Oral Abstract Session 5

New Paradigms in Rhinosinusitis and Nasal Polyps

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OAS-45

Age-Associated Changes in Chronic Rhinosinusitis Endotypes

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Objective: The objective of this study was to characterize age-related changes in immunologic profiles according to CRS subtypes and evaluate their clinical implications.
Methods: Subjects in Control, CRS without nasal polyps (CRSsNP), and CRS with nasal polyps (eosinophilic NP: ENP, non-eosinophilic NP: NENP) were enrolled in this study. Twenty-two markers for type 1/2/3 inflammation, and other inflammatory processes were measured in homogenates of sinonasal tissues and statistically analyzed.
Results: In control tissues, cytokines such as type 3, type 2, epithelial, S100A8, and TGF-β1, showed an inverse correlation with age, whereas BAFF was upregulated with age and showed an inverse relationship with TGF-β1. Non-type 2 CRS subjects such as the CRSsNP and NENP groups showed an age-related increase in type 2 cytokines and an age-related decline in type 3-associated cytokines. Interestingly, aging was inversely associated with CT scores, which were positively correlated with type 3 mediators in NENP. Type 2 CRS, ENP, showed an age-related increase in type 3-associated cytokines. Smokers with ENP demonstrated age-associated increases in type 2, type 3, and type 1 mediators as well as CT scores. Atopy status and smoking history affected age-related cytokine changes in CRS. After adjusting statistically for atopy status and smoking history, IL-17A decreased with aging in the CRSsNP group, whereas the ENP group showed an age-related increase in levels of IL-17A. Type 2 mediators such as periostin or CCL-24 increased with aging in non-type 2 CRS.
Conclusion: Age-associated cytokine changes differed among control subjects and CRS subtypes. The non-type 2 CRS group showed an age-related increase in type 2 inflammatory mediators, while the type 2 CRS group demonstrated an age-related increase in type 3 inflammatory mediators.

Key Words: Age, Endotype, Rhinosinusitis

OAS-46

The Diagnosis of Chronic Rhinitis in China with Cluster Analysis

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Purpose: Chronic rhinitis (CR) is currently regarded as a syndrome, which presents as several endotypes. The aim of this study was to identify the CR endotype clusters and investigate the inflammatory patterns associated with the different endotypes.
Methods: A total of 259 CR patients and 20 control subjects were enrolled in this prospective study. Twelve clinical variables were analyzed using cluster analysis and five inflammatory variables were measured to investigate the inflammatory patterns associated with the different clusters.
Results: Six endotype clusters of CR were defined in the Chinese CR patients. Patients in cluster 1 (38.6%) were diagnosed as allergic rhinitis (AR) without asthma, and in cluster 2 (13.5%) as AR with asthma; with all demonstrating positive results for local eosinophils and high levels of local and serum IgE. Similarly, patients in cluster 3 (18.6%) were diagnosed as nonallergic rhinitis with eosinophilia syndrome (NARES) without asthma and in cluster 5 (5.0%) as NARES with asthma; with all demonstrating positive result for local eosinophils, and negative results for both local and serum IgE. Patients in cluster 4 (4.6%), were diagnosed as local allergic rhinitis (LAR) and showed positive results for local eosinophils and local IgE, but negative results for serum IgE; whereas patients in cluster 6 (19.7%) were diagnosed as idiopathic rhinitis (IR) because of high symptoms scores, but negative findings for local eosinophils, local IgE and serum IgE.
Conclusions: Chinese CR patients may be clustered into six endotypes with different inflammatory patterns, which may help in delivering individualized treatment.

OAS-47

PI3K-δ-HIF-VEGF Axis Contributes to Develop Sinonasal Inverted Papilloma

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Sinonasal inverted papilloma (IP) is associated with the recurrent disease and invasion to adjacent tissues. In addition, IP has been regarded as a premalignant lesion, however, not enough information exists on the pathogenesis of the disease. Vascular endothelial growth factor (VEGF) is one of crucial mediators in airway inflammation in part through the regulation of vascular permeability. We previously demonstrated for the first time that vascular leakage and subsequent inflammation of airways can be modulated by PI3K-hypoxia-inducible factor (HIF)-1α-VEGF axis. Herein, we investigated the role of this axis in the pathogenesis of sinonasal IP. IP tissues were obtained from 10 patients during the endoscopic sinus surgery and inferior turbinate tissues as healthy control were obtained from 10 control subjects during septoplasty or skull base surgery. Western blot analyses showed that protein expressions of catalytic subunit of PI3K-δ (p110δ) and phosphorylated AKT, a key downstream mediator of PI3K-δ, were notably elevated in IP tissues compared to those in controls. Furthermore, confocal microscopic analysis demonstrated that expression of p110 δ was prominent in the epithelial and submucosal layers, which substantially co-localized to VEGF and HIF-1α in sinonasal IP tissues. Expression levels of VEGF and HIF-1α protein were strongly correlated with p110δ protein levels in these tissues. These data suggest that PI3K-δ-HIF-VEGF axis may play a role in the pathogenesis of sinonasal inverted papilloma, in part through modulating vascular leakage and plasma exudation.

Key Words: Inverted papilloma, PI3K-δ, HIF-VEGF axis

OAS-48

Predictive Significance of Charcot-Leyden Crystals for Eosinophilic Chronic Rhinosinusitis with Nasal Polyps

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Background: Eosinophilic chronic rhinosinusitis with nasal polyps (ECRSwNP) is a distinct phenotype, with many significantly different clinical features from non-eosinophilic chronic rhinosinusitis with nasal polyps (nonECRSwNP). Thus, identification of subtypes is crucial for precise treatment. Immunohistology is a reliable way to present the subtypes, however, the results mainly depend on the observation of pathologist, the method with automatic readout and the corresponding biomarkers is lacking. The purpose of our research was to explore the predictive value of qRT-PCR as an alternative method and mRNA expression of Charcot-Leyden crystals (CLC) as a corresponding target for ECRSwNP, which may benefit the automatized judgment.
Method: CLC mRNA levels in tissue samples from 48 CRSwNP patients and 10 controls were evaluated by quantitative real-time PCR (qRT-PCR). Hematoxylin and eosin (H&E) staining was performed for histological assessment of CRSwNP and subtyping as ECRSwNP and nonECRSwNP. Factors associated with ECRSwNP were determined with logistic regression analysis, the predictive value was presented by a receiver operating characteristic (ROC) curve and optimal cut-off points of the predictors were identified as Youden's index.
Results: mRNA level of CLC in ECRSwNP was significantly elevated compared to either nonECRSwNP group or control group (both $p<0.001$); with no significant difference between nonECRSwNP patients and controls. CLC mRNA levels were positively correlated with percentages of tissue eosinophil and peripheral blood eosinophil ($p<0.001$, $r=0.683$; $p=0.003$, $r=0.420$, respectively). Logistic regression analysis revealed CLC mRNA level and blood eosinophil percentages were pre-diagnosis factors ($p=0.007$, $p=0.045$, respectively) for ECRSwNP. ROC curves analysis indicated the area under the curve (AUC) of CLC mRNA level was 0.948 which was superior to the blood eosinophil percentage (AUC=0.797) ($p=0.044$) as an optimal biomarker to predict ECRSwNP.
Conclusions: CLC mRNA levels based on the qRT-PCR may serve as a reliable and alternative method for the identification of ECRSwNP.

OAS-49

The Effects of Wnt Signaling on Epithelial-Mesenchymal Transition in Chronic Rhinosinusitis with Nasal Polyp

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Background: Wnt signaling on epithelial to mesenchymal transition (EMT) in chronic rhinosinusitis with nasal polyp (CRSwNP) are not fully understood.
Objective: To evaluate the role of Wnt signaling on EMT of CRSwNP using a murine NP model and human tissues. To analyze molecular markers associated with tissue remodeling and EMT in sinonasal tissues from CRSwNP patients.
Methods: Nasal polypoid lesions were induced in wild type and ApcMin/+ mice and inflammatory markers and EMT-related molecules were analyzed using histopathological evaluation, immunohistochemistry, quantitative real time polymerase chain reaction (PCR) and gene PCR array. A Wnt inhibitor, indocyanine green-001 (ICG-001), was used in a murine NP model with BALB/c mice and the effects on inflammatory mediators were evaluated. Wnt signaling-associated mediators were analyzed using human sinonasal tissues from control subjects and CRS patients.
Results: ApcMin/+ NP mice exhibited more frequent polypoid lesions and nuclear β-catenin positive cells were markedly up-regulated compared to wild type NP mice. The percentage of EMT area and epithelial thickness were significantly increased in ApcMin/+ NP mice. The level of IL-17A and neutrophilic infiltration were increased in ApcMin/+ NP mice. In addition, EMT-related genes including SNAIL3 and TWIST1 were up-regulated in ApcMin/+ mice. Inhibition of Wnt signaling with ICG-001 in NP model mice showed significantly decreased nasal polypoid lesions compared with positive control group. EMT-related markers, the ratio of EMT lesions, and epithelial thickness were decreased and the mRNA levels of IL-4 and IL-17A were markedly suppressed in ICG-001 treated group. Finally, human tissue study showed that nuclear β-catenin was significantly increased in NP tissues and that expression levels of Wnt ligands and Wnd receptors were up-regulated in NP tissues from CRSwNP patients, suggesting increased Wnt singaling in CRSwNP tissue.
Conclusion: Wnt signaling could contribute to the pathogenesis of nasal polyps through EMT. Inhibition of Wnt signaling might be a possible therapeutic strategy for patients with CRSwNP.

Key Words: Nasal polyp, Wnt signaling, Epithelial-mesenchymal transition

OAS-50

Comparison of Comorbidities between Poly- and Mono-Sensitization to Common Aeroallergens in Adult Patients with Rhinitis

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Background: Recent studies have proposed a quantitative trait of IgE sensitization related to the multimorbidity of allergic diseases and the distinct phenotypes of mono-sensitization and poly-sensitization among children and adolescents.
Objective: We evaluated the clinical characteristics of adult rhinitis according to the quantitative trait of IgE sensitization to common aeroallergens.
Methods: The medical records of 1615 patients who were clinically diagnosed with rhinitis by an otolaryngologist based on clinical symptoms were evaluated. The severity of the rhinitis symptoms, comorbidities (asthma, conjunctivitis, and atopic dermatitis), family history of allergic disease, and the results of skin prick tests were reviewed.
Results: We reviewed 898 patients with non-allergic rhinitis (NAR), 392 with mono-sensitized allergic rhinitis (mono-AR), and 325 with poly-sensitized allergic rhinitis (poly-AR). The NAR patients exhibited late disease onset, milder symptoms, and aggravating factor profiles that differed from those of AR patients. Age at onset and rhinitis symptom severity did not differ between mono-AR and poly-AR patients. However, comorbid conjunctivitis and atopic dermatitis were more common in poly-AR than mono-AR patients. The age and age at onset of patients with NAR and mono-AR with comorbid conjunctivitis and atopic dermatitis were much younger than were those of patients without such comorbidities.
Conclusion: The clinical characteristics of adult patients with NAR and AR differed. Frequency of comorbid conjunctivitis and atopic dermatitis in adult rhinitis patients was differed by a quantitative trait of IgE sensitization, and each of the AR and NAR patients seems to have different mechanisms depending on whether they have such comorbidities.

Key Words: Rhinitis, Asthma, Conjunctivitis

OAS-51

Immunologic Modification in Mono- and Poly-Sensitized Patients after Sublingual Immunotherapy

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Objective: To compare immunologic modification and treatment outcomes after two years of sublingual immunotherapy (SLIT) with house dust mite extracts (HDM) between monosensitized and polysensitized patients with allergic rhinitis.
Methods: Among the patients who were prospectively enrolled in the SLIT cohort study, patients with allergic rhinitis who were sensitized to HDM and treated with SLIT for at least two years were studied. All participants underwent serologic tests at baseline and after SLIT to evaluate changes in immunologic parameters. The total nasal symptom score (TNSS) was measured before and after SLIT, and effective and less effective responder groups were categorized depending on whether patients had a TNSS reduction of 50%, as compared with baseline.
Results: The increase in Dermatophagoides pteronyssinus and Dermatophagoides farinae specific immunoglobulin G4 levels was significantly higher in monosensitized patients than those of polysensitized patients ($p=0.020$ and $p=0.005$, respectively). The TNSS significantly improved after SLIT in both the monosensitized and polysensitized groups ($p < 0.001$ in both groups). However, the difference in the changes in TNSS from baseline was not significant between the two groups ($p=0.374$).
Conclusion: This study demonstrated different immunologic modifications after SLIT between monosensitized and polysensitized patients. However, patients in the polysensitized group who were treated with single-allergen SLIT experienced comparable clinical improvement in TNSS to those in the monosensitized group despite demonstrating different immunologic changes.

Key Words: Allergic rhinitis, Immunologic modification, Sublingual immunotherapy

OAS-52

Serological Specific Immunoglobulin E in Nasal Secretion in Diagnosis of Allergic Rhinitis

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Purpose: To analyze the best method for the diagnosis of allergic rhinitis, comparisons were made among skin pick tests (SPTs), nasal secretion sIgE, and serum sIgE.
Methods: A meta-analysis was performed to evaluate the role of nasal secretion antigen-specific IgE (sIgE) in the diagnosis of allergic rhinitis (AR), involving a systematic search of literature in the Medline (1946-), Cochrane Library Databases (1944-), and Embase databases (1947-) up to August 2018, using the Meta-DiSc (vesion1.4) software.
Results: Seven studies were reviewed in the meta-analysis. The assessment indicated significant heterogeneity among the individual studies; thus, the ransomed effects model was used to pool data. The pooled sensitivity (95% CI) of nasal secretion sIgE, serum, and SPT was 0.84 (95% CI 0.79-0.88), 0.98 (95% CI 0.96-0.99), and 0.94 (95% CI 0.89-0.97), respectively, and the pooled specificity (95% CI) was 0.82 (95%CI 0.71-0.90), 0.91 (95%CI 0.82-0.97), and 1 (95%CI 0.78-1), respectively. The area under curves (AUC) of nasal secretion sIgE, serum sIgE, and SPT were 0.9036 (SE=0.0441), 0.9943 (SE=0.0098), and 0.9683 (SE=0.0239), separately. Therefore, sIgE measurement in serum is the superior method for diagnosis of AR, when compared to SPT and nasal secretion sIgE. In terms of high sensitivity and specificity, however, both SPT and sIgE detection in nasal secretion could help in the disease diagnosis.
Conclusions: Based on the available evidence, the measurement of nasal secretion sIgE is a non-invasive way to ascertain local inflammation, which, in combination with SPT and serum sIgE detection, can be beneficial in the diagnosis of AR.

Key Words: Allergic rhinitis, Antigen-specific IgE, Nasal secretion sIgE, Serum sIgE

OAS-53

Associated Factors for Developing Later Asthma Symptoms in Children with Allergic Rhinitis

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Background: Both allergic rhinitis and asthma are considered united airway disease which influence their developments and symptom aggravations each other. We evaluated the associated factors for subsequent asthma symptoms in the elementary school children with allergic rhinitis.
Method: We selected 343 children, aged 6 to 7 years old, who have rhinitis symptoms within 12 months and one more sensitization on skin prick test from 2,491 elementary school children. The questionnaires about symptoms, medical history and environments, blood eosinophil, serum total IgE, pulmonary function test, and bronchial provocation tests were performed. Using the multiple regression analysis, we evaluated the associated factors for later asthma symptoms in the 4 years follow-up.
Results: The independent risk factors for later asthma symptoms among children with allergic rhinitis were higher body mass index (aOR, 95% CI, P-value; 1.285, 1.058-1.561, 0.012), a parental diagnosis of asthma (1.285, 1.058-1.561, 0.008), and a history of bronchiolitis in the first 2 years (6.193, 1.594-24.063, 0.010). However, pulmonary functions, level of bronchial hyper-responsiveness, and the patterns of sensitization showed no significance. Children with the treatment of allergic rhinitis in the follow-up were less likely to have asthma symptoms later (0.168, 0.039-0.727, 0.017).
Conclusion: In the school-aged children with allergic rhinitis, an appropriate treatment of rhinitis and life style modification preventing obesity may decrease the later asthma symptoms.

Key Words: Allergic rhinitis, Asthma, Associated factors

OAS-54

Pathogenic Th2 Cells Develop the Symptoms of Japanese Cedar Pollen-Induced Allergic Rhinitis

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Purpose: Japanese cedar pollen-induced Allergic Rhinitis (JCP-AR) affects up to one-third of the Japanese population, and the patients have been suffering from severe nasal symptoms in pollen season. Allergic rhinitis (AR) consists of three developmental stages based on the presence of antigen-specific IgE and symptoms. The timing and mechanisms of onset in AR remain unclear.
In allergic disease, CD4 T cell subsets are flexible, and we have studied "pathogenic Th2 (Tpath2) cells", which constitute a population of Th2 cells with additional pathogenic characteristics. We investigated those stages of JCP-AR and the effects of sublingual immunotherapy with Tpath2 cells.
Methods: Patients with JCP-AR and healthy volunteers were divided into "non-sensitized," "asymptomatic sensitized (AS)," and "JCP-AR" groups. Moreover, patients with sublingual immunotherapy were enrolled. We analyzed the CD4 T cell in peripheral blood mononuclear cells (PBMCs) using flow cytometry and real-time polymerase chain reaction. We observed the aggravation of symptoms in the AS stage and the course of symptoms in patients with sublingual immunotherapy.
Results: The ST2 (IL-33 receptor) expression of T cells in PBMCs was upregulated only in the JCP-AR group by stimulation with JCP. In newly afflicted patients, the ST2 expression of T cells was upregulated after the season. Furthermore, even before the pollen dispersal season, the ST2 expression was upregulated. In good-responder of sublingual immunotherapy, the number of ST2 positive CD4 T cells had decreased year by year.
Conclusions: Several factors influence the development of T cell responses to allergen. Our study showed that the emergence and reduction of Tpath2 cells might have an impact on the symptom of allergic rhinitis. ST2-expressing memory Th2 cells may be involved in the onset of allergic rhinitis and the effects of sublingual immunotherapy.

OAS-55

Association of Allergic Rhinitis with New Development of Asthma and Bronchial Hyperresponsiveness in Schoolchildren

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Introduction: Allergic rhinitis (AR) has been well known to be associated with asthma and bronchial hyperresponsiveness (BHR). We investigated the relationship between AR and asthma and estimated the risk of newly diagnosed asthma and BHR in schoolchildren during two years follow-up period.
Methods: This study analyzed 2,308 elementary school children from the Children's HEalth and Environmental Research (CHEER) study, a 4-year, prospective, follow-up study with 2-year intervals. At every survey, skin prick tests (SPTs) and methacholine challenge tests with the International Study of Asthma and Allergies in Childhood questionnaire was performed.
Results: Regardless of atopy, allergic rhinitis was associated with asthma symptoms and treatment within the previous 12 months ($P<0.01$). Atopic AR and non-atopic AR increased the risk of new development of asthma after 2 years (adjusted odds ratio [aOR] 2.24, 95% confidence interval [CI] 1.05-4.77; aOR 3.21, 95% CI 1.78-5.77, respectively).
Compared with children with non-AR, children with atopic AR had a higher frequency of BHR ($P<0.01$) and no difference from children with non-atopic AR. Atopic AR was associated with an increased risk of new development of BHR after two years (aOR 3.69, 95% CI 2.01-6.79).
Conclusion: AR in school-aged children is associated with asthma and increased risk of newly diagnosed asthma. Atopic AR increased the risk of newly developing BHR. Controlling AR can play an important role in preventing asthma and BHR.

Key Words: Allergic rhinitis, Bronchial hyperresponsiveness, Asthma