Title: Allergies, asthma or hypersensitivity to NSAIDs - are they an equally important risk factor for the development of a specific CRS phenotype?

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Allergies, asthma or hypersensitivity to NSAIDs – are they an equally important risk factor for the development of a specific CRS phenotype?

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: CRS is a complex systemic disease affecting more than 10% of the population. There are two main types of CRS phenotypes: CRSwNP and CRSsNP. In the Caucasian population, the prevalence of inflammation markers typical of the Th1 profile is observed in CRSsNP, whereas Th2 and Th17 in CRSwNP. Th2 inflammation is observed in the CRSwNP phenotype with concomitant allergies, asthma or hypersensitivity to NSAIDs.

Objectives: The aim of the study was to evaluate, based on the authors' own material, whether allergies, asthma or hypersensitivity to NSAIDs were a risk factor for the development of a specific CRS phenotype. An attempt was also made to investigate the influence of comorbidities on the extent of sinus endoscopic procedures, which depended on the severity of inflammation.

Methods: In the years 2006–2015, ESS was performed on 2217 patients with different CRS phenotypes. Patients with an allergy, bronchial asthma and hypersensitivity to NSAIDs were subjected to analysis.

Results: Based on logistic regression, it was found that among the mentioned comorbidities, only asthma ($P < 0.0001$) and hypersensitivity to NSAIDs ($P = 0.0007$) significantly affect the occurrence of the phenotype with polyps, whereas the impact of allergies is statistically insignificant ($P = 0.1909$). The relationship between the type of ESS and CRS phenotypes is statistically significant ($P < 0.0001$).

Conclusions: Bronchial asthma and hypersensitivity to NSAIDs have a statistically significant effect on the occurrence of the CRSwNP phenotype. This effect was not observed in allergies. The impact of allergies, asthma and hypersensitivity on the phenotype was observed in the group of patients subjected to the most extensive surgery (ESS 4).

KEYWORDS: allergy, asthma, hypersensitivity, nasal surgical procedures, sinusitis

ABBREVIATIONS

AERD – aspirin-exacerbated respiratory disease
AFRS – allergic fungal rhinosinusitis
CF – cystic fibrosis
CRS – chronic rhinosinusitis
CRSsNP – CRS without nasal polyps
CRSwNP – CRS with nasal polyps
DCs – dendritic cells
EAACI – European Academy of Allergy and Clinical Immunology
ECP – eosinophil cationic protein
EFRS – eosinophilic fungal rhinosinusitis
ESS – endoscopic sinus surgery
GINA – Global Initiative for Asthma
ICS – inhaled corticosteroid
LABA – long-acting beta-agonists
NSAIDs – exacerbated respiratory disease
OR – odds ratio
pDCs – plasmacytoid dendritic cells
SABA – short-acting beta-agonists

INTRODUCTION

CRS is one of the most widespread chronic diseases in the world, affecting 10.9% of the Europe's population [1] and 12.5% of the US population [2]. Chronic sinusitis is a complex systemic disease. Clinically, based on endoscopic examination, two major CRS phenotypes can be distinguished, namely CRSwNP and CRSsNP. Clinically distinguished phenotypes do not reflect the profile of

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cytokines involved in the inflammation process. Tomassen et al. [3] defined CRS endotypes as „subtypes of disease with a unique pathomechanism, functionally and pathologically different from others by the involvement of a specific molecule or cell". Overlapping cytokines of the inflammation profile with the predominance of Th1, Th2 and Th17 helper lymphocytes are involved in CRS. In the Caucasian population, the prevalence of inflammation markers typical of the Th1 profile is observed in CRSsNP, whereas Th2 and Th17 in CRSwNP. Th2 inflammation with a high predominance of IL-5, causing subsequent tissue eosinophilia, is observed in the CRSwNP phenotype with concomitant asthma. Eosinophilic sinusitis is also observed in patients with respiratory diseases caused by IgE-related allergy or aspirin hypersensitivity (NERD) [4], EFRS [5] and AFRS [2]. CRSwNP with the predominance of neutrophilic inflammation (Th1 type) occurs in the case of blockage of the sinus ostia due to congenital anatomical malformations, chronic (allergic or nonallergic) rhinitis and CF or primary ciliary dyskinesia [4].

The aim of the study was to investigate whether comorbidities accompanied by inflammation with a predominant role of eosinophils such as allergies, asthma or NSAIDs hypersensitivity were equally important risk factors for the development of a specific CRS phenotype. Among Caucasians, eosinophilic infiltrates are mainly found in polyps, which suggests a common pathomechanism of upper and lower airway inflammation. In the existing literature, there are reports suggesting the impact of asthma, IgE-dependent allergy and AERD on the severity of CRSwNP and the extent and frequency of sinus reoperation [6–10]. This was a stimulus for verifying, based on the authors' own material, whether these comorbidities had an effect on the severity of inflammatory changes in the sinuses and, as a result, on the extent of endoscopic surgery.

The authors also decided to evaluate the relationships between CRS phenotypes and comorbidities such as allergies, asthma or hypersensitivity to NSAIDs and check if these relationships were similar in the groups divided based on the extent of endoscopic sinus surgery.

The authors of the study carried out a retrospective analysis of all the patients (only 1% of patients who met the exclusion criterion described below were excluded from the analysis) admitted, qualified and operated on due to CRS in the years 2006–2015. The demographic data, disease phenotype and concurrent conditions related to asthma, allergies and NSAIDs hypersensitivity as well as the extent of ESS were taken into account. The relationship between CRS phenotypes and the aforementioned diseases was assessed.

MATERIAL AND METHODS

Study population

In the years 2006–2015, ESS was performed on 2217 patients over the age of 18 with CRSsNP or CRSwNP. The study group consisted of 1021 women (46.05% of all patients) and 1196 men (53.95% of all). The average age of women was 48.03 ± 13.41, while that of men was 46.91 ± 14.55. They all belonged to the Caucasian race.

Extent of surgery

The extent of endoscopic sinus surgery is defined as type 1–4:

- the first type involves the removal of the uncinate process with the enlargement of the maxillary ostium (antrostomy with uncinectomy);
- the second type involves the opening of the anterior or anterior and posterior ethomoidal cells (anterior or anterior and posterior ethmoidectomy);
- the third type involves the opening of the frontal sinus (with or without antroethmoidectomy);
- the fourth one – the opening of the sphenoid sinus (operated in conjunction with other sinuses or not).

The authors adopted the above description of ESS types in order to group the procedures performed depending on the number and type of sinuses. The surgery was performed under general anaesthesia with hypotension.

Inclusion criteria

Patients who had reported nasal obstruction or discharge and at least one of the other symptoms, such as impaired olfaction or facial pain lasting over 12 weeks with no complete resolution after maximal medical therapy, were qualified for surgery in accordance with the EPOS 2012 guidelines [11]. For 504 patients (22.73% of the total number of patients), these were reoperations of the nasal cavity and sinuses. For the remaining 1713 (77.27%), these were the first operations. CRS phenotypes were identified after nasal endoscopy. CRSwNP was diagnosed when bilateral polyps were visualised at least in the middle nasal meatus. Nasal polyposis in CRSwNP was categorized using the Lund-Kennedy scoring system.

A CT scan of the sinuses was performed in each patient, on the basis of which the extent of inflammatory lesions was assessed according to the Lund-Mackay score (the degree of opacification in the maxillary, anterior and posterior ethmoid, frontal, and sphenoid sinuses as well as the obstruction of the ostiomeatal complexes were evaluated (on both sides) on a 0–2 scale – a maximum of 24 points), and then the extent of ESS was planned. The patients admitted to the ward for endoscopic surgery were diagnosed and treated on an outpatient basis due to chronic sinusitis and associated conditions such as allergies, bronchial asthma and hypersensitivity to NSAIDs. Tab. I. shows the number of patients with respect to the comorbidities. The patients were allocated to three groups depending on the comorbidities. However, one patient could belong to one, two or all three of them.

The first group included patients with IgE-dependent allergies to seasonal (early and late blooming trees, grasses, weeds) and perennial airborne allergens (mites and mould spores, cat and dog allergens). The patients had allergic reactions to one or several different allergens. The studied plant and fungal allergens were characteristic of the temperate climate of Central Europe. This group included patients reporting clinical symptoms caused by the allergens. Allergies were confirmed by a skin prick test or the presence of specific IgE antibodies in the patient's serum. The examinations were performed

on an outpatient basis and correlated with clinical symptoms occurring in the patients. The patients were under constant care of an allergist who applied the maximal medical therapy, some patients were also subjected to specific allergen immunotherapy. Skin prick or in vitro tests were not performed in every patient admitted to the ward. It was assumed that a positive test without clinical symptoms did not qualify patients to the group with allergies. The patients with clinical symptoms and positive pollen allergy tests were operated outside of the pollen season for specific allergens. Patients with allergic reactions occurring in other immunological mechanisms were not qualified here (non-IgE-dependent allergies).

The second group included patients with NSAIDs hypersensitivity. AERD is „a complex syndrome typified by underlying airway inflammation in which patients experience adult-onset asthma, nasal polyposis/chronic rhinosinusitis, and aspirin/nonsteroidal anti-inflammatory drug (NSAID) sensitivity" [12]. The authors adopted the term „hypersensitivity to NSAIDs" which is defined by the EAACI as objectively reproducible symptoms that are caused by exposure to a specific stimulus in a dose tolerated by other people. Clinical symptoms relate to the mucous membranes of the respiratory and digestive tract as well as the skin, and can be induced not only by aspirin, but also by one or more NSAIDs [13].

Patients, qualified to this group by the authors, who reported hypersensitivity to aspirin and other NSAIDs had dyspnoea attacks, serous fluid discharge/nasal mucosa oedema or acute urticaria after taking the drugs. Aspirin tests were not performed in patients after their admission to the ward. It was the medical history describing the symptoms resulting from taking the drug/s that played the crucial role. Information about unexpected symptoms after taking NSAIDs was provided during a medical interview, not in the form of a questionnaire. Not all patients with hypersensitivity to NSAIDs had asthma, some patients reported inhalant allergies.

The third group included patients with bronchial asthma diagnosed in the outpatient setting. According to GINA [14], asthma is a heterogeneous disease defined by a medical interview, with respiratory symptoms such as wheezing, dyspnoea, chest tightness and coughing, which vary over time and in terms of severity, including variable airway obstruction. Patients with co-existing asthma, depending on the severity of asthma (light, moderate, severe), took SABA, ICS combined or not with LABA and/or antileukotriene drugs. Chronic treatment in outpatient care was recommended by a specialist. The actual (the last 4 weeks before the surgical treatment) level of asthma control (good, partial or bad) was important for the authors. Asthma was considered well-controlled when the patient did not report any nocturnal symptoms, daily symptoms were less frequent than twice a week, drugs (SABA) were used less than twice a week, and if the disease had no effect on daily activities. In terms of the severity of asthma, assessed on the basis of recommended doses of inhalation drugs and the FEV1 index, patients with mild and moderately severe asthma were qualified for surgical treatment of the sinuses.

Exclusion criteria

Patients under 18 years of age with rhinosinusitis exacerbation less than 4 weeks prior to the admission to hospital, poorly controlled bronchial asthma, documented IgE-dependent allergies to grass, tree or weed pollen currently present in the environment, immunodeficiency, CF and those with tumours identified in the histopathological examination of the material collected from the sinuses were excluded from the study.

Tab. I. Number of patients with respect to comorbidities.

COMORBIDITY			DIAGNOSIS		TOTAL	
ALLERGY	HYPERSENSITIVITY	ASTHMA	CRSWNP	CRSSNP		
–	–	–	539	957	1496	1496
+	+	–	62	99	161	
–	–	–	35	48	83	
–	–	+	140	84	224	
+	+	–	8	3	11	721
+	+	+	50	24	74	
–	–	+	104	32	136	
+	+	+	25	7	32	
Σ+ = 278	Σ+ = 278	Σ+ = 466	Σ = 963	Σ = 1254	Σ = 2217	

„+" indicates the occurrence of a given disease, „–" means the absence of a given disease, e.g. in the second row of the table where „+" is only in the allergy column, 161 people out of all 2217 patients had allergies without co-existing hypersensitivity (–) or asthma (–); of the 161 patients, 62 had CRSwNP, the other patients (99) – CRSsNP; 721 out of 2217 patients had at least one comorbidity, and 32 patients had all three.

Tab. II. Relationship between comorbidities and diagnosis.

DIAGNOSIS COMORBIDITY		ALL PATIENTS N = 2217 CRSWNP N_{WP} = 963 (43,44% Z N)	CRSSNP N_{NP} = 1254 (56,54% Z N)	P – VALUE
Allergy	Yes (278 per.) 12,54% z n	52,16%	47,84%	p = 0.0017 *
	Nie (1939 per.) 87.46% z n	42,19%	57,81%	
Hypersensitivity	Yes (262 per.) 11,82% z n	65,65%	34,35%	p < 0.0001
	Nie (1955 per.) 88,18% z n	40,46%	59,54%	
Asthma	Yes (466 per.) 21,02% z n	68,45%	31,55%	p < 0.0001
	Nie (1751 per.) 78,98% z n	36,78%	63,22%	

* P < 0.01, P-values obtained from the Chi2 test, which checks whether there is a relationship between the occurrence of a particular comorbidity and CRS phenotype.

Statistical Analysis

Statistical analysis was performed using Statistica 12.5. The analysis was divided into two parts. First, the influence of each comorbidity (allergies, asthma or hypersensitivity) on CRS phenotypes was analysed separately (one-dimensional analysis, each comorbidity – dichotomous variable – was treated in the analysis as a single qualitative predictor). Thus, 3 groups were separated according to the

Tab. III. Distribution of the number of patients in relation to the diagnosis, extent of surgery and comorbidities.

COMORBIDITY			EXTENT OF SURGERY							
			ESS 1		ESS 2		ESS 3		ESS 4	
ALLERGY	HYPERSENSITIVITY	ASTHMA	DIAGNOSIS		DIAGNOSIS		DIAGNOSIS		DIAGNOSIS	
			CRSWNP	CRSSNP	CRSWNP	CRSSNP	CRSWNP	CRSSNP	CRSWNP	CRSSNP
–	–	–	114	545	198	227	12	16	215	169
+	–	–	10	56	23	24	——	1	29	18
–	+	–	9	26	16	13	1	1	9	8
–	–	+	23	44	44	21	6	1	67	18
+	+	–	1	1	1	——	——	1	6	1
+	–	+	5	11	16	7	2	——	27	6
–	+	+	12	6	40	13	——	——	52	13
+	+	+	——	——	8	3	1	——	16	4
razem			174	689	346	308	22	20	421	237

„+" indicates the occurrence of a given disease, „–" means the absence of a given disease.

description given in the „Inclusion criteria", and in each of them the relationship between the phenotype and one particular comorbidity was analysed individually. The same analysis was also performed after dividing each of the three groups into subgroups relative to the extent of surgery. For this purpose, the Chi2 test was used. In justified cases, the Chi2 test with the appropriate correction was used. In the second stage, it was examined which of the three comorbidities (three qualitative predictors in the analysis) affect the phenotypes. For this purpose, a multivariate analysis based on logistic regression (logit) was performed. OR was used as the measure of effect.

RESULTS

In the study group of 2217, there were 1254 (56.56% of total patients) patients with CRSsNP and 963 (43.44%) with CRSwNP. The group with CRSsNP included 616 women and 638 men. The CRSwNP phenotype occurred in 405 women and 558 men. The relationship between diagnosis and gender is statistically significant (P = 0.0009). Women were more likely than men to suffer from CRSsNP – 60.33% (616 out of 1021 women). A total of 53.34% of men (638 out of 1196 men) were diagnosed with CRSsNP, and polyps were present in 46.66%. However, the influence of gender on the occurrence of a particular phenotype was not taken into account in further analysis.

Allergy vs. CRS phenotype

Of all 2217 patients, 278 (12.54% of all the treated patients) had allergies (Tab. II.). Among patients with an allergy, 145 (52.16% of 278) had CRSwNP. The other 133 (47.84% of 278) – CRSsNP. As many as 1121 individuals (57.81% of 1939 patients without an allergy) were diagnosed with CRSsNP. The relationship between the occurrence of allergies and diagnosis is statistically significant (P = 0.0017) (Tab. II.). At this stage, the occurrence of the phenotype with polyps seems to be associated with the presence of allergies.

NSAID vs. CRS phenotype

Hypersensitivity to NSAIDs was present in 262 cases (11.82% of all the 2217 operated patients) (Tab. II.). Among patients with hypersensitivity to NSAIDs, 172 (65.65%) had polyps, and in 90 (34.35%) they were absent. Of all 963 patients with CRSwNP, 172 (17.86%) reported hypersensitivity. In the group without polyps, which included 1254 patients, only 90 (7.18%) reported hypersensitivity. The occurrence of hypersensitivity is associated with the presence of polyps (P < 0.0001) (Tab. II.).

Asthma vs. CRS phenotype

Bronchial asthma was present in 466 patients (21.02% out of 2217). In the group of patients with bronchial asthma, 319 (68.45%) had polyps, whereas in 147 (31.55%) they were absent. Among 963 patients with CRSwNP, 33.13% suffered from bronchial asthma. The relationship between the occurrence of bronchial asthma and the diagnosis is statistically significant (P < 0.0001) (Tab. II.). It is more common in the group with polyps.

ESS type vs. CRS phenotype vs. comorbidities

In this part, it was decided to check whether the above relationships were similar in nature in the groups divided in terms of the extent of surgery. For this purpose, the entire study group was divided with respect to the ESS type, thus obtaining four groups analysed independently.

Of all 2217 cases, the ESS 1 group was the largest (863; 38.93% of all the treated patients), whereas the ESS 3 group the smallest (42; 1.89% of 2217). In the other groups, namely ESS 2 and ESS 4, the numbers were comparable and amounted to 654 (29.50%) and 658 (29.68%), respectively (Tab. III.).

The relationship between ESS and primary diagnosis is statistically significant (P < 0.0001). In the CRSsNP group, ESS 1 accounted for more than half of all the cases (54.94%); the other types 2, 3 and 4 accounted for 24.56%, 1.59% and 18.9%, respectively. In the CRSwNP group, ESS 4 was most common (43.72%), and the other types, 1, 2, and 3 accounted for 18.07%, 35.93% and 2.28%, respectively. The ESS 1 group was mainly dominated by cases without polyps (79.84% of all people with ESS 1), whereas those with polyps prevailed in the other ESS groups: 52.91% (ESS 2), 52.38% (ESS 3), and 63.98% (ESS 4).

To assess the relationship between the type of diagnosis and comorbidities depending on the extent of surgery, the relationship between the diagnosis and comorbidities was analysed individually in each ESS group. Relevant P–values are provided in Tab. IV.

ESS 1 – CRS phenotype vs. comorbidities

In the ESS 1 group, there is no statistically significant relationship between the diagnosis and the occurrence of allergies (p = 0.7887). Patients with an allergy accounted for 19.05% in the group with polyps and 80.95% in the group without polyps. The distribution was similar in the non-allergic group – 20.28% had CRSwNP, and the remaining 79.72% had CRSsNP.

In the case of patients with hypersensitivity, the relationship between its occurrence and diagnosis is statistically significant (P = 0.0001). Among the patients with hypersensitivity, 40% were diagnosed with CRSwNP, and in the group without hypersensitivity, only 18.82% had polyps.

In the group of patients with asthma, the relationship between its occurrence and diagnosis is also statistically significant (P < 0.0001). A total of 39.60% of patients with asthma were diagnosed with CRSwNP, whereas 82.4% of patients without asthma had CRSsNP.

ESS 2 – CRS phenotype vs. comorbidities

In the ESS 2 group, there was also no statistically significant relationship between the existence of allergies and the type of diagnosis. In the group of 82 patients with an allergy, 58.54% were diagnosed with CRSwNP. Patients without an allergy diagnosed with CRSwNP accounted for a similar percentage, i.e. 52.10% out of 572 patients.

The relationship between the existence of hypersensitivity and the phenotype is statistically significant (P = 0.0006). Of the 94 patients with hypersensitivity, 69.15% had the CRSwNP phenotype, whereas in the group of 560 patients without hypersensitivity, it was 50.18% (CRSwNP).

The relationship between the occurrence of asthma and the phenotype is also significant (P < 0.0001). Of the 152 patients with asthma, 71.05% had the phenotype with polyps, whereas in the group of 502 patients without asthma, 52.59% had the phenotype without polyps.

ESS 3 – CRS phenotype vs. comorbidities

In the ESS 3 group consisting of 42 patients, only 5 patients had an allergy, 4 – hypersensitivity and 10 – asthma. Due to the large disproportion in terms of the number of patients with respect to the other types of ESS, only the relevant fractions were compared in the ESS 3 group.

In the group of 37 patients without an allergy, 19 (51.35%) had the CRSwNP phenotype. Three patients with an allergy (60%) had the same phenotype. In the case of 4 patients with hypersensitivity, half of them had the CRSwNP phenotype. In the group of the remaining 38 patients without hypersensitivity, 18 patients (47.37%) had the CRSsNP phenotype. Of the 10 patients with asthma, 9 were diagnosed with CRSwNP, and in the group of 32 patients without asthma – 59.38% had CRSsNP.

Tab. IV. Relationship between particular comorbidities and phenotypes for a specific ESS type.

	ESS 1	ESS 2	ESS 3	ESS 4
Phenotype vs. allergy	p = 0,7887	p = 0,2747	----------	p = 0,0358
Phenotype vs. hypersensitivity	p = 0,0001	p = 0,0006	----------	p = 0,0038
Phenotype vs. asthma	p < 0,0001	p < 0,0001	----------	p < 0,0001

ESS 4 – CRS phenotype vs. comorbidities

In the ESS 4 group, the relationship between the phenotype and the existence of allergies is important (P = 0.0358). In the group of 107 patients with an allergy, 72.9% had CRSwNP, whereas in the group of 551 patients without allergy, 62.25% had the same phenotype (CRSwNP). Thus, the impact of allergies on the phenotype with polyps is found to be significant only in the group subjected to the most extensive surgery.

The occurrence of the phenotype with polyps depends essentially on the existence of hypersensitivity (P = 0.0038). Of the 109 people with hypersensitivity, 76.15% had CRSwNP, whereas of the 549 people without hypersensitivity, it was 61.57%.

The phenotype is significantly dependent on the coexistence of asthma (P < 0.0001). Among the 203 patients with asthma, 79.8% had CRSwNP. A total of 59.92% out of 455 patients without asthma had the same phenotype.

Multivariate analysis (logistic regression)

Previous one-dimensional analysis enabled the authors to assess the impact of each of the three comorbidities on the phenotype independently of the other two. In order to further estimate the influence of comorbidities (three predictors at the same time) on the occurrence of a specific inflammatory phenotype, a logistic model was built, in which allergies, asthma and hypersensitivity were included as predictors. Of the selected predictors, only asthma and hypersensitivity were statistically significant, P < 0.0001 and P = 0.0007, respectively. The occurrence of allergies is statistically insignificant in this model (P = 0.1909). The resulting logistic regression equation has the following form:

$$\text{logit } P = 1.15 \times \text{asthma} + 0{,}51 \times \text{intolerance} - 0{,}59 \quad (1)$$

On the basis of the intercept parameter, it can be concluded that the chance of occurrence of the CRSwNP phenotype in the group of patients who did not have any of the analysed comorbidities was 0.55. According to the obtained model, there are 64.55% of correctly classified cases, which indicates an average quality of classification. The prediction of the lack of inflammation with polyps is high, i.e. 88%. However, the coexistence of asthma and hypersensitivity is not suf-

ficient to predict the occurrence of inflammation with polyps (the prediction is only 34%). By interpreting the calculated OR, it can be stated that the possibility of occurrence of the CRSwNP phenotype in the group of people with asthma is more than 3 times higher than in the group without diagnosed asthma (OR = 3.16). People who have hypersensitivity to NSAIDs have a 70% greater probability (OR = 1.67) of developing inflammation with polyps than people who do not have hypersensitivity. However, in the case of allergies, OR is only 1.19, so the chance of occurrence of the CRSwNP phenotype in the group of people with allergies is slightly higher (by about 20%) than in the group of people without allergies.

DISCUSSION

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses characterized by 2 or more symptoms, one of which should be either nasal obstruction or nasal discharge. Other symptoms can be facial pain, reduction or loss of smell, or both. Chronic rhinosinusitis is defined as symptoms lasting at least 12 weeks without complete resolution [11]. The authors of the study limited their observations to two CRS phenotypes distinguished on the basis of the presence of polyps revealed by nasal endoscopy. In the study group of 2217, there were 56.56% (1254) of patients with CRSsNP and 43.44% (963) with CRSwNP. The study has shown that CRSsNP is more frequent in women (616 out of 1021 women, 60.33%) than men (638 out of 1196 men, 53.34%). However, a higher percentage of men (558 out of 1196, 46.66%) than women (405 out of 1021, 39.67%) had the CRSwNP phenotype. A similar observation was made by Tan [15], who presented the results of retrospective observations of 446,480 clinic primary care patients in the years 2001–2010. CRSwNP was diagnosed in 595 patients and CRSsNP in 7523, CRSwNP was more common among men (54.5%) and CRSsNP among women (58.2%).

It should be borne in mind that there are other phenotypes. CRS can be clinically divided according to its severity (mild, moderate and severe), duration of inflammation (acute and chronic), colour of secretions, whether it is responsive or not to conventional therapy, and also according to the degree of disease control (fully controlled, partially controlled and uncontrolled inflammation) [16]. Certain subtypes of CRS, such as cystic fibrosis, primary ciliary dyskinesia, antrochoanal polyps, and fungal disease (allergic and invasive), systemic diseases, or immune deficiency are not specifically mentioned in the evidence-based guidelines because their medical treatment might not differ substantially from other phenotypes of rhinosinusitis [6, 16]. Clinical phenotypes do not provide full insight into all underlying cellular and molecular pathophysiologic mechanisms of CRS. This heterogeneity supports the concept that CRS consists of multiple biological endotypes, which might be defined by corresponding biomarkers [16]. The endotype of inflammation with the predominance of IL-4, IL-5, IL-10, IL-13 is associated with Th2-type lymphocytes. These interleukins influence the growth and proliferation of B lymphocytes [17], whereas under the influence of IL-5, eosinophilic inflammation develops within the sinus mucous membrane, usually of considerable severity.

A similar mechanism of inflammation was observed in bronchial asthma regardless of its phenotype [18]. The authors showed, based on their own material, that the development of the CRSwNP phenotype, which occurs in the Caucasians with the predominance of Th2 mediators and eosinophilia, was influenced by asthma and hypersensitivity to NSAIDs. The level of ECP in uncinate tissues of patients with CRSwNP, examined by Weibman [19], was higher in asthmatics and AERD patients, which was not observed in the case of co-existing allergies. This confirms the authors' observations that asthma and NSAIDs hypersensitivity affect the CRS phenotype.

Tan's study, whose aim was to observe what additional conditions occur more frequently in patients with CRS, also found that asthma was most strongly associated with the CRSwNP phenotype, whereas acute rhinosinusitis, otitis media, pneumonia and bronchitis were associated with the diagnosis of CRSsNP. In addition, allergic rhinitis was present in a similar proportion of cases in both sinusitis phenotypes.

CRSwNP is an inflammatory disease of the nasal cavity and paranasal sinuses of unknown cause and often accompanies respiratory diseases such as asthma, aspirin hypersensitivity and idiopathic bronchiectasis [20–22]. Jarvis [1], based on a multi–centre study in 12 European countries, has found a strong correlation between CRS and asthma especially when CRS was accompanied by allergic rhinitis. The incidence of asthma is more common in CRSwNP patients (7%) than in the general population (4%), predominantly in women [23, 24].

In the study group, bronchial asthma was present in 466 patients (21.02% of 2217). In the group of patients with bronchial asthma, 319 (68.45%) had polyps, whereas in 147 (31.55%) they were absent. Bilodeau [25] has observed that asthma patients with CRSwNP have more severe lower airway infections and worse asthma control compared to patients with CRSsNP.

In the study group, 12.54% of patients had clinically confirmed allergies, by skin prick and/or in vitro tests. The occurrence of IgE-dependent allergies to environmental allergens in CRS patients is estimated to be approximately 60% compared to 30–40% in the case of the general population. It is suggested that it may support rather than cause eosinophilic mucositis [2, 26]. The results of the multivariate analysis performed by the authors did not show the impact of allergies on the CRS phenotype. Similar results were obtained by Li Qc [27] in the study of 210 patients, which showed no relationship between the presence of atopy and polyps. Although allergies do not affect the CRS phenotype, hypersensitivity to NSAID seems to be strongly related to the presence of polyps.

AERD is characterized by hypersensitivity to aspirin, asthma and CRSwNP, and occurs in about 1% of the population, including 4.3%–20% of asthmatics and 14–22% of patients with polyps [11, 28–31]. In the studied material, hypersensitivity to NSAIDs was present in 262 cases (11.82% of the 2217 operated patients). The authors of the study confirmed the prevalence of asthma and hypersensitivity to NSAIDs in CRSwNP patients, especially in women. Women accounted for 65.27%, and men for 34.73%. Patients with aspirin hypersensitivity often have nasal polyps and asthma. This unique endotype is associated with tissue eosinophilia and an increase in the production of leukotrienes [16, 31]. Yamaguchi [32]

found that patients with asthma and aspirin hypersensitivity had a higher number of eosinophils in the sinus mucous membrane and a higher concentration of urinary leukotrienes E4 (U–LTE4) in urine than patients with asthma, and good tolerance to NSAIDs. Pezato's studies [33] showed that human DCs were significantly increased in CRSwNP compared to control nasal tissue, only the expression of pDCs decreased in asthmatic patients and in those with no IFN gamma production in the nasal tissue. It was shown that pDCs for asthmatic patients were dysfunctional and secreted less innate IFNs in response to rhinovirus exposure. Pezato [33] found that pDC decreased in more severe CRSwNP+asthma groups and aspirin hypersensitivity groups. These findings provide strong support for a unified airway concept in which the mucosal surfaces of the upper and lower airways share common pathogens and mechanisms of inflammation and innate immunity [15].

Patients with aspirin hypersensitivity were significantly more likely to have uncontrolled CRS, which was not observed in the case of asthma and atopy [34]. The sinusitis phenotype and presence of polyps did not significantly affect the degree of CRS control, as the percentages of patients in the three categories of control did not differ between CRSwNP and CRSsNP [34]. CRSwNP with accompanying asthma is characterized by older age, longer nasal congestion, a higher score in sinus computed tomography and nasal endoscopy, and more frequent nasal and sinus reoperations. This is especially true of the CRSwNP phenotype with hypersensitivity to NSAIDs [20, 24]. Bachert [6] reports that during the 12-year follow-up, 80% of patients with CRSwNP had polyp recurrence and about 37% required reoperation. This concerned mostly patients with eosinophil endothelium and AERD [5, 6].

In the studied material, ESS 1 was most commonly performed in the CRSsNP phenotype, whereas the CRSwNP phenotype required extensive surgery including the opening of all the sinuses, namely ESS 4 (it was sporadically limited to the opening of the sphenoid sinus only) or ESS 3. The need for reoperation followed by ESS 3 and 4 has been confirmed by the authors who found a higher Lund-MacKay computed tomography score and Lund-Kennedy endoscopy score in CRSwNP, especially in patients with atopy and hypersensitivity to NSAIDs [7]. Noon [35] has compared the findings of authors from the UK and North America, highlighting better postoperative outcomes in patients with CRSwNP who underwent extensive surgery, especially when they were affected by asthma and AERD. It should be remembered that apart from asthma and hypersensitivity accompanying CRSwNP, better postoperative results are obtained by performing extensive ESS also in other, not only neoplastic, sinus diseases [36]. The serum IgE level in patients with an allergy is a stimulant factor for more frequent recommendations for surgical treatment, but there was no difference in the outcomes of conservative and surgical treatment in patients with and without atopy [37, 38]. A higher level of ECP in uncinate tissues and nasal polyps significantly correlates with radiographic severity as determined by CT scores. Mucosal markers associated with comorbidities (asthma, atopy, and aspirin sensitivity) helps better establish the concept of unified airway inflammation [19]. The latest analysis of the clinical and biological parameters currently used for phenotyping and endotyping in CRSwNP ruled out allergy as a pathophysiological factor, which confirms our results of statistical analysis [39]. The study confirms the influence of eosinophilic inflammation with asthma and NSAIDs hypersensitivity on the development of the phenotype with polyps, more advanced inflammatory changes in the sinuses and the need for more extensive surgery.

CONCLUSIONS

1. Patients with co-existing asthma and hypersensitivity to NSAIDs have a greater chance of developing the CRSwNP phenotype;

2. In the case of allergies, the probability of the occurrence of the CRSwNP phenotype in the group of people with allergies is slightly higher (by approx. 20%) than in the group of people without allergies;

3. The impact of allergies, asthma and hypersensitivity on the phenotype was observed in the group of patients subjected to the most extensive surgery (ESS 4). In the other types of surgery, only the relationship between the phenotype with polyps and asthma and hypersensitivity was significant.

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