Oral Presentation 3

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· **Chairs:** Jae-Won Oh (Hanyang Univ.), Byung Jae Lee (Sungkyunkwan Univ.)

OP-25

The activation of transient receptor potential melastatin 8 (TRPM8) receptors of bronchial epithelial cells induces airway inflammation in bronchial asthma

Joo-Hee Kim[1]*, Young-Suk Jang[1], Ji Young Park[1], Yong Il Hwang[1], Sunghoon Park[1], Seung-Hun Jang[1], Ki-Suck Jung[1], Hae-Sim Park[2]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine Hallym University Medical Center, Hallym University College of Medicine, Anyang, [2]Department of Allergy and Clinical Immunology, Ajou Univerisity School of Medicine, Suwon, Korea

Background: The airway epithelium is exposed to a range of irritants in an environment which can trigger airway inflammation. Cold air is a major environmental factor that exacerbates bronchial asthma, and transient receptor potential melastatin family member 8 (TRPM8) receptor is a cold- and menthol-sensing cation channel expressed in sensory neurons as well as bronchial epithelial cells.
Objectives: We sought to explore the role of TRPM8 receptor expressed in bronchial epithelial cells in airway inflammation.
Methods: Human airway epithelial cell line, BEAS-2B, was treated with TRPM8 agonist (menthol), TRPM8 antagonist (BCTC, N-(4-tert-butylphenyl)-4-(3-chloropyridin-2-yl) piperazine-1-carboxamide) and dexamethasone in dose- and time-dependent manner. The mRNA of TRPM8 and epithelial driven cytokines such as IL-25, 33, and TSLP was determined by real-time quantitative PCR. The expression of TRPM8 in bronchial epithelial cells was determined by western blotting and immunofluorescence. ELISA of TRPM8 was performed using the induced sputum of asthmatics and normal controls.
Results: TRPM8 was expressed primarily in bronchial epithelial cells at both mRNA and protein levels. Activation of the TRPM8 receptors by menthol was coupled with the enhanced expression of the IL-25, 33, and TSLP and treatment with BCTC and dexamethasone attenuated the expression of the cytokines. TRPM8 protein expression was significantly increased in patients with asthma compared with healthy controls using ELISA of sputum supernatants. The expression of IL-25, 33, and TSLP mRNA increased in the sputum of asthmatics compared than normal controls. There was a significant association between these cytokines and TRPM8 mRNA expression.
Conclusions: Activation of the TRPM8 receptor of bronchial epithelial cells induces airway inflammatory cytokines, suggesting the TRPM8 receptor may involve in cold-induced asthma exacerbations

Key Words: Transient receptor potential melastatin family member 8 (TRPM8) receptor, cold air, airway inflammat

OP-26

Leukotriene receptor antagonist attenuates airway remodeling by suppressing TGF-β signaling

Jung Hur, Ji Young Kang, Chin Kook Rhee, Young Kyoon Kim, Sook Young Lee*

Division of Allergy and Pulmonary Medicine, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background/Objective: Asthma is a chronic airway disease characterized by airway eosinophilic inflammation and remodeling which are associated with a loss in lung function. Although both contribute significantly to asthma pathogenesis, mechanistic studies and drug discovery have focused on inflammatory targets. In this study, we investigated the effect of leukotriene receptor antagonist, pranlukast, on allergic airway inflammation and remodeling in vivo and in vitro.
Method: Four groups of female BALB/c mice [control (CON); ovalbumin-sensitized and challenged (OVA); DMSO treated OVA (OVA+DMSO); pranlukast treated OVA (OVA+Pran.)] were examined. Lung pathology, cytokine production and AHR measuring were compared among these groups. A human fetal lung fibroblast HFL-1 cell line was used in the peribronchial fibrosis analysis.
Results: OVA-sensitized and challenged mice exhibited allergic airway inflammation and significant increases in Th2 cytokines. Pranlukast treated mice showed significant attenuation of allergic airway inflammation. The pranlukast treatment decreased AHR and attenuated airway remodeling to goblet cell hyperplasia, collagen deposition, α-smooth muscle actin expression, pro-fibrotic gene expression. We further demonstrated that pranlukast not only inhibited TGF-β1-induced Smad signaling in human fetal lung fibroblast cells, but also simultaneously reduced the collagen synthesis and pro-fibrotic gene expression.
Conclusions: Leukotriene receptor antagonist, pranlukast, can reduce airway inflammation and remodeling by inhibiting TGF-β/Smad signaling in OVA-sensitization and challenged asthma mice model thus can suppress AHR.

Key Words: LTRA, Airway remodeling, Asthma

OP-27

Platelets Constitutively Express IL-33 Protein and Modulate Eosinophilic Airway Inflammation

Tomohiro Takeda[1,2], Hirotoshi Unno[2], Hideaki Morita[2], Hirohisa Saito[2], Akio Matsuda[2], Kenji Matsumoto[2]

[1]Department of Health Sciences, Kansai University of Health Sciences, Osaka; [2]the Department of Allergy and Immunology, National Research Institute for Child Health and Development, Tokyo, Japan

Purpose: Recent studies revealed that platelets are activated during asthma exacerbation and that depletion of platelets in a mouse model of asthma improves airway inflammation. However, the precise mechanisms of how platelets regulate allergic inflammation are not fully understood. IL-33, an IL-1 family cytokine, has recently attracted attention as a critical cytokine in the development, exacerbation and prolongation of allergic diseases, including asthma. In this study, we sought to determine the expression of IL-33 protein by platelets and its functional significance in airway inflammation.
Methods: IL-33 protein in human platelets, the human megakaryocyte cell line MEG-01, and bone marrow-derived mouse megakaryocytes, was detected by using Western blot analysis and fluorescent immunostaining. We examined the functional relevance of IL-33 protein in platelets by comparing platelet-intact and platelet-depleted groups in a murine model of IL-33-dependent airway eosinophilia elicited by intranasal inhalation of papain (25 μg/day x 3 days). We further compared the additive effect of administration of platelets derived from wild-type versus IL-33-deficient mice on the papain-induced eosinophilia.
Results: Platelets and their progenitor cells, megakaryocytes, constitutively expressed full-length IL-33 protein (31 kDa). Cytosol, but not nuclear, fractions of MEG-01 also expressed full-length IL-33 protein. Depletion of platelets resulted in a significant decrease in eosinophilic, but not neutrophilic, inflammation in papain-treated mouse airways. Conversely, concomitant administration of platelets derived from wild-type mice but not IL-33-deficient mice enhanced the papain-induced airway eosinophilia.
Conclusion: Our novel findings suggest that platelets might be important cellular sources of IL-33 protein in vivo and that platelet-derived IL-33 might play a key role in airway inflammation.

OP-28

The Distribution and Regulation of the Cadherin-related Family Member 3 Expression in Human Respiratory Epithelial Cells

Renee WY Chan[1]*, Kin P Tao[1], Joseph GS Tsun[1], Gary WK Wong[1], Samuel MW Chow[2], Judith CW Mak[3], Wai M Lee[5], John M Nicholls[4], Ting F Leung[1]

[1]Department of Paediatrics and [2]Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR; [3]Departments of Medicine and Pharmacology & Pharmacy, [4]Department of Pathology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR; [5]Biological Mimetics, Inc., Frederick, MD, USA

Purpose: Cadherin-related family member 3 (CDHR3, rs6967330) is identified as a susceptible gene locus for early childhood asthma with severe exacerbations in genome-wide association study published in 2014. In early 2015, the same transmembrane protein is found to be the cellular receptor for a newly identified human rhinovirus member, human rhinovirus C (RV-C). Intriguingly, the RV-C infection is the leading cause of childhood wheezing illnesses and asthma exacerbation. A susceptible CDHR3529Y had more cell surface expression and yielded ten-fold more RV-C progeny viruses. This finding infers that factors that could induce an overexpression of CDHR3 at the cell surface might lead to a greater susceptibility of RV-C. This study aimed to address the distribution and to identify relevant factors that regulate the CDHR3 expression.
Methods: Human respiratory tissue were stained for the CDHR3 expression from the upper to the lower airway. Nasopharyngeal, bronchial and alveolar type II epithelial cells were subjected to the incubation of cytokines (IL4, IL5 and IL13), aeroallergens (Cigarette smoke-conditioned medium (CSM), Lipopolysaccharides (LPS), dust mite extract), dexamethasone. The expression level and its cellular localization of CDHR3 were determined. An RV-C infection upon these treatments was performed as a functional test.
Results: CDHR3 is highly expressed in the epithelia of the nasopharynx and bronchus but is scant in the alveolar epithelium of adult. IL-5, CSE and LPS enhanced the CDHR3 expression in the respiratory epithelial cells. More importantly, the dexamethasone induced >6-fold expression of CDHR3 and both CSM and dexamethasone enhanced the replication of rhinovirus.
Conclusion: CDHR3 expression would be regulated upon the exposure of airway epithelial cells to relevant stimuli. The identification of the CDHR3 regulatory pathways may contribute to the airway remodeling in asthma and address part of the pathogenesis of asthma exacerbation.

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OP-29

Doxycycline down-regulates TGF-β1-induced extracellular matrix production in nasal polyp-derived fibroblasts

Jae-Min Shin[1], Joo-Hoo Park[2], Seung-Ae Lee[3], Il-Ho Park[1], Heung-Man Lee[1]*

[1]Department of Otorhinolaryngology-Head and Neck Surgery; [2]Division of Brain Korea 21 Program for Biomedical Science; [3]Research-Driven Hospital, Korea University Guro Hospital; Korea University College of Medicine, Seoul, Korea

Purpose: Doxycycline has been shown to have antibacterial and anti-inflammatory effects and suppresses collagen biosynthesis. The purpose of this study was to evaluate the effects of doxycycline on transforming growth factor (TGF)-β1-induced myofibroblast differentiation and extracellular matrix production in nasal polyp-derived fibroblasts (NPDFs). We also determined the molecular mechanisms of action for doxycycline.
Methods: NPDFs were isolated from nasal polyps from 8 patients. Doxycycline was used to pretreat TGF-β1-induced NPDFs. Cytotoxicity was evaluated using a 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl-tetrazolium bromide assay. Expression levels of α-smooth muscle actin (SMA) and fibronectin were measured using Western blot, reverse-transcription polymerase chain reaction, and immunofluorescence staining. Total collagen production was analyzed with the Sircol collagen assay, while mitogen-activated protein kinase (MAPK) and NF-κB activation were determined using Western blot analysis. Luciferase assay was used to evaluate the transcriptional activity of NF-κB.
Results: Although doxycycline (0 to 40 μg/mL) had no significant cytotoxic effects in TGF-β1-induced NPDFs, it significantly reduced the expression levels of α-SMA, fibronectin, and collagen in TGF-β1-induced NPDFs in a dose-dependent manner. Doxycycline also inhibited the TGF-β1-induced activation of p38, c-Jun NH2 -terminal kinase (JNK), and NF-κB, and its inhibitory effects were similar to those of the specific inhibitors for each.
Conclusions: Doxycycline has an inhibitory effect on TGF-β1-induced myofibroblast differentiation and extracellular matrix production via the p38 and JNK/NF-κB signal pathways in NPDFs.

Key Words: Doxycycline, extracellular matrix production, nasal polyp

OP-30

Phosphoinositide 3-kinase delta contributes to the formation of nasal polyp associated with eosinophilic inflammation

Yong Chul Lee[1*], So Ri Kim[1], Jong Seung Kim[2], Jae Seok Jeong[1], Kyung Bae Lee[1], Seung Yong Park[1], Yeong Hun Choe[1], Sam Hyun Kwon[2]

[1]Division of Respiratory Medicine and Allergy, Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, [2]Department of Otorhinolaryngology-Head and Neck Surgery, Chonbuk National University Medical School, Jeonju, Korea

Nasal polyp (NP) arising from sinonasal area is often associated with obstruction of sinus ostia and subsequent development of chronic rhinosinusitis (CRS). Previous researches have suggested that CRS associated with NP predominantly manifests eosinophil-dominant T helper type 2 cell (TH2)-associated inflammation, however, it is not known exactly how NP develops. Phosphoinositide 3-kinases (PI3Ks) are lipid signaling kinases which activate downstream cascades of protein phosphorylation. The important roles of PI3K-δ isoform in lung inflammation have been well demonstrated, however, potential role of PI3K-δ signaling in the formation of NP and associated inflammation in nasal cavity has not been characterized. In this study, we aimed to define the possible implication of PI3K-δ in nasal inflammation associated with NP through analyzing NP tissues obtained from patients with CRS. A total of 43 patients were enrolled in this study. Among them, 33 subjects had NP and concurrent CRS. We also obtained inferior turbinate tissues from 10 subjects who underwent other rhinological surgeries (e.g. septoplasty) as control samples. Results showed that protein expression of p110δ (catalytic subunit of PI3K-δ) in NP tissues were remarkably increased compared to those of control tissues. Levels of a key downstream mediator of PI3K-δ, AKT, were also elevated in NP tissues and increased p110δ expression was closely correlated with more severe endoscopic, radiographic, and symptomatic features of CRS in patients. Interestingly, p110δ expression were dramatically increased in eosinophilic NP, which is closely related to the complicated clinical courses of the disease, compared to those of non-eosinophilic NP. These findings suggest that PI3K-δ may be involved in the formation of nasal polyp, particularly eosinophilic nasal polyp associated with more severe clinical symptoms and radiological features.

Key Words: Nasal polyp, chronic rhinosinusitis, Phosphoinositide 3-kinase delta

OP-31

Establishment of the First Prospective Web-based Registry on Anaphylaxis in Korea and the Initial Report from the Registry

Kyunguk Jeong[1], Young-Min Ye[2], Ji-Won Kwon[9], Yoon Seok Chang[10], Yoon Hee Kim[3], Se-Ah Jeon[1], Young Sil Kang[11], Yoo Seob Shin[2], Kyung Won Kim[3], Kyung Hee Park[4], So-Yeon Lee[5], Song-I Yang[5], Joo-Hee Kim[6], Hye Mi Jee[7], Mi-Ae Kim[8], Sooyoung Lee[1]*

[1]Department of Pediatrics, Ajou University School of Medicine, [2]Department of Internal Medicine, Seoul National University Bundang Hospital, [3]Medsoft, [4]Department of Allergy and Clinical Immunology, Ajou University School of Medicine, [5]Department of Pediatrics, Severance Hospital, Institute of Allergy, Yonsei University College of Medicine, [6]Division of Allergy and Immunology, Department of Internal Medicine, Yonsei University College of Medicine, [7]Department of Pediatrics, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, [8]Division of Pulmonary, Allergy, and Critical Care Medicine, Hallym University College of Medicine, [9]Department of Pediatrics, CHA University School of Medicine, [10]Department of Pulmonary, Allergy, and Critical Care Medicine, CHA University School of Medicine, [11]Department of Pediatrics, Seoul National University Bundang Hospital

Purpose: To collect precise and standardized data and provide disease control strategy, we have developed the first prospective web-based registry of anaphylaxis in Korea, including all ages. Here we report the initial data from the registry.
Methods: The case report form was developed by experienced allergists, and the web-based registry was established in cooperation with a professional medical software team. Eleven departments from 6 hospitals took part during the first 5 months (Nov 2016 ? Mar 2017).
Results: The number of anaphylaxis cases registered was 112. The median age was 4 years, and 78.5% were less than 18 years old. In children, foods (87.5%) were the most common cause of anaphylaxis followed by drugs (5.7%), whereas in adults, drugs (50.0%) were more common than foods (29.2%). The most common food triggers were eggs (37.7%), milk (13.0%), and wheat (10.4%) in children, and crabs (57.1%) and wheat (42.9%) in adults. Among drug triggers in adults, antibiotics (58.3%) were the most common cause followed by NSAIDs and H2-blockers (16.7% each). The onset time was ≤ 10 minutes in 50.0%. In children, home was the place of occurrence in more than half of the cases, whereas adults experienced anaphylaxis in out-of-home settings more often. Co-factors were present in 30.4%. Among the 57 cases registered via the emergency department of participating hospitals, epinephrine was administered in 68.4% (54.5% in adults, 71.7% in children and the route of administration was IM in 87.1%, IV in 7.7%, both IM and IV in 2.6%, and subcutaneous in 2.6%. The number of epinephrine administration was single in 84.6%, twice in 12.8%, and thrice in 2.6%.
Conclusion: This multicenter prospective registry would provide a better understanding of anaphylaxis, and provide visionary modalities to improve the management and prevention of anaphylaxis in Korea. [Funded by the Korea Centers for Disease Control and Prevention (2016-E67001-00).]

Key Words: Anaphylaxis, Prospective registry, All age

OP-32

Early Introduction of Egg for Infants with Atopic Dermatitis to Prevent Egg Allergy: A Double-Blind Placebo-Controlled Randomized Clinical Trial

Osamu Natsume, Shigenori Kabashima, Junko Nakasato, Kiwako Yamamoto-Hanada, Masami Narita, Mai Kondo, Mayako Saito Ai Kishino, Eisuke Inoue, Hirohisa Saito, Yukihiro Ohya*

Division of Allergy, National Center for Child Health and Development, Tokyo, Japan

Purpose: We investigated whether the early introduction of small amounts of egg for infants with atopic dermatitis could prevent egg allergy at the first year of life.
Methods: This intervention was carried out as a design of a double-blind, placebo-controlled, parallel-group, randomized clinical trial (DBPCRCT). Infants with atopic dermatitis were randomly assigned into one of the two groups of placebo or egg consumption group. They were enrolled between 4 to 5 months of age and started taking the egg powder or placebo from 6 months until 12 months of age daily. Participants of intervention arm (egg group) took 50 mg of heated egg powder from 6 to 9 months and 250 mg from 9 to 12 months of age. The primary outcome was a prevalence of hen's egg allergy at 12 months of age proved with oral food challenges.
Results: This trial was completed based on the result of a scheduled interim analysis which showed significant difference between the two groups. The number of participants analyzed with intention-to-treat way was 121 (placebo group n=61; egg group n=60). The prevalence of egg allergy was 37.7% in placebo group and 8.3% in egg group (p=0.0013). There was no significant difference in adverse events between the both groups.
Conclusion: Introduction of small amount of heated egg at 6 months old followed by step up process on the way is the effective and safe way for infants with atopic dermatitis to prevent hen's egg allergy at the first year of life.Trial registration is UMIN-CTR 000008673.

OP-33

Clinical Value of Component-resolved Diagnosis in Fish Allergy

Nicki YH Leung, Agnes SY Leung, Gary WK Wong, Ting F Leung*

Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

Purpose: Current diagnosis of fish allergy relies on skin-prick test (SPT) or specific IgE test with a limited choice of commercial fish extracts. We investigated the diagnostic value of component-resolved diagnosis in fish allergy, using recombinant allergen components parvalbumin, enolase and aldolase from two commercially important species in Hong Kong.
Methods: The IgE reactivity of these patients to parvalbumin, enolase and aldolase from the grass carp *Ctenopharyngodon idella* and large yellow croaker *Larimichthys crocea* were measured by enzyme-linked immunosorbent assay (ELISA). IgE reactivity to cod parvalbumin was also measured to investigate whether the use of exotic fish for diagnosis is equally sensitive. Eighteen paediatric subjects with a clinical history of fish allergy and a positive SPT results to white fish mix or salmon were recruited.
Results: Eleven children were positive to parvalbumins, while two subjects were positive to enolase or aldolase. Despite the high similarity of parvalbumin sequences among grass carp, large yellow croaker and cod, only seven subjects were positive to all three parvalbumins. Nevertheless, all subjects exhibited the strongest reactivity towards grass carp parvalbumin. Competitive inhibition ELISA revealed that grass carp parvalbumin inhibited >85% of the binding of specific IgE to both large yellow croaker and cod parvalbumins, while reciprocally only inhibition of 60% and 50% could be achieved respectively, suggesting grass carp parvalbumin as the dominant fish allergen in our population.
Conclusion: Grass carp parvalbumin has the highest sensitivity of predicting IgE-mediated fish allergy in the Hong Kong population. This study highlights the superior sensitivity in using local fish species for diagnosis compared to exotic species. The use of component-resolved diagnosis also identified subjects outgrowing fish allergy which yielded false positive results in skin prick test with fish extracts.

[This study is supported by a research grant from the Hong Kong Institute of Allergy.]

OP-34

Tolerogenic Gene Signatures and Pathways Directing the Prevention of Shrimp Allergy in Murine Model in a Hypoallergen DNA Vaccine-based Immunotherapy

Christine YY Wai[1,2] Jing Qin[1], Nicki Y.H. Leung[1,2], Patrick S.C. Leung[3]*, Ka Hou Chu[1]*

[1]School of Life Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong; [2]Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; [3]Division of Rheumatology/Allergy, School of Medicine, University of California, Davis, CA 95616, USA

Purpose: Tolerogenic dendritic cells (tDCs) and regulatory T (Treg) cells were identified as key regulatory players in successful allergen-specific immunotherapy (AIT). However, the signaling events leading to the promotion of their recruitment, function and activity are largely unknown. We have previously constructed a DNA vaccine by expressing a shrimp tropomyosin hypoallergen, MEM49, in the plasmid pCI-Neo. BALB/c mice injected with the vaccine were protected against allergic sensitization. Based on this observation, we aim at dissecting the modulatory mechanism of this hypoallergen DNA vaccine-based formulation in the current study.
Methods: Total RNA from the ileum of naive mice (negative control), tropomyosin-sensitized mice (positive control) and pre-vaccinated mice (prophylactic group) are sampled for RNA-sequencing on the Ion Torrent Proton Platform.
Results: By differentially expressed genes (DEGs) annotation, we identified significant enrichment in genes related to a heightened energy metabolism, upregulation of tDCs markers *IDO1* and *CD274* (*PD-L1*), as well as Treg-specific markers including *NT5E* (*CD73*) and *ENTPD1* (*CD39*) in the pre-vaccinated mice. To infer the relationship among these DEGs and events, gene set enrichment analysis (GSEA) and transcription factor (TF) binding site determination were conducted. We propose that MEM49 DNA vaccine activates TLR9 and leads to a heightened PI3K/AKT signaling that manifests metabolic reprogramming in DCs. Such coupling also activates the TFs *AHR* and *IRF8* in DCs to induce *IDO1* expression and IDO1 catabolizes tryptophan into kynurenine and induces *CD39* and *CD73* expression in Treg cells. All these events then directed the prevention of shrimp allergic responses in our murine model.
Conclusion: Our data provides important clues to mechanisms linking AIT to tolerogenic cells induction. Future studies will be directed to cell-specific transcriptomic analyses to validate the proposed molecular pathways of MEM49 DNA vaccine.

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OP-35

Increasing prevalence of adult-onset food allergy due to nuts

Chang-Gyu Jung, Eun-Mi Yang, Hyun Mi Kim, Ji-Ho Lee, Young-Min Ye, Hae-Sim Park*

Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea

Nut allergy is a serious problem worldwide. While symptom onset of nut allergy occurs mostly during childhood, there is a considerable number of patients whose symptoms first begin to appear after the age of 19 years, but their clinical features are not well understood. The aims of this study were to evaluate the prevalence and clinical features of nut allergy in adults, especially adult-onset nut allergy.
96 adult patients who had suffered from allergic symptoms provoked by nuts were enrolled from Ajou University Hospital, Korea between January, 2011 and June, 2016. During the study period, a list of patients who received the diagnostic code of Food allergy and/or underwent ImmunoCAP tests to nuts were enrolled after receiving medical records. Two allergy specialists reviewed medical records and analyzed their clinical findings.
The number of patients with nut allergy and anaphylaxis has increased (11 and 2 in 2012; 26 and 8 in 2015). The female ratio was higher and the mean age was 41.41 years (range, 19-70 y). Major clinical symptoms were urticaria/angioedema (94.8%/41.7%), followed by respiratory symptoms (24.0%). Major causative nuts were peanut (57.3%), followed by walnut (31.3%). Adult-onset nut allergy patients accounted for 41.7% and anaphylaxis was noted in 28.1% which prevalence was significantly higher in the adult-onset group than in the childhood-onset group (45.0% vs. 16.1%, P=0.002). Among anaphylaxis reactions, respiratory (35.0% vs. 16.1%, P=0.032) and gastrointestinal symptoms (12.5% vs. 0%, P=0.007) were significantly higher in the adult-onset group. Overall, the positive rate of ImmunoCAP (20.8%) was higher than that of skin prick test (9.4%), and increased to 33.3% in the patient group with anaphylaxis.
The prevalence of food allergy due to nuts and anaphylaxis is increasing in an adult population in Korea in which anaphylaxis is more common in adult-onset group. ImmnunoCAP test is more useful than skin prick test to confirm causative nuts.

Key Words: Adult-onset nut allergy; ImmunoCAP

OP-36

The natural course of immediate-type cow's milk and hen's egg allergy in children

Minji Kim[1], Ji Young Lee[2], Hea-kyoung Yang[4], Jihyun Kim[2], Kangmo Ahn[2]*

[1]Department of Pediatrics, Dongtan Sacred Heart Hospital, Hallym University School of Medicine, [2]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [3]Environmental Health Center for Atopic Diseases, Samsung Medical Center, Seoul, [4]Department of Pediatrics, Kangnam General Hospital, Korea

Background: Although most of children with Cow's milk (CM) allergy and hen's egg (HE) allergy are known to outgrow their diseases with time, only a few studies have been reported about the natural course in Korea. The objective of the present study was to investigate the natural course of CM or HE allergy in Korean children and analyze the prognostic factors.
Methods: In this retrospective study, we reviewed data from 189 children with CM allergy and 171 children with HE allergy using medical records and parental telephone interview. Median duration of follow-up was 43.0 months in CM allergy and 36.0 months in HE allergy. Diagnosis of CM or HE allergy was based on a positive oral food challenge test or convincing history of immediate-type food allergy allergic symptoms in combination with the presence of allergen specific IgE ($\geq$0.35 kU/L). Acquisition of tolerance was defined by no allergic symptoms after reintroduction of the offending foods. Kaplan-Meier curve and Cox proportional hazard model was used for the statistical analysis.
Results: The median age at diagnosis of CM and HE allergies were 9.0 months (range 0-30.0 months) and 14.0 months (range 3.0-39.0 months), respectively. Half of children outgrow CM allergy at the median age of 8.7 years. CM-specific IgE level at diagnosis was a significant prognostic factor for oral tolerance in CM allergy. The median age to acquire oral tolerance in 50% of patients with HE allergy was 5.6 years. HE-specific IgE level at diagnosis and family history of allergic diseases significantly affect the prognosis in children with HE allergy.
Conclusions: In Korean children with CM and HE allergies, one half resolves at the age of 104.8 months and 67.6 months, respectively. Our results suggest that specific IgE level at diagnosis is the most significant prognostic factor to predict acquisition of oral tolerance in CM and HE allergies.

Key Words: Cow's milk allergy; Hen's egg allergy; Natural course