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LEVELS OF IMMUNOGLOBULIN E ANTIBODIES TO STAPHYLOCOCCAL ENTEROTOXIN A IN PATIENTS WITH NASAL POLYPOSIS WITH AND WITHOUT ASTHMA

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SUMMARY – Background: Recent investigations have shown that *Staphylococcus aureus* enterotoxins might be associated with inflammatory mucosal changes seen in chronic rhinosinusitis with nasal polyps (CRSwNP) or nasal polyposis (NP). Their involvement in disease maintenance is still unclear. The aim of this study was to determine the presence of immunoglobulin E specific to *Staphylococcus aureus* enterotoxin A (SEA-IgE) in the serum of CRSwNP patients and its involvement in the concomitant presence of asthma.

Methods: The study group consisted of 70 participants: 32 with CRSwNP without asthma, 13 with CRSwNP with asthma and 25 controls without an inflammatory disease of the nose/paranasal sinuses. A detailed medical history was obtained, and a clinical examination and skin prick test were performed. The diagnosis of CRSwNP was confirmed by nasal endoscopy and computed tomography. The levels of total immunoglobulin E (IgE) and SEA-IgE in the serum were measured using ImmunoCAP assays.

Results: Comparing CRSwNP patients with and without asthma, the patients with asthma had more severe symptoms, and higher endoscopic and radiological scores than those without asthma. SEA-IgE values were significantly higher in the CRSwNP group than in the control group. The presence of SEA-IgE antibodies was not associated with the presence of asthma.

Conclusion: Much controversy exists about the role of *Staphylococcus aureus* enterotoxins (SE) in the pathogenesis of NP. Although serum SEA-IgE values did not reach the established cut-off level, they were significantly higher in CRSwNP patients than in the control group. This may suggest that SE might be involved in CRSwNP pathogenesis or amplify inflammation in patients with CRSwNP. Serum SEA-IgE is not a reliable indicator of the concomitant presence of asthma in patients with NP.

Keywords: *Chronic rhinosinusitis*; *Nasal polyps*; Staphylococcus aureus *enterotoxins*

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Introduction

Chronic rhinosinusitis (CRS) represents a frequent health problem leading to significant morbidity, medical expenses and impact on general health. Research of potential etiopathogenetic factors in the occurrence of CRS is still a current topic within the scientific community with respect to the multifactorial mechanisms of the disease's occurrence. The division of CRS into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) is generally accepted. This division is certainly not final because the heterogeneity of the pathophysiological mechanisms within every group indicates the presence of multiple subtypes. A common topic for research in rhinology in the last 5 to 10 years are attempts to find corresponding biomarkers which would help endotype CRS. Any identified biomarkers would constitute direct diagnostic criteria in defining CRS and would also contribute to the development of personalized treatment[1]. CRSwNP is characterized by edematous masses in the nasal and paranasal cavities leading to nasal obstruction, secretion and loss of the sense of smell. It is estimated that the prevalence of CRSwNP in the general population is 4%[2]. The genesis of the disease is multifactorial and the pathophysiological mechanisms included in the disease's occurrence are still not fully explained. Possible mechanisms included in the occurrence of CRSwNP are mucociliary clearance disorder, allergic inflammation, aspirin sensitivity, biofilms and *Staphylococcus aureus* enterotoxins (SE) as superantigens[3]. The results of recent studies which examined the role of IgE-guided inflammation in the occurrence of CRSwNP indicate that there is a local production of specific IgE in the mucous membrane of the nasal and paranasal cavities despite negative skin prick test results. Alongside the development of a theory about the local production of IgE, a "staphylococcal superantigens hypothesis" is being developed too, which is founded in the fact that enterotoxins produced by *S. aureus* may cause a strong immune response by activating several types of immunocompetent cells, which primarily refers to polyclonal T lymphocyte activation. SE stimulates T lymphocyte activation by directly connecting to T-cell receptors without any interventions from antigen-presenting cells, due to the occurrence of the polyclonal activation of the humoral immune response, the production of B lymphocytes and the synthesis of IgE antibodies[4,5].

The role of SE as superantigens in the pathogenesis of nasal polyps was first mentioned in 2001 by Bachert et al., who noticed the presence of specific IgEs, produced against enterotoxins of *Staphylococcus aureus* A and B (SEA-IgE and SEB-IgE) in the nasal polyp tissue of CRSwNP patients[6]. The abovementioned studies found a significant connection between positive SEA-IgE test results and severe forms of diseases with concomitant asthma[7-10]. Research that tested the role of certain inflammatory markers in the occurrence of asthma as a comorbidity of CRSwNP found that the presence of SAE-IgE in nasal polyp tissues significantly predicted the development of asthma[11].

In accordance with the abovementioned results and with the goal to better understand the pathogenic mechanisms of this disease and introduce a specific treatment for it, it is important to determine the endotypes of CRS where systemic or local IgE would be included in the pathogenesis of CRSwNP. This research evaluated the presence of SEA-IgE in CRSwNP patients and its association with asthma, atopy and the patients' clinical, radiological and microbiological characteristics.

Patients and Methods

Participants

The research was conducted as a combination of a prospective and a cross-sectional study in our ENT department between January 2016 and December 2017. This investigation included 70 adult participants of both sexes: 45 CRSwNP patients (32 non-asthmatic and 13 asthmatic), who underwent surgical treatment after conservative management failed. CRSwNP was diagnosed based on EP3OS guidelines[1]. The control group included 25 subjects who underwent surgery of the nasal septum (septoplasty) and who did not suffer from any nasal inflammatory disease, according to the anamnesis, clinical features and standard radiography of the paranasal cavities. The exclusion criteria were: systemic use of corticosteroids during the previous two months, immunodeficiency, patients with antrochoanal polyps, cystic fibrosis and Aspirin-exacerbated

respiratory disease. Data on the presence of bronchial asthma were obtained based on data from the anamnesis and upon insight into previous medical records. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) by history and pulmonary function tests.

Clinical examination

The intensity of the symptoms experienced by the subjects belonging to the experimental group was assessed using the patients' subjective assessments based on the score achieved on the visual analogue scale (VAS). According to the scale, the disease was classified as mild (VAS = 0-3), moderate (VAS = 4-7) and severe (VAS = 8-10).

The severity of the disease present in the experimental group was clinically estimated based on endoscopic score[12]. Nasal endoscopy was performed with a rigid endoscope 2.7 mm in diameter at an angle of 0 and 30 degrees. The presence of polyps, nasal secretions and edemas was estimated. Allergic sensitivity was diagnosed according to a positive skin prick test to common inhalant allergens. A skin prick test was considered positive when the mean wheal diameter was 3 mm and larger than the negative control. According to recommendations, a standard allergy panel was used[13].

Biochemical analysis

In vitro concentrations of total serum IgE and specific serum SEA-IgE were measured in all subjects of both the experimental and control group using the fluoride-enzyme immunochemical method on an ImmunoCAP device (Phadia, Uppsala, Sweden), according to the manufacturer's instructions. A venous blood sample (8-10 ml) was taken via venipuncture. After that, venous blood was centrifuged at 3,000 revolutions for 10 minutes in order to separate the serum, which was preserved at -70 °C until testing. The method includes the bonded allergen (in a covalent bond with an encapsulated flexible hydrophilic carrier) from the reagent having a specific reaction with all or specific IgE antibodies from the serum. ImmunoCAP assays are based on the binding of allergen-specific IgE antibodies in the serum coupled in excess to a solid phase. After the non-specific IgE antibody is washed, a monoclonal anti-IgE antibody marked with β-galactosidase is added. After the substrate of 4-methylumbelliferyl-beta-galactoside is added, the emerging fluorescence is measured, proportionate to the concentration of all or specific IgE in the sample of the serum. Levels of total serum IgE antibodies above 120 kIU/L were considered positive. Levels of specific SEA-IgE ≥ 0.35 kUA/L were considered positive. Pursuant to the value of SEA-IgE, six classes are used: 0 (< 0.35), I (0.35-0.69 kUA/l), II (0.7-3.49 kUA/I), III (3.5-17.49 kUA/l), IV (17.5-49.9 kUA/l), V (50-100 kUA/l) and VI (> 100 kUA/l)[14].

Radiological examination

For the purpose of estimating the radiological characteristics of diseases present in the patients in the experimental group, computerized tomography findings were graded according to the Lund-Mackay scoring system[15].

Bacteriological evaluation

An experienced rhinologist carried out a middle meatus aspiration for all patients at day 0 and at the end of day 10. A fine catheter was connected to a suction unit and carefully introduced into the middle meatus under endoscopic control. Suction was stopped immediately when discharge was observed in the catheter. After that, the catheter containing the discharge was sent to the laboratory and samples were cultivated on Blood agar for *S. aureus* (HiMedia™ Laboratories, Mumbai, India) at 37 °C for 48 hours.

Ethics

Before the start of the study, the participants were informed about the study protocol, which was approved by the local Ethics Committee, and gave their informed consent for participation.

Statistical analysis

A descriptive analysis of the study population was performed. The analysis was carried out using the Statistical Analysis System (SAS Institute Inc. NC, USA) program, version 9.1.3. All variables were described for the total sample. The number of valid cases (N) was used in all tables, figures and graphics, and when calculating percentages or any other statistical consideration. Continuous variables were summarized based on the number of valid cases (N), mean, standard deviation, median and extreme values. Categorical

variables were described by means of the number of valid cases (N) and percentages in every category, while variables with an asymmetric frequency distribution were described using medians and their 25th to 75th percentiles. Other appropriate tests (chi-square, Mann–Whitney, or Kruskal–Wallis) were used in each case for other comparisons. Statistical significance was set at a *P*-value of < 0.05.

Results

The study group consisted of 70 patients, 32 with CRSwNP without asthma (45.7%), 13 with CRSwNP with asthma (18.6%) and the control group consisted of 25 subjects without an inflammatory disease of the nose/paranasal sinuses (35.7%). Demographic and clinical characteristics are presented in Table 1.

Demographic characteristics

There were 45 (64.3%) male and 25 (35.7%) female participants. The three groups did not differ significantly according to sex. The mean age of the control subjects was 29.2 ± 8.6 years (range 18-49 years), of the non-asthmatic CRSwNP patients 47.1 ± 12.4 years (range 24-70 years) and of the asthmatic CRSwNP patients 47.3 ± 14.4 years (range 27-69 years). Patients in the control group were significantly younger than the patients in the CRSwNP groups.

Clinical characteristics

Sensitivity to common inhalant allergens was found in 11 (34.4%) non-asthmatic CRSwNP patients and in 5 (38.5%) asthmatic CRSwNP patients. The two CRSwNP groups did not differ significantly according to prick test results. When we evaluated the mean VAS score for all nasal symptoms, it was significantly

Table 1: Demographic and clinical characteristics of participants

Variable		**CRSwNP-A (32)**	**CRSwNP+A (13)**	**Controls (25)**	***P*-value**
Sex	M/F	24 / 8	6 / 7	15 /10	$\chi2$ (2.70) = 3.66 *P* = 0.160
Age	mean ± SD	47.1 (12.4)	47.3 (14.4)	29.2 (8.6)	Kruskal-Wallis; $\chi2$ (2.70) = 25.98 ***P* = 0.000****
	n / range	32 / 44.97	13 / 44.15	25 / 18.88	
Prick test	positive; n (%)	11 (34.4)	5 (38.5)	_	$\chi2$ (1.45) = 0.067 *P* = 0.795
	negative, n (%)	21 (66.6%)	8 (61.5)	_	
Total IgE	positive, n (%)	16 (50)	6 (46.2)	4 (16)	$\chi2$ (2.70) = 7.505 ***P* = 0.023***
	negative, n (%)	16 (50)	7 (53.8)	21 (84)	
VAS	mild, n (%)	1 (3.1)	0 (0)	8 (32)	$\chi2$ (4.70) = 21.22 ***P* = 0.000****
	moderate, n (%)	21 (65.5)	7 (53.8)	17 (68)	
	severe, n (%)	10 (31.3)	6 (46.2)	0 (0)	
SEA-IgE	mean ± SD	0.14 (0.37)	0.09 (0.1)	0.01 (0.01)	Kruskal-Wallis; $\chi2$ (2.70) = 23.55 ***P* = 0.000****
	median (interquartile range)	0.04 (0.01, 0.10)	0.07 (0.01, 0.12)	0.00 (0.00, 0.01)	
	min – max	0.01-0.34	0.00-2.12	0.00-0.03	
Endoscopic score	mean ± SD	9.5 (1.9)	10.8 (1.1)	_	Mann-Whitney U = 649, Z = -2.22, ***P* = 0.026***
	n; range	32; 20.28	13; 29.69	_	
CT-scan score	mean ± SD	16.5 (4.0)	20 (1.5)	_	Mann-Whitney U = 97, Z= -2.78 ***P* = 0.005****
	n; range	32; 19.55	13; 31.50	_	

Abbreviations: CRSwNP = Chronic rhinosinusitis with nasal polyps; CRSwNP-A = CRSwNP without asthma; CRSwNP+A = CRSwNP with asthma; VAS = visual analog scale; SEA-IgE = immunoglobulin E specific to *S. aureus* enterotoxin A. *$P < 0.05$, **$P < 0.01$

higher in CRSwNP patients than in the control group ($P < 0.001$). In non-asthmatic and asthmatic CRSwNP patients, the category of "mild" VAS was almost completely absent, while in the control group, this category was present in 8 (32%) subjects. There were no participants who fell into the VAS category of "severe" in the control group. Asthmatic CRSwNP patients had higher endoscopic and CT scores than non-asthmatic patients ($P = 0.026$ and $P = 0.005$, respectively).

Biochemical and microbiological parameters

Total serum IgE was positive in 16 (50%) non-asthmatic CRSwNP patients, 6 (46.2%) asthmatic CRSwNP patients and 4 (16%) participants from the control group. The mean total serum IgE level was significantly higher in non-asthmatic CRSwNP patients than in the control group ($P = 0.023$) (Table 1). As shown in Table 2 and Figure 1, the level of SEA-IgE was significantly higher in the CRSwNP

Table 2. Serum SEA-IgE in the CRSwNP and control groups

SEA-IgE	**Mean ± SD**	**Median (interquartile range)**	**Min -Max**	
Controls (n=25)	0.01 ± 0.01	0.00 (0.00, 0.01)	0.00-0.03	***P* < 0.001**
CRSwNP (n=45)	0.12 ± 0.32	0.04 (0.01, 0.11)	0.00-2.12	
CRSwNP +A (n=13)	0.14 ± 0.37	0.07 (0.01, 0.12)	0.00-2.12	*P* = 0.820
CRSwNP–A (n=32)	0.09 ± 0.11	0.04 (0.01, 0.10)	0.01-0.34	
Total IgE positive (n=28)	0.22 ± 0.44	0.10 (0.06, 0.24)	0.00-2.12	***P* < 0.001**
Total IgE negative (n=17)	0.03 ± 0.04	0.01 (0.01, 0.04)	0.00-0.17	
Negative colonization with *S. aureus* (n=35)	0.07 ± 0.07	0.04 (0.01, 0.11)	0.00-0.30	*P* = 0.639
Positive colonization with *S. aureus* (n=10)	0.18 ± 0.44	0.07 (0.01, 0.22)	0.00-2.12	

Abbreviations: CRSwNP = CRS with nasal polyps; CRSwNP-A = CRSwNP without asthma; CRSwNP+A = CRSwNP with asthma; *S. aureus* = *Staphylococcus aureus*; SEA-IgE = immunoglobulin E specific to *Staphylococcus aureus* enterotoxin A. Median concentrations of SEA-IgE (min-max). *P*-values calculated with the Mann-Whitney U test.

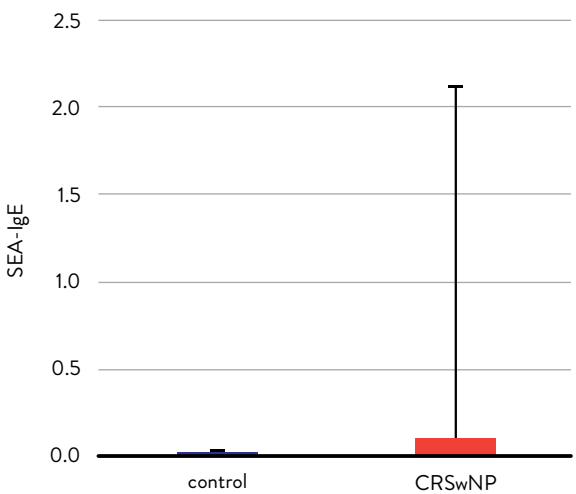

Figure 1. The concentration of SEA-IgE is significantly higher in patients with CRSwNP than in the control group (P < 0.001).

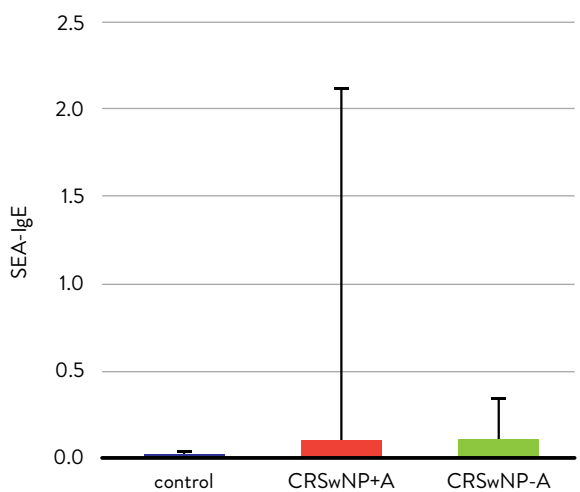

Figure 2. SEA-IgE in the serum of control subjects, asthmatic (CRSwNP+A) and non-asthmatic (CRSwNP-A) patients. We found no significant difference in SEA-IgE between non-asthmatic and asthmatic patients with CRSwNP (P = 0.820) (Kruskal–Wallis test)

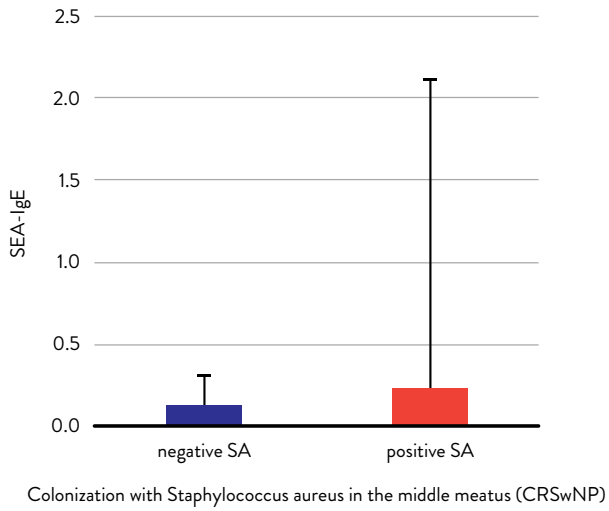

Figure 3. Serum SEA-IgE in CRSwNP patients, stratified by positive or negative Staphylococcus aureus *from the middle meatus (Mann-Whitney U test)*

Abbreviations

CRSwNP	Chronic rhinosinusitis with nasal polyps
CRSwNP+A	Chronic rhinosinusitis with nasal polyps with asthma
CRSwNP-A	Chronic rhinosinusitis with nasal polyps without asthma
SEA-IgE	Specific immunoglobulin E against *Staphylococcus aureus* enterotoxin A
VAS	Visual analog scale

groups than that in the control group ($P < 0.001$). The level of SEA-IgE in the CRSwNP groups showed an increasing trend compared to the control group, but only a few patients reached the cut-off level of 0.35 kUA/l. There was no significant difference in the level of SEA-IgE between non-asthmatic and asthmatic CRSwNP patients ($P = 0.820$) (Table 2). Non-asthmatic CRSwNP patients had significantly higher serum SEA-IgE levels than the control group ($P < 0.01$). There were significant differences between the two CRSwNP groups regarding the frequency of positive total IgE values and serum levels of SEA-IgE; SEA-IgE values were significantly higher in the CRSwNP group with a positive total serum IgE ($P < 0.001$). There was no significant difference between the prevalence of colonization with *S. aureus* in the middle meatus of CRSwNP patients with a positive serum SEA-IgE ($P = 0.639$) (Table 2, Figure 2).

Discussion

CRSwNP occurs due to a chronic inflammation of the nasal mucosa and paranasal sinuses that can be triggered by various factors. The mechanisms determining the inflammation are still not completely clear. One may say that the disease is a result of an inadequate or exacerbated immune response to external factors. We know that the basic pathophysiological mechanisms occurring in the majority of nasal polyps are mediated by the Th2 inflammatory profile characterized by high concentrations of interleukin-5 and IgE. The existence of plasma cells within nasal polyp tissue points to a local production of IgE, which is probably functional and polyclonal. The production of IgE antibodies in CRSwNP is probably a consequence of local activation and differentiation in plasma cells and B lymphocytes, which emerges after exposure to various allergens and infectious agents[3,5,16]. A previous study which investigated the role of IgE in the pathogenesis of allergic diseases showed that the value of total and allergen-specific IgE in tissues may be unrelated to its values in the serum. The authors suggested that the majority of circulating specific IgE antibodies do not originate from IgE-producing cells in blood, but that serum IgE originates from mucosa in different parts of the body[17].

We found positive serum values of total IgE in approximately half of the CRSwNP patients. The serum levels of total IgE were significantly higher in non-asthmatic CRSwNP patients than in the subjects without any nasal mucosa inflammation. At the same time, we determined that the values of serum SEA-IgE were significantly higher in the group

with positive total serum IgE, which is in line with previous studies, suggesting that SEA amplifies the immune response in CRSwNP patients, resulting in an overproduction of IgE[10]. Van Zele et al.[18] found significantly higher concentrations of IgE in nasal polyp homogenates compared to the nasal mucosa tissue of patients with chronic rhinosinusitis without nasal polyps and tissue from healthy nasal mucosa, but they did not find a significant correlation between total serum IgE and SEA-IgE in nasal polyp tissue or SEA-IgE in the serum of CRSwNP patients.

Despite the high prevalence of colonization with *S. aureus* (64%) in CRSwNP patients, the role of *S. aureus* in the pathogenesis of CRS still remains a controversial subject. The production of local specific IgE antibodies in polyp tissue is connected with a significant presence of a colonization of the nose with *S. aureus*. Moreover, current studies emphasize the role of the colonization of nasal cavity mucosa with *S. aureus* in CRSwNP patients in terms of not only the infective agent, but also the immunomodulatory factor. Previous studies indicated that nasal mucosa in patients with nasal polyps is more frequently colonized with *S. aureus* than the nasal mucosa of healthy subjects[19,20]. During this study, *S. aureus* in the secretion taken from the middle nasal meatus was detected in 10 (22.2%) CRSwNP patients. There was no significant difference between the prevalence of *S. aureus* and the values of SEA-IgE in patients with polyps[20]. A study conducted by Patou et al.[9] proved a lasting and significant colonization of the middle nasal meatus with *S. aureus* in CRSwNP patients compared to CRSsNP patients. It also showed that colonization with *S. aureus* in patients with CRSwNP is connected with increased values of total IgE and SEA-IgE in polyp samples[9]. However, the results of a prospective, multi-center European study which analyzed the colonization of the middle nasal meatus indicated that there are no differences between CRSwNP, CRSsNP and control groups[21].

Investigating the relationship between atopy, parameters of eosinophilic inflammation and local IgE concentrations, Bachert et al.[6] found the presence of local SEA-IgE and SEB-IgE in the homogenate of CRSwNP patients' tissues. The same study found increased values of total IgE and specific IgE in accordance with the results of the skin prick test to inhalant allergens in a certain number of patients with proven atopy[6]. According to the results of a study conducted by Seiberling et al.[8], 50% of polyp homogenates contained enterotoxins against *S. aureus,* and they found a significantly higher concentration of SEA-IgE in CRSwNP patients in comparison to CRSsNP patients and the control group with a healthy nasal mucosa.

Our results showed a significantly higher value of serum SEA-IgE in patients with CRSwNP than in the control group. A study conducted by Van Zele et al.[18] determined the presence of SEA-IgE in 33% of nasal polyp homogenates. Furthermore, in this SEA-IgE positive nasal polyp tissue group, 16% had positive SEA-IgE levels in the serum.

A study conducted by Bernstein et al.[22] showed that the polyclonal activation of Th1 and Th2 lymphocytes and the expression of interleukin (IL)-2, IL-4, IL-5, IL-10, IL-13 and interferon gamma were higher in the nasal polyp tissue of patients stimulated with SEB and SEA in comparison to the tissue of healthy subjects. A significant detection rate of *S. aureus* superantigens and their specific IgE in the CRSwNP group was also the reported in a meta-analysis including twelve studies[10]. However, a study conducted by Tripathi et al.[23], which investigated the values of serum SEA-IgE and SEB-IgE in CRSwNP patients, did not detect these specific IgE antibodies.

The results of a previous study conducted by Cui et al.[24] indicated a higher concentration of SEB-IgE in CRSwNP patients than in subjects with healthy nasal mucosa, implying the specific role of SEB-IgE in the pathogenesis of CRSwNP. On the other hand, a study conducted by Schiappoli et al.[25] did not confirm significant findings of specific IgE against SE in CRSwNP patients compared to healthy controls. One of the studies which did not confirm the importance of SAE in the pathogenesis of CRSwNP is a multi-center European study; its results did not show a significant correlation between staphylococcal enterotoxin genes and the presence of CRS with or without nasal polyps[21].

Nasal polyps with asthma represent the most severe form of airway disease and are characterized by, among other things, longer lasting nasal symptoms, a radiologically proven extended form of the disease, severe bronchial obstruction and sensitivity to perennial allergens[26]. It has been established that 20–60% of CRSwNP patients suffer from asthma. Also, a

significant connection has been found between the late occurrence of asthma in adults and CRSwNP, and the connection of CRSwNP and asthma is evident both from the aspect of frequency and the aspect of clinical manifestations at airway level[27,28]. The connection between CRSwNP and asthma can be definitely explained via joint inflammatory mechanisms, where eosinophils and the respiratory epithelium play an important role. There is a real possibility that the presence of specific IgE antibodies against staphylococcal enterotoxins could be a link between those two diseases at different levels of the airway. A study conducted by Bachert et al.[11] aimed to determine certain inflammatory phenotypes which are a potential link between CRSwNP and asthma. This research indicated that an increased expression of IgE and IL-5, together with positive specific IgE antibodies to the *Staphylococcus* enterotoxin in CRSwNP patients represent an increased risk for the occurrence of asthma[11].

In the present study, asthma was confirmed in 18.6% of CRSwNP patients. There was no significant difference between non-asthmatic and asthmatic CRSwNP patients regarding the serum concentrations of SEA-IgE. Patients with CRSwNP without asthma had significantly higher serum levels of SEA-IgE than controls. This study may not be considered confirmatory of previous studies regarding the positive findings of serum or tissue SAE-IgE in patients with nasal polyps and asthma[8,10]. With the goal to identify inflammatory endotypes of CRS, Tomassen et al.[29] found that SAE-IgE remains associated with nasal polyps and concomitant asthma. According to the results of studies which were following SAE-IgE, high levels of staphylococcal toxin-specific IgE antibodies were significantly associated with asthma, especially in patients with aspirin-exacerbated respiratory disease[30,31].

Conclusion

Much controversy exists about the role of SE in the pathogenesis of nasal polyposis. So far, limited knowledge of emerging etiopathogenetic factors of CRSwNP constitutes the greatest obstacle in the improvement of treatment procedures. Although serum SEA-IgE values did not reach the established cut-off level, they were significantly higher in CRSwNP patients than in the control group. This may suggest that SAE might be involved in the pathogenesis of CRSwNP as a possible causal factor, or just as a modulating factor. The use of a single SEA-IgE rather than a combination of different enterotoxins in a screening assay may be the reason why we did not find higher serum SEA-IgE concentrations in our samples. This study did not find a significantly higher level of SEA-IgE in asthmatic CRSwNP patients. A potential identification of clinical entities or endophenotypes within the group of CRSwNP patients based on a simple isolation of serum SEA-IgE remains, at least for now, unsuccessful. According to the results of this study, SEA-IgE can not be considered a biomarker for estimating the risk of concomitant asthma in patients with nasal polyposis. In accordance with this, a need for additional immunological studies researching the impact of systemic and local mucosal cellular and humoral immunological mechanisms in the pathophysiology of chronic rhinosinusitis with nasal polyposis emerges.

This paper represents the preliminary results of the doctoral dissertation of PhD candidate MD MSc Aleksandra Aleksić titled "Significance of local immunoglobulin E to *Staphylococcus aureus* enterotoxin in the pathophysiology of chronic rhinosinusitis with nasal polyposis."

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Sažetak

RAZINE IMUNOGLOBULINA E NA STAFILOKOKNI ENTEROTOKSIN A KOD PACIJENATA S NOSNOM POLIPOZOM I ASTMOM

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Uvod: Nedavna ispitivanja pokazala su da enterotoksini *Staphylococcus aureus* (SE) mogu biti povezani s upalnim promjenama sluznice prisutnim kod kroničnog rinosinuitisa s nosnosinusnom polipozom (CRSwNP) ili nosnim polipima (NP). Još uvijek nije jasna njihova uloga u održavanju tijeka upale. Cilj ove studije bio je utvrditi prisutnost specifičnog imunoglobulina E na *Staphylococcus aureus* enterotoksin A (SEA-IgE) u serumu pacijenata sa CRSwNP i njegovu uključenost u istodobnu prisutnost astme.

Metode: Ispitna skupina sastojala se od 70 sudionika: 32 s CRSwNP bez astme, 13 s CRSwNP s astmom i 25 kontrola bez upalne bolesti nosa/paranazalnih sinusa. Prikupljena je detaljna anamneza te su obavljeni klinički pregled i prick test. Dijagnoza CRSwNP potvrđena je endoskopijom nosa i kompjuteriziranom tomografijom. Razine ukupnog imunoglobulina E (IgE) i SEA-IgE u serumu mjerene su ImmunoCAP testom.

Rezultati: Uspoređujući bolesnike s CRSwNP s astmom i bez astme, pacijenti s astmom imali su teže simptome, viši endoskopski rezultat i izraženije radiološke promjene na razini sinusa od pacijenata bez astme. Vrijednosti SEA-IgE bile su značajno veće u skupini s CRSwNP nego u kontrolnoj skupini. Prisutnost SEA-IgE protutijela nije bila povezana s prisutnošću astme.

Zaključak: Postoji mnogo kontroverzi o ulozi enterotoksina *Staphylococcus aureus* (SE) u patogenezi NP. Iako vrijednosti SEA-IgE u serumu nisu dosegle utvrđenu referentnu razinu, one su bile značajno veće u bolesnika s CRSwNP nego u kontrolnoj skupini. Rezultat sugerira da SE mogu biti uključeni u patogenezu CRSwNP ili pojačati upalu kod pacijenata s CRSwNP. Serumski SEA-IgE nije pouzdan pokazatelj istodobne prisutnosti astme u bolesnika s nosnom polipozom.

Ključne riječi: *Kronični rinosinuitis*; *Nosni polipi*; *Enterotoksini* Staphylococcus aureus