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THERAPEUTIC-DIAGNOSTIC ALGORITHM IN DIFFERENT PHENOTYPES OF POLYPOUS RHINOSINUSITIS

Durdona D. Alimova

PhD, Associate Professor of the Department of Otorhinolaryngology,
Pediatric Otorhinolaryngology, Pediatric Dentistry,
Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
E-mail: dr.alimova@mail.ru

ABSTRACT

In recent years, there has been a noticeable increase in the proportion of rhinosinusitis polyps in the structure of nasal cavity and paranasal sinus diseases, which is due to a number of factors: changes in environmental conditions, an increase in the number of bacterial, viral, and professional pathogenic agents. The use of combined treatment regimens using topical and systemic corticosteroids has shown promising results, but requires further standardization in terms of drug selection, duration of administration, and safety monitoring. The aim of this study was to improve the methods of diagnosis and treatment of patients with polypous rhinosinusitis.

Key words: polypous rhinosinusitis, clinical examination methods, functional endoscopic sinus surgery.

INTRODUCTION

Polypous rhinosinusitis is fundamentally a chronic inflammatory hyperplastic process of the paranasal sinuses (PNS). The task of the treating physician in the management of children with polypous rhinosinusitis (PRS) is to achieve and maintain clinical control, which implies preventing the recurrence of polyp growth and increasing the interval between surgical interventions [2, 7, 11]. Ideally, it is necessary to achieve remission of polypous rhinosinusitis with minimal use of medication. At present, the need for systemic corticosteroid use or the necessity of surgical treatment are signs of an uncontrolled pathological process [3, 8, 10].

Different phenotypes of polypous rhinosinusitis have different mechanisms of the inflammatory process and different clinical course of PRS. Based on this, it is logical to assume that therapeutic measures in these children should be carried out taking into account comorbid PRS pathology in the form of respiratory allergy and

bronchial asthma. To identify PRS endotypes, the levels of various groups of cytokines, granulocytic leukocytes, or specific IgE in polyp tissue or blood are determined. However, endotyping or determining the pathophysiological mechanism of the pathological process flow is necessary in a limited number of cases. Conceptually, the structure of endotyping corresponds to the interests of personalized medicine and is used to develop targeted therapy methods, diagnostic sets of prognostically valid biomarkers, or, as in our work, to identify the dominant inflammation mechanism and demonstrate the relationship between coexisting respiratory diseases in different PRS phenotypes [9]. In contrast, determining the PRS phenotype directly involves analyzing only clinical characteristics without identifying the pathophysiological mechanisms of the disease.

In the routine work of a physician, accessible diagnostic markers are necessary for ranking children with polypous rhinosinusitis in real conditions [1]. Therefore, the advantage of phenotyping is undeniable, as the division of a heterogeneous group of children by the clinical criterion of the presence of concomitant pathology in the form of respiratory allergy and BA can be performed in most medical institutions, provided that an otorhinolaryngologist, allergist, and pulmonologist work together. Based on the available guidelines for PRS and the results of our own research, we have developed our own diagnostic algorithm for determining PRS phenotypes [5, 7].

Research aim.

To develop a therapeutic-diagnostic algorithm for polypous rhinosinusitis incorporating valid diagnostic methods and personalized treatment approaches, and to study its clinical effectiveness in different phenotypes.

Materials and Methods.

To identify the clinical and pathomorphological features of polypous rhinosinusitis in children, questionnaires were collected from 60 children with polypous rhinosinusitis who were referred for surgical treatment due to the ineffectiveness of conservative therapy from 2015 to 2020.

Based on the above, we examined 60 children aged 7 to 18 years. The examination was conducted at the Tashkent Pediatric Medical Institute clinic in the Department of Otorhinolaryngology with the direct participation of the problem laboratory of microbiology, immunology, and mycology at the microbiology department of the Tashkent Medical Academy. Among the patients, there were 24 boys and 36 girls, with an average age of 8.5 ± 3.75 years.

Concomitant pathologies of ENT organs were found in 45 (75.0%) children with PRS: adenoid vegetation of 2-3 degrees in 16 (25%), nasal septum deviation in 12 (18.8%), hypertrophy of palatine tonsils in 11 (17.2%), vasomotor rhinitis in

5 (7.8%), chronic tonsillitis toxic-allergic form in 5 (7.8%), allergic rhinitis in 4 (6.2%), conductive hearing loss in one ear in 8 (12.5%), in both ears in 3 (4.7%) children. Along with these, polypous sinusitis was detected in 13 (15.1%) cases.

Microbiological testing of nasal swabs in patients with PRS revealed the growth of various flora, with aerobic bacteria present in 86% of cases and anaerobic bacteria in only 8-10%. Among the aerobic microorganisms, Staphylococcus aureus (36%), coagulase-negative staphylococci (19.8%), and Streptococcus pneumoniae (17.4%) predominated.

The patient questionnaires included the following data: age, gender, nationality, heredity, extent of polyps spread, presence of NSAID intolerance, bronchial asthma, confirmed respiratory allergies, year of PRS diagnosis, number of PRS operations, interval between them, efficacy of conservative PRS treatment with detailed information on the medications used.

For the diagnosis of polypous rhinosinusitis and assessment of the nasal cavity dynamic state during all follow-up visits after mucosa decongestion with 0.05% xylometazoline solution, and if necessary, under topical anesthesia with 10% Sol. Lidocaine, endoscopic examination of the nasal cavity was performed with rigid endoscopes of 4.0 mm diameter with 0° optics angle from "Karl Storz" and "Azimuth" firms using the "Atmos" endovideoscopic complex with image visualization on a monitor screen via a camera connected to the endoscope eyepiece. The first stage involved examining along the floor of the nasal cavity towards the choana with visualization of the nasopharynx. The second stage examined the middle nasal passage, the condition of the anterior end of the middle nasal concha, and the extent of polypous vegetations according to EPOS recommendations:

Grade I - polyps located within the middle nasal passage;

Grade II - polyps extending beyond the middle nasal passage, occupying up to 2/3 of the common nasal passage, but without occlusion;

Grade III - polyps extending beyond the middle nasal passage and completely occluding the common nasal passage.

To refine the severity of the pathological process, extent of ENT involvement, diagnose the condition of the ostiomeatal complex and other intranasal structures, and identify nasal anatomical anomalies.

All patients underwent computed tomography (CT) of the paranasal sinuses in the coronal projection with subsequent reconstruction in coronal and sagittal projections with a slice thickness from 0.5 mm to 0.1 mm. Evaluation was performed using the Lund-Mackay scoring system.

For the confirmation of the clinical diagnosis of polypous rhinosinusitis and collection of operative material for further research, all patients under local anesthesia with 10% Lidocaine solution underwent endoscopic nasal polypectomy. At the time of material collection, all patients with PRS were not in an exacerbation stage of chronic rhinosinusitis or any comorbid diseases.

Results of the study.

The aim of medical control of PRS is to reduce the severity of clinical manifestations of chronic rhinosinusitis, slow the growth of polyps, and increase the time interval between surgeries. The integration of existing recommendations for the treatment of the pathological conditions we are considering allowed us to develop a therapeutic algorithm of step-by-step therapy for PRS with different phenotypes, according to which treatment starts with basic medications, and in the absence of control over clinical symptoms, progression to the next stage of therapy or surgical treatment is performed. The duration of treatment at each stage is 3 months. Upon achieving remission, when a decrease in the extent of polyps in the nasal cavity is observed during examination along with a regression of complaints associated with PRS, patients move to the next stage, reducing the volume of therapy or doses of recommended medications.

The first stage of disease treatment is not the starting therapy. It is indicated to patients with any PRS phenotype in remission stage in the absence of typical PRS complaints, absence or presence of polyps only within the middle nasal passage without negative dynamics during 3 months of being on the second stage of treatment. Essentially, this is a state of remission when the growth of polypoid tissue is absent without the use of ICS. However, it should be noted that even when polyp growth stops in children, nasal discharge may persist. Mucus is formed as a result of the pathological process in the mucous membrane of the paranasal sinuses, as a manifestation of chronic rhinosinusitis, and serves as a trigger for exacerbation of chronic inflammation, therefore, irrigation therapy with isotonic solution is recommended at this stage. In case of disrupted nasal cavity architecture due to frequent surgeries for mucus removal, the use of devices with a volume of more than 200 ml is recommended. In the event of polyp recurrence, even if the patient has been on the first stage for less than 3 months, they are immediately transferred to the second stage and prescribed ICS.

The second stage of PRS treatment is the first therapeutic stage. For all PRS phenotypes, ICS indicated in the instructions for PRS treatment are prescribed here as basic therapy at standard dosages for polyp recurrence. At the second stage, in case of exacerbation of allergic rhinitis, second-generation antihistamines are additionally prescribed according to standard treatment schemes for this condition.

This is especially relevant in the presence of hypersensitivity to seasonal inhalation allergens during the pollination season significant for the patient with PRS, combined with plant respiratory allergies. Patients on this stage take the intranasal glucocorticosteroid mometasone furoate at a dose of 100 mcg in each nostril twice daily (daily dose of 400 mcg).

The evaluation of treatment effectiveness should be conducted once every 3 months. Taking into account that according to the data obtained from our research, the inflammation mechanism of PRS in combination with AR or BA differs from other phenotypes, additional therapy is recommended from Stage I for Phenotypes 2 and 3. In the case of PRS+AR combination (Phenotype II), starting from Stage I of treatment, consideration should be given to AIT. The confirmed high efficacy of this method is realized through the suppression of effector cell activity by limiting the migration of eosinophilic granulocytes to the mucous membrane of all airway sections and inhibiting the degranulation of basophils and mast cells. As a result of the reshaping of T-cell response to allergens, there is a switch in the immune response from Th2 to Th1, manifested by a reduction in the proliferative response of T cells and the release of IL-4 while simultaneously increasing the synthesis of IL-10 and TGF-β. Accordingly, in the combination of PRS with AR or BA, AIT will contribute to slowing the progression of both PRS and allergic diseases directly. In the presence of BA, as well as in Phenotype III where PRS is accompanied by Non-BA, the key point is the parallel joint management of such children by an otolaryngologist and an allergist-immunologist or a pulmonologist, whose task in this case is the regular medication control of bronchial asthma. In case of therapy ineffectiveness, assuming full compliance with the prescriptions by the patient, they are moved to a higher stage.

Stage III. In the absence of treatment effectiveness, it is recommended to double the daily dose of ICS. For Phenotypes 2 and 3 of PRS, a leukotriene receptor antagonist montelukast (10 mg once a day) is added.

Stage IV. In case of therapy ineffectiveness in all PRS phenotypes, treatment with systemic corticosteroids for a short course is carried out, or the question of surgical intervention is considered. Also, in the 4th stage of PRS treatment for Phenotypes 2 and 3 with the presence of BA of any origin, there is an alternative to surgical treatment in the form of biological therapy. This type of therapy is prescribed only by an allergist-immunologist since the main indication for treating such children with monoclonal antibodies is solely BA, whereas for the treatment of nasal polyposis these drugs are at different stages of clinical trials or in the process of registration in Uzbekistan (Fig. 1).

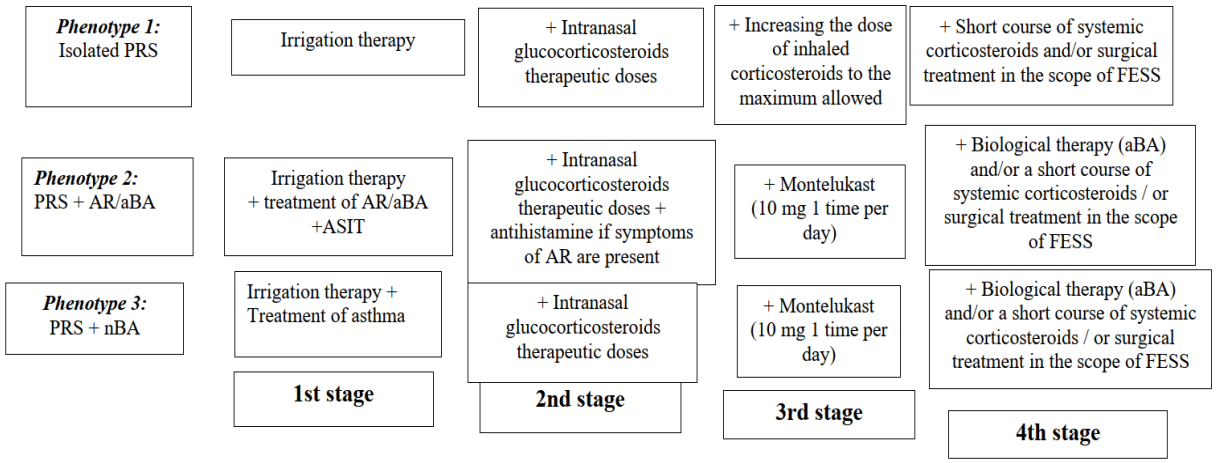

Fig. 1. Step-by-step therapy for different PRS phenotypes

In case of the development of rhinogenic intracranial or orbital complications at any stage of treatment, the patient is urgently hospitalized in the otolaryngological department for surgical treatment and all necessary therapeutic measures according to the rules of emergency otolaryngology. In order to confirm the effectiveness of the proposed step-by-step PRS therapy depending on its phenotype, an assessment of our treatment outcomes of children over 2 years is carried out.

Characteristics of children who participated in the study are presented in Table 1.

Table 1

Characteristics of children with PRS with different phenotypes

	Group 1 (PRS, n=20)	Group 2 (PRS+AR, n=20)	Group 2 (PRS+BA, n=20)
Age, years	14,4±1,3	15,2±2,28	16,8±2,7
Boys/Girls, %	65% / 35%	55,0% / 45,0%	30% / 70%
Duration of PRS, years	4 [1; 6,5]	5 [1,5; 10]	6 [3; 12]
CT of the Paranasal Sinuses (Lund-Mackay scale), scores	20,47±1,5	20,84±1,89	20,92±1,41
Polyp size grade, scores	5 [4; 6]	5 [4; 5]	5 [4; 6]

After surgical treatment, all patients, according to the 2nd stage of our algorithm, received mometasone furoate intranasal corticosteroids (ICS) in a total daily dose of 400 mcg. Then, every 3 months during follow-up endoscopic examinations, therapy adjustments were made. In cases of ineffectiveness of standard ICS doses, an increase in the dose of mometasone furoate by 4 inhalations (200 mcg each) in each half of the nose twice a day (total daily dose of 800 mcg) was recommended, according to the 3rd stage of our proposed algorithm. After 6 months, in 3 children (15%) without signs of recurrence, topical corticosteroids

were discontinued; in 2 children, standard ICS doses led to polyp growth, requiring an increase in the dose of mometasone furoate to 800 mcg daily.

One year after the start of observation, the absence of PRS recurrence without ICS was observed in 4 children (20%); 14 children received basic therapy with standard ICS doses (70%); 3 children received 3rd-stage treatment, and 2 children underwent FESS due to aggressive polyp growth and ineffective ICS at a dose of 800 mcg daily.

After 1.5 years of observation, FESS was performed in 1 more child (5%) in whom the growth of polypoid tissue was not controlled by ICS. Thirteen children were at the 2nd stage of control, and 4 children were at the 1st stage.

After 2 years, despite successful FESS, two patients had aggressive polyp growth 6 months after the operation, which decreased after a systemic corticosteroid course (4th stage). Thirteen children were at the 2nd stage of treatment, and 4 children were at the 1st stage.

Thus, out of 20 children in Group 1, the ineffectiveness of ICS medication control was observed in 4 individuals (20%). In 3 of them, additional surgical treatment in the form of FESS was performed, and two of them underwent a course of systemic corticosteroid therapy post-operation. Systemic corticosteroid administration was performed on 2 children (10.0%).

For children in Group 2 (Phenotype 2) with respiratory allergies, courses of allergen-specific immunotherapy (AIT) with pollen from trees, house dust, grass pollens, and composite flowers were conducted for 4 individuals over 2 years of observation. In cases of hypersensitivity to seasonal inhalant allergens during the flowering season, desloratadine was prescribed to all patients in addition to standard PRS therapy at 5 mg once daily orally. Desloratadine was prescribed according to standard AR treatment guidelines for patients with hypersensitivity to perennial allergens.

After 6 months of observation, 16 patients (80.0%) were at the 2nd stage, and 2 individuals (10.0%) were at the 3rd stage of therapy. After 1 year, remission of PRS was observed in 2 children (10.0%), allowing them to move to the 1st stage; 16 children were at the 2nd stage (80.0%), and 2 children were at the 3rd stage (10.0%). After 2 years, stabilization of the pathological process allowed 3 children (15.0%) to remain at the 1st stage without basic ICS therapy, 8 patients (40.0%) received standard ICS doses, and 2 children (10.0%) in addition to ICS were taking montelukast at a dose of 10 mg daily for the primary indication for AR treatment.

The group with Phenotype 3 of PRS had more complex disease control compared to the PRS+AR group, with more frequent episodes of acute respiratory infections. After 6 months post-endoscopic polypectomy, 8 individuals (40%) were

at the 3rd stage, with the addition of a leukotriene receptor antagonist, montelukast, at a dose of 10 mg daily to standard ICS doses, for the primary indication being bronchial asthma (BA). Eleven children (55.0%) were undergoing treatment at the 2nd stage. One patient underwent reoperation in the form of FESS due to lack of medication control and aggressive polyp growth.

Throughout the observation period, the treatment of patients with Phenotype 3 PRS+Non-BA was carried out jointly with an allergist-immunologist, who adjusted the BA treatment.

Therefore, the division of CRS patients into phenotypes, their constant dynamic observation by an otolaryngologist with treatment regimen adjustments every 3 months, and simultaneous parallel treatment of comorbidities in the form of respiratory allergies and bronchial asthma by an allergist-immunologist allowed to stabilize the course of the pathological process in the upper and lower airways, improve medication control of polyp recurrence, and reduce the number of surgical interventions in the nasal sinuses.

Conclusions.

The developed algorithm for the diagnosis and treatment, formed taking into account the phenotypes of CRS, is based on a multidisciplinary and personalized approach to patient management and ensures improvement in medical control when treating all phenotypes of CRS. The use of the algorithm reduced the number of patients at the 3rd and 4th stages from 70% to 36.8% when combining CRS with allergic bronchial asthma and avoided the 4th stage when combined with allergic rhinitis. In combination with non-allergic bronchial asthma, a slow but progressive positive dynamics in the course of CRS was observed, with 45.0% of children at stages 1 and 2 of treatment by the end of 2 years.

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