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Original Scientific Paper

ASSOCIATION BETWEEN SYMPTOM SEVERITY AND INTENSITY OF ACUTE PSYCHOLOGICAL DISTRESS IN NEWLY DIAGNOSED PATIENTS WITH CHRONIC RHINITIS AND CHRONIC RHINOSINUSITIS

Nia Naletilić[1], Nives Pondeljak[2], Liborija Lugović-Mihić[2], Vladimir Trkulja[3] and Livije Kalogjera[1]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;
[2]Department of Dermatovenereology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;
[3]Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia

SUMMARY – Chronic rhinitis and rhinosinusitis (CR and CRS) can lead to impairment of the health-related quality of life (HRQL) with higher psychological perceived distress, resulting in disease worsening and poor treatment outcomes. W aimed to evaluate the potential association between disease severity and HRQL impairment with the perceived acute psychological distress in newly diagnosed CR/CRS patients. This single-center cross-sectional study included otherwise healthy consecutive adults with newly diagnosed CR/CRS (European position paper on rhinosinusitis and nasal polyp criteria and International Consensus Statement on Allergy and Rhinology – Allergic Rhinitis criteria or non-allergic rhinitis), who were evaluated for CR/CRS symptom severity and HRQL (Sino Nasal Outcome Test 22 [SNOT-22], visual analog scale [VAS]) and acute perceived distress (Perceived Stress Scale [PSS]). Principal component analysis (SNOT-22 items, VAS) identified 6 components as CR/CRS severity indicators, i.e,, poor sleep, wakes-up tired, nasopharynx, obstruction, torment and rhinorrhea, which were evaluated for association with PSS score. Of the 63 included patients (20 men, age median 38, range 19-75 years), 27 suffered from CR and 36 from CRS. Upon adjustment for age and sex, higher total SNOT-22 (geometric means ratio [GMR]=1.04, 95% CI 1.01-1.06), higher "torment" (GMR=1.13, 1.04-1.24), higher "poor sleep" (GMR=1.11, 1.02-1.21) and higher "wakes-up tired" (GMR=1.11, 1.01-1.21) scores were each associated with a higher PSS score, overall and consistently in CR and CRS patients. In conclusion, more severe CR/CRS is associated with greater perceived psychological distress already at earlier stages of the disease. Paying attention to patient level of distress and anxiety over time may enable better understanding of the connection between exacerbations, symptom severity and psychological burden of the disease.

Key words: *Chronic rhinosinusitis; Chronic rhinitis; Psychological distress; SNOT-22; Perceived stress scale*

Introduction

Chronic rhinitis (CR) is a disease caused by inflammation of the nasal mucosa, and is often characterized by symptoms of obstruction, hypersecretion, sneezing or itching of the nose lasting for more than 12 weeks *per* year (International Consensus Statement on Allergy and Rhinology [ICAR])[1].

Rhinosinusitis is inflammation of the nasal cavity and paranasal sinuses with the presence of two or more of the following symptoms: nasal congestion or nasal secretion, facial pain, and smell impairment[2,3]. Furthermore, according to the criteria of the European position paper on rhinosinusitis and nasal polyps

Correspondence to: *Prof. Livije Kalogjera, MD, PhD*, Department of Otorhinolaryngology-Head and Neck Surgery, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: kalogjera@sfzg.hr

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(EPOS), endoscopic evaluation is required for a diagnosis of rhinosinusitis[2]. Unlike the acute form, where symptoms last for up to 12 weeks, chronic rhinosinusitis (CRS) lasts for more than 12 weeks, with constant exacerbations, and does not have complete resolution of symptoms[2,4]. Health related quality of life (HRQL) is most often measured by quality of life instruments in the form of questionnaires. The Sino-Nasal Outcome Test (SNOT-22) is the most appropriate questionnaire recommended for HRQL assessment and, in addition to visual analog scale (VAS), for the evaluation of disease and symptom severity in CRS and CR patients[2,5]. Impairment of HRQL drives patients to seek medical attention, which may result in higher perceived psychological distress, eventually leading to disease worsening and poor treatment outcomes. Studies suggest that chronic psychological distress, depression and anxiety may be the leading factors contributing to the severity of the disease and *vice versa*[6-8].

We aimed to evaluate the association between the severity of nasal/rhinosinusitis symptoms and level of HRQL impairment with the level of perceived acute psychological distress in newly diagnosed patients with CR or CRS. We hypothesized that the severity of perceived (acute) psychological test correlates with the severity of HRQL impairment and symptom severity.

Patients and Methods

This single-center cross-sectional study included consecutive adults (august 2018-May 2019) referred to the Department of Dermatovenereology for skin prick testing due to the upper respiratory system disorder suspected to be associated with CR or CRS. All patients had newly diagnosed CR/CRS in accordance with the EPOS and ICAR criteria[1,2], and were evaluated for symptom severity using SNOT-22, VAS for different symptoms, as well as for the level of perceived distress using the Perceived Stress Scale (PSS). The study was approved by the institutional Ethics Committee.

Subjects

Inclusion criteria were age ≥18 years; signed informed consent; and upper respiratory tract symptoms lasting >4 weeks with SNOT-22 score >3 for at least two of the major CR/CRS symptoms[2]. For clinical evaluation and classification of patients into the CR or CRS group, diagnosis was made in concordance with the EPOS criteria[2]. Patients that fulfilled CRS criteria were additionally endoscopically evaluated. Those with at least one positive endoscopic sign and Lund-Kennedy[9] score ≥2 were considered to suffer from CRS[2,10,11]. Patients suffering from asthma, aspirin-induced respiratory disease, malignant diseases or any chronic systemic disease, cystic fibrosis or ciliary dyskinesia, as well as patients with a known history of or an ongoing psychiatric disorder were excluded.

Instruments

The SNOT-22[12] is a self-reporting 22-item questionnaire addressing a range of individual sinonasal symptoms, as well as emotional and psychological functioning. SNOT-22 tackles 5 specific domains: nasal symptoms, extranasal symptoms, ear/facial symptoms, psychological/emotional dysfunction, and sleep dysfunction[12]. VAS were implemented to evaluate the intensity of nasal congestion, anterior rhinorrhea, postnasal drip, smell impairment, and facial pain/discomfort[5]. PSS is a 10-item self-reporting instrument quantifying the acute self-perceived psychological stress (addressing cognitive, emotional and behavioral domains of distress)[13].

Data analysis

Since individual items in SNOT-22 and VAS evaluated a number of similar CR/CRS severity aspects, principal component analysis (PCA) was performed to reduce dimensionality. Total SNOT-22 score and components identified by PCA were then used as indicators of CR/CRS severity. They were separately evaluated for a possible association with the PSS score by fitting generalized linear models to ln-transformed scores (maximum likelihood estimation with Gauss-Hermite quadrature). Each model included age, sex, type of disease (CR or CRS), indicator of disease severity, and CR/CRS severity indicator interaction to yield the 'effect' of disease severity indicator on PSS for the overall cohort and separately in CR and CRS patients. Effects were expressed as geometric mean ratios (GMR). Confidence intervals for the estimates derived from the interaction term are adjusted for multiplicity by the simulation method. The p-values for the effect in the entire cohort were *post-hoc* adjusted for multiplicity by the adaptive step-down Holm method.

Results

A total of 63 patients were included, 27 with CR and 36 with CRS (Table 1). Principal component analysis (PCA) identified the following 6 components: poor sleep (subsumes lack of a good night sleep,

Table 1. Subject characteristics, overall and by condition

	All	CR	CRS	d (CR-CRS)
N	63	27	36	---
Age (years)	38 (29-55; 19-75)	42 (28-60; 19-75)	38 (19-51; 22-69)	0.280
Men	20 (31.7)	7 (25.9)	13 (36.1)	-0.723
SNOT-22 score	43 (28-59; 9-82)	51 (36-64; 13-82)	40 (28-58; 9-82)	0.295
PSS score	19 (15-23; 7-39)	19 (15-24; 7-39)	18.5 (16-23; 8-29)	0.125
PCA component:				
Poor sleep	-0.30 (-0.68, 0.82; -1.69, 2.18)	-0.30 (-0.68, 0.79; -1.69, 2.06)	-0.26 (-0.70, 0.86; -1.62, 2.18)	0.030
Wakes-up tired	-0.11 (-0.79, 0.89; -2.22, 2.35)	0.01 (-0.64, 1.28; -1.40, 1.76)	-0.36 (-0.85, 0.54; -2.22, 2.35)	0.396
Nasopharynx	-0.08 (-0.73, 0.72; -1.68, 2.33)	-0.01 (-0.77, 0.72; -1.55, 2.33)	-0.24 (-0.73, 0.71; -1.68, 1.93)	0.230
Obstruction	0.10 (-0.88, 0.89; -2.06, 1.82)	0.33 (-0.59, 0.61; -1.85, 1.51)	-0.06 (-1.23, 0.96; -2.06, 1.82)	0.139
Torment	-0.15 (-0.75, 0.62; -2.35, 2.69)	0.17 (-0.72, 1.14; -2.35, 2.28)	-0.25 (-0.81, 0.31; -1.63, 2.68)	0.250
Rhinorrhea	0.08 (-0.55, 0.75; -2.95, 1.55)	-0.24 (-0.85, 0.36; -2.95, 1.26)	0.48 (-0.48, 1.09; -2.00, 1.55)	-0.556

SNOT-22 = sino-nasal outcome test; PSS = perceived stress scale; CR = chronic rhinitis; CRS = chronic rhinosinusitis. Data are median (Q1-Q3, min-max) or count (percent). Standardized differences (d) between CR and CRS patients are also shown. For components identified in the principal component analysis (PCA), higher coefficient indicates more pronounced difficulties.

waking-up during night, difficulties falling asleep); wakes-up tired (subsumes fatigue, waking-up tired, reduced productivity and concentration); nasopharynx (subsumes cough, postnasal discharge, thick nasal discharge, ear fullness and dizziness); obstruction (subsumes obstructed nose, and VAS for nasal obstruction, thick discharge and postnasal discharge); torment (subsumes facial pain, frustration and sadness); and rhinorrhea (subsumes need to blow nose, sneezing and runny nose) (Table 2). Compared to CRS group, patients suffering from CR were slightly older, had somewhat higher total SNOT-22, higher PSS score, and higher scores of all of the PCA-identified components (standardized differences between 0.125 and 0.396), except for "rhinorrhea", which was more pronounced in CRS patients, who were also more commonly men (Table 1). With adjustment for sex and age, higher total SNOT-22 (GMR 1.04, 1.01-1.06) and higher "torment" (from PCA) (GMR 1.13, 1.04-1.24) were each associated with higher PSS score (Table 3). A similar trend was observed for "poor sleep" and "wakes-up tired", whereas other indicators of disease severity were apparently not associated with PSS (Table 3). These associations were consistent in CR and CRS patients with adjustment for higher PSS score (Table 3).

Discussion

In patients suffering from chronic diseases, distress and anxiety are common and are associated with a more severe disease burden and exacerbations[14,15]. In patients with a long-term history of CR/CRS, pain – particularly facial pain and earache (two of the SNOT-22 items) – is clearly associated with a more pronounced impairment of HRQL[6,16]. Kara *et al.*[17] demonstrated association of emotional instability and psychological dysfunction with worse scores on the sleep and psychological subscales of SNOT-22 in CRS patients. The prevalence of anxiety is increased in CRS patients and comorbid anxiety is associated with worse preoperative quality of life (QOL) and reduced QOL improvement following endoscopic

Table 2. Summary of the Principal Component Analysis

	Principal components identified					
SNOT-22/VAS data	Poor sleep	Wakes-up tired	Nasopharyngeal issues	Nasal obstruction	Torment	Rhinorrhea
Needs to blow nose	-0.170	0.014	0.019	0.090	0184	**0.836**
Sneezing	0.073	0.257	0.082	-0.038	-0.216	**0.749**
Runny nose	0.155	-0.115	0.083	0.047	-0.041	**0.842**
Obstructed nose	0.128	0.442	0.119	**0.619**	-0.235	0.190
Cough	0.301	0.156	**0.658**	0.190	-0.063	0.110
Postnasal discharge	0.226	0.159	**0.628**	0.321	0.402	-0.063
Thick nasal discharge	0.050	0.258	**0.514**	0.335	0.150	0.308
Ear fullness	-0.290	0.306	**0.681**	0.058	-0.105	0.091
Dizziness	0.133	0.032	**0.834**	-0.134	0.084	0.021
Facial pain	-0.402	0.248	0.165	0.343	**0.636**	-0.016
Difficulties falling asleep	**0.812**	0.280	0.115	0.035	0.037	-0.047
Wakes-up during night	**0.813**	0.261	0.140	0.207	0.138	0.001
Lack of good night sleep	**0.796**	0.274	0.069	0.222	0.216	0.151
Wakes-up tired	0.408	**0.727**	0.255	0.144	0.074	0.077
Fatigue	0.400	**0.656**	0.331	.048	0.134	0.128
Reduced productivity	0.160	**0.804**	0.132	0.025	0.291	0.013
Reduced concentration	0.321	**0.725**	0.089	-0.135	0.374	-0.038
Frustrated	0.203	0.251	0.024	-0.246	**0.760**	0.030
Sad	0.405	0.212	0.022	-0.149	**0.702**	-0.044
Nasal obstruction (VAS)	0.104	0.083	-0.083	**0.895**	-0.120	-0.060
Thick discharge (VAS)	0.138	-0.274	0.275	**0.709**	-0.037	0.260
Postnasal discharge (VAS)	0.169	-0.074	0.454	**0.587**	0.396	-0.210
% variance explained 74.2%	14.3%	14.1%	12.9%	12.1%	10.5%	10.4%

In the 1st run, the SNOT-22 item "loss of smell" and visual analog scale (VAS) for "loss of smell" both had Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy <0.5 and were excluded; in the 2nd run, VAS for "facial pain" had KMO <0.5 and was excluded; in the 3rd run, SNOT-22 items "ear pain" and "embarrassed" had a communality <0.5 and were excluded; the remaining SNOT-22 and VAS items met the required criteria (overall KMO 0.685, all communalities >0.5 and factor loadings >0.5).

Table 3. Summary of the multivariate analysis of the association between PSS score (higher value= higher perceived stress) and indicators of the severity of rhinitis/rhinosinusitis for all patients and separately in patients with CR and CRS*

	GMR (95% CI)	Raw p	Adjusted p	GMR (adjusted 95% CI)
SNOT-22 score (by 5 points)				
All patients	1.04 (1.01-1.06)	0.0015	0.0060	
CR patients				1.04 (1.00-1.08)
CRS patients				1.03 (1.00-1.07)
Poor sleep				
All patients	1.11 (1.02-1.21)	0.0168	0.0672	
CR patients				1.10 (0.95-1.28)
CRS patients				1.12 (0.98-1.28)
Wakes-up tired				
All patients	1.11 (1.01-1.21)	0.0257	0.1028	
CR patients				1.18 (1.01-1.39)
CRS patients				1.03 (0.91-1.18)
Nasopharynx				
All patients	1.01 (0.92-1.10)	0.8990	1.0000	
CR patients				1.00 (0.86-1.16)
CRS patients				1.01 (0.88-1.17)
Obstruction				
All patients	0.95 (0.86-1.05)	0.2889	0.8667	
CR patients				0.92 (0.76-1.11)
CRS patients				0.98 (0.87-1.10)
Torment				
All patients	1.13 (1.04-1.24)	0.0070	0.0280	
CR patients				1.13 (0.98-1.31)
CRS patients				1.13 (0.98-1.31)
Rhinorrhea				
All patients	1.01 (0.92-1.11)	0.8015	1.0000	
CR patients				0.94 (0.80-1.11)
CRS patients				1.08 (0.95-1.24)

*A separate model was fitted to ln-transformed PSS scores for each of the indicators of severity of CR/CRS: type of disease (CR/CRS), symptom severity indicator, age, sex, and disease-severity indicator interaction. The effect of severity indicator in CR or CRS was derived from the interaction term (CIs adjusted for multiplicity). The raw p-values for the overall effects were *post-hoc* adjusted for multiplicity by the adaptive step-down Holm method; effects are expressed as GMR; GMR = geometric mean ratios; PSS = perceived stress scale; CR = chronic rhinitis; CRS = chronic rhinosinusitis; CI = confidence interval

sinus surgery[18]. Although a number of studies addressed the problem of distress in CR/CRS, in particular chronic perceived distress, most were focused on patients with a long history of the disease and on chronic distress instruments[6]. Duration of symptoms (i.e., history of the disease) has been typically addressed as a confounding factor in such studies, but newly diagnosed CR/CRS patients have been rarely addressed as a population of interest[19]. The present study was specific in that it was focused on patients

with newly diagnosed CR or CRS and evaluated the relationship between the severity of acute distress and symptom severity and HRQL impairment early in the course of the disease.

Our results did not show statistically significant difference in the severity of respiratory symptoms between the CR and CRS groups. Nevertheless, compared to CRS group, patients suffering from CR had somewhat higher total SNOT-22, higher PSS score and higher scores of all the PCA-identified components, except for rhinorrhea, which was more pronounced in CRS patients. The reason for these results could be the nature of patient recruitment into the study. Patients were primarily addressed to the skin prick test due to their respiratory symptoms. In this case, according to our results, the share of patients with positive skin prick test within the CRS group was 45.16%, while in the CR group it was 65.62%. We can hypothesize that this higher percentage of atopic patients within the CR group was responsible for those slightly higher scores of PCA-identified components. It is important to emphasize that all data were collected during the period of about 6 months (beginning in late August and ending in early March). In this period, given the pollen calendar, we can speculate that allergens such as *Ambrosia artemisiifolia* and dust mites were present in high concentrations, while allergens of inhaled pollen were not present. Among those with positive skin prick test, the majority (52.78%) were positive for one of the dust mite allergens and 42.86% were allergic to *Ambrosia artemisiifolia*. We can also assume that higher scores of the PCA-identified components correlated to somewhat higher SNOT-22 scores and disease severity.

Furthermore, PSS in long term suffering patients may differ from that in newly diagnosed patients due to changing treatment protocols over years and development of coping mechanisms. Longitudinal studies on this topic have been sparse. The present observations suggest that CR/CRS convey a certain level of distress already earlier in the course of the disease, when patients generally do not seem to deflect from the 'rest of the population' in this respect.

Limitations of the study

The present study was limited by a modest single-center cross-sectional sample that included only patients free of other comorbidities, which may affect the subjective outcomes. Exclusion of relevantly comorbid patients was intended to alleviate assessment of the relationship specifically between CR/CRS and the level of distress, which would otherwise need to be achieved through complex statistical models.

Another limitation of the study was the lack of specific sample categorization in CR and CRS groups. In other words, we did not conduct complete and additional diagnostic procedures to divide CR and CRS patients into infectious, allergic, or non-infectious non-allergic CR, and CRS with or without nasal polyps. Categorization of the sample would bring more detailed insight into the effect of perceived (acute) psychological stress on the severity of HRQL impairment and symptom severity specifically for mentioned categories. On the other hand, in the case of categorization, complex statistical analysis would not be possible to perform for the mentioned subgroups due to excessive variability within the sample that would probably end with too small final number of respondents in subgroups. This number of respondents would be too small to show statistically significant differences in investigated parameters. Larger study would be needed in this case.

Conclusion

Despite the limited sample size of otherwise generally healthy CR/CRS patients, the present observations suggest that the more pronounced CR/CRS is associated with greater perceived distress already at the earlier stages of the disease. Monitoring of both disease evolution and levels of distress and anxiety over time would help understand the interplay between the frequency of exacerbations, changes of symptom severity over time, and accompanying psychological burden, likely a bidirectional relationship.

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Sažetak

POVEZANOST TEŽINE SIMPTOMA I INTENZITETA AKUTNOG PSIHOLOŠKOG DISTRESA U NOVODIJAGNOSTICIRANIH BOLESNIKA S KRONIČNIM RINITISOM I KRONIČNIM RINOSINUSITISOM

N. Naletilić, N. Pondeljak, L. Lugović-Mihić, V. Trkulja i *L. Kalogjera*

Kronični rinitis i kronični rinosinusitis (KR i KRS) mogu poremetiti sa zdravljem povezanu kvalitetu života (*health-related quality of life*, HRQL) kroz višu razinu percipiranog psihološkog distresa, što dovodi do pogoršanja bolesti i loših ishoda liječenja. Cilj istraživanja bio je procijeniti moguću povezanost težine bolesti i poremećaja HRQL s percipiranim akutnim psihološkim distresom u novodijagnosticranih bolesnika s KR/KRS. U ovu presječnu studiju provedenu u jednom centru uključene su uzastopne inače zdrave odrasle osobe s novodijagnosticiranim KR/KRS (*European position paper on rhinosinusitis and nasal polyp criteria and International Consensus Statement on Allergy and Rhinology – Allergic Rhinitis criteria or non-allergic rhinitis*), kod kojih je procijenjena težina simptoma KR/KRS i HRQL (*Sino Nasal Outcome Test 22* [SNOT-22], vizualna analogna ljestvica [*visual analog scale*, VAS]) te akutni percipirani distres (Ljestvica percipiranog stresa, *Perceived Stress Scale* [PSS]). Analiza glavnih sastavnica (stavke *SNOT-22*, VAS) identificirala je 6 sastavnica kao pokazatelje težine KR/KRS, tj. slab san, osjećaj umora pri buđenju, nazofarinks, opstrukciju, bolnost i rinoreju, koje su procijenjene na povezanost sa zbrojem PSS. Od 63 uključenih bolesnika (20 muškaraca, medijan dobi 38, raspon 19-75 godina) 27 ih je imalo KR, a 36 ih je imalo KRS. Nakon prilagodbe na dob i spol utvrđeno je da su viši ukupni zbroj SNOT-22 (omjer geometrijskih srednjih vrijednosti, *geometric means ratio* [GMR]=1,04; 95% CI 1,01-1,06), viša razina bolnosti (GMR=1,13; 1,04-1,24), viša razina slabog sna (GMR=1,11; 1,02-1,21) i viša razina osjećaja umora pri buđenju (GMR=1,11; 1,01-1,21) svaki povezani s višim zbrojem na PSS, sveukupno i jednako tako u bolesnika s KR i onih s KRS. Zaključno, teži oblik KR/KRS udružen je s višim percipiranim psihološkim distresom već u ranijim stadijima bolesti. Pridajući pozornost razini distresa i anksioznosti kod bolesnika kroz vrijeme može doprinijeti razumijevanju povezanosti između pogoršanja bolesti, težine simptoma i psihološkog opterećenja ove bolesti.

Ključne riječi: *Kronični rinosinusitis; Kronični rinitis; Psihološki distres; SNOT-22; Ljestvica percipiranog stresa*