low (38mg/dl) and corrected with Dextrose 10%. The most likely cause of this seizure is hyponatremia. It is most likely due to SIADH, which is a significant cause of hyponatremia following craniofacial procedures including cleft palate repair but unlikely in cleft lip repair and tip rhinoplasty.

O 025

Cleft Lip Palate Profile and Influence of Distance from Hospital and Nutritional Status in Surabaya, Indonesia

Iswinarno Doso Saputro[1)], Rosalyn Devina Santoso[2)]
Plastics Surgery Department,
Premier Surabaya Hospital (Indonesia)

【Background】 Cleft lip and palate is one of the most common facial malformations in developing countries requiring multiple treatments on time to optimize feeding, facial growth, and speech. This study is to describe the profile of cleft patients and to investigate the correlation between a patient's distance from hospital and treatment delay, as well as correlation cleft type and nutritional status.

【Method】 This was a retrospective analysis of 408 patients underwent cleft lip and/or palate repair in Premier Surabaya Hospital, Indonesia between December 2017 and February 2019. Data obtained at the time of patient enrolment were gender, age, cleft type, surgery type, associated malformation, the timing of surgery, and complication. Patients' home was grouped to Surabaya-and-Surroundings and Other. The recommended timing of surgery 0-6 months of age for cheilonasoraphy and 10-12 months of age for palatoraphy. Patients aged 5 years old and younger was screened using WHO Weight-for-Age Z-score (WAZ). Correlations between patient's domicile and treatment delay and between WAZ and cleft type were analyzed using Pearson chi-square tests.

【Result and Discussions】 408 patients were enrolled in this study. Cleft lip and palate (CLP) type was the most common (310), followed by the cleft lip (CL) and cleft palate (CP). Of 251 male patients, 194 had CLP, 48 CL, and 9 CP. Unilateral left side cleft is more common than the right side. 26.75% (n=103) patients were found to be of later than suitable age for procedures. 76,62% (n=295) patients were of out of town origins, with 16 patients coming from out of state. However, Pearson chi-square test found no correlation between home distance and delay, with a p-value at 0.572 (α=0.05), as neither were found between state origin and delay (p value=0.321, α=0.05). Of 385 records of patients met inclusion criteria and were analyzed for correlation between WAZ and cleft type, with Pearson chi-square test revealed no correlation (p value=0.086, alpha=0.05) between both variables.

【Conclusion】 Male makes up the majority of cleft patients. Unilateral left sided cleft lip and palate is the most common type. This study shows no correlation between distance to hospital and treatment delay and no correlation between cleft type and nutritional status.

O 026

Improving orthognathic surgery in patients with bilateral cleft lip and palate.

Shuba M.I. , Evdokimov A.I.,
Fedotov R.N., Topolnitskiy O.Z.
Moscow State University of Medicine
and Dentistry (Russia)

【Background】 Patients with bilateral cleft pathology with late or poor quality surgical care without orthodontic treatment, and with the wrong tactics and algorithm of surgical treatment, leading to more distant consequences: growth retardation and position of the jaws, malocclusion. Those teeth and jaws deformities in patients with bilateral clefts most are often defined in the upper jaws, flattening of the midface, and has formed occlusion-type like mesial occlusion.

【Materials and methods】 Group 1- patients with bilateral cleft, who had orthognathic surgery with simultaneous

movement of the jaws in the correct ratio at the ages from 16 to 25 years. Group 2 includes patients who were treated for underdevelopment of the upper jaw using a distraction method at the age of 12–18 years. The first group included 13 patients with complete bilateral cleft lip and palate, who received treatment and orthognathic operations. Depending on the deformities of the jaw bones, the patients underwent an osteotomy of the upper jaw of Le Fort 1 with movement forward, only intercortical osteotomy of the lower jaw, or a combined movement of the jaws. The second group consisted of 4 patients with bilateral cleft, who were treated for underdevelopment of the upper jaw by the method of distraction.

【Results and Discussion】 Patients of the 1st group had a stable occlusion result after orthognathic surgery in 70% of cases. Relapse was observed in 30% of cases. A significant correlation was found between relapse and the quality of postoperative orthodontic treatment and preoperative preparation. ($P < 0.05$). Patients of the 2nd group. The distraction method was applied, a stable result was achieved in all 4 cases. Based on summarized recent research, it is necessary to correct and optimize the surgical orthognathic treatment of asymmetric jaw deformities according to the type of mesial occlusion in patients with bilateral cleft lip and palate, due to the predisposition to relapses. It is necessary to carry out the previous two-jaw surgery, the stage of distraction osteogenesis, showing a more stable result of the position of the upper jaw.

O 027

Unilateral Microform Cleft Lip Repair Through Intraoral and Intranasal Mucosal Incisions in adult patients

Yongqian Wang
Tao Song, Haidong Li, Di Wu,
Weiyi Sun, Ningbei Yin
Plastic Surgery Hospital, Peking Union Medical College (China)

【Background】 In microform cleft lip repair, it is elaborate work to restore the normal shape of the lip and nose without incision on the lip skin. We describe a new technique of unilateral microform cleft lip repair through intraoral and intranasal in adult patient .

【Methods】 According to the shape of Cupid's bow, a different small incision is used without creating an obvious cutaneous scar. A vertical incision is made on the mucosa in the oral cavity against the infused gap of the muscle. Another vertical incision was made on the nasal floor. The anatomical structure could be exposed clearly through the intraoral and intranasal incisions. First, the nasolabial muscle around the nasal floor is reconstructed and then the orbicularis oris muscle around the philtrum is reconstructed .

【Results】 From March 2011 to March 2018, the technique was used in 47 unilateral microform cleft lip repairs. All the patients were followed up for 12 to 36 months. The appearance of the nose, philtrum, and Cupid's bow peak improved. 42 patients had a satisfactory appearance. The nasal alar relapsed in 5 patients

【Conclusion】 The orbicularis muscle of mouth could be reconstructed through intraoral and intranasal incisions. The shape of the nose, Cupid's bow and philtrum could be restored without traditional skin incision.

【Keywords】 microform cleft lip; nasolabial muscle complex; intraoral incision; intranasal incision

O 028

Evaluation of lip symmetry after nasoalveolar molding in patients with unilateral cleft lip and palate – A four year follow up study

AlHayyan WA[1)],
Sharat P[2)], Hayek SM[3)]
[1)]ALJahra hospital (Kuwait)
[2)]Riyadh Elm University (Saudi Arabia)
[3)]King Abdulla children special hospital, Saudi Arabia (Kuwait)

【Background and Aim】 Presurgical Nasoalveolar Molding (P-NAM) has been shown to provide good post operative esthetic results in children with unilateral cleft lip and palate (UCLP). However there are few studies on the long term effects of P-NAM. This study aimed to compare the lip symmetry of children with UCLP who received P-NAM to children with UCLP who did not, and age matched controls without UCLP.

【Methdodology】 20 children with UCLP who had received P-NAM were matched for age and gender with 20 children with UCLP who had not received P-NAM. The children were recalled four years after the completion of surgery and were aged between 48 and 52 months and were compared to age and gender matched controls with no history of cleft lip and palate. A frontal photograph was taken from a distance of 150cm(5 ft) and Adobe Photoshop CS5 was used to define and measure the lip area. Upper lip area on either side of the midline and the combined upper and lower lip area on either side of the midline were measured. The differences in area were compared among groups using the one-way ANOVA and the Scheffe's post hoc test. Differences between the cleft and non cleft side (left and right for the control group) were measured using the paired t test.

【Results】 The control group showed greater lip area symmetry and upper lip symmetry when compared to the UCLP groups with or without P-NAM. The children who had received P-NAM showed significantly less upper lip asymmetry when compared to those without P-NAM.

【Conclusion】 Within the limitations of this study we can conclude that P-NAM appears to
Improve long term lip symmetry in patients with UCLP.

O 029

Prevalence of supernumerary teeth in children with cleft lip and/or palate: A CBCT study

Dr. Ravi Kumar Gudipaneni[1)],
Dr. S.M. Balaji[2)],
Dr. Shaifulizan Ab Rahman[3)],
Dr. Mohammad Khursheed Alam[4)],
Dr. Santosh R. Patil[5)]
[1)]PhD Scholar, School of Dental Sciences, Universiti Sains Malaysia (Malaysia)
[2)]Professor, Balaji Dental & Craniofacial Hospital, Chennai (India)

[3)]Professor & HOD, Oral & Maxillofacial Surgery, School of Dental Sciences, U niversiti Sains Malaysia (Malaysia)
[4)]Associate Professor, College of Dentistry, Jouf University (Saudi Arabia)
[5)]Assistant Professor, College of Dentistry, Jouf University, Saudi Arabia (India)

【Background】Dental anomalies are more commonly seen in children with cleft lip and/or palate than in normal subjects. They may affect both primary or permanent dentitions. The aim of the present study was to establish the prevalence of supernumerary teeth in children afflicted with cleft lip and/ or palate.

【Material and methods】The present study was carried out in Balaji Dental & Craniofacial Hospital, Chennai, India after obtaining ethical clearance. A total of 132 CBCT scans of 132 subjects, aging 2-12 years were analyzed. The CBCT unit used in the present study was Scanora 3D (Soredex, Tuusula, Finland) with 6 mA and 89 kVp and the scans were analyzed using the accompanying software (NewTom 3G: NNT, QR SRL; Scanora 3D: OnDemand®, Cypermed Inc, Irvine, CA). The scans were analyzed in all three dimensions by two examiners. To check the intraobserver variations, the same examiners carried out measurements after two weeks.

Presence of supernumerary teeth in the maxillary arch was evaluated the scans of cleft lip and/or palate patients. The evaluation comprised the cleft side as well as the unaffected side. The obtained data were statistically analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) by applying Chi-square bi-variate analysis in order to assess associations between the presence of supernumerary teeth and cleft lip and/or palate cases. The reliability of measurements was evaluated by Kappa statistic.

【Results】The reliability was very good, with Kappa values of 0.92 for intraoperator agreement and of 0.94 for interoperator agreement. Out of the 132 CBCT scans of the patients with cleft lip and/or palate analyzed, supernumerary teeth were observed in 22 Scans (16.6%). Twelve (9.0%) supernumerary teeth were observed in males and 10 (7.5%) in females. All the supernumerary teeth were found on the side of the cleft, the main location was the lateral incisor region (86.3%) and most cases occurred in the primary dentition (63.6%).

【Conclusion】Prevalence of supernumerary teeth was higher in males and mainly located in primary dentition, in the location of lateral incisors.

【Keywords】Cleft lip and palate, dental anomalies, developmental anomalies, supernumerary teeth.

O 030

Speech and neurologic development in cleft palate with and without Pierre Robin Sequence

Michael Krimmel, Sylva Bartel, Irene Steiner Wilke, Nadja Kaiser, Andreas Naros, Siegmar Reinert
University Hospital Tubingen (Germany)

【Introduction】Pierre Robin Sequence (PRS) is characterized by mandibular retrognathia, glossoptosis and possibly cleft palate (CP). Although upper airway obstruction and life threatening hypoxia are addressed early with various different techniques, children with PRS seem to have a worse neurological development. Therefore speech development also seems to be impaired in PRS with CP compared to children with isolated CP. Our hypothesis was, that children, that are treated with a preepiglottic baton plate in order to relieve airway obstruction, do not suffer from hypoxia and have a normal neurological development and in consequence also an equivalent speech development compared to children with isolate CP.

In a prospective monocenter survey study, speech and neurologic function of age-matched cleft palate children with and without PRS were compared.

【Patients and Methods】A consecutive series of children with cleft palate with and without PRS were enrolled at the age of 5 to 6 years. Cleft palate closure was performed in the technique of Sommerlad before the age of 18 months. All PRS children were treated with the preepiglottic baton plate during their first year of life. Children with other anomalies or syndromes or a prolonged necessity for a treatment with the preepiglottic baton plate (> 1 year) were excluded. Speech assessment was performed with the German version of the GOS.SP.ASS test (Great Ormond Street Speech Assessment). Audio and video taping were recorded and sent blinded to another university center, department of phoniatry, for evaluation according to the universal reporting parameters for cleft lip and palate deformities. The neuropsychological function was assessed with the WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence) and K-ABC-SED (Kaufmann Assessment Battery for Children).

【Results】From 2015 until 2018 forty-four consecutive children were inclosed to the study. 22 patients suffered from PRS with CP and 22 patients from an isolated CP. Their mean age was 6.1 years (±8.1 months). All children showed an almost normal and age appropriate speech function. There was no significant difference between PRS and non-PRS children concerning speech outcome. The physical and neurologic development was within the test specific reference values age adequate. Furthermore we did not observe any neurologic or cognitive developmental delays in the PRS group.

【Conclusion】Our results support the hypothesis, that the treatment of upper airway obstruction with the preepiglottic baton plate promotes not only a successful relief of hypoxia in PRS patients, but also ensures a normal speech and neurologic development equal to non-affected cleft palate patients.

O 031

Anthropometric measurements analysis in patients age 4-6 and patients age 9-11 with unilateral alveolar cleft prior to and after bone grafting.

Makeev A.V., Evdokimov A.I., Topolnitskiy O.Z.
Moscow State University of Medicine and Dentistry (Russia)

【Relevance】Secondary bone grafting has become one of the most common surgical procedures for dentoalveolar

reconstruction. Alveolar process reconstruction provides support for teeth adjoining the cleft, stabilizes fragments of the alveolar process and creates support for the wing of the nose.
Some maxillofacial surgery centers perform alveolar process bone grafting before the age of 6 on the basis of upper incisor eruption timeline to decrease maxillary fragments deformation and to reduce the risks of losing permanent teeth adjacent to the cleft. Presently, a comprehensive research with anthropometric measurements data for patients who had undergone bone grafting at ages 4-6 for alveolar cleft treatment has not been carried out yet. We have defined the objectives of the research: to acquire reliable information on the effect of bone grafting in patients age 4-6 and 9-11 it is necessary to study long-term results (5-7 years after the surgery).
【Objectives】Comparison of maxillofacial growth in patients with unilateral lip and palate cleft age 4-6 and 9-11.
【Materials and methods】Patients had been divided into two groups: group A - age 4-6 (n - 30 patients) and group B - age 9-11 (n- 60 patients). Patients had undergone X-ray examination prior to and 6 months after the surgery. Diagnostic casts were also made for further maxillary anthropometric measurements evaluation. Sagittal and transverse measurements were evaluated using «Dolgopulova technique».
【Results】Comparative study of anthropometric measurements using «Dolgopulova technique» had shown the following: in patients age 4-6 sagittal measurements were - in III-III region - 27,35(N- 27.2), V-V - 39.8(41) before bone grafting and 27.6 / 39.0 after bone grafting respectively; transverse measurements in the same group were - 26.2(N - 29.7) before and 26.2 after the surgery respectively. In patients age 9-11 sagittal measurements were - III-III - 29.53, V-V - 41.31 before and 30.08/41.44 after the surgery respectively; transverse measurements in the same group were - 28.75 before and 28.83 after the surgery respectively. Consequently, it can be concluded that there was no significant maxillary growth inhibition. Dolphin Imaging software was used to analyze morphometric growth measurements - SNA, SNB, ANB after 6 months after bone grafting in patients age 4-6 were: SNA -98.06 before the surgery, angular value 98.45.
【Conclusions】
1. According to the clinical study results, performing bone grafting in ages 4-6 is more effective and does not generally lead to maxillary growth inhibition, but it does not exclude the necessity to perform bone grafting at a later age.
2. Treatment of alveolar clefts with early (age 4-6) bone grafting allows to stabilize dental occlusion, provide benign conditions for canine eruption and reduce the severity of secondary maxillofacial deformations.

O 032

Premaxillary Osteotomy in Treatment of Bilateral Cleft Lip and Palate

LI Yang, YI Biao
Department of Oral and Maxillofacial Surgery,
Peking University School and Hospital of
Stomatology, Beijing (China)

【Background】Patients with bilateral cleft lip and palate may have severe premaxillary displacement, which is downwards and protruding. Premaxilla reposition is necessary for further treatment of orthodontics and bone grafting
【Purpose】To introduce a surgical technique for correction of secondary serious premaxillary deformity of bilateral cleft lip and palate with premaxillary osteotomy and discuss the indications and complications.
【Methods】We operated on 15 patients(9 boys, 6 girls) with bilateral cleft lip and palate ,who had secondary serious premaxillary deformity. Patient ages ranged between 8 and 12 years. All of them had undertaken repair surgery of cleft lip and palate at the appropriate time. Premaxillary osteotomy shifting premaxilla upwards and backwards was carried out in all patients. The premaxilla was immobilized in all patients using the individual labial arch and splint .
【Results】Proper positioning of the premaxilla was achieved in all patients. The bones had knit well after 3 months postoperation. There were no major complications, such as necrosis of the premaxilla or vascular compromise. All of them had underwent alveolar bone grafting and started orthodontic treatment post premaxillary osteotomy.6 of them had underwent repair surgery of secondary lip deformity .
【Conclusions】Premaxillary osteotomy allows repositioning of the premaxilla to its optimal preplanned position. This protocol proved advantageous in achieving good results. Premaxillary osteotomy may be one step of team approach in correction of bilateral cleft lip and palate patients with secondary serious premaxillary deformity.

O 033

Evaluation of The Airway Spaces in Patients With and Without Cleft Lip and Palate Using Cone Beam Computed Tomography

Kevser Tütüncüler Sancak,
Hakan Eren,
Aysegul Mine Tuzuner,
Ankara University (Turkey)

【Background】Patients with cleft lip and palate (CLP) suffer from several esthetic and functional challenges. A patient with a cleft generally has a Class III profile, and the comprehensive treatment plan involves orthognathic surgery mainly in the form of maxillary advancement or mandibular setback. Several cases of airway insufficiency, velopharyngeal incompetence, snoring, hypopnea, and obstructive sleep apnea have been reported in subjects with CLP. Hence, the conditions affecting pharyngeal airway space is of importance to the cleft team to create better understanding of the pharyngeal airway space (PAS) morphology and its associated disorders toward providing the possibility of modifying the airway by growth modifications or surgical modality of treatment. Cone-beam computed tomography (CBCT) has become a well-accepted diagnostic technique for the evaluation of airways because of its lower radiation doses and faster image acquisition times compared with the computed tomography (CT) technique.

We conducted this study to evaluate the pharyngeal airway space in unilateral cleft lip and palate (UCLP), and bilateral cleft lip and palate (BCLP) individuals and compare those

results to NC individuals. We hypothesized that individuals with UCLP and BCLP have smaller PAS in comparison to NC individuals.

【Method】The preliminary study consisted of 15 patients divided into 3 groups: unilateral cleft lip and palate (5 patients), bilateral cleft lip and palate (5 patients) and control group (5 patients). Volume of pharyngeal airway were measured and Kruskal-Wallis H test was used to evaluate differences between groups.

【Result and Discussions】The pharyngeal airway space was significantly reduced in BCLP group than in the UCLP and control groups. This reduced PAS should be taken into account while planning treatment for these individuals.

O34

OUTCOMES OF SECONDARY ALVEOLAR BONE GRAFTS IN CLEFT PATIENTS

Mabongo M, Machaka M,
Hlongwa P
University of the Witwatersrand
(South Africa)

【Background】Several radiographic studies have been conducted to assist with the assessment of long term outcomes. These studies include methods described by Bergland et al. (1986), Kindelan et al. (1997), and Witherow et al. (2002). The major flaw of these methods used 2D radiographs which overestimate the results, because they measure the height but not the volumetric infill within the defect of the cleft.

The emergence of CBCT scans has revolutionised the evaluation of the amount of bone post SABG.

Aim】The aim of this retrospective study was to determine the outcomes of secondary alveolar bone grafts (SABG) in cleft.

【Objectives】

- To record the demographic data of patients who had secondary alveolar bone grafts
- To assess the outcomes of SABG by evaluating the quantity of bone post SABG using Cone Beam computed Tomography scans (CBCT).

【Methods】Records of 19 patients with a total of 23 clefts were examined to evaluate the amount of bone at the cleft site following secondary alveolar bone graft. Socio-demographic information was collected as well as the clinical variables of the type of graft used, canine eruption, and closure or persistence of any oronasal fistula. The amount of bone at the graft site was measured on CBCT images using the Chelsea scale. SPSS ® 24 was used to analyse the data. All statistical tests were conducted at 5% significance level.

【Results】Most (52%) patients were male, with 78% having unilateral cleft. All patients received autogenous bone grafts from the chin. Most of the patients (65.2%) showed good clinical outcomes, whilst showing evidence of bone resorption in and around the graft site on CBCT images. Fifteen (62,5%) of the clefts were considered to have partial alveolar graft resorption.

【Conclusion】In the majority of patients, 3D CBCT images revealed bone resorption in areas that 2D images gave an impression of presence of bone. However, the majority of patients indicated good clinical outcomes despite the poor radiological findings.

O 035

Factors affecting the post-operative velopharyngeal function in adult patients

Yang Chen, Teng Wan
Oral-Craniofacial Surgery,
Shanghai Jiao Tong University,
School of Medicine (China)

【Background】To determine the factors affecting the post-operative velopharyngeal function of adult cleft patients.

【Method】The post-operative velopharyngeal function and possible factors including length and width of the cleft, length of soft palate, diagnosis was analyzed prospectively in 64 adult patients

【Result and Discussions】The length and with of the cleft, the length of soft palate in velopharyngeal competent group were not statistically different from the velopharyngeal incompetent group. The different in velopharyngeal competent rate was not significant in different diagnosis group.

Cleft size, shape and diagnosis are not the main factors affecting post-operative velopharyngeal function. Palatoplasty alone can achieve relatively high velopharyngeal competent rate, it is not recommended to use palatopharyngoplasty in primary surgery.

【Key words】Adult, Cleft palate, Velopharyngeal function, Influencing factors

References:

O 036

Multiple distraction osteogenesis in upper arch for maxillary three-dimensional hypoplasia on patients with cleft palate

Min Zhu, Yanfei Zhu, Minjiao Wang,
Xudong Wang, Guofang shen
Center of Craniofacial Orthodontics,
Department of Oral & Craniomaxillofacial Surgery,
Shaghai Ninth People's Hospital,
Medical School,
Shanghai Jiaotong University (China)

【Purpose】Patients with cleft palate always suffered from maxillary hypoplasia, severe crowding, crossbite on both anterior teeth and posterior teeth.

【Methods】30 Distraction Osteogenesis were operated in upper arch, usually between second premolar and first molar, or between first and second premolar. Customized distractors was designed using orthodontic lower expanders in different directions. The distractors were activated according to DO rules. Firstly DO were achieved anterior-posteriorly, then transversely until the patients profiles were improved significantly. After 6 month, the distractors were removed and the space were used to relieve severe crowding.

【Results】20 patients who were diagnosed with maxillary hypoplasia achieved satisfied profiles, and no need to orthognathic surgery. 10 patients who were diagnosed with both maxillary hypoplasia and mandibular hyperplasia were

achieve satisfied mid-face profiles, and only need to have BSSRO mandible to setback.

【Conclusion】Distraction Osteogenesis in upper arch can avoid extraction teeth when orthodontic treatment so that the depth of arch can be remained. Also Lefort I osteotomy to advance maxilla was no need so that the relapse was decreased. Since the posterior part of maxilla was not to move forward, the speech problem can't be worsen. Distraction osteogenesis in upper arch using customized distractors were seems better than conventional bimaxillary orthognathic surgery.

O 037

Rhinoplasty with combination of diced costal cartilage and caved framework for treatment of secondary nasal deformity of unilateral cleft lip

Bin Zhang, Qiang Liu*, Zeng-Jian Li ,
Xiao-Feng Bai, Li LU
Department of Oral-Maxillofacial Surgery,
the Affiliated Hospital of Stomatology
(Dentistry and Oral-Maxillofacial Surgery),
China Medical University (China)

【Objective】To evaluate the feasibility and outcomes of the rhinoplasty with combination of diced costal cartilage and caved framework for treatment of nasal deformity of unilateral cleft lip.

【Methods】25 patients, with unilateral cleft lip and similar deformities of the nose, have been enrolled in the clinical research in the period of Jun 2011 to Jun 2018. All the patients were treated with the same method. The diced costal cartilage was used for augmentation of nasal dorsum and alar base. The caved framework was made with plat pieces of costal cartilage as columellar struct, batten graft and spreader graft. Clinical evaluation was made on the times of pre-operation, post-operation and 6 to 24 months follow up.

【Results】Nasal tip was back to the central for 24 of the 25 patients. The deviation of the dorsal and lateral alar was redressed obviously. The divergence between bilateral nostrils was reduced and the base of the nose was higher than before. In one patient, the carved framework of costal cartilage became collapsed. The partial absorption of the diced cartilage happened in 10 patients in 6-12 months follow up, but the total appearance of the noses was not affected.

【Conclusion】Rhinoplasty with combination of diced costal cartilage and caved framework for treatment of nasal deformity is a effective and satisfactory method, and can be used as a treatment option for patients who do not pay attention to extra invasion on the chest.

O 038

Preliminary study of Electroglottography application on glottal stop in Mandarin cleft palate patients

Zhen Ren, Lian Ma
Department of Oral & Maxillofacial surgery,
Peking University School and Hospital of
Stomatology (China)

【Background】The glottal stop is a typical compensatory articulation error in cleft palate (CP) speech. It is produced by adducting the vocal folds as a substitution during the pronunciation of oral pressure consonants. The existence of glottal stop (GS) has a great impact on speech intelligibility, interfered the accuracy of perceptual analysis, decreased speech therapy effectiveness. Present lacking of effectiveness instrument of glottal stop, the Electroglottography (EGG) is proposed by its intrinsic mechanism of recording the vocal fold movement. It was never applied in CP patients with glottal stop. The aim of this study is to investigate the utility of vocal attack time (VAT) values in patients with cleft palate with and without GS, when unaspirated monosyllables are articulated in Mandarin, by using electroglottography.

【Method】Unaspirated monosyllables /pa/ /pi/ /pu/ /ta/ /ti/ /tu/ /ka/ /ki/ /ku/ with tone one were analyzed. A total of 575 tokens were obtained from 42 patients with cleft palate, divided into a GS category (n = 312 tokens) and a nonglottal stop (NGS) category (n = 263 tokens), as assessed perceptually by three judges. Sound pressure and electroglottography recordings were also obtained from these tokens. The time lag of the cross-correlation function was used to gain VAT values.

【Result and Discussions】The results showed that the mean VAT values of tokens from the GS category (–0.25 ms) was significantly shorter than that of tokens in the NGS category (3.19 ms) ($t = 7.326$, $P < 0.001$). The results also showed that there was no significant difference in VAT values between the different combined monosyllables both in GS and in NGS group. The conclusion that can be drawn from this study is that the VAT value was sensitively decreased in cleft palate Mandarin speakers with GS comparing to those without GS.

【References】

1. Stengelhofen J . Nature and causes of communication difficulties. In: J Stengelhofen (Ed.). Cleft Palate: Nature and Remediation of Communication Problems. Edinburgh: Churchill Livingstone.1989: 1-30.
2. Prathanee B, Pumnum T, Seepuaham C, Jaiyong P. Five-year speech and language outcomes in children with cleft lip-palate. Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery. 2016;44:1553-1560.
3. Kummer AW. Anatomy and physiology: the orofacial structures and velopharyngeal valve, cleft palate and craniofacial anomalies, the effects on speech and resonance. Cleft Palate and Craniofacial Anomalies: The Effects on Speech and Resonance. San Diego (CA): Singular 2001.
4. Warren DW. Compensatory speech behaviors in individuals with cleft palate: a regulation/control phenomenon?. The Cleft palate journal. 1986;23 (4):pp. 251-260.
5. Sell D, Harding A, Grunwell P. A screening assessment of cleft palate speech (Great Ormond Street Speech Assessment). International Journal of Language & Communication Disorders. 1994;29:1.
6. Konst EM, Rietveld T, Peters HF, Weersink-Braks H. Use of a perceptual evaluation instrument to assess the effects of infant orthopedics on the speech of toddlers with cleft lip and palate. The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association. 2003;40:597.

7. Kuehn DP, Moller KT. Speech and Language Issues in the Cleft Palate Population: The State of the Art. The Cleft Palate-Craniofacial Journal. 2000;37:348-348.
8. Whitehill TL. Assessing intelligibility in speakers with cleft palate: a critical review of the literature. Cleft Palate Craniofac J. 2002;39:50-58.
9. Kent RD. Hearing and Believing: Some Limits to the Auditory-Perceptual Assessment of Speech and Voice Disorders. Am J Speech-Lang Pat. 1996;5:7-23.
10. Howard S. Compensatory articulatory behaviours in adolescents with cleft palate: comparing the perceptual and instrumental evidence. Clinical linguistics & phonetics. 2004;18:313-340.
11. Fabre P. Un procédé électrique percutané d'inscription de l'accolement glottique au cours de la phonation: Glottographie de haute fréquence. Bulletin De Lacadémie Nationale De Médecine. 1957:66-69.
12. Taptapova SL, Ermakova J. [Electroglottography studies in patients with congenital cleft palate]. Revue de laryngologie - otologie - rhinologie. 1979;100:177-181.
13. Hamming KK, Finkelstein M, Sidman JD. Hoarseness in children with cleft palate. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009;140:902-906.
14. Robison JG, Otteson TD. Prevalence of hoarseness in the cleft palate population. Archives of otolaryngology--head & neck surgery. 2011;137:74-77.
15. Zajac DJ, Linville RN. Voice perturbations of children with perceived nasality and hoarseness. Cleft Palate Journal. 1989;26:226.
16. Garellek M. Voice quality strengthening and glottalization. Journal of Phonetics. 2014;45:106-113.
17. Pak M. How allomorphic is English article allomorphy? Glossa: a journal of general linguistics. 2016;1(1):20.
18. Solé M-J. Articulatory adjustments in initial voiced stops in Spanish, French and English. Journal of Phonetics. 2018;66:217-241.
19. Shen XR. The Acoustic Performances of Glottal Stop. Studies in Language & Linguistics. 2010 (3) :35-39.
20. Baken RJ, Orlikoff RF. Estimating vocal fold adduction time from EGG and acoustic records. Programme and abstract book: 24th IALP Congress, Amsterdam. 1998;15.
21. Orlikoff RF, Deliyski DD, Baken RJ, Watson BC. Validation of a Glottographic Measure of Vocal Attack. Journal of Voice. 2009;23:164-168.
22. Roark RM, Watson BC, Baken RJ. A Figure of Merit for Vocal Attack Time Measurement. Journal of Voice. 2012;26:8-11.
23. Watson BC, Baken RJ, Roark RM, Reid S, Ribeiro M, Tsai W. Effect of Fundamental Frequency at Voice Onset on Vocal Attack Time. Journal of Voice. 2013;27:273-277.
24. Watson BC, Baken RJ, Roark RM. Effect of Voice Onset Type on Vocal Attack Time. Journal of Voice. 2016;30:11-14.
25. Ma EP, Baken RJ, Roark RM, Li PM. Effect of tones on vocal attack time in Cantonese speakers. Journal of Voice. 2012;26: 670.e1.
26. Lee T-yT, 李 芷 茵 . The effects of vocal intensity on vocal attack time (VAT): The University of Hong Kong (Pokfulam, Hong Kong); 2010.
27. Tam K-cB, 譚家駿 . Effects of straw phonation on vocal attack time in Cantonese speakers: The University of Hong Kong (Pokfulam, Hong Kong); 2013.
28. Zhang R, Baken RJ, Kong J. Vocal Attack Time of Different Pitch Levels and Vowels in Mandarin. Journal of Voice. 2015;29:542-547.
29. Kong J, Zhang R. VAT of the lexical tones in Mandarin Chinese. Journal of Chinese Linguistics. 2017;45:275-289.
30. Roark RM, Watson BC, Baken RJ. Measures of vocal attack time for healthy young adults. Journal of Voice. 2012;26:12-17.
31. Paal S, Reulbach U, Strobel-Schwarthoff K, Nkenke E, Schuster M. Evaluation of Speech Disorders in Children with Cleft Lip and Palate. Journal of Orofacial Orthopedics / Fortschritte der Kieferorthopädie. 2005;66:270-278.
32. Whitehill TL. Assessing intelligibility in speakers with cleft palate: a critical review of the literature. Cleft palate-craniofacial journal. 2002;39:50-58.
33. Dowden, Patricia A. The effects of listener training on the speech intelligibility of severely dysarthric individuals. 1992;2814-2814.
34. Hikita R, Miyamoto JJ, Ono T, Honda E-i, Kurabayashi T, Moriyama K. Activation patterns in the auditory association area involved in glottal stop perception. Journal of Oral Biosciences. 2013;55:34-39.
35. Jiang C, Whitehill TL, Mcpherson B, Ng ML. Consonant accuracy in Mandarin-speaking children with repaired cleft palate. International journal of pediatric otorhinolaryngology. 2015;79:2270-2276.
36. Orlikoff RF, Deliyski DD, Baken RJ, Watson BC. Validation of a glottographic measure of vocal attack. Journal of voice : official journal of the Voice Foundation. 2009;23:164-168.
37. Moore P. Motion picture studies of the vocal folds and vocal attack. Journal of Speech Disorders. 1938;3: 235-238.
38. Hirose H, Gay T. Laryngeal Control in Vocal Attack. Folia Phoniatrica et Logopaedica. 1973;25:203-213.
39. Cerom JL, Macedo Cde C, Feniman MR. Can peripheral hearing justify the speech disorders in children with operated cleft palate? Int Arch Otorhinolaryngol. 2014;18:27-35.

O 039

Longitudinal study of vocal development and language environments in Korean-learning children with and without cleft palate

Seunghee Ha
Hallym University (Korea)

【Background】Few studies have thoroughly investigated vocal development and early language environment based on sufficient data in their natural environments in children with cleft palate (CP) before and after palatal surgery. The

Language Environment Analysis (LENA) enables researchers to collect a representative sampling of vocalizations in natural environments through a full day-long recording. This study aimed to investigate vocalization and language environment longitudinally through human coding as well as automated vocal analysis of naturalistic recordings in children with CP.

【Method】 Ten children with CP and age- and gender-matched 10 children without CP participated in the study. Their LENA data from a 16-hour recording at home were collected at 3-month intervals from 4–6 months to 22-24 months of age and therefore, each child provided vocalization samples at 7 different months of age. The recordings were analyzed using the LENA automated analysis program, which provided quantitative measures about infant vocalization and language environments. Human coding of the LENA recordings was also conducted for a detailed investigation of vocalization and language environment. Twenty 5-minutes segments at the child's highest vocalization rate determined by the LENA automated analysis were selected from each all-day home recording. Human coding was performed in real time using the Action Analysis Coding and Training software. Several measurements of vocalizations including the true canonical babbling ratio (CBR) were calculated for each time point of data collection for each child. Also, language environments were analyzed in detail based on measures including the ratio of the infant-directed speech. Statistical analyses were performed to conduct group and age comparisons through each measure on vocalization and language environments.

【Results and Discussion】 The results showed that children with CP did not show significant differences from children without CP in all the measures related to language environment across 4–6 months and 22–24 months of age. No group difference emerged in frequency of vocalization during the period of the study. Children with CP produced significantly fewer CBR and true CBR than children without CP at 13 to 15 months and at 19 to 21 months.

【Conclusion】 This study provides detailed information through naturalistic all-day home recordings about early language environments and vocal development in children with CP before and after palatal repair. Clinical implication for early intervention will be discussed.

【References】 This research has been supported by the National Research Foundation of Korea Grant funded by the Korean Government (NRF-2016S1A2911363).

O 040

Our 15-years experience for chelioplasty

Murod M. Jafarov, MD, PhD,
Mirjamol M. Jafarov, MD,
Timur Radjamatov MD,
Aziz Boykuvvatov, MD
Republican Center of pediatric plastic surgery
Clinic of Tashkent pediatric medical
Institute (Uzbekistan)

【Background】 Since 2003, we have operated on more than 3,000 children with cleft lips. The main method of operation was the Millard method with our modification.

【Method】 During the period 2003 - 2018, 3134 children with cleft lip were operated. Of these, 1835 were boys and 1299 were girls. Unilateral was 2478 and bilateral was 656. The main part of patients who underwent surgery was 4-7 months old child.

【Result】 Patients underwent a chelioplasty operation according to the Millard method with partial modification of it. We used an extreme flap on both sides to close the crevice from the back wall, i.e. from the side of the mucous lips. Flap fabrics for closure were sufficient and we could loosely close the widest crevices of the lips. The same method we used for bilateral crevices of the upper lip.

【Discussion】 All surgical interventions were without complications. During the chelioplasty operation, it was used; we observed patients for 3-6 years and received positive results. The free movement of the upper lip and the symmetry of its entire structure were noted.

O 041

Prevention of postoperative deformities in treatment of children with congenital cleft lip

Stepanova Y.V., Tsyplakova M.S.,
Baindurashvili A.A.,
The Turner Scientific Research Institute
for Children's Orthopedics (Russia)

【Bachground】 Congenital cleft lip and palate is a severe malformation of maxillofacial region. Prevention of postoperative deformities of the nose and upper lip in treatment of children with cleft upper lip and palate is one of the most difficult tasks of pediatric maxillofacial surgery.

【Method】 During the period 2010-2018, 412 children with unilateral and bilateral cleft lips were treated. All children from the first days of life were given preoperative preparation: early orthodontic treatment, use of an obturator, nose and upper lip massage. Primary rhinocheiloplasty was performed in children aged 2-6 months old. Regardless of the cleft shape, the operation was performed in one stage. To prevent postoperative deformities in the postoperative period, the nose and upper lip were massaged, orthodontic treatment was used for anatomic occlusion, conservative measures were taken in the postoperative period, individual tubes were used in the nasal passages.

【Result and Discussion】 Prevention of postoperative deformities in treatment of children with cleft lips should begin in the preoperative period, eliminating congenital deformity of the upper jaw and improving the condition of soft tissues. This greatly improves the conditions for primary rhinocheiloplasty. During the primary operation, it's necessary to completely eliminate abnormal pull of muscles, to restore the bottom of the nasal passage and the proper buccal cavity. When carrying out the stage of rhinoplasty in the primary operation, it is necessary to completely release the alar cartilage and move it to the correct position. Application of massage, myogymnastics, the use of individual tubes in the nasal passages in the early and late postoperative period allow not only to improve the condition of the postoperative scar, but also stimulates the normal growth of lip and nose tissues. When using this comprehensive treatment plan, 86% of children with unilateral cleft lip and 63% of children with bilateral cleft lip didn't need

corrective operations. Comprehensive treatment of children with cleft lips, orthodontic treatment from the first days of a child's life to the end of facial formation, conservative measures to prevent severe scars, the use of nasal tubes in the postoperative period significantly improve the results of treatment of children with cleft lips.

O 042

The Triangular Skin-white Roll Flaps Technique for Creation of Cupid's Bow in Bilateral Cheiloplasty

Geoff Williams
International Children's Surgical Foundation (USA)

【Background】For the surgeon contemplating bilateral cheiloplasty, creation of a beautiful and enduring Cupid's Bow with the degree of projection and definition in the normal lip is daunting.

【Method】Cupid's Bow essentially outlines a triangle, the creation of which is addressed through the use of two smaller triangular skin-white roll flaps, one on each of the two lateral lip elements, after which each flap is transposed inferiorly and medially to meet its counterpart in the midline to form Cupid's Bow. Over 200 patients with all varieties of bilateral cleft lip deformity underwent cheiloplasty using the triangular skin-white roll flaps technique from 2006 to 2018. Patients were followed long-term (yearly) when possible, using standard photography.

【Result and Discussion】More than ninety percent of patients exhibited significant projection, definition and form of Cupid's Bow at long–term follow-up. There were no instances of necrosis, infection or dehiscence of the Cupid's Bow construct. The triangular skin-white roll flaps technique is consistently reliable although it requires painstaking attention to detail performed under loupe magnification.

O 043

CAD-CAM construction of a pilot guide for a bone-anchored epithesis to replace an absent pinna

Olivier MJ Beckers, MD
Ana Tache, MD, DMD,
Erica Coppey, MD
Prof. Maurice Y. Mommaerts, MD, DMD, PhD,
European Face Centre,
Brussels University Hospital (Belgium)

【Background】Bone-anchored prosthetic devices have acquired an important role in the rehabilitation of craniofacial defects, not in the least for auricle reconstruction. Temporal bone quality and thickness are critical for osseointegration of the fixtures. Ipsilateral anatomical landmarks can be used as a guide for the future position of the ear epithesis but they give little information about the underlying bone and can be distorted in congenital malformations.

Many techniques have been described for the orientation of a surgical template but most of them are circumlocutory and none of them used a fully digital workflow . This article describes a digital workflow for computer-aided design and manufacturing (CADCAM) of a diagnostic and surgical template.

【Method】Two hemifacial microsomia patients with grade IV microtia were treated accordingly. The upper dental arch was optically scanned and a cone-beam computer tomography (CBCT) scan of the cranium was obtained. The created composite model and the soft tissue model were exported into 3D sculpting software. The unaffected ear was virtually mirrored to the affected site and two ideal implant positions were defined in relationship to bone thickness, contralateral symmetry and housing of the retaining bar. A bite wafer was virtually designed on the upper dental arch and connected to the mirrored ear. The pilot guide was 3D printed and allowed for correct positioning and orientation during surgery. The silicone prosthetic pinna was manufactured in a conventional way. A bar with retaining clips was used to anchor the prosthetic pinna.

【Results】Clinically satisfactory results were obtained in two grade IV microtia cases. One failing implant had to be replaced because of non-osseointegration.

【Discussion】The fully digital workflow presented to design and 3D print an optimal ear epithesis guide presents a good alternative to the existing techniques. Transfer to the operation field is very accurate since no intermediary steps are needed and fabrication of the clinical trial-in,the diagnostic and surgical template are all performed in a single fully digital environment.

【References】

1. Gumieiro EH, Dib LL Jahn RS, Santos Junior JF, Nannmark U, Granström G., Abrahão M (2009) Bone- anchored titanium implants for auricular rehabilitation: case report and review of literature. Sao Paulo Med J 127,160-165
2. Ciocca L, Mingucci R, Bacci G, Scotti R (2009) CAD-CAM Construction of an auricular template for craniofacial implant positioning: A novel approach to diagnosis. Eur J Radiol 71:253-256 10
3. Mevio E, Facca L, Mullace M, Sbrocca M, Gorini E, Artesi M, Mevio N (2015) Osseointegrated implants in patients with auricular defects: a case series study. Acta Otorhinolaryngil Ital 35:186-190
4. Gentile P, Bottini DJ, Gravante G, et al (2008) The use of bone-anchored implants for absent ear. J Craniofac Surg 19:744–747
5. Otero JJ, Vijverman A, Mommaerts MY (2017) Use of fused deposit modeling for additive manufacturing in hospital facilities: European certification directives. J Craniomaxillofac Surg 45:1542-1546

O 044

The development of a 3D printing trans-sinus maxillary distraction device on cleft patient

Ming Cai[1)], Guangwei Li[2)],
Guofang Shen[2)], Guomin Wang[2)]
[1)]Shanghai Ninth People's Hospital,
Shangha Jiaotong University,
School of Medicine
[2)]Department of Oral and
Cranio-Maxillofacial Surgery,
Shangha Jiaotong University (China)

【OBJECTIVE】To develop a customized trans-sinus maxillary distraction device by selective laser melting 3D printing

technique and compare the mechanic properties and clinical precision with conventional distractor.

【METHODS】 The 3D designing software was used to design the customized distractor based on a maxillary hypoplasia patient secondary to cleft lip and palate. The customized maxillary distractor was manufactured through combination of SLM printing technology and traditional technology. The mechanical properties of 3D distractors were tested compared with the commercial distractors. The skull model surgery was performed to assess the distraction accuracy of the customized distractor compare by pre and post 3D CT measurements.

【RESULTS】 The customized distractor can be fixed on the bony surface without pre-bending the distractor plate. The adjacent anatomic structures such as tooth root can be reconstructed by software which might reduce the intraoperative unexpected damage. The location of plate hole can be planned in the strut area of the maxilla which can provide sufficient mechanical support during distraction procedure. The biomechanical tests showed the appropriate properties of customized distractor compare with conventional devices. The skull model surgery showed higher precision and better degree of parallelism of customized trans-sinus distractors.

【CONCLUSIONS】 The 3D printing trans-sinus maxillary distractor has good mechanic properties which can transfer the surgical plan to the operation with high accuracy without damaging the adjacent structures. The potential application of this device can improve the clinical efficacy of maxillary distraction osteogenesis on cleft patients.

O 045

Utilization of Cleft Lip and Palate Post-Operative Care Guidebook for Caregivers Based on Local Wisdom for Rural Area Communities

Anindita Zahratur Rasyida,
Taufan Bramantoro,
David B. Kamadjaja,
Stanley S. Kamadjaja,
Ni Putu Mira Sumarta,
Universitas Airlangga,
Surabaya (Indonesia)

【Background】 Indonesia as a developing country is presumed to be high incidence of Cleft Lip and Palate (CLP). We held a cleft mission in Bima, Nusa Tenggara Barat, Indonesia, a rural area. Education barrier as well as facilities, socioeconomic status of the residents may contribute as challenges of post-operative care information. “Cleft Lip and Palate post-operative care guidebook for caregivers” with illustration and local wisdom may bridge this barrier to deliver proper explanation; besides its handiness and ease of use. The aim of this study was to describe the utilization of the guidebook for rural area communities.

【Method】 We provided the guidebook after CLP surgery in Bima, Nusa Tenggara Barat. A Total of 20 patient’s caregivers were enrolled in this study. They were asked to complete questionnaires in 2 weeks after surgery. We provided the descriptive data in this study.

【Result and Discussions】 Most of the CLPpatients were under 6 years old (80%) with the majority of the patients undergone palatoplasty (47.62%), followed by labioplasty (38.09%). Post-operative care is an important factor determining outcome after surgery. Local medical staffs are well trained in postoperative management despite limited in-hospital time after surgery in a cleft mission. Therefore, home-care management by the caregivers is mandatory. Parents counted the most as caregivers for the CLP patients (75%). They need to be informed and directly involved with postoperative care to achieve the best possible result. All caregivers agreed that this guidebook was easy to understand and had complete information related to post-operative CLP care. This guidebook was also considered attractive and the language used was understandable.

O 048

Articulation therapy for the clients with glottal stops accompanying velopharyngeal insufficiency -Prevention of oral-glottal double articulation-

Jin KAWAMURA[1)], Naohiro KIDO[1, 3, 4)]
Yuri FUJIWARA[2)], Naritaka KIMURA[3, 4)]
[1)]Hiroshima City Asa Citizens Hospital,
Dept. of Rehabilitation Medicine,
[2)]Osaka Health Science University,
Dept. of Speech Therapy
[3)]Hiroshima City Hiroshima Citizens Hospital,
Dept. of Plastic and Reconstructive Surgery,
[4)]Hiroshima City Hiroshima Citizens Hospital,
Cleft Lip and Palate Center (Japan)

Among the difficult cases with velopharyngeal insufficiency, oral-glottal double articulation is thought to be the major factor which prevent clients from increasing oral pressure during the primary stage of intervention, or from stabilizing the oral target in running speech at the final stage, in spite of the absence of severe velopharyngeal insufficiency, fistulas, or mental deficiency. This presentation will provide precautions and techniques to eliminate oral-glottal double articulation at the primary intervention stage based on our research.

Kido et al. (2000, 2006) reported that abnormal vocal folds adduction in oral-glottal double articulation helps to create pressure for consonant production above glottis. Once the client learned atypical supply method of air pressure, i.e. subglottic air pressure, it is generalized into every voiceless stops and affricatives. The client with glottal stops has never experienced to create oral pressure for consonant production. If a speech therapist takes her/him to atypical manipulation of air pressure, it will cause a chain of mislearning which responsibility lies with speech therapist. It is said that “Be careful not to mislead oral-glottal double articulation by speech therapy” in references, however, little has been mentioned how to lead normal articulation without acquiring abnormal laryngeal movement. Our strategy in primary intervention is 1) to let the client in on producing oral pressure consonants with abducted vocal folds, 2) to lead phonological awareness after acquiring typical articulatory movement (to be aware of target sounds).

In our institution, approximately 30 primary palatoplasties have been performed every year. There are no cases with oral-glottal double articulation during the course of speech therapy since 2000. It is sometimes difficult to perceptually judge oral-

glottal double articulation. Including discrimination method, our strategy for oral-glottal double articulation will be presented.

O 049

Costello syndrome phenotype with a de novo MRAS mutation

Hisato Suzuki[1)], Mamiko Yamada[1)], Tomoko Uehara[1)], Toshiki Takenouchi[2)], Hiroshi Yoshihashi[3)], Satoshi Takasago[4)], Satoshi Ihara[5)], Kenjiro Kosaki[1)]
[1)] Center for Medical Genetics, Keio University, School of Medicine
[2)] Department of Pediatrics, Keio University, School of Medicine
[3)] Department of Medical Genetics, Tokyo Metropolitan Children's Medical Center
[4)] Department of Cardiology, Tokyo Metropolitan Children's Medical Center
[5)] Department of Neurosurgery, Tokyo Metropolitan Children's Medical Center (Japan)

【Background】 RASopathy includes Noonan syndrome, cardio-facial-cutaneous (CFC) syndrome, and Costello syndrome. Disorders belonging to the RASopathy share overlapping characteristics including facial dysmorphisms, intellectual disability, cardiac defects, and growth delay. In 2018, two patients with a Noonan syndrome phenotype were shown to carry mutations in the yet another RASopathy gene, MRAS (muscle RAS oncogene homolog). Here, we report a patient with a de novo mutation (Q71R) in MRAS who had Costello syndrome-like phenotype.

【Clinical report】 The patient was a 2-year-old boy who was born to non-consanguineous Japanese parents with no significant family medical history. He exhibited cyanosis, tachycardia, and paroxystic sweating because of crying during the neonatal period and was diagnosed as having hypertrophic cardiomyopathy. Dysmorphic features included relative macrocephaly, a down-slanted palpebral fissure, hypertelorism, a depressed nasal bridge, bulbous nasal tip, low-set ears with thick lobes, and full lips. A whole exome analysis identified a de novo heterozygous mutation in MRAS (NM_001085049.2), i.e., c.212A>G, p.Gln71Arg.

【Discussion】 The MRAS Gln71Arg mutation corresponds to the codon Gln61Arg of HRAS KRAS, and NRAS which reportedly exert a gain-of-function effect in the RAS pathway in cancer cells and have been recurrently observed as somatic driver mutations in various tumors.

The relatively severer phenotype as Costello syndrome of the presently reported patient, compared with the previously reported patients as Noonan syndrome, can be explained by the strong degree of functional gain caused by the MRAS Q71R substitution, which was equivalent to an NRAS, KRAS, or HRAS Q61R substitution.

In summary, we reported the first patient with Costello–like syndrome and a MRAS Gln71Arg mutation. We suggest the MRAS gene would be yet another gene responsible for Costello syndrome.

【Funding】 This work was supported by the Initiative on Rare and Undiagnosed Diseases Program [Grant number JP18ek0109301] from the Japan Agency for Medical Research and Development.

【Conflict of Interest】 No conflict of interest

O 050

The mortality and morbidity of very low birth weight (VLBW) infants with trisomies in Japan.

Hidenori Kawasaki[1, 2)], Takahiro Yamada[1, 2)], Masatomo Oomiya[3)], Yoshimitsu Takahashi[4)], Takeo Nakayama[4)], Shinji Kosugi[1, 2)]
[1)] Graduate School of Medicine Kyoto University, School of Public Health, Medical Ethics and Medical Genetics
[2)] Kyoto University Hospital Clinical Genetics Unit
[3)] Graduate School of Medicine Kyoto University, School of Public Health, Biostatistics
[4)] Graduate School of Medicine Kyoto University, School of Public Health, Health Informatics (Japan)

【Background】 The mortality rate of very low birth weight (VLBW) infants is very low in Japan. Three to five percent of neonates have some kind of congenital anomalies and one fourth of them are chromosomal abnormalities. Little is known about prognosis of VLBW infants with chromosomal abnormalities in Japan.

【Purpose】 Our purpose was to investigate mortality and morbidity of VLBW infants with trisomy 21 (T21), trisomy 18 (T18) or trisomy 13 (T13).

【Method】 Maternal and neonatal data were collected prospectively for infants weighing less than 1,501 grams who admitted to centers of the Japanese Neonatal Research Network (NRN-J) during the period of January 2003 to December 2016. Statistical significance for unadjusted comparisons was determined using Fisher's exact test, Pearson's chi-square test, Student's t test and log-rank test. Poisson regression models were used to compare outcomes between the groups while adjusting for gestational age and other characteristics. This study was approved by Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

【Result】 Of 60,136 VLBW infants, number of T21, T18, and T13 was 327 (0.54 %), 564 (0.94 %) and 60 (0.10 %), respectively. As for maternal complication, T18 and T13 had significantly increased risk of hypertensive disorders of pregnancy and premature rupture of membrane, respectively. Male contribution was significantly high in T21 compared with the other two groups. More than 95 % of T18 VLBW infants were small for gestational age. Although both T18 and T13 had higher incidence of neonatal asphyxia, they had lower risk of chronic lung disease, patent ductus arteriosus, cystic periventricular leukomalacia, and retinopathy of prematurity, compared with T21. Mortality rate in NICU was 22.9 %, 70.4 % and 76.7 % for T21, T18 and T13, respectively. Mean length of hospital stay for survivors was 123.3 days, 202.7 days and 193.8 days for T21, T18 and T13, respectively.

【Discussion】 NRN-J database contains about two third of VLBW infants born in Japan and our data is the first national

survey for VLBW infants with trisomies. Although there is limitation that no data exists about the timing of diagnosis, which may affect the plan for care, our data showed that a little less than 30 % of VLBW infants with T13 or T18 could achieve to go home. This is a meaningful data for prenatal counseling, perinatal management and treatment.

O 051

Effectiveness of integrated interpretation of exome and corresponding transcriptome data in detecting splicing variants: Population and clinical studies

Mamiko Yamada[1)], Yuichi Shiraishi[2)], Hisato Suzuki[1)], Kenji Kurosawa[3)], Kenjiro Kosaki[1)]
[1)] Center for Medical Genetics, Keio University School of Medicine
[2)] National Cancer Center Research Institute
[3)] Division of Medical Genetics, Kanagawa Children's Medical Center (Japan)

【Background】 Sensitivity of exome analysis is yet suboptimal in defining molecular pathology of patients with multiple malformation syndromes. Weakness partly lies in its incapability to capture aberrant splicing. Whole transcriptome analysis would resolve this issue under scenarios where clinical diagnosis is relatively secure. Otherwise excessive number of potentially pathogenic splicing events hinders proper interpretation. Here we developed a protocol to detect aberrant splicing events and their triggering germline variants with a help of the Bayesian network method SAVNet that had originally been developed in cancer genomics.

【Methods】 We applied the algorithm to decipher abnormal splicing events and examined the correlation between these events and rare germline variants (MAF <0.03) among 179 phenotypically normal subjects whose RNA-seq data (lymphoblastoid cell lines) and corresponding exome data were publicly available. Only the 1913 causative genes of known autosomal recessive disorders were evaluated under the premise that the subjects could be carriers.

【Results】 Among 1913 genes, 1272 had expression levels that were sufficient to be analyzed by SAVNet. Forty aberrant splicing events associated rare germline variants were detected in 31 of the 179 subjects; creation of alternative 5' splice site (12/40 events), creation of alternative 3' SS (14) and exon skipping (13). The predicted effects on protein were as follows: mutation out of frame (29), and in-frame (11). Intriguingly, seven variants annotated as “missense” (5) or “silent” (2) per exome analyses had triggered abnormal splicing that disrupted the reading frame. Conventional exome analysis the 1272 genes detected a total of 144 putatively pathogenic variants including nonsense, frameshift, and canonical splice site (gt/ag) mutations.

【Clinical validation】

We applied the method to analyze a patient with craniosynostosis, cleft palate, and intellectual disabilities of whom diagnosis was unknown unknown through clinical evaluation or even by conventional exome analysis. Subsequent RNA-seq analysis of mRNA derived from peripheral blood and integrated analysis of exome data and RNA-seq data through the SAVNet analysis detected two rare variants that were shown to be associated with abnormal splicing. One of the two variants resided in the intron of HNRNPK gene that is causative of Au-Kline syndrome. Demonstration of de novo occurrence of this variant confirmed the diagnosis.

【Discussion】 Coupling interpretation of personal genomes with their corresponding transcriptomes successfully uncovered pathogenic splicing variants enhances performance of conventional exome analysis through proper interpretation of intronic variants that are outside of the consensus gt/ag-donor/acceptor sites.

No conflicts of interests

【Funding information】 Award Number: Research on Rare and Intractable Diseases; Japan Agency for Medical Research and Development, Grant/Award Number: JP18ek0109301

O 052

Mouse resource infrastructure for studies of genome functions and disease mechanisms

Atsushi Yoshiki, Shinya Ayabe, Toshiaki Nakashiba, Saori Mizuno, Masaru Tamura, Takanori Amano, and Hiroshi Masuya
RIKEN BioResource Research Center (Japan)

【Background】 Advancement of sequencing technology of genome and transcripts has generated exponentially increasing number of patient-derived genetic variants to be tested for the causality or pathogenicity of the disease condition. Currently, animal models, especially, laboratory mice are expected to play key roles and become more feasible tools by the genome editing and comprehensive phenotyping to validate whether the patient-derived genetic variants are disease-causing or not.

【Purpose】 As the core facility of laboratory mice in the National BioResource Project by MEXT/AMED, RIKEN BioResource Research Center (BRC) has collected, preserved, quality-controlled and distributed mouse models to promote studies of genes and diseases in the global biomedical research community. In addition, as a member of International Mouse Phenotyping Consortium (IMPC), we have generated and disseminated coding-gene knockout mouse resources associated with disease relevant and broad-based phenotypic data to build up the infrastructure for understanding genome functions and disease mechanisms.

【Achievement】 All our operation procedures including animals at RIKEN BRC have been approved by the Institutional Animal Care and Use Committee of RIKEN Tsukuba Branch. We have so far collected over 8,800 strains including genome-edited mice mainly developed by Japanese scientists and distributed the mice to 1,400 organizations around the world. The distributed mice were assured in high-quality by our strict microbial and genetic quality control programs. The IMPC has so far collectively produced 7,700 coding gene knockout (KO) mice, phenotyped the KO lines through standardized and comprehensive phenotyping platform. The phenotype data of over 6,000 KO lines with 69 million data points and approximately 369 K images has been

made freely available from the IMPC web portal.

【Discussion and future direction】 Thus, we have established high-quality mouse resources developed by Japanese scientists as well as global efforts, and built up KO mouse production pipeline by genome editing and disease-relevant phenotyping platform of global standard. To pursue precision mouse models of human genetic diseases, we will seek collaborative clinical partners to maximize the potential of our mouse resources, the production pipeline and the phenotyping platform, and facilitate the development of new therapies.

The author has no conflict of interest.

O 053

Reduction of CDK8 kinase activity induces human congenital defects through inhibition of WNT pathway

Tomoko Uehara[1)], Kota abe[2)], Masayuki Oginuma[2)], Nobuhiko Okamoto[3)], Hiroshi Yoshihashi[4)], Kenjiro Kosaki[1)], Tohru Ishitani[2, 5)]

[1)] Center for Medical Genetics, Keio University, School of Medicine

[2)] Department of Molecular Medicine, Institute for Molecular & Cellular Regulation, Gunma University

[3)] Department of Medical Genetics, Osaka Women's and Children's Hospital

[4)] Department of Medical Genetics, Tokyo Metropolitan Children's Medical Center

[5)] Department of Homeostatic Regulation, Research Institute for Microbial Diseases, Osaka University (Japan)

【Background】 Cyclin-dependent kinase 8, CDK8, is an evolutionarily conserved serine/threonine kinase. CDK8 is a member of the CDK/Cyclin module of the mediator complex that regulates a variety of transcription regulators including β-catenin and Notch. Mutations in other members of the CDK/Cyclin module including MED12 and MED13 are associated with syndromic intellectual disability and collectively referred to as "mediatropathies". As expected, a recent study reported 12 patients with heterozygous missense CDK8 mutations who presented with syndromic form of intellectual disability that resembles patients with mediatorpathies. Mechanistic basis of CDK8-related disorder and mediatropathies leading to specific defects is yet to be delineated. Here we report two patients with de novo missense mutations within the kinase domain of CDK8 and zebrafish model of these patients to delineate mechanistic basis of the CDK8-related disorder.

【Clinical report】 Patient 1 was a 2-year-old male who had short stature, intellectual disabilities, microcephaly, congenital heart defects and renal anomalies. Dysmorphic features included hypertelorism, epicanthal folds, low-set ears, prominent antihelix, a short philtrum, a high nasal bridge, a high arched palate, and a micrognathia. Patient 2 was an 8-year-old male who had short stature and intellectual disabilities. Dysmorphic features included hypertelorism, epicanthal folds, a short philtrum, a wide nasal bridge, protruding ears, and bifid uvula, cubitus valgus, and pes planus. Exome analysis showed both patients had heterozygous de novo missense variants in CDK8 (NM_003718) (Patient 1: p.G28A; Patient 2 p.N156S).

【Results】 Pathogenicity of the variants were evaluated by various in vitro and in vivo assays. 1) In vitro kinase assay of human CDK8 showed that enzymes with p.G28A or p.N156S substitution exhibited decreased kinase activity. 2) Zebrafish overexpression analyses showed that p.G28A or p.N156S alleles were hypomorphic alleles in vivo. Importantly, inhibition of CDK8 kinase activity in zebrafish embryos using morpholino antisense oligonucleotide or specific chemical inhibitor induced the craniofacial and heart defects related to the patients' phenotype.

【Discussion】 We suggest inhibition of Wnt/β-catenin signaling in developing neural crest cells may play a role in the pathogenesis of CDK8-associated disorder because of phenotypic overlap between inhibition of Cdk8 activity and Wnt/β-catenin signaling. In conclusion, zebrafish studies showed that missense mutations in kinase domain of CDK8 cause human congenital defects as hypomorphic alleles.

【Funding】 This work was supported by the Initiative on Rare and Undiagnosed Diseases Program [Grant number JP18ek0109301] and the Japanese Rare Disease Models and Mechanisms Program [Grant number JP19ek0109288h0003] from the Japan Agency for Medical Research and Development.

【Conflict of Interest】 No conflict of interest

O 054

A Three-Center Study of Dental Arch Relationships Outcomes Following Two-Stage Palatoplasty

Junya Kato[1)], Tadashi Mikoya[2)], Yumi Ito[1)], Yoshiaki Sato[3)], Setsuko Uematsu[4)], Yasumitsu Kodama[5)], Takafumi Susami[6)], Tadashi Yamanishi[4)], Ritsuo Takagi[5)], Kanchu Tei[1)]

[1)] Department of Oral and Maxillofacial Surgery, Division of Oral Pathobiological Science, Graduate School of Dental Medicine, Hokkaido University

[2)] Stomatognathic Function Center for Advanced Oral Medicine, Hokkaido University Hospital

[3)] Department of Orthodontics, Graduate School of Dental Medicine Division of Oral Functional Science, Hokkaido University

[4)] Department of Oral and Maxillofacial Surgery, Osaka Women's and Children's Hospital

[5)] Division of Oral and Maxillofacial Surgery, Graduate School of Medical and Dental Sciences, Niigata University

[6)] Department of Oral-Maxillofacial Surgery, Dentistry and Orthodontics, University of Tokyo Hospital (Japan)

【Introduction】 To compare Dental arch relationship outcomes of the patients with complete unilateral cleft lip and palate (UCLP) treated by three different treatment protocols with two stage palatoplasty.

【Materials&Methods】The inclusion criteria were as follows:complete UCLP, excluding patients with Simonart's band; Japanese ethnic background; Normal birth weight infants; and no associated congenital anomalies. 104 patients participated in this study. All patients in this study were carried out the presurgical orthopedic treatment advocated by Hotz and Goninski. In Hokkaido University Hospital (H.U.), Cheiloplasty was performed by modified Millard method at the mean age 5.0 months. Soft palate and the posterior half of hard palate closure was done using Perko method or modified Furlow method at the mean age of 1 year 7 months. In Niigata University Hospital (NU), Cheiloplasty was performed by Cronin method at the mean age 6.1 months. Soft palate was repaired using modified Furlow method at the mean age of 1 year 6 months. Hard palate was closed using Pichler method at the mean age of 5year 8months. In Osaka Women's and Children's Hospital (O.W.), Cheiloplasty was performed by modified Millard method at the mean age 3.0 months. Soft palate was repaired using modified Furlow method at the mean age of 1 year. Hard palate was closed using the Veau method or bridge flap at the mean age of 1 year 5 months. Dental casts were taken between 4.3 and 8.0 years. The casts were randomly numbered and assessed using the 5-Year-Olds'Index（5Y）and Huddart/Bodenham index（HB）. 5Y was performed by 5 raters, and HB was performed by 2 raters each twice.

【Result】Intrarater and interrater reliabilities evacuated using weighted kappa statistics were good or very good for the 5Y and HB rating. The mean 5Y score was 3.0 in H.U.,3.1 in O.W.,2.5 in N.U. (P value was not significant). There was no significant difference of the total HB mean score. The HB scores of canine and molars on minor segment were greater H.U. and N.U. than O.W. (P<.05).

【Conclusion】There were no significant differences at about 5 years old in different treatment protocols with two stage palatoplasty among these centers.

O 055

Rogdi plays an important role during enamel mineralization

Silvia Naomi Mitsui[1)], Akihiro Yasue[1)],
Shinya Horiuchi[1)], Seiichi Oyadomari[2)]
and Eiji Tanaka[1)]
[1)] Department of Orthodontics and Dentofacial Orthopedics, Institute of Biomedical Sciences, Tokushima University Graduate School
[2)] Division of Molecular Biology, Institute of Advanced Enzyme Research, Tokushima University (Japan)

【Background】Kohlschütter-Tönz syndrome (KTS) is a rare autosomal-recessive neurodegenerative disorder characterized by progressive dementia, epilepsy and amelogenesis imperferta (AI). Although several human ROGDI mutations have been associated with the disease, little is known about the function of ROGDI protein.

【Purpose】The aim of the present study is to create an animal model of the disease to elucidate the role of Rogdi during enamel formation.

【Methods】Rogdi disrupted mice were generated by targeting the start codon and fifth exon with CRISPR/Cas system. After verification of the correct targeting of the founders, mosaic mice were backcrossed with C57BL/6 mice. Scanning electron microscopy (SEM), micro-CT and histology were analyzed to study the phenotype. Calcein labeling of enamel was performed to analyze the ameloblast modulation cycle. Furthermore, P8 and P12 maxillary molar were isolated to analyze the expression of enamel proteins and proteinases by qPCR.

【Results】Three alleles with nonsense mutations in the start codon and one allele with a nonsense mutation in the exon 5 of Rogdi were obtained. All mice in the homozygous condition of these alleles showed chalky white enamel except the one with a nonsense mutation in the start codon. SEM and micro-CT images showed the loss of enamel in Rogdi-/- mice at 4 weeks, which was hypomineralized with altered enamel structure. Furthermore, ameloblasts at the maturation stage were shorter with altered polarization. There was no significant difference in the expression of enamel protein and proteinases between wild-type and Rogdi-/- mice. However, calcein labeling of enamel in Rogdi-/- mice did not show the bands of smooth ended ameloblasts observed in the wild-type.

【Discussion】Rogdi-/- mice generated with CRISPR/Cas system targeting the start codon and exon 5 showed AI, resembling the phenotype observed in KTS. The obtained results indicate that the enamel defect is due to disruption in the ameloblast modulation cycle and suggest that Rogdi plays an important role during enamel biomineralization. Regarding the mice with a nonsense mutation in the start codon showing normal enamel, illegitimate translation from the second methionine located downstream the start codon might be the reason for the unexpected phenotype.

【There is no conflict of interest to declare】This work was supported by JSPS KAKENHI Grant Number 18K17261 (S.N.M) and 16H05551 (A.Y).

O 056

New strategies to prevent Neural Tube Defects by folic acid supplementation with public-private partnership in Japan.

Seika Kamohara
DHC Corporation (Japan)

【Background】Neural tube defects (NTDs), major congenital anomalies of the central nervous system involve both genetic and non － genetic factors in their etiology. Mandatory folic acid（FA）fortification of food has proven to be highly effective in decreasing NTD cases, expanded globally whereas Japan does not yet have such a policy. The Japanese Government in 2000 recommended intake of 400μg of folic acid supplement per day during the period from 1 month before pregnancy to 3 months of pregnancy for potentially pregnant women. However, the prevalence of NTDs in Japan has not been declined yet.

【Purpose】To establish new effective strategies to prevent NTDs by folic acid supplementation with public-private partnership in Japan.

【Method】As of March 2019, DHC Corporation has signed comprehensive partnership agreements with 20 local governments for regional revitalization and health promotion.

As part of that, the enlightenment and distribution of folic acid supplementation during pregnancy were suggested for maternal and child health as one of their policies.

【Result】 As a result, nine municipalities have been carrying out the enlightenment activities with the distribution of DHC folic acid supplement at the time of issuance of the Mother and Child Handbook. In addition, there is a local government, which conducts the educational activity at the time of marriage registration also.

【Discussion】 The prevalence of NTDs did not decline, despite the recommendation of FA supplement intake by the Japanese Government in 2000. Because folate is essential for C1 metabolism, a network of pathways involved in several biological processes including nucleotide synthesis, DNA repair and methylation reactions, maternal folate throughout pregnancy may have other roles in offspring health, including neurodevelopment and cognitive performance in childhood. In fact, recent studies showed that the periconceptional folic acid improves pregnancy outcomes, in the prevention of miscarriage, premature birth, pregnancy hypertension syndrome, postpartum depression, and autism. Therefore, enlightenment and distribution activities of folate supplements applying the method of public-private partnership are considered to be rational and effective measures for the health of mothers and children.

N 501

3D computer-assisted two-layer and three-layer facial models of the congenital anomaly and AR technology

Misato Katayama, Daisuke Mistuno, Koichi Ueda
Osaka Medical College Plastic and
Reconstructive Surgery (Japan)

【Background】 Recently simulation surgery is progressively being introduced into surgical training in plastic surgery. However, there are few reports showing its usefulness. The models on which we developed and performed simulation surgery were realistic three-dimensional(3D), computer-assisted, two-layer elastic models(PRS 2017), three-layer models (PRS 2018) and separable two-layered elastic models (2018 PRSGO). On the other hand, our studies confirmed that AR technology using HoloLens from Microsoft Corporation with existing software is useful for evaluating body surface in several clinical applications (PRSGO 2017). Furthermore, we devised a new software to align surgical fields and holograms to perform precise simulation (PRS 2019).

【Purpose】 Our aim is to confirm the usefulness of these models in clinical cases and further explore how to utilize these 3D models and AR technology together in simulation surgery.

【Method】 The two-layer elastic model has the surface layer with polyurethane for skin and the inner layer with silicone for subcutaneous tissue and both the layers adhere to each other. The separable models can be detached the surface layer from the inner layer. The three-layer model has one more layer representing bone. HoloLens which is a head-mounted mixed reality device can display a precise 3D model stably on the real visual field as hologram. In the simulation surgery of many clinical cases including congenital anomaly, facial fracture, orbital tumor etc, we attempted HoloLens to display holograms of skin surface, facial bone, angiography on these models.

【Result】 The two-layer elastic models contributed to teach residents and young doctors how to make several typical local flaps and to perform cheiloplasty. And the three-layer models of facial multiple fracture cases led us to understand simulation of effective approaching method to the fracture site. Additionally, wearing HoloLens, it was possible to perform the typical flap design and simulation surgery on the separable two-layer models while viewing of holograms displayed on the models. Especially three-layer models of congenital anomaly cases enabled us to estimate the volume and size of bone and cartilage graft and to recognize the soft tissue profile change after osteotomy and bone grafting.

【Discussion】 We showed the simulation surgery could be performed more effectively in many clinical cases using these 3D models and AR technology. The possibility of collaboration of the simulation surgery with these 3D models and AR technology will be further explored in the future.

N 502

Prenatal exposure to thalidomide cause abnormalities of inhibitory neuron in rat olfactory nervous system

Ida-Eto M, Matsui Y, Shimotakahara Y,
Tsugiyama LE, Ohkawara T, Narita M.
Department of Developmental and Regenerative Medicine,
Mie University School of Medicine (Japan)

【Background】 Previously, we have demonstrated that prenatal exposure to thalidomide or valproic acid caused abnormalities of serotonergic neuronal system. These abnormalities were similar to human autism, and we reported as autism model rats (Narita et al., Pediatr Res 52: 576, 2002). Autism is a neurodevelopmental disorder and is associated with hypersensitivity to sensory stimuli. Recently, we reported that autism model rats have morphological abnormality of the nucleus of inhibitory pathway in auditory nervous system (Ida-Eto et al., Pediart Int 59: 2404, 2017).

【Purpose】 To clarify whether the other sensory nervous system of autism model rats have impaired, we performed morphological analysis of inhibitory neurons focusing on olfactory brain region, such as piriform cortex and amygdala.

【Methods】 All animal experiments were approved by the animal research committee at Mie University. Pregnant Wistar rats were exposed to thalidomide (500 mg/kg in 5% gum arabic) on embryonic day 9 and 10. The coronal brain slices on postnatal day 50 were cut at a thickness of 50 μm and performed immunohistochemical analysis using anti-parvalbumin antibody to inhibitory interneuron.

【Results】 In autism model rats, the number of parvalbumin immunopositive neurons were decreased in posterior piriform cortex and amygdala. No significant differences were found in anterior piriform cortex.

【Discussion】 Abnormalities of inhibitory neurons in autism model rats were found in the brain regions involving not only hearing but also olfactory sense, posterior piriform cortex. In addition, it has also been reported that human autism have abnormality of the amygdala. The inhibitory neuron of the amygdala may be involved in the mechanisms of sensory

hypersensitivity including olfaction in human autism.
COI: No

N 503

A novel de novo variant in the MAP3K7 gene causes Cardiospondylocarpofacial syndrome by dominant-negative effect.

Tadashi Kaname[1)], Kumiko Yanagi[1)], Takaya Tohma[2)], Shu Kondo[3)], Nana Kobayashi[1)], Kuniaki Saito[3)], Ituro Inoue[4)], Yoichi Matsubara[5)]
[1)] Department of Genome Medicine, National Center for Child Health and Development
[2)] Wanpaku clinic
[3)] Invertebrate Genetics Laboratory, National Institute of Genetics
[4)] Human Genetics Laboratory, National Institute of Genetics
[5)] National Center for Child Health and Development (Japan)

Cardiospondylocarpofacial syndrome (CSCF) is a genetic disease with autosomal dominant inheritance, which is characterized by growth retardation, dysmorphic facial features, brachydactyly with carpal-tarsal fusion, extensive posterior cervical vertebral synostosis, cardiac septal defects with valve dysplasia, and deafness with inner ear malformations. It has been reported that CSCF was caused by MAP3K7 pathogenic variant, but at the same time, reported that different disease, Frontmetaphyseal dysplasia 2 (FMD2) was also caused by MAP3K7 pathogenic variant. It is not clear enough what type of variant in the MAP3K7 gene causes CSCF or FMD2.

We met a four-year-old undiagnosed patient with short stature, dysmorphic facial features (macrocephaly, frontal bossing, long face, mid-face hypoplasia), scoliosis due to vertebral synostosis, coarctation of aorta, atrial septal defects, and cryptorchidism. The patient was dysmorphologically suspected to CSCF.

To analyze the genomic variants in the patient, whole exome sequencing was performed with trio after written informed consent obtained from his parents. Then, a novel heterozygous missense variant, c.574 A>G (p.S192G), in the MAP3K7 gene was found in the patient. The variant was de novo, which was confirmed by Sanger sequencing with trio analysis.

Next, we confirmed the pathogenicity of the variant by transgenic analysis in Drosophila. Expression constructs of the MAP3K7 gene with wild type or the variant type was introduced into a Drosophila mutant, which was overexpressed eiger (TNFalpha). The TNFalpha was at upstream of MAP3K7 in an apoptosis pathway and the eiger mutant was reduced the eye-size. The eiger effect was increased by expression of wild type of MAP3K7, But in contrast, the eiger effect was suppressed by expression of the mutant MAP3K7, suggesting that the variant displayed dominant negative effect.

We concluded that the patient was caused by the de novo missense variant of MAP3K7 and CSCF might be caused by dominant-negative effect in MAP3K7.

COI: nothing to disclose
【Grants】 Grant-in-Aid for Scientific Research, JSPS KAKENHI [18K07863], Grant from the Initiative on Rare and Undiagnosed Diseases in Pediatrics, AMED [16ek0109166h0002]

N 504

Effects of alveolar bone grafts on the quality of life (QoL) of patients with alveolar bone defects

Takao Minamidate[1)], Naoto Haruyama[2)], Ayako Inoue[1)], Shunsuke Nomura[2)], Kenshi Noguchi[3)], Keigo Yoshizaki[2)], Ichiro Takahashi[2)]
[1)] Section of Orthodontics and Dentofacial Orthopedics, Graduate School of Dental Science, Kyushu University
[2)] Section of Orthodontics and Dentofacial Orthopedics, Faculty of Dental Science, Kyushu University
[3)] Department of Orthodontics, Kyushu University Hospital, Fukuoka (Japan)

【Background】 Secondly bone grafting (SBG) for alveolar bone clefts in patients with cleft lip and/or palate (CL/P) is frequently performed prior to canine eruption along with orthodontic treatment. Few studies have focused on how these treatments affect Oral Health-Related QoL (OHRQoL) of the patients at this age.

【Objective】 The present study was performed to evaluate QoLs in patients with CL/P before and after SBG and to compare with those in patients without SBG.

【Method】 Seventy-two orthodontic patients from 8- to 10-year-old were divided into 3 groups: 33 CL/P patients with SBG (SBG group), 11 isolated cleft lip or cleft palate patients without SBG (w/o SBG group), and 28 general orthodontic patients without CL/P (Control group). Each patient completed the CPQ8-10 (self-report of OHRQoL), and PedsQL (self-report of Generic QoL) questionnaires; each parent completed "Parent Proxy-Report (PPR)" of PedsQL. SBG group was assessed at three time points: prior to SBG, 1 month after SBG, and 6 months after SBG. Other groups were assessed at any time after 6 months from their treatment started. Steel-Dwass test or Friedman test was performed for multiple comparisons or repeated measures, respectively (significant level: $P<0.05$).

【Result】 The total and subscale score "Social health" in CPQ8-10 from "w/o SBG group" indicated significantly lower OHRQoL than those from "Control group" ($P=0.024$ and $P=0.031$, respectively). As to the total score of PedsQL, Children's-self-report or PPR showed no significant differences either among the three groups or the three different time points of SBG group. On the other hand, the subscale score "School functioning" in PedsQL (PPR) from "w/o SBG group" indicated significantly lower QoL as compared with that from the "Control group" ($P=0.007$). The subscale score "Physical functioning" in PedsQL (PPR) showed significantly lower QoL at 1 month after SBG as compared to that at 6 months ($P=0.046$).

【Discussion】 Childrens' OHRQoL in SBG group was not

significantly different from other groups, suggesting that the surgical intervention for SBG does not affect the children's QoL dramatically at this age. Additional assessment for sociogeographical status may be required for identifying the reason why "w/o SBG group" showed significantly lower OHRQoL than the "Control group". Several subscales in PPR shows significant differences or changes between groups or time point, respectively, which is inconsistent with patients' self-report. We may need to keep things above in mind for improving the psychological care for both of the patient and parent with or without CL/P. (398/400 words)

N 505

Immunohistological study for the connection between the testis and epididymis

Takuya Omotehara, Miyuki Kuramasu,
Kenta Nagahori, Xi Wu, Shinichi Kawata,
Zhong-Lian Li, Hidenobu Miyaso,
Masahiro Itoh
Department of Anatomy,
Tokyo Medical University (Japan)

【Background】Cryptorchidism is one of the most frequent congenital disorders in a male child. Although some hormonal factors have been identified for a descent of a testis, other factors may be involved. For example, majority of the cases are reported to be unattached at somewhere between the testis and epididymis. When the seminiferous tubules are not connected to epididymal tubules, the fertility is hardly improved by surgical treatment because sperm transport is impossible. However, the mechanism to induce the connection between them is still unclear.

【Purpose】When and where the connection between the testis and epididymis, especially the testis cord and Wolffian duct, is induced in the mouse embryo are investigated.

Materials and Methods:

Paraffin sections of a gonad-mesonephros complex at each developmental day were serially cut, and some marker proteins were detected on them by sequential immunohistochemistry method. This method enables to repeatedly detect each immunoreactivity with different antibodies on the same sections. The markers used in the present study were Ad4BP (Adrenal 4 Binding protein) for gonadal somatic cells, Pax2 (Paired box gene 2) for mesonephric tubules and Wolffian duct, Collagen type IV for basal membrane, and E-cadherin for epithelial cells.

【Results】Ad4BP was detected in the surface of a ventral region in the mesonephros at E10.5. On the other hand, Pax2 was detectable in the epithelial cells of mesonephric tubules underneath the region. A basal membrane which was positive for collagen type IV was found around the tubules. It was, however, incomplete especially at a ventral curve of them with facing the gonadal region. Such tubules were negative for E-cadherin, and Pax2-positive cells were neighbored by Ad4BP-positive cells. At the later developmental stage, basal membrane beneath Pax2-positive cells was serial to that beneath the Ad4BP-positive cells.

【Discussion】The testis cord and Wolffian duct possibly starts to connect between Ad4BP-positive gonadal cells and Pax2-positive mesonephric tubules as early as the gonadal formation.

COI: No

【Funding】KAKENHI for MI, HM, and SK

Invited Poster Presentations

P 101
IMMUNOHISTOCHEMICAL STUDIES OF DENTIFICENTAL SYSTEM TISSUES UNDER THE EFFECT OF ECOTOXICANTS IN THE PERINATAL PERIOD

To prove the effect of ecotoxicants in the prenatal period of development of laboratory animals on the morphogenesis of the dental system.

Sergei Vasilyevich Chuykin,
Oleg Sergeevich Chuykin,
Sergey Vitalyevich Averyanov,
Georgy Levanovich Chuykin,
Alik Dinarovich Valiullin
Bashkir State Medical University (Russia)

【Background】Congenital cleft lip and palate (CLP) among the other congenital malformations of children in the Republic of Bashkortostan takes the first place and is 1: 554 newborns. A situational analysis of the effect of pollutants from industrial emissions into the atmospheric air, water, and soil in the regions of the Republic of Bashkortostan with petrochemical industry on the incidence of CLP in children showed the relationship between environmental pollution and the number of births of children with CLP. Indicators of environmental pollution in the regions with petrochemical industry are 3–5 times higher than those in regions without petrochemical industry.

【Method】Experimental studies on the toxic effects of ecotoxicants on bone tissue and the rudiments of teeth of laboratory animals were performed on white outbred rats weighing 180-250 grams. In total, 60 animals were involved in the experiment. All animals were divided into 4 groups: control and 3 experimental. During the entire pregnancy, the females were in the seed chambers.

In the course of the experiment, animals of the 1st experimental group were subjected to inhalation exposure to gasoline vapors, the 2nd experimental group - formaldehyde and the 3rd experimental group were exposed to the combined exposure to gasoline and formaldehyde. The animals of the control group were in the seed chambers and they were fed ordinary air around the clock. After birth, the pups were taken out of the experiment by inhalation overdose of ether vapor on the 14th day of life.

Histological sections were prepared on a LEICA RM microtome - 2145 (Germany), stained with hematoxylin and eosin and by the method of Van-Gieson. Immunohistochemical studies were performed using an indirect streptavidin-biotin method using monoclonal antibodies to TGF-b1-transforming growth factor - b (Santa Cruz Biotechnology). The expression level of TGF-b1 was determined by measuring the relative area of specific staining on histological sections of bone tissue and tooth germs using the AXIO IMAGER-Z1 hardware-software image analysis complex from CARL ZEISS (Germany).

Proliferative activity and apoptosis of cells was studied by staining with propidium iodide followed by cytofluorimetry. Determination of ectosirezorufin-O-diethylase activity and benzyloxyresorufin-O-diethylase activity was carried out

using a Versa Fluor fluorimeter.

【Result and discussions】 The effects of the toxic effects of ecotoxicants appeared when evaluating the functional properties of splenocytes. In the group of rats, whose mothers were exposed to formalin, an increase in the spontaneous mitotic activity of splenocytes was observed.

In the group of rats, whose mothers received a combined toxic effect, a maximal, statistically significant increase in apoptosis was observed, indicating a violation of the mechanisms of cell cycle regulation, a statistically significant decrease in the liver metabolizing function was also observed.

In rats, whose mothers were exposed to inhalation of gasoline, CYP2B / 3A impaired the monooxigenase activity of rat rat hepatocytes was disturbed — a statistically significant inhibition of benzyloxyresorufin and de-ethylase activity was observed. The decrease in the activity of cytochromes that neutralize ecotoxicants indicates their increased expenditure in neutralization or is a consequence of genetic shifts and impaired expression of cytochrome genes.

The toxic effects of formalin, gasoline, and their combination on laboratory animals in the antenatal period leads to disruption of the proliferative potential of cells of the lymphoid organs and the inhibition of the mechanisms of cytochrome P450-dependent monooxygenation in hepatocytes, conjugated as AhR-receptor-dependent isoforms of CYP1A1 / 2 (formalin, benzine and their combination) and isoforms of the subfamilies CYP2B and CYP3A (gasoline, a combination of gasoline and formalin). This indicates violations of the regulation of the cell cycle and cell reproduction, which, of course, can affect the cells of the jaw bone tissue and dental germs.

A morphological study of the rudimentary teeth of rats (14 days after birth), born from females who underwent inhalation poisoning with ecotoxicants during pregnancy (formalin, gasoline, combined effect of formalin and gasoline), we found pronounced signs of impaired histogenesis of the teeth and pathological changes of the dental-toothed tissues .

In rat dental germs, deformed odontoblasts with signs of pronounced vacuolar degeneration of cytoplasm formed random, irregular rows. Individual cells underwent destructive processes. Their processes were necrotized with disintegration into separate fragments, which can lead to disruption of the morphogenesis of the dental system

Measurement of the optical density of the stained areas on sections when a transforming growth factor-betta1 - TGF-β1 was detected in rat tissues showed that the greatest amount of cytokine is expressed in tissues in the combined poisoning of rats with formalin and gasoline.

【References】 The data of morphological and immunohistochemical studies indicate that the influence of ecotoxicants (formalin, gasoline or their combination) in the antenatal period of laboratory animals causes significant disturbances in the histogenesis of bone tissue and tooth germs in the offspring of laboratory animals, which is the basis of violations of embryogenesis and congenital development pathology of the dental system.

P 102
ALGORITHM FOR REHABILITATION OF CHILDREN WITH CLEFT LIP AND PALATE IN REGIONS WITH ECOTOXICANTS
When constructing an algorithm of rehabilitation of children with CLP adapted to the conditions of our region with the petrochemical industry, we took into account the environment and especially the somatic status of these children.

Sergey Vasilievich Chuykin, Nazim Namikovich Dzhumartov,
Oleg Sergeevich Chuykin, Kristina Nikolaevna Kuchuk,
Anna Grigorievna Bilak, Eduard Aleksandrovich Grin,
Dilara Rafaelevna Khamitova,
Bashkir State Medical University (Russia)

【Background】 According to the analysis of gross emissions of pollutants into the air in different areas of the Republic of Bashkortostan, we have analyzed the relationship between the level of emissions of pollutants into the atmosphere and the frequency of birth of children with congenital cleft upper lip and palate (CLP) in cities and regions of the Republic of Bashkortostan with the petrochemical industry. The importance of high somatic morbidity in children with CLP, living in regions with the petrochemical industry (PCI), and the need for additional rehabilitation measures in the rehabilitation algorithm, taking into account the impact of adverse environmental factors on the child's body. Based on this, we propose an algorithm for the rehabilitation of children with CLP living in the region of Republic of Bashkortostan with PCI.

【Results and discussion】 As the basis of our algorithm we used one introduced by Prof. Ad.A. Mamedov (2009) and L.V. Aheeva in et. al, in which we have introduced additional rehabilitation measures.

When constructing an algorithm of rehabilitation of children with CLP adapted to the conditions of our region with the petrochemical industry, we took into account the environment and especially the somatic status of these children.

The rehabilitation process occurred during the childhood and a number of individuals and at an older age, however, it should be divided according to the periods identified in pediatrics at the 7 periods:

1. Prenatal
2. The neonatal period - from 0 t.o 1 month;
5. The period of infancy - 1 month. - 1 year;
4. The period of toddlers - 1 year - 3 years;
5. The pre-school period - 3 - 6 years;
6. The period of primary school age - 7 - 11 years;
7. The period of school age - 11 - 18 years.

Given the peculiarities of rehabilitation of children with CLP in the regions of the Republic of Bashkortostan with PCI, we have developed the following algorithm rehabilitation.

Given the environmental factors of the environment, data on the presence of pregnant women in the urine and blood toxicants, exceeding the maximum allowable con-centration, we introduced an algorithm of rehabilitation consultation toxicologist, which indications may appoint examination of urine or blood ecotoxicants and indications appoint detoxification.

【References】 Pregnant women need to consult an ecologist and a professional pathologist (according to the indications) to plan therapeutic and preventive measures. The proposed algorithm of rehabilitation of children with CLP takes into account the peculiarities of somatic status, developed taking into account the impact on the body of adverse environmental factors in the Republic of Bashkortostan, clinical and anatomical forms of the cleft, and the peculiarities of the use of their own methods of treatment and examination, which reduces the number of early and long-term postoperative complications, improve functional results and quality of life, reduce the duration of disability, achieve full medical and social rehabilitation of patients.

P 103
PREVALENCE AND CLINICAL AND ANATOMIC FORMS OF CLEFT LIP AND PALATE IN REGIONS WITH ECOTOXICANTS

To study the epidemiology, the frequency of birth of children with cleft lip and palate (CLP) in the Republic of Bashkortostan - a region with unfavorable environmental factors for the clinical and epidemiological rationale for the prevention and rehabilitation of children with CLP.

Oleg Sergeevich Chuykin, Nail Airatovich Davletshin,
Sergey Vasilyevich Chuykin, Anna Grigorievna Bilak,
Nazim Namikovich Dzhumartov, Marsel Venerovich Gilmanov,
Eduard Aleksandrovich Grin
Bashkir State Medical University (Russia)

【Background】 Congenital clefts of the upper lip and palate are among the most frequent (87%) and severe malformations of the maxillofacial region. The Republic of Bashkortostan, being an industrial region of Russia, is composed of large petrochemical enterprises that pollute the soil, water and air with industrial waste containing ecotoxicants, which accounts for the birth rate of children with HWPW higher than the national average.

Knowledge of the epidemiological situation of the CLP, the causes of and the timing of timely surgical interventions will help to organize prevention and a multicomponent period of treatment and rehabilitation.

【Method】 A retrospective analysis of the medical documentation in the Department of Maxillofacial Surgery of the Republican Children's Clinical Hospital for the period from January 1, 1985 to December 31, 2018 was conducted to study the specific features of the structure of the clinical-anatomical forms of CLP in children living in the Republic of Bashkortostan. During the analyzed period, there were treated and dispensary observation of 3463 children from birth to 18 years old with CLP.

【Results and discussion】 When analyzing the frequency of CLP, it was found that the frequency of birth of children with CLP per 1000 births in industrial cities (2.43) and districts (3.26) of the Republic of Bashkortostan is higher than in environmentally friendly cities (1.14) and districts (0.96).

After analyzing 3463 children with this pathology, the clinical forms of CLP in accordance with the MMSI classification were distributed as follows: 1) an isolated cleft of the sky - in 1506 (43.49%) children; 2) the combined cleft of the upper lip, alveolar process, soft and hard palate - in 1110 (32.05%); 3) an isolated cleft of the upper lip - in 847 (24.46%) children.

Among congenital clefts of the palate, registered in 1506 patients, crevices of the soft and hard palate prevailed - 1076 (71.45%), followed by congenital cleft of the palate - 211 (14.01%), then congenital total cleft of the soft and hard palate and alveolar the appendix - 151 (10.02%), then the congenital cleft of the alveolar process and the anterior part of the palate - 68 (4.52%).

In the structure of the combined crevices of the upper lip, alveolar process, soft and hard palate, 1110 cases were dominated by incomplete crevices - 622 (56.04%), followed by complete - 388 (34.95%) and hidden crevices - 100 (9.01%).

【References】 The study revealed the dependence of the ecological disadvantage of cities and districts of the Republic of Bashkortostan with the highest rates of birth of children with CLP, the structure of types of CLP, among which the most severe forms were found, and also identified the need for prevention, surgical intervention and rehabilitation of children with CLP in adverse environmental factors.

P 104
RESULTS OF MONITORING OF CONGENITAL DEVELOPMENTAL DISEASES IN CHILDREN IN THE REGIONS WITH ECOTOXICANTS
Monitoring congenital malformations in children in regions with ecotoxicants, and to identify the frequency of associated diseases in children with congenital cleft lip and palate.

Sergey Vasilievich Chuykin, Rezeda Yamilevna Azmetova,
Kristina Nikolaevna Kuchuk, Elvira Zinfarovna Snetkova,
Georgy Levanovich Chuykin, Sofia Marsovna Mansurova,
Irina Alekseevna Karimova, Almaz Fanzulevich Sultanov,
Bashkir State Medical University (Russia)

【Background】 congenital malformations are usually regarded as one of the important indicators of the harmful effects of adverse environmental factors in areas with high man-made stress. The Republic of Bashkortostan is a major center for the petrochemical and oil refining industries. A high degree of concentration of industry in the Republic creates a certain chemical load on the environment and the resident population. Congenital cleft lip and palate is the most common malformation of man.

【Method】 An analysis was made of the results of the state observation network for the state of the environment, and the excess of chemicals that are most dangerous to health in the atmospheric air was detected. The analysis of congenital malformations of children in the region with ecotoxicants was carried out.

【Result and discussions】 The highest average pollution levels in 2018 in the Republic of Bashkortostan: suspended solids - 1.6 MPC, nitrogen dioxide - 1.1 MPC, benzo (a) pyrene - 0.82 MPC, formaldehyde - 0.6 MPC, ethylbenzene, ammonia, carbon monoxide.

Gross emissions are dominated by: carbon monoxide - 398900 tons, volatile organic compounds - 175000 tons, sulfur dioxide - 57400 tons, nitrogen dioxide - 89800 tons.

The maximum single concentrations reached: sulfur dioxide - below 1 MPC, nitrogen dioxide - 1.5 MPC, nitrogen oxide - 1.5 MPC, suspended solids - 4.6 MPC, carbon monoxide - 3.4 MPC; The maximum concentration of benzo (a) pyrene is 2.9 MPC. The average annual concentration of hydrogen sulfide is 0.000 mg / m3, xylene - 0.014 mg / m3, toluene - 0.035 mg / m3, ethylbenzene - 0.004 mg / m3, formaldehyde - 0.005 mg / m3 or 0.5 MPC (taking into account the old standards - 1 , 7 MPC), other impurities of the permissible norms.

The maximum single concentrations were: hydrogen chloride - 2.4 MPC; hydrogen sulfide - 9.5 MPC; benzene - 1.6 MPC; for ethylbenzene - 9.5 MPC; xylenes - 4 MPC; phenol - 2.6 MPC; toluene - 3.5 MPC, other impurities - below the permissible norms, including formaldehyde - 1 MPC (taking into account the old standards - 1.5 MPC).

The frequency of congenital cleft lip and palate in the Republic of Bashkortostan was analyzed. In 2018, according to the results of monitoring in the structure of all congenital malformations, the congenital cleft of the lip and palate was 18.02% and ranked first among other malformations.

Structure of congenital malformations in the Republic of Bashkortostan for 2011-2018.

【References】 our situation analysis of the impact of industrial emissions into the air, water, soil in the regions of the Republic of Bashkortostan with the petrochemical industry on the incidence of congenital lip and palate clefts in children clearly showed the role of adverse environmental factors in the etiology and pathogenesis of the congenital cleft of the upper lip and palate and other malformations.

P 105
Concomitant premaxillary setback and bilateral nasolabial repair

Young-Wook Park,
Min-Keun Kim
Department of Oral and Maxillofacial Surgery,
College of Dentistry,
Gangneung-Wonju National University (Korea)

【Background】Functional closure of the orbicularis oris muscle and esthetic reconstruction of nasolabial components are impossible in patients with severely deformed premaxilla. Here, we review a surgical strategy for patients with unremedied premaxilla retrospectively.

【Results】Vomerine ostectomy and premaxillary setback with nasolabial repair were performed in 12 patients with bilateral cleft lip and palate. The mean age of patients was 21.7 months. The extent of ostectomy varied between 3 and 11 mm. There were no serious complications from defective perfusion to the premaxilla or the philtral flap. The follow-up period ranged from 2 to 25 months. Proper positioning of the premaxilla and satisfactory nasolabial esthetics were achieved in all patients.

【Conclusions】We performed nasolabial repair after premaxillary setback without jeopardizing the premaxillary segment or the philtral flap. Our surgical strategy could be recommended in poor socio-economic circumstances due to the cost effectiveness of limiting the number of surgeries.

【Keywords】Bilateral cleft lip and palate, Vomerine ostectomy, Premaxilla setback, Primary rhinoplasty

P 301
International volunteer surgical project for Cleft lip and/or palate patients in Ethiopia

K. Nishihara[1)], T. Kibe[2)], N. Takahashi[3)], F. Yamauchi[5)],
N. Nakamura[2)] H. Furukawa[4)], N. Natsume[5)],
[1)]Department of Oral and Maxillofacial Functional Rehabilitation,
Graduate School of Medicine,
University of the Ryukyus
[2)]Department of Oral and Maxillofacial Surgery,
Graduate School of Medical and Dental Sciences,
Kagoshima University
[3)]Department of Dentistry, Chiba Cancer Center
[4)]Department of Health Sciences,
Faculty of Psychological and Physical Science,
Aichi-Gakuin University
[5)]Division of Research and Treatment for Oral and
Maxillofacial Congenital Anomalies,
School of Dentistry, Aichi-Gakuin University (Japan)

【Introduction】Babies with cleft lip or/and palate (CL/P) are born at a rate of 1.49–1.61 per 1000 population in Ethiopia. Many of these babies do not undergo appropriate treatment because of the poor economic development in this country. Our charitable activity for CL/P patients was launched with support and funding from the Japan Cleft Palate Foundation for 2011 to 2019. The aim of this study was to better understand the results of this program and the effects of CL/P treatment in this population and to establish future guidelines for our charitable activities in Ethiopia.

【Subjects and Methods】Altogether, 20 oral and maxillofacial surgeons and 4 anesthesiologists have visited Yekakit 12 Hospital at Addis Ababa and Grarbet Hospital at Butajira, Ethiopia.

【Results and Discussion】A total of 85 patients were evaluated for CLP/P preoperatively in these hospitals. In all, 90 patients underwent surgery to correct their CL/P. The diagnoses were 24 cleft lips and palates (CLPs) and 66 cleft lips and/or cleft alveolus (CL/A). There were fewer CLP than CL/A surgical cases. We believe that suckling failure in a CLP infant could lead to death. With this in mind, a senior surgeon performed 84 cheiloplasties, 4 palatoplasties, and 2 lip reconstructions. The mean age for cheiloplasty was 6 years 4 months (range 3 months to 33 years), which was significantly older than that in a corresponding Japanese population.

【Conclusions】We believe that a program that requires our continuing surgical and economic cooperation is needed for making progress in the multidisciplinary treatment of CL/P.

P 302
THE CHARITABLE OPERATION PROJECT FOR PATIENTS WITH CLEFT LIP AND PALATE IN LAOS

Takahiro Goto,
Kazuhide Nishihara,
Akira Arasaki
Department of Oral and Maxillofacial Functional Rehabilitation,
Graduate School of Medicine,
University of the Ryukyus (Japan)

【Background】With the support of the Japanese Cleft Palate Foundation, we have engaged in activities such as free-of-charge surgery for cleft lip and palate (CLP) for a total of 14 times from 2001 to 2018 in the Lao People's Democratic Republic (Laos). The aim of this study was to assess the state of Lao patients with CLP in our project.

【Subjects and Methods】In total, we have conducted CLP-related surgery on 319 patients. While most surgical procedures were performed on patients at the Setthathirath Hospital, located in Vientiane, the capital city of Laos, the Japanese medical team also performed surgical procedures by visiting provincial cities three times. The 319 patients were divided into surgical methods, age and cleft types.

【Results】The specific surgical procedures performed were as follows: cheiloplasty (200 cases; 62.3%), palatoplasty (88 cases; 27.4%), and lip reconstruction (33 cases; 10.3%). Specific cleft types were as follows: cleft lip and/or alveolar (144 cases; 45.2%); cleft lip and palate (143 cases; 44.8%); cleft palate (35 cases; 11.0%). The distribution of age at the first cheiloplasty operation from 2001 through 2018 was analyzed. A linear regression analysis showed a significant difference between the age at first lip plasty and the year of first operation ($\beta = -0.35$; $P < 0.001$), indicating that the age dropped as the years passed.

【Discussion】Our activities spanning 18 years appear to have contributed to lowering the age at first cheiloplasty in CLP patients in Laos. This was likely an effect of continuing to train local medical staff in surgical techniques and donating surgical tools and facilities over a period of 18 years while building a good relationship with local staff. However, the healthcare system in Laos is an obstacle to some patients who still cannot undergo CLP surgery in infancy for financial reasons. We therefore need to support Laos in developing an adequate healthcare system and in allowing local medical staff and facilities to provide treatment on their own as we continue to carry out our activities for CLP patients.

P 303
The Nursing Reports of Medical Supports Cooperation for Patients with Cleft lip and Cleft Palate in Ben Tre Province, Vietnam

Harumi Ejiri[1)], Kaoru Kanno[2)], Akiko Sumi[2)],
Akiko Koga[3)], Sayaka Toyonaga[4)], Reizo Baba[1)],
Hideto Imura[5)], Teruyuki Niimi[5)], Nagato Natsume[5)],
[1)] Chubu University, College of Life and Health Sciences
[2)] Hokkaido University Hospital
[3)] Hirose Hospital
[4)] Oita University Hospital
[5)] Aichi Gakuin University, School of Dentistry (Japan)

【Backgrounds】Japanese Cleft Palate Foundation, (JCPF), a Non-Profit Organization in Japan, has dispatched voluntary medical support teams to Vietnam that perform cleft lip and/or palate repair for these 26 years. Another mission of JCPF is to educate Vietnamese surgeons about the treatment of these abnormalities.

【Purpose】To report the performances of the nursing team activities in JCPF 2018 at Nguyen Dinh Chieu General Hospital in Ben Tre Province, Vietnam.

【Methods】We inductively described the tasks and the performances of our nursing activity in Vietnam.

【Results】In the 2018 JCPF medical support team, seven nurses, including one perioperative nursing specialist, have participated from several districts in Japan. Five nurses now work, and two others previously worked in operating rooms in Japanese hospitals. Three of them have multiple experiences of participating in the JCPF medical support teams. In the 2018 dispatch mission, a total of 46 patients underwent cleft lip and/or palate repair surgery. The nursing activities were performed largely in the operating and the recovery rooms. The main activities of the nurses in the operating room were: 1) assistance to the anesthesiologists, 2) assistance to the surgeons during the surgical procedures, 3) cares on the patients in the operating room, 4) preparations and sterilization of surgical instruments. The main activities of the nurses in the recovery room were: 1) assistances of patients before surgery, 2) close observation and cares on the postsurgical patients, and 3) to support doctors in the recovery room. These nursing practices were operated in cooperation with the Vietnamese nurses. However, due to difficulties in the linguistic barriers, communication to each other was often difficult, especially in dealing with emergencies.

【Discussion】The missions of the JCPF were successfully performed. Communications between nurses and doctors, between nurses of Japan and Vietnam were crucial. Systematic information exchange meeting would be necessary. Furthermore, discussion among nurses of the two countries, especially about the comfort and ethics of the patients, would be necessary. These procedures would improve the qualities of nursing practices of the nurses of the two countries. In addition, advance orientation for Japanese nurses who participate for the first time, as well as the augmentation of the manuals would be necessary. It is also necessary to create an education system that enables the participation of nursing students.

P 304
The Orthodontic management of Apert syndrome

Tadashi Morishita[1)],
Nobuyuki Mitsukawa[2)]
[1)]St.Mary's Hospital Department of Orthodontics
[2)]Chiba University Department of Plastic,
Reconstructive and Aesthetic Surgery (Japan)

【Background】There is severe crowding and labial inclination of upper and lower anterior teeth due to hypoplasia of the midface and characteristic form of the palate and alveolar ridge. As a result, the tongue chamber is narrow and secondary to the lower tongue. Eruption of their permanent teeth is delay.

【Purpose】It is difficult to improve the oral environment of this syndrome. The purpose of this presentation is to present the two cases treated by our team

【Cases】History: Immediately after birth, they were diagnosed with Apert syndrome. In infancy, they were performed cranial distraction of osteogenesis (anteroposterior) for craniosynostosis by plastic surgeon. One of them boy was judged as respiratory insufficiency of the upper airway by SPG examination at the age of 4 and received a maxillary distraction of osteogenesis by LeFort III type osteotomy. The other girl was also treated with maxillary distraction to improve breathing, at her mixed dentition age.

【Orthodontic Therapy】At the age of 14 the boy was referred to our orthodontic department. His problem was reversed occlusion, narrow arch of maxillae, palatal protuberances and severe crowding. First, we aligned lower arch, simultaneously the SARME (surgical assisted rapid maxillary expansion) was done. Subsequently, leveling of the maxilla was also started. At age of 16 he was operated secondly maxillary distraction of osteogenesis for eye closing function and the normal occlusion.

The girl also was aligned her dentition as pre-surgical orthodontic treatment, then was operated second distraction of maxilla. She was finished occlusion, wearing retainers.

【Result】They gained acceptable occlusion with orthodontic treatment and twice maxillary distraction of osteogenesis.

【Discussion】Craniofacial anomaly affect various functions. Cranial vault distraction osteogenesis has been performed to improve intracranial pressure, and maxillary distraction osteogenesis has been performed very early phase to improve respiratory function. The mid-facial hypoplasia is the reason why we need surgery as well as orthodontic treatment to acquire oral function during the growth phase.

P 305
History and perspective of Congenital Anomalies

Yuji Nakajima,
Toshiyuki Yamagishi
Editorial Office of Congenital Anomalies,
Department of Anatomy and Cell Biology,
Osaka City University (Japan)

【Background and purpose】Congenital Anomalies (CGA), the official journal of the Japanese Teratology Society (JTS), has been published since 1963. However, the JTS members do not know much about the history and current state of CGA. The purpose of this poster is to present (record) the history/activities of CGA and to encourage further progress of our journal.

【Method】We explored the already-published CGA and used "The 50th Anniversary of the Japanese Teratology Society" as a reference to investigate the activities and history of CGA. We also investigated recent 10-year state of CGA by Web of Science and Journal Citation Reports.

【Result and discussion】The official journal of the Japanese Teratology Society, "SENTENIJYOU, NIHON SENTENIJYOU GAKKAI KAIHOU, Official Journal of Congenital Anomalies Research Association of Japan Vol. 1 & 2, No1" was first published in 1963 and has been published continuously without any discontinuation until now. The journal has published only articles written in English since 1981. English abstracts of the annual meeting have been published in the journal since 1985. The title of the journal was changed from "SENTENIJOU and Congenital Anomalies" to "Congenital Anomalies (CGA)" in 1987 and the cover design of the journal was changed to the current one from Vol 40, No1 published in 2000. To globalize CGA, the journal performed following changes: internet delivery was started in 1996, included in PubMed/Medline in 2004, issued from Blakwell (currently Wiley) from 2004, introduced an electronic submission/review system ScholarOne in 2008, included in Web of Science in 2010, 2012 IF=1.0 was released in 2013, introduced a plagiarism detection system CROSSREF in 2013, discontinued printed version in 2014, and published bimonthly from quarterly in 2017. In 2009, "Terminology of Developmental Abnormalities in Common Laboratory Animals version 2", which was developed by the International Federation of Teratology Societies (IFTS) including JTS, has been published and widely used in developmental toxicity test until now. To further make development of CGA, following key words must be focused on: next generation sequencer, responsive gene causing rare congenital disease of etiology unknown, developmental mechanisms of the disease, new therapeutic procedure; embryonic/fetal environment, developmental disorders and adult diseases, developmental biology, neurobehavioral study, large-sized epidemiology; high-throughput toxicity model system, zebrafish, iPS-derived organoid culture; iPS-derived tissue/organoid, new therapeutic material and drug discovery. No COI, JSPS Grant #17HP2011

P 306
Genomic backgrounds of Japanese patients with undiagnosed neurodevelopmental disorders

Toshiyuki Yamamoto[1,2], Taichi Imaizumi[1,3],
Keiko Yamamoto-Shimojima[1,2], Tomoe Yanagishita[1,4],
Toshiyuki Seto[5], Nobuhiko Okamoto[6]
[1]Institute of Medical Genetics, Tokyo Women's Medical University, Tokyo
[2]Tokyo Women's Medical University Institute of Integrated Medical Sciences, Tokyo
[3]Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki
[4]Department of Pediatrics, Tokyo Women's Medical University, Tokyo
[5]Department of Pediatrics, Osaka City University Graduate School of Medicine, Osaka
[6]Department of Medical Genetics, Osaka Women's and Children's Hospital, Izumi (Japan)

【Background】Recently, many genes related to neurodevelopmental disorders have been identified by high-throughput genomic analysis; however, a comprehensive understanding of the mechanism underlying neurodevelopmental disorders remains to be established. To further understand these underlying mechanisms, we performed a comprehensive genomic analysis of patients with undiagnosed neurodevelopmental disorders.

【Methods】Genomic analysis using next-generation sequencing with a targeted panel was performed for a total of 133 Japanese patients (male/female, 81/52; median age, 4.0 years) with previously undiagnosed neurodevelopmental disorders, including developmental delay (DD), intellectual disability (ID), autism spectrum disorder (ASD), and epilepsy. Genomic copy numbers were also analyzed using the eXome Hidden Markov Model (XHMM).

【Results】Thirty-nine patients (29.3%) exhibited pathogenic or likely pathogenic findings with single-gene variants or chromosomal aberrations. 67 patients (50.4%) were analyzed through "Trio" analysis. There was no difference in diagnostic yields when patients are associated with clinical condition other than DD/ID.

【Conclusion】A diagnostic yield of 29.3% in this study was nearly the same as that previously reported from other countries. Thus, we suggest that there is no difference in genomic backgrounds in Japanese patients with undiagnosed neurodevelopmental disabilities. Although most of the patients possessed de novo variants, one of the patients showed an X-linked inheritance pattern. As X-linked recessive disorders exhibit the possibility of recurrent occurrence in the family, comprehensive molecular diagnosis is important for genetic counseling.

This work was supported by the Practical Research Project for Rare/ Intractable Diseases from the Japan Agency for Medical Research and development (AMED), and a Grant-in-Aid for Scientific Research from the Health Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare, Japan, and JSPS KAKENHI.

P 307
Genetic mapping of male subfertility locus on mouse chromosome 4

Hideo Gotoh[1)],
Ikuo Miura[2)],
Shigeru Wakana[3)]
[1)] Reproductive Biology Unit, Division of Animal Sciences,
Institute of Agrobiological Sciences, NARO, Tsukuba
[2)] Technology and Development Team for Mouse Phenotype Analysis,
RIKEN BioResource Research Center, Tsukuba City,
[3)] Department of Gerontology, Institute of Biomedical
Research and Innovation, Kobe-city (Japan)

【Background】Reproductive problems are common in both humans and domestic animals. Recent estimates indicate that male infertility accounts for approximately half of the cases of infertility in humans. The B10.M/Sgn mouse strain exhibits inherited male subfertility as indicated by an approximate ~50% reduction in litter size.

【Purpose】The purpose of this study is to map the responsible locus for the male subfertility of the B10.M/Sgn.

【Method】Genetic mapping was performed by the quantitative locus analysis using the GigaMUGA markers (UNC).

【Results】The major responsible locus for male factor subfertility 1 (Mfsf1) was mapped onto chromosome 4 within the 137,048,759–138,615,338 bp interval. Two other factors interacted with the Mfsf1 locus were also found. A factor located near 39.97 cM on chromosome 5 interacted with the Mfsf1 locus to suppress male fertility, whereas the other factor located near 20.89 cM on chromosome 12 interacted with the Mfsf1 locus to enhance male fertility.

【Discussion】The results of this study will improve our understanding of male reproductive problems.

P 308
Prenatal exposure to valproic acid induces dysplasia of the neocortex and neuro-inflammation in mice.

Munekazu Komada,
Haruka Kamiyama,
Nao Kagawa,
Tetsuji Nagao
Human Embryology, Life Science,
Kindai University (Japan)

【Background】Prenatal exposure to chemical substances affects brain morphogenesis by affecting the proliferation, differentiation, and migration of neurons. We have shown that prenatal exposure of bisphenol A (BPA) and ethanol induces dysplasia of cortical layer structure of neocortex. These chemicals prenatal exposure showed that microglial abnormalities and neuro-inflammation were induced in the neocortex at the developmental stage, which is a cause of morphogenesis. Valproic acid is used as an antiepileptic drug, and has shownthe teratogenicity such as neural tube defects.

【Purpose】We analyzed the neurodevelopmental effects of valprolic acid (VPA) on neocortical morphogenesis and intracerebral inflammation.

【Methods】ICR pregnant female mice were administrated intraperitoneally VPA (400mg/kg/day) at embryonic day (E) 14. To determine whether prenatal VPA exposure induces neuro-inflammation and results in abnormal microglial activation, we examined the effect of the anti-inflammatory agent pioglitazone on VPA exposure. Pregnant females were administrated either 12.5 mg/kg/day pioglitazone or water by gavage on E11 through E15.

【Results】Prenatal exposure of valproic acid affected neurogenesis of the developing neocortex. As a result, it was shown that abnormality was found in the lamination of the neocortex. In addition, the number of microglia increased and the expression of inflammatory related factors was changed, resulting from prenatal exposure to VPA. It was revealed that neuro-inflammation caused by VPA was ameliorated by co-treatment with pioglitazone.

【Discussion】These results show that prenatal exposure to VPA causes abnormalities in the layer formation of neocortex by affecting cell proliferation, neural differentiation, and neural migration. Furthermore, neuro-inflammation and activation of microglia occurred in the developing neocortex. The neuro-inflammation and microglial abnormalities might induce the malformation of developing neocortex. Congenital anomalies of neocortex are thought to be one of causes of developing disorders and mental disorders. Congenital dysplasia of neocortex following prenatal exposure to chemicals might prevent by co-administration of anti-inflammatory agents.

Conflict of interest (COI) of the principal presenter: No potential COI to disclose. This work was supported by JSPS KAKENHI Grant Numbers 17K00572, 17K08500.

P 309
Survey of female nursing students on their consciousness of "congenital anomalies"

Takuya Matsuo
Faculty of Medicine
Kindai University (Japan)

【Background】Currently, outbreaks of infectious diseases affecting fetuses, such as rubella, are prevalent. The media has been using the expressions "affects the fetus" and "there is a possibility of miscarriage". However, it may be difficult to have a concrete image and understanding of the onset of “congenital anomalies”.

【Purpose】To survey female nursing students on their consciousness of "congenital anomalies".

【Method】Female nursing students (First year: 76 students and second year: 76 students) were included. The reported tasks were "phrases related to congenital anomalies" for first year students and "phrases combined with congenital anomalies at the time of searching and search results" for second year students.

【Result】Commonly known phrases, such as “chromosomal abnormalities including Down syndrome (31%)” and “cleft lip and cleft palate (24%)”, were frequent among the first year students. Phrases related to congenital anomalies, such as "the definition of congenital anomalies (28%)", "cause (14%)", and "treatment and nursing (25%)", were frequent among most of the second year students.

【Discussion】First year students may only have common knowledge because there are few learning opportunities for “congenital anomalies”. On the other hand, second year students have had many opportunities to study cases and symptoms of “congenital anomalies”. Therefore, more learning opportunities are necessary.

P 310
Analysis of dentocraniofacial morphology in patients with achondroplasia

Michiko Tsuji, Ayumi Shoji, Kyoko Hirabayashi,
Yukiho Kobayashi, Keiji Moriyama
Department of Maxillofacial Orthognathics,
Division of Maxillofacial and Neck Reconstruction,
Graduate School of Medical and Dental Sciences,
Tokyo Medical and Dental University (Japan)

【Background】Achondroplasia (ACH) (#10800) is an autosomal dominant disease arising most frequently in individuals with short-limb dwarfism with an estimated incidence of 2.6/100,000 live births. Affected individuals exhibit short stature caused by rhizomelic shortening of the limbs. The majority of patients with ACH have one of the two point mutations in fibroblast growth factor receptor 3 (FGFR3), resulting in amino acid substitution (G380R). Several common findings relating to morphometric analysis of the craniofacial configuration in patients with ACH have been reported. That is, patients with ACH often show macrocephaly with frontal bossing, a low nasal bridge, and midfacial hypoplasia with a prognathic mandible.

【Purpose】The aim of this study was to investigate dentocraniofacial morphological characteristics in Japanese patients with ACH.

【Method】Four patients with ACH (1 male and 3 female patients; mean age, 21.0 years) at the Tokyo Medical and Dental University Dental Hospital participated in this study, which was approved by the Ethical Committee of the Tokyo Medical and Dental University (approval number 419). Lateral cephalograms, orthopantomograms, dental casts, medical interview records, and facial and intraoral photographs were analyzed. Z-scores were calculated based on sex- and age-matched Japanese standard values.

【Result】Half of the patients with ACH presented with macrocephaly (2/4), and hypoplasia of the nasal bone was observed in all patients. Cephalometric analysis revealed that patients with ACH presented strikingly enlarged anterior cranial base length (median of S-N: +6.0 standard deviation (SD)), shortened posterior cranial base length (median of S-Ba value: -5.5 SD), and low cranial base angle (median of N-S-Ba value: -1.2 SD). Additionally, all patients showed the skeletal class III jaw relationship with long mandibular ramus (median of Ar-Go value: +1.8 SD) and mandibular body length (median of Go-Pog value: +2.0 SD).

【Discussion】Despite the small number of patients, our study clarified that mid-facial depression in patients with ACH was more likely to be formed by enlarged anterior cranial base length with shortened posterior cranial base length, nasal bone hypoplasia, and relative mandibular prognathism. This observation suggests that sutural growth in the sphenoethmoidal synchondrosis may be more dominant in patients with ACH. Early closure of the spheno-occipital synchondrosis may result in hypoplasia of cartilaginous bones. Further studies including a larger number of patients with ACH are demanded to clarify the mechanism responsible for the development of dentocraniofacial morphological aberrations in patients with ACH.

P 311
Application of a rapid and nondestructive tissue clearing system for immunohistochemistry

Hiromi Sakata-Haga[1)],
Maimi Uchishiba[2)],
Tsuyoshi Tsukada[1)],
Hiroki Shimada[3)],
Natsumi Masuda[1)],
Hiroki Shoji[4)],
and Toshihisa Hatta[1)]
[1)]Department of Anatomy, Kanazawa Medical University
[2)]Hidaka General Hospital
[3)]Department of Medical Science,
Kanazawa Medical University
[4)]Department of Biology, Kanazawa Medical University (Japan)

We previously reported a new rapid and nondestructive tissue clearing system for whole-mount bone staining (RAP-B; Sakata-Haga, et al., 2018). In the present study, we optimized the procedure for immunohistochemistry. Pregnant ICR mice were deeply anesthetized and the embryos were removed on gestational day 10 or 11. The embryos were immersed in 4% paraformaldehyde phosphate buffer (PFA). Adult ICR mice were perfused with 4% PFA and their brains were removed. Frozen 500 μm thick slices of the brain were prepared. As pre-treatment, the embryos and brain sections were immersed in RAP fixative containing PFA, Triton X-100, and KOH, then immersed in decoloring enhancement solution containing ethylene glycol, Triton X-100, and KOH (RAP enhancer), followed by the regular immunostaining procedures. For whole-mount immunostaining of mouse embryos using an anti-neurofilament antibody, pre-treatment substantially improved staining and resulted in clearer detection of peripheral nerve fibers of the trigeminal nerve and spinal nerves compared to the conventional procedure without pre-treatment. The brain sections underwent free-floated fluorescent immunostaining using an anti-glial fibrillary acidic protein (GFAP) antibody and nuclear staining using EZ fluoro stain DNA, then immersed in a high-refracting index medium to transparentation. Fluorescent signals were detected by deep scanning by confocal microscopy (LSM710, Zeiss), and the obtained Z-stack images were reconstructed as 3D images using Amira (ver.6.2, FEI) or Imaris (BITPLANE). GFAP-immunoreactivity was clearly detected throughout the whole section depth, suggesting that the antibody was well permeated and the sections were sufficiently transparent. Given these results, we conclude that tissue clearing by RAP is available for immunohistochemistry. This may also be a useful tool for whole-mount immunostaining and thick tissue sections due to the ability to improve the staining property and permeation of antibodies.

This work was supported by KAKENHI (15K09713 and 18K11659). COI: None

P 312
A patient with bilateral cleft lip and alveolus associated with bilateral Tessier no. 7 clefts and accessory maxillae.

Naoto Haruyama[1)], Shunsuke Nomura[1)], Kenshi Noguchi[2)], Keigo Yoshizaki[1)], Takeshi Mitsuyasu[3)], Akira Suzuki[4)], Seiji Nakamura[5)], Ichiro Takahashi[1)]
[1)] Section of Orthodontics and Dentofacial Orthopedics, Graduate School of Dental Science, Kyushu University. Fukuoka
[2)] Department of Orthodontics, Kyushu University Hospital, Fukuoka
[3)] Department of Oral & Maxillofacial Surgery, Kyushu University Hospital, Fukuoka
[4)] Suzuki Dental Office, Fukuoka
[5)] Section of Oral and Maxillofacial Oncology, Graduate School of Dental Science, Kyushu University. Fukuoka (Japan)

【Objective】 Transverse facial cleft associated with accessory maxillae is one of the most rare congenital anomalies. The purpose of this case report is to present a summary of the clinical history and features of a patient with bilateral cleft lip and alveolus, combined with bilateral transverse facial clefts: Tessier no. 7, accessory maxillae, and severe mandibular hypoplasia.

【Case】 Abnormalities in cranial shape was initially identified at 23 weeks of gestation by ultrasound tomography in utero. Intrauterine growth restriction became evident from 30 weeks. The patient was delivered as a male light-for-dates infant of 2348g weight at 40 weeks by urgent cesarean section because of severe variable deceleration during uterine contraction. Bilateral cleft lip and alveolus combined with bilateral transverse facial clefts was observed at birth. The maxilla was hyperplastic in contrast to the severely hypoplastic mandible. The ears were low-set and the right and left ears had mild and severe conductive deafness, respectively. Accessory maxillae were located on both sides of the maxilla: two in right and one in left. Noncraniofacial associations were observed.

Bilateral cleft lip and transverse facial clefts were repaired when he was 5- and 9-month-old, respectively. Excision of the accessory maxillae and distraction for mandibular advancement were initially planned; however, follow-up without any surgical intervention was eventually attempted since the anteroposterior discrepancy between hyperplastic maxilla and hypoplastic mandible became smaller along with their growth, lead to no respiratory obstruction.

At growth completion, intra-oral examination revealed prolonged retention of deciduous teeth, with a 25 mm overjet and severe anterior open bite. Computed tomography demonstrated that the accessory maxillae carried extra sets of teeth and were attached to the inferior border of the zygoma or zygomatic arch on both sides. The left mandibular ramus and condyle were hypoplastic as compared to those in the right side, and left coronoid process was absent.

【Discussion and Summary】 Consistent with previous reports about Tessier no. 7 clefts, this patient accompanied the accessory maxillae in bilateral molar regions. In contrast, Tessier no. 7 cleft with bilateral cleft lip and alveolus in anterior region is extremely rare. Unfortunately, the pathogenesis of these anomaly is not well understood; his clinical features suggested the possibility of neural crest disturbances during embryonic development, i.e. neurocristopathy.

Comprehensive treatment including orthognathic surgery, orthodontics and prosthodontics is required for the improvement of his quality of life.

P 313
Dental Care for Pediatric Cases of Severe Motor and Intellectual Disabilities with Cleft Lip and Palate

Yuko Umezu[1)], Saya Takahashi[1)],
Kyoko Matsuo[1)], Toshiomi Shirase[1)],
Miho Kodama[2)], Reiko Machida[2)]
[1)]Department of Pediatric Dentistry, The Nippon Dental University Hospital
[2)]Division of Rehabilitation for Speech and Swallowing Disorders,
The Nippon Dental University Hospital (Japan)

【Introduction】It is difficult to perform cheiloplasty or palatoplasty for pediatric cases of severe Motor and Intellectual Disabilities because of complications involving organic disorders, such as respiratory disorders, and perioperative risks are high. This paper reports dental care and swallowing training for pediatric cases of severe physical and psychological impairments with cleft lip and palate in which the appropriate timing for cheiloplasty or palatoplasty had not been determined.

【Cases report】Patients with physical and psychological impairments who had cleft lip and palate were referred to our department from a pediatrics department for swallowing training and dental management. The cases comprised five patients (two males and three females), aged eight months to two years and six months at the time of initial consultation; none of them had undergone cheiloplasty nor palatoplasty. The patients had the following diseases: trisomy 13, hydrocephalus, and holoprosencephaly. Considering the potential impact on respiration, we consulted the physicians responsible for the cases about using Hotz-type plates before commencing oral food intake; the plates were created following their approval. Hotz-type plates were created and oral hygiene instructions, dental treatment, and preventive care were provided by the pediatric dentistry. The cases were assessed and swallowing function therapy with indirect training was provided by the division of rehabilitation for swallowing disorders. The design of the plates was examined in both the department and the division.

【Results and Discussion】Early dental intervention in pediatric cases of severe physical and psychological impairments with cleft lip and palate improves swallowing and oral functions, prevents dental diseases, and contributes to normal development of the maxillofacial area. Additionally, we maintained the oral environment of the patients through control measures, including prevention of soft tissue damage, restoration of hypoplastic teeth, and caries prevention. We consider that we could also provide psychological support to the patients and their families through continued interaction for swallowing training and oral care. Dental intervention in pediatric cases with severe Motor and Intellectual Disabilities may need to address pathologies with poor prognosis depending on the severity of the diseases; therefore, it is necessary for the doctors, nurses, and parents or guardians of patients to understand the situation and collaborate with each other so the patient can be provided with treatment and support based on consultation with the patient's family and circumstances specific to the patient.

General Poster Presentations

P 202

ORTHODONTIC MANAGEMENT OF CLEFT LIP AND PALATE- AN OVERVIEW

Dr. Abdul Baais Akhoon[1*)],
Professor (Dr.) Mohammad Mushtaq[2)]
and Dr. Syed Zameer[3)]
[1)] Resident, Department of Orthodontics and Dentofacial Orthopaedics, Govt. Dental College and Hospital, Srinagar, J & K
[2)] Professor and Head of The Department, Department of Orthodontics and Dentofacial Orthopaedics, Govt. Dental College and Hospital, Srinagar, J & K
[3)] Associate Professor, Department of Orthodontics and Dentofacial Orthopaedics, Govt. Dental College and Hospital, Srinagar, J & K (India)

Cleft of the lip and/or the palate is a congenital birth defect which is characterized by complete or partial clefting of the lip and/or the palate. The severity of clefting may vary from the trace of notching of the upper lip to complete non-fusion of the lip, primary palate and secondary palate.

Facial clefts are seen due to non-fusion of the facial process. The cleft of the lip, palate and face may be seen as an isolated birth defect, non-syndromic cleft or as a part of a syndrome with multiple congenital anomalies called as 'syndromic clefts'.

Patients with cleft lip and palate routinely require extensive and prolonged orthodontic treatment. Orthodontic treatment may be required at any or all of four separate stages: 1) in infancy before the initial surgical repair of the lip, 2) during the late primary and early mixed dentition, 3) during the late mixed and early permanent dentition, and 4) in the late teens after the completion of facial growth, in conjunction with orthognathic surgery.

This article discusses the various aspects of cleft lip and palate and its management from the orthodontic perspective.

Key words : Cleft lip, Cleft palate, Orthodontics.

P 203

Pre surgical orthopedics in a complicated cleft case.

Barra, Jorge.[1, 2)], Tapia, María.[1)], Osses, Claudia.[2)],
Rojas, Tircia .[2)], Muñoz, Jaime.[2)]
[1)]Orthodontics Department, School of Dentistry, U. of Concepcion
[2)]Pediatric Surgery Department of the Regional Hospital of Concepcion
CONCEPCION (Chile)

【Background】 Pre surgical orthopedics therapeutical techniques [1] are used to mold the infant´s maxillary segments, alveolar and nasal tissues with a unilateral or bilateral cleft lip and palate. This case report presents a 39-week gestational new born female patient with multiple congenital anomalies born in the Regional Hospital of Concepcion, Chile, who was treated with a modified pre surgical orthopedics appliance technique. The infant presented a bilateral cleft lip and palate with a pre maxilla completely rotated and displaced, in addition to craniofacial anomalies, possibly product of an amniotic band, with loss of the left eye, cranial cleft with absence of parietal bone and exposure of the brain.

Method: Almost immediately after her birth, she was undergoing surgery to close the brain exposure and started her pre surgical orthopedics appliance technique. A silicone dense impression was taken five days after his birth. A primary cast was prepared using dental stone, and undercuts were blocked with wax. The passive acrylic appliance was made covering only the hard palate and the pre maxilla was repositioned using a tape-elastic system.

After three months of treatment the patient was referred to the cleft palate clinics of the Regional Hospital of Concepcion for repairing plastic surgery.

【Result and Discussions】 This complicated and cleft case is rare and sparsely reported in the literature and it's possible to obtain very good results with pre-surgical orthopedics. In summary a difficult case and her multidisciplinary treatment approach.

【References】 1. Grayson, B., Santiago, P., Brecht, L. & Cutting, C. (1999). Pre surgical Nasoalveolar molding in infants with cleft lip and palate. Cleft Palate Craniofacial Journal, 36, 486–498

P 204

Uncommon complication after primary taijima limited rhinoplasty for cleft lip/nose deformity

Dr. Paula Tang (Hong Kong)

【Background】 Current literature favours early primary limited rhinoplasty at the time of primary cheiloplasty, as it would potentially minimize the nasal cleft deformity during the patient's formative years, and sometimes even obviate the need for definitive rhinoplasty in the teenage years. However, data on early post op complications after primary taijima limited rhinoplasty is lacking.

【Method】 We described three patients who underwent primary taijima limited rhinoplasty at the time of primary cheiloplasty by a single surgeon in our center.

【Results】 Three consecutive patients with cleft lip deformity (one bilateral cleft lip, two unilateral cleft lip) underwent primary cheiloplasty with limited taijima rhinoplasty at three months of age. All of them went through the post cheiloplasty management protocol: topical antibiotic ointment (chloramphenicol) and systemic antibiotic (oral augmentin) for a week, followed by laser treatment to lip scar and post op nasal silicon stenting, starting at 4 to 6 weeks post primary

cheiloplasty. All three patients developed nasal abscess at the site of taijima incision (at the cleft side) or at the rim incision (at the non-cleft side) at 6 weeks post op. Additional topical antibacterial ointment (bactroban and chloramphenicol) was given with poor clinical response and increasing size of the abscess. Needle drainage of the abscess was performed and microbiological culture came back to be positive for (non-methicillin resistant) staphylococcus aureus. However, the nasal abscess recurred requiring repeated bedside drainage and they finally subsided completely at about 5 months post primary cheiloplasty.

【Discussion】 While we are not certain of the exact etiology in causing the recurrent nasal abscesses in the three patients with unilateral cleft lip repair, we remain cautious in managing these abscesses, especially in view of the potential risk of cartilage damage and nasal deformity with uncontrolled infection. Long term follow up would be required for these patients. Relapse of cleft nasal deformity is one of the most commonly quoted "complication" of primary taijima limited rhinoplasty. Herewith we presented an uncommon early complication of primary rhinoplasty.

P 205

Submucous cleft palate: what are the good speech outcome predictors?

Dr. Paula Tang (Hong Kong)

【Background】 Submucous cleft palate is characterized by a bifid uvula, a translucent zone in the soft palate (zona pellucida) and a bony notch in the posterior edge of the hard palate. When the submucous cleft palate is symptomatic, surgical repair is indicated. However, long term data on the speech outcome on patients after palatoplasty for submucous cleft palate is lacking.

【Aim】 To review our center's data on the operative timing, surgical technique and speech outcome of patients with submucous cleft palate surgically repair in the past ten years.

【Methods】 Medical records of patients with primary surgical repair of submucous cleft palate in our center in January 2008 to December 2018 were retrospectively reviewed.

【Results】 26 patients' medical records were reviewed (12M:14F) (age range: 10 month-old to 15 year-old). Six patients (23%) underwent von Langenbeck primary palatoplasty repair and twenty patients (77%) underwent Furlow primary palatoplasty repair. Out of the 26 patients, six patients (23%) had other co-morbidities apart from the cleft palate: one had left hemi-microsomnia with left microtia, one had Klippel Feil syndrome, one had Simpson Golabi Behmel syndrome, one had confirmed 22p & 11q duplication with mental retardation and language delay, one had pineal gland tumor and global delay and one had Kabuki syndrome. For the speech outcome of these 26 patients, 3 patients (two von Langenbeck primary palatoplasty and one Furlow primary palatoplasty) were reported to have significant hyper-nasal speech by perceptive speech assessment by an independent speech therapist, one of them who had previous von Langenbeck primary palatoplasty repair performed at 3 year-old (patient with Kabuki syndrome) opted to have a revision Furlow palatoplasty at 7 year-old, with subsequent satisfactory speech outcome. For the other two patients with hypernasal speech, one had received primary Furlow palatoplasty at 15 year-old due to delayed presentation of the submucous palate and one had von Langenbeck primary palatopalsty repair at 10 month-old.

【Conclusion】 Patients with submucous cleft palate represented a heterogenous groups of patients with a wide spectrum of co-morbidities. We postulate that a delayed primary repair of the submucous cleft palate would probably complicate the subsequent speech outcome due to the likely development of compensatory speech in the patient's formative years with the unrepaired submucous cleft palate. Patient receiving von Langenbeck primary palatal repair also seems to be more likely to develop suboptimal speech outcome, although our sample size is too small to reach a statistical significance.

P 206

Hemifacial microsomia with cleft palate: is this a distinct entity?

Paula Tang
United Christian Hospital (Hong Kong)

【Background】 Hemifacial microsomia is often considered as the second most common craniofacial birth defect after isolated cleft lip/palate deformity. It consists of variable clinical manifestation, involving the orbit, maxilla, mandible, ear, cranial nerves, soft tissues and extra-craniofacial anomalies. When hemifacial microsomia occurs together with cleft palate, it is frequently associated with hemipalatal neuromuscular deficiency and velar hypoplasia, resulting in suboptimal speech outcome secondary to underlying velopharyngeal insufficiency.

【Aim】 Data on the speech outcome of Asian patients with hemifacial microsomia and cleft palate are scanty. We aim to review our center's experience in managing these patients.

【Method】 We retrospectively reviewed patients with cleft palate and hemifacial microsomia seen at our center, their demographic data and latest speech outcome were analyzed.

【Results】 Five patients were identified and selected for the review.

Patient A

F/6yo with submucous cleft palate surgically repaired at our center with Furlow palatoplasty at age 3. She also has concommittent left microtia and left hemifacial microsomia. Speech assessment at 6 yo showed good articulation with no hypernasality.

Patient B

M/31yo with submucous cleft palate surgically repaired at our center with Furlow palatoplasty at age 31 due to delayed presentation. He also has concommittent right microtia and right hemifacial microsomia. Speech assessment showed improved articulation with mild hypernasality.

Patient C

M/23yo with cleft palate and right microtia with primary palatoplasty done in China at aged 2. Severe velopharyngeal insufficiency with pharyngeal flap repair at age 20. Speech assessment showed residual hypernasality.

Patient D

M/15month old with cleft soft palate with Furlow palatoplasty at our center at age 12months. He also has left

hemifacial microsomia and left microria. Unable to have formal speech assessment due to young age.

Patient E

M/31yo with cleft palate repair in china at aged 10. He has concommittent right hemifacial microsomia and right microtia. Recent speech assessment showed severe hypernasality and significant palatal fistula.

【Conclusions】Clinical presentation for patients with hemifacial microsomia and cleft palate is highly variable. More data and longer term follow up would be required to assess their musculo-skeletal development and speech outcome.

P 207

Elimination of the soft tissue defects in patients with oblique and transvers facial clefts

Ms. Salimat A. Dyshekova (Russia)

Among all the pathologies of the maxillo-facial area, oblique and transverse clefts are of prime interest. Their clinical manifestations are extremely diversified, thereby requiring to use individual approach to each particular case. The oblique and transverse clefts are localized in the area of eyes and cheeks, nose and eyelids as well as in form of macro- and microcharacters. However, the nasoocular and oroocular forms are more frequently detected. Severity of the defect is determined by its form: it can be in the form of clefting and dystopia of soft tissues fragments or in combination with split of the osseal fragments of the same facial parts. The final stage of any surgical intervention is cicatrisation. In order to optimize this natural but hardly manageable process it's considered to be reasonable to divide the cleft into three main zones: the lip region, the cheek region and orbit region. Experience shows that the functional load effects on the rate of cicatrisation in these areas. In this regard the lip area holds a special place.

It is necessary to take into account the main condition while planning multi-stage surgical treatment, which is reflecting in desire to achieve bilateral functional symmetry, that influences on the growth rate and development of the facial skeleton. The technique of reconstruction for soft tissue defects is ensured by the implementation of a number of basic principles:

1. Maximum use of local tissues for replacement of rotatory flaps with mobilization of mucosal, muscles, and skin layers;
2. Correction of the upper lip and nose as uni- or bilateral rhinocheiloplasty;
3. Use of forehead flap with large soft tissues defect in combination with coloboma;
4. Forming of nasolacrimal canal (oroocular cleft) after lower eyelid repair;

However, despite reaching the positive outcomes of the primary reconstruction, it was found out that in functionally active zones or age-related gravity zones, the face configuration changes over time. As a rule, scar revision is required, and in combinations with gravitational ptosis - extended mobilization of the skin with movement of muscle and fascial structures, liposuction in the most deformed zones or lipofilling for eliminating of volume deficit.

P 208

Upper Lip Symmetry after the Straight Line Repair of Unilateral Complete Cleft Lip: in Comparison with the Rotation-Advancement Repair

Jeong Hyun Ha[1)], Youn Taek Koo[2)],
Jeehyeok Chung[3*)], Sukwha Kim[1*)]
[1)] Division of Pediatric Plastic Surgery, Seoul National University Children's Hospital,
[2)] Wonjin Plastic Surgery
[3)] Department of Plastic and Reconstructive Surgery, Myongji Hospital, Gyeonggi (Korea)

【Background】Rotation-advancement repair has been the most widely used technique for unilateral cleft lip repair. Recently, we have used a straight-line repair technique with assumption that it could minimize upper lip asymmetry when muscle reorientation is performed properly. The purpose of this study was to compare the results of these two techniques for cleft lip repair.

【Method】We conducted a retrospective cohort study of patients with unilateral complete cleft lip who underwent cheiloplasty at Seoul National University Children's Hospital from January 2009 to January 2017. The patients were divided into two groups according to cheiloplasty technique: rotation-advancement repair (RAR group) or straight-line repair (SLR group). Outcomes were evaluated by assessing 12 to 48-month follow-up photographs using three methods : (1) glance impression using a five-point scale, (2) Manchester Scar Scale, and (3) indirect anthropometry

【Result and Discussions】A total of 39 patients with unilateral complete cleft lip were analyzed: 19 in the RAR group (12 males, 7 females) and 20 in the SLR group (12 males, 8 females). The glance impression (p=0.336) and Manchester Scar Scale (p=0.667) scores did not differ significantly between groups. According to the symmetry ratio (SR; cleft side value / noncleft side value) assessed by indirect anthropometry, vertical lip height (sbal-cph), horizontal lip length (cph-ch), and Cupid's bow width (cph-ls) did not differ significantly between groups (p=0.411, p=0.496, and p=0.879, respectively). Preoperative lip height discrepancy was not significantly correlated with the postoperative vertical lip height (sbal-cph).

Straight-line repair method can be regarded as a successful tool for symmetric repair of unilateral cleft lip without causing a short lip deformity. Since skin incision type did not affect the surgical outcome, muscle reorientation appears to be more important for cleft lip repair than skin incision.

P 209

POST OPERATIVE SEIZURE FOLLOWING CLEFT LIP SURGERY

Santoso RD[1)], Saputro ID[2)], Hardiono[3)]
[1)]Resident Medical Officer
[2)]Division of Plastics Reconstructive Surgery
[3)]Division of Anesthesiology and Reanimation, Consultant of Intensive Care and Cardiovascular
Premier Surabaya Hospital (Indonesia)

【Background】Cleft lip surgery is regarded as a minor procedure that usually goes uneventful. In this study, we report a postoperative seizure as a serious complication following

cleft lip surgery. This case report serves to increase awareness about this previously rarely reported complication

【Method】This case report is using data from electronic based medical record and direct observation of the registered patient. A 4-month old boy with congenital left unilateral complete cleft lip palate without associated congenital anomaly, allergy and medical history underwent primary cleft lip repair and tip rhinoplasty. He was categorized as PS ASA 1. The procedure and perioperative were uneventful. Six hours after surgery, he vomitted and developed generalized tonic clonic seizure, leading to cardiac arrest. ROSC was aechieved, seizure was managed, patient was intubated and put under controlled ventilation, followed by transfer to Intensive Care Unit. Initial blood gas analysis and serum electrolyte showed respiratory acidosis (PH 7.187 PCO2 63.8) and severe hyponatremia (Sodium 117 meq/L). Head CT and chest xray results were unremarkable. Hypoglycemia was found (38mg/dl).

【Result and Discussions】Seizure was controlled with Midazolam and Propofol, while airway and breathing was managed under assisted ventilation. Sodium level of 117 was corrected with Saline to the point of 134. Blood glucose was low (38mg/dl) and corrected with Dextrose 10%. The most likely cause of this seizure is hyponatremia. It is most likely due to SIADH, which is a significant cause of hyponatremia following craniofacial procedures including cleft palate repair but unlikely in cleft lip repair and tip rhinoplasty.

P 210

Cleft Lip Palate Profile and Influence of Distance from Hospital and Nutritional Status in Surabaya, Indonesia

Iswinarno Doso Saputro[1)], Rosalyn Devina Santoso[2)]
Plastics Surgery Department,
Premier Surabaya Hospital (Indonesia)

【Background】Cleft lip and palate is one of the most common facial malformations in developing countries requiring multiple treatments on time to optimize feeding, facial growth, and speech. This study is to describe the profile of cleft patients and to investigate the correlation between a patient's distance from hospital and treatment delay, as well as correlation cleft type and nutritional status.

【Method】This was a retrospective analysis of 408 patients underwent cleft lip and/or palate repair in Premier Surabaya Hospital, Indonesia between December 2017 and February 2019. Data obtained at the time of patient enrolment were gender, age, cleft type, surgery type, associated malformation, the timing of surgery, and complication. Patients' home was grouped to Surabaya-and-Surroundings and Other. The recommended timing of surgery 0-6 months of age for cheilonasoraphy and 10-12 months of age for palatoraphy. Patients aged 5 years old and younger was screened using WHO Weight-for-Age Z-score (WAZ). Correlations between patient's domicile and treatment delay and between WAZ and cleft type were analyzed using Pearson chi-square tests.

【Result and Discussions】408 patients were enrolled in this study. Cleft lip and palate (CLP) type was the most common (310), followed by the cleft lip (CL) and cleft palate (CP). Of 251 male patients, 194 had CLP, 48 CL, and 9 CP. Unilateral left side cleft is more common than the right side. 26.75% (n=103) patients were found to be of later than suitable age for procedures. 76,62% (n=295) patients were of out of town origins, with 16 patients coming from out of state. However, Pearson chi-square test found no correlation between home distance and delay, with a p-value at 0.572 (α=0.05), as neither were found between state origin and delay (p value=0.321, α=0.05). Of 385 records of patients met inclusion criteria and were analyzed for correlation between WAZ and cleft type, with Pearson chi-square test revealed no correlation (p value=0.086, alpha=0.05) between both variables.

【Conclusion】Male makes up the majority of cleft patients. Unilateral left sided cleft lip and palate is the most common type. This study shows no correlation between distance to hospital and treatment delay and no correlation between cleft type and nutritional status.

P 211

Association study between haplotypes of WNT pathway genes and non-syndromic oral clefts among Chinese populations

Mengying Wang[1)], Hongchen Zheng[1)], Siyue Wang[1)],
Wenyong Li[1)], Ren Zhou[1)], Dongjing Liu[1)],
Hongping Zhu[2)], Zhibo Zhou[2)], Tao Wu[1)],
[1)]School of Public Health,
Peking University, Beijing
[2)]Peking University School of
Stomatology, Beijing (China)

【Background】WNT pathway is an important metabolic pathway influencing the risk of non-syndromic oral clefts (NSOC). Previous studies have explored the associations between haplotypes in WNT pathway genes and NSOC yet the results remain inconclusive among different studies. This study aimed to explore whether WNT pathway genes were associated with NSOC based on haplotypes analyses among Chinese populations.

【Method】We used genome-wide association study (GWAS) data of NSOC among 806 Chinese non-syndromic cleft lip with or without cleft palate (NSCL/P) case-parent trios and 202 Chinese non-syndromic cleft palate (NSCP) case-parent trios selected from an international consortium established. Haplotypes association studies were performed though transmission disequilibrium test (TDT) using plink (v1.07). The threshold of significance level was set as 3.47×10-4 using Bonferroni correction.

【Result and Discussions】A total of 144 SNPs in seven genes passed the quality control process in NSCL/P trios and NSCP trios, respectively. The results showed 29 haplotypes were associated with NSCL/P ($p<0.05$), and 15 haplotypes showed nominal significant association with NSCP ($p<0.05$), while none of them reached statistical significance level after Bonferroni correction ($p>3.47\times10\text{-}4$). Conclusion: This study failed to detect significant associations based on haplotypes of seven WNT pathway genes and the risk of NSOC. This study failed to detect significant associations based on haplotypes of seven WNT pathway genes and the risk of NSOC.

【References】The study was supported by National Natural Science Foundation of China (81102178, 81573225) and Beijing Municipal Natural Science Foundation (7172115).

P 212

A New Technique to Improve Secondary Alveolar Bone Grafting by Applying a Palatal-side Approach in Cleft Lip and Alveolus: Long-Term Effects on Alveolar Bone Formation

Chao Yang, Kun Liu, Pin Ha, Qian Zheng, Bing Shi
[1)]Department of Cleft Lip and Palate Surgery, West China Stomatology Hospital, Sichuan University, Chengdu
[2)]State Key Laboratory of Oral Disease, West China Stomatology School, Sichuan University, Chengdu (China)

【Introduction】The typical surgical approach for alveolar bone grafting（ABG）is through labial side, which may result in a shallow oral vestibular sulcus and can hardly achieve satisfied bone grafting volume and long-term bone formation. The purpose of this study was to evaluate the sufficiency of the ABG by applying a palatal-side approach for unilateral and bilateral cleft alveolar.

【Methods】A total of 30 patients from age 5 to 14 years old with non-syndromic cleft lip and palate were included in the study. These patients have received cheiloplasty and palatoplasty surgery before receiving cleft alveolar repair. An ABG through a palatal-side approach was performed by one surgeon on every patient. Cone beam computer tomography (CBCT) was taken before, 1-week after, and 1-year after surgery. All the CBCT images were measured and analyzed by Image-Pro Plus 5.1 Software.

【Results】The overall bone mass ratio between transplanted volume and defect volume was 93%, 1-week after surgery. The ratio dropped slightly to 85%, 1-year after surgery (Figure 1). Only 2 out of all the 30 patients had a shallow oral vestibular sulcus and received a secondary surgery to reconstruct the sulcus.

【Conclusions】Both short-term and long-term outcomes of the new ABG technique showed good results. ABG through a palatal-side approach solved the bone insufficiency on the palatal side of cleft alveolar, and avoid a large relaxation incision on the labial side.

P 213

Exploring the rare haplotype associations between SPRY genes and non-syndromic cleft lip with/without cleft palate among Chinese populations

Ren Zhou[1)], Hongchen Zheng[1)], Mengying Wang[1)], Siyue Wang[1)], Nan Li[2)], Zhibo Zhou[2)], Hongping Zhu[2)], Tao Wu*[1)], Terri H. Beaty[3)]
[1)] School of Public Health, Peking University, Beijing
[2)] School of Stomatology, Peking University, Beijing (China)
[3)] School of Public Health, Johns Hopkins University, Baltimore, Maryland (USA)

【Key words】genetic association study; cleft lip and palate; case-parent trios; haplotypes

【Background】Non-syndromic cleft lip with or without cleft palate (NSCL/P) is one of common birth defects with a complex genetic architecture. Although genome-wide association studies (GWASs) have identified multiple loci or candidate genes associated with the risk of NSCL/P, these genes could explain only about 20% of the heritability. Rare variants have been proposed to be more deleterious than common variants. Recently a family-triad-based logistic Bayesian Lasso (famLBL) method has been developed to detect rare variants based on data of common variants using case-parent trios, which provides a cost-effective approach to identify potential target regions for subsequent sequencing study. SPRY gene family has been reported to be associated with NSCL/P, while roles of rare variants in this gene family remained unknown. This study aimed to investigate potential risk rare variants in SPRY gene family associated with NSCL/P based on famLBL method, using GWAS data of 806 Chinese case-parent trios recruited from an international consortium for oral clefts.

【Method】Four exclusion criteria were adopted for quality control: missing genotype information in the 806 trios >10%, minor allele frequency (MAF) among founders <0.05, significant deviation of Hardy-Weinberg equilibrium among parents <0.001, or Mendelian errors >5%. A total of 200 single nucleotide polymorphisms (SNPs) of SPRY genes remained for analyses after the process of quality control. Haplotypes required in famLBL method were established by two or three adjacent SNPs. FamLBL method provided Bayesian factor for each haplotype, while haplotypes might contain susceptibility rare variants if Bayesian factors exceeded 100. The analyses were conducted by famLBL package in R 3.5.1.

【Result】The famLBL analyses yielded 11 2-SNPs haplotypes and 3-SNPs haplotypes with Bayesian factors more than 100. These haplotypes mainly located at 47kb-85kb downstream of SPRY1 and 8kb-24kb downstream of SPRY2.

【Discussion】This study explored regions potentially containing risk rare variants for NSCL/P among SPRY genes using data of common variants by famLBL method. The results indicated that two segments respectively located at downstream of SPRY1 and SPRY2 might contain susceptibility rare variants. The segments were located in non-coding regions, yet they may influence the risk of NSCL/P by regulating gene expressions. The results needed to be verify, nevertheless, this study provided candidate regions in SPRY genes for subsequent sequencing studies by a cost-effective approach.

P 214

Analysis of parent-of-origin effect on genes in the folate/homocysteine pathway among Chinese orofacial cleft triads

Hongchen Zheng[1)], Mengying Wang[1)], Siyue Wang[1)], Wenyong Li[1)], Ren Zhou[1)], Dongjing Liu[1)], Hongping Zhu[2)], Zhibo Zhou[2)], Tao Wu[1)],
[1)]Department of Epidemiology and Biostatistics, School of Public Health, Peking University
[2)]Department of Oral and Maxillofacial Surgery, School of Stomatology, Peking University (China)

【Background】Non-syndromic cleft lip with or without cleft palate (NSCL/P) is a common heritable birth defect but with little of the heritability explained by the genetic variants identified so far. Previous studies suggested that genes in the folate pathway were potentially associated with NSCL/P. While, although both the maternal and paternal alleles are present in the offspring, they may not operate at the same

level. Thus, we explored the potential parent-of-origin (PoO) effects and PoO-environment interaction in the genes in the folate/homocysteine pathway on the risk of NSCL/P in Chinses triads.

【Method】 Study participants were recruited from 4 sites in China and totally 806 NSCL/P case-parent trios were involved. We selected 268 SNPs in the folate/ homocysteine pathway. R-package Haplin (version 7.0.0) was used to test for the PoO effect with the maximum likelihood method. Relative risk ratio was used to estimate the PoO effect, and Bonferroni correction was applied to control multiple comparisons. We also tested interaction of PoO effect with environmental tobacco smoke (ETS) and maternal multivitamin supplementation during pregnancy.

【Result】 After quality control, 233 SNPs were included for the analysis. Nominal significant PoO effect was found as 3 SNPs (rs2034900, p=0.028; rs1805074, p=0.028; rs10514154, p=0.042) for maternal effect and 5 SNPs (rs9988559, p=0.021; rs2431332, p=0.025;rs250513, p=0.030;rs28326, p=0.035;rs631305, p=0.038) for paternal effect. However, no SNP survived Bonferroni correction (p=2*10^-5). In the further analysis, the interaction of PoO effect with ETS and maternal multivitamin supplementation during pregnancy showed no significant results.

【Conclusion】 Our study explored the potential PoO effect and PoO-environment interaction in the folate pathway on the risk of NSCL/P. Although no SNP survived Bonferroni correction, the results still suggested that PoO effect may be the potential mechanism of NSCL/P. This study needs to be verified with more samples in the future.

【References】 Project is supported by the National Science Foundation for Young Scientists of China (Grant No. 81102178) and the National Natural Science Foundation of China (Grant No. 81573225).

P 215

The genetic association between genes in the folate/ homocysteine metabolic pathway and non-syndromic oral clefts

Siyue Wang[1)], Mengying Wang[1)], Wenyong Li[1)], Ren Zhou[1)], Hongchen Zheng[1)], Zhibo Zhou[2)], Tao Wu*[1)], Hongping Zhu[2)],
[1)]School of Public Health, Peking University, Beijing
[2)]School of Stomatology, Peking University, Beijing (China)

【Background】 Oral clefts (OFCs), including cleft lip with/ without cleft palate (CL/P) and cleft palate (CP), are among the most common craniofacial malformations in human. Previous genome-wide association studies (GWAS) have identified several OFCs genetic risk variants, yet cumulatively explained 20%-30% of total genetic variance. It's hypothesized that complex diseases risks may be driven by the joint action of many SNPs with modest effects well below genome-wide significance. In addition, a biologically driven pathway-wide study that combines pathway genes effect altogether with polygenic risk score (PRS) is proposed for better understanding the genetic architecture. The folate/homocysteine pathway were extensively studied for its biological function in orofacial development. However, none of previous GWASs found significant effects for genes in the pathway. This study aimed at understanding the role of folate/homocysteine genes in OFC risks, using case-parent trios recruited for an oral cleft GWAS.

Method】 Participants recruited including 1008 Chinese OFC trios (806 CL/P ; 202 CP) and 2458 Asian & Europe trios (1908 CL/P ; 550 CP). SNPs located in or near 18 genes of folate/homocysteine pathway (268 SNPs totally) were selected for this analysis. Genetic quality control was performed on PLINK (version 1.90). Pseudo-controls with consideration on haplotypes were generated with trio package in R 3.5.0. PRS was calculated with minor allele numbers, with weights derived from log odds ratio in transmission disequilibrium tests (TDT). Conditional logistic regression was performed to test for PRS main effects.

【Result and Discussions】 After quality control, 233 SNPs in Chinese CL/P ,230 SNPs in Chinese CP, 138 SNPs in pooled CL/P and 191 SNPs in pooled CP were included for the analysis. The combined odds ratio (OR) of folate/homocysteine genes among Chinese was 1.305 (95% CI: 1.204-1.414, P =7.6*10-11) among CL/P trios and 1.359 (95% CI: 1.258-1.467, P = 4.92*10-15) among CP trios. The combined effects were also significant among pooled CL/P trios (OR=1.435, 95% CI: 1.265-1.628, P = 2.11*10-8) and pooled CP trios (OR=1.495, 95% CI: 1.369-1.633, P < 2*10-16). Significant combined genetic effects of folate/homocysteine metabolic pathway genes were found among case-parent trios with Chinese, Asian and European ancestries. Results suggested consistently that the folate/homocysteine pathway was of significance in controlling OFC genetic risks, which corresponded with the biological evidence. In addition, this study tentatively proposed a way for exploring the roles of etiological SNPs with genetic effects below genome-wide significance and provided more evidence in understanding the genetic risks of OFCs.

【References】 National Natural Science Foundation of China (81102178); National Natural Science Foundation of China (81573225); Beijing Municipal Natural Science Foundation (7172115)

P 216

Gustatory perception in children after palatoplasty with a tongue flap.

Fedotov RN, Grigorova EA, Budylina S.M. S.V. Dyakova, S.A. Ulyanov, Topolnitsky OZ,
Moscow State University of Medicine and Dentistry (Russia)

【Objectives】 Domestic and foreign specialists have accumulated considerable experience in surgical rehabilitation of patients with residual palate defects after uranoplasty.

The plastic using tongue flap is more often applied in case of the defects of a hard palate anterior part.

Since this method involves the excision of a part of the tongue, it is likely to suggest a violation of the sensory function of the latter, since it is rightly considered to be a kind of sensory organ.

The purpose of this research was to analyze a taste

sensitivity in children with congenital clefts who underwent plastic surgery on the palate using a flap from the tongue.

【Methods】 A group of 7 children aged 10 to 18 years was under supervision.

The research was carried out using the method of functional mobility developed by N.S. Zayko and S.M. Budylina. The patients were supervised during different periods: before surgery, 15 days after surgery, 6 months and 1 year 2 months after surgery.

【Results】 Gustatory perception research of the reference group in the preoperative period showed that the level of the tongue taste buds mobilization is on the average 85%, which is somewhat higher than the norm (70%).

The study in the early postoperative period revealed a significant increase in the level of the tongue taste buds mobilization off to 100%.

The study of the patients after 6 months of the surgery revealed a decrease in the level of the tongue taste buds mobilization to 85%, and after 1 year 2 months of the operation, the level of the tongue taste buds mobilization was 70%, which corresponds to the age norm.

Such dynamics is probably connected with the adaptation of the organism to the new conditions that have developed in the oral cavity after the surgery, with the addiction to the new conditions. As a result, the redundancy in the reactions of sensory systems is eliminated, which is manifested in a decrease in the level of the tongue taste buds mobilization to normal values.

Along with this, we paid attention to the lingual flap, moved to the palate. Visually the transplant had a pale pink color, it was normally moistened, and 3-4 some mildly expressed mushroom-shaped papillas were preserved.

Filiform papillas were of an ordinary anatomical structure. We conducted preliminary studies of the taste, tactile and temperature sensitivity of the transplanted lingual flap. At the same time it was revealed that the taste buds did not react to the suprathreshold stimulus. However, the patients felt touches and distinguished the temperature stimuli.

We also conducted a morphological study of the lingual flap moved to the palate, after 1 year and 6 months of the surgery. Histopreparations revealed a heterogeneous morphological picture: regions with well-marked mushroom-shaped papillas were visualized. The papillas were covered with a multilayer keratinizing epithelium, typical for mucous membranes of the oral cavity. The mushroom-shaped papilla is normally covered with multilayer, flat, nonkeratinized epithelium. There were signs of fibrosis and diffuse macrophage infiltration in the submucosal base.

【Conclusions】 It should be noted that the research of gustatory perception in case of surgery on the palate using a flap from the tongue can be used as an indicator of dynamic processes in sensory systems, in which compensatory mechanisms take part that ensure the normalization of taste perception in the postoperative period.

This indicates that the use of a flap from the tongue to obturate a hard palate defect does not lead to a significant disruption in the taste perception and does not adversely affect the quality of life.

P 217

For cleft lip and palate patients with special wound care compared to the advantages traditional wound dressing

Yun Wang
Beijing Smileangel Children's
Hospital (China)

【Abstract】 The importance of postoperative wound dressing change for wound recovery is well known .Especially for the special population such as cleft lip and palate, special parts are particularly important .

【Objective】 To approve that the specialized wound care is more beneficial to the special population of cleft lip and palate than traditional wound care.

【Methods】 Specialized wound care is based on different surgical methods to adopt the corresponding dressing change process .Traditional wound care is a single dressing change process .To analyze the difference between the two kinds of wound care, By statistics of wound healing, doctor satisfaction, when patient is discharge. And the parents' satisfaction rate after 1 month.

【Results】 Due to specialized wound care, the recovery of wound is better than traditional wound care, thus shortening the length of hospital stay. Improved patient' satisfaction with wound recovery.

【Conclusion】 In order to ensure cleft lip and palate wound the recovery, we should be more standardized and more professional in wound care

P 218

Anthropometric evaluation of unilateral complete cleft lip and Palate after Presurgical Nasoalveolar Molding therapy

Xieli Chen
Beijing Smileangel Children's
Hospital (China)

【Objective】 To evaluate the outcome of presurgical nasoalverolar molds (PNAM) therapy in the patients with non-syndromic unilateral complete cleft lip and palate (UCCLP) comparing with PNAM group and no PNAM groups.

【Design】 a retrospective study with blinded measurement.

【Patients】 21 patients with UCLP with PNAM treatment (PNAM groups), and 22 age-matched subjects with UCLP without PNAM treatment (no PNAM groups) from 2011 to 2017

【Interventions】 The starting age for PNAM therapy was 15.3 days, and the average length of treatment was 98.5 days.

【Main outcome measures】 measurements of facial casts were made, and statistical analyses were used to compare the differences between two groups.

【Results】 In PNAM groups, cleft width, vertical distance between double philtrals and columellar deviation were smaller than that in no PNAM groups. And nostril height was larger than that in no PNAM groups. The difference between two groups were statistically significance ($p<.05$). Although the difference of nostril width between two groups was not statistically significance, the difference between two group was on average 1.2mm.

【Conclusion】 Our result indicated that, PNAM therapy decreases cleft width and vertical distance between double

philtrals. It also increases nasal symmetry by decreasing columellar deviation, increasing nostril height.

【Key words】 Nasoalveolar molding (NAM); cleft lip and palate; anthropometry; nasal deformity;

P 219

Improvement of suturing method for levator palatine velum retropositioning in the repair of cleft palate

Han Zhang, Xiaoju Jin
Beijing Smileangel Children's Hospital (China)

Cleft palate is one of the common congenital diseases that affects multiple functions including speech and swallowing. Reconstruction of the palatal muscle and restoration of the levator palatine velum ring can improve the velopharyngeal function and speech. Reconstruction of the the levator palatine velum ring has two ways of apposition suture and overlapping suture. This article reviews the improvement of the splitting muscle suture method.

P 220

Clinical effect comparison of different filling methods of iodoform gauze for the relief incision after palatoplasty

Wenjun Xie
Beijing Smileangel Children's Hospital (China)

【objective】 to study the postoperative body temperature, feeding, secondary bleeding and healing of patients with different filling methods of iodoform gauze in relief incision after palatoplasty.

【Methods】 30 cases of surgery for Bardach, langley, Furlow of cleft palate patients were randomly divided into 2 groups, intraoperative use of high frequency electric knife to provide adequate hemostasis, postoperative group A in two small section of the iodoform gauze filled respectively within the bilateral relief incision, postoperative group B ues of iodoform gauze bag pressurized fixed above the relief incision and hard palate, and don't fill in the bilateral relief incision.

【Results】 there was no significant difference in postoperative fever, recovery rate of feeding, postoperative healing in the operative area ($P > 0.05$), and the secondary bleeding in group B was significantly less than that in group A, with statistically significant difference ($P < 0.05$).

【Conclusion】 the choice of iodoform gauze bag for pressurized fixation in the bilateral relief incision and the upper part of the hard palate showed no significant difference in postoperative fever, recovery rate of feeding and postoperative healing, but it could significantly reduce postoperative secondary bleeding, which had good clinical application value.

【Key words】 postoperative of palatoplasty; iodoform gauze; relaxed incision; Clinical effect.

P 221

PREVALENCE OF CLEFT LIP AND PALATE ANOMALIES IN SOUTH-EAST ASIA: SYSTEMIC REVIEW

Ahmed Abumustafa, Bushra Alkhen, Marie M. Tolarova
Department of Orthodontics, Arthur A. Dugoni School of Dentistry, University of the Pacific, San Francisco (USA)

【BACKGROUND】 South-East Asia consists of eleven countries (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar (Burma), Philippines, Singapore, Thailand, Timor Leste, and Vietnam) that are diverse in religion, history and culture. Population of 642 million people lives on area of 1.7 million sq. miles. Birth defects cause a significant proportion of infant and childhood mortality and morbidity. Regional offices of WHO are working towards improvement of this situation. Cleft lip and palate (CLP) anomalies are the second most common congenital malformations with average birth prevalence 1 in 500 – 1 in 1000 worldwide, while higher numbers occur in low-income and developing countries. Because of insufficient resources in many of these countries, CLP anomalies create a burden on individuals, families, and society. The first step to effectively plan improvement of this situation is to know how many babies with CLP are born in each specific country or location.

Purpose of our study was to review literature on prevalence of CLP in the South-East Asian countries.

【MATERIAL AND METHODS】 A systematic review of literature was done using four search engines (PubMed, Scorpius, Google Scholar, and Science Direct) and keywords cleft lip, cleft lip and palate, cleft palate, prevalence, and names of eleven South-East Asian countries. The search was run with no language restrictions and covered the 1980 – 2018 time period.

【RESULTS AND DISCUSSION】 Twelve articles and two WHO reports matched the inclusion criteria and were reviewed in detail. No individual data from Brunei, Cambodia, Indonesia, Laos, Myanmar and Timor Leste were found in the reviewed literature.

Vast majority of studies were hospital-based and no division to syndromic and non-syndromic clefts was done. The highest birth prevalence was reported in Singapore - 1 per 574 live births.

Studies from Malaysia reported birth prevalence 1.24/1,000, Philippines 1.94/1000 and 5.7/10,000, Singapore 1.87-2.07/1000, Thailand 1.1-1.51/1000, and Vietnam 1.4/1,000 live births.

【CONCLUSIONS】 Birth prevalence of CLP anomalies in South East Asian countries seems to be high and varies by country. Birth defect registry and further studies focusing on environmental and genetic factors are needed to get a better understanding of etiology of CLP in South East Asia.

P 222

Classification of Submucous Cleft Palate Bone Defect

Changjiang DU, Xia ZHOU, Feifei SHANG, Lian MA (China)

Submucous cleft palate is a special subgroup of cleft palate. Clinical studies have shown that there existed various degrees of the palatal bony defects in patients with submucous cleft palate, which may effect on choice of treatment methods, the prognosis of speech outcomes and in identifying the genes expression involved. Objective: To classify the degree and shape of palatal bony defect in patients with submucous cleft palate. Materials

and Methods: 91 patients with submucous cleft palate who were treated in Peking University School and Hospital of Stomatology from 2013.01.01 to 2014.12.31 were included into this study. Bony defects of the hard palate were divided into three types, type I: half of secondary palate or less was involved; type II: more than the half of secondary palate was involved; type III: the alveolar bone was involved. In addition, according to the shape of the bony defect, it was divided into " 𠆢 " shape, inverted "V" shape , inverted "U" shape and atypical shape. Five judgers were used to perform the assessment individually. Results: 1. The proportions of three types of bony cleft palate were determined to be as follows: type I, 39.6% (36/91); type II, 49.4% (45/91); type III, 11.0% (10/91). 2. The shape of submucous cleft palate bony defect can be divided into four types: " 𠆢 " shape, inverted "V" shape, inverted "U" shape and atypical shape. In the patients of type I, the proportions of the four types of bony cleft palate were determined to be as follows: " 𠆢 " shape: 30.6% (11/36); inverted "V" shape: 69.4% (25/36); inverted "U" shape: 0% (0/36); atypical shape: 0% (0/36). In the patients of type II, the proportions of the four types of bony cleft palate were determined to be as follows: " 𠆢 " shape: 73.3% (33/45); inverted "V" shape: 13.3% (6/45); inverted "U" shape: 13.4% (6/45); atypical shape: 0% (0/45). Conclusions: The degree and shape of palatal bony defect are different in patients with submucous cleft palate. The different degrees and shapes of submucous cleft palate bony defects are of great significance for the selection of surgical methods and the effect of speech rehabilitation.

【KEY WORDS】Submucous cleft palate, Bony defect, Classification

P 223

A family case of congenital cleft lip and palate: clinical and genetic markers and a multidisciplinary approach.

Khachatryan L.G., Mamedov A.A.,
Morozova N.A., Areian D.E., Makeeva I.M.,
Maclennan A.B., Admakin O.I., Kasanabe E.V.
I.M.Sechenov First Moscow State Medical University
(Sechenov University), Moscow (Russia)

【Introduction】Congenital cleft lip and palate (CCLP) is the most common manifestation of maxillofacial malformations. CCLP occurs in 0.6-1.6 cases per 1000 newborns, of which 63.1% have various changes of chromosomal and genetic nature. Every year from 3500 to 5000 children are born in Russia with CCLP. The examination of family cases of CCLP will enable to reveal new mechanisms of inheritance of this pathology.

【Discussion】We observed a family - a father and two sons, who had different anomalies of the facial area. The father had a corrected monolateral cleft lip and polycystic dysplasia of the kidneys, the eldest son (16 years old) also had a monolateral cleft lip and febrile seizures. The most serious picture was observed in the younger child. His clinical manifestations included the following symptoms:

1. Age 3 years. Weight - 11.5 kg, height - 86 cm, (physical developmental delays);
2. One-sided cleft lip and palate, cicatricial deformity of the upper lip after cheilo uranoplasty;
3. Polymorphic convulsions and dystonic attacks;
4. Polydactyly of the right hand (additional rudimentary little finger);
5. Arterial hypertension (kidney origin);
6. Cryptorchidism.
7. Microcephaly and Tetraparesis.

A comprehensive study of the child revealed the following:

1. According to the MRI of the brain, there was a picture of diffuse cortical and subcortical atrophic changes in the cerebral hemispheres, hypoplasia of the corpus callosum, hypoplasia of the cerebellum, expansion of the outer cerebrospinal fluid spaces.
2. The electroencephalographic monitoring registered multiregional epileptiform activity in the form of spikes, sharp waves, peak-wave complexes, and an acute slow wave.
3. According to the CT scan of angiography of the kidneys, hypoplasia of the renal artery on the right was found.
4. The genetic analysis immediately revealed 2 mutations: C.113T> A in the MEF2C gene in 5q14.3, a mutation in the MKS1 gene in 17q23. Despite partial clinical manifestations in the boy's father (polycystic kidney disease and lip cleavage characteristic of Meckel–Gubler syndrome), the complete gene sequencing did not reveal any disorders. The boy's brother had a microdeletion in 5q14.4, which was also determined in the mother who was clinically healthy.

【Conclusion】The syndrome of cleft lip and palate is a polyetiological and clinically diverse condition. Studying and demonstrating a family case is an attempt to find new mechanisms of the inheritance of this pathology, and its clinical polymorphism requires a multidisciplinary approach to the management of these patients.

P 224

EVALUATION OF PALATAL DIMENSIONS IN PATIENTS WITH UNILATERAL COMPLETE CLEFT LIP AND PALATE WITH DIFFERENT TIMING OF PRIMARY LIP SUTURE

Tereza Petrova, DMD
Magdalena Kotova, MD, PhD
Department of orthodontics and cleft anomalies,
Kralovske Vinohrady University Hospital,
Prague (Czech Republic)

【Background】The aim was to evaluate transversal and sagittal dimensions of upper jaw in patients with unilateral complete cleft lip and palate with different timing of primary lip suture

【Method】We have evaluated the distance between the cusps of primary canines, the distance between the centres of distal side of primary second molars and the perpendicular going from the reconstructed position of papilla incisiva to the tangent uniting both tuber maxillae. The measurements were performed on plaster models using a sliding scale. In the first part of the study we have evaluated a group of 16 patients with mean age 8 with unilateral complete cleft lip and palate, who have undergone the neonatal suture of the lip. The second group consisted of 18 patients with the same defect, but the primary lip suture has been performed at the age of 3 months. Their mean age was 9. Both groups were then compared with healthy control and with

data of Dr. Peterka (1975), who observed patients with later timing of lip suture as well as palate suture.

【Results】We have found differences in some of the observed parameters in between all the three groups of cleft patients and when compared to the healthy control.

【Discussion】The growth of the upper jaw in cleft patients shows important connotations with the results of primary operations. Therefore it is important to observe the effectiveness of the particular treatment protocols.

P 225

Growth and development of Craniofacial structures in patients with unrepaired submucous cleft palate.

Yan Wang[1,2], Congcong Cao[1,2], Qian Zheng[1,2], Bing Shi[1,2]
[1)]State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China School of Stomatology, Sichuan University, Chengdu
[2)]Department of Cleft Lip and Palate Surgery, West China Hospital of Stomatology, Sichuan University, Chengdu (China)

【Objcetive】to compare the craniofacial morphology cephalometrically of patients at children, adolescence and adulthood with SMCP and age-matched non-clefts, attempted to observe the craniofacial growth and development of patients with SMCP and to study the changement of differences between SMCP cases and non-clefts during ageing.

【Materals and methods】The study included consecutive thirty-nine nonoperated patients with SMCP of Han nationality. Patients were divided into three subgroups: children group ranging from 5 to 6 years, adolescent group ranging from 10 to 11years, adult group ranging from 18 to 30 years. Winceph 7.0 was used to fixed measure points and measure lengths, angles and ratios. 22 measurements were used in this study, including 13 linear measurements, 9 angle measurements. Measurements used reflect cranial length, cranial angle, maxilla sagittal length and protrusion, maxilla vertical height, pharyngeal depth, facial height, mandible length and protrusion. Spss 16.0 was used to analyze data.

【Results】

1) Children: The cranial base lengths (S-N, N-Ba, N-Ba) and angle(∠ N-S-Ba), maxillary sagittal length(PMP-ANS,PMP-A) and retrusion (Ba-A,Ba-ANS, ∠ S-N-ANS, ∠ SNA), anterior and posterior maxillary height(N-ANS, R-PMP), bony nasopharyngeal depth(Ba-PMP),the length of mandibular body (Pog-Go), protrusion of mandible(∠ S-N-B, ∠ S-N-Pog), mandibular ramus (Ar-Go) and gonial angle(∠ Ar-Go-Gn), facial height(N-ANS, N-Me,ANS-Me) and ∠ A-N-B were similar（$p > 0.05$）in patients with SMCP and non-clefts.
2) Adolescents: The cranial base lengths(S-N, N-Ba, N-Ba) , the cranial base angle (∠ N-S-Ba)were similar（$p > 0.05$）in alolescents with SMCP and non-clefts. The SMCP patients showed decreased（$p < 0.05$）maxillary sagittal length(PMP-ANS,PMP-A), retrusion of maxillary(Ba-A, Ba-ANS, ∠ Ba-N-ANS, ∠ S-N-ANS, ∠ S-N-A).The posterior maxillary height(R-PMP), bony nasopharyngeal depth(Ba-PMP), the length of mandibular body(Pog-Go) and mandibular ramus(Ar-Go), protrusion of mandible(∠ S-N-B, ∠ S-N-Pog), gonial angle(∠ Ar-Go-Gn) and gacial height(N-ANS, ANS-Me, N-Me)were similar（$p > 0.05$）in patients with SMCP and non-clefts.
3) Adults: The cranial base lengths(S-N, N-Ba, N-Ba), the cranial base angle (∠ N-S-Ba)were similar in adults with SMCP and non-clefts($p > 0.05$). The maxillary sagittal length(PMP-A, PMP-ANS), retrusion of maxillary(Ba-A, Ba-ANS, ∠ Ba-N-ANS, ∠ S-N-ANS, ∠ S-N-A) and upper and total facial height(N-ANS, N-Me), mandibular body length(Pog-Go),mandibular ramus length(Ar-Go) and gonial angle(∠ Ar-Go-Gn) were signifcantly shortended（$p < 0.05$）in adults with SMCP , while the bony nasopharyngeal depth(Ba-PMP),posterior maxillary height(R-PMP) and protrusion of mandible(∠ S-N-B, ∠ S-N-Pog) were normal($p > 0.05$).

【Conclusions】The craniofacial morphology were similar in children with SMCP and non-clefts, while the rate of craniofacial growth and development in patients with SMCP were slower than non-clefts, gradually showed the median facial dysplasia in adolescence, with the adapative growth of mandible demonstrated mandible depression in adults.

【Key words】submucous cleft palate, hard and soft cleft palate, craniofacial, growth and development, lateral cephalometric analysis.

P 226

Cross cultural adaptation and validation of a health related quality of life assessment (COHIP- Children's Oral Health Index Profile) for adolescents with Cleft Lip and Palate in Sri Lanka.

Mirihagalla Kankanamalage Inoka, Dr. Wendy Cohen, Dr. Joanne Cleland (UK)

【Background】Cleft lip and/or palate (CL/P) is one of the most common orofacial congenital malformations in live births and has varied incidences in different regional populations (Augsornwan & Prngapagatip, 2011). The current worldwide incidence is estimated as 1-2/1000. Treatment processes for CL/P and associated difficulties is a long term process, usually from birth and lasting until early adulthood, leading to long term quality of life (QOL) implications for these individuals. Measuring QOL in adolescents requires care to ensure that questions are valid and appropriate, particularly where there may be discrete QOL concerns relating specifically to CL/P. Some questionnaires are available in some languages for this population, but not all in Sinhalese, the principal language spoken in Sri Lanka.

The objectives of this study are to culturally adapt and validate an existing QOL assessment for CL/P the "Childrens Oral Health Index Profile (COHIP)" (Broder., 2017) alongside a measure of speech intelligibility, the "Intelligibility in Context Scale (ICS) " (McLeod, Harrison &McCormack, 2012) to Sinhalese. These tools will then be used to measure the QOL of young people with repaired CL/P in Sri Lanka.

【Method】The COHIP and ICS were translated into Sinhalese using cross cultural adaptation guidelines (Gulimen et al., 1993). This requires two forward translations from English to Sinhalese, followed by reconciliation and agreement and

a backward translation from Sinhalese to English of the reconciled forward translated questionnaire. Bilingual English and Sinhalese speakers are required for all steps in the process, with three bilingual (Sinhalese and English) Speech and Language Therapists (SLT's) undertaking these tasks.

【Results】Two bilingual SLTs whose mother tongue is Sinhalese and one SLT, whose mother tongue is English, together produced the final Sinhalese translation of COHIP and ICS. The forward, reconciliation and backward steps of the translation process were completed leading to a final translation of both the COHIP and ICS ready for future validation in Sri Lanka. The process undertaken will be presented along with the final translations of the two questionnaires.

【Discussion】The time taken in preparing and completing the forward-backward-forward translation process should not be underestimated when preparing existing questionnaires for use in other cultural contexts. The next stage in this study will involve trialing the questionnaires with 400 Sri Lankan typically developing adolescents and 30 young people with repaired CL/P, all aged 12-15 years. This will lead to validation of the COHIP and ICS Sinhalese questionnaires for use in the Sri Lankan context.

P 227

Report Humanitarian Surgery Activities For Children With Cleft Palate Between Japanese Cleft Palate Foundation (JCPF) And Ninh Binh General Hospital

Le Chinh Chuyen
Ninh Binh General Hospital (Viet Nam)

【Introdution】Brief introduction about Ninh Binh province and Ninh Binh General Hospital (Total number of hospital staff, Total number of planned beds, departments)

- Introduction of cooperation activities between JCPF and Ninh Binh General Hospital since 1998 up to now (Introducing the context of cooperation, sponsored activities of jcpf, working time, working schedule, composition of the cooperation team…)

【Contents of cooperation activities over the years】Organize meetings to meet and discuss between JCPF's member with hospital leaders, agree on a plan to coordinate activities with hospital leaders and related departments.

Organize screening examination for patients with cleft palate, consult and appoint surgery for patients:

Coordinate to organize surgery for patients and transfer technology to doctors and nurses of Ninh Binh General Hospital on surgery, anesthesia, care after surgery:

Doctors and professors in the surgical team also had lectures in the field of surgery and treatment of dentomaxillofacial for doctors and nurses of the provincial general hospital.

【Results】

* From 1998 to present:

Total number of examination: More than 1000 cases

Total surgery: 530 cases

* In 2019:

Examination: 112 patients, aged from 2 months to 32 years.

36 cases were considered for surgery:

+01 case: not come.

+01 case: not healthy enough for surgery.

34 surgeries:

+Age from 3 months to 12 years old.

+Weight: 8kg to 32 kg.

On average, 6 children are operated daily.

【Discussion】

・Difficulties

+Insufficient consultation time for patients

+Insufficient recording time (surgical records)

+Shortage of member

+Limited number of operations

+Difficulties Introduction of new technique e.g. orthodontic treatment, alveolar bone grafting, orthognathic treatment, speech therapy

・Direction of cooperation in the coming years

+Continue the annual surgical coordination program

+Supplement and improve new techniques related to grafting bone and orthodontic treatment

+Creating conditions and opportunities for doctors of the Ninh Binh General Hospital to exchange experience, learn and transfer technology on dentomaxillofacial surgery, cleft lip - palate, anesthesia ...

+Enhancing the exchange of learning between doctors of Ninh Binh General Hospital with Japanese doctors and experts through direct training and through Telemedicine system

P 228

Craniofacial Characteristics and Management of Melnick-Needles Syndrome: A Case Report

Lunjanasatienchai Kornkamol, Tantidhnazet Syrina, Raocharernporn Somchart, Siew Peng Neoh, Chaweewannakorn Chaiyapol, Peanchitlertkajorn Supakit
Department of Orthodontics, Faculty of Dentistry, Mahidol University (Thailand)

【Background】Melnick-Needles syndrome (MNS) is an extremely rare genetic disorder, caused by mutation in exon 22 of the FLNA gene. The syndrome is characterized as the most severe form in the otopalatodigital disorders spectrum. Common characteristics include short stature, scoliosis, bilateral exophthalmos, prominent forehead, arachnodactyly, fullness of cheeks, micrognathia, oligodontia, delayed dental development, and malocclusion. The incidence is less than 1:1,000,000, with fewer than 100 cases reported worldwide. Previous case reports emphasized the need for a combined orthodontics and orthognathic surgery, specifically mandibular distraction osteogenesis. The aim of this report is to present clinical characteristics and our treatment approach for MNS.

【Method】A 17-year-6-month-old Thai female diagnosed with MNS was referred to our Craniofacial clinic. The patient presented with short stature, scoliosis, long fingers and toes, and bowed arms. Notable facial features include prominent forehead, bilateral exophthalmos, convex profile, maxillary retrognathia, and mandibular micrognathia. Dentally, she is still in mixed dentition with prolonged retention of multiple deciduous teeth. Her molar relationship is Class II on the left, and Class III on the right. The canine relationship is Class III on the left, and unclassified on the right. The overjet and overbite are 2.5, and 3 mm respectively. Radiographic exam reveals tooth # 18, 17, 15, 14, 13, 12, 22, 24, 25, 27, 37, 35, 41,

44, 45, 47, 48 are congenitally missing. Significant hypoplasia of coronoid process and shortening of rami are observed bilaterally. Cephalometric analysis demonstrates skeletal type II with bimaxillary retrusion, steep mandibular plane, retroclination of upper and lower incisors.
【Result】Combined orthodontics and orthognathic surgery is planned. The surgery will be performed in 2 stages. The first stage is to perform LF III distraction to advance the midface. The second stage is to advance the mandible to harmonize maxillomandibular relationship and reduce facial convexity. The LF III advancement is performed first to allow for additional mandibular advancement and elimination of exophthalmos. Comprehensive orthodontics will be performed to facilitate surgical procedures and refine dental occlusion. Prostheses to replace missing teeth will be performed after the completion of surgical-orthodontic treatment.
【Discussion】This is the first case report of MNS in Thailand. The surgical approach of this patient differs from previous reports as the LF III distraction is included to address midfacial hypoplasia and exophthalmos. Because patients with MNS have a defective collagen synthesis, special considerations such as bone healing after distraction osteogenesis will also be discussed.

P 229

SPECIALIZED HELP TO CHILDREN WITH A CLEFT PALATE IN MODERN CONDITIONS OF DEVELOPMENT OF THE CHECHEN REPUBLIC OF RUSSIA

Akhmetkhanov S-M.S-A.,
Mamedov A.A.,
M. Khamidova
[1)] Republican Childrens' Dental Polyclinic, Grozny
[2)] Moscow, FSAEI about I.M. Sechenov First Moscow State Medical University Ministry of Health of Russia (Sechenov University), Department of Pediatric Dentistry and Orthodontics, Children's Dental (Russia)

【Relevance of the problem】Problems with congenital maxillofacial pathology has always attracted a lot of attention from many researchers, what can be proved by an amount of congresses and symposia with doctors and biologists, also a large number of publications about different congenital pathologies. The problem of treating children with congenital cleft lip and palate remains relevant due to unsufficiently qualified, specialised care for children with such pathologies.
【Frequency and prevalence in Russia】on the basis of the research conducted in some regions, there is a tendency to increase the number of children born with cleft lip and palate.

So in the Lipetsk region over the past 10 years, the birth rate of children with CLP increased from 1: 954 to 1: 800 newborns. However, the frequency of birth of children with CCLP in the Orenburg region over the past 20 years has remained unchanged at 1: 750. Research has shown that children living in a city with industry (NHP) and exposed to chemical factors of low intensity of polluted atmospheric air, have a higher birth rate of children with CCLP. In some areas it reaches 1:200, despite a stable figure of 1: 750.

【CENTERS IN RUSSIA】There are a lot of successfully working Centers in Moscow, Yekaterinburg, regional centers in St. Petersburg, Perm, Ufa, Voronezh and Orenburg.
【COOPERATION OF ORGANIZATIONS】To improve the effectiveness of care for children with congenital disorders of the cranio-maxillofacial area, it is necessary, first of all, for organizations like cooperation, such as the Ministry of Health and Social Development of Russia, social protection of the population, organs, Dental association of Russia (STAR), Health departments (regional), specialized Centers, regional Urban Children's hospitals , children's dental clinics, universities, (departments of children's country dentistry), charity foundations, medical health insurance companies.

Together with the Russian Charitable Foundation "Congenital cleft lip and palate" created and registered on June 1 (by Professor Mamedov), with the support of parents of our patients, as well as on the basis of the decision of the Board of the Ministry of Health of the Russian Federation of October 21, 2003, Minutes No. 14 "On Improvement of dental care for children in the Russian Federation ", legal integrated regional centers for clinical examination of congenital maxillofacial pathology were organized in Yuzhno-Sakhalinsk, Tula, Lipetsk. Activities of medical examination centers in Orenburg, Volgograd, Samara, Tver are supported. The registration in the Department of Health of Belgorod Region and the Chechen Republic is planned.

We have conducted over one thousand consultations. Especially : primary pathology and recovery operations, over 500 operations. Patient age from 1 month to 18 years. Patients older than 16 years old are operated on in adult clinics (departments). Our patients are pathological primary and reconstructive, in need of medical care and are over 18 years old, because reconstructive-restorative interventions are in order of patients needs. Not only aesthetic operations are performed at will, but also the elimination of defects and deformations made in childhood after primary operations.
In modern conditions, a comprehensive solution to the problem of treating children with the CLP requires the collection and analysis of large volumes and diverse forms of information, the timely and high-quality processing of which is impossible without using automation tools and creating a single information space.

Informational computer space is a new technology of medical, psychological, educational and social rehabilitation of patients with CLP. Sources of information support in this case can be systems of expert assessments; diagnostics, planning of rehabilitation tactics, data processing (recovery, quick filtering, data compression).

Highly qualified rehabilitation of patients with congenital abnormalities of the cranial-maxillofacial area in modern conditions is possible only in specialized centers that allow to provide assistance from the day the child is born and at all its stages.

A significant increase in the list and scope of informatization tasks, their applied focus due to the specificity of treatment in various departments of the specialized Center, implemented in the networked version of a computer system, is focused on solving the following tasks: maintaining a child's medical history, including medical, social, pedagogical, psychological

information coming from different specialists from different departments and accumulated in a single database; Formation of summarizing documents that are, in essence, epicrises (if necessary, an extract from the child's development history) - providing all the specialists with necessary information about the child, including those working in geographically remote divisions of the center (data exchange); development and formation of a comprehensive treatment and rehabilitation plan with monitoring the implementation of prescriptions and turnout for follow-up and activities; - operational control of the treatment and diagnostic process by the administration.

Static data processing and their presentation in tabular form (in the subsequent receipt of a hard copy in graphic, textual form), in accordance with the requirements of the user; maintenance of reference information; -creation of educational multimedia complexes for training, advanced training of medical personnel who are able to interactively reveal educational topics with hypertext and display video images imitating the student's visual, tactile and auditory sensations. We have proposed an automated system for managing and recording data in the comprehensive rehabilitation of patients with CLP in the Center for the Clinical Examination of Children with Congenital Maxillofacial Pathology.

The automated system for managing and recording data in the form of a hypertext, multimedia database (DB) allows not only to perform basic tasks for the comprehensive rehabilitation of patients with cleft lip and palate, but it is also an educational and methodological knowledge base for system training of specialists in the form of a modular knowledge base. In this case, the specialist can visually view and have a hard copy of the complete algorithm for the rehabilitation of such patients.

P 230

Development of in vitro developmental toxicity using human iPS cell technology

Yasunari Kanda and Shigeru Yamada
Division of Pharmacology, NIHS (Japan)

Environmental chemicals have potential effects on children's neurodevelopmental toxicity, leading to neurobehavioral outcomes such as attention deficit hyperactivity disorder and autism. Since the developing brain is much more vulnerable to chemicals compared with the adult brain, exposure to neurotoxic chemicals during prenatal period can cause delayed neural disorders. Current developmental neurotoxicity (DNT) guideline (OECD TG 426) using in vivo studies is expensive, takes a lot of time and requires large numbers of animals. Large numbers of chemicals have been identified for testing (e.g., pesticide) with no risk-based criteria for setting testing priorities. Here we tried to develop an in vitro DNT method as animal alternative in vitro testing. To search suitable endpoints for evaluation of chemicals with DNT hazard, we have focused on neural differentiation process which is induced by the dual Smad inhibitors in human iPS cells. Positive compounds inhibited the induction of Pax6, a key transcription factor that regulates neurogenesis in human iPS cells, whereas negative compounds did not. Next, we examined mitochondrial dynamics, because differentiation requires ATP production that is a critical function of the mitochondria. Staining with mitochondrion-selective fluorescent dye Mito-Tracker revealed that positive compounds induced mitochondrial fragmentation in human iPS cells. Recent studies have shown that the mitochondrial dynamics is regulated by fusion factors, such as mitofusin (Mfn) and optic atrophy 1 (Opa1), and fission factors, such as fission protein 1 (Fis1) and dynamin-related protein 1 (Drp1). Positive compounds selectively induced degradation of Mfn protein among mitochondria-regulated factors in human iPS cells. We further examined the role of Mfn on neural differentiation in human iPS cells. Knockdown of Mfn gene in iPS cells mimicked the effects of positive compounds on ATP production and neural differentiation, suggesting that Mfn mediates neural differentiation in human iPS cells. Taken together, these results suggest that positive compounds induces neurotoxicity via Mfn-mediated mitochondrial impairment in human iPS cells. Further studies need to confirm the relationship between in vitro data and in vivo data.

This work was in part supported by MHLW research grant.

P 231

Interkinetic nuclear migration in the trachea and esophageal epithelia of the mouse embryo

Regassa Dereje Getachew[1)], Akihiro Matsumoto[1)], Jun Udagawa[2)], Hiroki Otani[1)]
[1)] Department of Developmental Biology, Faculty of Medicine, Shimane University
[2)] Department of Anatomy, Shiga University of Medical Science (Japan)

【Background】 Interkinetic nuclear migration (INM) is the migration of nuclei of the epithelial cells in synchrony with cell cycle, undergoing cell division at apical and back to basal during interphase.

【Purpose】 To investigate the inter-organ and regional differences of INM in the epithelium of trachea and esophagus of mouse embryos.

【Method】 DNA synthesizing stem cells nuclei were labeled with EdU (5-ethynyl-2'- deoxyuridine). The pregnant mice received single intraperitoneal EdU injection at embryonic day 11.5 (E11.5) and E12.5 and were sacrificed 1, 4, 6, 8, and 12hr later to obtain one embryo per dam (N=1 for each time point). The labeled stem cell nuclei distribution along the apicobasal axis was chronologically analyzed in the total, ventral and dorsal side of the trachea and esophagus using the histogram and multi-dimensional scaling (MDS). We analyzed the total cell count and EdU-labeled index in the trachea and esophagus.

【Result】 In the trachea, at E11.5 the total EdU-labeled nuclei positions were basal at 1hr and apical at 4 and 6hr and back to basal at 8hr and again fully basal at 12hr. At E12.5, the nuclei positions showed a similar pattern with E11.5 except at 6hr the more apical positions. In the esophagus, at E11.5 the total EdU-labeled nuclei positions were basal at 1hr, and apical at 4hr and shifting to basal at 6 and 8hr, and again fully basal at 12hr. At E12.5, a similar pattern of nuclei distribution except at 12hr which was not fully basal. The total cell count showed more cell population in trachea than esophagus at E11.5 and E12.5, whereas EdU-labeled index showed no significant difference between trachea and esophagus at E11.5 or E12.5, neither in the trachea between E11.5 and E12.5, nor in the esophagus

between E11.5 and E12.5.
【Discussion】 We previously reported that the INM exists at E11.5 in the trachea and esophagus. In the present study, we further investigated the inter-organ and/or regional difference between ventral and dorsal part. There was a slight inter-organ dissimilarity in the INM mode between trachea and esophagus at E11.5 and E12.5. These findings suggests that an inter-organ INM mode difference exists between trachea and esophagus which may be involved in the later different development of the epithelia of these organs.
This work was supported by MEXT KAKENHI (23112006).
COI: None

P 232

Leukemia inhibitory factor upregulates corticotropin-releasing hormone through activating AKT and MAPK signaling in mouse trophoblasts

He Wang[1)], Tsuyoshi Tsukada[1)], Hiromi Sakata-Haga[1)], Hiroki Shimada[2)], Hiroki Shoji[3)], and Toshihisa Hatta[1)]
Departments of [1)]Anatomy
[2)]Medical Science, and
[3)]Biology, Kanazawa Medical University (Japan)

Previous studies of rodents have shown that maternal leukemia inhibitory factor (LIF) induces the secretion of adrenocorticotropic hormone (ACTH) from the placenta, which in turn stimulates fetal nucleated red blood cells to secrete LIF in rodents (the maternal-fetal LIF-ACTH signal relay pathway proposed by Simamura et al., 2010). Here we examined the effects of LIF on the expression and secretion of corticotropin releasing hormone (CRH) in mouse trophoblasts in vitro. The mouse trophoblast stem cells (mTSCs) which we used in this study were capable of differentiating into various types of mouse trophoblasts, including giant trophoblasts, spongiotrophoblasts, and syncytiotrophoblasts. At several time points, we measured the expression of Crh mRNA in mTSCs by quantitative RT-PCR and CRH levels in culture media containing LIF (10 ng/ml of recombinant mouse LIF) by Sandwich ELISA. At 3 and 5 days after LIF supplementation, the expression of Crh mRNA was significantly increased in the mTSCs with LIF treatment compared to those with control treatment. The concentration of CRH in the culture media also increased. We then examined the effect of LIF downstream pathways, including JAK/STAT3, AKT, and MAPK signaling, on the induction of CRH in mTSCs. The LIF-induced upregulation of CRH in mouse trophoblasts was attenuated by the inhibition of AKT and MAPK phosphorylation, but not by that of JAK/STAT3. These findings suggest that LIF induces CRH in mouse trophoblasts via the AKT and MAPK pathways, contributing to the induction of ACTH secretion from the placenta.

This work was supported by KAKENHI (15K15405, 16H05364, and 16K19674). COI: None

P 233

Histological analysis of the smooth muscle cell layer and epithelial lumen in the mouse developing duodenum.

Nusrat Jahan[1)], Esrat Jahan[1)], Regassa Dereje Getachew[1)], Noriko Ogawa[1)], Ashiq M Rafiq[2)], Satoru Hirano[1)], Hiroki Otani[1)]
[1)] Department of Developmental Biology, Faculty of Medicine, Shimane University,
[2)] Center for the Promotion of Project Research, Organization for Research, Shimane University (Japan)

【Background】 The mechanism of the development of smooth muscle (SM) layer, epithelium as well as mesenchyme of the gut during embryogenesis is important to understand whole gut development. SM layer of the gut, which develops from mesenchyme, consists of two inner circular (IC) and outer longitudinal (OL) layers. Previously we reported regional differences of SM layers in ileocecal junction (ICJ) during developmental period. Understanding the mechanism of these regional differences needs further research.
【Purpose】 To clarify the common features in the regional difference in the development of SM layers, mesenchyme and epithelium of the duodenum for elucidating their possible relationship with the overall macroscopic morphogenesis of the duodenum.
【Method】 We used C57BL/6 mouse embryos at embryonic day (E) 13.5, 15.5, 17.5 (each day, n=3). After fixation, embryos were processed to make sections. We did HE staining and immunohistochemistry for α-SM actin, followed by histomorphometric analysis. The angle of the epithelial lumen against the mesentery was also measured.
【Result】 From histological analysis, The duodenum IC layers were in 2-3 layers at E13.5, at E15.5 mostly arranged in 2 layers, and at E17.5 layers were 3-4, showing a slight temporary decrease at E15.5. Number of IC layers showed a regional difference related to the mesentery, and it was higher at the mesentery axis than at the vertical-to-mesentery axis. OL layers first appeared at E15.5 and remained in one layer at E17.5. These findings on SM layer were different from those of our previous study on ICJ. The epithelial lumen orientation against the mesentery generally rotated in a clockwise direction along the long axis of the duodenum at E13.5.
【Discussion】 At E13.5, E15.5 and E17.5, IC layers arrangement showed a similar regional differences against the mesentery position, suggesting that IC layer development is related with the position of (factors from) the mesentery. We noticed some difference in IC and OL development between duodenum and ICJ. These regional differences along the long axis of the intestine may be involved in their differential macroscopic morphogenesis. The results of luminal angle against mesentery suggest its possible relation to the development of other layers and macroscopic morphogenesis of the duodenum, but need further research to draw any conclusion. The present findings suggest that a possible relationship between the regionally differential development of the SM layers and epithelium may contribute to the macroscopic morphogenesis of the duodenum.

This work was supported by MEXT KAKENHI (23112006).
COI: None

P 234

Dlx5-augmentation in neural crest cells induces ectopic calvarial cartilages

Tri Vu Hoang[1)], Masaki Takechi[1)], Miki Shimizu[2)], Taro Kitazawa[2)], Hiroki Higashiyama[2)], Akiyasu Iwase[2)], Hiroki Kurihara[2)], Sachiko Iseki[1)].
[1)]Section of Molecular Craniofacial Embryology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU)
[2)]Department of Physiological Chemistry and Metabolism, Graduate School of Medicine, The University of Tokyo (Japan)

【Background】 Although the cranial vault is formed by intramembranous ossification, cartilaginous structures are also observed in this area, suggesting a potential of both osteoblast and chondrocyte differentiation in cranial vault formation. Distal-less homeobox 5 (Dlx5) is a homeobox transcription factor that induces osteoblastic and chondrogenic differentiations. Endogenous Dlx5 is not expressed in the forming calvaria, but we have found that the augmentation of Dlx5 in the mouse NCC (Wnt1-Cre;Rosa26Dlx5/+, called thereafter NCC-Dlx5) induces conspicuous ectopic cartilages in the apical region of the cranium. This is an important implication for understanding molecular mechanisms of the calvaria formation.

【Purpose】 To elucidate developmental basis of calvaria formation by disrupting gene expression involved in bone and cartilage formation.

【Methods】 In this study, in situ hybridization, immunohistochemistry, alizarin red & alcian blue skeletal staining, hematoxylin & eosin staining, toluidine blue staining, transmission electron microscopy, and micro-CT analyses were performed.

【Results】 Newborn NCC-Dlx5 mice showed the ectopic cartilage formed under developing frontal bone, which expanded to the posterior and displayed patchy bone defects. Histological analysis demonstrated the ectopic cartilage seemed to be formed in the dura mater derived from NCC-derived head mesenchyme. To reveal developmental process leading to the phenotype, gene expression patterns of Dlx5, osteoblast (Runx2) and chondrocyte (Sox9) markers were examined in earlier fetal stages of the NCC-Dlx5. At E10.5, Dlx5 was transcribed in the maxillary processes, supraorbital regions, where Dlx5 is not normally detected, but no difference was found in the histological structure. To E11.5, in the NCC-derived head mesenchyme of NCC-Dlx5, Dlx5 is expressed ubiquitously, Runx2 is expressed in both osteoblasts and chondrocytes, Sox9 was found in the chondrocytes. Those expressions were not found in the counterparts of the control. The head mesenchyme was thickened, accompanied by increased number of PHH3-positive cells in the NCC-Dlx5. The mesenchymal condensation started at E12.5 near the apical cranium. Dlx5 expression mainly remained in the differentiating chondrocytes and osteoblasts, and Runx2 expression level in chondrocytes became faint. By E13.5, Runx2 expression diminished in the cartilaginous structure.

【Discussion】 The augmentation of Dlx5 in NCC developed ectopic cartilage in the dura mater layer, and enlarged the frontal bone. It is suggested that Dlx5 overexpression stimulates proliferation, subsequently, differentiation of chondrocytes and osteoblasts in NCC-derived head mesenchyme. However, the calvarial phenotype, together with temporal changes of Runx2 and Sox9 expression during development suggest that Dlx5-induced osteogenesis and chondrogenesis compete each other at the apical cranium.

P 235

Statin and Other Lipid-Lowering Therapy During First Trimester, Lipoprotein Apheresis Between the Second Trimester, and Lactation Period and Pregnancy Outcome in Heterozygous Familial Hypercholesterolemia: A Case Report

Ayami Miyai[1)], Naotake Maruyama[1)], Hiromi Sekimoto[1)], Mitsuo Kinugasa[2)], Kyosuke Takeuti[3)]
[1)]Department of pharmacy, Kobe medical center
[2)]Department of Cardiovascular medicine
[3)]Department of Obstetrics and Gynecology (Japan)

【Background and Purpose】 Pregnancy in heterozygous familial hypercholesterolemia (HeFH) is related to further elevation of already markedly elevated low-density lipoprotein cholesterol (LDL-C) levels, especially if lipid-lowering therapy is discontinued. This increases the cardiovascular risk of the mother and fetus. Lipoprotein apheresis is the current recommended treatment for HeFH patients; however, this is costly and time consuming. Furthermore, HeFH women who are taking statins may become pregnant in future. In Europe and many other countries, statins are considered as contraindicated drugs, signifying that they have potential fetal risks. If HeFH women under statin therapy become pregnant, they may become anxious on the detrimental effects of statins on the fetus, and proper counseling is necessary.

【Case Presentation】 We present the case of a 31-year-old Japanese woman who was diagnosed with effort angina pectoris (EAP). Her total cholesterol level was 433 mg/dl, which was quite high, and FH was suspected before admission. She had also previously taken conjugated estrogen and synthetic progesterone for infertility treatment. She underwent coronary angiography (CAG) and percutaneous coronary intervention (PCI) for EAP. Her chief complaint was anterior chest wall pain. She started to take low-dose aspirin, ezetimibe, rosuvastatin, prasugrel, and esomeprazole. Subsequently, prasugrel was switched to clopidogrel. After PCI, she was diagnosed with HeFH and discerned PCSK9 gene negative. We advised her that she needs to consider a planned pregnancy and continue to take her medications; however, one year later, she got naturally pregnant and got anxious about the effects of her medications on her baby. We counseled her and explained how the medications could affect the fetus, such as that described in case studies and prospective cohort studies, and recommended apheresis during pregnancy. Then she decided to continue the pregnancy. She continued to take her medications until she was 16 weeks and 6 days pregnant. In her 17th week of pregnancy, she was referred to the National Cardiovascular Center to undergo LDL apheresis. Successful childbirth was achieved as well as management of LDL, without any adverse events. When she was 38 weeks and

4 days pregnant, she gave birth to a 3270 g baby boy via normal spontaneous vaginal delivery under epidural anesthesia.
【Conclusion】 HeFH is a severe health condition and has an influence on life expectancy. Although numerous women with HeFH have a high cardiovascular risk, pregnancy is not rare.
For women of childbearing age anticipating LDL-C reduction, proper counseling must be considered.

P 236

Deregulation of histone methylation is implicated in the etiology of frontonasal dysplasia.

Honami Ogoh[1)], Kazutsune Yamagata[4)], Tomomi Nakao[1)], Lisa L. Sandell[2)], Ayaka Yamamoto[1)], Aiko Yamashita[1)], Naomi Tanga[1)], Mai Suzuki[1)], Takaya Abe[3)], Issay Kitabayashi[4)], Toshio Watanabe[1)], and Daisuke Sakai[5)]
[1)]Department of Biological Science, Graduate School of Humanities and Science, Nara Women's University, Nara
[2)]Department of Oral Immunology and Infectious Diseases, University of Louisville, School of Dentistry, Louisville, KY (USA)
[3)]Animal Resource Development Unit and Genetic Engineering Team, RIKEN Center for Life Science Technologies, Kobe
[4)]Division of Hematological Malignancy, National Cancer Center Research Institute, Tokyo
[5)]Division of General Education, Biology, Kanazawa Medical University, Ishikawa (Japan)

【Background】 Frontonasal Dysplasia (FND) is a very rare congenital disorder characterized by midfacial malformations, such as bifid nose, bifid philtrum and hypertelorism. Although some responsible genes for FND have been identified, environmental factors are suggested as possible causes for FND as well. Epigenetic processes are thought to play as interface between environmental factors and alterations of gene expression resulting in the increase of the severity of midfacial malformation. However, it is still unclear if epigenetic machinery is involved in the severity of midfacial malformation. Recently, we found that Af10, one of the important factors for methylation of histone H3 on lysine 79 (H3K79me) is intensely expressed in craniofacial tissues, suggesting the association with craniofacial development.
【Purpose】 The purpose of this study is elucidation of the relationship between H3K79me and midfacial development.
【Methods】

(1) We generated knockout mouse of Af10 (Af10-KO), and investigated the role of H3K79me in midfacial development.
(2) We examined the role of H3K79me in cranial neural crest development.
(3) We identified down- and up-regulated genes in Af10-KO embryos.
(4) We examined if the treatment of mouse embryo with specific chemical inhibitor of H3K79me mimics the phenotype of Af10-KO.

【Results】 Af10 homozygous knockout mutants (Af10-KO) exhibited midline facial cleft and hypertelorism, reminiscent of FND. The midfacial defects of Af10-KO embryos were associated with reduced proliferation of cranial neural crest-derived mesenchyme in developing nasal processes and adjacent tissue. We demonstrated that H3K79me level was significantly decreased in nasal processes of Af10-KO embryos. Importantly, the loss of Af10 leads to down-regulation of AP2α, a gene critical for cranial neural crest development in nasal processes and adjacent tissue. Furthermore, inhibition of H3K79me completely mimicked the Af10-KO phenotype.
【Discussion】 Taken together these data demonstrate that Af10-dependent H3K79me is essential for nasal process and adjacent tissue development, and consequent midfacial formation. We elucidate that H3K79me regulates the growth of neural crest cells in nasal process and adjacent tissue through the activation of AP2α expression. Our results indicate the contribution of H3K79me to the severity of midfacial malformations in FND induced by environmental factors.

P 237

17-Year Follow-up After Distraction Osteogenesis Performed in a 4-month Old Infant With Robin Sequence.

COI Disclosure

Takako Nakao, M.D.[1)], Misato Katayama, M.D.[2)], Yumi Lee, M.D.[3)], Hiromi Kino, M.D.[4)], Daisuke Mitsuno, M.D., Ph.D[5)], Shuichi Kawai, D.D.S., Ph.D[6)], Koichi Ueda, M.D., Ph.D[7)]
[1)]Department of Plastic and Reconstructive Surgery, Osaka Medical College
[2)]Kawai Orthodontic Dental Clinic (Japan)

All authors have no financial conflicts of interest to disclose
【Background】 The main manifestation of Pierre Robin Sequence (PRS) is mechanical obstruction of the upper respiratory tract caused by depression of the tongue. Mandibular distraction osteogenesis (MDO), first described in 1992 by McCarthy, has become popular as the definitive technique to address the issues associated with PRS by relieving airway obstruction, improving facial cosmesis, and correcting malocclusion. There are some reports in Europe and the United States that infants with severe airway distress who undergo MDO are able to be more quickly weaned off mechanical ventilatory support. However there are few studies like these in Japan. Furthermore, there is no report about long follow-up containing occlusion after MDO.
【Purpose】 We performed distraction osteogenesis in a 4-month old infant with Robin Sequence. The purpose of this study was to obtain long-term follow-up, especially given the paucity of data on long-term outcomes in patients with Robin Sequence who undergo MDO.
【Method】 Case report: The patient was a 1-month old infant with PRS. The patient had episodes of spontaneous oxygen desaturations during feeding and crying. He was deemed to be a candidate for surgery due to his poor oral intake, inspiratory stridor, and cyanosis in prone positioning.

Tracheotomy and Tongue-lip adhesion(TLA) was performed at the age of 30 days. After 3 months, bilateral MDO was done by an internal traction device. The range was

1mm per day. After 20 days, the mandibular was bilaterally lengthened by 17.5mm and expansion of the airway after distraction was confirmed by a X-ray. The distraction devices are removed after 6 months of consolidation phase. There was good bone osteogenesis after the procedure.

In addition, we performed a cleft palate operation at the age of 17 months. At the age of 3 years the tracheostomy orifice was closed with an otolaryngologist. After these surgical interventions, speech/language training and orthodontics were begun.

【Result】 Computerized tomography and X-ray were performed after MDO. Here we have shown the results after 17 years with earlier invasive surgery and orthodontics.

【Discussion】 In this article, we show that permanent molars were formed normally on a PRS patient receiving MDO. We also discussed the methods of osteotomy, distraction devices and orthodontics used to achieve normal occlusion.

P 238

Perception of Cleft Palate Speech by Naïve Listeners —Influence of Impact of Final Particle to Listeners' Perception on Speech Assessment—

Yoshiko Aihara[1,2], Toko Hayakawa[1,4], Chisako Inoue[1,3], Tomoko Mori[3], Hideto Imura[1,3], Hiroo Furukawa[1,4], Teruyuki Niimi[1,3], Kazuo Katayama[4], Nagato Natsume[1,3]
[1]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University, Aichi
[2]Junior College Division of Aichi Gakuin University, Aichi
[3]Division of Speech Language Hearing Therapy, Aichi Gakuin University Hospital, Aichi
[4]Faculty of Psychological and Physical Science, Aichi Gakuin University, Aichi (Japan)

【Background】 Our laboratory continues research on public awareness of cleft palate speech :CPS, with the aim of establishing a new method of speech therapy for relieving mental burden of CPS carried by children with cleft palate and their family members. In our studies, Aihara et al. directed attention to particles using final particles (Japanese particle appears in the sentence end, and expresses speaker's attitude to listener), reporting that addition of final particles may give a positive perception about cleft palate speakers. We have discussed the effects that final particle in CPS have on speech assessment, and the relation between speech assessment and assessment of speakers' perception.

【Method】 100 listeners were men in and 100 were women. Perception was evaluated according to the adjective pair of 16. In addition, auditory perception if the speech sample was normal or abnormal on each sample speech was evaluated. The speech disorder was "consonant distortion caused by Nasal Emission (NE)". The each speech sample included 11 sentences, and each sentence was added with final particles of "ne" which were common particles. Chi-square test was performed to find listenes' judgment of "normal" or "abnormal". Then, we conducted a logistic regression analysis with the normal perception group and the abnormal perception group as the reference variables and the scores on the 16 perception assessment scale items regarding the speaker as the explanatory variables. We performed the analysis for each final particle.

【Results and discussion】 1)The comparison of the proportion of the speech assessment has revealed that, with regard to all the final particle, the percentage of judgment as "abnormal" was clearly higher than that of judgment as "normal." 2)It has turned out that any final particle are not effective for improving assessment of nasal emission speech produced by those with an insufficient velopharyngeal function. In addition, our study has revealed that final particle had no or little influence on enhancement of the assessment of "perceived as strange—not perceived as strange". 3) Not all the characteristics of the listeners' perception items affected the speech assessment, and final particle also had an influence. Thus, we consider that it is significantly meaningful to introduce final particle to a new training method for boosting the perception of those who make CPS.

This work was supported by JSPS KAKENHI Grant Number JP24593018.

P 239

Psychology in Prenatal Diagnosis of Mothers with Cleft Lip and/or Palate Children

Yoshiko Aihara[1,2], Toko Hayakawa[1,4], Chisako Inoue[1,3], Tomoko Mori[3], Hideto Imura[1,3], Hiroo Furukawa[1,4], Teruyuki Niimi[1,3], Kazuo Katayama[4], Nagato Natsume[1,3]
[1]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University, Aichi
[2]Junior College Division of Aichi Gakuin University, Aichi
[3]Division of Speech Language Hearing Therapy, Aichi Gakuin University Hospital, Aichi
[4]Faculty of Psychological and Physical Science, Aichi Gakuin University, Aichi (Japan)

【Background】 We are conducting continuous surveys with the purpose of clarifying changes in the mother's mental state at each treatment stage from the notification of cleft lip and/or palate(CL/P) in children. Among them, this time we report the psychology of the mother who received prenatal diagnosis.

【Method】 A self-administered questionnaire survey was conducted on 136 mothers of children with CL/P who went to CLP Center, Aichi Gakuin University Hospital. Survey items 1) received / didn't receive prenatal diagnosis, 2) feelings when receiving prenatal diagnosis, 3) better to receive prenatal diagnosis / better not to receive it, 4) their reasons, more than 4 items.

【Results】 The subjects were mothers of 71 with CLP, 33 with CL alone, and 32 with CP alone. 1) 27.2% of mothers received prenatal diagnosis. 2) "The feeling at the time of prenatal diagnosis " had many "anxiety" "chaos / shock" "despair". A few mothers didn't want to give birth. 3) "It was good to receive " was different depending on different cleft types: CLP 67.6%, CL 51.5% alone, CP alone 37.5%. 4) It was good to receive prenatal diagnosis, their reason was "collection of information about CL/P before giving birth" and "preparation of the mind".

【Discussion】 CL/P cause psychological distress and confusion in families, especially mothers, because they are accompanied

by esthetic disorder and dysfunction. From the results, it was revealed that there are many mothers who desire prenatal diagnosis for CL alone and CLP where aesthetic problems are large. In addition, for the reason for wishing for feelings and announcements after antenatal prenatal diagnosis, it has become clear that the mother's psychological condition of mothers who will try to receive the disease of her parents who prepares information and prepares information about CL/P . That is, it can be said that the provision of sufficient knowledge and information to the mother is essential for the treatment of CL/P over a long period of time. It is important to have an individual understanding of how to treat your child's ailments in order to get a better mother's cooperation.
This work was supported by JSPS KAKENHI Grant Number JP24593018.

P 240

Perception of Cleft Palate Speech by Variations in Speech Speed

First report: Articulation Distortion from Nasal Emission

Hiyori Makino, ST[1,4)], Toko Hayakawa, ST[1,2,3)], Teruyuki Niimi, DDS, PhD[1)], Katsuhiro Minami, DDS, PhD[1)], Tomoki Kato, DDS[1)], Nagato Natsume, DDS, PhD, DMSc[1,2)]
[1)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry , Aichi-gakuin University
[2)]Cleft Lip and Palate Center, Aichi-gakuin University Hospital
[3)]Faculty of Physiological and Physical Science, Aichi-gakuin University,Japan 4 Division of Speech Therapy, Nagoya Isen (Japan)

【Introduction】 The previous study on the perception of the naive listeners for the cleft palate speech (CPS) showed that naive listeners could accurately distinguish the non-cleft palate speech (non-CPS) from the CPS. The previous study suggests the possibility of reducing the psychological burden of the patients by changing the perception of the CPS from negative to positive among other people.

【Objectives】 To investigate, analyze, discuss, and clarify whether the naive listeners accurately distinguish speech samples of CPS of articulation distortion from nasal emission (NE) and non-CPS in changes of speech speed as the CPS or the non-CPS.

【Material and Methods】 From the CPS samples on the market in Japan, we used the speech sample of 4 years old boy with NE. The speech intelligibility of the CPS sample is grade 2.5 by The Japan Societry of Logopedics and Phoniatrics . As a control sample, we recorded the speech by a non-cleft palate child matched in age and gender and with context edited to match that of the CPS sample. Based on the 2 samples, we created 6 speech samples with the following three speeds without changing the prosody and intonation with the usage of the software of Audacity1.2,6a：Camaguey Mellon University: faster than the original speed as A, original speech speed as B, and slower than the original speed as C. Speeds of each sample were measured by the software of AVS Audio Editor6,1,2,375:Online Media Technolobies Ltd. Each speech speed was as follow; A= 7.64mora/second, B=4.95mora/second, C=3.96mora/second. 88 people in their 20's listened to 6 samples and judged if they were CPS or non-CPS. A likelihood ratio test was conducted to analyze the rates of distinguishing CPS and non-CPS within and between each speech sample.

【Results】 Of all 6 samples, there were significant differences in terms of the accuracy of distinguishing the CPS and the non-CPS ($P<0.001$). Most naive listeners could accurately distinguish the CPS and the non-CPS in any speeds.

Within the non-CPS samples, there were no significant differences in A, B and C for distinguishing non-CPS or CPS. Within the NE samples, comparing B to A and C, B was significantly distinguished as non-CPS in comparison with the others ($p<0.001$).

【Conclusion】 It is said that the speed of A is corresponding to the daily conversation speed and B is best speed of presentation in lectures, meaning slower than A and C is slower than B. This study indicated that NE, which is frequently shown among CPS with velopharyngeal insufficiency, with a certain speech speed was less perceived as CPS, faster and slower speeds than a certain speed were perceived as CPS more frequently.

P 241

The approach to cleft lip and palate patients in Aichi-Gakuin Cleft Lip and Palate Center

– Our idea in obtaining a finer lip and nasal alar form –

Hiroo Furukawa[1,2)], Hideto Imura[1,3)], Teruyuki Niimi[1,3)], Katsuhiro Minami[1,3)], Satoshi Suzuki[1,3)], Maya Yoshida[1,3)], Akihiro Mori[1,3)], Shinichi Nakahara[1,3)], Chisato Sakuma[1,3)], Masaaki Itoh[1,3)], Yumiko Ikegami, Yasunori Akiyama[1,3)], Yuki Akiyama[1,3)], Akira Arasaki[1,3)], Nagato Natsume[1,3)]
[1)]Cleft lip and palate center, Aichi-Gakuin University Dental Hospital
[2)]Department of Health Science, Faculty of Psychological and Physical Science, Aichi Gakuin University
[3)]Devision of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University (Japan)

【Introduction】 We have long-term stability of external nasal form by combining the our presurgical nasoalveolar molding method (PNAM-AGU method) with keeping wear the postoperative nostril retainer for cleft lip (and palate) patients. We have reported on the acquisition effect. Though the PNAM-AGU method can significantly improve the external nasal form before the operation, the nasal alar is extended when do the method. So, the cheiloplasty method that takes this into consideration is required. In this report, we will report on our approach to better external nose shape by adding the cheiloplasty method.

【Treatment】 Pre-intra-post operative series treatments such as PNAM-AGU method and cheiloplasty with triangular valve method and long-term nostril retainer wearing for cleft lip (and palate) patients are adopted.

【Result and consideration】 A good lip and nasal alar form has been obtained for a long time by our series therapy. However, if the post operative nostril retainer wear is not sufficient, continuation of the external nasal form taking advantage of the preoperative and intraoperative effects is insufficient. So, it is

important to continue the post operative nostril retainer wear.
Based on these facts, in addition to devising cheiloplasty, we will work on the development of a preoperative treatment method that does not extend the nasal alar, a device for wearing the nostril retainer for a long period after surgery, or a post-operative treatment method.

【Cited literature】Niimi T, Natsume N, Tsukawaki T, Furukawa H, Masuda H, Kobayashi M.
Treatment of the nostrils in patients with cleft lip by a nostril retainer.
Br J Oral Maxillofac Surg. 2000; 38: 224-226. 10864730

P 242

Replication of GWAS Candidate Genes in non-syndromic Cleft lip and / or Cleft palate in Vietnamese population.

Suzuki S[1,2)], Ono M[1)], Niimi T[1)], Yamamoto M[6)], Imura H[1)], NGUYEN C[8)], Leslie E[3,4)] Cooper M.E[5)], Natsume N[1)], NGUYEN M[8)], Marazita M.L[3,5)], Murray J.C[2,7)].
[1)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, Aichi-Gakuin University, Nagoya (Japan)
[2)]Department of Pediatrics, University of Iowa (USA)
[3)]Center for Craniofacial and Dental Genetics, Department of Oral Biology, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA (USA)
[4)]Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA (USA)
[5)]Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA (USA)
[6)]Faculty of Psychological and Physical Science, Aichi-Gakuin University (Japan)
[7)]University of Iowa, Departments of Pediatric Dentistry, Epidemiology and Biology, Iowa City, IA
[8)]Odonto Maxillo Facial Hospital Ho Chi Minh City (Vietnam)

【Background】Non-syndromic cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO) are among the most common human birth defects caused by both genetic and environmental factors and/or their interactions. Genome wide association studies (GWAS) and meta-analyses of CL/P have been identified multiple genetic risk loci including MAFB, VAX1, PAX7, FOXE1 and ABCA4. Previous studies of the DMD gene also showed significant association with oral clefts that include cleft palate.

【Purpose】we analyzed genotyping data of the cleft lip and/or cleft palate in Vietnam as a GWAS replication study.

【Method】We used 404 independent case-parent trios from three case groups: non-syndromic cleft lip only (CLO; 104 case-parent trios), cleft lip and palate (CLP;135 case-parent trios) and cleft palate only (CPO;165 case-parent trios). Participants were genotyped by either TaqMan assays® or Fluidigm®. We genotyped 48 SNP markers, which were utilized and found statistically significant in previous GWAS studies. Transmission disequilibrium tests were performed by the Family based Association Test and PLINK. This study was approved by institutional review boards and informed consents were obtained from the patients.

【result】Statistically significant associations were observed with SNPs in genes IRF6, FOXE1 and MAFB. Regarding CL/P, TDT analysis showed associations with IRF6 (rs2235371, p= 6.80E-06 and rs2013162 p= 0.03486) and MAFB (rs17820943, p= 0.002266, rs13041247 and rs11696257, p= 0.001862). Also FOXE1 (rs894673 and rs3758249, p= 0.02) was slightly associated with CL/P(Table-1,2,3). We could not confirm statistical significance between VAX1 markers and the Vietnamese population that have previously shown an association in the Mongolian population. However, after Bonferroni correction of the above results, only IRF6 showed significant association.

【Discussion】Our study replicated previous GWAS findings in 48 markers from 22 genes for the Vietnamese population and identified that IRF6 may contribute to a part of the cleft lip and/or cleft palate etiology. Our findings of this study also suggest that MAFB might be associated with CL/P, similar to our previous study of the Mongolian population.

P 243

Replication of genome wide association findings for Cleft Lip and Palate a role for variants in MAFB, VAX1 and PAX7 in Asian populations.

S. Suzuki[1,2,3)], ML. Marazita[4,5)], ME. Cooper[4)], E. Dragan[1)], A. Butali[1)], M. Mansila[1)], N. Natsume[2)], Y. Suzuki[2)], T. Niimi[2)], M. Yamamoto[3)], G. Ayanga[8)], T. Erkhembaatar[8)], H. Furukawa[2)], K. Minami[2)], H. Imura[2)], K. Fujiwara[2)], J. L'Heureux J[1)], K. Durda[1)], AC. Lidral[1)] and JC. Murray[1,6,7)]
[1)] Dept of Pediatrics, Univ Iowa, Iowa City, IA (USA)
[2)] Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi-Gakuin University (Japan)
[3)] Faculty of Psychological and Physical Science, Aichi-Gakuin University (Japan)
[4)] Center for Craniofacial and Dental Genetics, and Dept of Oral Biology, and Dept of Human Genetics, Univ of Pittsburgh, Pittsburgh, PA (USA)
[5)] Dept of Psychiatry, Univ of Pittsburgh, Pittsburgh, PA (USA)
[6)] Dept of Pediatric Dentistry, Epidemiology and Biology, univ of Iowa, Iowa City, IA (USA)
[7)] College of Nursing, University of Iowa, Iowa City, IA (USA)
[8)] Maternal and Children's Health Research Center Hospital, Ulaanbaatar (Mongolia)

【Background】Nonsyndromic cases of cleft lip with or without cleft palate (NSCL/P) and cleft palate only (NSCPO) are among the most common human birth defects caused by both genetic and environmental factors and/or their cross talks. With an average birth prevalence of 1/700 live births, in general, Asian populations have a higher birth prevalence of clefting (1/500 births) But interestingly, prevalence of clefting in Mongolia is the lowest (1/1300) in Asian populations.

【Purpose】To investigate GWAS signals from previous studies could show positive association.

【Method】TaqMan® chemistry as designed by Applied Biosystems. SNP Genotyping Assays detected 8 SNP Markers on a 7900 HT sequence system (Applied Biosystems)

Analysis: SNP makers at each genes were tested for association with CL(P) using PLINK and FBAT(http://pngu.

mgh.harvard.edu/purcell/plink/) (http://www.biostat.harvard.edu/~fbat/default.html)

PLINK showed same p-value as FBAT, but gives (un) transmitted counts and odds ratio of having the associated allele versus having the other allele. It also is able to give the parent-of-origin results and their associated Odds Ratios.

【result】1. Most of SNPs in VAX1,MAFB and PAX7 were in HWE. However in both populations, two SNPs in PAX7 (rs4920520 and rs766325) were not in HWE.

2. Results in Mongolian population SNP maker rs7078160 in VAX1 showed most significant association in all cleft group (p = 5.32E-05)

3. Results in Japanese population. SNP maker rs7078160 in VAX1 showed strong significant association in all cleft group (p = 0.005114)

【Discussion】These results support a role for variation of VAX1 and MAFB in orofacial cleft and suggest that examination of additional members of this pathway and deeper investigation of SNPs at the locus may disclose etiologic variants. Previous GWAS has been showed strong associations with clefting from numerous loci. And also we obtained significant association signals from TDT using same markers and different populations. It helped to support previous study identified real associations.

P 244

Rat palatine fissure for evaluating bone graft materials in human alveolar cleft reconstruction

Masaaki Ito, DDS[1)], Taku Toriumi, DDS, PhD[2)], Hideto Imura, DDS, PhD[1)], Yasunori Akiyama, DDS[1)], Nagato Natsume, DDS, PhD[1)], and Masaki Honda, DDS, PhD[2)]
[1)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University
[2)]Department of Oral Anatomy, Aichi Gakuin University School of Dentistry (Japan)

The bone reconstruction in the congenital alveolar cleft of human is mainly based on autologous bone graft. In many cases, the animal experimental models in bone regeneration studies have been artificial bone defects. These models are not anatomically similar to the congenital alveolar cleft of human because the defects are not congenital and away from nasal cavity. An animal experiment model that is similar to the congenital alveolar cleft of human is needed. The palatine fissure of a rat exists in the center of the palate of a rat, and connected to nasal cavity. In this study, we examined potential bone repair by an autologous bone implant and beta-tricalcium phosphate (β-TCP) using rat palatine fissure as a model. The results of the implants were evaluated by micro-computed tomography and histological analysis. The study was performed using 15 male SD rats. The rats were subdivided into the 3 experimental groups, each containing 5 animals (group 1: received an autogenous bone graft. group 2: received β-TCP. group 3: received a blank defect with no implant at the implant site.). Before operation, and after 4,8,12, and16 weeks, the palatine fissures were evaluated radiologically. At 16weeks the rats were sacrificed and evaluated histologically. The results are as follows. The hard tissue was observed by 16weeks after operation in group 1 and group 2 but not group 3. In group1, the volume of newly hard tissue was 1.41 mm3 and the density was 745 mg/cm3, and in group2, the volume of newly hard tissue was 0.72 mm3 and the density was 590 mg/cm3.The hard tissue volume and density of group 1 were significantly higher than those of group 2 at 16 weeks. In group1 and group 2, the formation of newly bone was visible in the rat palatine fissure histologically at 16 weeks. Osteoblasts and osteoclasts were observed on the surface of the newly bone.

Conclusion: we have provided the first demonstration of the suitability of the rat palatine fissure as the implant site for bone graft materials to simulate the implantation of bone graft materials into human alveolar cleft. Thus, the palatine fissure can be considered as a congenital bone defect that is similar to the alveolar cleft conditions in humans.

P 245

Report of Cleft lip and/or Palate in Division of Speech Language Hearing Therapy, Aichi-Gakuin University Hospital

Chisako Inoue[1)], Tomoko Mori[1)], Toko Hakawa[1)], Yoshiko Aihara[1)], Yoshio Akiyama[1,2)], Naoki Saitou[2)], Hideto Imura[1,2)], Katsuhiro MInami[1,2)], Teruyuki Niimi[1,2)], Hiroo Furukawa[1)], Nagato Natsume[1,2)]
[1)]Division of Speech Language Hearing Therapy, Aichi-Gakuin University Hospital
[2)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies (Japan)

【Purpose】Our division at the Cleft Lip and Palate Center provides several assessments and language and speech therapies to patients with cleft lip/palate. The purpose of this survey is to clarify the status of new patients.

【Method】The subjects were patients with cleft lip/palate who were new to the division in 16 years through 2002 to 2017.
We investigated the number of new patients, sex ratio, and the distribution of residential area.

【Result】The total number of new patients with cleft lip/palate within 16 years was 1,510. 95% of the patients' residential area was Aichi, Gifu and Mie prefectures (Tokai area) where the center located in.

The number of new patients with cleft lip/palate in 2017 was 80. The estimated birth rate of babies with cleft lip/palate in the Tokai area from the number of births in 2017 was 73.2 to 168.1.

【discussion】The result showed that most patients with cleft lip/palate in the Tokai area visited our center. It indicated that the division played an important role in the sequence of cleft treatment, especially in the speech therapy for cleft palate speech in the Tokai area.

P 246

The clinical study on non-operated patients with submucous cleft palate —The first report about the comparison between non-operated and post-operated cases—

T.Mori[1,2)], C.Inoue[1,2)], T.Hayakawa[1)], Y.Aihara[1,2)], H.Imura[1,2)], M.Yoshida[1,2)], C.Sakuma[1,2)], K.Minami[1,2)], T.Niimi[1,2)], N.Saito[2)], N.Natsume[1,2)]

[1)] Division of Speech Language Hearing Therapy, Aichi-Gakuin Dental Hospital, Aichi
[2)] Cleft Lip and Palate Center, Aichi-Gakuin Dental Hospital, Aichi (Japan)

【Purpose】We recently think that not all submucous cleft palate (SMCP) patients need to be operated on by all means, and perform conservative treatment such as speech therapy to those. This study shows the comparison of a long-term progress of velopharyngeal function (VPF) and articulation between non-operated and post-operated patients with SMCP.

【Objects and Method】15 patients (age 9-18, mean age 12±3) diagnosed with SMCP in our center, who chose the medical option without an operation because of the family's hope after a careful informed consent, were in this study. We performed a test set including a nasal mirror test, cephalogram, the articulation test, and an assessment of VPF. In addition, post-operative data from the same test set from patients were collected.

【Result and Discussion】At the final assessment, 80.0% of patients showed "good" VPF or "very mild" VPD, and their VPF did not show decreasing during the period. The ratio of good VPF or very mild VPD was higher than post-operated patients in our center (79.1%) and a precedent study (70.4%). Articulation disorder was observed in 60.0% of patients without operation, and the most types of error they showed were nasal articulation and weakened/nasalized consonants due to nasal emission. Some patients had glottal stops but those population was less than post-operated patients. The result of this study indicates that it's important to know that operation for SMCP is not the only option but also carefully observing progress of VPF may be the other option for some patients.

P 247

The clinical study on non-operated patients with submucous cleft palate —The second report about the long-term progress of velopharyngeal function and articulation—

T.Mori[1,2)], C.Inoue[1,2)], T.Hayakawa[1)], Y.Aihara[1,2)], H.Imura[1,2)], M.Yoshida[1,2)], C.Sakuma[1,2)], K.Minami[1,2)], T.Niimi[1,2)], N.Saito[2)], N.Natsume[1,2)]
[1)] Division of Speech Language Hearing Therapy, Aichi-Gakuin Dental Hospital, Aichi
[2)] Cleft Lip and Palate Center, Aichi-Gakuin Dental Hospital, Aichi (Japan)

【Purpose】We recently pointed out the importance of the long-term follow-up for the patients with submucous cleft palate (SMCP). In this study we report the long-term progress of velopharyngeal function (VPF) and articulation.

【Objects and Method】15 patients (age 9-18, mean age12+3) with a diagnosis of SMCP in our center and they chose the medical option without the operation because of the family's hope after informed consent. We carried out nasal mirror test, cephalogram, articulation test, and assessment of VPF. In addition, we calculated rhinopharynx form ratio (ratio of soft palate length for the depth of the cavity of pharynx) from cephalogram and analyzed them.

【Result and Consideration】At the final assessment, more than 80% of patients were with "good" or "slight imperfection" VPF, and there was no case who showed decreasing VPF. The patients complicated with "slight imperfection" VPF and intellectual retardation, an effect of the speech therapy was not obvious. Due to no significant correlation between rhinopharynx form ratio and VPF by the cephalogram measurement, it indicated that the influence on VPF cannot be measured from rhinopharynx form ratio at rest. This study revealed that not all patients with SMCP need surgery at early childhood, and we should judge operation adaptation carefully when we can see an effect of speech therapy.

P 248

A case of cleft soft palate patient acquired good speech without operation

Tomoko.Mori[1,2)], C.Inoue[1,2)], T.Hayakawa[1)], Y.Aihara[1,2)], H.Imura[1,2)], M.Yoshida[1,2)], C.Sakuma[1,2)], K.Minami[1,2)], T.Niimi[1,2)], N.Saito[2)], N.Natsume[1,2)]
1) Division of Speech Language Hearing Therapy, Aichi-Gakuin Dental Hospital, Aichi
2) Cleft Lip and Palate Center, Aichi-Gakuin Dental Hospital, Aichi (Japan)

【Purpose】Usually most of patients with cleft palate require surgical intervention, but we report a case acquired "good" velopharyngeal function (VPF) and articulation skill without surgery.

【Object and Method】17 years old male with cleft soft palate who was made a diagnosis of cleft at age 1 by pediatrician. He had not had difficulty in feeding and speech affected by the cleft, and they didn't demand surgery after the careful informed consent. We observed his VPF during speaking syllables and sample sentences by cephalogram, nasoendoscope, and audible evaluation.

【Result and Consideration】At age 6, he showed "good" VPF and appropriate articulation, but adenoids helped velopharyngeal closure. Although adenoids reduced with growth at age 17, his VPF and articulation stayed "good". It may be because, his cleft was not long enough to reach the levator palati, and a scar from surgery was not formed, and adenoids helped velopharyngeal closure in childhood. The result of this report indicates that not all patients with slight cleft soft palate need surgery when they have enough portion of velar muscle and not large pharyngeal cavity. We should judge operation adaptation carefully after detailed anatomical, functional and speech assessment.

P 249

A maxillary and mandibular surgical treatment case of CLP patient without maxillary protraction

Motoko Yoshioka, Tatsunori Shibazaki, Katsuhiro Minani, Hideto Imura, Nagato Natsume
Asami Orthodontic Clinic (Japan)

Maxillary undergrowth is often seen in cleft lip and palate patients because of their multiple factors. Orthodontic treatment is difficult and time consuming especially in severe case. Maxillary protraction and upper arch expansion are often use to release sagittal and transverse intermaxillary discrepancy in first phase orthodontic treatment. In our clinic, we always carry out maxillary protraction and expansion in maxillary deficiency cases. In this report, we show a surgical treatment case without maxillary protraction in first phase of orthodontic

treatment. A female patient was introduced to our clinic at the first time at the age of 18. She had never treated orthodontically before, so she had severe crowding and anterior and posterior crossbite. We treated her with maxillary and mandibular lateral expansion, Le Fort I osteotomy and SSRO in order to correct severe skeletal discrepancy and malocclusion. This treatment resulted with good stability in occlusion, however with not good in facial proportion. Compared with normal mandibular protrusion cases (Skeletal 3 cases), middle face depression was not recovered completely. In conclusion, maxillary protraction in first phase of orthodontic treatment is important and effective for CLP patients with maxillary growth retardation.

P 250

Treatment effects of maxillary protraction appliance in unilateral cleft palate patients

Tatsunori Shibazaki, Motoko Yoshioka,
Hideto Imura, Nagato Natsume
Asami orthodontic Clinic (Japan)

【Background】To evaluate the stability of results of maxillary protractor appliance is valuable for skeletal contribution. Inhibit usually occurred after maxillary protraction. Maxillary front growth stops as the reason temporarily, and it is said that the front growth of the mandibular becomes remarkable.

【Purpose】The purpose of this study is to investigate the treatment effects of maxillary protraction appliance in unilateral cleft lip and palate (UCLP) patients and cleft palate (CP) patients.

【Method】14 patients (9 UCLP and 5 CP) were treated by maxillary protractor with lingual arch, and used lingual arch or quad-helix for labial tipping on incisors after maxillary protraction. The protraction period was 1~2 years. Lateral cephalogram was taken before, after and 2 years after maxillary protraction and measured the changes of facial growth.

【Result】Facial axis showed clockwise turn in both groups, and slightly counter-clockwise turn in both groups 2 years after treatment. Posterior facial height was significantly larger in CP group. Positions of upper first molars changed more former in UCLP group. Convexity was significantly larger in UCLP group, however inhibit 2 years later was too. Positions of pogonion was restrained by mandibular clockwise turn, however 2 years after protraction, growth to the front was showed.

【Discussion】The positions of Maxilla changes forward by maxillary protraction in both groups. In this study, change to the front was larger in UCLP group. However, inhibit appeared under the influence of lip force, moreover, mandibular growth appeared, too. Thus, in conclusion, UCLP patients should be protracted maxillary extra.

P 251

Treatment result of dental implant for the patients with cleft lip and/or palate

Katsuhiro MINAMI[1,2], Hideto IMURA[1,2],
Maya YOSHIDA[1], Akihiro MORI[1,2],
Nagato NATSUME[1]
[1]Division of Research and Treatment for Oral and
Maxillofacial Congenital Anomalies,
Aichi-Gakuin University School of Dentistry
[2]Division of Dental Implantology,
Aichi-Gakuin University Hospital (Japan)

【PURPOSE】We think that an important goal in the treatment of cleft lip and/or palate patients is to normalize the function and anatomy of cleft region. Complete skeletal and dental reconstruction of alveolar cleft is of great importance because of congenital missing of lateral incisor. Most of cleft patients have benefited from alveolar bone grafting and orthodontic realignment and require little or no prosthodontic treatment. In addition, dental implant has been utilized for dental reconstruction for cleft patients. The purpose of this study was to evaluate the long term results of dental implant placement into the grafted alveoli.

【MATERIAL and METHODS】22 patients (9 male and 13 female) were selected. They had been performed dental implant treatments and set final restoration more than 5 years at Cleft Lip and Palate Centre, Aichi-Gakuin University Hospital. Eight patients were CLA and fourteen were CLP patients. All patients were performed orthodontic treatment from mixed dentition periods and put removable retainer.

【RESULTS】19 patients were received secondary alveolar bone grafting from ilium during orthodontic treatment. 3 patients were performed tertiary alveolar bone grafting for the purpose of implant placement. 17 patients were needed alveolar augmentation for the purpose of implant placement. We applied 33 implants to 25 alveolar cleft, and only one implant loss was observed (success rate :97%).

【DISCUSSION】In many CLP patients, prosthetic rehabilitation is essential after orthodontic treatment because of congenital missing of lateral incisor. However there are many difficulties of prosthetic treatment in CLP patients. Recently alveolar bone graft was applied to the serial treatment of CLP patients. Alveolar bony reconstruction with bone grafting enabled us to apply almost same prosthetic protocol in CLP patients. Dental implant prosthesis has been thought to be one of the prosthetic option. In our cases, alveolar augmentation was necessary for fixture installation in many cases though secondary bone graft was performed formerly.

P 252

Experience of medical aid project for cleft lip and palate patients in Ninh Binh Province, Vietnam

Katsuhiro MINAMI[1], Yoshihide MORI[2],
Akihiro MORI[1], Nagato NATSUME[1]
[1]Division of Research and Treatment for Oral and
Maxillofacial Congenital Anomalies,
Aichi-Gakuin University School of Dentistry
[2]Section of Oral and Maxillofacial Surgery,
Kyushu University Faculty of Dental Science (Japan)

【Purpose】We have been carried out medical aid project for CLP patients in Ninh Binh Province, Vietnam. Japanese Cleft Palate Foundation sponsored this project, as a part of Official Development Assistance, Ministry of Foreign affairs, Japan. In this paper, we report the aim, outline, and results of our project.

【Method】Ninh Binh Province is located in the northern part of Vietnam and about 100km far from Ha Noi city. The Province was lack of hospitals where surgical treatment for

CLP patients could be conducted. The purpose of our project is to support technically and financially and to treat untreated CLP patients. For these purpose, we carried out medical activities 18 times from 1998 to 2018.

【Results】 We examined and registered 550 CLP patients, and performed cleft surgery for 530 patients successfully with Vietnamese staff under general anesthesia.

【Discussion】 From our assessments of the efficacy of technical transfer, we recognized their capability of primary cleft surgery. 3 surgeons acquired the ability to perform primary cleft surgery by themselves. Anesthesiologists acquired the knowledge and technique to manage inhalation general anesthesia during operation. Co-medical (nurse etc) acquired the ability to manage during and after operation. However many problems to be solved are remaining. In Vietnam, speech and orthodontic treatment had not established yet. From now on, we want to continue this project and overcome these challenges.

P 253

Herlyn-Werner-Wunderlich Syndrome with double hematocolpos in one side hemivaina

Kim Youjin, Lee Kihwan,
Yoo Heon Jong, Yang Jung Bo
Chungnam National University (China)

【Abstract】 Herlyn-Werner-Wunderlich syndrome (HWWS) is a rare mullerian anomaly consisting of uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis. Although a few HWWS had been reported in gynecologic literatures, most of cases were combined with single hematocolpos.

In this report, we present a rare case of Herlyn-Werner-Wunderlich syndrome with double hematocolpos in one side hemivagina which has never been reported before. In addition, highlighting the clinical presentation and natural history of this rare anomaly through case presentations. Surgical treatment and our follow-up data are also presented.

P 254

A consideration about ending period and procedure of nostril retainer.

Teruyuki Niimi[1)], Hiroo Furukawa[2)], Hideto Imura[1)],
Satoshi Suzuki[1)], Maya Yoshida[1)],Yuki Akiyama[1)],
Nagato Natsume[1)]
[1)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi-Gakuin University, Nagoya
[2)]Faculty of Psychological and Physical Science, Aichi-Gakuin University, Nagoya (Japan)

【Introduction】 Patients with cleft lip have severe midfacial deformities as a result of the tissue defects of the upper lips and the contraction of scars after the operation, and it is difficult to restore the shape of the nostrils by operation alone. We use a nostril retainer to maintain and improve the shape of the nostril.

According to the manufacturer, the nostril retainer is for preoperative nostril correction and post-operative deformation prevention. We have been using it for developmental guidance until the end of growth. We have obtained good results this way and we have reported so far1). However, the end time of the nostril retainer has not been sufficiently considered.

We considered about ending period and procedure of nostril retainer.

【Procedure】 The use of the nostril retainer ended in the following procedure.

1. After wearing the nostril retainer all day for 6 months after surgery, it continues wearing at home.
2. Assuming that age 18 is the end of growth, stop the nostril retainer after confirming that there has been no change in height since 6 months ago.
3. Take a picture once every one to two months and confirm that there is no significant change in nostril shape.
4. End the use of the nostril retainer if there is no significant change in nostril shape for 1 year.

In addition, when correction surgery of the nose is performed at the age of 17 to 18 years, after wearing for 6 months after surgery in all day, wearing is continued at home for 1 year, and use is suspended. Also, if the deformation progresses, resume use and stop again one year later.

【Discussion】 The stop period was initially 3 months because the nostril form had some relapse about 2 months after stop of using the nostril retainer. However, there was a case where the relapse even after 3 months, so the stop period was 1 year. More than 10 years have passed since the one-year stop period, but no cases have relapse since then. It is considered that the use of the nostril retainer may be ended if no significant deformation of the nostril is recognized even one year after stopping the nostril retainer.

【Reference】 1) Niimi T., et al., Treatment of the nostrils in patients with cleft lip by a nostril retainer., British Journal of Oral & Maxillofacial Surgery., 38 : 224-226. 2000.

P 255

A method of dermabrasion

Teruyuki Niimi[1)], Hiroo Furukawa[2)], Satoshi Suzuki[1)],
Maya Yoshida[1)], Yuki Akiyama[1)], Nagato Natsume[1)]
[1)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi-Gakuin University, Nagoya
[2)]Faculty of Psychological and Physical Science, Aichi-Gakuin University, Nagoya (Japan)

【Introduction】 We have been conducting a dermabrasion for cases of visible scars at postoperative wound in cleft lip patients in whom the postoperative shape of lip and nasal ala are esthetically acceptable. Dermabrasion has an effective method for the smoothening of the scared skin surface and making it inconspicuous. Formerly we performed dermabrasion with local anesthetic injection. However, there were many patients who disliked an operation by pain of an injection in children. Thus we perform dermabrasion with surface anesthesia using lidocaine tape recently, furthermore we use hydrocolloid dressing material to apply on the wound. Here we report our procedure of dermabrasion including anesthesia and dressing.

【Method】 Ninety minutes before the dermabrasion, lidocaine tape (PENLES®, Wyeth K.K.) is put on the part where the treatment will be applied. We abrade scar using dental stone wheel cooled by rinsing with normal saline. During dermabrasion, 4% lidocaine dipped in sponge is applied when pain occurs.

After dermabrasion, hydrocolloid dressing material (ABSOCURE® - SURGICAL, NITTO DENKO) is put for a week to reduce postoperative pain and skin redness. Antibiotics and painkillers are not necessary.

【Result】 This method was undertaken in 92cases (male : 38, female : 54) without any wound infections nor complications. There were no cases which necessitate local anesthetic injection during the treatment. All patients healed without scab formation and epithelized in a week.

【Discussion】 It is said that the origin of dermabrasion is Kromayer smoothened skin surface using machinery in 1905. This method indicated for scar, discoloration and tattoo. Dermabrasion does not cause any scar formation as long as the abrasive depth remains dermis stratum papillare.

Lidocaine tape (PENLES®, Wyeth K.K.) was invented for distress of injection. This material is bioadehesive film and contains 60% lidocaine. Application time for the reduction of injection pain is 30 minutes, but we think it is too short for dermabrasion.

Hydrocolloid dressing materials have the adhesion side containing hydrocolloid particles. It is easy to transfer new epithelial tissues. Since hydrocolloid particles forms gel by absorbs exudates and keeps wet condition, wound healing is promoted. This material is comparatively thin thing with thickness 0.4mm, so it is easy to put on curved surface such as upper lip.

P 256

Williams syndrome of Submucosal cleft palate

Yasunori Akiyama, Hideto Imura, Akihiro Mori, Maya Yoshida, Tomoko Mori, Naoki Saito, Yoshitaka Toyama, Masaaki Itoh, Yoshio Akiyama, Nagato Natsume (Japan)

【Purpose】 Williams syndrome is the first syndrome reported in 1961 by Williams in four patients with supravalvular aortic stenosis who have very characteristic facial and mental developmental disorders. Arate of incidence of the williams syndrome is 1 in 20,000 to 30,000. We report the complaint was speech disorder williams syndrome with submucosal cleft palate and multiple congenital tooth missing.

【Case】 The patient was 9-year-old. She was diagnosed with Williams syndrome at another hospital.She was diagnosed with submucosal cleft palate because she has three signs of calnan. We evaluated for the pronunciation and developmental examination.Velopharyngeal function was unstable and quite mild. She was 9 years old and her intelligence quotient 3 years old. In the panoramic XP examination, permanent teeth numbered 15, 13, 12, 24, 25, 45 were congenitally missing.

【Discussion】 Velopharyngeal function was severe dysarthria. We have not found any reports of williams syndrome that have accompanied submucosal cleft palate in our search.We have never seen the reports of williams syndrome revealed details about the tooth phenotype.We reported cases of williams syndrome in which there were 6 teeth congenital defects of permanent teeth. From this report, it is thought that multiple congenital missing tooth are submucosal cleft palate areas new phenotypes of williams syndrome.

P 257

Cleft palate after palatal fusion in mice exposed to TCDD

Chisato Sakuma[1, 2)], Hideto Imura[1, 2, 5)], Tomohiro Yamada[3)], Yayoi Ikeda[4)], Toshio Sugahara[5)], Nagato Natsume[1, 2, 5)]
[1)] Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi-Gakuin University
[2)] Aichi-Gakuin University Hospital Cleft Lip and Palate Center
[3)] Section of Oral and Maxillofacial Surgery, Division of Maxillofacial Diagnostic and Surgical Science, Faculty of Dental Science, Kyushu University
[4)] Department of Anatomy, School of Dentistry, Aichi-Gakuin University
[5)] Division of Genetics and Philology for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi-Gakuin University (Japan)

【Introduction】 We had reported that the mice embryos exposed TCDD, the minimum concentration to induce a 100% cleft palate rate, occurred cleft palates after palatal fusion. We studied to reveal the involvement of intercellular adhesion in the cleft palates after palatal fusion.

【Method】 In this study, on GD 12, ICR pregnant mice were administered with TCDD diluted in olive oil at a dose of 40 μg/kg body weight, the minimum concentration to induce a 100% cleft palate rate (TCDD-exposed embryos). The palates with fusion of TCDD-exposed embryos compared with the palates of control embryos in morphology and immunohistochemistry.

【Result】 In the individual TCDD-exposed mouse embryos that showed healing at the anterior part of the palatal processes and posterior dissection, it was observed that the oral mucosa invaded upward as it went backward, and it was torn from the palate midline part. The appearance of intercellular adhesion factor was different at the fusional palate between control embryos and TCDD-exposed embryos.

【Discussion】 From this study, we suggested that the intercellular adhesion concerned the epithelial split and the mesenchymal defect of the fusional palate, and there was a possibility that the weakness of intercellular adhesion led to the cleft palate after palatal fusion.

This work was supported by KAKENHI (No. 16K15830, No.16K11773).
COI: None

P 258

Validation study for Language ENvironment Analysis system (LENATM)in Japanese

Toko Hayakawa[1)], Hiyori Makino[1)], Hideto Imura[2),] Nagato Natsume[2),], Adriane Baylis[3)]
[1)] Faculty of Psychological and Physical Science, Aichi-Gakuin University
[2)] Division of Speech-Language-Hearing Therapy, Aichi Gakuin University Hospital
[3)] Nationwide Children's Hospital (USA)

【Background】 The Language ENvironment Analysis (LENA)

system is a system developed and standardized based on US English that measures conversations with children from the pre-language period, which is considered to be an important element of early brain development. It is used in research and clinical settings in US for the purpose of promoting language development and improving the delay in development of cognition, emotion and social skills. This study was preliminary conducted because the validation of whether LENA can be used in Japanese has not been performed yet.

【Purpose】 To assess the validity of the use of LENA in Japanese

【Method】 The participants of 5 children (median: 39 months, 2 male, 3 female) aged 13 to 47 months with DQ <100 on the KIDS infant development scale were in this study. The participants wore a special vest with a recorder and recorded at home for over 10 hours continuously. 60 minutes were extracted from each participant's recordings, and the listener whose first language was Japanese calculated Adult Word Count (AWC) and Child Vocalizations (CVs) of each participant's recording. The intraclass correlation (ICC) and correlation of AWC and CVs between by the listener and calculated by the dedicated LENA software were studied.

【Result】 Both LENA and the listener's calculated overall AWC and CVs showed high ICC and correlation. As for ICC in each participant, it was high in any AWC, but CVs was low in the child aged 13-month. As for the correlation in each participant, AWC showed significant high correlation in all participants, but CVs showed the correlation in only 1 case. There were no significant differences in both AWC and CVs between by the listener and the LENA.

【Discussion】 LENA's AWC was correctly calculated in Japanese. As for CVs, there was a possibility that CVs could not be counted accurately depending on the level of language development, but in this study, only one person was at the canonical babbling stage. LENA can measure the language environment for children from the pre-language period, and the results from LENA can be used for training and environmental adjustment to promote language development and communication skill. In the future, we would like to increase the number of subjects and divide those into age groups to evaluate their relevance in Japanese.

P 259

Case report: Outcome from speech therapy for the patient with laryngomalacia and VPD

Emina Hashimoto[1)], Chisako Inoue[2)], Tomoko Mori[2)],
Yoshiko Aihara[3)], Nagato Natsume[2)], Toko Hayakawa[1)]
[1)]Faculty of Psychological and Physical Science,
Aichi-Gakuin University
[2)]Division of Speech-Language-Hearing Therapy,
Aichi Gakuin University Hospital
3) Department of Dental Hygiene,
Aichi Gakuin University (Japan)

Laryngomalacia is the most common congenital laryngeal anomaly. Patients present with different degrees of stridor and feeding problems that usually resolve by 18 months of age. Also cleft lip/palate is the most common congenital maxillofacial anomaly.

As a trainee of Speech-Language-Hearing therapist, I experienced the patient with laryngomalacia and cleft palate.

The patient had a palate plasty at age two. She was assessed as having a good velopharyngeal function at age four though, her VPF decreased to mild dysfunction at age five. She did not present cleft related articulation errors such as glottal stops and pharyngeal fricatives, however her phonological skill was clearly immature and she needed the speech therapy targeting at substitution of /p/ to /t/, of /d/ to /m,b/.

What we learned from this case was even VPF was good at some young age, we need to routinely check and assess patients' status because some of those may demonstrate decrease of VPF along with their physical development.

P 260

Case report: Outcome from speech therapy with a speech prosthesis – a case with cleft palate and 22q11.2 deletion syndrome-

Ayane Endo[1)], Chisako Inoue[2)], Tomoko Mori[2)],
Yoshiko Aihara[3)], Toko Hayakawa[1)]
[1)]Faculty of Psychological and Physical Science,
Aichi-Gakuin University
[2)]Division of Speech-Language-Hearing Therapy,
Aichi Gakuin University Hospital
[3)]Department of Dental Hygiene,
Aichi Gakuin University (Japan)

Patients with 22q11.2 deletion syndrome often present developmental delay and borderline intelligence and velopharyngeal dysfunction(VPD) with/without cleft and other multiple comorbidities. Due to VPD and developmental delay, those often encounter speech therapy. As a trainee of Speech-Language-Hearing therapist, I experienced the case with 22q11.2 deletion syndrome improved his speech from eliminating glottal stops though his VPD was remained.

This speech therapy outcome may indicate that having speech therapy to eliminate glottal stops may have led improvement of velopharyngeal muscles mobility and clinicians could eventually assess the nature of patient's VPD. The patient could have the further treatment options after the appropriate assessment of VPD.

P 261

ASSOCIATION OF MEOX2 POLYMORPHISM WITH NONSYNDROMIC CLEFT PALATE ONLY IN A COMPARISON BETWEEN A JAPANESE POPULATION AND A VIETNAMESE POPULATION.

Duy Le Tran[1, 2)], Hideto Imura[1)], Akihiro Mori[1)],
Satoshi Suzuki[1)], Teruyuki Niimi[1)], Toko Hayakawa[1)],
Tham Thi Hong Nguyen[1)], Phuong Thi Pham[2)],
Ut Cong Nguyen[2)], Viet Hoang[2)], Hiep Minh Trinh[2)],
Minh Duc Nguyen[3)], Tan Van Ngo[4)], Mai Van Phan[5)]
and Nagato Natsume[1)].
[1)]Division of Research and Treatment for Oral and
Maxillofacial Congenital Anomalies,
School of Dentistry, Aichi Gakuin University,
Nagoya (Japan)
[2)]Nguyen Dinh Chieu General Hospital,
Ben Tre City

[3)]Odonto and Maxillofacial Hospital, Ho Chi Minh City
[4)]Department of Health in Ben Tre
[5)]Ben Tre People Committee, Ben Tre (Vietnam)

【Objective】 To evaluate the association between the single nucleotide polymorphism (SNP) rs227493 in the MEOX2 gene and nonsyndromic cleft palate only, this research was conducted as a case-control study by comparing a nonsyndromic cleft palate only (NSCP) group with an independent, healthy, and unaffected control group who were both examined by specialists.

【Methods】 Based on clinical examination and medical records, we analyzed a total of 570 Vietnamese DNA samples, including 277 cases and 293 controls, which were extracted from dry blood spot samples collected from both the Odonto and Maxillofacial Hospital in Ho Chi Minh City and Nguyen Dinh Chieu Hospital in Ben Tre province respectively; whereas, in Japanese, we collected 91 patients with NSCP (61 females and 30 males), compared to 104 controls data (48 females and 56 males) extracted from gene database of 1000 Genomes Browser (Phase 3). The standard procedures of genotyping the specific SNP (rs2237493) for MEOX2 were performed on a StepOneTM Realtime PCR system with TaqMan® SNP Genotyping Assays (Thermo Fisher).

【Results】 In Vietnamese, significant statistical differences were observed in allelic frequencies (allele T and allele G) between the NSCP and control groups in female subjects, with an Allelic Odd Ratios (AORs) of 1.455 (95% CI: 1.026 – 2.064) and $p < 0.05$. Meanwhile, in Japanese females, genotypic frequencies in three genotypes (TT, TG, and GG) showed a significant difference ($p < 0.05$), particularly in the dominants (TT) with Genotypic Odd Ratios (GORs) at 3.47 (95% CI: 1.39 – 8.66, $p < 0.05$) and in the heterozygous (TG) with GORs at 0.36 (95% CI: 0.16 – 0.79, $p < 0.05$). Making a data integration between the two studied racial groups in case-control study, also in females, significant differences were revealed not only in alleles (T and G) of AORs: 1.46, 95% CI: 1.09 – 1.95, $p < 0.05$) but in genotypes (TT, TG, and TG, $p < 0.05$). In which, the dominant genotype TT appear to overwhelm the others (GORs: 1.66, 95% CI: 1.11 – 2.47, $p < 0.05$).

【Conclusion】 These study findings suggest that nonsyndromic isolated cleft palate might be influenced by the variation of MEOX2, especially SNP rs2237493 in a Vietnamese female population as well as the Japanese female population.

P 262

Experimental Study on Cleft Lip and Palate: The Effects of Cheese on the Mouse Strain with High Incidence of Spontaneous Cleft Lip and/or Palate.

Duy Le Tran[1, 2)], Teruyuki Niimi[1)], Toko Hayakawa[1)], Tham Thi Hong Nguyen[1)], Ut Cong Nguyen[2)], Viet Hoang[2)], Hiep Minh Trinh2, Tan Van Ngo[4)], Mai Van Phan[5)] and Nagato Natsume[1)].
[1)]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University, Nagoya (Japan)
[2)]Nguyen Dinh Chieu General Hospital, Ben Tre City
[3)]Department of Health in Ben Tre
[4)]Ben Tre People Committee, Ben Tre (Vietnam)

【Objective】 We reported the incidence of cleft lip and palate in Mongolian people is lower than that in of the other Asian races. Based on the fact that the Mongolian have a high consumption of dairy products, A/J inbred mice strain with spontaneous development of cleft lip and palate was employed to investigate the association between high intake of a kind of milk-related product and these clefts.

【Method】 8-week-old mice were initially fed with Mongolian cheese and solid diet CA1 and then mated at ten weeks of age. C-section operations were performed on the 18th gestational day, and fetuses with and without oral clefts were observed and recorded. Incidentally, a group of mice being fed by CA1 only was used as the control. Also, the X2 test was employed for data analysis with significant level is lower than 5%.

【Results】 With a number of fetuses in the control group at 291 and in the experimental group at 297, the fetal mortality rate in the experiment is significantly lower than that in controls, with percentages at 7% and 20.6% respectively. The incidence of cleft lip and palate showed a considerable disparity with the percentage of the experimental group at 6.5% of 276 alive fetuses, compared to 11.7% of 231 alive controls.

【Conclusion】 The present study suggested that dietary intake of cheese seems to give a preventive effect on fetal mortality and occurrence of cleft lip and palate in A/J mice.

P 263

Clinical, radiographic, and genetic characteristics of hypohidrotic ectodermal dysplasia: A cross-sectional study

Vo Truong N. Ngoc[1)], Tong M. Son[1)], Nguyen M. Duc[1, 2)], Nguyen T. Tra[1)]
[1)]School of Odonto Stomatology, Hanoi Medical University, Hanoi (Vietnam)
[2)]Division of Research and Treatment for Oral Maxillofacial Congenital Anomalies, Aichi Gakuin University, Nagoya (Japan)

【Aim】 Hypohidrotic ectodermal dysplasia (HED) is a hereditary disorder affecting the development of ectodermal structures such as skin, hair, nails, teeth, and sweat glands, consequently diminishing patients' quality of life. The knowledge of clinical characteristics as well as the molecular mechanisms underlying HED development benefits the development process of methods for disease's prevention and treatment. This research paper aims to determine the clinical, radiographic, and genetic characteristics of this disease in a cohort of 16 HED cases collected during the period of 2013 to 2017.

【Methods】 A cross-sectional study was conducted in 16 cases of HED collected from 2013 to 2017. Epidemiological data, clinical conditions, radiographs and genetic characteristics were analyzed.

【Results】 13/16 had typically clinical characteristics of HED including sparse scalp hair, partial/total anodontia and hypohidrosis. 16/16 cases had undeveloped mandibular ridge showed by radiographs. 8/10 cases found mutations in the EDA gene.

【Conclusion】Typical features of HED are hypotrichosis, hypohidrosis and hypodontia. Mutations in the EDA gene are present in most cases (80%).

P 264

Cleft lip and palate management in Vietnam

Nguyen M. Duc[1, 2)], Nguyen T. Tra[1)], Dong N. Quang[3)], Truong M. Nga[4)], Tran L. Duy[2, 5)], Tran D. Thong[2)]
[1)] School of Odonto Stomatology, Hanoi Medical University, Hanoi (Vietnam)
[2)] Division of Research and Treatment for Oral Maxillofacial Congenital Anomalies, Aichi Gakuin University, Nagoya (Japan)
[3)] Hanoi National Hospital of Odonto – Stomatology, Hanoi
[4)] Department of Dentistry, Hanoi Medical University- Thanh Hoa Campus, Thanh Hoa
[5)] Nguyen Dinh Chieu General Hopsital, Ben Tre (Vietnam)

The prevalence of cleft lip and palate of Vietnam is about 19,7 per 10.000 live births, cleft lip with/without palate 14.33, cleft palate only 5.37. There are many hospitals able to perform cleft lip and palate repair. According to statistics of Hanoi National Hospital of Odonto – Stomatology, 2443 cleft lip palate cases were performed from 12/2015 to 6/2019. A comprehensive treatment is currently more focused on interdisciplinary approach, providing adequate treatments, early consultation, and long-term follow-up. Cleft centers were established along the country, like Hanoi National Hospital of Pediatrics, Ho Chi Minh National Hospital of Odonto-Stomatology (NHOS). Patients with cleft lip are diagnosed by ultrasound images after 16 weeks of pregnancy, access to early intervention like nasoalveolar molding (NAM) as a pre-surgery treatment, chelioplasty from 6 months old, cleft palate repair from 16-18 months of age, speech therapy from 2-3 years old, orthodontics from primary dentition, alveolar bone graft, orthognathic surgery, rhinoplasty, etc. The cleft lip and palate management in Vietnam remains problems and difficulties, especially, speech and language therapy. The lack of Speech language pathologists (SLPs) contributes to exacerbating the problem. A few hospitals and medical centers starting to treat speech like Vietnam National Hospital of Pediatrics (Hanoi), Hanoi NHOS, Ho Chi Minh NHOS, however, are still in a very first step. The most crucial problem of individuals with cleft lip and palate is unaffordable treatment cost. Most patients only affordable access with chelioplasty and palatoplasty with the support from charity associations. Thus, other treatments like orthodontics, alveolar bone graft, speech therapy have been omitted and consequently diminished patients' quality of life. To date, through a period of over 30 years, there have been Associations, NGOs coming to Vietnam for charity activities like funding, health care technology transfer, co-operating operation: Japanese Cleft Palate Foundation, Operation Smile, Smile Train, etc.

Clinical, radiographic, and genetic characteristics of hypohidrotic ectodermal dysplasia: A cross-sectional study

Vo Truong N. Ngoc1, Tong M. Son1, Nguyen M. Duc1,2, Nguyen T. Tra1
1. School of Odonto Stomatology, Hanoi Medical University, Hanoi, Vietnam
2. Division of Research and Treatment for Oral Maxillofacial Congenital Anomalies, Aichi Gakuin University, Nagoya, Japan

【Aim】Hypohidrotic ectodermal dysplasia (HED) is a hereditary disorder affecting the development of ectodermal structures such as skin, hair, nails, teeth, and sweat glands, consequently diminishing patients' quality of life. The knowledge of clinical characteristics as well as the molecular mechanisms underlying HED development benefits the development process of methods for disease's prevention and treatment. This research paper aims to determine the clinical, radiographic, and genetic characteristics of this disease in a cohort of 16 HED cases collected during the period of 2013 to 2017.

【Methods】A cross-sectional study was conducted in 16 cases of HED collected from 2013 to 2017. Epidemiological data, clinical conditions, radiographs and genetic characteristics were analyzed.

【Results】13/16 had typically clinical characteristics of HED including sparse scalp hair, partial/total anodontia and hypohidrosis. 16/16 cases had undeveloped mandibular ridge showed by radiographs. 8/10 cases found mutations in the EDA gene.

【Conclusion】Typical features of HED are hypotrichosis, hypohidrosis and hypodontia. Mutations in the EDA gene are present in most cases (80%).

P 265

THE SURVEY QUESTIONNAIRE FOR CLEFT LIP AND/OR PALATE (CL/P) AT MANDALAY UNIVERSITY IN MYANMAR

Thong Duc Tran[1)], Satoru Ozeki[2)], Takeshi Mitsuyasu[3)], Nagato Natsume[1)], Duy Le Tran[1)]
[1)] Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, Aichi-Gakuin University Hospital, Aichi
[2)] National Hospital Organization Kyushu Medical Center, Fukuoka
[3)] Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Higashi-Ku, Fukuoka (Japan)

【Introduction】Republic of the Union of Myanmar is a country in Southeast Asia. The population is about 54 million people (2017). Due to various reasons, medical quality hasn't been taken seriously. Currently, the insufficiency of professional doctors is one of the biggest problems. There are nearly between 6.000 and 8.000 children with CL/P average yearly. (According to Central Women's Hospital).

【Method】The method of this survey is designed to answer in a set format, including open-ended and close-ended questions and conducted on the 166 dental students at the Mandalay

University by asking some questions related to their knowledge of CL/P.

【Purpose】 Providing general knowledge, the information processing approach and evaluation perspectives such as prejudice and discrimination remarks of dental students for a child with CL/P. Offering positive support solutions for the long-term development of a child with CL/P.

【Result】 According to the statistics result, more than half of the dental students are likely to know CL/P. Therefore, this problem is prevalent in Asian countries. However, there are few people (4,8%) who understood well CL/P. If the knowledge isn't enough, it will be challenging to figure out how to treat in the right ways.

The number of dental students who receive information through hospitals or clinics is 32,6%. However, promoting knowledge via health center isn't the right way in Myanmar at the moment. This situation indicates education hasn't developed synchronously.

More than haft of people (59,6%) think CL/P will affect the social life of the child. The knowledge for education at school is also crucial for the children.

The idea of preparing the necessary knowledge and information about CL/P is raised by the majority of people (24,7%).

【Discussion】 The activities and introductions of valuable information related to CL/P are relatively effective in Myanmar through the hospital, clinic and social media network. Therefore, treatment methods and necessary reference materials for the family who has the children with CL/P is the priority.

Not only family members, but also health workers, neighbors and local authorities need to support the local community. Creating a pleasant environment for children with CL/P, enabling them to have excellent community integration is necessary. Medical staffs should support the mother's mental state regarding the child with CL/P.

P 266

A case of cleft alveolar and palate without cleft lip.

YOSHIDA Mitsuna, FUJIWRA Kumiko,
NAKAMICHI Naomi, NOGUCHI Makoto
Department of Oral and Maxillofacial Surgery,
Graduate School of Medicine and Pharmaceutical
Sciences for Research, University of Toyama (Japan)

【Backgoround】 Cleft Lip and/or Palate is one of the most common anomaly. It does not clear that how to occur the cleft lip and/or palate. Cranio-Maxillofacial is formed by a number of facial process. Cleft Lip and Alveolar are caused by maxillary process imperfection. This is a rare case that there is a cleft alveolar without cleft lip.

【Case】 The patient was born at 2,714 g at GD37w and was Apgar Score 9/10. He has a cleft alveolar and cleft palate, but the other abnormality (including microform cleft lip) was not accepted. The nostril has the impression that the left side is slightly wide, but the functional aesthetic appreciation problem does not clear.

【Discussion】 Nakahara S.(2017) reported that there are 102 cleft types of Cleft Lip and/or Palate. This case, the alveolar and palatal cleft without cleft lip, does not belong to these types. As for the primary development of palate, there were many points that did not yet become clear, but the possibility that cleft alveolar occurred regardless of cleft lip was suggested.

P 267

Clinical research of Van der Woude syndrome.

Maya Yoshida, Niimi Teruyuki,
Imura Hideto, Natsume Nagato
[1)] School of Dentistry Aichi Gakuin University,
Division of research and Treatment for Oral
and Maxillofacial Congenital Anomalies.
[2)] Cleft lip and palate center, Aichi-Gakuin
University Hospital (Japan)

【Background】 Van der woude syndrome (VWS) is autosomal dominant disease with cleft lip/palate occupied 0.5-2.0% of the total patients of cleft palate/lip. The causative gene for both of the syndromes was previously isolated, which was interferon regulatory factor 6 (IRF6) gene that was a family of interferon regulatory factors. However, the relationship of mutation and cleft type is unidentified.

【Method】 We have analyzed sequence of the IRF6 gene in new 5 familial cases of VWS. One family had nonsense mutation in the patient, and other 4 families had missense mutation in the patients. We reviewed position of the mutation in IRF6 previously reported, and discussed the phenotype and genotype of the mutations.

【Result】 The cleft type was classified into cleft lip and palate; 5 cases, cleft lip and alveolus; 1 cases. The cleft type of incomplete cleft lip was not seen in the patients.

We have analyzed sequence of the IRF6 gene in new 5 familial cases of VWS. One family had nonsense mutation in the patient, and other 4 families had missense mutation in the patients.

As a result of investigating the gene analysis results of VWS cleft pattern model and IRF6, the relationship between exon position and amino acid mutation was not regular, and the relationship between VWS phenotype and IRF 6 base substitution was unknown.

【Discussion】 In VWS, lip pits were observed in around 85% of affected individuals, which is one of the major symptom of the VWS with IRF6 mutation. However the lip pit is also phenotype of incomplete penetrance in VWS familial case. Although the VWS is Mendelian inheritance disease, the incomplete penetrance of the each oral abnormality may explain by concept of biological threshold, like a multifactorial disease resulted in relatively large effects on risk for VWS with IRF6 mutation in the two critical domains, while in small effect of the common variant of the IRF6 and other gene in isolated cleft lip/palate with environment factors. In the future, by increasing the number of cases and investigating more detailed data on the relationship between pharyngeal phenotype and heredity, it is thought that it may lead to future treatment, prevention and genetic counseling.

P 268

Effect of "Carbonate Apatite " bone regeneration on Cleft lip and palate in SD rat

Ichinnorov Chimedtseren[1,2], Motoko Yoshioka[2,3], Ito Masaaki[1,2,3,4], Toriumi Taku[1], Akiyama Yasunori[1,2,3,4], Ariuntuul Garidkhuu[5,6], Amarsaikhan Bazar[5], Anar-Erdene Gantugs[7], Tsolmon Jadamba[5], Masaki Honda[1] and Nagato Natsume[2,3,4].

[1]Department of Oral Anatomy, Aichi Gakuin University School of Dentistry

[2]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, Aichi Gakuin University, School of Dentistry

[3]Cleft Lip and Palate Center, Aichi Gakuin University Dental Hospital

[4]Division of Speech, Hearing, and Language, Aichi Gakuin University Dental Hospital,

[5]Mongolian National Medical University, School of Dentistry

[6]School of Medicine, International University of Health and Welfare (Japan)

7) Mongolian National Medical University, School of Pharmacy (Mongolia)

【Acknowledgment】 This research support by Grant-in-Aid for Young Scientist (18K17212-Motoko Yoshioka)

One of the stages of treatment is alveolar bone graft for Cleft lip and palate patients. The most common procedure is the autograft to repair Cleft Lip and Palate, however its lead to complications such as pain, swelling infection, abnormal bleeding, and donor-site morbidity. Therefore, bone defects can be repaired with artificial bone substitutes.

As such, hydroxyapatite compounds are the most, have been used as bone substitutes. Of these compounds, the hydroxyl group is the most popular because of its very good biocompatibility, but it is poorly resorbed in the body, similar to autogenous bone has been waiting. The bone contains about 7% carbonate and consists mainly of carbonate apatite, not stoichiometric hydroxyapatite. Recently it was reported that carbonate apatite more than hydroxyapatite upper level of new bone formation and easily absorbed in the body.

The purpose of this study, based on this report, the effect of carbonate apatite on cleft lip and palate regeneration, was studied used for female, ten weeks age a total amount of 10 SD rats.

Throughout the experimental process, 0.02g carbonate apatite implanted into the right side of the palatine fissure. During the experimental process analysis of bones by sagittal, horizontal, and frontal section for one week four week eight, week 12 week and 16 weeks examine bone volume for micro-computed tomography (CT). Carbonate apatite is an impermeable graft material; an opaque image is observed on CT from the time of transplantation. However, carbonate apatite was quickly resorbed, and the implantation side increased by bone wide. It might be new bone formation. Additional histological analysis (Histomorphometry) is performed to confirm the absorption, period, and bone formation.

P 269

Experimental effects of licorice solution on fetal mortality and cleft lip and/or palate in A/J mice

Ichinnorov Chimedtseren[1], Teruyuki Niimi[1,2,3], Tran Duy[1], Hideto Imura[1,2,3], Satoshi Suzuki[1,2,3], Akihiro Mori[1,2,3], Maya Yoshida[1,2,3], Ariuntuul Garidkhuu[4,5], Amarsaikhan Bazar[4], Tsolmon Jadamba[4], Anar-Erdene Gantugs[6] Ito Masaaki[1,2,3], Akiyama Yasunori[1,2,3], Chisato Sakuma[1,2,3], Minami Katsuhiro[1,2,3] and Nagato NATSUME[1,2,3].

[1]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, Aichi Gakuin University, School of Dentistry

[2]Cleft Lip and Palate Center, Aichi Gakuin University Dental Hospital

[3]Division of Speech, Hearing, and Language, Aichi Gakuin University Dental Hospital

[4]Mongolian National Medical University, School of Dentistry

[5]School of Medicine, International University of Health and Welfare (Japan)

[6]Mongolian National Medical University, School of Pharmacy (Mongolia)

During pregnancy, estrogen can increase the risk of cleft lip and palate in human and animals. Licorice (Glycyrrhiza glabra¬) dry root extract and its major compounds have been reported to exhibit varying degrees of estrogen receptor agonism in various tissues in vitro and in vivo.

Here, we evaluated the effects of licorice extracts on fetal mortality and incidence of cleft lip and/or palate using A/J mice. Throughout the experimental process, different dose compared to four groups. Group I is 0.03mg/ml, Group II is 0.06mg/ml, Group III is 0.09mg/ml and Group IV is 0.3mg/ml. Those mice were mated, and licorice solution instead of usual tap water was provided as drinking water to the experimental group of A/J mice.

At the age of eight weeks. Those mice were mated and humanely sacrificed on eighteenth gestation day, and the fetuses were examined. The results more than effected group III, there was indicated that fetal mortality (6.2%) was for the control group whereas (5.6%) for the experiment group. The percentages of fetuses with cleft lip and palate were (3.4%) of 144 alive fetuses and (8%) of 187 alive fetuses for control and experiment groups, respectively. There were significant differences between the experiment group (with ingestion of the licorice solution of 0.09mg/ml) there was Cleft palate only 2 fetuses (1.3%) and Unilateral cleft lip and palate 3 fetuses (2.0%) of 149. There were no fetuses have Bilateral cleft lip palate in that group.

It seems that licorice solution of 0.09mg/ml does effect the rate of cleft lip and/or palate in A/J mice.

P 270

Association of SNP rs2237493 in MEOX2 and Cleft Palate in Japanese population

Akihiro Mori[1,2,3], Hideto Imura[1,2,3], Satoshi Suzuki[1,2,3], Satoru Takumi[1,2,3], Maya Yoshida[1,2,3], Toko Hayakawa[1,2,4],

Katsuhiro Minami[1, 2, 3], Teruyuki Niimi[1, 2, 3], Hiroo Hurukawa[1, 2, 4], Nagato Natsume[1, 2, 3]
[1] Cleft Lip and Palate Center, Aichi Gakuin Dental Hospital, Nagoya
[2] Division of Speech, Hearing and Language Aichi Gakuin Dental Hospital, Nagoya
[3] Division of Research and Treatment for Oral Maxillofacial Congenital Anomalies, Aichi Gakuin University, Nagoya,
[4] Department of Health Science, Faculty of Psychological and Physical Science, Aichi Gakuin University, Nagoya (Japan)

【Abstract】Cleft lip with or without cleft palate (CL/P) is a common congenital deformity worldwide with multifaceted etiology. Interaction of genes and environmental factors has been indicated to be related with susceptibility to CL/P. Some of genetic factors associated with cleft lip and palate was identified, such as BMP4, MSX1, TBX22, IRF6 and SUMO1 genes. Meox2 is candidate gene linked with cleft palate in genetically engineered mice. In this study, we aimed to investigate a potential link between MEOX2 mutations and cleft palate in human subjects. We analyzed 108 DNA samples which obtained from Japanese Non-syndromic cleft palate (NSCP) patients. We compared the genotyping data with healthy 170 individuals without cleft palate and/or any other congenital defect. The DNA was extracted from the venous blood of each sample, and Taqman fluorescent quantitative polymerase chain reaction (qPCR) technique was used to detect rs2237493 in MEOX2 gene. In dominant models, odds ratio (OR) of (TT/TG+GG) was 1.79 (P=0.028*). In heterozygotes models, OR of (TG/TT+GG) was 0.70 (P=0.16). In recessive models, ORs of (GG/TT+TG) was 0.79 (P=0.46). In summary, T/T genotype was associated with a 1.82 times significantly higher risk of cleft palate than others. This study suggests that rs2237493 T/T genotype might constitute a predisposing genetic factor of cleft palate disorders in Japan.In conclusion, genotype TT at rs2237493 in MEOX2 gene has association with the incidence of NSCP, and prevalence risk.

P 271

Prevalence and incidence estimates for infectious disease in The First Central Hospital of Mongolia, 2014-2017

A.Davaasuren[1], G.Enkhtsatsral[1], M.Bold[2], P.Ulanbayar[2], P.Bulgan[2], G.Bayarmunkh[2] P.Davaadorj[2]
[1]Mongolian National University of Medical Science, School of Dentistry
[2]Department of Oral and Maxillofacial Surgery, The First Central Hospital of Mongolia (Mongolia)

【OBJECTIVES】To estimate adult prevalence and incidence of oral facial cellulitis (L03.2), furuncle (L02.0), adenophlegmon (L04.0) and osteomyelitis (K10.3) in The First Central Hospital of Mongolia, over 2014-2017.

【METHODS AND FINDINGS】The records of 1812 patients treated for only oral facial cellulitis, furuncles, adenophlegmon and osteomyelitis at the Department of Oral and Maxillofacial Surgery, The First Central Hospital of Mongolia during the period from 2014 to 2017 were retrospectively reviewed. Their demography, symptoms, etiology, seasonal distribution, bacteriology, radiology, site of head and neck infection, duration of the hospital admission and hospital stay, treatment, complications, and outcomes were evaluated. The findings were compared to those in the available literature.

【CONCLUSIONS】One thousand eight hundred twelve charts were recorded; 1135 (62.64%) were men, and 677 (37.36%) were women, with ages between 18-25 years were 563 (31.07%), 26-35 years were 512 (28.26%), 36-45 years were 300 (16.56%), 46-55 years were 210 (11.59%), and two hundred twenty-seven (12.53%) of the patients were older than 56 years old. There were 1126 patients (62.1%) who had cellulitis, 354 patients (19.54%) had osteomyelitis, 211 patients (11.64%) had furuncles, 121 patients (6.68%) had adenophlegmon. Fifty-five percent of them came from Ulaanbaatar city, others came from the suburbs. We found a cellulitis incidence rate is increased during the last four years. The percent of cellulitis was 56.59% in 2014, 60.45% in 2015, 64.2% in 2016, 66.45% in 2017.

【Keywords】Oral and Maxillofacial surgery, oral facial cellulitis, facial furuncle, osteomyelitis

P 273

Social/medical problems of patients with cleft lip and palate in Mongolia

Davaasuren Amgalanbaatar[1], Azbileg Batbold[1], Amarsaikhan Bazar[1], Ariuntuul Garidkhuu[1]. Unurjargal Khadbaatar[2], Susuki Toshio[3], Ando Takuya[4], Suzuki Satoshi[3, 5], Nagato Natsume[5]
[1]Mongolian National University of Medical Science, School of Dentistry
[2]Department of OMS, National Maternal and Children Health Center (Mongolia)
[3]Suzuki Dental Clinic, Nagoya city
[4]Matsukage Hospital, Nagoya city
[5]Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies,School of Dentistry, Aichi-Gakuin University (Japan)

In Mongolia, a cleft lip and palate is a very common (1:1000) facial congenital abnormality. We are doing all kinds of operations, orthodontic treatment, and step by step treatment for CLP patients, according to world standards. International organizations like Operation Smile, Chang Gun Memorial Hospital, Japanese Cleft Palate Foundation, Smile Train, and other independent doctors have helped Mongolia advance its oral surgical technique. The people of Mongolia are spread throughout a vast area of land, and towns are often 500-1000km apart, so it is difficult for every citizen to go to the hospital.

Since 1999, oral surgeons have offered to do operations and treatments for people in three to four regions across the countryside. In 2011, We established Center of Cleft lip and palate in the National Maternal and Child Health Center (NMCHD) in Mongolia.

Our doctors are improving their surgical skills and in countries with more advanced medical knowledge. They also team up with international organizations to volunteer in underdeveloped countries. Every Tuesday these doctors

examine patients who have a cleft lip and palate in The Center of CLP.

We have two big problems about CLP patients in Mongolia. The first is a problem about adult patient with CLP. There are no specialized staff who treat them in our country. Therefore, they are examined and treated by ordinary oral and maxillofacial surgeons. Doctors operate on adults who apply for treatment cooperate with The First Central Hospital of Mongolia (FCHM) and the National Maternal and Child Health Center at FCHM. But there are no specialized department for adults. What makes the problem worse is a little bit complicated. Adults with CLP receive benefit from The National Welfare Institute monthly until they are completely treated. Though it is a good policy, many adults avoid having operations, because if they are operated, they won't receive benefits anymore.

The second is a problem regarding the National Maternal and Child Health Center. This is the only advanced institute for pediatric patients in Mongolia. The doctors specialized for CLP are just a few. Thus, patients are too many in comparison with the doctors, beds, medical instruments, and the budgets from the government. For example, nostril retainers, which are supposed to be made for each patient, are expensive because the national budget is too small to cover them. So, there are not enough retainers for patients. Therefore, retainers are rented to them for around 5000 yen and re-use it.

References

・Ariuntuul G, Furukawa H, Uetani M, Suzuki S, et al. The Prevalence of Cleft Lip and/or Palate in Mongolia.J Jpn Cleft Palate Assoc. 31:267-273, 2006.
・Ayanga G, Davaanyam L, Purevjav N, Ariuntuul G, Agiimaa D, et al. The Prevalence and types of Cleft Lip and Palate, current condition of Cleft Palate repair in Mongolia, 2009 Acknowledgments
・This story is a headline story of "Japanese Cleft Palate Foundation" quarterly newsletter.
・Special thanks to Ando Takuya (Matsukage Hospital) and Suzuki Toshio (Suzuki Dental Clinic) supporting to my stay and live in Japan.

P 274

Upper Lip Symmetry after the Straight Line Repair of Unilateral Complete Cleft Lip: in Comparison with the Rotation-Advancement Repair

Jeong Hyun Ha[1)], Youn Taek Koo[2)], Jeehyeok Chung[3)]*, Sukwha Kim[1)]*
[1)] Division of Pediatric Plastic Surgery, Seoul National University Children's Hospital, Seoul
[2)] Wonjin Plastic Surgery, Seoul
[3)] Department of Plastic and Reconstructive Surgery, Myongji Hospital, Gyeonggi (Korea)

【Background】 Rotation-advancement repair has been the most widely used technique for unilateral cleft lip repair. Recently, we have used a straight-line repair technique with assumption that it could minimize upper lip asymmetry when muscle reorientation is performed properly. The purpose of this study was to compare the results of these two techniques for cleft lip repair.

【Method】 We conducted a retrospective cohort study of patients with unilateral complete cleft lip who underwent cheiloplasty at Seoul National University Children's Hospital from January 2009 to January 2017. The patients were divided into two groups according to cheiloplasty technique: rotation-advancement repair (RAR group) or straight-line repair (SLR group). Outcomes were evaluated by assessing 12 to 48-month follow-up photographs using three methods : (1) glance impression using a five-point scale, (2) Manchester Scar Scale, and (3) indirect anthropometry

【Result and Discussions】 A total of 39 patients with unilateral complete cleft lip were analyzed: 19 in the RAR group (12 males, 7 females) and 20 in the SLR group (12 males, 8 females). The glance impression (p=0.336) and Manchester Scar Scale (p=0.667) scores did not differ significantly between groups. According to the symmetry ratio (SR; cleft side value / noncleft side value) assessed by indirect anthropometry, vertical lip height (sbal-cph), horizontal lip length (cph-ch), and Cupid's bow width (cph-ls) did not differ significantly between groups (p=0.411, p=0.496, and p=0.879, respectively). Preoperative lip height discrepancy was not significantly correlated with the postoperative vertical lip height (sbal-cph).

Straight-line repair method can be regarded as a successful tool for symmetric repair of unilateral cleft lip without causing a short lip deformity. Since skin incision type did not affect the surgical outcome, muscle reorientation appears to be more important for cleft lip repair than skin incision.

P 275

Indoor exposure to the PM2.5 particle and the need in protective and preventive services in Mongolia

Tselmuun Chinzorig[1)], Purevdorj B. Olkhanuud[2)], Davaalkham Dambadarjaa[2)], Ken Osaka[1)], Koji Wada[3)], Shunya Ikeda[3)], Ariuntuul Garidkhuu[3, 4)]
[1)]School of Dentistry, Tohoku University (Japan)
[2)]School of Public Health, Mongolian National University of Medical Sciences (Mongolia)
[3)]School of Medicine, International University of Health and Welfare (Japan)
[4)]School of Dentistry, Mongolian National University of Medical Sciences (Mongolia)

【Introduction】 Ulaanbaatar – capital city of Mongolia, is the coldest in the world and topographically lies in the deep valley. It is subject to high air pollution peaking in the winter. Extensive burning of raw coal for the heating have led to the serious environmental and occupational health issues. The School of Dentistry, Mongolian National Univeristy of Medical Sciences locates in the city suburb ger district with high PM2.5 air particulate that have severe implications for health where as School of Public Health in the downtown of Ulaanbaatar.

【Aim】 The purpose of the study is to evaluate the indoor environmental air pollution and personal exposure to the PM2.5 particle.

【Methods】 Personal Exposure

For the measurement used TSI SidePak AM510 Aerosol Monitor for 5 days during the highest peak of PM2.5 in winter

(9-14 January) between 10:00 am -16:00 pm.
In total 30 faculties were included in the study: 20 faculties from the School of Dentistry (SD) and 10 faculties from the School of Public Health (SPH). In addition, 30 faculties from SD had Pulmonary Function Test (PFT) by Koko Spirometer and questionnaires are used to collect information on health symptoms of study subjects.
【Environmental Exposure】Dust Trak II Aerosol Monitor was placed at the work place to assess the indoor PM2.5. Descriptive statistics are used to analyze data.
【Results】The environmental exposure of PM2.5 among faculties at the School of Dentistry, MNUMS are 40 times higher (2,005 μg/m3) than the accepted level (50 μg/m3 within 24 hours, Air Quality standard of Mongolia) where is the School of Public health is 7 times higher (399 μg/m3). The Personal Exposure of PM2.5 among faculties the School of Dentistry was 3.84 times higher despite both schools were exceeded from the Mongolian air quality standard.
【Conclusion】The long-term higher levels of PM2.5 particulate matter exposure may negatively affect the health and wellbeing of faculty at the School of Dentistry, especially women of childbearing age. Occupational health management as one of the preventive measures might reduce possible risk of complications. This study is preliminary and matter for future continuity with larger sample.
Key words: Air quality, PM2.5, Mongolia

P 276

Standardization of nasalance scores in Mongolian speaking children: A population based study

Batsukh Shagdar[1)], Davaa Gombosuren[2)], Koji Wada[3)], Shunya, Ikeda[3)], Nagato Natsume[4)], Ariuntuul Garidkhuu[1, 3)]
[1)]School of Dentistry, Mongolian National University of Medical Sciences
[2)]School of Public Health, Mongolian National University of Medical Sciences (Mongolian)
[3)]School of Medicine, International University of Health and Welfare
[4)]School of Dentistry, Aichi-Gakuin University (Japan)

【Introduction】In Mongolia, there are no studies on the development of nasalance scores for the use of in clinical speech therapy for children with clefts. Therefore, necessity in the establishment of the normative nasalance scores based on native Mongolian language and dialect prompted us to conduct present study.
【Aim】To evaluate a mean nasalance scores of Mongolian speaking children.
【Methods】A total of 2280 normal speaking children were selected in the population based study in order to represent all khalkh dialects. Participants from central region, 4 aimags and 3 cities were included. Subjects were divided into 4 groups, aged (i) 4–5, (ii) 6–8, (iii) 9–11 and (iv) 12-13, respectively. Children repeated each of the seven speech stimuli (high pressure consonants and low pressure consonants, nasal consonants and 7 passages) which were developed by our research team, individually. Nasalance scores were obtained using a Nasometer TM II (model 6400). For statistical analysis used SPSS 20.0 paired-sample t-test, One- way ANOVA and p value calculated for the significance differences ($p<0.05$).
【Results】Normative a mean nasalance scores obtained for the all passages were 30.9%. Normative a mean nasalance scores obtained for 4-5 years old were 26.8±5.0%, 6-8 years 32.0±7.5%, 9-11 years 34.0±6.6% and 12-13 years 35.0±8.7%, respectively. There was statistically significant gender dependence for the all passages ($p<0.001$). A mean normative nasalance score for Mongolian speaking boys were 31.44%±7.45%, where as for girls was 32.71%±7.96 and showed statistically gender significance ($p<0.001$).
【Conclusion】Mongolian normative data will provide reference information in the evaluation and treatment of resonance problems in children with repaired cleft and it is the first research study of its kind in Mongolia.
【Key words】nasometer, nasalance score, Mongolian, cleft

P 277

26 years of JCPF operation in Ben Tre, Vietnam.

Nguyen Cong Ut
Nguyen Dinh Chieu Hospital (Vietnam)

Ben Tre is a province in the southern Vietnam, with a population of over 1 million 400,000. Cleft lip and cleft palate patient ratio is 1/1000[1]. Before 1993, CL, CP patients are not surgical in an international program. Since the Japanese Cleft Palate Foundation (JCPF) has been implementing surgical programs for CL and CP patients since 1993 continuously. It has been 26 years with the result of 1443 cases successful surgeries. So, as you can see, in its 26 years of operation, JCPF has become a household name in Bentre, Vietnam. JCPF also contributes to the construction of a new operating rooms with medical equipments. JCPF also supports other health programs in Ben Tre, Vietnam.
1) According to research results of the NDC hospital 1997
BS UT biên soạn để in ấn trong CLEFT 2019 tại Nagoya Nhật Bản 26-29/07/2019

P 279

A case of hematoma arising from wounds caused by toothbrush during hematopoietic stem cell transplantation

Yumiko Ikegami[1, 2)], Nagati Natume[2)], Hideo Imura[2)]
[1)] Department of Nursing, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo
[2)] Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University, Nagoya (Japan)

【Introduction】In this report, we report a patient with hematopoietic stem cell transplantation for acute myeloid leukemia who has experienced a case of hematoma that has formed and become worse from a toothbrush injury.
【Case and progress】Patient: 46-year-old woman (weight: 45.3 kg, the number of nucleated cells at the time of cord blood freezing: 12.47 × 10 ∧ 8)

Active history: Acute myeloid leukemia

Course: Acute myeloid leukemia first recurrence, with complications such as drug-induced cardiac dysfunction, transferred to hospital for the purpose of early cord blood transplantation.

Intervention was requested by perioperative oral function management review and request for oral care. There was no risk of infection in the oral cavity and oral hygiene was good. For transplantation pretreatment, FLu + Mel + TBI was performed and MTX administration was performed. After implantation, oral mucositis appeared around the mandibular anterior teeth from a wound caused by a toothbrush (SS) at d5. Blood test data became severe several hours later with WBC 0.01 PLT 1.5 CRP 4.54 and myelosuppression. For oral care, in cooperation with the nurse, we carried out care with a soft sponge brush and cotton ball and provided cooling. Although oral mucositis was alleviated in d21, survival was unsuccessful in d23 and steroid high-dose therapy was performed, resulting in pneumonia, which made it impossible to control infection, resulting in deterioration of respiratory condition and death. (D29) We also performed oral care for terminal care and angel care.

【Discussion】 Patients undergoing hematopoietic stem cell transplantation have received thorough oral hygiene instruction prior to transplantation. However, self-care alone makes it easy to make WSD, gum shortening and wounds. Even if PCR is good, professional evaluation and instruction are essential.

Deterioration of the oral mucosa at d5 after transplantation was one of the causes of deterioration as it was cord blood transplantation at the bone marrow suppression pole stage and survival was slow and wound healing was delayed and control of infection was difficult. During this period, severe sepsis often occurs, and in cooperation with hematologists, early infection control is essential. In addition, I think that it is very important that a team with advanced specialized oral care technology closely cooperates with nurses so that oral function management can be performed continuously.

【Conclusion】 We report that a patient with hematopoietic stem cell transplantation for acute myeloid leukemia experienced a case that hematoma was formed and aggravated from a wound by self-care toothbrush. The importance of oral care in hematopoietic stem cell transplantation has been confirmed.

P 280

Nonsyndromic Cleft Lip and/or Palate and the 5, 10-Methylenetetrahydrofolate Reductase C677T Polymorphism in Mongolians

Ariuntuul Garidkhuu[1, 2], Waka Yoshida[3], Tselmuun Chinzorig[4], Ayanga Gongorjav[5], Koji Wada[1], Shunya Ikeda[1], Nagato Natsume[3]
[1]School of Medicine, International University of Health and Welfare
[2]School of Dentistry, Mongolian National University of Medical Sciences
[3]School of Dentistry, Aichi-Gakuin University
[4]School of Dentistry, Tohoku University (Japan)
[5]Department of Oral and Maxillofacial Surgery, National Center for Maternal and Child Health (Mongolia)

【Introduction】 Cleft lip and/or palate (CL/P) are the most common and easily recognizable major congenital abnormalities in the world. The pathogenesis of CL/P is complex, presumably implicating the interaction of several genetic and environmental factors. MTHFR (5,10-methylenetetrahydrofolate reductase) gene C677T functional mutation and insufficient folic acid intake during pregnancy were proposed to increase the risk of CL/P. However, this finding is still debated.

【Methods】 A case-control study carried out on 307 nonsyndromic CL/P (cleft lip (CL) 92, cleft lip and palate (CLP) 162, cleft palate (CP) 53) Mongolian patients, their 158 fathers, 220 mothers and 220 controls to examine whether the MTHFR C677T mutation was associated to an increased risk of the anomaly in Mongolia. Genotype frequencies were compared using a chi-squared test.

【Results】 No indication of significant differences for the proportions of CC, CT, TT genotypes was observed between total patients (CC 54.7%; CT 36.8%; TT 8.5%) and control groups (CC 54.5%; CT 37.7%; TT 7.7%) for either their parents or the controls. Nevertheless, when patients group were divided by cleft types and gender, a difference tendency ($p=0.09$) was found between female CP patients (CC 53.0%; CT 23.5%; TT 23.5%) and female control groups (CC 53.0%; CT 37.0%; TT 10.0%), respectively. Further significant differences were found between male CL and female CL ($p=0.01$), as well as male CP and female CP ($p=0.04$) when cases were compared by their subtypes of oral clefts.

【Conclusion】 The discrepancy in the distribution of MTHFR genotype among types of oral clefts reflects some heterogeneity in the development mechanism of nonsyndromic CL/P. The TT genotypes might contribute to the pathogenesis of cleft palate in Mongolian females.

【Key words】 nonsyndromic cleft lip with or without cleft palate; cleft palate; 5,10-methylenetetrahydrofolate reductase; polymorphism; Mongolians

P 281

Toward an evidence-based speech-audio-verbal therapy practice in Mongolia: 12 years of experience

Ariuntuul Garidkhuu DDS., PhD., FICD
School of Medicine, International University of Health and Welfare (Japan)
School of Dentistry, Mongolian National University of Medical Sciences (Mongolia)

In 2007, the School of Dentistry, Health Sciences University of Mongolia with the support of the Japanese Cleft Palate Foundation, established the first Speech Treatment Clinic for children with clefts, pioneering the development of Speech Pathology nationwide. Respectively, since August of 2009 the team successfully started Audio Verbal Therapy (AVT) for the very first congenitally deaf child with cochlear implantation in Mongolia by laying foundation for future progress of AVT nationwide. This joint project represents common model of international cooperation with grassroots in developing countries to transfer knowledge and . Exploring effective “university - international institution” relations and the

issues facing within the process of operation of clinical speech therapy practice, thu. It might serve as an example and good practice for the countries, where speech, audio verbal therapy is launching or developing. The strength of the current "university-international institution" model is that it based on the local academic higher education institution – country`s catalyst for innovation, research and development. Without research and knowledge-based platform it is challenging to think about sustainability. Thus, the goal of founding evidence-based speech pathology in Mongolia intended to carry out preliminary and population-based studies beside clinical practice. Even though in the past 12 years tangible progress was made in the area of speech therapy for disabled Mongolian children, comprehensive studies and assessments are still limited.

The latest development of research-based speech pathology and treatment will be shared. Future building of human capacity and strategic planning at the governmental level as well as joint research projects are needed.

P 401

The role of extracellular matrix proteins in enteric neural crest cell migration

Hisayoshi Yoshizaki, Shoichi Nishida, Yoshitomo Yasui, Tuyoshi Kuwahara and Miyuki Kohno
Department of Pediatric Surgery, Kanazawa Medical University (Japan)

【Background and purpose】 Hirschsprung's disease (HSCR) is a rare congenital disease (1 in 5000 live births) in which the enteric nervous system (ENS) is missing from distal bowel. The ENS is a network of neurons and glia, which are derived from enteric neural crest cells (ENCCs). In many cases, genetic mutations that suppress ENCC motility lead to HSCR. Therefore, to understand the pathology of HSCR, we investigated the molecular mechanisms of ENCC migration and colonization in the intestine for the formation of the ENS.

【Methods】 For analysis of mouse intestinal development by microarray, RNA were purified from whole intestines that were surgically dissected at E11.5 and E15.5. Labeled cRNA were synthesized from sample RNA using a GeneChip WT PLUS Reagent Kit and were hybridized on a Clariom™ D Assay, Mouse (Affymetrix). The microarray data were analyzed by using Transcriptome Analysis Console Software (Affymetrix). Embryonic mouse ENCCs were grown as neurospheres before adhesion assay or transplantation into mouse hindgut explants. Cell adhesion, engraftment and neural differentiation were confirmed using immunofluorescence microscopy.

【Results】 We first compared gene expression in the intestine between at E11.5 and E15.5 and identified 1355 transcripts that were differentially expressed. Among those transcripts, we found gens coding for extracellular matrix (ECM) proteins were enriched. Of note, collagen VI family members were upregulated in E15.5 mouse intestine at the mRNA and protein levels, while fibronectin was decreased. To understand the mechanisms of collagen VI and fibronectin in ENCCs migration, we examined neurosphere or individual ENCCs adherence capabilities toward ECM. collagen VI suppressed fibronectin-induced cell migration of ENCCs. Finally, we show the new method to avoid the inhibition of transplanted ENCCs invasion by treatment of collagenase to recipient colon.

【Discussion】 In this study, we demonstrate that ECM expression significantly altered during mouse intestinal development by microarray analysis. These significantly altered genes involved many known genes related to ENS development and HSCR. This suggest that our dataset can help to elucidate the gene function for ENS development and their role in HSCR.

【Conflict of interest】 There is no conflict of interest for the studies in this presentation.

【Grants】 This work was supported by JSPS KAKENHI (Grant Numbers 16K15743 and 17K17008)

P 402

Application of X-ray micro-computed tomography (micro-CT) for fetal skeletal examination in developmental toxicity study in rats

Ryo Ihara, Terumasa Taniguchi, Kensho Matsuda, Katsumasa Iwashita, Toru Utsumi
Sumitomo Chemical Co., Ltd. Environmental and Health Science Laboratory (Japan)

【Background】 In developmental toxicity study, fetal skeletal abnormalities have been consistently evaluated by alizarin red staining method for over 50 years. Recently, high-resolution imaging modalities have been developed and the use of micro-CT is expected to be an alternative method for fetal skeletal examination. Micro-CT evaluation has some advantages over the traditional staining method. For example, skeletal examination can be conducted immediately after the caesarian sectioning and the procedures without fetal fixation and staining allow for both skeletal and visceral examinations of all fetuses even in rats. However, few studies have reported that micro-CT is utilized for fetal skeletal examination so far because of new technology and method.

【Purpose】 The purpose of this study was to evaluate the practical applicability of micro-CT for fetal skeletal examination in developmental toxicity study in rats.

【Method】 RCC:Han Wistar pregnant female rats (10 animals/group) were administered vehicle or boric acid at 100, 200 and 400 mg/kg/day from Day 6 to 11 of gestation. After caesarean sectioning on Day 20 of gestation, fetuses were imaged by micro-CT. Scan conditions were set as follows; voltage: 50 kV, current: 160 μA, voxel size: 90 μm, scan time: 4 minutes. After micro-CT scanning, fetuses were eviscerated, fixed with alcohol and then stained with alizarin red S. Fetal skeletal 3D images constructed by micro-CT and stained specimens were examined separately, and those evaluations were compared with each other.

【Result】 In all the treated groups, several skeletal alterations were observed. Those alterations included fused cervical arches, cervical ribs, absent/short 13th ribs, presacral vertebra 25, and/or bipartite ossification of sternebra. In addition, incomplete ossification of skull and unossified bones as well as reduced number of ossified sacrococcygeal centrums, which were indicative of growth retardation as manifested by low fetal body weight, were observed in 400 mg/kg/day group. Micro-CT could detect almost all types of skeletal alterations and the incidences of those alterations were comparable with alizarin red staining evaluation. Although some rudimentary

skeletal elements and low-density skeletal bones could not be detected by micro-CT, these differences did not impact on the evaluation of skeletal alterations.

【Discussion】 These results indicate that skeletal alterations as well as ossifications can be evaluated properly by micro-CT, and micro-CT could be shown to be well suited for high-throughput fetal skeletal evaluations in rat developmental toxicity study.

P 403

Factors determining the timing of closure and opening of eyelids in the Hatano rats

Haruka Nishiya[1)], Kenta Morinaga[2)], Mieko Shimizu[2)], Ryo Ohta[3)], Mariko Shirota[4)]
[1)]Laboratory of Comparative Toxicology, School of Veterinary Medicine, Azabu University (Sunplanet Co., Ltd.)
[2)]Laboratory of Comparative Toxicology, School of Veterinary Medicine, Azabu University
[3)]Hatano Research Institute, Food and Drug Safety Center
[4)]Laboratory of Comparative Toxicology, School of Veterinary Medicine, Azabu University (Faculty of Agriculture, Tokyo University of Agriculture and Technology) (Japan)

【Background】 In the course of development, the eyelids close for a certain time during the fetal period and then open. The timing of eyelid opening is one of the landmarks for physical development of the offspring in the reproductive/developmental toxicity studies; however, factors affecting the timing have not been well established. Inbred strains of Hatano rats consist of two sub-strains, low-avoidance animal (LAA) and high-avoidance animal (HAA). Even after accelerating neonatal growth under foster dams, LAAs complete eyelid opening at an older age than HAAs. Histological examination of eyelid tissues toward the time of opening has revealed that epithelial development of the eyelid commenced later in the LAAs, but the timing of eyelid closure has not been determined.

【Purpose】 To examine the involvement of the intrauterine environment and genetic factors in determining the timing of closure and opening of the eyelids, we compared the timing of eyelid closure and fetal growth between LAAs and HAAs and between their crosses from LAA dams (LH) and HAA dams (HL). The timing of eyelid opening was also compared between the LHs and HLs.

【Methods】 Fetuses were obtained on day 18 of pregnancy by caesarean section and were individually weighed. The number of fetuses that completed closure of both eyelids was determined to calculate the ratio of rats with closed eyelids to the litter size (eyelid closure rate). Skeletons were stained by the Dawson's method and were examined for ossification to determine fetal growth. To determine the timing of eyelid opening of the LHs and HLs, dams were allowed to deliver spontaneously and nurse their own offspring.

【Results and discussions】 The eyelid closure rate of LAA was higher than that of HAA. LAA also exhibited heavier weight and higher degree of ossification than HAA. Since birth weight of LAAs is known to be higher than that of HAAs, the LAAs seem to grow faster in utero and to complete eyelid closure earlier than HAA. LHs and HLs are genetically identical, but the eyelid closure rate of LH was higher than that of HL and LHs also exhibited heavier weights than HLs. In contrast, the timing of eyelid opening was comparable between LH and HL, although HL was heavier than LH probably because of better nursing conditions under the HAA dam. From these results, the timing of eyelid closure and opening could be strongly affected by the intrauterine environment and genetic factors, respectively.

COI: No conflicts of interest, financial or otherwise, are declared by the authors.

P 404

Nutritional study in L-proline on cultured rat embryo

Masaharu Akita[1)], Atsushi Yokoyama[2)], Hiroshi Yokoyama[3)] and Roberto Los[3)]
[1)] Kamakura Women's University (Japan)
[2)] Life Science Laboratory of Kanagawa
[3)] University of Baltimore (USA)

【Purpose】 We have developed the teratogen test for drug and chemical compound of food by the use of rat whole embryo culture. The advantages of whole embryo culture are to examine the direct effects of the L-proline on rat cultured embryo.

【Method】 Rat embryos on day 11.5 of gestation (plug day = 0) were cultured for 48 hours with L-proline. In this whole embryo culture system, rat embryos were explanted on day 11.5 gestation and cultured of rat serum with complex gas (95 % O2 and 5 % CO2) using improved rotator for 48 hours.

【Results and Discussion】 The group of treated embryos of L-proline were not exchanged in the heart beats (157 ± 3), the crown-rump length (8.9 ± 0.1 mm), the embryonic protein contents (4,700 ± 44μg) and the embryonic total number of somites (56 ± 0.9). The malformation was not observed in the cultured embryos with L-proline. On the other hand, L-proline (the metabolite of L-arginine) treatment group was not changed in blood flow on the tail of cultured rat embryos.

P 405

Study of the mechanism(L-arginine) on cultured rat embryo

Atsushi Yokoyama[1)], Masaharu Akita[2)], Hitoshi Yokoyama[3)]
[1)] Life Science Laboratory of Kanagawa
[2)] Kamakura Women's University
[3)] Laboratory of Hyogo Clinical Medicine (Japan)

【Purpose】 The mechanism of the L-arginine effect on cultured rat embryos is important to understand gut development of rat embryo. We were reported to the effect of L-citruline on cultured rat embryos in the 58th annual meeting of the Japanese teratology society. In this meeting, the advantages of whole embryo culture are to examine the direct effects of the L-arginine of L-citruline metabolite on rat cultured embryo.

【Method】 Rat embryos on day 11.5 of gestation were cultured for 48 hours with L-arginine. In this whole embryo culture system, rat embryos were explanted on day 11.5 gestation and cultured of rat serum with 95 % O2 and 5 % CO2 using improved rotator for 48 hours.

【Result and Discussion】 The group of treated embryos of

L-arginine were not exchanged in the heart beats (153 ± 2), the crown-rump length (8.6 ± 0.2 mm), the embryonic protein contents (4,670 ± 41μg) and the embryonic total number of somites (56 ± 0.3). The malformation was not observed in the cultured embryos with L-arginine. On the other hand, the group of treated embryos of L-arginine significantly increased in blood flow on the tail of cultured rat embryos.

P 406

Decreased Gelatinase Activity at the Optic Fissure Margins in Murine Colobomatous Eyes

Yuta Iizuka, Kiyokazu Ozaki, Atsushi Miyazaki and Tetsuro Matsuura
Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University, Hirakata (Japan)

【BACKGROUND】 Failure of basement membrane degradation at the optic fissure margins causes ocular coloboma in human and mouse. We have reported that matrix metalloproteinases (MMPs) including gelatinase might involve in basement membrane degradation during normal murine eye development.

【PURPOSE】 In this study, we attempted to clarify the relationship between gelatinase activity and disturbed basement membrane disintegration in murine colobomatous eyes.

【METHOD】 Serial coronal frozen sections of eyes from FLS and F1 (FLS×CBA) fetuses at gestation day (GD) 11.5 to 13.0 were prepared at each stage, and gelatinase activity was examined using an in situ FITC-conjugated zymography technique. The same sections were also immunohistochemically stained with anti-type IV collagen for detection of basement membrane.

【RESULT】 The mean positive ratio of FITC fluorescence at the optic fissure margins reached a peak at GD 12.0, and the fluorescence became less active after that with no significant difference between FLS and F1 mice. However, in some eyes of FLS fetuses at GD 12.0, rolling on one side of fissure margins and asymmetry were observed, and type IV collagen-positive basement membranes clearly persisted at the optic fissure margins. Thus, these abnormal eyes were judged as ocular coloboma. The mean positive ratio of FITC fluorescence in the colobomatous eyes was significantly lower compared to normal F1 eyes at GD 12.0. Meanwhile, there was no significant difference in the mean positive ratio of FITC fluorescence of normal eyes between FLS and F1 fetuses at GD 12.0.

【DISCUSSION】 Decreased gelatinase activity may be involved in disturbed basement membrane degradation at the optic fissure margins of colobomatous eyes in FLS fetuses.

P 407

Relation between Macrophage Recruitment and Basement Membrane Disintegration at Optic Fissure Margin in Murine Ocular Coloboma

Atsushi Miyazaki, Kiyokazu Ozaki, Yuta Iizuka and Tetsuro Matsuura
Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University, Hirakata (Japan)

【Background】 Typical coloboma is a congenital ocular anomaly in human, and is caused by a failure in closure of the embryonic fissure of the optic cup due to disturbed basement membrane disintegration at the optic fissure margins. Previous studies have suggested that macrophage recruitment might involve in basement membrane disintegration at the optic fissure margins during normal murine ocular development.

【Purpose】 This study was attempted to clarify the relationship between macrophage recruitment and disturbed basement membrane disintegration at optic fissure margins in colobomatous eye.

【Method】 Female FLS mice were mated with male FLS mice or male CBA mice, and fetuses at gestation day (GD) 11.5 to 13.5 were obtained from dams. Coronal serial sections through the eye were made and the sections were followed by immunohistochemical stain with anti- F4/80 or anti-MMP 2 antibodies. Then the sections were examined by light microscopy.

【Result】 In normal eyes of F1 (FLS×CBA) fetuses, the number of F4/80-positive cells at the ventral optic cup increased or decreased during experimental period, and showed 2 peaks at GD 12.0 and GD 13.0 on the serial paraffin sections. Meanwhile, in eyes of FLS fetuses, the number of F4/80-positive cells was significantly reduced at GD 12.0 compared to F1 fetuses. In addition, some of macrophage was positive for MMP 2 (gelatinase A), and the number of MMP 2-positive cells at the anterior side (beneath the lens) of ventral optic cup in FLS fetuses at GD 12.0 tended to decrease compared to F1 fetuses.

【Discussion】 Disturbed macrophage recruitment and decrease of intramacrophage MMP 2 expression may cause failure of basement membrane disintegration at optic fissure margins in colobomatous eyes of FLS fetuses.

P 408

Relationship between hydronephrosis and eosinophil infiltration in mutant mice derived from C57 BL/6 strain

Matsumoto A, Ozaki K, and Matsuura T
Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University, Hirakata (Japan)

【Background】 We have reported relatively frequent incidence of a characteristic hydronephrosis in a colony of C57 BL/6 strain of mice. The mutant line was established as an inbred strain (abbreviated as B6-Hy strain) from brother and sister mating. The incidence of hydronephrosis was approximately 20% after 7 weeks of age, and hydronephrotic kidney showed severe atrophy of renal parenchyma accompanied by stenosis of the proximal ureter with epithelial proliferation and substantial inflammation consisting of eosinophils, lymphocytes, macrophages and plasma cells at ureteropelvic junction. Meanwhile, dilatation of renal pelvis was hardly detected macroscopically in both sexes of B6-Hy strain aged 5 weeks, whereas the number of eosinophils in urinary tract was increased compared to ICR mice.

【Purpose】 We considered eosinophil recruitment was important for hydronephrosis formation in B6-Hy strain, and tried to clarify when and how the eosinophil inflammation might involve in hydronephrotic lesion in this strain.

【Method】 As an inherited hydronephrosis model, male and female B6-Hy mice were examined at 1, 2, 3, 5, and 8 weeks

of age. Age-matched C57 BL/6N strain of mice was used as control animals. Kidney along with ureter was removed, hydronephrosis (dilatation of renal pelvis) was judged macroscopically from cutting surface of kidney, and they were subjected to histopathological examination after making serial sections. Then, the number of eosinophils at ureteropelvic junction showing no dilatation of renal pelvis was counted light microscopically at each stage.

【Result】 Even at 1 week of age in B6-Hy strain, the number of eosinophils invading the submucosal tissue and the peri-ureter tissue has significantly increased compared to C57 BL/6N strain. Eosinophils extended to the epithelia of ureter at 3 weeks of age in B6-Hy strain, and the number of eosinophils significantly ascended compared to C57 BL/6N strain at 5 weeks of age. Meanwhile, the number of eosinophils invading the submucosal and peri-ureter tissue has slightly increased with age in C57 BL/6N strains, but there was no highly-developed inflammation and following epithelial proliferation in C57 BL/6N strain.

【Discussion】 Eosinophil infiltration precedes the other inflammatory cells accompanied by stenosis of the proximal ureter with epithelial proliferation in B6-Hy strain. Eosinophils may response to minute amounts of Ym proteins first of all at preweaning stage in this strain.

P 409

Normal process of cerebellar cortical histogenesis during postnatal life in ferrets

Shiori Kamiya , Kazuhiko Sawada
Department of Nutrition, Faculty of Medical and Health Sciences, Tsukuba International University, Tsuchiura (Japan)

【Background】 A disturbance of morphological lateralization of the cerebellum is reportedly involved in human neurodevelopmental disorders such as autism and schizophrenia. Ferrets have a striking asymmetric aspect of the cerebellar morphology, as well as humans and non-human primates. However, many studies have been reported with regard to cerebellar cortical histogenesis mainly in mice and rats, but a few in other mammals including ferrets.

【Purpose】 The purpose of this study was to characterize immunohistochemically the normal process of the cerebellar cortical histogenesis in ferrets.

【Method】 Ferrets consisting of three animals each at postnatal days (PDs) 4 to 90 were perfused. Cryosections were made in the midsagittal plane, and immunohistochemistry with DAB detection was performed using markers for cerebellar neurons and glial cells.

【Result】 On PD 4, Calbindin D-28k-immunopositive Purkinje cells were arrayed in 2 to 3. GAD 65/67 immunostaining appeared in puncta with rosette-like arrangements at glomeruli in the inner granular layer (IGL). PCNA-positive cells were seen in the outer stratum of the external granular layer (EGL). At PD 10, Calbindin D-28k-positive Purkinje cells aligned in a monolayer, and some of their somata exhibited weak parvalumin immunostaining. GFAP-positive Bergman glial processes aligned vertically in the molecular layer and EGL. At PD 21, the EGL including PCNA-positive outer stratum were still sustained. Purkinje cells were strongly stained with anti-parvalbumin, as well as anti-Calbindin D-28k, and their dendritic arbors were further developed. Parvalbumin immunostaining also appeared in basket cell somata located in the lower half of molecular layer. At PD 42, the EGL disappeared. PCNA immunostaining was seen alternatively in cells aligned throughout the Purkinje cell layer. A similar alignment of S100 protein-positive cells (Bergman glial somata) was obtained by PD 90. By PD 42, Calbindin D-28k- and parvalbumin-defined Purkinje cells formed their mature aspects, and parvalbumin-positive stellate cells were observable in the upper half of the molecular layer. In the IGL, the rosette-like arranged GAD 65/67-positive puncta were increased in number.

【Discussion】 The results reveal that ferrets experience cerebellar corticohistogenesis during postnatal life in similar sequences with rodents. The findings will provide useful information for investigating neurodevelopmental disorders with disturbed cerebellar asymmetry such as autism and schizophrenia using ferrets as a model animal.

P 410

Maternal nutritional status during pregnancy in Shimane Prefecture: Second report - A comparison by meal skipping -

Yukiko Kagohashi[1)], Yoko Nakatani[1)],
Reiko Nagashima[1)], Aiko Katsube[2)],
and Hiroki Otani[3)]
[1)]The University of Shimane
[2)]Shimane Prefectural Central Hospital
[3)]Faculty of Medicine Shimane University (Japan)

【Background】 It is reported that the birth rate of low birth weight babies in Shimane prefecture is the third largest nationwide, and the average of birth weight is reported to be about 30 g less than the national average, and there is a possibility of various risks in the future of the babies.

【Purpose】 We investigate nutritional intake situation, dietary behavior, and food consciousness of pregnant women in Shimane Prefecture and we are studying the relevance to birth weight of babies.

【Methods】 In this study, we examined the frequency of food intake in 26 pregnant women from 10 to 12 weeks (early), around 26 weeks (middle) and 36 weeks (late), and compared the nutrient intake by the difference in the state of meal skipping (skipped vs non-skipped) during pregnancy and birth weight of babies.

【Results & Discussion】 In the early pregnancy group, 38.4% of pregnant women skipped meals more than once a week, and it was suggested that many of the nutrients were less than the amount recommended by the Ministry of Health, Labour and Welfare, Japan. In the middle and late pregnancy groups, 23.0% and 30.7% of pregnant women skipped meals more than once a week, respectively. The average of birth weight of babies were 2993.3 ± 384.1 grams in the non-skipped group and 3102.7 ± 273.8 grams in the skipped group at the early pregnancy and there were no significant differences. We are currently increasing the case number and investigating nutritional situation during pregnancy. This study was approved by the institutional Ethics Committee. COI: NONE

P 411

A case of 4p- Syndrome with cleft palate treated with push-back palatoplasty

Goro Sugiyama[1)], Tomohiro Yamada[1)], Azusa Nakashima[1)], Kosuke Yasuda[1)], Shiho Tajiri[1)], Sachiyo Hasegawa[2)] and Yoshihide Mori[1)]
[1)]Section of Oral and Maxillofacial Surgery, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University
[2)]Department of Oral and maxillofacial Surgery Kyushu University Hospital (Japan)

【Background】 4p- Syndrome is a syndrome with multiple congenital anomalies caused by the deletion of genomic material in the short arm of chromosome 4p. Patients have multiple symptoms such as growth and psychomotor retardation, a characteristic facial appearance, heart trouble and ophthalmologic abnormality. Cleft lip and palate are also occurred relatively a lot with 4p- syndrome. Hence, feeding difficulties and articulation disorders are clinical problems in oral and maxillofacial region. Here we report a case of 4p- Syndrome patient with cleft of soft palate treated with conventional push-back palatoplasty.

【case】 The female patient was born after 40-week pregnancy at 2010 g and Apgar score 8/9, and was referred to our department because of cleft palate. Because postnatal growth disturbance was gradually actualized, investigation of chromosome aberration was performed on and revealed 4p-syndrome. Although feeding difficulties was not remarkable, the palatoplasty by push-back method was performed on under general anaesthesia at 2 years and 8 months old (height; 72.9cm, weight ; 6.1 kg) because of risk for articulation disorder in the future. Two years after surgery, the postoperative course of the patient is favorable, and gain of speech function is advancing.

P 412

Maternal nutritional status during pregnancy in Shimane Prefecture : Second report
- Comparison among early, middle and late pregnancy –

Yoko Nakatani[1)], Yukiko Kagohashi[1)], Reiko Nagashima[1)], Aiko Katsube[2)] and Hiroki Otani[3)]
[1)]The University of Shimane
[2)]Shimane Prefectural Central Hospital
[3)]Faculty of Medicine Shimane University (Japan)

【Background】 In Shimane prefecture, the birth rate of low birth weight infants is higher than the national average, and the incidence of future non-communicable disease may increase.

【Purpose】 To investigate relationship between nutritional intake and birth weight of offspring in pregnant women in Shimane prefecture.

【Methods】 In this study, we examined the food intake, We examined food intake, dietary and health consciousness in 26 pregnant women (average age, 29.8 ± 4.6 years) from 10 to 12 weeks (early), around 26 weeks (middle) and 36 weeks (late) of gestation. We then analyzed the relationship between nutrient intake in each pregnancy period and birth weight.

【Results & Discussion】 Among 26, 14 were primiparas (53.8%) and 12 were multiparas (46.2%). Twenty-three (88.5%) had occupation, and three (11.5%) did not. Four (15.4%), 21 (80.8%), and one (3.8%) women had pre-pregnancy BMI in the "low body weight (≦ 18.5)" , "normal(18.5 ≦ ＜ 25.0)", and "obese (25.0 ≦ ＜ 30.0)" range, respectively. The average hemoglobin values were 12.5 ± 0.6 g/dl, and 11.2 ± 0.7 g/dl in early and late pregnancy, respectively. The average increase in body weight during pregnancy was 10.4 ± 3.2 kg, and the average birth weight of the offspring was 3035.4±344.2 g. The average birth weight of boys (15, 57.7%) and girls (11, 42.3%) was 3112.7 ± 346.1 g and 2929.9 ± 327.5 g, respectively. One (3.8%) was less than 2500 g. There was no correlation between the birth weight and pre-pregnancy BMI or weight gain during pregnancy. The amount of nutrient intake in most of the pregnant women in each pregnancy period is less than that recommended by the Ministry of Health, Labor and Welfare. Among 26, twenty-two (84.6%, early), 20 (76.9%, middle), and 16 (61.5%, late), respectively, reported having stress and fatigue. The average birth weight tended to be heavier in the non-stressed group than in the stressed group. The total scores for dietary behavior and food consciousness were not different at each pregnancy period. We are currently investigating the nutritional status at the one-month checkup. This study was approved by the institutional Ethics Committee. COI: NONE

P 413

Morphological differences of rib and transverse process of lumber vertebra between two rat strains

Yoshinori Hosokawa, Kensho Matsuda, Misaki Matsumoto, Katsumasa Iwashita, Toru Utsumi
Sumitomo Chemical Co., Ltd. Environmental Health Science Laboratory (Japan)

【Background】 Supernumerary ribs are a common skeletal variation and defined as any degree of ossification lateral to the first lumbar vertebrae. It is known that the supernumerary ribs of rat fetuses are reversible during postnatal development; however, the morphological characteristics of supernumerary ribs and lumber vertebra, and the reversible process of the ribs have not been investigated in detail.

【Purpose】 The purpose of this study is to investigate the characteristics of rib and lumbar vertebra during reversible process in two rat strains with different incidences of spontaneous supernumerary ribs.

【Method】 The incidences of supernumerary ribs were examined in fetuses, neonates, and adult rats. In addition, the morphological characteristics of rib and lumber vertebra were also examined in adult rats. This experiment was conducted on two rat strains; BrlHan:WIST@Jcl(GALAS) rats with a high spontaneous incidences of supernumerary rib and Crl:CD(SD) rats with a low one. Fetuses and neonates were examined after alizarin red S staining, and adults were scanned by micro-CT.

【Result】 Short supernumerary ribs (SR) occurred in 74.3 % of fetuses and 82.8% of neonates in GALAS rats, and in 1.8 % of fetuses and 9.3 % of neonates in SD rats. Full supernumerary ribs (FR) occurred in approximately 15% of fetuses and neonates in GALAS rats, but not in SD rats. In adult rats, the incidences of SR and FR occurred in 9.5 and

13.5 % in GALAS rats, respectively, whilst these SR or FR were not observed in SD rats, implying that the occurrence of SR in both strains were restored. Also, various morphological structures in transverse process of first lumber vertebra were found, and these findings occurred in 37.8 % and 10.0% in GALAS and SD rats, respectively. In proximal portion of 13th rib, various morphological structures were observed in 25.0 % of SD rats, and the structures are similar to the supernumerary ribs observed in GALAS rats.

【Conclusion】 These results indicate that there are differences in the incidences of supernumerary ribs and in structural characteristics of rib and transverse process of lumber vertebra between two rat strains, whilst from a fact that GALAS rats with high spontaneous incidences of supernumerary ribs do not show any negative performance of viability, growth, behavior, reproduction and so on as compared with those of SD rats, it is considered that supernumerary ribs not accompanying any malformation have little toxicological impact.

P 414

Research on the mechanism of thoracolumbar supernumerary rib development after birth using CT scanning in rats.

Makiko Kuwagata[1)], Fumiaki Kumagai[2)], Mika Senuma[2)], Mai Todoroki[2)]
[1)]Division of Cellular and Molecular Toxicology, Center for Biological Safety and Research, National Institute of Health Sciences
[2)]Division of Safety, Hatano Research Institute, Food and Drug Safety Center (Japan)

【Background and Purpose】 Thoracolumbar supernumerary rib (TSR, 14th rib) is classified as a variation and has been observed with relatively high incidence in rodent reproductive and developmental toxicity studies.

To investigate the toxicological significance of TSR, postnatal morphological changes of TSR in the same animal were monitored using 3D micro X-ray computed tomography scanning.

【Method】 0 (vehicle, 0.5% sodium carboxymethyl cellulose solution), 35 or 75 mg/kg of 5-flucytosine (5-FC), which is an oral antifungal drug and is known to inhibit cell division, was administered to Sprague-Dawley rats orally on gestational day 9, as in previous studies. After delivery, offspring were examined for rib morphology using 3D pictures and the lengths of the ribs were measured by maximum intensity projection (MIP) images, until 9 weeks of age. The types of TSR were categorized into rudimentary, short and full types based on their shape and length.

【Result and Discussion】 5-FC induced TSR in offspring in a dose dependent manner without maternal toxicity. In order of decreasing incidence, the TSR types were rudimentary, full and short types, in both 5-FC treated groups. In the control groups, only rudimentary TSR were observed.

CT scanning revealed that TSR developed and that the lengths of the 13th and 14th ribs extended with growth. However, the ratio of the14th rib to the 13th rib did not change during the postnatal period. These results indicate that the extension of TSR does not exceed the normal range after birth.

Supported by
The Food Safety Commission, Cabinet Office, Government of Japan (Research Program for Risk Assessment Study on Food Safety, Grant No. 1607)

P 415

The effect of granulocyte macrophage-colony stimulating factor on histogenesis of the mouse embryonic brain

Akihiro Matsumoto[1)], Ashiq M Rafiq[2)], Fumio Satow[1)], Ryuju Hashimoto[3)], Toshihisa Hatta[4)], Hiroki Otani[1)]
[1)] Department of Developmental Biology, Faculty of Medicine, Shimane University, Shimane
[2)] Center for the Promotion of Project Research, Organization for Research, Shimane University, Shimane
[3)] Department of Clinical Nursing, Faculty of Medicine, Shimane University, Shimane
[4)] Department of Anatomy I, Kanazawa Medical University, Ishikawa (Japan)

【Background】 Granulocyte macrophage-colony stimulating factor (GM-CSF) is a multifunctional cytokine, originally found as one of hematopoietic cytokines. Recent studies reported its activities on neuronal progenitor cells in vitro, however, its function in the brain development in vivo remains unclear.

【Purpose】 The purpose of this study is to elucidate the function of GM-CSF in the brain development in vivo by creating the mouse embryo model of excess GM-CSF in the cerebrospinal fluid by injecting GM-CSF into lateral ventricle exo utero, and to analyze the effect of excess GM-CSF in the histogenesis of developing mouse brain.

【Method】 We injected GM-CSF into the lateral ventricle of embryos on embryonic day (E) 13 and let them develop until E15 by exo utero development system. Whole brain tissues were dissected from E15 embryos, and then fixed in fixative containing 10% formalin and 70% methanol overnight. By following conventional tissue processing, paraffin section slides were prepared. Tissue sections were examined by immunohistochemistry; primary antibodies against GM-CSF, GM-CSF-receptor-α, bromodeoxyuridine (BrdU), doublecortin, γ-tubulin, and phalloidin were used for analysis.

【Result】 From histological analysis, luminal surface of the ganglionic eminence became irregular and formed ‘bulge’ by disarrangement of the neuroepithelial cells in the GM-CSF-injected brain, whereas these histological changes were not observed in the other parts of cerebrum such as the cerebral cortex. There seemed to be a regional specificity of such a histological change in the brain. From immunohistochemical analysis, these irregular cells were positive for doublecortin which is expressed in neuronal progenitor cells, whereas negative for BrdU which is incorporated into S-phase cell nuclei. Moreover, the apico-basal cell polarity that is normally observed in neuroepithelial cells was disturbed in these cells from observation of the distribution of primary cilia and cytoskeletons.

【Discussion】 Previous in vitro studies reported that effects of GM-CSF were modulation of proliferation, differentiation, and apoptosis of neuronal progenitor cells. In this study, the

observed irregular cells in the GM-CSF-injected brain appeared to have lost proliferative activity, expressed doublecortin to start differentiation, but their migration was prevented, and then they were accumulated at the luminal surface around the ganglionic eminence. These results suggest that GM-CSF signaling may be related with regulation of proliferation of neuroepithelial cells, apico-basal cell polarity, and migration of post-mitotic neuronal progenitor cells in the ganglionic eminence of mouse embryonic brain.
This work was supported by KAKENHI (15K08135).
COI: None

P 416

DYRK1A-related syndrome in 2 individuals with facial asymmetry and microphthalmia

Yuma Takahashi[1,2], Toru Kato[1], Takeshi Tsuji[1], Toshifumi Suzuki[3], Noriko Miyake[4], Naomichi Matsumoto[4], Kenjiro Kosaki[5], Seiji Mizuno[6]
[1] Department of Pediatrics, Okazaki City Hospital
[2] Department of Pediatrics, Nagoya University School of Medicine
[3] Department of Obstetrics and Gynecology, Juntendo University School of Medicine
[4] Department of Human Genetics, Yokohama City University Graduate School of Medicine
[5] Center for Medical Genetics, Keio University School of Medicine
[6] Department of Clinical Genetics, Central Hospital, Aichi Developmental Disability Center (Japan)

【Background】 DYRK1A located in chromosome 21 carries out different functions during development, and has an important role in controlling brain growth through neuronal proliferation and neurogenesis. Recently, truncating variant and deletion in DYRK1A have been shown to be responsible for intellectual disability and are characterized by microcephaly, developmental delay and distinctive facial features. Other common observations in the patients include febrile seizures, vision defects, brain abnormalities, and cardiac anomalies. We present two individuals with DYRK1A pathogenic variant showing facial asymmetry and microphthalmia; these features are less commonly seen in this syndrome.

【Case presentation】 Both individuals presented with the characteristic features of DYRK1A-related syndrome including developmental delay, intellectual disability, microcephaly, facial asymmetry, and microphthalmia. Both of them had low birth weight and unilateral microphthalmos with congenital cataract. Patient 1 presented with high muscle tone while Patient 2 had prominent ears. De novo mutations, 〔c.787C>T:p.Arg263*〕 and 〔c.247C>T:p.Gln83*〕 in DYRK1A were identified by whole-exome sequencing in Patients 1 and 2, respectively.

【Discussion】 Among hundreds of congenital anomaly syndromes caused by pathogenic variants of a single gene, only a few show facial asymmetry as their characteristic phenotype. These two cases suggest facial asymmetry to be one of the characteristic phenotypes of DYRKA1-related syndrome. Though OMIM only describes autosomal dominant mental retardation syndrome as a phenotype of DYRK1A heterozygous disruption, taken together with deep set eyes, nose, and ear shape, and intellectual disability, DYRKA1 syndrome can be considered to be a unique recognizable congenital anomaly syndrome. Long term follow-up of psychomotor development and growth would be needed to confirm delineation of its phenotype.

P 417

Preparation of whole-mount bone staining specimens in adult mice using a rapid tissue clearing system

Nobuo Kariyama[1], Hiromi Sakata-Haga[1], Tsuyoshi Tsukada[1], Hiroki Shimada[2], Toshihisa Hatta[1]
[1] Department of Anatomy, Kanazawa Medical University, Ishikawa
[2] Department of Medical Science, Kanazawa Medical University, Ishikawa (Japan)

We previously developed a rapid whole-mount bone staining procedure (RAP-B) for small fish and Xenopus laevis (Sci Rep, 2018), and for fetal rodents. Here, we present a novel procedure for whole-mount bone staining of adult mice based on RAP-B.

First, we examined hair removal treatments for adult mice. ICR or C57BL/6J mice were fixed with 4% paraformaldehyde phosphate buffer (PFA) by perfusion under deep anesthesia, and skin was collected from their backs. Skin pieces were immersed in a solution containing KOH with either calcium mercaptoacetate (CaMA) or sodium MA (SMA). The optimal solution composition for effective hair removal treatment was determined to be immersion in 2% SMA/3% KOH for 16 hours at 42°C. Next, we attempted to combine hair removal treatment with RAP-B using limbs of adult mice. Limbs were collected from mice perfused with 4% PFA and immersed in RAP fixative at 42°C for ≥24 h. After hair removal by immersion in 2% SMA/3% KOH at 42°C for 16 h, the limbs underwent RAP-B and were subsequently immersed in BABB (benzyl alcohol and benzyl benzoate mixture) after dehydration. Using this method, it was possible to prepare highly transparent bone-stained limb specimens within five days. This new procedure combining hair removal treatment and RAP-B was also effective for whole-mount bone staining in adult mice after evisceration. Because this procedure is faster and easier than conventional procedures, it has the potential to become the new standard procedure for whole-mount bone staining. Using this method, highly transparent soft tissues, such as brain, spinal cord, and most skeletal muscle and blood vessels, can be preserved without destruction; therefore, making the procedure suitable for deep imaging.

This work was supported by KAKENHI (15K09713 and 18K11659). COI: None

P 418

Functions of fibroblast growth factor signaling in osteoblast differentiation.

Erika Kubota[1], Masaki Takechi[2], Michiyo Miyashin[1], Sachiko Iseki[2]
[1] Pediatric dentistry, Graduate School of Medical and Dental Sciences, Tokyo Medical

and Dental University (TMDU),
[2)]Section of molecular craniofacial embryology,
Graduate School of Medical and Dental Sciences,
Tokyo Medical and Dental University (TMDU) (Japan)

【Background】It has been well known that fibroblast growth factor (FGF) signaling is involved in skeletal development. Since there are several FGFs among total 22 and three receptors reported to be involved in skeletal development, precise functions of FGF signaling have not been revealed, especially in osteogenesis.

【Purpose】In order to get some insights into functions of FGF signaling in osteogenesis, we carried out in vitro and in vivo studies by using FGF2 and 18, which are reported to be associated with osteogenesis.

【Method】KUSA-O (osteoprogenitor-like cell line) cells were used to study osteoblast differentiation. Calcification was induced by osteogenesis inducing medium (OIM; 10%FBS, 10mM β-glycerophosphate, 0.28mM ascorbic acid). Real-time RT-PCR was carried out with KUSA-O cDNA made from extracted RNA at subconfluent and 1 week after OIM treatment stages.

Heparin-coated acrylic beads soaked in PBS, FGF18 or FGF2 was transplanted subcutaneously in embryonic day 15.0 C57BL/6 mouse coronal suture area by ex utero surgery. The fetuses were collected after 48, 72 or 96 h. and directly embedded in O.C.T. compound for in situ hybridization. In situ hybridization of Fgfrs and osteoblast marker genes was carried out with digoxygenin (DIG)-labeled RNA probes visualized by nitro blue tetrazolium/5-bromo-4-chloro-3-indolyl-phosphate together with immunohistochemistry of N-cadherin, a marker of osteoblast.

【Result】KUSA-O cells demonstrated mineralization one week after treatment with OIM. At that time point RT-PCR showed Col1a1, Fgfr1, -2, and-3 expression levels increased during differentiation. Fgfr3 expression levels became robustly high in mineralizing period.

Expression of Fgfrs and osteogenic related genes and marker was investigated in the coronal suture area after bead treatment. FGF2 beads treatment caused decreased expression of osteogenic related genes, consistent with decreased N-cadherin expression. Fgfr1 expression was increased in the subcutaneous tissue area around the beads but not in bone forming layer. In bone forming layer, expression of Fgfr1, -2 and -3 was decreased. FGF18 beads treatment upregulated osteoblast marker gene expression and thickening of expression domains of osteoblast markers and Fgfr1, -2 and -3 at 96 h, which leads to the ambiguous frontal and parietal bone domain boundary.

【Discussion】This study demonstrated that Fgfr1, -2 and -3 signaling is positively involved in osteoblast differentiation. Especially, Fgfr3 expression was strongly upregulated according to calcification of Kusa-O cells in vitro. Although Fgfr3 signaling is related to chondrocyte differentiation marker, it is suggested it is also involved in mineralization stage of osteoblasts.

P 419

Expansion of phenotypic spectrum of EP300 mutations: Normal thumbs, coloboma, and imperforate anus

Rika Kosaki[1)], Kenjiro Kosaki[2)]
[1)] Division of Medical Genetics, National Center for Child Health and Development
[2)] Center for Medical Genetics, Keio University School of Medicine (Japan)

【Background】Rubinstein-Taybi syndrome (RSTS) is an autosomal dominant congenital malformation syndrome characterized by typical facial appearance (down slanting palpebral fissures, columella below the alae nasi), broad thumbs and halluces, and intellectual disability. Heterozygous mutations in CREBBP (50-60%) or EP300 (8-10%) have been detected among patients with clinical features of RSTS. Recently, a heterogeneous group of patients with CREBBP or EP300 mutations who have clinical features atypical for RSTS have been reported though exome analysis of undiagnosed patients. We here report three unrelated patients with EP300 mutations to expand phenotypic spectrum.

【Methods】Informed consent from the parents and approval from the local institutional review board were obtained prior to the molecular studies. Medical exome analysis [TruSight One V1] was performed following the GATK best practice guideline.

【Results】All the three patient had heterozygous mutation of EP300. Patient 1) 5-month-old male with some of RSTS including intellectual disability, broad thumbs, and ventricular septal defect. Nonsense mutation p.Gln965* was detected. Patient 2) 2-year-old female with atypical features of RSTS including intellectual disability, and normal thumbs. Missense mutation p.Val1656Ala was detected. Patient 3) 11-month-old female with double outlet right ventricle, myelomenigocele, hydrocephalus, imperforate anus, coloboma, and hearing impairment. Dual mutations were detected: EP300 frameshift mutation p.Gln2048Thrfs*24 and SOS1 Thr778Pro mutation.

【Discussion】We demonstrated the clinical variability of patients with EP300 mutations. Patient 1 with p.Gln965*, which truncates the HAT domain, exhibited classic RSTS features. Patient 2 with p.Val1656Ala, a missense mutation within domain carboxyl to the HAT domain, exhibited atypical features for RSTS. Patient 3 with dual mutations p.Gln2048Thrfs*24 and SOS1 Thr778Pro exhibited unusual features for RSTS such as coloboma and imperforate anus. These features could not be accounted for by the SOS1 mutation. Furthermore, the combination of coloboma and imperforate anus has been reported in a patient with a frameshift mutation (p.H815Tfs*128) in EP300 (Masuda et al. 2015). Recurrence of such a specific combination of defects suggests causal relationship. Phenotypic spectrum of EP300 mutations may be much broader than has been previously appreciated.

There are no conflicts of interest to declare.

P 420

Higher amount of the Fgf10 gene product is required for the accessory lobe formation and type 2 alveolar cell differentiation in the mouse lung as revealed by Fgf10-mosaic mutants generated by genome-editing

Munenori Habuta[1)], Akihiro Yasue[2)], Ken-ichi T Suzuki[3)], Hirofumi Fujita[1)], Tetsuya Bando[1)], Keita Sato[1)], Seiichi Oyadomari[4)], Eiji Tanaka[2)], Hideyo Ohuchi[1)]
[1)]Department of Cytology and Histology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,

[2)]Department of Orthodontics and Dentofacial Orthopedics, Institute of Biomedical Sciences, Tokushima University Graduate School,
[3)]Department of Mathematical and Life Sciences, Hiroshima University,
[4)]Division of Molecular Biology, Institute for Genome Research, Tokushima University (Japan)

【Background】 The genome-edited mice at founder generation (F0) often exhibit somatic mosaicism in the targeted gene(s). When the mouse Fgf10 gene is knocked out by the CRISPR-Cas9 system, a fraction of the founder mice exhibits typical limbless and lungless phonotypes as the classical gene-targeting technique was employed. The severity in the limbless phenotypes nearly depends on the mutation rate in the Fgf10 gene. However, lung phenotypes of Fgf10-mosaic mutants have not been studied.

【Purpose】 Here we examined variable lung phenotypes of Fgf10 genome-edited F0 mice to know relationship between lung and limb phenotypes, and whether the lung phenotype is correlated to the amount of the functional gene product for Fgf10 in the mutants.

【Method】 Fgf10-mosaic embryos were classified into three types according to Hashimoto and Takemoto (2015): type I, no limb; type II, limb defect; and type III, normal limbs. Deep sequencing of the Fgf10 mutant genomic DNA was performed. Histology of the mutant lung at embryonic day 16.5 (E16.5) was examined and immunohistochemistry of lung in the type III embryo (E18) was performed.

【Result】 Percentage of wild-type plus in-frame mutations, retaining nucleotides for the functional amino acids was 8.5 ± 8.6% (in type I), 25.3 ± 3.8% (type II), 54.3 ± 13.4% (type III), respectively (mean ± SD). In type II embryos, the accessory lung lobe was absent while in type I embryos, all lobes were absent or only a residual lobe was observed. The number of the lung tubules per unit area was counted and significantly decreased in type I and type II embryos, while that of type III embryos was not altered. Immunostaining by use of anti-prosurfactant protein C antibody showed that alveolar type 2 epithelial cells did not differentiate and development of the lung ceased at the canalicular stage while control (Cas9-minus) lung developed to the saccular stage.

【Discussion】 Thus, it is suggested that there is a correlation between the severity of lung phenotypes and that of limb phenotypes in the Fgf10-mosaic mutants. Higher amount of the Fgf10 gene product is needed to generate the accessory lobe in the mouse and to differentiate type 2 alveolar cells as well as to develop lung tubular morphogenesis to the saccular stage. (COI: none)

P 421

Quantitative analysis of lower extremity muscles in human fetuses using three-dimensional models

Yutaka Yamaguchi[1)], Ami Murase[2)], Hiroko Hashimoto[1)], Motoki Katsube[3)], Akira Yamamoto[4)], Kaori Togashi[4)], Shigehito Yamada[1, 2)]
[1)] Congenital Anomaly Research Center, Kyoto University Graduate School of Medicine
[2)] Department of Human Health Sciences, Kyoto University Graduate School of Medicine
[3)] Department of Plastic and Reconstructive Surgery, Kyoto University Graduate School of Medicine
[4)] Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine (Japan)

【Background】 Congenital and developmental musculoskeletal anomalies of the lower extremities are observed both sporadically and in association with various congenital disorders. The effect of impaired fetal movement on skeletal development has been reported in studies on animal models of fetal mechanical stimulation, and recent research suggests that normal prenatal musculoskeletal development is affected by mechanical forces generated by active fetal movements. Therefore, visualization of the normal developmental process in human fetal leg muscles can contribute to understanding of congenital and developmental musculoskeletal anomalies.

【Purpose】 Over 45,000 human embryo and fetal specimens are stored as the Kyoto Collection of the Congenital Anomaly Research Center, Kyoto University Graduate School of Medicine. Using this collection, this study aimed to reconstruct 3-dimensional (3D) models of human fetal leg muscles to visualize the developmental process and analyze the volume of these models.

【Method】 We selected 13 formalin-fixed human fetal specimens ranging from 90 mm to 225 mm in crown-rump length (CRL) from the Kyoto collection, and 3D-imaging of the selected specimens was performed using 3-T magnetic resonance imaging (MRI) at the Kyoto University Hospital. The lower limb length was measured and the developing muscles were segmented manually using MR data. Finally, the 3D models of the fetal leg muscles were reconstructed, and the muscle volume was determined with Amira software.

【Result】 We reconstructed 3D models of each leg muscle in 13 specimens. The measurements showed a correlation between CRL and lower limb length ($R2 = 0.96349$). The volume of each developing lower limb muscle increased sharply after 20 weeks. The rates of increase in the volume of the triceps surae, hamstrings, adductors, and quadriceps (except for the rectus femoris) were relatively prominent, and the triceps surae showed the most rapid increase after 20 weeks.

【Discussion】 Several studies reported that the frequency of movement peaks during the second trimester, followed by a decrease in frequency towards full term. This study showed an exponential increase in lower extremity muscle volume. Lower extremity movement occurs regularly starting at 15 weeks; therefore, it is presumed that muscle volume is correlated with fetal movement. Future research is needed with a larger sample size and more fetal specimens less than 15 weeks of age for analysis of quantitative changes during development.

P 422

Effects of feeding restriction in juvenile rats

Yuko Izumi, Tomoya Sano, Kiyoshi Matsumoto
Drug Safety Research and Evaluation, Research, Takeda Pharmaceutical Company Limited (Japan)

【Background】 In toxicology studies, body weights and food consumption are major toxicological endpoints, and decreases

in these parameters occur frequently as toxicological changes. In order to examine the effects of decreased food consumption on other toxicological parameters, feeding restriction (FR) was conducted in juvenile rats.

【Method】 Juvenile rats on postnatal day (PND) 21 were kept with FR of 40%, 50%, and 60 % to controls for 4 or 8 weeks, and the following examinations were conducted: clinical observations, body weights, morphological differentiation, hematology, blood chemistry, macroscopic and microscopic observations.

【Result】 Body weights were decreased depending on the degree of FR, but the body weight ratio to the control was reached at steady state around PND 40. Cleavage of the balanopreputial gland were delayed and cell debris in epididymal lumen was noted after 4-week FR as a related finding. Vaginal opening was also delayed and some histopathological findings were noted in reproductive organs after 8-week FR. Red blood cells were increased after 4-week FR, and were slightly decreased only in males after 8-week FR, and extramedullary hematopoiesis in the spleen were noted after both 4- and 8-week FR. White blood cells were decreased after both 4- and 8-week FR, and the degree was mitigated after 8-week FR. In blood chemistry, total protein including globulin, glucose, triglyceride, calcium were decreased, and sodium and chloride were increased after both 4- and 8-week FR. Increased total bilirubin was noted after 4-week FR, but recovered after 8-week FR. Atrophic changes were noted after 4-week FR, but mitigated or disappeared after 8–week FR.

【Conclusion】 FR induced various effects on toxicological parameters, and some effects were considered to be related to growth retardation. Some findings noted after 4-week FR were mitigated or disappeared after 8-week FR, and the phenomenon might be adaptation to malnutrition.

P 423

Prenatal exposure of rats to 2,2',4,4',5,5'-hexachlorobiphenyl facilitates early eye opening in F1 offspring

Kenichi Kobayashi[1)], Muneyuki Miyagawa[1, 2)], Rui-Sheng Wang[1)], Megumi Suda[1)], Soichiro Sekiguchi[1)], Takeshi Honma1)
[1)] National Institute of Occupational Safety and Health
[2)] Department of Sport and Medical Science, Faculty of Medical Technology, Teikyo University (Japan)

Prenatal exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) and coplanar polychlorinated biphenyl (PCB) congeners has been reported to hasten the occurrence of eye opening in rodents, but the effects of exposure to non-coplanar PCB congeners on the time of eye opening remain unclear to date. TCDD binds to the cytosolic ligand-activated transcription factor aryl hydrocarbon receptor (AhR), leading to adverse effects by altering AhR target gene expression. In contrast, non-coplanar PCB congeners show little or no binding to AhR. PCB 153 has been detected in wildlife as well as in human plasma and breast milk, and could thus serve as an appropriate biomarker for exposure to PCBs. Therefore, we examined whether gestational exposure to 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153), a di-ortho-substituted non-coplanar PCB congener, affects the time of postnatal eye opening in F1 rat offspring. Pregnant Sprague-Dawley rats were orally treated with PCB 153 (0, 16, or 64 mg/kg/day) in corn oil vehicle from gestational day (GD) 10 through 16, and maternal body weights during gestation and lactation, the duration of gestation, somatic growth, and the onset of eye opening in pups were evaluated. On postnatal day (PND) 1, all live births were counted and sexed. Body weight, body length (nose-anus length), and tail length were measured on PND 1, 7, 14, and 21. F1 Pups were observed for bilateral eye opening on each day. The percentage with opened eyes was calculated on PND 10-16. No statistically significant differences were observed between the control group and the PCB 153-exposed groups in terms of maternal body weights during gestation and lactation, the duration of the gestational period, or the number of live births per litter. The values of body weight, body length, and tail length in the PCB 153 groups were lower than those in the control group on PND 1, 7, 14, and 21 in a dose-dependent manner in both sexes. The day of eye opening in PCB 153-exposed pups was earlier and dose-dependent in both sexes. These findings suggest that gestational exposure (GD 10-16) to PCB 153 suppresses postnatal somatic growth but induces unexpected facilitation of early eye opening that might not occur through interaction with AhR. The underlying mechanism(s) of early-onset eye opening and its toxicological significance due to in utero PCB 153 exposure remain unknown.

The authors thank Mr. T. Murase and Mr. S. Numajiri throughout this study. This study was conducted as part of contract research with the Ministry of Health, Labour and Welfare, which was supported by funds from the Ministry of the Environment.

P 424

Maternal poly(I:C) injection induces the initial placental immune response at maternally derived cells in decidua in mice

Tsuyoshi Tsukada[1)], Hiromi Sakata-Haga[1)], Hiroki Shimada[2)], He Wang[1)], Hiroki Shoji[3)], and Toshihisa Hatta[1)]
Departments of [1)]Anatomy
[2)]Medical Science, and
[3)]Biology, Kanazawa Medical University (Japan)

【Background】 Interleukin 6 induced by maternal immune activation has been shown to be produced in the placenta and implicated in the pathophysiology of neruodevelopmental disorders such as autism spectrum disorders. However, the initially immune activated site in the placenta in response to maternal polyriboinosinic-polyribocytidylic acid [poly (I:C)] injection are not clear.

【Purpose】 In this study, we evaluated that initial Toll like receptor 3 (TLR3) signaling site where the inflammatory response occurs in the placenta.

【Methods】 Female wild-type C57BL/6J and male C57BL/6-Tg (CAG-EGFP) mice were crossed to obtain placenta in which cells of maternal origin can be distinguished from those of paternal origin by EGFP signals. At 12.5 days post-coitum, dams were administered an intraperitoneal poly (I:C) injection (20 mg/kg BW). We quantitatively analyzed the

phosphorylation of interferon (IFN) regulatory factor 3 (pIRF3) level in the placenta by western blotting and investigated the distribution of pIRF3 positive cells by immunohistochemistry.
【Results and discussion】 At 3 hours after poly (I:C) injection, level of pIRF3 was increased. At the same time, maternally derived mesenchymal cells in the decidua were mainly positive for pIRF3. In addition to these results, Ifnb mRNA expression was upregulated in the placenta. These results suggest that the decidual cells are initially activated for inflammatory response in the placenta

This work was supported by KAKENHI 16K19674. COI: None

P 425

Questionary survey about the folic acid intake in Wakayama Rosai Hospital

Nobuko Takinami[1)], Shiho Hongo[1)], Miki Fujii[1)], Ryosuke Nakatani[1)], Yoshie Yoshimoto[2)], Tomoko Okawa[2)], Kayoko Fukuchi[2)], Atsushi Matsumoto[1)]
[1)] Japan Organization of Occupational Health and Safety Wakayama Rosai Hospital Pharmaceutical Department
[2)] Japan Organization of Occupational Health and Safety Wakayama Rosai Hospital Nursing Department (Japan)

【Background and Purpose】 The increase of a folate intake is recommended to reduce the risk of occurrence of neural tube obstruction disorder in the foreign countries. The Ministry of Health, Labor and Welfare of JAPAN issued a notice "Promotion of appropriate information provision on the intake of folic acid to women of childbearing age for reducing the risk of neural tube obstruction disorder" in 2000. However, it is reported that a folic acid intake before the pregnancy does not advance in the present state of Japan. Therefore we conducted a questionnaire to grasp the state of a folate intake of pregnant women who were consulted at Wakayama Rosai Hospital.
【Method】 We conducted questionnaires for pregnant women who visited Wakayama Rosai Hospital from October 2018 to March 2019.We investigated age, a gravida, the folate intake situation and intake time, presence or absence of knowledge on the reason for recommending folic acid, presence or absence of knowledge on recommendation of intake of folic acid among pregnant women who do not take folic acid. We made the brochure about folic acid intake recommendation and distributed after a questionnaire.
【Result】 67% of pregnant women took in folic acid, but the ratio of pregnant women who had taken folic acid before the pregnancy was 31 % of pregnant women who took folic acid. (Only 21% of pregnant women ingested folic acid before pregnancy.) The ratio pregnant women who understood the reason why folic acid was recommended was 73%. The pregnant woman who did not take folic acid was 33% and 85% of those knew the recommendation of a folic acid intake. So that means 95% of all pregnant women knew the recommendation of the folic acid intake.
【Discussion】 The low rate of folate intake before pregnancy was obtained for pregnant women who received Wakayama Rosai Hospital was as with the present state of Japan. Initially, we thought that the low ratio of folic acid intake was due to ignorance about the recommendation about folic acid intake. However the majority of pregnant women who don't take folic acid knew the recommendation about folic acid intake. This result was unexpected. We think that it is necessary to investigate the reason why pregnant women and women of childbearing age don't take folic acid and grope the way to increase the ratio of folic acid intake.

P 426

Dog testis toxicity of glucagon receptor antagonist monitored using monthly sperm assessment, followed by recovery

Isobe Y[1)], Bowman CJ[2)], Papanikolaou A[2)], Geoly FJ[2)], Updyke LW[2)] and Cappon GD[2)]
[1)] Pfizer R&D (Japan)
[2)] Pfizer, Groton, CT (USA)

【Background】 Microscopic effects on spermatogenesis were observed in the testis and epididymis with 3 months of dosing dogs at ≥150 mg/kg/day with PF-06291874, a glucagon receptor antagonist. No effects were observed in shorter duration dog studies or in any rat studies at similar doses.
【Purpose】 To better characterize the onset and reversibility of this toxicity in dogs, serial sperm evaluation (motility, density and count) of ejaculate was monitored monthly during a 9-month study with a 5-month recovery period.
【Method】 In the 9-month study, male beagle dogs were dosed once daily by oral gavage with 0, 10, 50, 100, or 500 mg/kg with 8, 5, 5, 8, and 8 male dogs per group, respectively (female dogs were also part of the study but are not described here). Five males per group were necropsied after 9 months and 3 males in the control, 100 and 500 mg/kg groups were necropsied after a 5-month recovery. Post-mortem evaluation included weights and microscopic evaluation of the reproductive organs. Semen from all animals was collected approximately monthly for automated evaluation of sperm motility, density, and total counts using a Hamilton Thorne IVOS sperm analyzer.
【Result】 The microscopic findings in the testes at the end of the dosing phase included degeneration of spermatids and high incidence and severity of multinucleated spermatids at ≥100 mg/kg and degeneration of spermatocytes at 500 mg/kg. Considered secondary to the testis damage, hypospermia and cellular debris were noted in the epididymis at ≥100 mg/kg. The monthly sperm analysis resulted in test article-related lower sperm motility, sperm density and/or total counts during the dosing phase at ≥100 mg/kg. These effects on sperm generally started during month 3 of the dosing phase and generally correlated with the microscopic findings in the testis and epididymis. Although 2 out of 3 recovery animals at 500 mg/kg indicated lower sperm counts and motility at the end of dosing, there were no male reproductive effects observed at the end of the recovery period, including recovery of sperm endpoints.
【Conclusion】 In conclusion, serial sperm evaluation provided time-course information complementary to the terminal testicular toxicity observed, as well as a potential predictive biomarker of recovery in the testis and epididymis.
【Acknowledgements】 We would like to thank Dr. Shana R. Dalton from Covance Laboratories Inc., Madison, WI, USA for conducting the study as the Study Director.

P 427

Relationship between fusion of lateral palatal shelves and mandible growth (Meckel's cartilage)

Aoi Nohara[1)], Natsumi Owaki[1)], Clara Manesco[1)], Motoki Katsube[2)], Shigehito Yamada[1, 3)], Hirohiko Imai[4)], Tetsuya Matsuda[4)], Akio Yoneyama[5)] and Tetsuya Takakuwa[1)]
[1)]Human Health Science, Graduate School of Medicine, Kyoto University, Kyoto
[2)]Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Kyoto University, Kyoto
[3)]Congenital Anomaly Research Center, Graduate School of Medicine, Kyoto University, Kyoto
[4)]Department of Systems Science, Graduate School of Informatics, Kyoto University, Kyoto, Japan
[5)]SAGA Light Source, Saga (Japan)

【Background】 The development of the pharyngeal cavity into oral and nasal cavities takes place in the human embryonic period between Carnegie Stage (CS) 22 and CS23 (unpublished data). In the present study, the relationship between secondary palate and mandible formation was analyzed, and we used Meckel's cartilage as an anatomical landmark.

【Materials & Methods】 Magnetic resonance imaging (MRI) and phase-contrast X-ray computerized tomography (CT) images from six human embryos between CS22 and CS23 were selected from the Kyoto collection at the Congenital Anomaly Research Center of Kyoto University, Japan. Five human embryos were divided into two groups by the percent of lateral palatal shelve fusion, namely Fusion (-) [fusion <50 %] and Fusion (+) [50% <]. Secondary palate and surrounding anatomical structures, including Meckel's cartilage, were 3-D reconstructed and subjected to morphometry with Amira software (Ver. 5.50; Visage Imaging; German).

【Results & Conclusion】 The total Meckel's cartilage length differed between Fusion (-) (4.48 mm) and Fusion (+) (6.01 mm) . The angle between the middle part of the bilateral Meckel's cartilage differed between Fusion (-) (58.6 degree) and Fusion (+) (43.6 degree). The angle between the posterior part of the bilateral Meckel's cartilage differed between Fusion (-) (81.2 degree) and Fusion (+) (69.2 degree). The distance between bilateral Meckel's cartilages did not significantly differ between the groups. Morphometric data of Meckel's cartilage may reflect the differential growth of the mandible. The present data suggests that anterior-posterior elongated and sharp pointed mandibles may contribute to the fusion of lateral palatal shelves. (COI: NO)

P 428

Upper incisors are most susceptible to phenytoin-induced hypoxic stress during mouse tooth development

Kotono Kibe[1, 2)], Mitsushiro Nakatomi[1)], Shinji Kataoka[1)], Takashi Toyono[1)], Yuji Seta[1)]
[1)]Division of Anatomy, Department of Health Improvement, Kyushu Dental University
[2)]Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University (Japan)

【Background】 Congenital anomalies are caused by gene-environmental interactions during embryonic development. Among environmental factors, hypoxic stress can be induced by smoking, arrhythmia, sleep apnea syndrome, living at high altitudes, and uptake of medicine. Compared with other organs, it has not been fully understood how hypoxic stress affects tooth development.

【Purpose】 This study aimed to address the effect of hypoxic stress during odontogenesis using mouse embryos.

【Method】 Pregnant wild-type mice were intraperitoneally injected with phenytoin, an anti-epileptic drug and a known arrhythmia inducer, at various stages from embryonic day (E) 13 to E16. Dissected embryonic tooth germs were histologically analyzed by H&E staining and immunohistochemistry detecting hypoxic markers Hif1a, VEGFa, and Hydroxyprobe. Quantitative RT-PCR analysis was carried out using cDNA derived from phenytoin-treated and non-treated upper and lower incisor germs and Hif1a, VEGFa, and GAPDH primers. In addition, pregnant mice were kept in a chamber in which oxygen concentration was maintained at 10% from E14 to E17 and fetal tooth germs were histologically analyzed.

【Results】 Phenytoin injection induced vascular dilation of 100 μm or more in diameter in the dental pulp in 21 of upper incisors and 2 of lower incisors but not in molars among 110 right and left jaws (55 individuals). No such phenotype was observed in tooth germs obtained from the hypoxic chamber group. Upper incisors of the group of phenytoin injection at E15-16 and dissected at E17 exhibited the highest incidence rate of vasodilation. Hif1a, VEGFa, and Hypoxyprove were immunopositive in phenytoin-treated odontoblasts. Quantitative RT-PCR analysis revealed that the expression of Hif1a and VEGFa was significantly up-regulated in phenytoin-treated group than in non-treated.

【Discussion】 Our data indicated that upper incisors were most susceptible to phenytoin-induced hypoxic stress than other tooth types. One reason why incisors are more susceptible than molars would be that the size of molar germs is bigger than that of incisors due to being multi-rooted and therefore vascularization could easily occur in molars. However, it remains unclear why upper incisors are more susceptible than lower incisors. One possible explanation to no phenotype of hypoxic chamber group is that phenytoin can pass through the placenta and affect the embryos directly, whereas lower oxygen concentration influences the embryos indirectly via mothers. In conclusion, our results suggest that hypoxic stress caused by medication during pregnancy would increase the risk of dental malformation especially in single-rooted teeth.

【COI】 The authors declare no conflicts of interest.

【Grant】 This work was supported by the Japan Society for the Promotion of Science KAKENHI (Grant Number 15K11019 to M.N.).

P 429

Effect of Reveromycin A on Continuous Tooth Movement with Reveromyicin A in Osteoprotegerin Knockout Mice

Fumika Kimura[1)], Chisato Minamoto[1)], Ken Miyazawa[1)], Masako Tabuchi[1)], Makoto Kawatani[2)], Hiroyuki Osada[2)], Shigemi Goto[2)]
[1)]Department of Orthodontics, School of Dentistry, Aichi Gakuin University, Aichi
[2)]Chemical Biology Research Group, RIKEN CSRS, Wako (Japan)

【Background】Recent studies have revealed that juvenile Paget's disease is related to the lack or mutation of a gene encoding Osteoprotegerin (OPG). Additionally, it was reported that this disease is quite similar to that of OPG knockout (KO) mice. Bisphosphonates (BP) are used as the drug of choice for this disease. In our previous studies, inhibition of resorption of alveolar bone, reduction of tooth movement, and normalization of bone metabolism after bisphosphonate administration were observed in OPG KO mice. Since it has been reported that BP remains the bone for a long time with adverse dental side-effects, including osteonecrosis in the jaw, we therefore focused on reveromycin A (RMA) which has an extremely short half-life and suppresses osteoclast-specific activity.

【Purpose】Tooth movement experimentation has been accepted as a useful method to elucidate the process of bone metabolism. Therefore, in this study, we hypothesized that tooth movement would be suppressed by BP even after discontinuation because of its long half-life and bone avidity but tooth movement would resume after discontinuation because of its short half-life. So continuously we administered BP to one group and RMA to another group and then discontinued their administration to compare their effects on tooth movement, and surrounding alveolar bone, to verify the positive effects of RMA.

【Method】OPG KO and wild type mice were developed as tooth movement models under constant orthodontic force. A nickel-titanium closed coil spring with a force of 10g was placed on the maxillary incisors and left first molar to mesially move the molar for 14 days. The mice were divided into three groups (n=4 each) for the continuous administration of physiological saline for 14 days (SA group), RMA (1.0 mg/kg) for the first 7 days followed by saline for 7 days (RMA+/− group), and RMA for the entire 14 days (RMA+ group). Saline or RMA was administered intraperitoneally twice daily starting 3 days before spring placement. BP (1.25 mg/kg) was administered to all three groups (SA, BP+/−, and BP+), but administration was only once daily starting 5 days before spring placement.

【Result】Continuous of both BP and RMA administration suppressed osteoclast activity and preserved alveolar bone around the roots, apparently normalizing bone metabolism. Tooth movement remained suppressed after BP discontinuation but resumed after discontinuation of RMA.

【Discussion】RMA appears useful for controlling orthodontic tooth movement because it can be suppressed and resumed through administration and discontinuation.

P 430

Pre-treatments of developing palates with tyrphostin AG1517 may prevent the induction of cleft palate by glucocorticoid treatments in mice.

Naoko Endo, Akira Sato, and Hiroaki Aoyama
Institute of Environmental Toxicology (Japan)

【Background】Our previous studies have shown that cleft palate induction by exposures to glucocorticoids can be replicated in an in vitro suspension organ culture system with developing mouse palates. We have also demonstrated that the pre-treatment of developing palates with tyrphostin AG1517 (tyrphostin), a specific inhibitor of EGFR phosphorylation, could partially prevent cleft palate inductions by the treatment with triamcinolone acetonide (TC), a synthetic glucocorticoid with this experimental system: the pre-treatment with tyrphostin allowed palatal shelves to contact each other following TC treatment, in which inhibition of EGFR activation reduced MAPK activity in palatal nasal epithelial cells and prevented epithelial thickening at the nasal area and tip of palatal shelves, although the process of palatal fusion did not recover completely.

【Purpose】The present study aimed at examining whether inhibition of EGFR activation would prevent cleft palate induction by the treatment with corticosterone (COR), natural glucocorticoid, by inactivating EGFR-mediated signal transduction cascade.

【Method】Developing palates collected from ICR mouse embryos on gestation day 13 were exposed to COR at concentrations of 0, 100 and 150 μg/mL for 60 hours with or without the tyrphostin pre-treatment (1 μM for 1 hour) in the suspension organ culture system. Palatal development was examined morphologically under a dissecting microscope. Additional palatal shelves were collected from embryos for total RNA extraction at 1, 3 or 6 hours after glucocorticoid treatments of mothers: these mice were subcutaneously injected COR at 0 and 400 mg/kg or TC at 0 and 15 mg/kg on gestation day 12. Expressions of Egf and Tgfα mRNA were analyzed by real-time PCR.

【Result】Pre-treatments with tyrphostin significantly increased the incidences of fused palate following the COR-treatment at each concentration, although they were not comparable to that in the control group. Real-time PCR analyses revealed that maternal exposures to TC significantly increased mRNA expression levels of Egf at 1 and 3 hours after injection when compared with the corresponding controls, although the effect was less clear in COR-treated palates.

【Discussion】These results suggest that the EGFR-mediated signal transduction cascade was involved, at least in part, in the process of cleft palate induction by glucocorticoid treatments and that glucocorticoid-induced cleft palates can be rescued by inhibiting EGFR activation if the condition is appropriate.

P 431

Developmental delay and dysmorphic features in a girl with a de novo 5.4 Mb deletion of 13q12.11-q12.13

Kenji Kurosawa[1)], Makiko Tominaga[1, 2)], Toshiyuki Saito[3)], You Umeda[2)], Mitsuo Masuno[4)]

[1)] Division of Medical Genetics, Kanagawa Children's Medical Center, Yokohama
[2)] Children's Medical Center, Showa University Northern Yokohama Hospital, Yokohama
[3)] Department of Clinical Laboratory, Kanagawa Children's Medical Center, Yokohama
[4)] Genetic Counseling Program, Graduate School of Health and Welfare, Kawasaki University of Medical Welfare, Kurashiki (Japan)

【Background】 Proximal interstitial deletions of chromosome 13q are very rare, and only 4 patients with a deletion of 13q12 have been reported with detailed clinical and molecular cytogenetic information.

【Purpose】 We report a female patient with moderate intellectual disability, short stature, and dysmorphic facial features and a de novo deletion of a 5.4 Mb interval of 13q12.11-q12.13.

【Methods】 By using molecular cytogenetic methods, we refined the critical region for the syndrome.

【Results and Discussion】 These results suggested that FGF9 happloinsufficiency could account for the variable phenotypes of the patients. The microdeletion may uncover autosomal recessive disease or minor dominant traits. Exome sequencing could identify further additional variants associated with the phenotypes of the patient. Haploinsufficiency of a combination of genes in this region could lead to the developmental delay and dysmorphic facial appearance of the reported patients. Further analysis with animal models and a patient cohort could provide an insight to the underlying mechanism.

P 432

Atretic Cephalocele: Three Cases Report and Review of the Literature

Noriaki Kikuchi[1)], Akiko Yano[2)]
[1)] Division of Plastic and Reconstructive Surgery, Okitama public general Hospital
[2)] Division of Plastic and Reconstructive Surgery, Yamagata University Hospital (Japan)

【Background】 Cephaloceles is a congenital herniation of intracranial contents through a defect in the skull. It is considered a type of Neural Tube Defect (NTD).

They have an incidence of 0.3-3 in 10,000 live births.

Atretic cephaloceles (ACs) represent 37.5% of all types of cephaloceles. They are abortive rudimentary cephaloceles, benign malformative small, skin-covered subscalp lesions consisting of meningeal and vestigial tissues arising in the vertex midline. ACs are rare entity of NTD.

【Cases】 Three cases with parietal ACs are presented. All of three are girls. They were born by normal delivery with no neurological deficit. Their first visit to us were during October 2012 to February 2017. Their age at first visit were one month each two cases, and five months. One case was treated surgically, the other two cases have been following up conservatively.

【Discussion】 They can be considered rare forms of cranioschisis, and various hypotheses have been proposed to explain their origin. The development of an ACs is usually explained by a partial failure of the neural tube to close. The cranial bone defect is secondary to the formation of the ACs, and it is due to a failure of mesodermal interposition between the cutaneous ectoderm and neuroectoderm.

The average number of births per year is about 7300 in our prefecture. The estimate prevalence of cephalocele is 0.2-2.1 per year. In a short period, we found out three cases with ACs.

Empirical evidence shows that optimal folic acid intake (400 μg/day) by mothers before and during early pregnancy can effectively prevent spina bifida in most cases. However, when we look at long-term trends of NTDs in Japan, prevalence of NTDs did not decline, despite the recommendation of supplement intake by the Japanese Government in 2000.

【Conclusion】 It seemed there are some limitations of the effect of voluntary supplementation of folic acid on NTD prevalence. We hope this presentation reminding us not to overlook small ACs lesions and enlightening the people about pericoceptional folic acid supplementation.

P 433

Welcome to Tanpopo ~Let's talk ! To create bright tomorrow.~

Self help group for Cleft Lip and Palate " Tanpopo " (Japan)

Self help group for CLP "tanpopo" was established in 1978. The members are mainly composed of people in the Tokai region. The baby with CLP is born about 1 in 500, and the treatment takes about 20 years. However, the social understanding is low, and the treatment system and social security are not sufficient. We carry out various activities to realize a society where we can get treatment at ease.

Example:Information exchange, Providing advice, Exchange of Opinions with medical personnel, Calling to govorment, society and media.

P 434

Medical cooperation and academic research for cleft lip and palate in the Federal Republic of Ethiopia

Nagato Natsume[1, 2)], Hideto Imura[1, 2)], Toko Hayakawa[2 3)], Kazuhide Nishihara[4)], Akira Arasaki[1, 2, 4)], Naoki Takahashi, Toshiro Kibe, Fuko Yamauchi[1, 2)], Maya Yoshida[1, 2)], Satoshi Suzuki[1, 2)], Tran Le Duy[1)], Hiroo Furukawa[2, 3)]
[1)] Division of Research and Treatment for Oral and Maxillofacial Congenital Anomalies, School of Dentistry, Aichi Gakuin University, Aichi
[2)] Cleft Lip and Palate Center, Aichi-Gakuin University Dental Hospital, Aichi
[3)] Department of Health Science, Faculty of Psychological and Physical Science, Aichi Gakuin University, Aichi
[4)] Department of Oral and Maxillofacial Functional Rehabilitation, Graduate School of Medicine, University of the Ryukyus, Okinawa
[5)] Chiba Cancer Center, Chiba
[6)] Department of Oral and Maxillofacial Surgery, Kagoshima University, Kagoshima (Japan)

【Objectives】Medical cooperation in Africa is important to us. We have 15 years experience in medical cooperation in African Continent from Tunisia and I would like to report our experience in Ethiopia.Ethiopia has an area of 1097,000 square meters, which is about three times bigger than that of Japan, with a population of about 102,400,000 people. It plays a diplomatic central role of the African region, and the headquarters of the African Union (AU) and the United Nations Economic Commission for Africa (ECA) are located in there.
【Methods】We are conducting several researches in Ethiopia by Grant-in-Aid for Scientific by the Japan Society for the Promotion of Science of Japan. It has been said the incidence of cleft lip and palate varies on races, and African people have a low incidence of cleft lip and palate, but any detailed research have proven our common view.We alongside have been operating charitable surgeries as a medical assistance in Ethiopia, and been receiving and training Ethiopian oral-maxillo surgeon in Japan, and we published the book about cleft lip and palate in Ethiopian.
【Results】These researches and charitable medical activities have resulted in being evaluated by the country.
【Conclusions】These researches and charitable medical activities have been evaluated by Prime Minister of Hailamariam and they established the Honorary Consulate of the Federal Democratic Republic of Ethiopia in Japan after all and cultural and economic exchange cooperation between the two countries has been active besides the charitable medical activities. This presentation reports the results currently acquired from these researches and activities. This study is supported by Grant-in-Aid for Scientific Research:Japanse Gavernment (A) 26257509 by the Japan Society for the Promotion of Science.
【three (3) keywords】Cleft Lip and/or Cleft Palate, Medical support in Ethiopia , epidemiology in Etiopia

P 435

Preventing Postoperative Fistula after Double-Opposing Z-plasty with Collagen Interposition Graft in Isolated Cleft Palate

Jeong Hyun Ha[1)], Hyeonwoo Kim[1)],
Youn Taek Koo[2)], Yeon Woo Jeong, M.D., Ph.D.[3)],
Jeehyeok Chung[3)], Sukwha Kim[1)]
[1)]Division of Pediatric Plastic Surgery,
Seoul National University Children's
Hospital, Seoul
[2)]Wonjin Plastic Surgery, Seoul
[3)]Slow Plastic Surgery, Seoul
[4)]Department of Plastic and Reconstructive Surgery,
Myongji Hospital, Gyeonggi (Korea)

【Background】Palatal fistula remains a challenging complication following cleft palate repair. The authors tried to delineate the usefulness of collagen interposition graft in primary palatoplasty to prevent fistula.
【Method】We conducted a retrospective cohort study of isolated cleft palate patients who underwent primary palatoplasty (Furlow's double opposing z-plasty). In attempt to decrease the incidence of palatal fistula, we used collagen membrane/graft (GENOSS) in cases with incomplete closure of nasal lining. Cleft width(X), palatal shelves width (Y1,Y2), palatal index [X/(Y1+Y2)] were reviewed. Association between collagen interposition graft and postoperative fistula rate was analyzed considering palatal index.
【Result and Discussions】A total of 204 isolated cleft palate patients (male : female = 69:135, median age 15 months) underwent primary palatoplasty from 2015 to 2018 at Seoul National University Children's Hospital. Postoperative fistula was observed in 16 patients (7.8 percent). Collagen interposition graft was used in 32 patients. Average palatal index was 0.28(±0.23) in whole population and 0.37(±0.11) in collagen interposition graft group. Logistic regression analysis considering index and collagen graft showed that collagen interposition graft significantly reduced fistula rate. Receiver operating characteristic curve analysis indicated that fistula rate significantly increased when palatal index was over 0.235. In subgroup analysis with palatal index over 0.235, collagen interposition graft significantly reduced fistula formation. None of collagen interposition graft cases was complicated by infection or local inflammation.

Collagen interposition graft is an effective tool for palatal fistula prevention when used in cases of incomplete closure of nasal lining, especially in wide palatal clefts.

CONTENTS

Author Index Oral Presenters

Name	Date	Time	VENUE
Akai, T	27	18:30-18:45	3
Akita, M	28	10:00-10:15	4
Alberto, A	27	17:30-17:45	4
Alkhayat, A.M.S	28	16:45-17:00	2
Alhayyan, W.A	28	13:45-13:52	2
Amin, M.M	27	17:45-18:00	4
Amin, M.M	27	18:00-18:15	4
Amin, M.M	27	18:15-18:30	4
Assawakawintip, T	27	17:52-18:00	2
Balaji, S.M	28	10:00-10:30	2
Baylis, A. L	27	13:00-14:30	2
Cai, M	28	13:00-13:07	2
Cha, J-Y	28	9:22-9:30	2
Chen, Y	28	16:00-16:07	2
Choi, J-Y	27	16:37-16:52	4
Chuykin, S.V	28	17:00-17:15	2
Crerand, C.E	27	13:00-14:30	2
Elliott, M	27	14:45-15:00	2
Endo, M	28	16:15-16:30	1
Fomenko, I	28	9:07-9:15	2
Fujimoto, T	27	17:00-17:15	2
Fujiwara, Y	26	16:00-16:15	2
Fushimi, Y	28	9:00-12:00	3
Gudipaneni, R.K	28	13:07-13:15	2
Ha, S-G	27	16:22-16:30	4
Hall. C. E.	27	13:00-14:30	2
Hamada, H	28	15:05-16:00	3
Hamanoue, H	28	16:00-16:15	3
Hanai, U	27	14:45-15:00	3
Harada, A	27	14:00-14:15	4
Hashimoto, R	27	18:00-18:15	3
Hayakawa, T	26	14:30-14:45	2
Hayashi, N	28	16:45-17:00	1
Hayashi, N	28	11:45-12:00	2
Higashimoto, K	28	16:30-16:45	3
Hiraoka, M	27	14:15-14:30	3
Hirata, A	28	11:22-11:37	4
Honda, M	28	10:30-11:00	1
Hong, M	28	13:52-14:00	2
Hoshi, K	27	17:15-17:30	1
Ida-Eto, E.M	28	10:45-10:52	4
Ikeda, K	27	15:00-17:00	3
Imai, Y	26	11:00-11:15	2
Imura, H	28	9:00-10:00	1

Name	Date	Time	VENUE
Inoue, A	27	15:00-17:00	3
Iseki, S	28	10:30-10:45	2
Ivanov, A	28	15:00-15:15	2
Jafarov, M.M	27	16:3716:45	2
Jafarov, M.M	27	17:15-17:22	4
Jia, Y	28	9:15-9:22	2
Kamohara, S	28	15:15-15:22	2
Kaname, T	28	10:52-11:00	4
Karoon, A	27	14:30-15:00	4
Katayama, M	28	11:15-11:22	4
Kato, J	28	15:37-15:45	2
Katsube, M	27	18:30-18:45	1
Kawamura, J	27	16:00-16:15	4
Kawasaki, H	27	18:00-18:15	1
Kawasaki, H	28	14:07-14:15	2
Kido, N	27	15:45-16:00	4
Kim, H-W	28	11:30-11:37	2
Kirschner, R. E	27	13:00-14:30	2
Kitamura, C	28	15:45-16:00	2
Kondo, A	28	17:15-17:30	3
Kosaki, K	27	16:30-17:00	1
Krimmel, M	28	14:00-14:07	2
Kurasawa, K	28	9:00-10:00	1
Kurosaka, H	28	14:45-15:00	1
Kurosawa, K	28	9:00-10:00	1
Kushima, S	28	16:30-16:45	2
Kyozuka, H	28	9:00-10:00	1
Lewis, E.M	28	15:45-16:15	1
Li, Y	28	9:37-9:45	2
Li, Y	28	15:30-15:37	2
Liu, J	28	11:07-11:15	2
Ma, L	27	15:30-15:45	4
Mabongo, M	27	18:52-19:00	2
Maclennan, A.B	27	17:00-17:15	1
Maeda, M	28	9:00-12:00	3
Makeev, A.V	28	15:22-15:30	2
Mamedov, A.A	28	17:00-17:15	1
Mikoya, T	26	11:15-11:30	2
Min. Z	28	16:07-16:15	2
Minamidate, T	28	11:00-11:07	4
Mishima, H	28	16:15-16:30	3
Mitsui, S.N	28	14:37-14:45	2
Mitsukawa, N	26	16:15-16:30	2
Mizuno, S	28	10:15-10:45	4

Name	Date	Time	VENUE
Mori, Y	26	10:45-11:00	2
Morillas, A.C	27	15:15-15:30	4
Murasugi, R	28	9:45-10:00	4
Murotsuki, J	28	9:30-9:45	4
Nagata, J	27	17:15-17:30	3
Natsume, N	27	11:20-12:00	1
Niimi, T	26	14:00-14:15	2
Nishihara, K	26	9:30-9:45	2
Noguchi, M	26	9:00-9:15	2
Ogata, Y	26	15:45-16:00	2
Oh-Nishi, A	27	14:00-14:15	3
Ohno, A	28	9:00-12:00	3
Okamoto, N	28	9:15-9:30	4
Omotehara, T	28	11:07-11:15	4
Otani, H	27	15:00-15:30	1
Ozaki, N	28	13:00-14:00	1
Ozawa, S	26	14:15-14:30	2
Park, S-H	28	9:45-9:52	2
Park, Y-W	27	16:00-16:15	2
Prabodha LLB	27	17:15-17:30	2
Rachmiel, A	28	14:00-14:15	1
Rachmiel, A	28	14:15-14:30	1
Rasyida, A.Z	27	16:30-16:37	2
Reinert, S.W	27	14:45-15:00	1
Ren, Z	27	16:15-16:22	4
Romero, M	27	15:15-16:00	2
Ruslin, M	27	18:37-18:52	2
Saijo, H	26	10:00-10:15	2
Saito, N	26	14:30-14:45	2
Saitsu, H	28	13:55-14:50	3
Salyer, K.E	26	13:00-14:00	2
Salyer, K.E	27	13:00-13:30	1
Salyer, K.E	28	11:00-12:00	1
Salyer, K.E	28	14:0017:00	Agals2402
Sancak, K.T	28	16:15-16:22	2
Sandor, G.K	27	14:30-14:45	1
Santoso, R.D	28	13:15-13:22	2
Santoso, R.D	28	13:22-13:30	2
Sasaguri, M	26	11:30-11:45	2
Sasaki, M	27	15:00-17:00	3
Savitha, V.H	27	15:00-15:15	4
Sawada, K	27	18:45-19:00	1
Sawada, M	27	18:07-18:22	2
Sawamura, H	28	9:00-9:15	4
Shafeta, O	27	14:30-14:45	2
Shang, F	28	11:37-11:45	2
Shiga, M	27	17:00-17:15	3
Shimizu, H	27	15:00-17:00	3
Shimomura, K	28	9:00-12:00	3
Shiota, K	27	15:30-16:00	1

Name	Date	Time	VENUE
Shuba, M.I	28	13:30-13:37	2
Singh, S	28	9:00-9:07	2
Solaeche, N	27	17:45-17:52	2
Stepanova, Y	27	17:22-17:30	4
Suda, N	26	15:00-15:15	2
Sunakawa, H	27	16:45-17:00	2
Suzuki, H	28	11:00-11:07	2
Suzuki, K	27	18:15-18:30	1
Suzumori, N	28	16:30-16:45	1
Tache, A	27	16:30-16:37	4
Tache, A	27	16:52-17:07	4
Takakuwa, T	28	10:45-11:00	2
Takeya, R	27	18:15-18:30	3
Takimoto, M	28	15:00-15:30	1
Tanaka, S	28	14:30-14:45	1
Tolar,M	28	15:30-15:45	1
Tolarova, M. M	27	13:30-14:30	1
Tosa, Y	26	9:45-10:00	2
Tuzuner, A.M	27	17:30-17:45	1
Uchino, S	27	15:00-17:00	3
Ueda, K	26	10:30-10:45	2
Uehara, T	28	14:30-14:37	2
Volk, A.S	27	16:15-16:30	2
Waga, C	27	15:00-17:00	3
Wang, Y	28	13:37-13:45	2
Watanabe, A	27	18:45-19:00	3
Williams,G	27	17:07-17:15	4
Wu, D	28	11:15-11:30	2
Yagi, H	28	17:00-17:15	3
Yamada, A	27	14:15-14:30	4
Yamada, A	28	11:00-12:00	1
Yamada, A	28	14:0017:00	Agals2402
Yamada, M	28	14:15-14:22	2
Yamada, S	28	10:00-10:30	1
Yamada, T	26	16:30-16:45	2
Yamada, T	28	16:45-17:00	3
Yamamoto, I	26	15:30-15:45	2
Yamamoto, M	28	13:00-13:55	3
Yamasaki, H	28	9:00-12:00	3
Yamawaki, Y	27	18:22-18:37	2
Yasuda, M	27	16:00-16:30	1
Yokoyama, A	27	14:30-14:45	3
Yoshida, N	26	15:15-15:30	2
Yoshiki, A	28	14:22-14:30	2
Yoshiura, K	27	17:30-18:00	3
Young, SE-L	27	17:45-18:00	1
Yuzuriha, S	26	9:15-9:30	2
Zhang. B	28	16:22-16:30	2
Zhou, X	28	9:30-9:37	2
Zhu, H	27	18:00-18:07	2

Notebook

The 59th Annual Meeting of
The Japanese Teratology Society
The 13th World Congress of
The International Cleft Lip and Palate Foundation
- CLEFT 2019 -

July 26-29/ 2019

Nagato Natsume

Aichi-Gakuin University,
School of Dentistry Division of Research and Treatment for
Oral and Maxillofacial Congenital anomalies
Aichi-gakuin University Hospital, Cleft lip and palate center
2-11 Suemori-dori, Chikusa-ku, Nagoya, 464-8651, Japan

Printed by Neomedix Co., Ltd.
5-22-28 Chiyoda, Naka-ku Nagoya 460-0012 Japan
Kenji Kinoshita

2,000 JPY (tax included)
20 US dollar (tax included)