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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Characteristics of patients with diagnosed chronic fungal rhinosinusitis surgically treated in the past five years

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SUMMARY

Introduction/Objective Fungal rhinosinusitis comprises of a wide range of immune-pathological responses, including invasive, chronic, granulomatous, and allergic diseases.
Aim of this study was to determine total number of patients, their characteristics, frequency of symptoms, the manner of disease manifestation and the success of therapy.

Methods Study included 21 patients with fungal rhinosinusitis diagnosis made according to the 2020 EPOS guidelines.

Results Based on the visual analogue scale, feeling of localized pressure, i.e., facial pain, was dominant with a score of 9.57 ± 0.98, followed by the secretion from the nose with 8.14 ± 1.62, problems with breathing through the nose with 6.67 ± 3.25, and reduction the sense of smell with 2.14 ± 3.00. The t-test showed a statistically significant difference between mucosal changes on the diseased and healthy sides of the patient's face ($p < 0.0001$). Only one sinus was affected intraoperatively in 18 (85.71%) patients. The most commonly affected sinus was the maxillary one, in 13 (54.17%) patients, followed by the sphenoid sinus in five (20.83%) patients. *Aspergillus* was proven as the couse of rhinosinusitis in 12 (57.14%) patients.

Conclusion The dominant symptom of patients with fungal rhinosinusitis was localized pain/pressure in the area of the affected sinus. Endoscopically, on the side of the affected sinus, the pathological mucosa with thick, pithy, mucous secretion dominated. The maxillar sinus was primarily unilaterally affected, in more than half of the patients. *Aspergillus* has been proven to be the most common cause of rhinosinusitis.

Keywords: fungal rhinosinusitis; chronic rhinosinusitis; headache; facial pain/pressure; nasal discharge; nasal obstruction

INTRODUCTION

Fungal rhinosinusitis (FRS) comprises of a wide range of immunopathological responses, including invasive, chronic, granulomatous, and allergic diseases. They differ in clinical picture, histological phenomena, and biological significance [1, 2].

During the course of the disease, we distinguish between the acute form, which lasts up to four weeks, and the chronic form, with the duration of the symptoms longer than 12 weeks. Acute rhinosinusitis is well categorized. Controversy exists around the concept of chronic rhinosinusitis (CRS), i.e., the role of fungi in this condition. Based on histopathological findings, FRS can be broadly divided into two categories: invasive and noninvasive. The noninvasive form of FRS behaves clinically like chronic bacterial rhinosinusitis. Three noninvasive FRS have been described: saprophytic fungal infection, fungal ball (fungus ball or sinus mycetoma), and fungal-associated eosinophilic rhinosinusitis, including allergic fungal rhinosinusitis (AFRS). Invasive forms of FRS, in which the infection results in a mass that behaves like a malignant neoplasm, eroding the bones and spreading to the adjacent tissue, are the following: acute (fulminant) invasive, granulomatous invasive, and chronic invasive types. The granulomatous invasive type is mainly described in chronic cases of FRS from Sudan, India, and Pakistan, where patients are immunocompetent, almost exclusively identified with *Aspergillus flavus* and presented as non-seated granulomas, almost all of which have proptosis in clinical manifestations. These cases differ from chronic invasive FRS, which has a chronic course, often in subtly immunocompromised patients, such as those with diabetes mellitus and/or treated with corticosteroids, with a dense accumulation of hyphae attacking the tissue, sometimes associated with orbital apex syndrome [1, 2, 3].

AFRS is a type of chronic rhinosinusitis, as a reaction of hypersensitivity to fungi that colonize the sinus. It mainly affects young, atopic, immunocompetent patients, who often have nasal polyps and asthma. It is characterized by eosinophilic inflammation of the mucous membrane and thick mucin, the consistency of peanut or cheese butter, brownish to black, rich in eosinophils. Bent and Kuhn criteria are used to diagnose AFRS: nasal polyps, the presence of fungi in a microscopic finding or culture of sinus contents, eosinophilic mucin without

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fungal invasion of the sinus tissue, type 1 hypersensitivity to fungi, proven by skin or *in vitro* tests, and a characteristic CT finding (computed tomography of the paranasal sinuses – sinus expansion or heterogeneous shading). The therapy is surgical: all fungal material and nasal polyps are removed. Postoperative nasal lavage with salt water and intranasal corticosteroids improves the likelihood of long-term cure.

Fungus ball or sinus mycetoma is a dense accumulation of hyphae inside one or more sinuses, usually maxillary, without tissue invasion. Clinical signs and symptoms are nonspecific or absent, so the diagnosis of fungus ball is made mostly by chance, radiologically. Like AFSR, it can be associated with the presence of nasal polyps. The therapy is surgical: all fungal material is removed. There is no need for drug therapy postoperatively [2–6].

The aim of this research was to determine the total number of patients with FRS, their distribution by sex, age, to identify the leading symptom, most common localization, endoscopic and radiological characteristics, the extent of the disease and the success of therapy.

METHODS

In this prospective-retrospective study during the previous five years, among 557 operatively treated patients with diagnosed CRS, FRS was microbiologically and pathohistologically verified in 21 patients. They were operatively treated at the Clinic for Ear, Throat and Nose Diseases of the Clinical Centre of Vojvodina, Novi Sad, Serbia. Fungal rhinosinusitis diagnosis was made according to the 2020 EPOS guidelines [1]. Patients' data were collected from the medical histories (sex, age, diabetes mellitus, use of corticosteroids, lifestyle, smoking, chemical contaminants, chronical inflammations, allergens). Diagnostic protocol included the VAS (visual analogue scale), intraoperative nose swab, endoscopic intraoperative finding, CT finding, laboratory test (eosinophils in nasal secretions, total immunoglobulin E (IgE), and complete blood count). The patients assessed their symptoms intensity on the VAS from 0 to 10, with 0 indicating no trouble and 10 indicating the maximum intensity of symptoms. The VAS assessed the following: nasal breathing, nasal secretions, secretions flowing through the posterior wall of the pharynx, decreased sense of smell, and pressure or pain in the affected sinus.

Endoscopic examination of the nose assessed the appearance of the mucosa (0 – mucosa without changes, 1 – there is mild edema, 2 – polypoid degeneration), the presence of secretion (0 – none, 1 – a small amount of clear secretion, 2 – thick and/or mucopurulent secretion), the presence of polyps (none, first degree, second degree, third degree), and deviation and deformities of the nasal septum.

The study was carried out according to the principles of the Helsinki Declaration and it was approved by the local ethics committee, decision number 00-15/1700. All the patients were fully informed on the study itself and they signed their consent to participate. Numerical data are presented as measures of central tendency (mean, median), the measures of variability (standard deviation, minimum, maximum), and categorical data are presented as frequencies and percentages. Statistical analysis was performed using IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 557 operatively treated patients diagnosed with CRS, during five years, 21 (3.8%) patients had microbiologically and pathohistologically verified FRS. CRS with polyposis was found in nine (42.9%) patients. There were 11 (52.4%) female patients, as opposed to 10 (47.6%) male patients. The average age was 45.33 ± 16.51 years (18–75 years).

Of the associated diseases, allergies were present in 14 (66.67%) patients, headache in six (28.57%) patients, hypertension in six (28.57%) patients, asthma in five (23.8%) patients, cardiovascular disease in three (14.29%) patients, diabetes in two (9.52%) patients, hearing impairment in two (9.52%) patients, and hemophilia, urticaria, gastric ulcer and hypocroticism in one (4.78%) patient. Patients were predominantly allergic to inhaled allergens – in nine (42.9%) patients, while drug allergy was reported by seven (33.3%) patients, and food allergy by one (4.8%). The most common inhaled allergens are mites, in five (15.5%) cases, followed by weed pollen in four (12.1%) cases, house dust in three (9.1%) cases, mold/mildew/fungi in three (9.1%) cases, grass pollen in three (9.1%), tree pollen in one (3%) case.

In the laboratory findings, we were interested in the following data: eosinophils in nasal secretions, total IgE, and complete blood count. Eosinophilic granulocytes were found in nasal secretions in 12 (57.14%) patients. Total IgE was elevated in nine (42.85%) patients and decreased in two (9.52%) patients. Blood of seven (33.33%) patients showed eosinophilia, in one (4.76%) patient anti-*Aspergillus* antibodies were isolated, and the remaining 13 (61.9%) patients did not show peculiarities in the blood.

Based on the visual analogue scale, feeling of localized pressure, i.e., facial pain, was dominant with a score of 9.57 ± 0.98, followed by the secretion from the nose with 8.14 ± 1.62, problems with breathing through the nose with 6.67 ± 3.25, and reduction of the sense of smell with 2.14 ± 3.00 (Figure 1).

The appearance of the mucosa on the patient's side was evaluated by endoscopic examination in all patients with a grade of 2 (mean value: 2 ± 0). Nasal secretion was evaluated with 1 in four (19.05%) patients, with 2 in 17 (80.95%) patients (mean: 1.81 ± 0.4). The presence of polyps was evaluated with 0 in 12 (57.14%) patients, the first degree of polyposis was found in two (9.52%), the second degree in five (23.81%), and the third degree was found in two (9.52%) patients (mean: 0.86 ± 1.11). Deviation and deformities of the nasal septum were present in 12 (57.14%) patients. Using the obtained results, we compared the diseased and the healthy side of the patient. The obtained results are shown in Table 1.

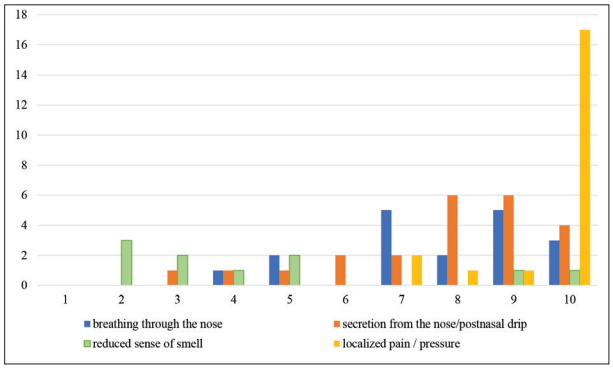

Figure 1. Visual analog scale score of nasal symptoms (nasal block, secretion/postnasal drip, hyposmia/anosmia, local pressure of the sinuses)

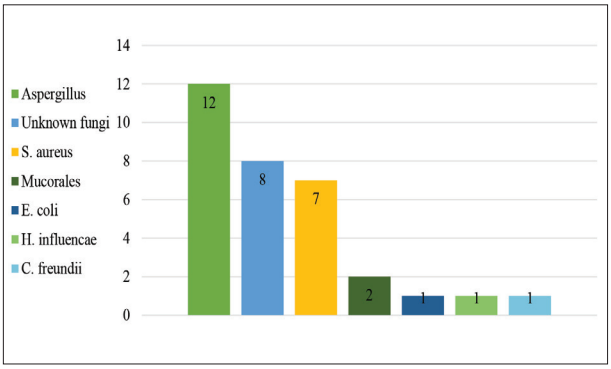

Figure 2. Pathogenic microorganisms isolated in nasal swab/material from the affected sinuses

Table 1. Endoscopic analyses of the nose

Parameter	Mucosa	Nasal secretion	Polyp	Nasal deviation	
				Yes	No
Diseased side (M ± SD)	2 ± 0**	1.81 ± 0.4**	0.86 ± 1.11	12 (57.14%)	9 (42.86%)
Healthy side (M ± SD)	0.76 ± 0.83**	0.33 ± 0.67**	0.33 ± 0.8	4 (19.05%)	17 (80.95%)

M – middle value; SD – standard deviation;
*p < 0.05;
**p < 0.001

Table 2. Analyses of the CT scan of the paranasal sinuses

Sinus	Maxillar	Ant. ethmoidal	Post. ethmoidal	Sphenoidal	Frontal	Osteomeatal complex
Diseased side (M ± SD)	1.33 ± 0.91**	1.43 ± 0.81**	0.9 ± 0.77*	0.62 ± 0.92*	0.67 ± 0.58*	1.48 ± 0.87**
Healthy side (M ± SD)	0.24 ± 0.54**	0.19 ± 0.51**	0.19 ± 0.51*	0.14 ± 0.48*	0.09 ± 0.3*	0.24 ± 0.54**

M – middle value; SD – standard deviation;
*p < 0.05;
**p < 0.001

The t-test showed there is a statistically significant difference between mucosal changes on the diseased and healthy sides of the patient's face ($p < 0.0001$). There is a statistically significant difference between the amount and properties of secretions on the diseased and healthy side of the patient's face ($p < 0.0001$). Also, there is no statistically significant difference in the presence of nasal polyps on the diseased and healthy side of the patient's face ($p = 0.0835$).

Binomial test showed that there is no statistically significant difference in whether or not there is a deviation on the affected side ($p = 0.664$).

Intraoperative in 18 (85.71%) patients only one sinus was affected, in the remaining 3 (14.29%) two sinuses were affected. The most commonly affected sinus was the maxillary sinus, in 13 (54.17%) patients, followed by the sphenoid sinus in five (20.83%) patients, the posterior ethmoid in three (12.5%) patients, the anterior ethmoid sinus in two (8.33 %) patients, and the frontal sinus was affected in only one (4.17%) patient (Table 2).

Nasal swab or analysis of the material obtained from the affected sinus showed the presence of fungi in all the patients. *Aspergillus* was proven in 12 (57.14%) patients, and mucormycosis (a fungus of the order Mucorales) was diagnosed in one (4.76%) patient. Fungal material was found in eight (38.1%) patients, and was not examined in more detail. In addition to fungi, we also isolated the following: *Staphylococcus aureus* in 33.33% (seven patients), *Escherichia coli* 9.25% (two patients), *Haemophilus influenzae* and *Citrobacter freundii* 4.76% each (one patient) (Figure 2).

Using the t-test, we determined whether there was a statistically significant difference in the changes on the CT finding on the healthy and sick side of the patient's face. There is a statistically significant difference of the shading of the maxillary sinus on the diseased *vs.* the healthy side of the patient's face ($p < 0.0001$) (Table 2).

There is a statistically significant difference between the shading of the anterior ethmoid and of the posterior ethmoid sinus on the diseased and the healthy side of the patient's face ($p < 0.0001$). There is a statistically significant difference between the shading of the sphenoid sinus on the diseased and the healthy side of the patient's face ($p = 0.0403$). There is a statistically significant difference between the shading of the frontal sinus on the diseased and the healthy side of the patient's face ($p = 0.0002$). There is a statistically significant difference between the shading of the osteomeatal complex on the diseased and the healthy side of the patient's face ($p < 0.0001$).

DISCUSSION

The incidence of chronic rhinosinusitis in European countries has been continuously growing over the years. There

is an increasing presence of non-invasive fungi, i.e., "fungus ball" in the intraoperative finding in affected sinuses, patients undergoing surgical treatment. This phenomenon is explained by the increased and uncontrolled use of antibiotics, immunosuppressive therapy and changes in life habits (primarily increased stay in air-conditioned rooms and vehicles). While some authors cite the use of more advanced diagnostic methods as a reason for detecting fungi in the sinuses [6].

The study analyzed 557 patients diagnosed with CRS, surgically treated at the Clinic for Ear, Throat and Nose Diseases of the Clinical Centre of Vojvodina, Novi Sad, Serbia. In 21 (3.77%) patients the presence of non-invasive fungi in the affected sinus was proven intraoperatively, and of that number, 12 (57.14%) had CRS without polyposis and nine (42.86%) had nasal polyps [7]. Of the 21 patients examined, 11 (52.4%) were female and 10 (47.6%) were male. A higher incidence of the female sex in FRS is also found in other papers [7, 8]. Cho et al. [9] and Jiang et al. [10] also note that the disease is more common in middle-aged women, for no apparent reason. The average age of our respondents was 45.33 years, which is in line with the literature – the disease is characteristic of adult patients, while it is rarely found in children and adolescents [7].

The most common comorbidities in the study were allergies (66.67%). Of these, inhaled allergens (42.9%), drug allergies (33.3%) and nutritional allergens (4.78%) were noted. Of other diseases, headache was present in 28.6%, hypertension in 28.6%, lower respiratory tract disease in 23.8%, and bronchial asthma in 19% of the patients. Tyler et al. [11]. report allergic rhinitis in 48% of their patients, bronchial asthma in 33.8%, hypertension in 25.8% of patients, and aspirin intolerance in 22.5%. Diabetes mellitus was found in our patients in only two (9.5%) cases. In the study by Tyler et al. [11] it was also among the less common comorbidities (3.2%). Diabetes mellitus, as well as other immunodeficiency conditions, is characteristic of invasive forms of fungal rhinosinusitis, such as acute necrotizing and chronic invasive fungal rhinosinusitis [12].

In relation to sinus involvement, the changes can be unilateral and bilateral. All patients in our study had changes exclusively unilaterally, which is in line with most studies, which more often find that only one side of the face is affected [7, 8]. The maxillary sinus was most commonly affected, in 13 (54.67%) patients. The sphenoid sinus was the second most affected, in five (20.83%) patients. Although such epidemiology is confirmed by other studies, they state that the increased frequency of jaw sinus disease is associated with dental procedures performed on the upper jaw [7, 8, 12, 13, 14]. In our study, we had no data on previous dental interventions. Other sinuses were less frequently affected by fungal infection: the posterior ethmoid three (12.5%) times, the anterior ethmoid two (8.33%) times, and the frontal ethmoid only once (4.17%).

The microbiological findings of the examined patients showed the presence of fungi in all (100%) the patients. *Aspergillus* is the most common isolated fungus, in as many as 12 (57.14%) patients, which is in line with other studies [10, 11, 15, 16]. In eight (38.1%) specimens in which fungal material was found, the type of fungus was not defined, and fungi from the order Mucorales, which cause mucormycosis, were found once (4.7%). The presence of *Staphylococcus aureus* in the findings of seven (33.33%) patients is interesting. Tyler et al. [11] and Singh [12] found frequent infections with this bacterium. *Escherichia coli* was isolated in two (9.5%) patients, *Haemophilus influenzae* and *Citrobacter freundii* in one (4.8%).

The dominant problem in the VAS, in all the patients, was the characteristic localized pain, i.e., facial pressure, with an average score of 9.57. The second most severe symptom was nasal discharge or discharge down the throat, with an average score of 8.14. Nasal congestion was reported by 18 (85.7%) patients with a mean score of 6.6. Mild odor disorder with a mean score value of only 2.14 was registered in only 10 (47.62%) patients. These findings differ from the claims of Fadda et al. [7], according to which the most common symptom of the maxillary sinus involvement is nasal congestion (76.9%), followed by rhinorrhea (61.5%), with facial pain in the third place (46.1%). Compared to the same paper, when the sphenoid sinus is affected, our findings are similar given that the most common symptom for their patients is facial pain (77.8%), followed by rhinorrhea (66.7%), and cacosmia (33%), while only 11% of the patients complained of nasal congestion. Comparing the endoscopic findings of the healthy and diseased (fungal infiltrate-affected) sides of the nose, the t-test showed a statistically significant difference in the appearance of the mucosa ($p < 0.0001$). There is a significant difference in the quality and quantity of nasal secretions ($p < 0.0001$). The presence of polyps was not shown to be a statistically significant characteristic of chronic fungal rhinosinusitis ($p = 0.0835$), nor was the existence of nasal septal deviation or deformity ($p = 0.664$). In a study by Tyler et al. [11], diagnostic nasal endoscopy showed polypoidal changes in 71 patients (37.3%), blackish debris in 14 patients (7.4%), and mucopurulent discharge in middle meatus in 49 cases (25.8%) out of 81 cases of fungal sinusitis. A CT scan of paranasal sinus cavities was done for all the cases and sinus involvement. Using the t-test and comparing the score of the diseased and of the healthy side of the nasal cavity and the patient's sinuses, a statistically significant difference in the appearance of all sinuses was proved. For the maxillary, anterior ethmoid, and frontal sinuses, and the osteomeatal complex, statistically extremely significant differences were shown between shading on the healthy and the diseased sides ($p < 0.0001$). These findings correspond to the published data [15, 16]. In a study by Fadda et al. [14], unilateral involvement was seen in 83.3% of cases and 33.3% cases of fungal rhinosinusitis show features of dense metal deposits and 30.9% of cases show bony erosion.

CONCLUSION

The dominant symptom of patients with fungal rhinosinusitis in the study was localized pain/pressure in the area of the affected sinus, followed by secretion/discharge of nasal

secretions, and nasal congestion. Nasal endoscopy in all the patients was dominated on the side of the pathologically fungally altered sinus by pathological mucosa with thick, pithy, mucous secretion. Intraoperative findings revealed unilateral involvement of the affected sinus in all the patients, primarily the maxillary sinus, which was affected in more than half of the patients. *Aspergillus* has been proven to be the most common cause of the disease.

Conflict of interest: None declared.

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Карактеристике болесника са дијагнозом хроничног гљивичног риносинузитиса хируршки лечених у протеклих пет година

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САЖЕТАК

Увод/Циљ Гљивични риносинузитис обухвата широк спектар имунопатолошких одговора, укључујући инвазивне, хроничне, грануломатозне и алергијске болести носа и параназалних шупљина.

Циљ овог истраживања био је да се утврди укупан број болесника, њихове карактеристике, учесталост симптома, начин манифестовања болести и успех терапије.

Методе У нашу студију је укључен 21 болесник са микробиолошки и патохистолошки верификованим гљивичним риносинузитисом.

Резултати На основу визуелне аналогне скале болови у лицу били су доминантни са оценом 9,57 ± 0,98, секреција из носа са оценом 8,14 ± 1,62, проблем дисања на нос са 6,67 ± 3,25, док је смањење чула мириса било са оценом 2,14 ± 3,00. *T*-тест је показао да постоји статистички значајна разлика између промена слузокоже на болесној и здравој страни лица болесника ($p < 0,0001$). Интраоперативно је код 18 (85,71%) болесника захваћен само један синус, и то најчешће максиларни у 13 (54,17%) случајева, потом сфеноидни синус у пет (20,83%) случајева, задњи етмоид у три (12,5%) случаја, предњи етмоид у два (8,33%) случаја и фронтални синус само код једног (4,17%) болесника. *Aspergillus* је дијагностикован код 12 (57,14%) болесника, а мукор микоза (гљива реда *Mucorales*) код једног (4,76%) болесника.

Закључак Доминантан симптом болесника са гљивичним риносинузитисом је локализован бол/притисак у пределу захваћеног синуса. Ендоскопски, на страни захваћеног синуса, доминирала је патолошка слузница са густим, пихтијастим, мукозним секретом. Првенствено је унилатерално захваћен вилични синус, код више од половине болесника. *Aspergillus* је доказан као најчешћи узрочник риносинузитиса.

Кључне речи: гљивични риносинузитис, хронични риносинузитис; главобоља; бол/притисак у лицу; секреција из носа; опструкција носа; поремећаји мириса; визуелна аналогна скала