Japan Korea conjoint session in rhinology
（日韓鼻科学ジョイントセッション）

10月2日（金）

10:00～11:30

司会：Prof. Heung-Man Lee（KRS会長 / Korea University），
増山　敬祐（山梨大学）

1. T helper 1 (T_H1), Th2, and Th17 cytokine-profiles during long-term sublingual immunotherapy for Japanese cedar pollinosis.
   演者：Takechiyo Yamada
   （Department of Otorhinolaryngology, University of Fukui, Japan）

2. Preoperative Assessments for Sinonasal Inverted Papilloma
   演者：Yuji Nakamaru
   （Department Otolaryngology Head and Neck Surgery Hokkaido University School of Medicine）

3. Technical Advancements in Sinonasal Surgery
   演者：Chang-Hoon Kim
   （Yonsei University College of Medicine）

4. Olfactory event-related potentials: normative data in Koreans
   演者：Jae Hoon Cho
   （Konkuk University School of Medicine）

T helper 1 (T_H1), Th2, and Th17 cytokine-profiles during long-term sublingual immunotherapy for Japanese cedar pollinosis.

T Yamada, M Sakashita, K Ogi, Y Kato, K Saito, S Fujieda

Department of Otorhinolaryngology, University of Fukui, Japan

Introduction: Sublingual immunotherapy (SLIT) for Japanese cedar pollinosis (JCP) has also started to be covered under the national health insurance system in Japan. The mechanisms of action of SLIT also include early desensitization effects, modulation of T cell and B cell responses, and induction of blocking antibody, as well as decreased migration of eosinophils, basophils, and mast cells to tissues and the release of their mediators. Regulatory T cells have also been identified as key regulators of immunologic processes in peripheral tolerance to allergens. We performed long-term sublingual immunotherapy (SLIT) for patients with JCP, screened molecules as candidate biomarkers, and investigated the serum levels of T helper 1 (T_H1), Th2, and Th17 cytokines in order to evaluate whether these molecules show changes correlated to symptom scores.

Method: The patients received SLIT from a pre-seasonal period (October) through to the end of the high-pollen season (April) for four consecutive years. The symptom medication scores were evaluated in accordance with the Japanese guidelines for allergic rhinitis. Blood samples were obtained and the serum was stored at −80°C. We measured the levels of molecules including T_H1, Th2, and Th17 cytokines in the serum at the peak of pollen dispersion using ELISA or multiple assay system using kits.

Results: The levels of IL-4 showed a significant decrease at year 4 compared with those at year 1. On the other hand, the levels of IL-5, IL-13, and IFN-γ at year 4 did not change significantly compared with those at year 1. The long-term SLIT reduced the serum levels of IL-17A and TSLP. Significant positive correlations were found between the symptom medication scores and the levels of IL-17A or TSLP during long-term SLIT. The scores in the group in which the IL-17A or TSLP levels decreased were significantly lower than those in the group in which these levels did not decrease.

Conclusion: IL-17A and TSLP might be involved in pathological features of JCP or mechanisms of SLIT efficacy, suggesting that it could be one of the suitable biological parameters for SLIT efficacy. Further studies are needed to evaluate the difference between responders and non-responders in SLIT. In addition, collaboration among scientists and pharmaceutical companies is necessary to produce new therapeutics for non-responders in whom serum IL-17A and TSLP levels are still higher at year 4 for JCP.

Preoperative Assessments for Sinonasal Inverted Papilloma

Yuji Nakamaru, Dai Takagi, Masanobu Suzuki, Aya Homma, Satoshi Fukuda

Department Otolaryngology Head and Neck Surgery Hokkaido University School of Medicine

Objective: Sinonasal inverted papillomas (IP) originally have a benign entity but they can be locally aggressive and have a high potential of recurrence. The precise assessments of the attachment site of IP before surgery are mandatory for complete surgical resection and prevention of complications. The aim of this study is to compare the performance of 3.0Tesla (3.0T) MRI and 1.5Tesla (1.5T) MRI and CT in terms of sensitivity and specificity in predicting the attachment site of IPs on the sinus walls before surgery.

Methods: Ten consecutive patients with pathologically proven IPs who were treated at the Department of Otolaryngology, Head and Neck Surgery, Hokkaido University Hospital were enrolled in the study. Two radiologists predicted the IP attachment site from 3.0T MRI and 1.5T MRI and CT.

Results: The sensitivity, specificity, PPV, NPV and accuracy of the 3.0T MRI images were all slightly better than those obtained by 1.5T MRI. However, there were no significant differences in sensitivity or specificity between the two groups. CT showed the highest sensitivity ($P < .0001$), although both MRI formats showed greater specificity ($P < .0001$).

Conclusion: Although there were no significant differences, the values for sensitivity specificity, PPV, NPV and accuracy were better for 3.0T MRI than those for 1.5T MRI. Therefore, the use of 3.0T MRI for the preoperative imaging is thought to be the useful in the detection of attachment sites.

Technical Advancements in Sinonasal Surgery

Chang-Hoon Kim

Yonsei University College of Medicine

3-D Endoscope

Traditionally, endoscopic sinonasal surgery is performed using 2-dimensional (2D) endoscopes, which lack depth of field and contribute to image distortion. Recently, a new generation of 3D endoscopes has been introduced for improved endoscopic depth perception. In this lecture, our initial experience with a new 3D-endoscope in sinonasal surgery will be presented. The diseases included chronic sinusitis, CSF leakage, olfactory neuroblastoma, sphenoid mucocele, juvenile angiofibroma, adenoid cystic carcinoma of maxilla, squamous carcinoma involving sphenoid sinus, nasal malignant melanoma. The 3D technology facilitated depth perception and completeness of surgery without increase in complications, and may improve performance for novices. The 3D-endoscope may be a safe and feasible tool for endoscopic sinus and skull base surgery. I will also discuss the advantages and disadvantages of endoscopic sinonasal surgery using the 3D endoscopes. In addition, I will present the way we teach the residents for sinonasal surgery in our institution.

Navigation

The use of image-guided surgery (IGS) (also known as navigation-assisted surgery) has played an important and expanding role in endoscopic sinus surgery (ESS) nowadays. Although IGS is considered a valuable tool, its impact on the detailed parameters of IGS, such as instrument setup time, actual operation time and rate of complications, remains unclear. This study presents the comparative analysis of IGS experienced in the Severance Hospital between December 2011 and July 2014 with standard ESS cases.

A total of 149 patients underwent image-guided endoscopic sinus surgery at Sinchon Severance hospital during December 2011 and July 2014. 4 cases were excluded by using external approaches together. We analyzed total 145 cases with parameters of basic demographic data, diagnosis, procedure, instrument setup time, actual operation time, outcome and complications. To compare characteristics of IGS, a group of 145 patients underwent ESS in 2011, before application of image-guided instrument, was analyzed as a control group using same parameters.

The most common diagnosis with image-guided ESS was chronic sinusitis (n=89, 61.4%), followed by tumor (n=28, 19.3%) and mucocele (n=9, 6.2%). Of all the tumors, inverted papilloma (n=15, 53.6%) was the most common, followed by maxillary sinus cancer (n=3, 10.7%) and nasal cavity cancer (n=3, 10.7%). Control group showed that 76.6% (n=111) of cases were chronic sinusitis, followed by tumor (n=14, 9.7%) and POCC (n=9, 6.2%). Number of revision cases was higher in image-guided ESS (n=54, 37.2%) compared to control group (n=31, 21.4%). In image-guided ESS group, complications were observed in 8 cases (5.5%); 3 cases were minor bleeding which spontaneously stopped after vising ER and others were revision-required cases, otherwise no major complications such as CSF leakage, orbital complications were observed. Complication rate in the control group was 7.6% (n=11), slightly higher than image-guided group. Instrument setup time took 29.3 minutes in average, significantly longer than control group (24.4 min). Actual operation time was also significantly longer in image-guided ESS cases (81.99 min), compared to control (52.94 min). Other parameters showed no significant differences between the control and image-guided ESS group.

Image-guidance in ESS provides more accurate and secure skills, extending its indications and reducing rate of complications, residual lesion or recurrence. If preoperative finding shows suspicious mass lesion, anatomical variations or distortions due to previous operations, it would be safer and more efficient to use image-guidance during operation, despite of longer operation time.

Olfactory event-related potentials: normative data in Koreans

Jae Hoon Cho

Konkuk University School of Medicine

Olfactory event–related potential (OERP) has been considered as an important alternative method to evaluate olfactory function. OERP correlates directly with neuronal activation, has an extremely high temporal resolution in the range of microseconds, and allows the investigation of the sequential processing of olfactory information. OERP also has been used to investigate the processing of odorous information in olfactory dysfunction. The purpose of the current study is to further define the effects of age, gender, and their interactions on the olfactory evoked potential in Koreans. Participants were 71 people (who were) screened for nasal health and olfactory dysfunction. The odor stimulus was βmercaptoethanol 1 M, presented at nasal temperature in a humidified airstream delivered by an air-dilution olfactometer at a constant flow rate, using a 60 second inter-stimulus interval. OERPs were recorded at Fz, Cz, and Pz electrode sites, (BrainAmp MR plus 32, Brain product GmbH, Germany) amplified and averaged over trials. Amplitudes of the N1/P2 and P3 and latencies of the P2 and P3 were analyzed. Amplitudes of the N1/P2 and P3 were decreased across the life span, significantly. Especially an age-related decline of N1/P2 amplitude was prominent in both male and female. Latencies of the P2 and P3 were increased across the life span, significantly. Latency of P3 was increased in male and female, significantly. Normative data will be useful in research on olfactory function and in clinical assessment of olfactory functional status.

韓国鼻科学会会長講演

10月2日（金）

11:30～12:00

Tissue remodelling in upper airway; epigenetic regulation

司会：平川　勝洋（広島大学）

演者：Heung-Man Lee
（The President of Korean Rhinologic Society / Korea University College of Medicine）

Tissue remodelling in upper airway; epigenetic regulation

Heung-Man Lee[1,2]

[1]The President of Korean Rhinologic Society
[2]Korea University College of Medicine

The pathogenesis of CRS with nasal polyp is unclear, but may involve anatomic abnormalities, local immunologic derangement, and genetic and/or epigenetic factors. Chronic rhinosinusitis with nasal polyps is characterized by both a chronic inflammation and tissue remodelling; as indicated by extracellular matrix protein deposition, basement membrane thickening, goblet cell hyperplasia and subepithelial edema, with reduced vessels and glands. Fibroblasts, which are found in the stroma, are the cellular source of extracelluar matrix (ECM) proteins and are involved in the tissue remodelling of CRS. Tissue remodelling is a critical aspect in all organs which associates matrix production and degradation in reaction to an inflammatory insult leading to a normal reconstruction process or a pathological one. Epigenetics is the study of heritable changes in gene expression that occur without direct changes in the DNA sequence. Epigenetic mechanisms regulate gene expression at the DNA, mRNA, and the chromatin level. Regulation of gene expression occurs at DNA level by DNA methylation and small noncoding RNAs such as microRNAs regulate mRNA translation. Histone modifications result in chromatin remodeling which regulates gene expression. Trichostatin A (TSA) is one of the histone deacetylase (HDAC) inhibitors and induces hyperacetylation of histones. In CRS with nasal polyp, TSA inhibits expression of HDAC2 and increases the hyperacetylation. Inhibition of HDAC2 by TSA reduces TGF-β1-induced myofibroblast differentiation and ECM accumulation in nasal polyp-derived fibroblasts. Epigenetic regulations such as inhibition of HDAC2 by TSA can be clinically useful target for inhibition of remodeling in CRS with nasal polyp.

海外招聘講演 1

10月2日（金）

14:30〜15:30

1. CSF leak closure—When and How?
2. Contemporary Management of Nasal Polyposis.
3. The Watery eye—How to manage and What is the Evidence?

司会：春名　眞一（獨協医科大学）

演者：Raymond Sacks
（Dept ORL/ Head & Neck Surgery-Macquarie University
Clinical Professor-University of Sydney）

1. CSF leak closure—When and How?

2. Contemporary Management of Nasal Polyposis.

3. The Watery eye—How to manage and What is the Evidence?

Raymond Sacks[1,2]

[1]Professor and Head Dept ORL/ Head & Neck Surgery-Macquarie University

[2]Clinical Professor-University of Sydney

1. CSF leak closure

This talk will focus on the surgical options for closure of both small and large skull base defects. There will be multiple videos depicting the treatment options for both small spontaneous leaks and the vascularized flap options for large defect closure in endoscopic skull base surgery. A review of the literature will be presented and our results will be discussed.

2. Nasal Polyposis

This talk will detail the treatment philosophy for CRS with Nasal polyposis and both the medical and surgical management will be detailed. There will also be an analysis of current treatment regimens and our rationale for the pre-operative, operative and post-operative approaches in our department will be discussed and analysed.

3. The Watery eye

This talk will focus on—

1. How to approach a patient presenting with epiphora
2. How to clinically establish those cases that would benefit from a DCR
3. How to perform an endoscopic DCR
4. Tips on surgical technique to improve success rate
5. Review of the literature and our unit recommendations

海外招聘講演 2

10月3日（土）

11:00～12:00

Evolution of endoscopic surgery of the ventral skull base.

司会：森山　　寛（東京慈恵会医科大学 名誉教授）

演者：Richard John Harvey
（Program Head and Conjoint Professor, Rhinology & Skull Base Surgery, University of New South Wales & St Vincent's Hospitals / Clinical Professor, Macquarie University）

Evolution of endoscopic surgery of the ventral skull base.

Richard John Harvey[1,2]

[1]Program Head and Conjoint Professor, Rhinology & Skull Base Surgery, University of New South Wales & St Vincent's Hospitals
[2]Clinical Professor, Macquarie University

Skull base pathologies present many challenges for management. The endoscopic approach has evolved in the past decade and now encompasses surgical access to the ventral skull base that was not possible with open craniofacial approaches without significant approach morbidity. The endoscopic route is still limited to areas that can be accessed without crossing major neurovascular structures. The ability to expose the petro-cavernous carotid and gain complete access to the olfactory groove are still the anatomical areas that define a endoscopic skull base surgeon. The petro-cavernous carotid is anatomical structure that belongs to the experienced skull base surgeon with few other surgical groups equipped to manage pathology in this area.

International Session 1

10月3日（土）

14:00～14:45

司会：太田　伸男（山形市立病院済生館），竹野　幸夫（広島大学）

1. Posterior nasal neurectomy in Hiroshima
   演者：Kazunori Kubota
   （Department of Otorhinolaryngology, Head and Neck Surgery, Hiroshima University）

2. Recent advances in management of allergic rhinitis in Egypt
   演者：M A Ragaee
   （Department of Otorhinolaryngology, Assiut University, Faculty of Medicine, Assiut, Egypt）

3. The Epidemiology of Chronic Rhinosinusitis and Allergic Rhinitis in Indonesia
   演者：Abdul Kadir
   （Dr. Wahidin Sudirohusodo Hospital Makassar）

Posterior nasal neurectomy in Hiroshima

Kazunori Kubota, Sachio Takeno, Takayuki Taruya, Atsushi Sasaki, Takashi Ishino, Katsuhiro Hirakawa

Department of Otorhinolaryngology, Head and Neck Surgery, Hiroshima University

Sensory irritation to nasal mucosa is perceived by inferior turbinate sensory nerves derived from the trigeminal nerve. The stimulation of nasal mucosa is reflected by organs such as the superior salivary nucleus via the central nerve ganglion. There are parasympathetic preganglionic cells in this ganglion, and they send parasympathetic preganglionic nerve fibers to the pterygopalatine ganglion and submandibular ganglion on the same side. In severe perennial allergic rhinitis patients, the thresholds of nerve reflection are greatly decreased, resulting in sneezing and itchiness. Rhinorrhea symptoms result from exacerbated nasal secretions due to the excitement of the cholinergic efferent parasympathetic nerve. Posterior nasal neurectomy (PNN) is a surgery invented in Japan. A PNN improves the nasal symptoms of allergic rhinitis patients by identifying the sphenopalatine artery in the posterior part of the nasal cavity and amputating the afferent and efferent nerve fibers accompanying the artery.

We demonstrated previously that the PNN procedure can lead to an inhibited orchestration of allergic inflammatory responses. Histological examinations showed that the number of inflammatory cells is markedly reduced in the lamina propria, and the empty space they leave is filled by collagen fibers. The epithelial layer is covered with stratified columnar cells. The changes in cytokine levels in nasal lavage after PNN were remarkable. The levels of interleukin (IL)-5 and eotaxin were significantly decreased after PNN (Ogawa et al. ANL 2007).

Here we provide the surgical protocol for a PNN as performed at our department, and we report the effectiveness of PNN performed for severe allergic rhinitis patients at our department within the past 3 years following our analysis of the changes in symptoms and drug scores from before to after the surgery and the changes in the nitric oxide concentration in the nasal cavity.

Recent advances in management of allergic rhinitis in Egypt

M A Ragaee, A Anter, A H Monib, M M Osman, A Abdelaleem, M M Ragab

Department of Otorhinolaryngology, Assiut University, Faculty of Medicine, Assiut, Egypt
Affiliated to Department of Otorhinolaryngology, Hiroshima University, School of Medicine, Hiroshima, Japan

Respiratory tract allergies are known diseases from ancient Egyptian ages as delineated in the Ebers Papyrus (c. 1550 BC), which contained an impressive number of remedies for maladies including asthma.

Allergic rhinitis has been rising throughout the late 20th and 21th centuries and it is more obvious in Egypt due to over crowdedness and low socioeconomic level for most of the Egyptian population. Usually patients come with complications as chronic rhinosinusitis, sleep disorders and lower respiratory tract infection.

The treatment modalities became widespread including medical and surgical ways. Medical treatments includes topical corticosteroids, nasal douches, oral corticosteroids, antihistamines and mast cell stabilizers and to lesser extent immunotherapy.

Surgical intervention is limited to cases of hypertrophied inferior turbinate, complicated with chronic rhinosinusitis and nasal polyposis.

In this session, I will present the recent topics and some recent methods used in management of allergic rhinitis in the last 5 years in Egypt either introduction of new medicines or new surgical techniques.

The Epidemiology of Chronic Rhinosinusitis and Allergic Rhinitis in Indonesia

Abdul Kadir

Dr. Wahidin Sudirohusodo Hospital Makassar Makassar

Background: Epidemiological and prevalence data for chronic rhinosinusitis (CRS) and allergic rhinitis (AR) in Indonesia —the fourth-most-populous country, with an estimated population of over 252 million people— are relatively rare. Purpose and settings: Our initial survey was aimed to measure the prevalence of chronic rhinosinusitis and allergic rhinitis among the patient visiting secondary to tertiary ENT care unit (or University Hospitals and it's satellites clinic). Our data has been collected secondary from medical records during 2009 until 2014. Result: On epidemiologic grounds, chronic nasal complaints represent about 50% of the total number of outpatient visits to an average Indonesian ENT practice, 18% of them have some typical symptoms of allergic rhinitis. Some association has been found between CRS prevalence and air pollution (include occupational background), active cigarette smoking, secondhand smoke exposure, allergic rhinitis, and gastroesophageal reflux. Rhinosinusitis is still the most common diagnosis for which an antibiotic is prescribed.
Keyword : Rhinosinusitis, Allergic Rhinitis, Epidemiology, Indonesia

International Session 2

10月3日（土）

14:45～ 15:50

司会：清水　猛史（滋賀医科大学）
Chang-Hoon Kim（Yonsei University College of Medicine）

1. The expression of CST1 in eosinophilic chronic rhinosinusitis
   演者：Yukinori Kato
   （Departments of Otorhinolaryngology Head and Neck Surgery, Faculty of Medical Sciences, University of Fukui, Japan）

2. Regulatory effect of TLR3 signaling on staphylococcal enterotoxin-induced eosinophilia-associated cytokine production by nasal polyps
   演者：Takaya Higaki
   （Department of Otolaryngology-Head & Neck Surgery, Okayama University School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan）

3. A recently established murine model of nasal polyps: similarities and differences with human nasal polyps
   演者：Dong-Young Kim
   （Seoul National University College of Medicine, Seoul, Korea）

4. Obesity & Inflammatory Airway Diseases: Roles of Mucin Gene as a Connecting Link
   演者：Yong-Dae Kim
   （Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Yeungnam University, Daegu, Republic of Korea / Regional Center for Respiratory Diseases, Yeungnam University Medical Center, Daegu, Republic of Korea）

The expression of CST1 in eosinophilic chronic rhinosinusitis

Y Kato, T Takabayashi, Y Imoto, S Fujieda

Departments of Otorhinolaryngology Head and Neck Surgery, Faculty of Medical Sciences, University of Fukui, Japan

Eosinophilic chronic rhinosinusitis (ECRS) is the inflammation disease of nasal sinuses characterized by significant eosinophilic infiltration and is progressively increasing in Japan. Patients with ECRS have nasal polyps which are refractory and recurrent easily and can have complications; severe hyposmia, asthma, and eosinophilic otitis media. It is very hard to treat ECRS, yet the pathogenesis of ECRS is largely unknown.

Cysteine proteases are widely expressed proteolytic enzymes that play role in inflammatory tissue destruction. The proteolytic activity of these enzymes is controlled by a family of inhibitors known as the cysteine superfamily, and cystatine inhibit cysteine proteases by forming tight but reversible complexes with their target enzymes.

Cystain SN (CST1) is protease inhibitor and is one of the type 2 cystatine subfamily. CST1 is expressed in the submandibular gland, bladder, and uretus. CST1 has been shown to bind tightly to the cysteine protease, papain, which is a potent allergen, and to inhibit the cysteine protease activity of papain. Thus, the cystatin family may play protective roles against allergens with protease activity.

In the previous study, we performed a microarray analysis of nasal epithelial cells from seasonal allergic rhinitis (SAR) patients to the Japanease ceder and control subjects. We observed that the expression of CST1 was upregulated specifically in SAR patients during natural allergen exposure. Immunohistochemical staining confirmed the increased expression of CST1 in the nasal epithelial cells of SAR patients. We have been analyzing the function of CST1 in allergic rhinitis. Additionally, we think that CST1 has the important role in eosinophilic chronic rhinosinusitis, which is the representative chronic inflammation disease such as allergic rhinitis.

In this study, samples of nasal mucosa and nasal polyp of ECRS patients and non-ECRS patients were collected and compared the expression of CST1. Furthermore, we analyzed the function of CST1 by using cultured mast cells.

Regulatory effect of TLR3 signaling on staphylococcal enterotoxin-induced eosinophilia-associated cytokine production by nasal polyps

T Higaki, M Okano, S Kariya, T Haruna, Y Noyama, K Nishizaki

Department of Otolaryngology-Head & Neck Surgery, Okayama University School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Background: Toll-like receptor 3 (TLR3) is expressed in upper airways, and signals through TLR3 induce the production of pro-inflammatory cytokines including interleukin (IL)-6 and IL-8 by sinonasal tissue cells. However, little is known regarding whether TLR3 signals exert a regulatory effect on the pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP), especially on eosinophilic inflammation.

Objective: We sought to investigate the effect of Poly(IC), the ligand for TLR3, on cytokine production by dispersed nasal polyp cells (DNPCs).

Methods: DNPCs were pretreated with or without Poly(IC), and were then cultured in the presence or absence of staphylococcal enterotoxin B (SEB), following which the levels of IL-5, IL-10, IL-13, IL-17A and interferon (IFN)-γ in the supernatant were measured. To determine the involvement of IL-10 and cyclooxygenase in Poly(IC)-mediated signaling, DNPCs were treated with anti-IL-10 monoclonal antibody and diclofenac, respectively. Poly(IC)-induced prostaglandin E_2 (PGE_2) production was also determined.

Results: Exposure to Poly(IC) induced a significant production of IL-10, but not of IL-5, IL-13, IL-17A or IFN-γ by DNPCs. Pretreatment with Poly(IC) dose-dependently inhibited SEB-induced IL-5, IL-13 and IL-17A, but not IFN-γ production. Neutralization of IL-10 significantly abrogated the inhibitory effect of Poly(IC). Treatment with diclofenac also abrogated the inhibitory effect of Poly(IC) on SEB-induced IL-5 and IL-13 production. However, unlike exposure of diclofenac-treated DNPCs to lipopolysaccharide, the ligand for TLR4, exposure of these cells to Poly(IC) did not enhance IL-5 or IL-13 production. Poly(IC)-induced release of PGE_2 by DNPCs was transient and not significantly higher than controls.

Conclusions & Clinical Relevance: These results suggest that TLR3 signaling regulates eosinophilic inflammation in CRSwNP, at least in part, via IL-10 production. For clinical implications, these observations may provide a basis for novel therapeutic approaches targeting Poly(IC) and other viral components in the management of eosinophilic airway diseases such as CRSwNP, allergic rhinitis and bronchial asthma.

A recently established murine model of nasal polyps: similarities and differences with human nasal polyps

Dong-Young Kim

Seoul National University College of Medicine, Seoul, Korea

Animal model systems are valuable for investigating human diseases and developing new therapeutic targets. Our laboratory recently established a murine model of nasal polyps (NP) and investigated similarities and differences between this murine model and human NP. It was previously demonstrated that B cell–activating factor of the TNF family (BAFF), a key B-cell survival factor, is highly expressed in NP tissue from patients with chronic rhinosinusitis with nasal polyps (CRSwNP). Several reports also have shown increased levels of various isotypes of immunoglobulins, including IgG, IgE, and IgA, in sinus tissue from patients with CRS. Therefore, we aimed to focus this investigation on B cell activation in this murine NP model.

Mice were sensitized with an intraperitoneal injection of PBS or 25 μg of ovalbumin (OVA; grade V; Sigma, St. Louis, MO) plus 2 mg of aluminum hydroxide gel (Alum) on days 0 and 7. After general sensitization, mice were locally challenged with PBS or 6% OVA into their nostrils daily from day 14 to day 20. To generate NP-like tissues, 6% OVA with *Staphylococcus aureus* enterotoxin B (SEB, 10 ng) was instilled into the nasal cavity of mice 3 times a week for 8 weeks after induction of an OVA-induced allergic rhinosinusitis. Negative control mice did not receive either OVA or SEB. The OVA group mice were challenged nasally with only 6% OVA without SEB. The development of NP was confirmed by hematoxylin and eosin staining. The mRNA and protein levels of various inflammatory cell markers and mediators were measured by real-time PCR in nasal tissue and by ELISA in nasal lavage fluid (NLF), respectively. Total immunoglobulin isotype levels in NLF were also quantitated using the Mouse Immunoglobulin Isotyping Multiplex kit (EMD Millipore, Billerica, MA) on a Luminex 200 instrument (Life Technologies, Grand Island, NY), and normalized to total protein.

The H & E staining of nasal tissue revealed that mice challenged with OVA plus SEB (NP group) developed multiple edematous polypoid lesions with heavy eosinophilic infiltrations, whereas mice challenged with only OVA (OVA group) showed eosinophilic infiltrations, but no polypoid lesions. Similar to human NP, there were significant increases in gene expression of inflammatory cell markers such as CD19 (2-fold), CD138 (3-fold), CD11c (9-fold), and MCP-6 (300-fold) in nasal tissue samples of the NP group compared with those of the control group ($P < 0.05$). In further investigations of B cell activation, mRNA expressions of BAFF (3-fold) and A Proliferation Inducing Ligand (APRIL, 2.5-fold) were found to be significantly increased in murine NP tissue ($P < 0.05$). BAFF protein concentration in NLF was significantly higher in the NP group than in the control group (1.5-fold, $P < 0.05$). IgA and IgG_1 levels in NLF were significantly higher in the NP group compared with the control group ($P < 0.05$).

In conclusion, this study demonstrated that the NP mouse model confirms enhanced B-cell responses, reminiscent of the activation of B cells in human NP. The value of mouse models in general, and this model of CRS in particular, is that genetically manipulated mice are available and can be used to test the importance of various therapeutic targets for therapeutic intervention, such as BAFF. Mouse models can also be utilized to explore pathogenic mechanisms and to identify novel biomarkers of disease.

Obesity & Inflammatory Airway Diseases: Roles of Mucin Gene as a Connecting Link

Yong-Dae Kim[1,2]

[1]Department of Otorhinolaryngology-Head and Neck surgery, College of Medicine, Yeungnam University, Daegu, Republic of Korea
[2]Regional Center for Respiratory Diseases, Yeungnam University Medical Center, Daegu, Republic of Korea

Obesity has emerged as an important risk factor for inflammatory airway diseases. There has been a remarkable increase in the prevalence of obesity worldwide as a consequence of the modern eating habits associated with a sedentary lifestyle. Along with the growing prevalence of obesity and metabolic syndrome, a concomitant rise in the incidence of inflammatory airway diseases, such as, asthma, COPD, rhinitis has been observed in the last few years. Nevertheless, clinically, obesity is known to increase disease severity, impair the efficacy of medications, and worsening disease control in patient with inflammatory airway diseases.

Mechanisms underlying obesity-related inflammatory airway diseases are not well comprehended yet. Distribution and location of adipose tissue and its adipokine release are determinant factors influencing this correlation. Furthermore, hormones involved in glucose homeostasis and in the pathogeneses of obesity are likely to directly or indirectly link obesity and inflammatory airway diseases. Recently, clinical and basic studies highlighted the association between adipokines or insulin with pro-inflammatory mediators and showed that in accordance with other obesity-associated diseases, low-grade inflammation may be determinant for the pathogeneses of inflammatory airway diseases in obese patients. One key factor in clarifying the association between inflammatory airway diseases and obesity is to understand the intercommunication between the respiratory epithelium and the adipocytes, and to know how insulin and adipokines mediate this conversation.

Mucins play essential roles by regulating mucociliary clearance, protecting airway mucosa from bacteria and toxins, and by aiding the maintenance of airway hemostasis under normal and inflammatory conditions. Major secreted and membrane-bound mucins, are overexpressed in inflammatory airway diseases such as asthma, chronic bronchitis, chronic obstructive pulmonary disease, and rhinosinusitis. They lead to airway obstruction, increasing susceptibility to infection, and decreasing pulmonary function. In addition, it is also regulated by stimulating several inflammatory cytokines and hormones. Therefore, we focused on the relationship between obesity-related pathologic conditions (increased adipokines, hyperinsulinemia) and the regulation of major mucin genes expression. Through review of our previous studees, we want to talk about the changes in mucin gene expression in obesity, as one of the major causes of the severity of airway disease in obese patients.

International Session 3

10月3日（土）

15:50～17:00

司会：川内　秀之（島根大学），岡野　光博（岡山大学）

1. Shifting concepts for surgery in CRS: from ventilation to access for topical therapy
   演者：Richard Harvey
   （Program Head and Conjoint Professor, Rhinology & Skull Base Surgery, University of New South Wales & St Vincent's Hospitals / Clinical Professor, Macquarie University）

2. Role of ESS in sinonasal papillomas
   演者：BS Gendeh
   （Department of ORL-HNS, National University Malaysia Medical Center, Kuala Lumpur, MALAYSIA）

3. SCUAD in adult and pediatric population.
   演者：Emmanuel Prokopakis
   （Department of Otorhinolaryngology, University of Crete, Faculty of Medicine, Crete, GREECE）

4. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study
   演者：Stephan Vlaminck
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Shifting concepts for surgery in CRS: from ventilation to access for topical therapy

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Chronic sinus disease, for the majority of patients, is not a disease of ostial obstruction. While simple clinical examples exist where occlusion of ostia, the ostio-meatal complex or simply poor ventilation, these cases are easily treated with a variety of surgical techniques. However, many CRS suffers have diffuse disease, associated lower airway involvement and areas of severe oedema/polpys next to near-normal mucosa. Simple surgical interventions are not the answer for these patients. The goals of surgical intervention must align with what pathophysiological alteration is to be brought about to change the underlying condition. Creating a surgical neo-sinus cavity is critical for success as it allows effective topical therapy. This talk highlights the evidence for such an approach and discusses the outcomes for patients with significant polyposis that has changed the fundamental way in which such patients are treated. Revision polypectomy operations are uncommon in our centre as management is better aligned with our current understanding of the condition.

Role of ESS in sinonasal papillomas

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Inverted papilloma are benign sinonasal tumors that have a propensity to recur after surgical resection and may undergo malignant transformation. For this reason, complete resection is essential for the successful management of these tumors. Advances in endoscopic techniques and experience, as well as improved radiologic accuracy and navigation, are increasing the role of minimally invasive, endoscopic approaches for surgical resection of inverted papilloma. The following represents a review of the important and recent literature on the pathophysiology, diagnosis, and management of inverted papilloma.

RECENT FINDINGS:

Studies of altered epithelial cell proliferation and cell cycle regulation have elucidated mechanisms of inverted papilloma pathogenesis. Radiographic findings, such as thickening of bone or osteitis, have been demonstrated to be useful in determining preoperative staging and for surgical planning. Outcomes studies suggest that endoscopic and combined endoscopic/external approaches now equal the effectiveness of traditional open procedures with decreased morbidity and reduced hospital stays.

SUMMARY:

A better understanding of alterations in epithelial cell proliferation and cell cycle regulation in inverted papilloma may lead to adjuvant medical therapies to decrease recurrence rates and improve treatment. Endoscopic approaches continue to gain acceptance and have become the standard of care for resection of sinonasal inverted papillomas.

SCUAD in adult and pediatric population.

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We address recent research findings on recalcitrant chronic rhinosinusitis (CRS) in relation to "Severe Chronic Upper Airway Disease" (SCUAD).

Complex pathophysiological mechanisms characterize various forms of chronic rhinitis and rhinosinusitis (CRS), where inflammation persists in spite of adequate medical treatment. In these cases, a multifactorial etiology often underlies the development of sino-nasal inflammation. The interaction between chronic upper and lower airway inflammation via neurogenic and systemic pathways may complicate the therapy of these patients, and lead to insufficient symptom control.

The recently introduced definition of "Severe Chronic Upper Airway Disease" (SCUAD) increases awareness of those patients with persistent inflammation and symptoms despite guideline-driven pharmacologic treatment. The concept of SCUAD may prove helpful in directing research towards clarifying the definition, diagnosis and pathophysiology of rhinitis and rhinosinusitis, their limits and overlap.

Pediatric SCUAD represents a heterogenous group of patients and has significant clinical and socioeconomic implications. Relevant literature is generally lacking and questions regarding definition and pathogenesis remain unanswered.

Accurate definition and acknowledgement of pediatric SCUAD cases may lead to better design of future clinical and molecular research protocols. This may provide improved understanding of the underlying disease processes, more accurate data regarding socioeconomic burden, and, above all, more successful treatment and prevention strategies.

A hypothesis on SCUAD immunopathology is also presented.

The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study

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BACKGROUND: Patients with chronic rhinosinusitis with/without nasal polyps (CRSwNP/CRSsNP) benefit from endoscopic sinus surgery (ESS), with an estimated success rate of 80%. At present, it remains unclear to what extent the presence of eosinophils, eosinophilic mucin (EM) and fungal hyphae (FH) in secretions influence the clinical outcome and recurrence of disease after ESS.
OBJECTIVE: By delineating CRS groups and subgroups based on the finding of eosinophils, EM and FH, differences in the frequency of recurrent disease after ESS over a longer period of time were investigated.
METHODS: A prospective mono-centre study including 221 CRS patients who were unresponsive to medical treatment and underwent ESS, was performed. All tissue and sinonasal secretions were microscopically examined for the presence of eosinophils, EM and FH. Patients were followed for 3 years after surgery. Recurrence was defined according to the EPOS clinical control assessment, based on nasal endoscopy, symptoms and the need for systemic treatment.
RESULTS: In total, 96 CRSwNP and 125 CRSsNP patients were included. Tissue eosinophils were found in 78% of CRSwNP patients compared to 42% in CRSsNP. Eosinophilic mucin was observed in 52% of the CRSwNP group versus 20% of the CRSsNP group. Furthermore, secretion analysis revealed FH in 7% of CRS. Recurrence in the total group was 22% over 3 years. CRSwNP patients with tissue eosinophilic involvement showed a recurrence rate of 48%. When the airway mucus secretions were positive for EM the recurrence rate was 51%.
CONCLUSION: The presence of eosinophils in the tissue or secretions greatly increases the risk of recurrent disease in CRSwNP patients. The finding of tissue eosinophilia and EM in the collected sinonasal airway mucus secretions provides valuable information regarding the clinical outcome and the increased likelihood of CRS recurrence after ESS, whereas the finding of FH does not.