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Original Scientific Paper

UNILATERAL VS. DIFFUSE CHRONIC RHINOSINUSITIS

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ABSTRACT – Chronic rhinosinusitis (CRS) is a widespread disease with various symptoms. It is defined as an inflammation of the nasal mucosa and paranasal sinuses lasting for 12 weeks, with symptoms of nasal obstruction and/or congestion and facial pain and/or pressure as well as decreased sense of smell. Despite the widespread prevalence of the disease, the diagnosis and treatment of CRS are still not adequately developed, so many patients remain misdiagnosed. This study involved 150 patients who, according to EPOS guidelines, met the diagnosis of CRS without nasal polyposis. Each patient underwent a computerized tomography (CT) scan of the paranasal sinuses, which was evaluated according to the Lund-Mackay scoring system. Furthermore, patients completed a visual analog scale (VAS) score questionnaire which examined the severity of their symptoms. The aim of this study was to find an association between the degree of mucositis and the clinical symptoms reported by the patient. Our results showed a low positive correlation between nasal secretion and Lund-Mackay score for the bilateral ostiomeatal complex (OMC). Furthermore, a low positive correlation was found between the severity of reduced sense of smell and severity of anterior ethmoid and sphenoid sinusitis. The results demonstrated a low negative correlation between the severity of facial pain or pressure and the severity of inflammation of the anterior ethmoid and sphenoid sinus. The results of statistical testing did not show statistical differences in severity of subjective symptoms for almost all of the observed symptoms in persons with unilateral inflammation and persons without unilateral inflammation, except for cough. People who did not have unilateral inflammation had a more pronounced cough compared with people who had unilateral inflammation. However, these correlations were very mild and not clinically significant, so we cannot say that the distribution of sinusitis significantly affects the occurrence of characteristic symptoms in chronic rhinosinusitis.

Key words: *Chronic rhinosinusitis (CRS); Lund-Mackay score (LM score); Visual analog scale (VAS); Clinical symptoms*

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disorder of the nose and the paranasal sinuses lasting longer than 12 weeks. It is common in the general population.[1,2] According to The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) guidelines, CRS is characterized by two or more symptoms, one of which is either nasal blockage, obstruction, congestion, or nasal discharge (anterior/posterior), with or without facial pain or pressure, and reduction or loss of smell lasting for at least 12 weeks.[2]

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Endoscopic signs that confirm CRS diagnosis based on symptoms include the presence of nasal polyps and mucopurulent discharge from the middle meatus, with or without oedema of the nasal mucosa and ostiomeatal complex.[2,3] Radiological signs of rhinosinusitis are mucosal changes within the ostiomeatal complex and/or sinuses.[2,4,5] The latest EPOS 2020 guidelines classify CRS as primary or secondary, and each of these is further classified according to anatomic distribution as localized or diffuse disease.[2] In primary CRS, the disease is classified by endotype dominance, either T helper 2 cells (Th2) or non-Th2. Localized primary CRS is then subdivided into two phenotypes – allergic fungal rhinosinusitis or isolated sinusitis. For diffuse primary CRS, the clinical phenotypes are predominantly eosinophilic CRS (eCRS) and non-eCRS, based on histological quantification of the number of eosinophilic. Secondary CRS can again be divided into primary and secondary. It is then split into four categories depending on local pathology and mechanical, inflammatory, and immunological factors.[2,6]

There are two different phenotypes of CRS: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyps (CRSsNP). The differential diagnosis of these phenotypes is based on endoscopic findings, depending on the presence or absence of polyps. In most cases, CRSwNP is characterized by a type 2 inflammatory response with predominant tissue eosinophilia, while CRSsNP is followed by a type 1 inflammatory response and tissue neutrophilia.[2,7] However, the Th17 inflammatory pathway has been reported as an alternative inflammatory pathway in CRSsNP.[8]

In addition, CRS also affects the social aspect of a patient's life; patients with CRS are significantly more limited by their health status in social functioning than patients with other chronic diseases.[9]

Different HRQL instruments have been developed to assess the severity of the disease and the impact of CRS on the health-related quality of life (HRQL) of an individual.[10-12] In practice, the SinoNasal Outcome Test with 22 questions (SNOT-22) is used to identify the burden of CRS on a patient's life. Since this might be impractical in the everyday clinical setting, recent research indicates that visual analog scale (VAS) scores in 4 subdomains might adequately reflect the information from the SNOT-22 questionnaire.[12]

The aim of our study was to assess the severity of major and minor subjective symptoms of CRS measured in VAS scores and to compare outcomes in patients with unilateral (local) and diffuse CRS.

Patients and methods

A cross-sectional study was conducted at the Department for Otorhinolaryngology and Head and Neck Surgery, University Hospital Center Sestre milosrdnice, as part of the Ministry of Science project number 065-235-0145. The project was approved by the Ethical Committee of University Hospital Center Sestre milosrdnice, the Ethical Committee of the Faculty of Dentistry, and the Ethical Committee of the Medical Faculty of the University of Zagreb.

Patients who met the EPOS 2020[2] clinical criteria for CRS and who showed no response to medical treatment according to the guidelines for at least 3 months were included in the study, which was confirmed by the evidence of objective signs of disease on endoscopy and a computerized tomography (CT) scan. Patients were excluded if they had an acute exacerbation of rhinosinusitis, trauma or tumors of the nasal/sinus cavities, cystic fibrosis, granulomatous disease affecting the sinus or nasal cavity mucosa, or age <18 years. We also excluded patients with CRSwNP, as it is a diffuse disease by definition.[2]

The visual analog scale (VAS) was used to determine major and minor symptoms according to the recommendations by the Rhinosinusitis Task Force. The symptoms assessed by the VAS were: nasal discharge, nasal obstruction, postnasal discharge, smell impairment, facial pain/pressure, facial fullness, headache, dental pain, halitosis, cough, ear pain/fullness, and fatigue. Patients graded their subjective symptoms with the VAS scale, marking the intensity of the symptoms on a straight line from 0 to 10 cm. Patients also underwent CT imaging, and their findings were graded according to the Lund-Mackay system, scoring the ethmoidal, frontal, sphenoidal, and maxillary sinuses and the ostiomeatal complex to assess the condition of the mucosa. The degree of sinus opacification was scored from 0 to 2; 0 indicating no opacification and 2 representing a completely opacified sinus.

Statistical analysis of results

We used Pearson's correlation coefficient to compare the severity of inflammation (Lund-Mackay score) for individual sinuses and the severity of the observed symptoms. We used a parametric T test to test the differences in symptom severity in patients with unilateral inflammation and patients without unilateral inflammation.

Table 1. Testing the difference in the severity of individual symptoms of patients with unilateral inflammation and without unilateral inflammation

Unilateral inflammation		N	Arithmetic mean	Standard deviation	F (Leven's test for equality of variances)	Significance (p)	t	Df	Significance (p)
VAS 1 nasal secretion	No	103	4,44	2,93	,166	,684	,774	149	,440
	Yes	48	4,04	2,90					
VAS2 postnasal secretion	No	103	5,99	3,02	1,947	,165	-,233	149	,816
	Yes	48	6,12	3,39					
VAS3 nasal congestion	No	103	6,18	3,06	,035	,852	,113	149	,910
	Yes	48	6,12	3,25					
VAS4 reduced sense of smell	No	103	2,83	3,26	,628	,429	,363	149	,717
	Yes	48	2,63	3,18					
VAS5 facial pain or pressure	No	103	5,14	3,39	,412	,522	,526	149	,600
	Yes	48	4,83	3,23					
VAS6 sense of fullness in the face	No	103	3,92	3,58	,029	,866	,441	149	,660
	Yes	48	3,64	3,53					
VAS7 headache	No	103	5,17	3,49	,076	,783	1,270	149	,206
	Yes	48	4,40	3,32					
VAS8 toothache	No	103	1,99	3,07	,016	,901	-,207	149	,836
	Yes	48	2,10	2,93					
VAS9 fatigue	No	103	3,95	3,20	,535	,466	,297	149	,767
	Yes	48	3,79	2,99					
VAS10 ear pain or pressure	No	103	2,35	3,12	,631	,428	-1,186	149	,238
	Yes	48	3,01	3,32					
VAS12 halitosis	No	103	1,55	2,38	3,796	,053	-1,530	149	,128
	Yes	48	2,21	2,69					
VAS13 cough	No	103	3,25	3,25	14,078	,000	2,556	115,396	0,012*
	Yes	48	2,01	2,54					

*p<0,05

Results

The study included 150 patients diagnosed with CRSsNP. Of the 150 respondents, 65 were men and 85 are women. The youngest respondent was 18 years old and the oldest was 76 years old. The average age of the respondents was 42.7 years.

A low positive correlation between VAS 1 symptoms (nasal secretions) and LM score for OMC (bilateral) was found (r = 0.184, p =0.024). Furthermore, a low positive correlation was found between the severity of VAS 4 symptoms, i.e. reduced sense of smell and severity of anterior ethmoid sinusitis (r = 0.173, p =0.034), and severity of sphenoid sinusitis (r = 0.180, p =0.027) for unilateral inflammation.

There was a low negative correlation between the severity of facial pain or pressure and the severity of inflammation of the anterior ethmoid sinus (r = -0.207, p =0.011) and the severity of inflammation

of the sphenoid sinus (r = -0.166, p =0.043).

Low negative correlations were also found between the severity of VAS 6 symptoms (sense of fullness in the face) and inflammation of the anterior ethmoid sinus (r = -0.199; p =0.015); between VAS 7 symptoms (headache) and inflammation (LM score) of maxillary sinus (r = -0.179; p =0.029), frontal sinus (r = -0.167; p =0.041), sphenoid sinus (r = -0.214 ; p =0.008) and OMC (r = -0.186; p =0.023); between the severity of VAS 8 symptoms (toothache) and the severity of inflammation of the anterior ethmoid sinus (r = -0.162; p =0.048); between VAS 9 symptoms (fatigue) and severity of anterior ethmoid sinusitis (r = -0.164; p =0.045), and severity of frontal sinusitis (r = -0.231; p =0.04).

In addition, the parametric T test tested differences in symptom severity measured on the VAS scale in patients with unilateral inflammation and patients without unilateral inflammation, which we defined as the diffuse CRS subgroup.

The results of statistical testing (Table 1) did not show statistical differences in severity of subjective symptoms for almost all of the observed symptoms (p> 0.05) in persons with unilateral inflammation and persons without unilateral inflammation. The only difference was found in VAS scores for cough (t = 2.56, p =0.0012). People who do not have unilateral inflammation have a more pronounced cough (M = 3.25) (VAS 13) compared to people who have unilateral inflammation (M = 2.01).

Discussion

CRS is a common disease that can be presented with different clinical symptomatology.[1,2] CRS is often characterized by the disproportion of the clinical picture, radiological imaging, and the severity of symptoms that concern patients. [10, 13-15] The disease may be misdiagnosed or underdiagnosed. Lack of proper diagnostic workout may lead to inadequate treatment, which in the end may lead to more pronounced nasal and pain symptoms in CRS patients and impaired quality of life,[12] Since the prevalence of CRS is around 9-11% in developed countries, the proportion of this problem is also high in the population. Epidemiological studies have confirmed an increased prevalence of allergic rhinitis and asthma in patients with CRS, although the clear role of these comorbidities in the pathogenesis of CRS has not yet been elucidated. [2,15,16] Some studies suggest the presence of a bacterial biofilm (clusters of microorganisms surrounded by glycocalyx that can communicate and are resistant to the effects of antibiotics) as one of the factors exacerbating the disease.[2,5,17] In addition to CRS, biofilm is thought to play a role in other otorhinolaryngological diseases, such as adenoiditis, tonsillitis, and otitis media.[17]

Histopathological mucosa of patients with CRSwNP shows the presence of loose connective tissue, while in CRSsNP the presence of thick collagen fibers is increased.[18] CRSsNP is characterized by fibrosis, thickening of the basement membrane, and subepithelial oedema of the nasal mucosa.[18] In addition to the above histopathological features, patients with CRSwNP are more likely to have more pronounced symptoms, such as hyposmia. Hyposmia occurs because of eosinophilic infiltration of the mucosa, not as a consequence of the presence or size of the polyp itself. [19,20]

Smell impairment has been recognized as an important factor of the quality of life in patients with CRS.[2,20] It has been shown that loss of smell leads to changes in mood, social functioning, appetite, and nutrition and can jeopardize environmental safety.[21] In this study we have tried to find a correlation between CT scan findings and severity of smell related symptoms according to patients. Results of the study showed that patients with greater inflammation extension in the anterior ethmoid and sphenoid sinus had a more reduced sense of smell.

Results have also shown a negative correlation between the pain symptoms (like headache and teeth pain) and tiredness and opacification of anterior ethmoid sinus, which would mean that patients with pronounced anterior inflammation have fewer pain and tiredness symptoms. A low negative correlation between the severity of pain or pressure in the face and the severity of inflammation of the anterior ethmoid sinus may be explained as higher number of inflammatory cells (mast cells and eosinophils) in the mucosa of the ethmoid with more extensive inflammation. These cells release proteases (like tryptase or chymase) which degrade neurokinins, like substance P, which is a pain mediator. Although we analyzed only patients with CRSsNP, more hyperplastic mucosa in the ethmoid may be related to type 2 inflammation, which occurs also in some proportion of patients without nasal polys. It has been found that headache and facial pain is less pronounced in CRSwNP than in CRSsNP, and this finding goes along with the previous hypothesis.

However, these correlations are also very mild (correlation coefficient below 0,4), so the results should be carefully interpreted, and further studies should be done to elucidate these findings. On the opposite, this study has also shown that obliteration of OMC leads to more pronounced nasal symptoms like nasal obstruction and secretion.[22] That finding is in concordance with the presumed pathogenesis of CRS according to which the absence of normal infundibular ventilation and drainage (OMC blockage) leads to long-term inflammation of nasal and sinus mucosa.[2]

Furthermore, results have shown that patients with diffuse CRS have more pronounced cough than those with unilateral disease. That is in concordance with the united airway hypothesis (patients with asthma, COPD, and lower respiratory tract diseases in general) which stresses the importance of controlling upper respiratory tract disease like CRS.[2,23-26] In some patients other co-morbidities which are often found with CRS are responsible for cough like laryngopharyngeal reflux, adenoiditis, COPD or asthma. [2,26] So this could contribute to the expression of this symptom in patients with diffuse CRS also.

Regression analysis that was done in the study has shown that we cannot predict the expression of every single symptom by using objective disease scores (like LM score). However, the expression of symptoms in CRS can inform us about disease control in these patients, and with a VAS score, we can easily assess this important issue.

The strength of the study is a relatively large cohort of patients who are well defined according to the phenotype of the disease, and subjective scores were taken at the moment of objective measure of the disease severity (CT score). Results were analysed to test the difference in the disease severity according to the most recent classification of CRS. The drawback of the study is that we did not analyse the HRQL impairment in our CRS, which may have shown the difference in the disease severity between patients with localized vs. diffuse disease, even though individual symptoms have not been different, except for the cough.

In conclusion, the study has not shown the difference between the severity of individual CRS symptoms in patients with unilateral and diffuse CRS, except for the severity of cough which was more pronounced in patients with diffuse disease. Further research regarding HRQL impairment comparing localized and diffuse disease is needed.

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Sažetak

USPOREDBA JEDNOSTRANOG I DIFUZNOG KRONIČNOG RINOSINUITISA

A. Vrljičak, A. Penezić, T. Gregurić, M. V. Grgić, T. Baudoin i *L. Kalogjera*

Kronični rinosinusitis (KRS) široko je rasprostranjena bolest koja se očituje različitim simptomima. Prema EPOS 2020 smjernicama, KRS karakteriziraju dva ili više simptoma, od kojih bi jedan trebao biti začepljenje nosa, opstrukcija, začepljenost ili sekrecija iz nosa (prednja/stražnja), sa ili bez boli ili pritiska na licu, te smanjenje ili gubitak mirisa koji traje najmanje 12 tjedana.

Unatoč širokoj rasprostranjenosti bolesti, dijagnoza i liječenje KRS-a još uvijek nisu dovoljno razvijeni, pa se mnogim pacijentima i dalje postavlja pogrešna dijagnoza. U ovoj studiji sudjelovalo je 150 pacijenata koji su, prema smjernicama EPOS-a, imali dijagnozu KRS bez nosnih polipa. Svakom bolesniku učinjena je CT snimka paranazalnih sinusa, a svaka snimka evaluirana je prema Lund-Mackay zbroju. Nadalje, pacijenti su ispunili VAS upitnik koji je ispitivao izraženost njihovih simptoma. Cilj ovog istraživanja bio je pronaći povezanost između stupnja upale sluznice i kliničkih simptoma koje je pacijent prijavio.

Naši rezultati pokazali su nisku pozitivnu korelaciju između nazalne sekrecije i Lund-Mackay rezultata za bilateralni OMC. Nadalje, pronađena je niska pozitivna korelacija između smanjenog osjeta mirisa i težine upale u prednjem etmoidnom i sfenoidnom sinusu. Rezultati su pokazali nisku negativnu korelaciju između jačine boli ili pritiska u licu i težine upale prednjeg etmoidnog i sfenoidnog sinusa. Rezultati statističkog ispitivanja nisu pokazali statističke razlike u izraženosti subjektivnih simptoma za gotovo sve uočene simptome u osoba s jednostranom upalom i osoba bez jednostrane upale, osim za kašalj. Osobe koje nemaju jednostranu upalu imaju izraženiji kašalj u odnosu na osobe koje imaju jednostranu upalu. Međutim, te su korelacije vrlo blage i nisu klinički značajne, stoga se ne može reći da raspodjela sinusitisa značajno utječe na pojavu karakterističnih simptoma kod kroničnog rinosinusitisa.

Ključne riječi: *Kronični rinosinuitis; Njuh; Lund–Mackay zbroj; Vizualno-analogna skala (VAS)*