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Self-reported Cough in Chronic Rhinosinusitis

Samoocena kašlja pri kroničnem rinosinuzitisu

ABSTRACT

KEY WORDS: cough, chronic rhinosinusitis, retro nasal drip, congestion, upper airway cough syndrome

BACKGROUNDS. Cough is an essential protective reflex of the respiratory tract, which is triggered by various chemical or mechanical stimuli. It can be caused by acute or chronic upper aerodigestive tract conditions, alone or in combination. Cough can be initiated voluntarily from the cortical system or as an involuntary reflex. The upper airway cough syndrome (i.e., previously post nasal drip syndrome) has been identified as the most common cause of acute and chronic cough. This syndrome can present in chronic rhinosinusitis, which is a common disease marked by an inflammation of the sinonasal mucosa. However, to our best knowledge, the association between chronic rhinosinusitis and cough has not been quantified yet. This paper aims to determine whether there is difference in self-reported cough between patients with chronic rhinosinusitis and the control group. METHODS. Cough was self-reported on the Likert scale with values 0–5 derived from the 22-item sino-nasal outcome test (SNOT-22). The analysis included patients with chronic rhinosinusitis and patients without chronic rhinosinusitis with the latter being the control group. RESULTS. The study included 477 patients with chronic rhinosinusitis and 73 controls. The median self-reported score for controls was 0 (interquartile range (IQR) 1) and 3 (IQR 3), $p < 0.001$ for chronic rhinosinusitis was. Even the ratio of those who cough is higher in the chronic rhinosinusitis group (23.3% vs. 72.1%), $p < 0.001$. This study has shown a difference in self-reported cough depending on whether chronic rhinosinusitis is present ($x^2(1,N=550)=66.9$, $p<.00001$). DISCUSSION. This study underlines the intricate relationship between nasal symptoms in chronic rhinosinusitis and cough. Now that this relationship has been statistically confirmed, one can further question which specific chronic rhinosinsusitis symptoms (from the sino nasal outcome test questionnaire) are related to cough. A symptomatic evaluation of cough in the presence of chronic rhinosinusitis could be developed.

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IZVLEČEK

KLJUČNE BESEDE: kašelj, kronični rinosinuzitis, izcedek iz nosu, nosna kongestija, sindrom zgornjih dihalnih poti

IZHODIŠČA. Kašelj je eden izmed osnovnih zaščitnih refleksov respiratornega trakta. Sproži ga vrsta kemičnih ali mehanskih sprememb na sluznici dihal. Po trajanju ga delimo na akutni in kronični kašelj. Redko se kašelj pojavlja samostojno ali v povezavi z drugimi boleznimi, kašljamo pa lahko tudi hoteno ali nehoteno (refleksno). Klinični sindrom kašlja v zgornjih dihalnih poteh so včasih enačili z izcedkom iz nosu navzad. Ta sindrom naj bi bil eden najpogostejših vzrokov akutnega in kroničnega kašlja. Kronični rinosinuzitis je pogosta bolezen, ki jo zaznamuje vnetje sluznice nosu in obnosnih votlin. Izcedek navzad je eden pogostih simptomov kroničnega rinosinuzitisa. Povezava pojavnosti kašlja pri bolnikih s kroničnim rinosinuzitisom in kontrolah še ni bila ustrezno raziskana. METODE. Članek opisuje pojavnost in oceno obremenjenosti s kašljem pri bolnikih s kroničnim rinosinuzitisom in kontrolah. Kašelj je bil ocenjen s pomočjo Likertove lestvice z vrednostmi 0–5. Pri tem smo uporabili uveljavljen vprašalnik 22-predmetni test sinusno-nosnega izvida (angl. *22-item sino-nasal outcome test*, SNOT-22). REZULTATI. V raziskavi je sodelovalo 550 preiskovancev (447 s kroničnim rinosinuzitisom in 73 kontrol). Mediana ocen kašlja je bila 0 (kvartilni razmik (angl. *interquartile range*, IQR) 1) pri kontrolah in 3 (IQR 3) pri bolnikih s kroničnim rinosinuzitisom. Tudi delež tistih, ki kašljajo, je bil pri kroničnem rinosinuzitisu višji (72,1 % proti 23,3 %). S tem smo dokazali statistično pomembno razliko v pojavnosti kašlja pri bolnikih s kroničnim rinosinuzitisom. RAZPRAVA. Raziskava poudarja razmerje med nosnimi simptomi pri kroničnem rinosinuzitisu in kašljem. Smiselno bi bilo raziskati tudi vpliv ostalih simptomov, ocenjenih z vprašalnikom SNOT-22, za razvoj ustreznejših diagnostičnih in terapevtskih načinov za kroničen kašelj, povezan s kroničnim rinosinuzitisom.

BACKGROUNDS

Cough is an essential protective reflex of the respiratory tract. Its prevalence in the average population in Europe and the USA has been recorded to be 9–33%. It is used to clear the larynx, trachea, and large bronchi of secretions such as mucus, noxious substances, foreign particles, or infectious organisms *(1)*. It is a process triggered by various inflammatory or mechanical changes, typically occurring in the upper airways. Most episodes of cough are a physiological response to stimuli and tend to be self-limiting. Even so, it can also be a symptom of an underlying disease such as pneumonia, lung cancer or laryngeal cancer *(2)*.

Acute cough (lasting between 1–3 weeks) is a typical symptom of a cold, which is experienced by the majority of the population. In this scenario, cough is an essential symptom for the resolution of the cold, and in preventing further complications. This crutial function is illustrated when looking at patients with neuromuscular disease. The latter have a weakened cough, meaning a decreased airway clearance, predisposing these patients to respiratory infections. Thus, it is recommended that these patients receive airway clearance support *(3)*. This highlights the possible consequences of a dysfunctional cough mechanism.

In spite of this symptom's importance, a chronic persistant cough can be the manifestation of an underlying disease. It can be associated to vomiting, urinary incontinence, syncope, tiredness, rib fractures and depression *(1, 4, 5)*. This significant decrease in the health related quality of life of the affected patients makes it even more important to find the underlying cause and treat the symptom accordingly.

Chronic rhinosinusitis (CRS) is an upper airway condition that is often related to the upper airway cough syndrome (UACS), which is one of the leading causes of chronic cough *(1, 6)*. UACS includes any rhinosinus conditions associated with cough. The precise association between CRS and cough has not been quantified to our knowledge. This article presents the general pathophysiology of cough and its pathogenesis in CRS to emphasize the significance of cough in CRS. It aims to determine the influence of the presence of CRS on self-reported cough in a retrospective controlled clinical study. We predict that there will be higher cough scores in CRS patients rather than in those from the control group.

Cough Pathogenesis

Cough is characterized by three discinct phases, which are a deep inspiratory phase, an intense, forced expiratory phase against a closed glottis, and a final expiratory phase with the glottis opening *(1)*. An effective cough is marked by the capacity to push gas through the airways, and interactions between the flowing gas and the mucus lining. This process is dependant firstly on the ability of the respiratory muscles to increase intrathoracic pressure and compress the airways to push air outside and secondly on the effective closure of the glottis to maintain the pressure gradient in the airways *(3)*.

Cough can be initiated voluntarily from the cortical system or involuntarily as a reflex. The latter depends on sensory afferents from cough receptors into the vagus nerve *(1)*. Both mechanical and chemical cough receptors converge to initiate a cough response *(3)*.

The sensory nerves are characterized by their conduction and their specific triggers. For instance, some fibers (C fiber receptors) are activated predominantly by chemical stimuli (e.g., hydrogen ions, capsaicin, bradykinin), while others have a wider variety of triggers such as acidity/alkalinity, mechanical stimulation, pulmonary congestion, or other modifications of pulmonary compliance (rapid-acting receptors) *(1)*. This array of possible cough triggers and sensory pathways complicate the identification of the cough's etiology.

Cough Etiology

Cough can be further separated into acute and chronic according to the duration of the symptom. Acute cough lasts between 1–3 weeks, typically due to an upper respiratory tract viral infection, pneumonia or pulmonary emboli *(7)*. Sub-acute cough lasts between 3–8 weeks, and chronic cough persists for more than 8 weeks *(1)*. The diagnosis can be made by exploring other associated symptoms.

The most common causes of chronic cough are referred to as the triad of cough and include UACS, asthma and gastro-oesophageal reflux disease (GERD) *(1, 5, 8)*. One study showed that 94% of chronic cough cases are caused by one of these three phenomena, either alone or in combination. Asthma and GERD are specific disorders that have straightforward diagnostic procedures. At the same time, UACS encompasses any condition of the upper airways presenting with cough. UACS has been named the most common cause of acute and chronic cough. Indeed, in 87% of patients consulting American physicians the cough was attributed to rhinological causes *(5)*. Several clinical and epidemiological studies agree that UACS is the most commonly identified

cause of chronic cough *(8, 9)*. Although this has been named a specific syndrome since 2006, there is minimal consensus concerning its exact causes, mechanisms, and management *(8, 10, 11)*.

Upper Airway Cough Syndrome

UACS encompasses all nasopharyngeal conditions (allergic rhinitis, rhinosinusitis, laryngopharyngitis, etc.) that present with cough *(8)*. It includes disease of the nose or paranasal sinuses, anatomic abnormalities of the respiratory tract, and pharyngeal disease *(11)*. There is no single pathognomonic finding in this syndrome, which complicates its identification. The general clinical presentation of UACS includes several common complaints reported by the patients. These are as follows: the sensation of something draining in the back of the throat, a need to clear the throat, a tickle in the throat, nasal congestion or nasal discharge. Hoarsness can also be present aswell as a history of a previous upper respiratory illness. The diagnosis can be made by identifying one or more of the following: drainage in the posterior pharynx, throat clearing, nasal discharge, cobblestone appearance of the oropharyngeal mucosa, or mucus in the oropharynx.

These clinical findigs are linked to high specificity but low sensitivity, making their presence difficult to interpret. *(8)*. Some researchers even stipulate that the presence of clinical manifestations is not compulsory. There is still a lot of debate regarding it's validity *(11)*. As a consequence, the diagnosis of this syndrome is made by considering a combination of criteria including symptoms, physical examination, radiographic findings and the response to specific therapy *(9)*.

The exact pathogenesis of UACS is not yet elucidated. The current theories are the following *(14)*:

- post nasal drip stimulates cough receptors in the hypopharynx or larynx,
- direct irritation and sensitization of the cough receptors in the nasal mucosa,
- inflammation and irritation of both the upper and lower airways and
- cough reflex sensitization.

Although UACS is described in many articles, the pathogenesis and diagnosis are still inconsistent. As previously cited, many studies report a high prevalence of UACS. The Japanese respiratory society does not report such a high frequency. They instead propose the categorization of the sinobronchial syndrome (SBS), which they find to be the most common cause of cough together with atopic cough *(12)*. SBS is characterized by a cough related to CRS and chronic lower airway inflammation. In light of this controversy, it seems paramount to investigate the link between cough and CRS more specifically.

Chronic Rhinosinusitis and Cough

CRS is a common condition with a prevalence of 5.5–28% of the population worldwide and 10.9% of Europeans *(14, 15)*. Its prominent marker is the inflammation of the mucosa in the nose and paranasal sinuses *(14)*. The physiological function of the mucosa is to provide a barrier to regulate interactions with the immune system. This will provide tolerance, symbiosis, while also limiting inflammation. Hence, in patients with CRS, there is a dysfunction of this barrier. The hypothesis for the aetiology of this syndrome has signficiantly evolved in the past 15 years. There is a clear role of both environmental and predisposing factors in the host. However, several other components are frequently associated to a worstening of this syndrome such as bacteria, fungus and smoking *(14)*. The pathogenesis of CRS is thus attributed to a combination of environmental triggers and genetic predispositions working together to penetrate this protective barrier. This will induce an immune response through cellular

interactions and various cytokine releases, eventually leading to the diverse phenotype of CRS.

This syndrome can present itself in many ways, and in different severities. Hence, a standard assessment tool is a patient-completed survey to quantify the patient-specific presentations of the disorder and analyze the treatment options. The Sino-Nasal Outcome test (SNOT-22) is commonly used as a validated Quality of Life (QoL) tool in patients with CRS *(16, 17)*. It is a 22 domain score exploring the self-reported severity of different symptoms, both physical and psychological *(17, 18)*.

Rhinosinusitis-associated cough is one of the items reported on the SNOT-22 questionnaire. This symptom is typically categorized as UACS. Nevertheless, there is no consensus regarding upper airway cough syndrome and its link to CRS. The proposed theories of cough in CRS are *(6)*:

- cough reflex hypersensitivity,
- post nasal drip,
- aspirated secretions from the lower airways and
- enhanced sensitivity to environmental factors.

These theories strongly overlap those for cough in UACS, underlining the similarities between the two. The understanding of the lack of objective critera for these syndromes and their relative ambiguity supports the lack of consensus between authors *(19)*.

METHODS

Study Design

The study was designed as a retrospective single-center controlled trial conducted at the Department of Otorhinolaryngology and Cervicofacial Surgery of the University Medical Centre Ljubljana from 2011 to 2021. The National Medical Ethics Committee Slovenia approved the study. Written informed consent was obtained from all individual participants included in the study. There were two study groups: CRS patients and patients without CRS (control group).

Inclusion and Exclusion Criteria

See Table 1.

Diagnosis of Chronic Rhinosinusitis

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines for the diagnosis of CRS are the following: the obligated presence of at least one of these symptoms: nasal blockage/obstruction/nasal discharge (anterior or posterior) and the optional presence of facial pain/pressure or the loss of smell, for more than 14 days, with positive endoscopy or CT signs of the disease in the paranasal sinuses *(14)*.

Table 1. Inclusion and exclusion criteria for the patients and the control groups. CRS – chronic rhinosinusitis, EPOS – European Position Paper on Rhinosinusitis and Nasal Polyposis.

	CRS patients	Controls
Inclusion criteria	patients above 18 years old consulting for rhinological complaints diagnosed CRS (according to the EPOS criteria)	patients above 18 years old consulting for rhinological complaints
Exclusion criteria	diagnosed tumor (benign or malignant) any non-related pathology (identified neoplasia and autoimmune disease of non-CRS related immunodeficiencies such as cystic fibrosis or primary ciliary dyskinesia)	

Quality of Life Related to Chronic Rhinosinusitis (Sino-Nasal Outcome Test Questionnaire)

All patients fitting the inclusion criteria for this study were asked to complete the SNOT-22 questionnaire. The questionnaire had previously been translated, adapted, and validated in the Slovenian language *(20)*. Patients score the severity of 22 items (nasal symptoms and their health-related quality of life) on a Likert scale of 0–5. In addition to the SNOT-22 questionnaire, the age and gender were systematically recorded. Finally, the diagnosis of CRS and its subtypes was documented following EPOS guidelines *(14)*. All patients with CRS were regarded as a uniform group (disregarding the diagnostic categories with/without nasal polyps).

Statistical Analysis

The Kolmogorov-Smirnov and the Shapiro-Wilk test were used to determine the distribution of our data. We found a non-normal distribution of the results. Therefore, we represented our data using medians and interquartile ranges and further analyzed it using non-parametric tests *(21)*.

The next step was to use the Kruskal-Wallis test to compare the distribution of gender in our data. The same was performed for the age distribution analysis.

Cough was graded on a Likert scale of 0–5 according to the SNOT-22 questionnaire. In addition to this, we decided to binarize the cough symptom. A score of 0–1 was graded as »no cough,« and 2–5 signified the presence of a cough. This cut-off point was chosen because, when looking at all our patients, the median of the cough scoring was 2. A binomial test was performed to determine the distribution of patients with and without cough within the two groups.

The Mann-Whitney U test was used to determine the statistical difference between the medians of cough score between our two groups. Then, we used the x^2 test to determine the difference in binarized cough between the groups. A p-value of < 0.05 was considered statistically significant. All statistical analyses were done using the SPSS statistics program version 27 (IBM, Armonk, USA).

RESULTS

The patient characteristics for our study are shown in table 2. A total of 550 patients participated in our study. 477 had CRS and 73 were controls. There was no statistically significant difference between the genders or across age disctibution ($p > 0.05$) in either of the groups.

In the 73 patients from the control group, the median self reported sino-nasal outcome test (SNOT) score was 9 (interquartile range (IQR) of 24). In the 477 CRS patients it was 53 (IQR of 30). These results indeed showed a significant statistical difference ($p > 0.05$). The exact difference between the two medians is 44, this represents a 40% increase in the total SNOT score (the range is from 0–110 points). The IQR of the total SNOT score was 24 for the control group and 30 for the CRS patients. Concerning the specific cough SNOT scores, the median was 0 (IQR 1) for the control group and 3 (IQR 3) for the CRS patient groups. Again, showing a statistically significant difference ($p < 0.05$). The number of people in the control group who had a cough score higher than 1 was 17 (23.3%) versus 56 who reported a score of 0 or 1 (76.7%). In the CRS patients, 344 reported a cough score higher than 1 (72.1%) and 133 equal to or less than 1 (27.9%). A statistically significant difference ($p < 0.05$) was found between the two diagnostic groups, and in the cough versus no cough categories, with a result of $x^2(1,N=550)= 66.9$, $p<.00001$. The IQR was 1 for the control group and 3 for the CRS patients, reflecting a larger range of cough scores in the latter group.

Table 2. Baseline characteristics of the patients. CRS – chronic rhinosinusitis, N – number of patients, SNOT-22 – 22-item Sino-nasal Outcome Test, Mdn – median value, IQR – inter quartile range.

	Controls (N=73)	CRS patients (N=477)	p-value[a]
Gender			
Male (n, %)	35 (47.9%)	274 (57.4%)	0.128[b]
Female (n, %)	38 (52.1%)	203 (42.6%)	
Age			
Mdn years; IQR	42; 27	51; 23	0.384[b]
SNOT-22			
Mdn score; IQR	9; 24	53; 30	<0.001[b]
Cough score[c]			
Mdn score; IQR	0; 1	3; 3	<0.001[b]
Yes (n, %)	17 (23.3%)	344 (72.1%)	<0.001[b]
No (n, %)	56 (76.7%)	133 (27.9%)	
p-value[a]	<0.001[d]	<0.001[d]	

[a] p-value < 0.05 denotes a statistically significant difference
[b] Mann-Whitney U test
[c] the specific score given to the symptom of cough on the SNOT-22 questionnaire
[d] Binominal test

DISCUSSION

A significant difference between SNOT scores of both groups was observed. This reflects a higher severity and frequency of symptoms in CRS patients, which translates to a lower health related QoL. The same is seen concerning the specific cough scores. The higher IQR for cough in CRS patients (3 points) mirrors the heterogeneity of the severity of these symptoms, contrasting the IQR of 1 point in control groups. Both the general SNOT score and the specific cough score show that there are more symptoms present in patients with CRS and are reported to be more severe. By performing a x^2 test, we can confidently say that our data supports our hypothesis that CRS patients report more severe cough than other patients.

CRS was historically connected to cough, but according to the EPOS 2020, the diagnosis is not associated with cough unless pediatric CRS is diagnosed *(6, 14)*. Yet, it is one of the domains of a widely used QoL questionnaire for CRS, SNOT-22 *(18)*. To our best knowledge, no published studies examine the exact relationship between CRS and cough or compare the symptom of cough in patients with or without CRS. We set up a study to compare the self-reported cough score in controls and CRS patients. We had previously established a valid diagnosis of CRS using the EPOS 2020 criteria. Our control group consisted of patients who did not have CRS. We have opted for a self-reported cough score due to the lack of a simple objective cough evaluation scheme. Morevorer, it has been previously established that cough significantly deteriorates the QoL *(22)*. Consequently, the use of the SNOT-22 questionnaire seems adequate. The use of the Likert scale allowed us to compare quantifiable results. We confirmed that self-reported cough is present in a higher proportion of patients with CRS compared to patients without CRS, and that cough has a more considerable negative impact on the QoL. This

study also implies a relationship between CRS and cough. Especially since the ratio of subjects with cough is higher in the CRS group.

Cough is one of the most common symptoms worldwide, often associated with acute, self-resolving conditions. Yet, it can be chronic and represent a health burden for the affected subjects. Contrary to asthma and GERD, the two other most common causes of chronic cough, UACS does not have some specific, objective diagnostic criteria *(5, 14)*. Previous research observes that this diagnosis is broad and is made with any upper airway symptoms. These are associated with a multitude of diseases affecting the upper airway. Our study provided an insight on the association between CRS and cough. This is important as CRS is a heterogeneous syndrome and should perhaps be considered individually when associated with cough rather than be associated with an equally heterogeneous syndrome such as UACS. Perhaps we should rethink the classification of UACS into smaller, more specific diagnoses.

The shortcomings of our study begin with the possible overestimation of patient-reported cough scores (SNOT-22). This starts with the problem of exact cough measurement. The SNOT-22 questionnaire is a subjective estimation of the severity of symptoms, meaning that it depends on an individual's personal evaluation of the symptom. Moreover, both the control groups and the CRS patients were consulting the ear, nose, and throat (ENT) clinic for rhinological complaints. We therefore cannot generalize our data to the general population since we do not represent CRS patients with mild symptoms who do not necessarily seek medical care *(12)*. Similarly, we placed all CRS subtypes in one single category. Perhaps there are notable differences in the incidence of cough between those groups that cannot be observed with our present methods. Although uncommon, it is important to consider that a psychological aspect may play a role in the representation of cough *(4)*. It is especially prevalent in CRS patients, where psychological comorbidities are common, and can be associated with pain catastrophization, leading to worsened health-related QoL for those specific patients *(23)*. It could be interesting to record possible psychiatric comorbidities in those patients. Finally, our study does not differentiate cough in terms of duration. We assumed that patients had a chronic cough. However, the SNOT-22 questionnaire explicitly asks subjects about the last 14 days. It is also vital to mention cultural differences when evaluating symptoms *(24)*. Hence, these results are not generalizable to any population as most of the patients were Slovenian. To lessen score exaggeration and acquire a more generalizable set of data, it would be essential to apply a population-based method with a more heterogeneous group of people. Nonetheless, our methods provided sufficient data and showed significant differences in cough between both the controls and the CRS patients.

This study has shown a difference in self-reported cough depending on whether CRS is present or not. This confirms the broad relationship between the symptom of cough and CRS and draws attention to the ambiguity of the UACS as an endpoint diagnosis.

Comparing self-reported cough in the control group and in patients with CRS has shown a higher cough score and a higher ratio of cough in the CRS group. Our study underlines the intricate relationship between nasal symptoms in CRS and cough. One can now wonder which symptoms graded on the SNOT-22 questionnaire are related to cough and whether there is a decrease in self-reported cough and well-controlled CRS. In the long term, a specific symptomatic evaluation and treatment for chronic cough associated to CRS could be developed.

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