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ORIGINAL ARTICLE

Analysis of the impact of bronchial asthma and aspirin hypersensitivity on the clinical course of chronic sinusitis with nasal polyps

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:

Background: Despite significant developments in immunology, microbiology and genetics, we still do not know enough about the etiology and pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP). The incidence of that disorder has been steadily increasing in the recent years. The co-occurrence of CRSwPN, bronchial asthma (BA) and aspirin intolerance (AI) what is called the aspirin triad, constitutes an adverse prognostic factor, increasing the individual predisposition of patients to disease relapse.

Aim: The aim of this work was to compare the severity of CRSwNP in patients undergoing surgery depending on the coexistence of BA and/or AI. The study included 204 patients treated for CRSwNP between 2009 and 2013 with a minimum 5-year follow-up period.

Results: We demonstrated greater severity of polypoid lesions in endoscopic examination among people with the aspirin triad (P = 0.0005), with CRSwNP and bronchial asthma (P = 0.0030), as well as in the CT of the sinuses according to the Lund-Mackay scale (P <0.0001 and P = 0.0009, respectively). At the same time, more profound exacerbation of symptoms associated with CRSwNS acc. to VAS scale prior to surgery was observed among patients with concomitant bronchial asthma (P = 0.0126) and in patients with the aspirin triad (P = 0.0390) compared to the remaining patients with CRSwNP. Similarly, increase in symptoms during the 6 months following surgery in these patient groups (aspirin triad: P <0.0001, CRSwNP and AO: P = 0.0174) was shown. Moreover, patients with aspirin triad were statistically more likely to have undergone surgery in the past (P = 0.001), indicating high recurrence rate of the inflammatory process and frequent persistence of polypoid lesions despite proper conservative treatment. No similar differences have been shown for patients with CRSwNP and isolated aspirin hypersensitivity (without accompanying bronchial asthma).

Conclusions: Allergy to inhaled allergens and hypersensitivity to aspirin significantly aggravate the course of CRSwNP. It would be indicated to consider, despite the absence of history of aspirin intolerance, performing an aspirin provocation test in patients with a particularly severe course of CRSwNP, especially accompanied by bronchial asthma. It also seems appropriate to carry out such a test in every patient with newly diagnosed CRSwNP and bronchial asthma in order to adequately plan further treatment in this group of patients, including biological therapy (antimonoclonal therapy against interleukin 4, 5 or 13).

KEYWORDS: bronchial asthma, chronic sinusitis with nasal polyps, clinical course, hypersensitivity to aspirin, treatment

ABBREVIATIONS

AERD – Aspirin-Exacerbated Respiratory Disease
AIA – Aspirin-Induced Asthma
AIANE – European Network on Aspirin-Induced Asthma
BA – Bronchial Asthma
EPOS – European Position Paper on Rhinosinusitis and Nasal Polyps
FESS – Functional Endoscopic Sinus Surgery
AI –Aspirin Intolerance
NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
NP – Nasal Polyps
CRS – Chronic Rhinosinusitis
CRSwNP – Chronic Rhinosinusitis with Nasal Polyps
TENOR – The epidemiology and natural history of asthma: Outcomes and Treatment Regimens
CT – Computed Tomography
VAS – Visual Analog Scale

INTRODUCTION

The etiology and pathogenesis of CRSwNP remains insufficiently elucidated despite the developments in immunology, microbiology and genetics. It is defined as the occurrence of symptoms, such as: obstruction of nasal passages, excessive production of

secretions flowing on the back of the throat, often in conjunction with sinus pain, feeling of distension and/or a reduced sense of smell lasting more than 12 weeks [1]. In the recent years, the incidence of CRS with and without nasal polyps has been steadily increasing [1]. The number of people suffering from these conditions in Europe amounts to 10.9% on average [2]. In Poland, the incidence of CRS is 12% [3]. Despite many studies, pathomechanism of CRSwPN has not been elucidated to date. According to the hypothesis of multifactorial pathogenesis of nasal polyps according to Bernstein, dysfunction of endothelial cells and eosinophilic mucositis are important in the development of nasal polyps [4]. Function of the nasal mucosa is impaired due to the action of damaging factors, such as bacteria, including bacterial biofilm, viruses, allergens, toxic substances, or hypoxia, resulting from, i.a. mechanical air flow obstruction (e.g. deviation of nasal septum, concha bullosa) [5].

Despite the use of advanced surgical techniques and long-term adjuvant pharmacotherapy, recurrences of CRSwNP occur with a varying and difficult-to-predict frequency in an individual patient. It is estimated that up to 30% of patients with CRSwNP suffer from bronchial asthma, while in 15–25% it coexists with intolerance of aspirin and other NSAIDs [6]. Such a hypersensitivity, known as respiratory disease exacerbed by non-steroidal anti-inflammatory drugs, is associated with type 2 inflammatory reaction and facilitates frequent disease recurrence. The exact pathomechanism of its development has not been recognized to this date, resulting in diagnostic difficulties and restricted possibilities of pharmacological intervention. The combination of CRSwNP, bronchial asthma and aspirin intolerance is called the aspirin triad, which usually constitutes an adverse prognostic factor, augmenting individual predisposition to relapse.

AIM

The aim of the work was to compare the severity of chronic sinusitis with nasal polyps in patients undergoing surgery depending on the coexistence of BA and/or AI.

MATERIAL AND METHODS

Study included 204 patients treated surgically for CRSwNP over the years 2009–2013 at the Department of Otolaryngology and Oncological Laryngology at the Medical University of Lodz. Study group included 84 women (41.18%) and 120 men (58.82%). The Bioethical Committee approved the study protocol (RNN/187/13/KE). Patients enrolled in the study group were adult, without contraindications to surgery, without cancer or history of immunological disorders. Four subgroups of CRSwNP patients were formed: (1) without coexisting BA and AI, (2) with BA, (3) with AI, (4) with aspirin triade (CRSwNP + BA + AI). The subgroup of patients with aspirin hypersensitivity was identified based on the positive result of aspirin provocation test, which confirmed it in 41 of 204 individuals operated on due to CRSwNP, accounting for 20.01% of the study group. More than a quarter of patients were diagnosed with bronchial asthma (52 people; 25.49%). Among them, hypersensitivity to aspirin was diagnosed in 31 subjects (15.20% of the study group). Therefore, the majority of patients hypersensitive to aspirin (75.61%) presented all symptoms of the aspirin triad. The group of 31 people with aspirin triad comprised of 16 women (51.61%) and 15 men (48.39%). The characteristics of the test group are presented in Tab. I.

VAS was used to assess the severity of PZZP symptoms before and after endoscopic surgery. Patients in the study group assessed the severity of CRSwNP symptoms before endoscopic surgery and 6 months after treatment. During the post-operative period, they remained under laryngological care and were receiving intranasal glucocorticoids. The severity of the symptoms on a 10-cm-long numerical scale has been converted into numerical values, which allowed comparison of the severity of symptoms before and after treatment in individual patients. CRSwNP was divided according to VAS scores: light (0–3 points), moderate (4–7 points) and severe (8– 10 points) [1].

After taking medical history, patients underwent complete laryngological examination as well as 0-degree endoscopy following constriction of the nasal mucosa. The severity of the polypoid changes was assessed, as follows:

- „0" – no nasal polyps,
- Grade „1" – polyps present under the middle nasal turbinate,
- Grade „2" – polyps below the middle nasal concha,
- Grade „3" – polyps filling the common nasal duct.

The Lund-Mackay scoring system (1997), in accordance with the recommendations of the 2012 EPOS consensus, was used to assess the severity of inflammatory lesions in the nasal sinuses in CT examination [1]. Involvement of individual sinuses was assessed on a scale from 0 to 2 points („0" – no inflammatory changes within the examined sinuses, „1" – partial shading of the sinus, „2" – total shading of the sinus). To the points calculated for each sinus we added points depending on on the patency of the ostiomeatal complex („0" – patent, „2" – obstructed) on the right or left side respectively. The maximum number of points that could be obtained with the greatest exacerbation of inflammatory lesions within all paranasal sinuses and on both sides of the ostiomeatal complexes was 24 points. The advancement of nasal polyps was described as follows: light (0–7 pts), intermediate (8–15 pts) or severe (16–24 pts).

Variables were presented as arithmetic means, medians, minimum and maximum values, and standard deviations. The Shapiro-Wilk test was used to assess for the normality of distribution. Inter-group comparison for independent variables was performed using the Mann-Whitney U test. Wilcoxon test was used to compare dependent variables. ANOVA was used to perform comparisons between study groups with regard to the age of patients at the time of inclusion, age at diagnosis, assessment of disease burden by visual analogue scale before and 6 months after surgery. Tukey's test was used for post-hoc testing. Due to the non-normal distribution of variables, inter-group comparisons of the severity of lesions in nasal endoscopy and CT were performed using Kruskal-Wallis test. The Dunn test was used for post-hoc tests. Wilcoxon test was used

Tab. I. Clinical characteristics of the study group of CRSwNP patients (N = 204) divided into four subgroups: (1) without coexisting BA and AI, (2) with BA, (3) with NA, (4) with aspirin triad (CRSwNP + BA + AI) [BA – Bronchial Asthma; AI –Aspirin Intolerance; aspirin triad: CRSwNP + BA + AI; FESS – Functional Endoscopic Sinus Surgery]. Age at the time of surgery, age at onset, VAS scale score before and 6 months after surgery presented as mean +/-standard deviation; advancement of polyps in endoscopy and CT presented in points as median and interquartile range.

VARIABLE	ALL PATIENTS (N = 204)	CRSWNP WITHOUT BA AND AI (N = 142)	CRSWNP + BA (N = 21)	CRSWNP + AI (N = 10)	ASPIRIN TRIAD (N = 31)	P
Women N (%)	84 (41.18)	53 (37.32)	11 (52.38)	4 (40)	16 (51.61)	
Men N (%)	120 (58.82)	89 (63.68)	10 (47.62)	6 (60.0)	15 (48.39)	
Age (years)	46.22 +/- 13.59	45.33 +/- 13.63	49.48 +/- 13.96	51.00 +/- 12.62	46.55+/- 13.45	<0.3835
Age at first diagnosis (years)	39.99 +/- 13.52	40.06 +/- 13.63	41.10 +/- 13.50	46.00 +/- 11.60	37.00 +/- 13.44	<0.3054
VAS score before FESS (pt)	7 (6–9)	8 (6–8)	8 (7–10)	8 (7–9)	8 (7–9)	0.0032
VAS score afterFESS (pt)	1 (0–2)	1.00 (0.00–2.00)	2.00 (1.00–3.00)	1.00 (1.00–2.00)	3 (2–3)	<0.0001
Advancement of CRSwNP in Endoscopy (pt)	3 (2–4)	3 (1–4)	4 (4–5)	3 (0–5)	4 (4–5)	<0.0001
Advancement of CRSwNP in CT (pt)	16 (10–20)	22 (16–23)	20 (16–24)	16 (10–22)	14 (8–18)	<0.0001

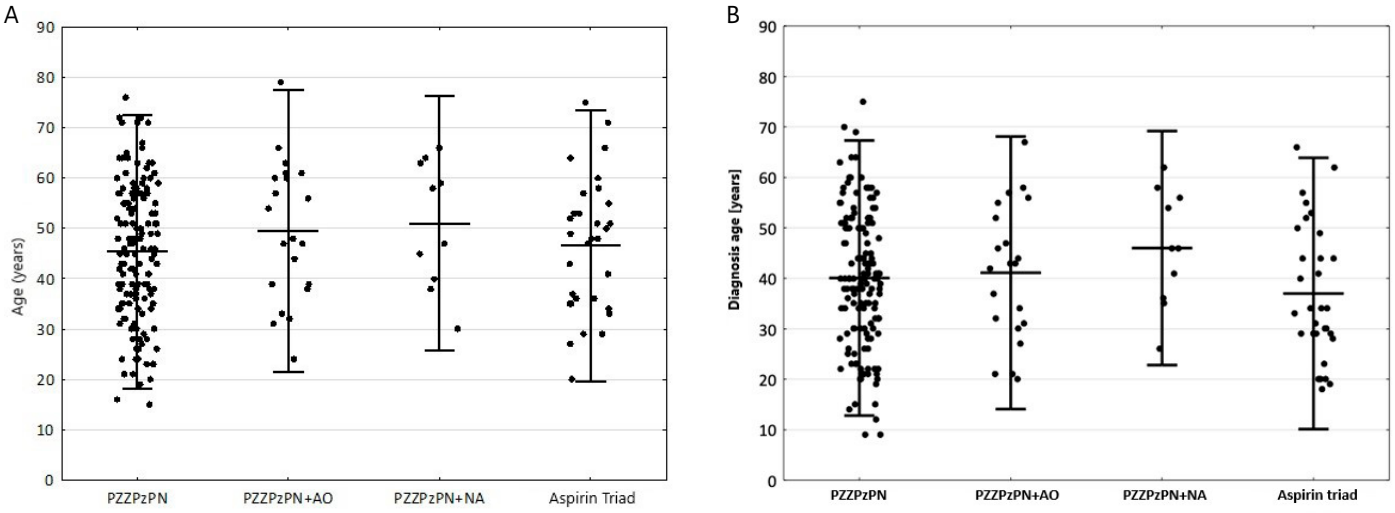

Fig. 1. Age of patients with CRSwNP divided into four groups depending on the coexistence of aspirin hypersensitivity and/or asthma: a. before FESS procedure; b. at the time of diagnosis (mean +/-two standard deviations).

to perform analysis of subjective severity of CRSwNP symptoms (assessed by VAS scale) before and after endoscopic surgery. The interaction between groups and results acc. to VAS scale before and after surgery was demonstrated graphically using generalized linear model. The exact Fisher test (Freeman-Halton Extension) was used to analyze previous surgery to remove polypoid changes in selected patient groups. Calculations were made using the Statistica 12 software (StatSoft, United States). The statistical significance threshold was set at 0.05.

RESULTS

No significant differences were observed between the groups when comparing the mean age of patients at the time of the examination before planned endoscopic surgery of the nasal and paranasal sinuses (Fig. 1a).

Based on thorough history taking, we obtained data regarding patient age at the time of diagnosis of CRSwNP. There were no significant differences with regard to the age of patients at the time of diagnosis of CRSwNP, but the lowest age at the time of definite diagnosis was noted in patients with aspirin triad (Fig. 1b).

The analysis of subjective severity CRS symptoms before and after endoscopic treatment using the VAS scale showed statistically significant reduction in the severity of discomfort associated with CRSwNP in the entire study group (Fig. 2a). When comparing changes in the severity of perceived symptoms for individual groups, there were no statistically significant differences with regard to the change in VAS scores before and after surgery. This means that the presence of coexisting diseases had no influence on the perceived effect of surgery half a year after it has been performed (P = 0.6073). However, in a similar analysis comparing the severity of patients' symptoms assessed on the VAS scale prior to surgery, a statistically significant increase in the severity of discomfort was noted in people with nasal polyps accompanied by bronchial asthma (post-hoc Tukey test P = 0.0126) and in patients with the aspirin triad (P = 0.0390). Similarly, when comparing the severity of the symptoms experienced in relation to CRSwNP 6 months after surgery, a significantly higher severity was demonstrated in the same groups of patients (aspirin triad P <0.0001; CRSwNP

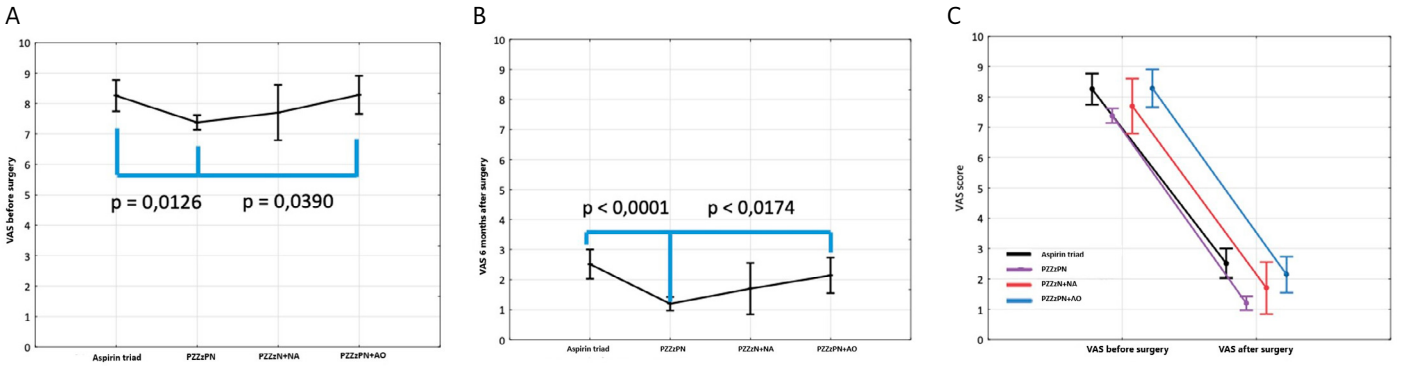

Fig. 2. Severity of symptoms in CRSwNP assessed according to VAS scale: a. before surgery; b. 6 months after FESS; c. before and 6 months after surgery in individual patient groups.

+ AO P = 0.0174) (Fig. 2). This indicates that, although subjective improvement in all groups was significant and similar both before and after surgery, patients with aspirin triad and CRSWNP and coexisting bronchial asthma were characterized by a greater severity of discomfort.

Endoscopic examination showed greater severity of polypoid lesions in patients with aspirin triad (P = 0.0005) and in the group where nasal polyps were accompanied by atopic bronchial asthma (P = 0.0030) compared to patients with CRSwNP without concomitant diseases (Fig. 3a). Comparing the severity of inflammatory lesions in CT examination of paranasal sinuses acc. to the Lund-Mackay point scale, patients with aspirin triad (P <0.0001) and with bronchial asthma and associated nasal polyps (P = 0.0009) (Fig. 3b) were characterized by significantly greater severity of lesions.

At a further stage of the study, we analyzed the number of previous surgeries to remove polypoid lesions in individual patient groups. It has been demonstrated that there is a relationship between the number of operations and the diagnosis of aspirin triad. People with aspirin triad were significantly more likely to undergo surgery for recurrent inflammatory process presenting as nasal and sinus polyps not responding to conservative treatment compared to those without such a condition (P = 0.001). This relationship was not observed in groups with CRSwNP without concomitant bronchial asthma and aspirin intolerance and in patients with CRSwNP and bronchial asthma (Tab. II.).

Summarizing the results of the conducted analysis, it should be noted that there was greater severity of polypoid lesions in endoscopic examination as well as greater severity of inflammatory lesions in the CT of paranasal sinuses according to the Lund-Mackay scale among patients with aspirin triad and in those with CRSwNP accompanied by bronchial asthma. At the same time, those patients experienced a significantly more severe acute exacerbations of symptoms associated with CRSwNP both before and after surgery, as indicated by the score on the VAS scale. Moreover, patients with aspirin triad were statistically more likely to undergo surgery in the past, indicating high recurrence rate of inflammatory processes and frequent persistence of polypoid lesions following conservative treatment with both topical (topical glucocorticoids) and systemic (oral glucocorticoids, antibiotics) agents. No similar differences have been shown for patients with CRSwNP and isolated hypersensitivity to aspirin (without accompanying bronchial asthma).

DISCUSSION

Pathogenesis of chronic sinusitis with nasal polyps continues to be an important diagnostic and therapeutic problem, which is further hindered by the lack of knowledge of the pathogenesis of this common disease. CRS without NP usually affects women and is more common than its polypoid form, which occurs in about 20% of cases of CRS [7]. CRSwNP mainly develops in males, especially after the age of 60 years [7]. In our own studies on 204 patients with CRSwNP we also observed the predominance of males (120 patients; 58.82% of the study group). Mean age of the study population was 46.22 years (range: 18–79).

It is observed that polyps recur at variable frequency that is difficult to predict in an individual patient, despite the use of advanced surgical techniques (FESS) and pharmacological treatment. Many people require reoperation, which carries a greater risk of surgical complications, including intracranial. In our study, the average number of procedures was 1.40 (median 1.00, SD 1.02489) and was significantly higher in patients with aspirin triad.

One of the causative factors, facilitating its persistence and often unfavourable course, includes hypersensitivity to aspirin. It was first described in 1902 by a physician from Poznan, Hirschberg, who noticed an abnormal response to the medicine in a patient presenting with acute angioedema and urticaria. Precise determination of the prevalence of aspirin hypersensitivity in a population is not easy due to low sensitivity and specificity of surveys in its detection. People who have never taken aspirin are unaware of their problem. Other respondents may not associate the drug with signs of hypersensitivity that appear after some time [8]. Jenkins, Costello and Hodge [9] performed a meta-analysis of publications on bronchospastic form of hypersensitivity after NSAIDs. By compiling studies where provocative tests have been performed, they demonstrated aspirin hypersensitivity in 21% of adults and 5% of children with asthma. However, when taking into account only those studies that consisted of an oral history taking, sensitivity to aspirin in asthma was identified in only 4% of adults and 3% of children [9]. In a questionnaire study performed in Poland, which included 12970 people selected randomly from general population,

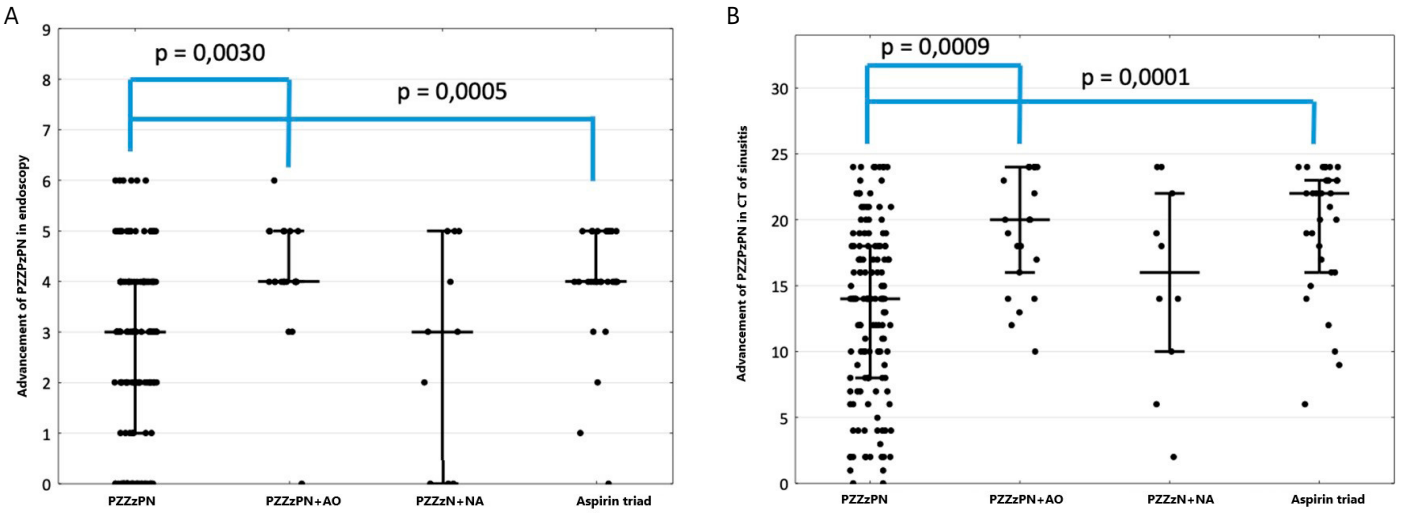

Fig. 3. Advancement of CRSwNP in the study group depending on the coexistence of aspirin hypersensitivity and/or bronchial asthma in: a. endoscopy; b. computed tomography.

the incidence of hypersensitivity to aspirin was estimated at 0.6% of all surveyed individuals and at 4.3% of asthmatic patients [10]. It is now predicted that as much as 25% of nasal polyps may be associated with hypersensitivity to aspirin and other NSAIDs [11]. In our own studies, hypersensitivity to aspirin and other NSAIDs was confirmed in 41 of 204 patients treated surgically for CRSwNP, corresponding to 20.01% of the study group. It should be emphasized that in our study, the criterion for inclusion into the aspirin sensitivity group was a positive result of an aspirin provocation test performed under hospital conditions. Such a challenge was performed in 120 people with nasal polyps and with medical history that might indicate aspirin intolerance and hypersensitivity was confirmed in only 41 patients with CRSwNP (34.2%).

In 1968, Max Samter and Roland Beers introduced the concept of an ‚aspirin triad', defined as the coexistence of bronchial asthma, chronic paranasal sinusitis with nasal polyps and hypersensitivity to aspirin. Currently, in addition to the notion of asthma with aspirin hypersensitivity, we also use the concept of aspirin-exacerbated respiratory disease [8]. This term indicates chronic inflammation taking place in the upper and the lower respiratory tract at the same time. According to Szczeklik et al. [12], in cases of coexisting asthma and aspirin hypersensitivity nasal polyps occur in approximately 60% of patients. In our study, hypersensitivity to aspirin coexisted with bronchial asthma and CRSwNP in 31 subjects, corresponding to 15.20% of study population. Notably, bronchial asthma was diagnosed in 75.61% of patients with CRSwNP and aspirin hypersensitivity. Simultaneously, provocation test confirmed aspirin hypersensitivity in the majority of patients with CRSwNP and bronchial asthma (59.62%).

Asthma associated with aspirin hypersensitivity is more frequent in women. Moreover, it is diagnosed earlier and progresses faster than in men [12]. In our study, we also observed this predominance: there were 16 women (51.61%) and 15 men (48.39%) among 31 patients with aspirin triad. Chronic sinusitis with nasal polyps and bronchial asthma associated with aspirin hypersensitivity usually runs a severe course with frequent exacerbations. Patients with AIA require treatment with high doses of inhaled glucocorticoids and often require administration of oral glucocorticoids [13]. Chronic oral steroid therapy is required in some patients. Szczeklik, Niżankowska and Duplaga [12], while analyzing the data generated in the AIANE project from 16 European research centers, demonstrated that 80% of patients with asthma associated with aspirin hypersensitivity were treated with inhaled glucocorticoids, 51% received oral steroids at a mean dose of 8 mg prednisone per day and 24% required intravenous glucocorticoid administration at least once in the last 12 months [12]. In an American TENOR study, Mascia et al. [14] showed that patients with asthma and aspirin hypersensitivity suffered from more severe disease course compared to patients with asthma and good aspirin tolerance according to physicians' assessment (66% vs. 26%), had more exacerbations requiring treatment with systemic steroids and more often presented with asthmatic state requiring intubation. These patients were treated with higher doses of inhaled glucocorticoids and leukotriene receptor antagonists. Similarly, the course of CRSwNP in a group of people with bronchial asthma and hypersensitivity to aspirin is more severe and procedures for removal of nasal polyps are often repeated, posing a risk of orbital and intracranial complications [14]. In our study, in the group of patients with aspirin triad, the severity of paranasal lesions in endoscopic examination as well as in CT was significantly higher. At the same time, for 45.2% of patients in this group it was the second nose surgery at the least. For comparison, in the subgroup without known hypersensitivity to aspirin and without bron-

Tab. II. The number of endoscopic procedures of the nose and paranasal sinuses performed due to disease relapse among CRSWNP patients by group: (1) without BA and AI, (2) with BA, (3) with AI, (4) with aspirin triad (CRSWNP + BA + AI) [BA – Bronchial Asthma; AI – Aspirin Intolerance; aspirin triad: CRSwNP + BA + AI; FESS – Functional Endoscopic Sinus Surgery].

STUDY GROUP	NUMBER OF FESS 0–2 N (%)	NUMBER OF SURGERIES ≥ 3 N (%)
CRSwNP without BA and AI (N = 142)	129 (76.33)	13 (37.14)
CRSwNP + BA (N = 21)	15 (8.88)	6 (17.14)
CRSwNP + AI (N = 10)	8 (4.73)	2 (5.71)
Aspirin triad (N = 31)	17 (10.06)	14 (40.00)

chial asthma, it was the first surgery for 76.33% of patients. In the recent years, the effectiveness of desensitization to acetylsalicylic acid for causative treatment of CRS has been demonstrated [15]. Reduction in the symptoms of the disease was observed after 18 months of aspirin use at a dose of 500 mg of acetolosalicylic acid after surgery compared to the control group [16]. Ultimately, this resulted in a reduction in the number of surgical procedures and prolonging the time between procedures from 3 to 9 years [17]. There was also a beneficial effect on the course of bronchial asthma with a reduction in the number of exacerbations and the need for hospitalization. In patients with CRSwNP the target daily dose is 325 or 625 mg of acetylsalicylic acid BD, but its tolerability lasts only 2 to 5 days [18]. Bachert et al. [19] recently reported the efficacy and safety of monoclonal antibody against interleukin 4 and 13 in a multicentre, randomized, double-blind and placebo-controlled study in patients with severe chronic paranasal sinusitis and nasal polyps. This opens up a new pathway for treatment of people with particularly severe and difficult to treat form of this disease as an adjunct to primary therapy.

Allergy to inhaled allergens and aspirin hypersensitivity are factors influencing poorer course of CRSwNP. Therefore, it would be advisable to consider performing an aspirin provocation test despite the absence of medical history of aspirin intolerance in patients with particularly severe CRSwNP, especially those with associated bronchial asthma. It also seems appropriate to carry out such a test in each patient with newly diagnosed CRSwNP and bronchial asthma in order to be able to adequately plan further treatment in this group of patients. However, the use of biological therapies with monoclonal antibodies against selected interleukins involved in type 2 inflammatory reaction, such as: IL-4 and IL-13 (dupilumab), IL-5 (benralizumab) or IgE (omalizumab), creates new possibilities for effective control of the disease. However, this requires confirmation in further studies.

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