



Increased TSLP, IL-33, IL-25, IL-19, IL 21 and amphiregulin (AREG) levels in chronic rhinosinusitis with nasal polyp

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Abstract

Objective Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease. The surrogate indicating biomarkers in patients with CRSwNP need further evaluation. The aim of this study was to investigate the association of thymic stromal lymphopoietin (TSLP) and amphiregulin (AREG) cytokines in patients with CRSwNP.

Methods Sinonasal tissue samples were collected from 33 patients with CRSwNP and 29 controls. Levels of AREG, IL-19, IL-21, IL-25, IL-33 and TSLP in nasal polyp and control sinonasal tissues were determined following the enzyme-linked immunosorbent assay method.

Results We found that AREG, IL-19, IL-21, IL-25, IL-33 and TSLP levels were significantly higher in the CRSwNP group compared to the control group ($p < 0.000$; $p < 0.000$; $p < 0.000$; $p < 0.000$; $p < 0.003$; $p < 0.021$, respectively).

Conclusions Our findings indicated that AREG, IL-19, IL-21, IL-25, IL-33 and TSLP were significantly increased in tissue samples of CRSwNP patients and may be considered as molecular indicators and targets for therapeutic developments for patients with CRSwNP.

Keywords Nasal polyp · Chronic rhinosinusitis · Cytokine · Amphiregulin

Introduction

Chronic rhinosinusitis (CRS) is characterised by inflammation of the sinonasal mucosa for at least 12-week duration and affects potentially 8–10% of the world population. CRS is generally classified into two subtypes based on the presence or absence of a nasal polyp: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [1]. In patients with CRS, the presence of sinonasal polyps has been suggested to be a significant factor for the treatment, resistance and recurrence of the disease [2, 3]. Although phenotypes of CRSwNP are similar, the underlying immunological mechanisms may differ. There are recent studies of different CRS endotypes based on response to treatment, recurrence, and underlying etiological factors [4, 5]. Medical and/or surgical treatment results and recurrences may differ in patient

groups with similar phenotype. Using the biomarkers that play a role in the etiopathogenesis of CRSwNP, the classification of the endotype is promising in terms of determining optimal treatment. However, there is no accepted classification on this subject and the data are insufficient.

CRSwNP is a heterogeneous inflammatory disorder with a poorly understood pathophysiology. Although the exact pathways underlying the genesis and development of CRSwNP are not well clarified, pieces of evidence suggest that exacerbation of the inflammatory cytokines derived from increased numbers of inflammatory cells such as eosinophils, neutrophils and Type 2 T-helper lymphocytes in the development of chronic airway disorders such as CRSwNP is involved [6, 7].

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine molecule that has been shown to cause a release of chemokines from neutrophils [8]. IL-21 improves the production of pro-inflammatory cytokines in the mucosa as well as increasing the number of neutrophils [8]. IL-25 has been identified as a key component in the induction and modulation of Th2 inflammatory processes [9] and IL-25 also enhances inflammation via the production of IL-4, IL-5 and IL-13 [10]. IL-19 is clearly implicated in playing an

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important role in asthma. Bacterial toxins and Th2-sourced cytokines (IL-4, IL-13) may stimulate expression and/or release of IL-19. Higher levels of IL-19 may actively contribute to exaggerating the inflammatory responses in CRSwNP patients [11].

Pace et al. reported the over-expression of IL-19 in the epithelium in patients with CRSwNP [11].

AREG is a member of the epidermal growth factor family and binds EGFR to promote cell proliferation and tissue homeostasis [12]. Over-expression of AREG has been demonstrated after pulmonary infection [13]. During the infection, AREG is produced primarily by ILC2s, Tregs and Th2 cells at the stage when adaptive immunity dominates. The role of AREG in CRS pathogenesis has not yet been studied.

The aim of this study was to investigate the role of the mediators of inflammation in CRSwNP pathogenesis by comparing TSLP, IL-19, IL-21, IL-25, IL-33 and AREG levels in the tissue samples of patients with CRSwNP with those of normal controls. From this point of view, the aim was to contribute to data that could be used in the development of target molecules for use in determining the endotype of CRSwNP and future treatment modalities.

Methods

Patient and tissue samples

This prospective clinical study was carried out in collaboration with the otolaryngology and biochemistry clinics in a university hospital and was approved by the university's Ethical Review Board (2017/1084). Patients who were planned to undergo surgery with the diagnosis of CRSwNP (Group 1) and those planned to undergo conchoplasty, endoscopic dacryocystorhinostomy, and concha bullosa surgery with or without septoplasty surgeries (Group 2 or the control group) were enrolled. The control group was formed in accordance with the age and gender of the patient group. Written informed consents were gathered from verbally informed patients who wanted to be included in the study. Surgical and medical histories were taken and comprehensive ENT examinations and paranasal CT scans were performed for the patients who were planned to undergo functional endoscopic sinus surgery with the diagnosis of CRSwNP. Patients were diagnosed according to the European position paper on rhinosinusitis and nasal polyps 2012 [14].

Exclusion criteria for patients in the study were as follows: under 18 years old, smokers, a diagnosis of asthma, aspirin-exacerbated respiratory disease, immunodeficiency, immunological disease, any malign disease, previous sinus surgery, previous CRS diagnosis, any systemic disease, or any systemic/nasal drug treatment. Also, patients who had

used any immunomodulator drug or nasal/systemic steroid within 4 weeks of surgery were not included.

Tissue samples were taken during surgery from patients who met the inclusion criteria. Gathered tissue samples were stored at -85°C for the further analysis of inflammatory mediators.

Tissue ELISA analysis

Tissues were homogenised in 50 mM phosphate buffer at pH 7.4 as 1/10, w/v. Buffer contained protease inhibitor, 0.2 μM phenylmethanesulfonyl fluoride (PMSF) and 1 mM ethylenediaminetetraacetic acid disodium salt (Na_2EDTA), at 4°C for 15 s. Homogenates were centrifuged at 10,000 rpm for 10 min at 4°C and the supernatants used for ELISA analysis. TSLP (cat. no.: E-EL-H1598), IL-25 (cat. no.: E-EL-M0187) IL-33 (cat. no.: E-EL-H2402), IL-19 (cat. no.: E-EL-H0254), IL-21 (cat. no.: E-EL-H2450), and AREG (cat. no.: E-EL-H0237) concentrations were determined with commercial Elabscience® ELISA kits using an ELX800 microplate reader.

Statistical analysis

IBM SPSS Statistics 25 software was used for the statistical analysis. Shapiro–Wilk test was used to check the normality assumption. Statistical analysis was performed through a non-parametric Mann–Whitney U test, since the variables did not show a normal distribution. Hypothesis tests were performed as two sided at significance level $\alpha = 0.05$.

Results

Data of 62 individuals were investigated. The CRSwNP group had 33 patients (11F/22M) with a mean age of 48.2 ± 16.3 years. The control group had 29 patients (9F/20M) with a mean age of 46.3 ± 17.4 years. There was no statistically significant difference between the two groups in terms of age and gender ($p = 0.817$ for age, $p = 0.563$ for gender).

Atopy was detected in 15 patients (45.4%) in the CRSwNP group. There were no patients with atopy in the control group.

Mean Lund–Mackay score on the paranasal CT scans of the patients was 9.1 for the right side and 8.6 for the left side.

Median, mean and maximum cytokine levels of CRSwNP patients are presented in Table 1.

Median, mean and maximum cytokine levels of control patients are presented in Table 2.

Measured levels for each cytokine type were found to be statistically significantly higher in the CRSwNP than in the control group. Statistical significance levels (p values)

Table 1 Cytokine levels in CRSwNP group

Cytokines (pg/mg)	Median	Min	Max
AREG	1.372	0.676	14.583
IL-19	0.662	0.083	4.092
IL-21	3.744	1.454	21.78
IL-25	5.702	0.874	43.989
IL-33	6.718	1.071	30.038
TSLP	2.545	0.887	12.76

Table 2 Cytokine levels in control group

Cytokines (pg/mg)	Median	Min	Max
AREG	1.272	0.346	9.668
IL-19	0.391	0.024	3.251
IL-21	0.756	0.136	4.133
IL-25	2.795	0.526	9.725
IL-33	3.471	0.771	14.882
TSLP	1.643	0.984	3.482

Table 3 Cytokine levels compared between CRSwNP and control groups

Cytokines (pg/mg)	CRSwNP median	Control median	<i>p</i> value
AREG	1.372	0.676	<0.001
IL-19	0.662	0.083	<0.001
IL-21	3.744	1.454	<0.001
IL-25	5.702	0.874	<0.001
IL-33	6.718	1.071	0.003
TSLP	2.545	0.887	0.021

indicating the difference between CRSwNP and control groups for each cytokine are presented in Table 3.

Box plot graphics indicating the distribution of levels of TSLP, IL-19, IL-21, IL-25, IL-33 and AREG in CRSwNP and control groups are presented in Figs. 1, 2 and 3.

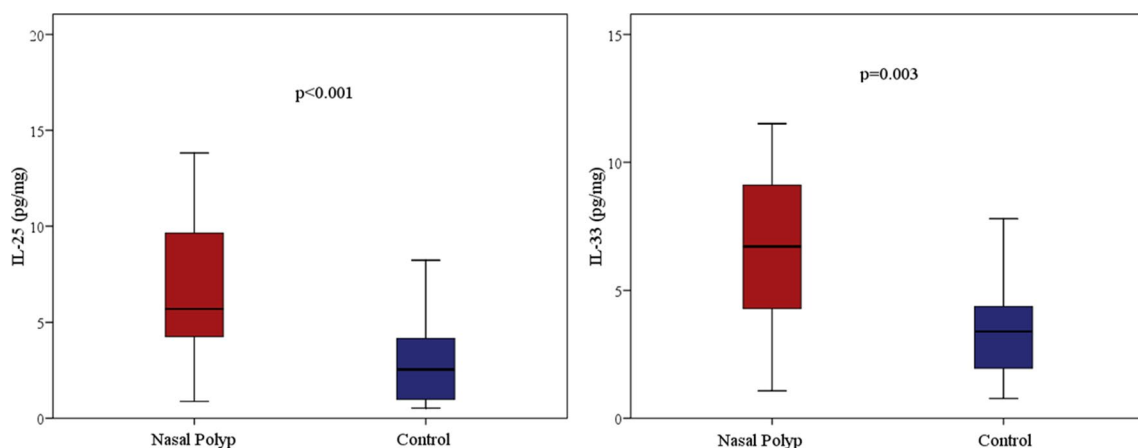
Correlation coefficient (*r*) values between AREG and the other cytokine levels in the CRSwNP group according to the Pearson Correlation test were as follows: 0.523 for IL-19, 0.469 for TSLP, 0.452 for IL-21, 0.516 for IL-25, and 0.313 for IL-33.

Discussion

There have been many studies investigating the role of cytokines in the pathogenesis of CRSwNP. We found statistically significant differences for each cytokine level in the CRSwNP group when compared to the healthy nasal tissues: IL-19 ($p < 0.001$), IL-21 ($p < 0.001$), IL-25 ($p < 0.001$), AREG ($p < 0.001$), IL-33 ($p < 0.01$) and TSLP ($p < 0.05$). This finding suggests that these cytokines could play a role in the development of CRSwNP and could be used for the management of these patients.

It is suggested that impaired cytokine and chemokine balance in the nasal mucosa in patients with CRSwNP can cause inflammation. The immunological mechanism in CRS is not yet fully understood. Although many theories have been presented in the literature for nasal polyp aetiopathogenesis, all these studies acknowledged oedema of the nasal mucosa as the primary pathology leading to polyp formation. Inflammatory mediators, cytokine and adhesion molecules are considered to cause mucosal oedema [15, 16].

Kimura et al. reported in vivo TSLP over-expression in patients with CRSwNP and stated that upregulated TSLP expression can cause Th2-type inflammation in nasal polyps

**Fig. 1** Comparison of IL-25 and IL-33 levels in nasal polyp tissues

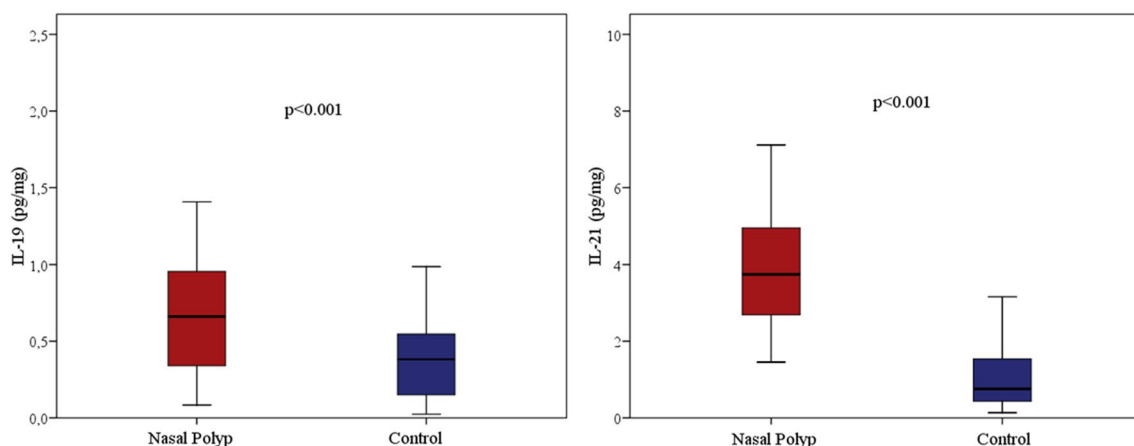


Fig. 2 Comparison of IL-19 and IL-21 levels in nasal polyp tissues

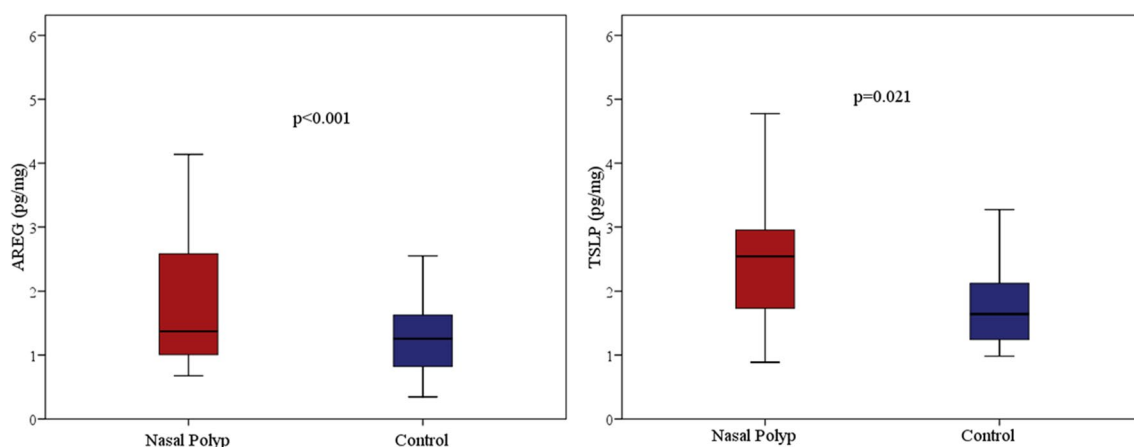


Fig. 3 Comparison of AREG and TSLP levels in nasal polyp tissues. *AREG* amphiregulin, *TSLP* thymic stromal lymphopoietin

[17]. They also analysed the relationship between TSLP and eosinophilic inflammation in nasal polyps and found a significant correlation between the numbers of TSLP⁺ cells and the number of eosinophils [3, 17].

Xiao et al. found that the tissue samples of the patients with CRSwNP had significantly higher IL-21 levels compared to the normal mucosa [1] and demonstrated that as the level of IL-21 expression increases, the severity of the disease increases. In their study, IL-21 levels correlated positively with polyp size and surgical recurrence rate [1]. Their findings suggested that IL-21 could be used as a biomarker for the disease activity in CRSwNP patients and may be considered as a therapeutic target [1].

In patients with asthma and chronic obstructive pulmonary disease, increased IL-19 levels have been found to correlate with increased IL-4 and IL-13 levels [18]. Similarly, in patients with CRSwNP, higher IL-19 expression was found to correlate with increased IL-5, IL-13 and GATA-3 levels, which are typically associated with Th2 responses [16].

The increased levels of IL-19 may cause a proliferation and a differentiation of the nasal epithelium in CRSwNP [11]. However, research into IL-19 expression in human nasal mucosa is limited.

Hong et al. studied the cytokine levels in IL-25^{high} and IL-25^{low} nasal polyp tissues. They found that the levels of Th2-relevant cytokines (IL-4, IL-5, IL-9 IL-13 and IL-25) were significantly increased in the IL-25^{high} subgroup as compared to the IL-25^{low} subgroup [19]. Tissue levels of IL-25 were demonstrated to be significantly higher in CRSwNP patients compared to CRS patients without nasal polyp and healthy controls [20, 21]. These findings of both Shin et al. and Lam et al. supported our results [20, 21]. We found similar higher IL-25 levels in nasal polyp tissue compared to the control group. Additionally, other levels of cytokines that could contribute polyp formation, together with IL-25, were found to be higher in the polyps.

Unlike previous literature studies that support our results, Ozturan et al. mentioned that they did not find any

statistically significant difference in tissue IL-25 levels ($p = 0.698$) between CRSwNP and CRSsNP, and control groups [22]. The same study declared that the mean tissue IL-33 level in the CRSwNP group was found to be significantly lower than those of CRSsNP and control groups. They stated a negative correlation between the severity of CRS and IL-25 and IL-33 levels. Different types of inflammatory cells and adhesion molecules that are the targets for these cells might cause negative correlation. More studies are needed to investigate the roles of IL-25 and IL-33 levels in the aetiopathogenesis of CRSwNP and their relationship with the severity of the CRSwNP. In our study, it is speculated that the high levels of cytokine in the polyps were an inflammatory response based on eosinophils.

An epithelial proliferation stimulator, AREG, plays a role in the normal physiology of tissue repair and immune response. Exacerbated production of AREG can lead to tissue damage. For instance, elevated AREG levels have been shown in some chronic airway diseases such as asthma [23]. Chronic inflammation also plays a key role in CRSwNP aetiopathogenesis. Okumura et al. indicated that there is an increased AREG expression from upper airway epithelium, basophil and mast cells in patients with asthma [24]. Another study conducted by Val et al. showed that AREG increases expression of pro-inflammatory cytokines such as IL-8, which has an important role in the pathogenesis of upper airway inflammation and obstruction [25]. There is no study in the literature concerning AREG tissue levels in patients with CRSwNP. We consider that measuring the significantly higher AREG levels in patients with CRSwNP contributes to the literature for the first time. Moreover, the AREG level had a positive correlation with the other cytokines such as IL-19, IL-21, IL-25, IL-33 and TSLP. This finding suggested the role of AREG in CRSwNP aetiopathogenesis.

What differentiated our study from other aetiopathogenic studies was that amphiregulin has not been studied before in the pathophysiology of CRSwNP. We believe that with further studies this molecule will contribute to endotyping and targeted treatment.

Data can be obtained to increase the success of the treatment and follow-up processes by future studies of the markers and mediators that are thought to be specific to the patient and the disease. This approach, which may be specific to the patient, is currently costly and difficult to apply in daily clinical practice. Most research results have been primarily based on clinical features or on a limited number of inflammatory biomarkers. With the current data, it is recommended not to use only clinical features or clusters based on molecular and cellular factors.

Liao et al. identified seven multidimensional endotypes using 28 clinical variables and 39 cellular and molecular parameters and linked them to treatment outcomes [26]. Seven separate clusters were formed using both clinical

features and different mediator types. When we evaluated our data in terms of biomarker and polyp presence, Cluster 5 was similar to our patient group. Again, in Cluster 5, similar to our patient group, AREG-like growth factors were elevated along with IL-25 and IL-33 levels. In our study, because of the number of cases and the number of biomarkers studied, cluster classification could not be performed for the determination of endotype. However, patients showing an absence of asthma, aspirin desensitisation, cystic fibrosis and primary ciliary dyskinesia can be considered as a separate group of endotypes when evaluated together with other cluster studies. In the literature, the biological marker(s) that can be used to determine the efficacy of treatment and recurrence of CRSwNP are not yet defined.

Liao et al. reported that in patients with predominant neutrophils and eosinophils and low IL-10 levels, recurrence may be more frequent and disease control may be more difficult [26]. Hong et al. evaluated the factors that may affect oral-corticosteroid treatment outcome in CRSwNP and declared that IL-25 levels in the nasal polyp tissue and in blood serum could be used to predict the clinical efficacy of oral-corticosteroid sensitivity [27]. Further studies are needed to investigate predictive tissue markers for prognosis and recurrence.

The use of anti-interleukin-5 agents such as reslizumab and mepolizumab for treatment of patients with inadequately controlled, moderate-to-severe asthma improved treatment outcome [28, 29]. There have been recent studies into biological agents targeting some specific inflammatory mediators and/or pathways, such as anti-IgE, anti-IL-5 and anti-IL-4 and IL-13 receptor antibodies that have shown promising effects for the treatment of CRSwNP. In a multicentre study of topical steroid and mepolizumab in patients with severe bilateral nasal polyposis, the symptoms regressed compared to the placebo group and a significant reduction in surgical necessity was reported [30]. In his study, Liao et al. have speculated that the group identified as Cluster 1 (Type-2-response-dominated eosinophilic CRSwNP with severe clinical manifestations and poor treatment outcomes) might benefit from such steroid/nonsurgical treatments [26]. Also, it was reported that a neutralising antibody that targeted IL-25 reduced the number of polyps and the inflammatory status in a murine nasal polyp animal model [20]. For example, it was stated that addition of a human monoclonal antibody to the interleukin-4 (IL-4) receptor α subunit (dupilumab) to mometasone furoate nasal spray reduced endoscopic nasal polyp burden [31]. The results of our study may contribute to future management modalities of CRSwNP. Similarly, further studies are needed into the treatment of CRSwNP using anti-interleukin agents. Studies are also needed to contribute to the development of specific

therapies by identifying and expanding mediators involved in the aetiopathology of CRSwNP, as we have tried to do. Thus, we can protect patients from unnecessary/excessive treatments and their related side-effects.

A limitation of our study was the lack of inflammatory cell type determination in the tissues. Therefore, a correlation between cytokine levels and cell type (neutrophil, eosinophil, etc.) could have been investigated. Although peripheral blood cytokine levels could be affected by many factors, not measuring serum cytokine levels may be considered as a deficiency of our study.

The absence of a CRSsNP group was another limitation. We thought the reason for this was that most patients were not responding to previous medical treatment, were referred to our clinic for surgery, and/or had a history of previous surgery. In addition, our study method was not included in a treatment follow-up. Another patient group, such as CRS plus asthma, was not included for comparison in this study. Comparing cytokine levels, especially AREG, in patients with asthma plus CRSwNP, and CRSwNP only, could be another subject of study.

In our study, cluster analysis and endotype determination were not performed. We were unable to cover all the molecules critical for the pathogenesis of CRS due to the limited sample size and technique limitations. In addition, the number of cases in our prospective study was insufficient to perform these analyses. There is a need for further research on this subject, which is not sufficiently clarified in the literature.

In conclusion, inflammatory mediators such as AREG, IL-19, IL-21, IL-25, IL-33 and TSLP play a role in CRSwNP pathophysiology. We think that the findings of our study can be useful in determining the target molecules to be developed. Amphiregulin is another potential target for therapeutic development. We believe that the results of our study will contribute to advanced studies in endotype determination, diagnosis and treatment of CRSwNP patients. Further studies are needed to confirm the precise role of AREG and the other cytokines in CRSwNP pathogenesis and management.

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Compliance with ethical standards

Conflict of interest The authors declared that there was no conflict of interest between the authors.

Ethical standards This study was approved by the university's Ethical Review Board (2017/1084).

Informed consent Informed consent was obtained from all individual participants included in the study.

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