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THE CLINICAL CHARACTERISTICS OF PATIENTS AND TREATMENT OF CHRONIC POLYPOUS RHINOSINUSITIS

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ABSTRACT

The article presents modern views on the etiology and pathogenesis of polypous rhinosinusitis. Based on the analysis of domestic and foreign protocols, clinical research data, and observations, an evaluation of the existing conservative and surgical treatment methods for polypous processes in the nasal cavity and paranasal sinuses has been conducted. Special attention is given to the pathogenetic justification, safety, comprehensive approach, and level of evidence of the proposed treatment and prevention schemes for the recurrence of polypous rhinosinusitis.

Key words: polypous rhinosinusitis, corticosteroids, surgical treatment, pathogenesis.

INTRODUCTION

Polypous rhinosinusitis (PRS) among inflammatory diseases of the nasal mucosa and paranasal sinuses represents one of the most pressing issues in modern rhinology. In recent years, there has been an increase in the prevalence of this condition in the structure of nasal and paranasal sinus pathology. This is due to changes in the ecological environment, as well as an increase in the number of bacterial, viral, and occupational pathogenic factors.

In Uzbekistan, approximately 500 thousand people suffer from nasal polyps, while in the USA, this number reaches 30–35 million people [1, 2]. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012, polypous rhinosinusitis (PRS) occurs in 2–4.3% of the European population.

Manifested forms of PRS in industrial cities, according to data on patient visits to various clinics, range from 1.3 to 13.1 cases per 10,000 people [3–5]. Clinical manifestations of PRS are present in approximately 3% of the population, and according to some data, in up to 5%. Moreover, patients with nasal polyps often seek medical help for the first time not from an otolaryngologist, but from an allergist, pulmonologist, or general practitioner. Prolonged examination and monitoring by allied specialists, on the one hand, allows for a comprehensive assessment of the patient's somatic status; on the other hand, in our opinion, it increases the time needed for diagnosis and leads to a significant rise in the prevalence of subclinical forms of this disease. Recently, both foreign and domestic literature has emphasized the heterogeneity of PRS patients in terms of age and the nature of the polypous process [2, 4]. According to our observations, this disease occurs in all age groups. The polypous process in the nasal cavity and paranasal sinuses is most commonly diagnosed in individuals of working age and occurs twice as often in men as in women. Prolonged nasal obstruction, frequent exacerbations, and recurrences of the polypous process significantly affect the quality of life of patients [6]. This disease is often associated with various congenital or acquired bronchopulmonary pathologies, as well as allergic reactions. Patients with the asthmatic triad represent the most complex category of patients. The presence of bronchial asthma and nonsteroidal anti-inflammatory drug intolerance in patients with PRS contributes to the most severe course of both the polypous process and bronchial asthma. Additionally, when infectious agents are involved, it stimulates the development of widespread damage to the upper and lower respiratory tracts [7–10].

To this day, the issues of the etiology and pathogenesis of PRS remain subjects of discussion. In monographs and periodicals, reports on PRS relapses are contradictory, ranging from 19% to 60% [11]. Among the factors contributing to the development and recurrence of the polypous process, the involvement of allergies, bronchial asthma, chronic inflammatory processes in the paranasal sinuses caused by bacterial flora, viral agents, the influence of various anatomical anomalies that contribute to impaired aeration and the maintenance of the inflammatory process, and genetic predisposition are all discussed. However, there is still no consensus on the origin of PRS and the main triggering mechanisms that activate this pathology in the body [12, 13].

According to the infectious-allergic theory, the triggering factor in the etiology and pathogenesis of PRS is the infectious process, which predisposes the body to allergy and leads to the development of the polypous process in the nasal cavity [11, 14].

From the perspective of the fungal theory, PRS is considered an immuno-mediated disease. In these patients, T-lymphocytes activate eosinophils and stimulate their migration into the mucous membrane of the paranasal sinuses. In the presence of fungal flora, eosinophils release toxic proteins, leading to the formation of thick mucus, which damages the mucous membranes of the nasal cavity and paranasal sinuses, ultimately creating favorable conditions for the development of chronic inflammation [15].

Supporters of the chronic inflammatory process theory of the nasal mucosa point out that PRS develops due to mucociliary insufficiency, deepening deficits in secretory antibodies, imbalance in the functional activity of immune cells, and pathological transformation of the antigenic structure of the mucosa [16].

The participation of infectious agents that trigger allergic and autoimmune reactions in the mucous membrane of the nasal cavity is also significant. Disruption of immune homeostasis in the form of secondary immunodeficiency leads to the persistence of immune eosinophilic inflammation. This, in turn, leads to the remodeling of the nasal mucosa and the development of nasal polyps [17].

In connection with the clear sequence of inflammatory-degenerative changes in the mucous membrane of the nose and paranasal sinuses with the onset of various forms of PRS, the presence of certain pathological conditions within the paranasal sinuses and anatomical anomalies of the nasal septum or osteomeatal complex that cause gradual and persistent disruption of nasal aerodynamics cannot be excluded. Constant irritation of the mucous membrane in the nasal cavity and paranasal sinuses may lead to their morphological remodeling, contributing to the development of catarrhal or wall-hyperplastic forms of inflammation, which then lead to the formation of polyps. The next stage in the development of PRS is defined by the aggressiveness of the accompanying microflora, which results in the formation of bacterial PRS and creates the need for a course of antibacterial therapy [18, 19].

The question remains debated regarding the influence of prolonged colonization of the mucous membrane of the nasal cavity and paranasal sinuses by Staphylococcus aureus in patients with PRS. It is hypothesized that the development of the polypous process is supported by a specific superantigen produced by this microorganism in the respiratory tract. This superantigen contributes to the increased formation of immunoglobulin E (IgE) antibodies to staphylococcal enterotoxins, induces the synthesis of total IgE in the tissue of nasal polyps, and affects the severity of eosinophilic inflammation [20]. Several researchers note a persistent correlation between staphylococcal colonization and the tissue immune response of nasal polyps to the action of this bacterial

superantigen, particularly in patients with concomitant bronchial asthma, which may possibly stimulate the formation of polyps in the nasal cavity and causes combined damage to the lower respiratory tract. However, the obtained data are contradictory, which requires further in-depth study of the role of Staphylococcus aureus in the pathogenesis of PRS [19, 20].

Viral agents are also considered as one of the main triggers in the activation of the chronic pathological process in the paranasal sinuses. By persisting in the body, they initiate the inflammatory process and trigger a cascade of immunological reactions that lead to the development of PRS [15].

The existence of genetically determined defects that are activated when interacting with environmental factors cannot be excluded. The involvement of gene mutations in the development of PRS is indicated by the close association of this pathology with cystic fibrosis and Kartagener syndrome [17].

In our opinion, PRS is a multifactorial disease. The influence of mechanical and physical factors, as well as the penetration of microbial, fungal, and viral agents into the surface of the nasal mucosa, and disturbances in neurovegetative regulation gradually lead to the activation of local immunity mechanisms. These mechanisms represent a complex of specific and nonspecific reactions that ensure the barrier function of the mucous membrane. Prolonged exposure to various agents contributes to a decrease in the activity of the protective barrier of the nasal mucosa and stimulates the development of infection-dependent allergic processes.

The treatment of patients with PRS has a long history and includes a wide range of different conservative and surgical approaches.

Currently, surgical interventions in the nasal cavity and paranasal sinuses are performed using modernized instruments and state-of-the-art video-endoscopic techniques, such as microdebriders and navigation systems. These tools help minimize traumatic damage during surgery and preserve the normal anatomy of the nasal cavity. Visual control not only allows for the maximum preservation of the anatomical integrity of the paranasal sinuses but also contributes to the rapid recovery of mucociliary transport and nasal aerodynamics, thus shortening the rehabilitation period for patients.

The use of liquid nitrogen, high-energy lasers, ultrasound, and electrocoagulation for the treatment of PRS is currently limited due to the lack of significant advantages over functional endoscopic surgery. These aforementioned surgical methods are more time-consuming and are often performed in several stages. However, for patients with a complicated somatic history related to bronchial asthma, the asthmatic triad, and cardiovascular pathology, as well as blood coagulation disorders, they can significantly reduce the risk of bleeding and

are applied in certain cases [15]. The cornerstone of surgical treatment is the absence of direct impact on the etiopathogenetic mechanisms of the polyposis process [13, 15]. The analysis of the results of surgical interventions in PRS patients over the past 10-15 years does not allow for prioritizing surgical approaches in the treatment of this disease, as the results do not always meet expectations.

The first attempts at conservative treatment of PRS date back to ancient Greece, but for a long time, they were unsuccessful. It was only with the advent of corticosteroid drugs and their successful use by H. Migind in 1975 that a new era began in the development of conservative methods for treating nasal polyps. Since the late 20th century, this disease has been considered by leading specialists from a therapeutic perspective, focusing on finding and developing pathogenetically justified treatment methods.

Currently, corticosteroid therapy is considered the "gold standard" for treating PRS, as established in both national recommendations and international protocols and consensus agreements, including the 2012 EPOS guidelines.

The pharmacological properties of corticosteroids allow them to affect almost all pathogenetic mechanisms of the polyposis process. Corticosteroids reduce the number of mast cells and the mediators they release, as well as the number of eosinophils, T-lymphocytes, and Langerhans cells in the mucosa of the respiratory tract. By inhibiting the synthesis of arachidonic acid, corticosteroids reduce the production of prostaglandins and leukotrienes, thereby decreasing plasma extravasation and tissue edema. These drugs also reduce gland secretion and the sensitivity of nasal mucosa receptors to histamine and mechanical irritants [16].

In the modern period, topical corticosteroids are successfully used as monotherapy, lasting from several weeks to several months, for newly diagnosed chronic rhinosinusitis with nasal polyps (CRSwNP) in patients with the asthma triad, and are often used in the pre- and postoperative periods as a long-term anti-relapse therapy. High efficacy in alleviating the main clinical symptoms and reducing the size of polyposis tissue, as well as the safety and high local activity of topical corticosteroids, have been proven in numerous clinical studies [2, 13].

In Uzbekistan, fluticasone propionate (Flixonase), mometasone furoate (Nasonex), and budesonide (Tafen Nasal) are registered. The lack of positive dynamics when prescribing this group of drugs may primarily be due to the presence of fibrous polyps, which, unlike "young" edematous polyps, are more appropriately removed and then followed by a prolonged course of intranasal corticosteroids. The need for a differentiated approach in choosing conservative treatment for CRSwNP is also indicated by the structural division of polyps into

neutrophilic and eosinophilic. Typically, in cases of neutrophilic infiltration, the first step is to suppress the inflammatory process using antibacterial therapy, followed by polypotomy. In contrast, with abundant eosinophilic infiltration of the polyposis tissue, the preference is given not to surgical intervention, but to corticosteroid therapy [5].

The appropriateness of using systemic corticosteroid therapy has been actively discussed over the past decade. This situation is due to the known side effects of these drugs and the withdrawal syndrome that develops with their complete discontinuation or a sharp reduction in dosage after long-term use. In Russia, systemic corticosteroid therapy is prescribed only for the treatment of CRSwNP associated with bronchial asthma and acetylsalicylic acid intolerance, as well as in severe forms of allergic rhinitis resistant to all other nonsurgical treatments, or when there are contraindications to surgical intervention and in cases where polyps relapse very quickly. However, there is currently no unified protocol for the prescription of systemic corticosteroid therapy. In Russian guidelines, the most commonly used approach is a pharmacological polypotomy scheme, which involves the oral administration of prednisone for 10 days. Over the past decade, short courses of systemic corticosteroids have been reported as effective in patients with CRSwNP, but studies evaluating the effectiveness of this treatment method are numerous and vary in methodological approaches. International organizations are engaged in the systematization and qualitative assessment of such studies organizations, such as The Cochrane Collaboration [17]. Studies conducted between 2012 and 2016 presented an analysis of the effectiveness and level of evidence for short courses of oral corticosteroids in the treatment of CRSwNP, as well as the combination of these drugs with topical corticosteroids. The high effectiveness of this therapy in alleviating the main symptoms of the polyposis process and reducing the size of polyps was reported. However, the methodology of the studies often did not meet international standards and lacked high levels of evidence. The studies did not include long-term follow-up or describe the side effects of the treatment.

According to the EPOS 2007 and EPOS 2012 guidelines, corticosteroid therapy remains one of the leading treatments for CRSwNP. Intranasal steroids are used as first-line therapy for newly diagnosed CRSwNP, as well as for the treatment and prevention of recurrences of polyposis in the nasal cavity and paranasal sinuses in long-term courses. Systemic corticosteroid therapy is prescribed, according to the protocol, as a first step only in stages III and IV of the polyposis process, in combination with intranasal steroids, and to prevent side effects at minimal doses that provide an anti-inflammatory effect, for no more than

14 days in the postoperative period, followed by prolonged antibacterial therapy and/or in combination with topical steroids [18].

According to our observations, the use of a short course of systemic corticosteroid therapy followed by long-term use of topical corticosteroids shows high therapeutic effectiveness and safety in the treatment of CRSwNP, provided there is step-by-step monitoring of fluctuations in free and bound cortisol concentrations. In the case of polypoid-purulent rhinosinusitis, this systemic corticosteroid therapy regimen should be combined with a short course of antibacterial drugs due to the reduced activity of nonspecific resistance mechanisms and contamination of the mucosal surface by pathogenic and opportunistic microorganisms [19].

The introduction of systemic corticosteroids into the nasal cavities and directly into the tissue of polyps is not advisable, as, in addition to known systemic effects, it poses a risk of retinal vessel embolism and blindness in patients [30].

The broad scientific search and variety of drugs stimulate the inclusion of different medications in the treatment of CRSwNP, including furosemide, leukotriene receptor antagonists, topical (amphotericin B) and systemic (itraconazole) antifungal drugs [11]. However, their effectiveness lacks solid evidence, and according to the EPOS 2012 guidelines, the use of these drugs is only recommended in specific cases, as the development of side effects during therapy outweighs the therapeutic effects of the medications. Regarding the use of systemic antibacterial therapy, particularly macrolides, in the treatment of CRSwNP, these drugs may be used in the case of a purulent-polypoid inflammatory process in patients with newly diagnosed CRSwNP, in combination with prolonged courses of topical corticosteroids [12]. Some researchers highlight the need for immunostimulatory therapy as an adjunct to topical corticosteroids in the treatment of nasal polyps. This choice is primarily due to the immunodependent nature of the disease. Clinical observations have shown that intramuscular administration of the immunomodulator polyoxidonium for 10 days extends the effect of the inhaled corticosteroid fluticasone, limits polyp growth, reduces episodes of respiratory viral infections, improves immunological parameters, and enhances the patients' quality of life. Similarly promising results were observed with the intramucosal administration of the synthetic drug immunofan for 3 days in the preoperative period and 8 days before endoscopic polyp removal [13].

Increasing attention is being paid by researchers to the use of monoclonal antibodies, which act by suppressing specific elements of the immune system in CRSwNP patients. It has been reported that the most significant improvement in

endoscopic, clinical, and radiological changes was observed in patients with CRSwNP after subcutaneous injections of dupilumab for 16 weeks, compared to the intranasal use of mometasone furoate in the control group [14]. However, the proposed scheme and the drug itself require more detailed investigation within clinical trials. In a number of studies regarding the treatment of CRS, the role of staged therapy is emphasized, in accordance with a significant number of studies are dedicated to selecting effective post-surgical recurrence prevention therapy. Traditionally, topical corticosteroids are used to prevent recurrences of the polypoid process, but the regimens for these medications vary widely and are often supplemented with medications from other pharmacological groups, such as macrolides and leukotriene receptor antagonists.

The use of the alkaloid capsaicin in the form of intranasal applications before and after polisinusotomies in patients with CRS is controversial. The action of the drug is based on blocking neurogenic inflammation. Capsaicin reduces the manifestations of nasal symptoms and prevents polyp recurrence for up to 9 months after treatment.

One of the new methods for preventing recurrences of CRS is extracorporeal hemocorrection: ultraviolet irradiation of autologous blood, therapeutic plasmapheresis, and the use of capsaicin alkaloid in the form of intranasal applications before and after polisinusotomies. This approach to preventing nasal polyp recurrences has shown promising results in patients with CRS in combination with concurrent lung pathology.

Treatment of patients with asthma triad presents a particular challenge in rhinology. The proposed conservative and surgical approaches are diverse. Short courses of systemic or inhaled corticosteroids as preoperative preparation and the use of these drugs in combination with topical corticosteroids in the early postoperative period help prevent recurrences of the polypoid process, relieve bronchial asthma exacerbations, and enhance the effectiveness of surgical treatment. The need for aspirin desensitization in these patients has not been fully justified, but a number of studies show its high therapeutic efficacy in treating patients with asthma triad.

Thus, the priority approach in selecting the management strategy for patients suffering from CRS today is a comprehensive and differentiated approach.

An expanded study of the pathophysiological mechanisms of CRSwNP at the molecular level has shown that one of the triggering factors in the development of this pathology is the production of the HMGB1 protein. The latter, when released into the extracellular space, initiates a cascade of inflammatory reactions. In this case, the application of a drug based on mannitol and 18β-glycyrrhizic acid has an

inhibitory effect on HMGB1 protein, reducing disease symptoms and preventing the recurrence of nasal polyps [15]. The diversity of proposed conservative methods for treating CRS requires further in-depth study, pathogenetic justification, and the formation of an evidence base for their effectiveness and safety. The surgical approaches used should not be considered as a competing method of treatment for the polypous process, but rather as one of the important stages of multi-component therapy for chronic CRS.

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