



I.V. Koshel

## Major Clinical Phenotypes of Polypous Rhinosinusitis

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

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aspirin-intolerant polypous rhinosinusitis; clinical phenotype

### Abstract.

Polypous rhinosinusitis remains one of the major problems of modern otorhinolaryngology, its prevalence in general population reaches 4%. There is a wide range of variants of clinical course and a different response to traditional methods of treatment, however all these cases are diagnosed as “polypous rhinosinusitis”. It suggests the heterogeneity of a group of patients diagnosed with “polypous rhinosinusitis” and the need for a detailed study of various clinical variants of nasal polyposis, i.e. clinical phenotypes of the disease.

**The objective** of the research was to assess clinical features of chronic polypous rhinosinusitis depending on trigger of the disease as well as to determine clinical phenotypes of nasal polyposis.

**Materials and methods.** The article presents the results of clinical and anamnestic investigations, radiology examinations and laboratory studies of 150 patients with various types of polypous rhinosinusitis. Patients were divided into three groups: Group I included 50 patients with aspirin-intolerant polyposis; Group II consisted of 50 patients with polyposis due to violations of aerodynamics of the nasal breathing; Group III included 50 patients with Ig-E-dependent (allergic) polyposis,

**Results.** The research revealed significant differences in studied indicators between different clinical groups. The presence of differences in gender, age, severity of clinical symptoms and the character of pathological changes allowed us to determine the most common clinical phenotypes of polypous rhinosinusitis.

**Conclusions.** The onset of the disease affecting primarily females in adulthood, severity of clinical manifestations, total or subtotal lesions of sinuses resulting in resistance to traditional methods of treatment are typical for patients with aspirin-intolerant polyposis. The above mentioned phenotypes are considered within a clearly defined pathology and allow us to optimize the diagnostic process as well as to determine adequate therapeutic tactics for each clinical case.



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***Problem statement and analysis of the recent research***

Polypous rhinosinusitis is a chronic inflammatory disease of the nasal mucosa and paranasal sinuses characterized by the formation of polyps. Epidemiological and statistical studies indicate that the prevalence of polypous rhinosinusitis in general population of Europe is between 2% to 4%. Patients with polypous rhinosinusitis account for 5% of the total number of patients consulting ENT specialists and 4% of patients visiting allergologists [1, 2, 3, 4, 5]. However, there are other data that the disease manifests itself in 15-25% of patients with ENT diseases [6].

Clinically, the term "nasal polyposis" involves all types of nasal polyps, found within the ethmoid bone, the middle meatus, and the middle turbinate which appear as gray-blue evaginations. Larsen P.I. and Stammberger H. consider the mucous membrane of the middle turbinate and the middle meatus to be the origin of polyps while the inferior turbinate has no tendency of nasal polyp formation [7, 8, 9]. The reasons are unknown. Nowadays there is no adequate definition of nasal polyps, or nasal polyposis. According to Stedman's Medical Dictionary (1995) polyp is a general descriptive term used with reference to any mass of tissue that bulges or projects outward or upward from the normal surface level, thereby being macroscopically visible as a hemispheroidal, spheroidal, or irregular mound-like structure growing from a relatively broad base or a slender stalk [10]. It means that any spherical outgrowth of the nasal mucosa or paranasal sinuses should be considered as nasal polyp. Some authors consider chronic sinusitis and nasal polyposis as various diseases of the mucosa [11]. Nowadays there is a consensus that chronic rhinosinusitis is a major disease and nasal polyposis is its subpopulation [12].

Histologically, nasal polyps are characterized by swelling and/or fibrosis, reduced vascularization, decreased number of glands and nerve endings, and damaged epithelium. Histological examination of polyps allows us to differentiate eosinophilic polyps constituting approximately 65-90% of all cases from neutrophilic polyps [13, 14]. Neutrophil-dominant polyps are detected histologically in 15-20% of cases. Neutrophils are associated with the growth of polyps in cystic fibrosis, Young's syndrome, Kartagener's syndrome and immotile cilia syndrome [15-18]. They are usually connected with a certain genetic functional defect in the mucociliary apparatus due to violations of the rheological properties of nasal mucous or damage to the cilia of the ciliated epithelium. In this case chronic polypous rhinosinusitis is syndromic in nature with co-existent lesions of respiratory and other systems.

Eosinophilic polyps received their name due to the presence of tissue eosinophilia accompanied by mononuclear cell infiltration, plasma cell infiltration, and T-cell infiltration. Pathogenetically, a large number of tissue eosinophils on the background of their normal content in the blood is explained by increased transendothelial migration and inhibition of programmed cell death (apoptosis) of eosinophils [19,20]. Impregnation and accumulation of plasma proteins (albumin) is considered as the link between tissue eosinophilia and polyp growth.

Over recent years nasal polyposis is considered as a heterogeneous disease that could fail to impact its classifications. In modern otorhinolaryngology, there are many different classifications of polypous rhinosinusitis. In particular, according to the prevalence of polypous process in the nasal cavity, lesions of the paranasal sinuses, their localization [3, 21, 22, 27]. In addition to clinical classifications there are also clinical and morphological classifications of polypous rhinosinusitis. The development of nasal polyps is classified into two phases: the initial phase is edematous or glandular and cystic one and the second stage is fibrous one. The use of topical corticosteroids at the first stage can cause regression of polyposis, and at the fibrous stage only surgical treatment is effective. [23]. Another classification distinguishes antrochoanal polyps, large isolated (choanal) polyps, chronic non-eosinophilic dominant polypous rhinosinusitis, chronic eosinophilic dominant polypous rhinosinusitis and polyps associated with specific conditions (fibrous cysts, malignancy, etc.) [15-18, 24]. A significant number of classifications indicates that despite the large amount of diverse research there is no consensus on the etiology

and pathogenesis of polypous process. Current research proves quite convincingly that polypous rhinosinusitis is significantly different from other forms of chronic inflammation not only in the pathogenesis, morphological pattern and clinical course, but also in the nature of local tissue response to surgery and medication. However, all researchers refer polypous rhinosinusitis to diseases treatment of which is ineffective due to frequent relapses. Relapses of polypous rhinosinusitis after surgical treatment reach 60-80%. 20% of patients develop recurrent nasal polyposis within 1 month after surgery, 42% of patients develop it a year after surgery, and in 81% of patients recurrent nasal polyposis is diagnosed 2 years after surgery [2, 3, 4, 5, 13, 26].

Particular attention is given to treatment of polyposis in comorbidity, since there was observed that nasal polyposis is often associated with severe diseases such as asthma, chronic obstructive pulmonary disease, aspirin intolerance, allergy and others. There is a wide range of variants of clinical course and a different response to traditional methods of treatment, however all these cases are diagnosed as "polypous rhinosinusitis". It suggests the heterogeneity of a group of patients diagnosed with "polypous rhinosinusitis" and the need for a detailed study of various clinical variants of nasal polyposis, i.e. clinical phenotypes of the disease.

The closest approach to modern understanding of polyposis phenotypes was made by S.Z. Piskunov who described the following clinical and pathogenic variants of polypous rhinosinusitis:

- related to changed architectonics of the nasal cavity;
- allergic (Ig-E-dependent);
- fungal (allergic fungal sinusitis);
- syndromal: cystic fibrosis, Young's syndrome, Kartagener's syndrome, large group of so-called tubulopathies, or immotile cilia syndrome;
- polyposis associated with intolerance to aspirin (aspirin triad).

However, the indicated types of polyposis are determined when defining triggers of the disease that is insufficient for clinical practice. The identification of the features of clinical course of each polyposis form is relevant in terms of allocation of a specific patients' phenotype. Phenotypic characteristics are convenient to use as diagnostic and prognostic criteria for various ethiopathogenetic forms of polypous rhinosinusitis.

**The objective** of the research was to assess clinical features of chronic polypous rhinosinusitis depending on trigger of the disease as well as to determine clinical phenotypes of nasal polyposis.

### **Materials and methods**

The study included 150 patients diagnosed with "chronic polypous rhinosinusitis" who were hospitalized in the ENT department of the Regional Clinical Hospital within 2011-2014. Patients were divided into three groups: Group I included 50 (33.3%) patients with aspirin-intolerant polyposis; Group II consisted of 50 (33.3%) patients with polyposis due to violations of aerodynamics of the nasal breathing; Group III included 50 (33.3%) patients with Ig-E-dependent (allergic) polyposis.

Clinical peculiarities determining the phenotype features include age-related and chronological aspects of the disease, sex-specific prevalence of the disease, prevalence and morphological characteristics of inflammation, type of the disease course, the efficiency of its treatment using the most effective conventional methods.

### **Results and discussion**

The moment of disease manifestation (diagnosis of polypous rhinosinusitis) and disease duration were determined according to the patient's words or date when diagnosis was made as indicated in his/her outpatient medical record. At the moment of making a diagnosis all patients were divided into 2 groups according to the age classification:

Group 1 – young people (17-35 years old);

Group 2 - mature and elderly people (36-70 years old).

Among patients of Group I - aspirin-intolerant polyposis was first diagnosed in mature and elderly people in most cases - 41 (82%) patients. The number of patients in Group II - polyposis due to violations of aerodynamics of the nasal breathing - was divided almost equally - 26 (52%) young people versus 24 (48%) older people. Among patients of Group III - Ig-E-dependent (allergic) polyposis there were 36 (72%) young people.

Thus, the incidence of chronic polypous rhinosinusitis in age groups was divided very unevenly. The peak incidence of aspirin-intolerant polyposis compared to other types of rhinosinusitis prevailed in the mature age group. It developed in 82% of people within the age range of 36-70 years. 72% of young patients suffered from Ig-E-dependent polyposis. The incidence of polyposis due to violations of aerodynamics of the nasal breathing had no age-dependence, as patients were distributed evenly - 52% of young people versus 48% of older people.

Gender is one of the most important criteria determining the phenotype. There was an obvious trend towards higher prevalence of polyposis in males of Group II and Group III. There were 32 (64%) men in Group II being 28% more than women - 18 (36%) and 27 (54%) men in Group III. Among patients with aspirin-intolerant polyposis, female patients prevailed - 58% (29 patients); there were 42% (21 patients) of males, respectively. These data are significantly different from gender differences in other groups with polyposis, where the incidence among women is significantly less than among men.

Age and gender indicators characterize the incidence of polyposis at the time of initial diagnosis. However, the period of disease in most patients was probably significantly longer, and visit to a doctor was preceded by a latent period, long-term compensation of the symptoms of the disease, impaired nasal breathing as a result of self-medication in particular, or banal indifference of patients. The duration of the disease is important when assessing clinical peculiarities of any chronic processes. Therefore, we studied the age of onset depending on gender (Fig.1).

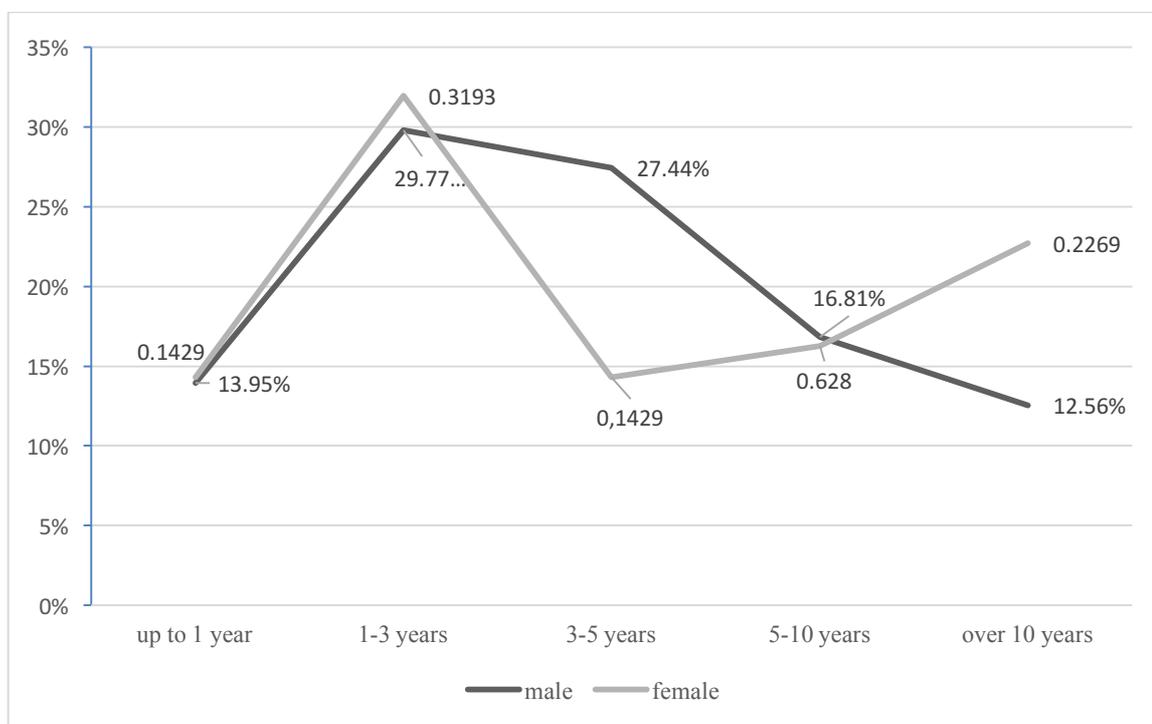


Fig.1. PMH (past medical history) duration

It is noteworthy that patients with disease duration of more than three years constituted the largest part among men and women. The relatively short duration in both sexes was almost the same: up to 1 year in 13.95±2.36% of males and 14.29±3.21% of females; 31.93±4.27% of men and 29.77±2.52% of women reported on the duration of 1-3 years. Within the range of 3-5 years the disease duration in men was significantly higher than in women – 27.44±3.04% versus 14.29±3.21%. The difference in the indicators was 13.15%. Within the range of 5-10 years of disease duration the indicators were aligned: indicators of men significantly reduced by 11.36% while those of women tended to increase. However, the duration of the disease of over 10 years in women significantly dominated over the indicators of men: 22.69±3.84% versus 12.56±2.26%. The difference in the indicators was 10.13%. The indicated dynamics may indicate a more severe course of polyposis in females.

Clinical manifestations of polyposis do not cause special difficulty in its detection. Common symptoms are difficult breathing through nose, nasal discharge and presence of polyps in the nasal cavity. To determine the duration of the disease is also not difficult. However, in the context of determining the phenotype, the relevant problem is to diagnose the extent of sinus lesions. Therefore, the diagnosis in all patients was based on the patient's complaints and history taking, results of otorhinolaryngological and routine X-ray examination, as well as the results of nasal endoscopic examination, computed tomography of the nasal cavity, sinuses and elements of the osteomeatal complex. According to the results of examinations considering ICD-10 requirements patients were divided into groups depending on the number of affected sinuses. People with a lesion of one or several sinuses on one side constituted a group of mono-hemisinusitis, people with bilateral lesions (not of all sinuses were affected) constituted a group of polysinusitis, and people with pervasive lesions of the sinuses constituted a group of pansinusitis.

Among patients of Group I - aspirin-intolerant polyposis - in most cases (84.73%) pervasive lesions of the sinuses (pansinusitis) were diagnosed and in 15.27% of cases subtotal lesions of the sinuses (excluding the basilar sinus) were detected.

Among patients of Group II - polyposis due to violations of aerodynamics of the nasal breathing - lesions of the sinuses were mainly observed in the form of maxilla-ethmoidal sinusitis with a slightly swollen mucosa of other sinuses on the same side being conventionally regarded as hemisinusitis. Among patients of Group III - Ig-E-dependent (allergic) polyposis - the number of patients with pansinusitis accounted for more than half of cases - 63.48%. In 36.52% of patients of this group multiple bilateral lesions were diagnosed. The represented data indicated the unquestionable dominance of multiple forms of sinus lesions over isolated ones in patients of Group I and Group III. This feature characterized aspirin-intolerant polyposis and Ig-E-dependent (allergic) polyposis as the pathology with severe course. The severity significantly affects the treatment outcomes. Therefore, we conducted a detailed study of the course of the disease in patients of these groups.

The distinctive feature of patients with Ig-E-dependent (allergic) polyposis was the fact that patients with disease duration of more than three years but not more than ten years constituted the largest part (73.3%). The number of patients with relatively short duration of the disease (3-5 years) among patients with aspirin-intolerant polyposis was significantly less - 41.7%. Within the range of 3-5 years the duration of the disease in patients did not exceed 19.6% versus 57.1% among patients with Ig-E-dependent (allergic) polyposis. The difference in the indicators was 37.5%. Within the range of 5-10 years of disease duration indicators were aligned: in Ig-E-dependent polyposis they reduced by 22.1% and in aspirin-intolerant polyposis they tended to increase by 16.2%. However, disease duration of more than 10 years in patients with aspirin-intolerant polyposis increased progressively and significantly exceeded the indicators in patients with allergic polyposis: 56.4% versus 12.5%. The difference in the indicators was 43.9%. The above-mentioned dynamics indicated a more severe course of the disease in patients with aspirin-intolerant

polyposis and higher efficiency of treatment of allergy-dependent form of the disease. Since among patients with aspirin-intolerant polyposis women prevailed these data correlated with peculiarities of the age of onset. Disease duration of over 10 years in women significantly prevailed indicators in men:  $22.69 \pm 3.84\%$  versus  $12.56 \pm 2.26\%$ . These data indicated the prevalence of severe forms of the disease in female population.

The disease of long duration (over 10 years) reflected the progressive course of polyposis and was associated with frequent relapses. The vast majority of patients developed from 4-5 to 16-20 and more polypotomias. Frequent recurrence, in turn, was an evidence of resistance to the most effective methods of treatment (surgery, steroids). These features characterized aspirin-intolerant polyposis as the pathology with particularly severe course of the disease.

When analyzing age-related and chronological aspects of chronic polypous rhinosinusitis there was found that the peak incidence among patients with aspirin-intolerant polyposis prevailed in the mature age group. Within the range of 36-70 years 82.3% of patients were diagnosed with the disease, the number of women dominated over that of men. However, taking into consideration the duration of the disease, the onset of the disease probably occurred significantly earlier in the young age group as this group was characterized by long duration of the disease.

72.3% of young patients suffered from Ig-E-dependent polyposis. The incidence of polyposis due to violations of aerodynamics of the nasal breathing had no age-dependence, as patients were distributed evenly – 50.87% of young people versus 49.13% of older people. Among patients of these groups the number of men prevailed. When disease occurred in all groups of patients its clinical symptoms had no special manifestations and were peculiar for chronic rhinosinusitis. They were often diagnosed as chronic catarrhal or allergic rhinosinusitis.

The predominance of patients with long disease duration can indicate the prevalence of severe forms of the disease as their specific feature is low efficiency of treatment and, therefore, progressive course.

### Conclusions

Thus, as a result of comparative study of clinical features of the disease, certain phenotypes of polypous rhinosinusitis were determined. It is characterized by the following indicators:

- Gender is one of the most important criteria that determine the phenotype. Our study clearly showed that among patients with severe polyposis females prevailed - 58% compared to other types of polyposis.

- Age is also a significant criterion for the formation of pathological phenotype. Clinical pattern of the disease in different age groups had its peculiarities. Most patients with severe forms of polyposis (aspirin-intolerant polyposis) belonged to the mature age group - 36-70 years. When the onset of the disease occurred in childhood or adolescence then we could observe hereditary malformations (polyposis due to violations of aerodynamics of the nasal breathing) or Ig-E-dependent (allergic) polyposis.

- Severity of the disease. Severity of clinical course of polypous rhinosinusitis has several features that deserve special allocation into phenotypic marker. The severity of disease in these patients is associated with a progressive, relapsing course and resistance to the most common and effective methods of treatment. Although severity is used as an additional criterion for phenotype allocation, its degree is often determined arbitrarily, but depends on age. Frequent recurrence, progressive course of the disease, especially in young people, regardless of gender, should be considered as a severe course. These severity criteria should include long duration of the disease that along with recurrence indicates the resistance to treatment.

- Nature of pathological changes. In patients with severe forms of polyposis tendency to pervasive or subtotal lesions of the sinuses was determined. This marker is particularly important

in the onset of the diseases, especially at a young age, when clinical manifestations are often considered as symptoms of chronic catarrhal or vasomotor rhinosinuitis.

### **Perspectives for further research**

The possibility of forming phenotypic diagnostic features is promising as polypous rhinosinuitis is a heterogeneous disease, and the phenotypes mentioned above are considered within clearly defined pathology. The recommendations considering different markers will assist in optimization of diagnostic process and determination of adequate therapeutic tactics.

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