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Cutaneous reactivity pattern and nasal smear cytology in patients with chronic rhinosinusitis with nasal polyps; is it associated with the course of the disease?

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Abstract

Background and Objectives: To determine the association of hyper-reactivity to environmental allergens and mucosal secretion cytology with the course of disease in patients with chronic rhinosinusitis and nasal polyps (CRSwNP).

Methods: A cross sectional study was conducted at Tehran Clinic of Asthma and Allergy in 2016. Adult patients who earned the definite diagnosis of CRSwNP and were free of serious underlying disease were selected. A comprehensive history regarding the course of disease was taken. Success or failure of previous interventions was defined as subsiding the symptoms and no need for further invasive intervention of surgery. Physical examination, pulmonary function test, nasal smear from both nasal cavities and skin prick test were performed for all enrolled subjects. The results were compared among participants with different course of disease.

Results: A total of 45 patients with mean age of 35.8±11.7 (18 to 60 years) were enrolled. Of the participants, 30 (66.7%) had asthma, medical treatment was failed in 23(51.1%), 25 underwent surgery in whom it was failed in 5 (11.1%). Regardless of course of disease, neutrophilia was the predominant cytology of nasal smear. Of the participants, 17 (37.8%) had no sensitization, while, 11(24.4%) showed mono-sensitization and 17(37.8%) were poly-sensitized. Seasonal allergy was found in 16(35.5%), while, perennial sensitization was in 19 (42.2%). Failures of medical treatment were more sensitized to seasonal allergens (45.2% vs 14.3%, p=0.045). Failures of surgery, were found to have poly sensitization to both of perennial and seasonal allergens (66.7% vs 21.1%, p=0.037).

Conclusion: Atopy is frequently present in patients with CRSwNP and pattern of sensitization can affect the outcome of intervention. With respect to different pattern of sensitization among failed and successful interventions, determining the sensitizations prior to any intervention is suggested. Patient counseling regarding the recurrence of disease can be done in accordance with atopic profile.

Keywords: Chronic rhinosinusitis, Allergy, Asthma, Atopy

Background

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease of nasal cavity and paranasal sinuses (1). There is a broad spectrum of diversity in underlying etiologies, associated comorbidities and outcome of CRS (2). Tow accepted categories of CRS include polypoid (CRSwNP) and non-polypoid (CRSsNP) subtypes that may be distinct in underlying pathophysiology and outcome (3). Opening insights into the different categories of CRS help treat patients with more appropriate modalities. Indeed Individualized based treatment seems important when some studies suggests the refractory behavior of atopic CRS to medical and surgical treatment modalities (4).

In addition to general modulators of immune system such as corticosteroids, targeted treatments like monoclonal antibodies and specific allergen immunotherapy (SIT) can be tested in

these cases. In this way, disclosure of sensitization pattern of patients with CRS is inevitable to determine the atopic status is perennial or seasonal, monosensitized or polysensitized and which environmental allergen should be used in SIT.

One patient with CRS may experience allergic rhinoconjuctivitis, airway hyper-responsiveness and asthma more than general population conferring the idea of unified airway (5). Additionally, the prevalence of asthma incidence in CRSwNP is more than CRSsNP(6). However the role of atopy is well described in pathophysiology of comorbidities associated with CRS such as asthma; there are many unanswered questions upon the place of atopy in pathophysiology of CRS and treatment implications.

We aimed to find the sensitization pattern of patients with CRSwNP using skin prick test (SPT) and the cytology of inflammatory cells infiltrated in nasal secretions. We also investigated the differences in sensitization pattern in patients with different response to treatment modalities.

Methods

Study population

A cross sectional study was conducted at Tehran clinic of Asthma and Allergy from January 2016 to December 2016 to investigate the association between cutaneous reactions to environmental allergens and nasal smear cytology with the course of CRS. Inclusion criteria of this study were adult patients (aged >18 years) with definite diagnosis of CRSwNP that was made by an experienced physician and using of both of American Academy of Otolaryngology Head and Neck surgery task force criteria of CRS(7) and Lund-MacKay scoring system (scores more than 5) of computed tomography (CT) results(8). All the patients had documented evidence of nasal polyps in their medical files with comprehensive endoscopic evaluations. Patients who underwent medical treatments including antibiotics and corticosteroids during previous month or surgical management of nasal polyposis during previous 3 months and patients with immunodeficiencies, cystic fibrosis and autoimmune disorders or any serious underlying comorbidities needed hospitalization or receiving immunomodulatory drugs were excluded from the study. Furthermore, subjects who previously received SIT or who with incomplete data as described in follows were excluded. Our local ethic committee and institutional review board approved this study. All the participants signed informed consents prior to enrollment. Enrolled subjects were compared in different subgroups according to their clinical manifestations and comorbidities; (1) patients with asthma versus free of asthma; (2) patients in whom medical treatment was failed versus those in whom medication was successful with subsiding the symptoms and no need for surgery; (3) patients in whom surgery was failed and needed further surgeries versus who were managed successfully by first surgery.

Data acquisition

All the participants were examined by one experienced physician regarding the presence of possible comorbidities. Symptoms like recurrent experience of cold, disrupted sleep, snoring, sneezing, reduced sense of taste, dyspnea, skin disorders like urticarial and gastrointestinal problems like food intolerability were asked. Additionally, they were asked for presence of allergic disease including eczema, angioedema, anaphylaxis, conjunctivitis, rhinitis, food allergy, drug allergy, acetylsalicylic acid (ASA) hypersensitivity and allergy to bee venom. Then patient's history regarding the initial manifestation of CRS including nasal congestion, headache, fullness or tenderness of head, reduced sense of smell, age at the time of diagnosis, nasal polyps and surgery for its management were extracted from medical records.

Pulmonary function tests

Spirometry was obtained from all patients who fulfilled the selection criteria and with accordance to standard guidelines (9). More than 12 percent increase in peak expiratory flow following salbutamol administration was confirmatory of asthma in this study.(10) Our goal from performing this test was to assess the presence of asthma and airway hyper-responsiveness (AHR).

Nasal smear

Nasal secretions of all participants were obtained using an appropriate clean swap under clean conditions. The specimens were stained by Hematoxylin and eosin (H&E) and reviewed by one blinded pathologist to the study. Total number of neutrophils and Eosinophils were counted in 10 distinct high power field of light microscope and proportional percent of neutrophils and Eosinophils to all counted leukocytes in each nasal cavity was calculated

Table 1. Patient characteristics in asthmatics versus non asthmatics and failed versus successful of medical or surgical treatments

Variable (%)		CRSwAS	CRSsAS	P	CRSfMT	CRSsMT	P	CRSfSur	CRSsSur	P
Age		35.4±13.1	38.0±10.4	0.580	35.4±12.0	37.0±12.8	0.567	45.8±10.3	34.6±12.6	0.102
Gender	Male	7 (24.1)	8 (50)	0.078	11 (64.5)	4 (28.6)	0.649	4 (66.7)	7 (36.8)	0.199
	Female	22 (75.9)	8 (50)		20 (11.5)	10 (71.4)		2 (33.3)	12 (63.2)	
ASA hyper-sensitivity		6 (20.7)	2 (12.5)	0.492	5 (16.1)	3 (21.4)	0.667	2 (33.3)	1 (5.3)	0.065
Conjunctivitis		10 (34.5)	5 (31.3)	0.826	10 (32.3)	5 (35.7)	0.820	2 (33.3)	5 (26.3)	0.739
Eczema		10 (34.5)	2 (12.5)	0.110	9 (29)	3 (21.4)	0.593	3 (50)	5 (26.3)	0.278

CRSwAS: chronic rhinosinusitis with asthma, CRSsAS: chronic rhinosinusitis without asthma, CRSfMT: chronic rhnosinusitis with failed medical treatment, CRSsMT: chronic rhnosinusitis with successful medical treatment, CRSfSur: chronic rhnosinusitis with failed surgery, CRSsSur: chronic rhnosinusitis with successful surgery.

Skin prick test (SPT)

Cutaneous reactivity of patients to allergens including grass pollens, house dust mites, molds, animal dander, mosquito, cockroaches, latex and foods such as nuts were assessed using skin prick test. It was applied to the forearm of participants with histamine and control dilution (ALK, Abello) under close supervision of experienced physician in order to management of possible anaphylaxis. Finally, with compare to wheal area as the indicator, the area greater than 8 mm^3 in compare to negative control was considered as positive response after 20 minutes. It is of value to state that atopy in this study was considered as documented sensitization to at least one environmental allergen using SPT

Statistical analysis

Data analysis was performed using SPSS (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Illinois, USA). Kolmogorov Smirnov test was used to test the normality of continues variables. Data were expressed as mean ± standard deviation and range of changes. Student t test and chi square was employed to compare continues and categorical normally distributed variables, respectively. Fishers' Exact Test was performed as applicable. All the tests were two sided and the probability less than 0.05 was considered statistically significant.

Results

Overall findings

A total of 45 patients with CRS who fulfilled the selection criteria were included in the study. They were 30 (66.7%) female and 15 (33.3%) male participants with mean age of 35.8±11.7 (ranged from 18 to 60 years). The most common initial presentation of the CRS was nasal obstruction that was found in 37 (82.2%). Asthma was detected in 29 (64.4%) of the participants. Of the participants, 12 (26.6%) had no history of allergy to environmental allergens and 33 (73.3%) experienced at least one of aforementioned allergic conditions; allergic rhinitis in 28 (62.2%), food

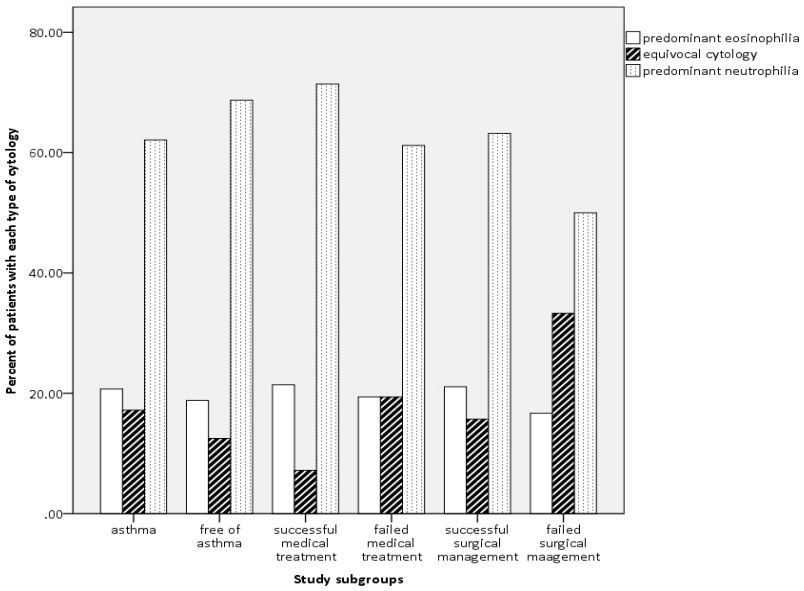

Fig. 1. Neutrophilia was the predominant pattern of inflammation in CRSwNP

Table 2. Patient characteristics in asthmatics versus non asthmatics and failed versus successful of medical or surgical treatments according to sensitization

Variables (%)	CRSwAS	CRSsAS	p	CRSsMT	CRSfMT	p	CRSsSur	CRSfSur	p
Only seasonal	4 (13.3)	2 (12.5)	0.903	1 (7.1)	5 (16.1)	0.412	4 (21.1)	1(16.7)	0.815
Only perennial	6 (20.4)	3 (18.8)	0.876	4 (28.6)	5 (16.1)	0.334	3 (15.8)	0	0.299
Seasonal	12 (41.4)	4 (25)	0.272	2 (14.3)	14 (45.2)	0.045	8 (42.1)	5(85.3)	0.078
Perennial	14 (48.3)	5 (31.3)	0.268	5 (35.7)	14 (45.2)	0.553	7 (36.8)	4 (66.7)	0.199
Both	8 (27.6)	2 (12.5)	0.244	1 (7.1)	9 (29)	0.102	4 (21.1)	4 (66.7)	0.037

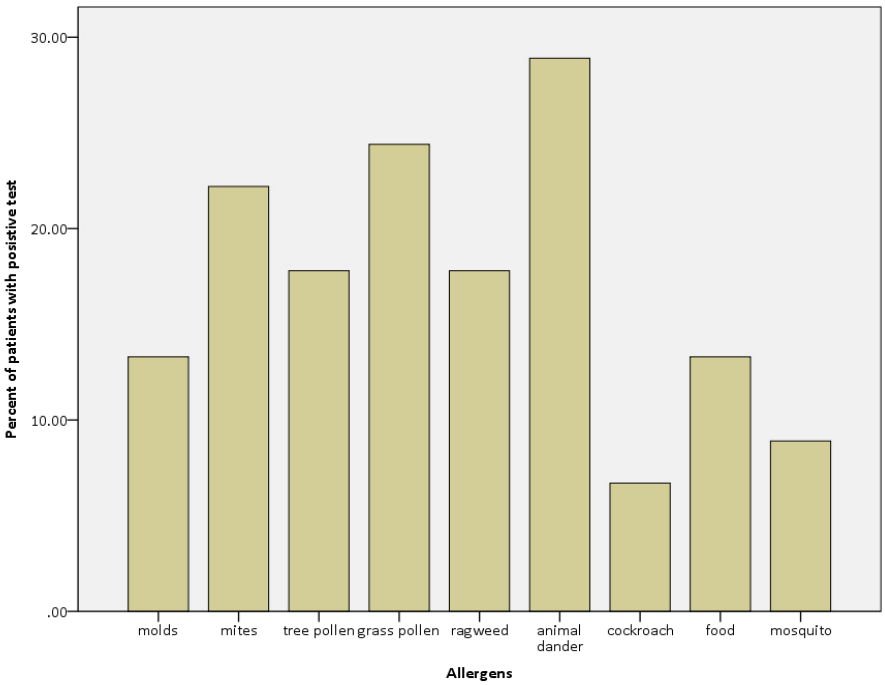

Fig. 2. Sensitivity to animal dander, grass pollen and mites were the most common, respectively.

allergy in 16 (35.6%), conjunctivitis in 15 (33.3%), eczema in 12 (26.7%) and allergy to bee venom in 2 (4.4%) of participants were reported.

Medical treatment was successful in 14 (31.1%) and failed in 31 (68.9%). Of the failures of medical treatment 25 underwent surgery for polyp removal; it was successful in 19 (76%) and failed in 6 (24%). Patient characteristics in asthmatics versus non-asthmatics and failed versus successful of medical or surgical treatments has been depicted in Table 1.

Nasal smear cytology; which inflammatory cells are predominant in nasal secretions of CRSwNP?

Leukocyte infiltration was present in most of the specimens and was not found in only 7 (15.5%) patients. Neutrophil infiltration was predominant in 29 (64.4%) and eosinophilia in 9 (20%). Neutrophil infiltration was the predominant pattern whether patient suffered from asthma or not (p=0.887). Furthermore, no significant difference was found in cytology pattern of nasal secretions between failed and successful cases of either medical or surgical treatments (p=0.557 and p=0.647, respectively, Figure 1).

Cutaneous reactivity pattern; is it related to the course of disease?

SPT revealed that 17 (37.8%) patients had no sensitization, while, 11 (24.4%) showed monosensitization and 17 (37.8%) were polysensitized. Of them, 16 (35.5%) were only sensitized to seasonal allergens while 19 (42.2%) to perennial allergens (p<0.001, Table 2).

Overall sensitivity pattern has been depicted in figure2. In both of asthmatics and who were free of asthma sensitization to animal dander was seen more but it did not attain significance compared to other allergens (31% and 25%, respectively, p>0.05). In failures of either medical or surgical management sensitization to animal dander was predominant but successful treatments were more sensitized to mites or grass pollens, respectively (Figure 3).

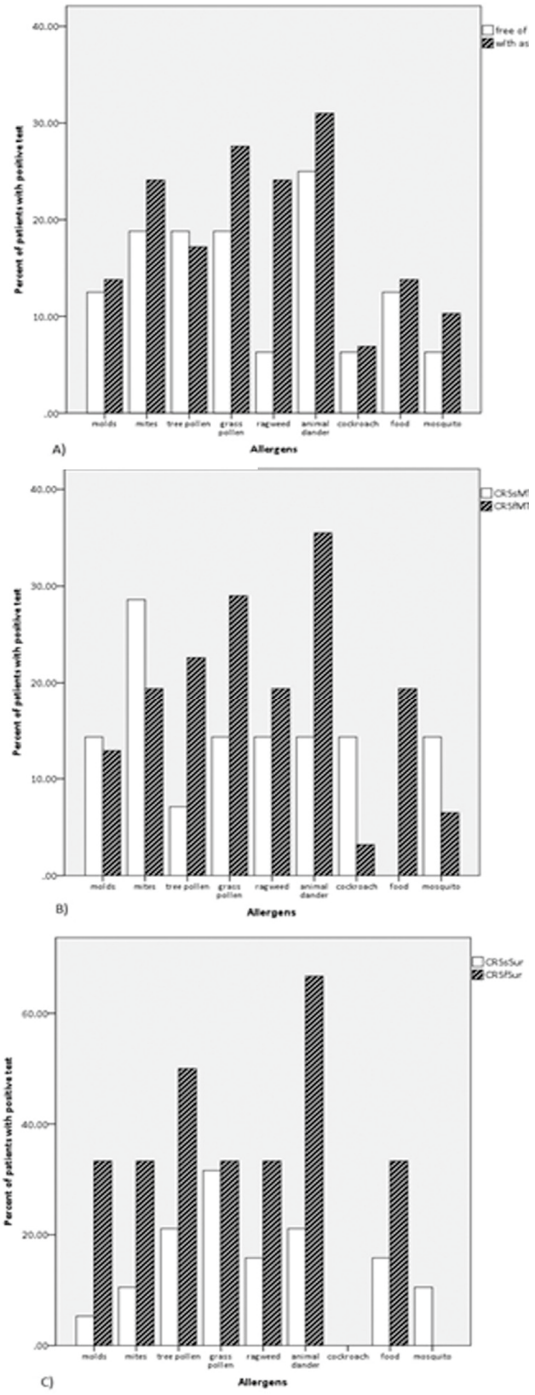

Fig.3. Sensitization pattern in patients with CRSwNP A) in the presence or absence of asthma, B) failing medical therapy or when it was successful (CRSfMT and CRSsMT, respectively) and C) failing surgery or when it was successful (CRSfSur and CRSsSur, respectively).

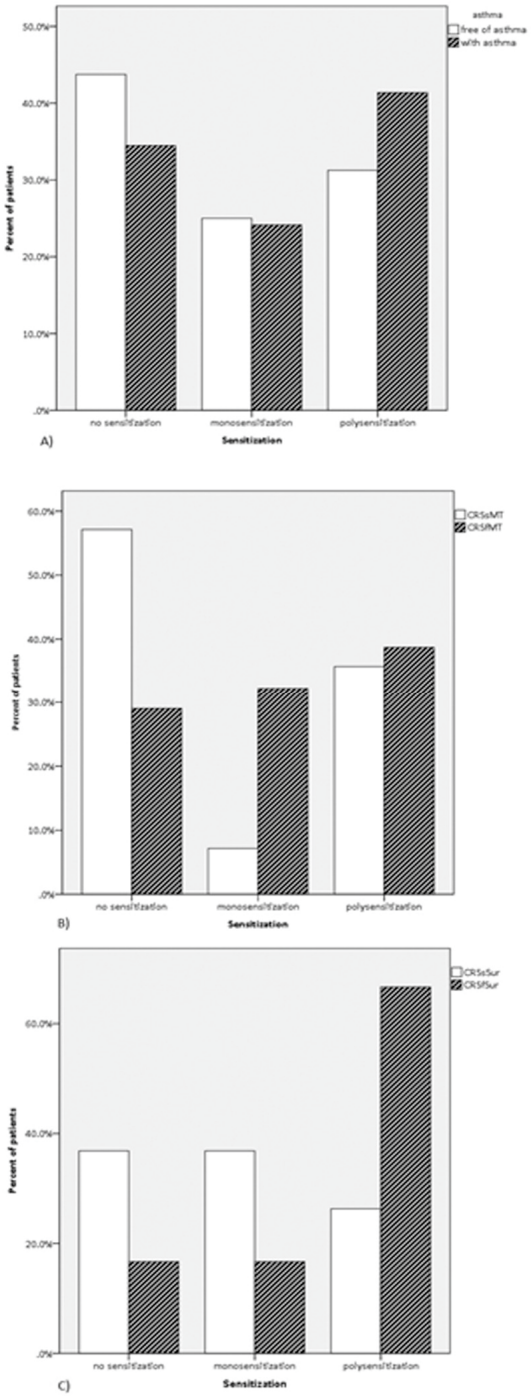

Fig. 4. atopic status in patients with CRSwNP A) in the presence or absence of asthma: of asthmatics 65.5% and of non-asthmatics, 56.3% had atopy without significant difference (p=0.539) B) failing medical therapy or when it was successful (CRSfMT and CRSsMT, respectively); Of CRSfMT, 71% and of CRSsMT, 42.8% had atopy without significant difference (p=0.072) C) failing surgery or when it was successful (CRSfSur and CRSsSur, respectively); Of CRSfSur, 83.4% and of CRSsSur 63.2% had atopy(p=0.356). Poly-sensitization was more than mono/non-sensitization in asthmatics, CRSfMT and CRSfSur.

Failures of surgical intervention were more poly-sensitized compared to successful surgeries (p=0.073, Figure 4).

Discussion

This study investigated the association of atopy in terms of cutaneous reactivity pattern to environmental allergens and predominant type of inflammation in nasal secretions of patients with CRSwNP with the course of disease. We focused on patients with CRSwNP from population with CRS because presence of nasal polyps in the setting of CRS may change the course of disease with idiopathic etiology and poorer response to medical and surgical therapies compared to CRSsNP. Indeed, it seems that CRSwNP should be considered as a distinct disease and it is unlikely to say that CRSwNP is advanced-stage of CRSsNP (11).

We found a high prevalence of atopy among patients suffering from CRSwNP in which 73.3% had a history of allergic conditions and SPT confirmed atopy in 62.2% of participants. In atopic patients, exposure to aeroallergens leads to expression of pro-inflammatory cytokines, infiltration of inflammatory cells to the exposure site (upper airway in these cases) vascular congestion and tissue edema (3). These changes are recurrent and justify the chronic pattern of disease. Furthermore, local inflammation of nasal and paranasal cavities facilitates microbial infection and muco-cilliary dysfunction. On the other hand, epithelial barrier dysfunction adjunct to viral, bacterial or even fungal infections would propagate the inflammation (12, 13). In this overwhelming cycle, mucosal inflammation that can be seen with (atopy) or without (entopy) systemic allergic response plays an important role (14). Most of previous studies suggested eosinophilic inflammation derived by T helper 2 cytokines such as interleukin 5 in patients with CRSwNP. These results were achieved with samples from Caucasian people while studies on Asian revealed predominant pattern of neutrophilia conferring the role of racial parameters and genetics in response to environmental allergens (15). In this study, we found predominant pattern of neutrophilia in nasal secretions of patients with CRSwNP regardless of course of disease. Whether mucosal inflammation is predominantly neutrophilic or eosinophilic, imbalance in immunological response to aeroallergens or superantigens exists and justifies the implications of medical therapy with corticosteroids and macrolides as immunomodulators (14). In this study, patients who were failed with medical therapy showed atopy (70.9%) more than who succeeded with medical therapy (42.8%), while, medical therapies with blunt immunosuppressant agents like steroids had been employed. The authors suggest that maybe local treatment or the dosage is not enough when the patient has atopy and specially poly-sensitization.

However the role of allergy in development of CRS is controversial but there are evidences that it may be the complication of allergy especially perennial type (16, 17). Gutman et al found that 57.4% of patients with chronic or acute recurrent rhinosinusitis had atopy with predominance of perennial allergy (18). Perennial allergy and poly-sensitization were the predominant pattern of sensitization in experience of Emmanuel et al with prevalence of atopy as 84% in a total of 200 patients with CRS failing medical therapy (19). In our experiment, there was a significant predominance of perennial allergy rather than seasonal one ($p<0.001$), However, predominant pattern of sensitization in all of patients underwent Surgery either failed or succeeded was seasonal allergy. Additionally, it was equivocal in failures of medical treatments and perennial in successful medical managements and patients with asthma. Recent study by Tan et al revealed no significant difference between seasonal or perennial allergies in patients with CRSwNP failing medical therapy but poly-sensitization was higher than patients with CRSsNP or rhinitis (6). Accordingly, identification of sensitization status is helpful to select patient for medical or surgical therapy, patient counseling regarding the prognosis of treatment and application of specific tailored medications such as SIT (20). Delineation of specific sensitivities is the key point to target the trigger of inflammation cascade and induction of tolerance. We found that the most common allergy was to animal dander (cat and dog) and unfortunately it was frequently observed in whom failing medical or surgical interventions. In these cases application of SIT with the knowledge of sensitivity status may help to reduce the inflammation and need for revisions of conventional therapies.

Airway hyper-responsiveness manifested as asthma was detected in 64.4% of patients with CRSwNP in our experience and from them 64.5% were atopic. This was similar to results of Tan et al with 62.9% prevalence of asthma in patients with CRSwNP(6). On the other hand, Pearlman et al showed that Asthmatics are more prone to have nasal polyps compared to those who are free of asthma(21). These findings support the idea of unified airway and justify the comprehensive taking history of respiratory system and performing PFT for patients with documented CRSwNP (22, 23). Asthma in the setting of CRSwNP is more likely to be atopic as we

observed, while, one half of asthmatic adults are estimated to be atopic (24).

Interestingly, more than aeroallergens, drug and food sensitization was observed in patients with CRSwNP. It is unclear that sensitization to these allergens and re-exposures is responsible for chronic mucosal inflammation or sensitization to other aeroallergens is the key point as there were no atopic cases with only food sensitivity in present series of patients with CRSwNP. Previous studies suggested that many patients with aspirin hyper-sensitivity will experience severe form of asthma and extensive nasal polyps and poor course of disease (25). Smater's triad or aspirin-exacerbated respiratory disease as defined with CRSwNP, asthma and ASA hypersensitivity was found to be 8/45 (17.7%) in patients with CRSwNP in this study. No difference between numbers of patients with ASA hypersensitivity was found between who were failed with medical or surgical therapies versus who successfully managed. However, there was a trend towards failure of surgical therapy in patients with ASA hyper-sensitivity. Medical therapy with oral corticosteroids is an appropriate option for management of CRSwNP in the setting of ASA hyper-sensitivity (25) but if it is failed the possibility of recurrence following surgery will be higher than patients with only CRSwNP (26). This combination in aspirin-exacerbated respiratory disease is totally poor responsive to standard therapeutic approaches than other forms of CRSwNP (27).

Some of the limitations of this study that should be addressed its retrospective nature, referral bias and absence of a large sample to validate the results. Furthermore, for clinical applications and patient counseling it was better that the SPT and smear cytology to be obtained prior to medical or surgical intervention. The strength of this study is its comprehensive insight to the atopy in the course of CRSwNP not only in whom failed with medical therapy as previous studies did but also considered different response to surgical management and presence of prevalent comorbidities together.

As a whole, there is a link between atopy and comorbidities originated from atopy with CRSwNP. The response of the patient to medical and surgical therapies is under the influence of sensitization status. Perennial allergy is the most common pattern in patients with CRSwNP but seasonal one is not rare and is more frequently seen in whom failing with surgery. Polysensitization is associated with poor response to conventional therapies. SIT may play an important role in the future of management of patients with CRSwNP regarding the specific sensitization status. Further studies is needed to investigate the safety and efficacy of SIT in treatment of patients of with CRSwNP and its cost-effectiveness compared to conventional treatment modalities.

Conclusion

Atopy is frequently present in patients with CRSwNP and pattern of sensitization can affect the outcome of intervention. With respect to different pattern of sensitization among failed and successful interventions, determining the sensitizations prior to any intervention is suggested. Patient counseling regarding the recurrence of disease can be done in accordance with atopic profile.

Conflicts of interest: None declared.

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