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Cognitive dysfunction associated to pain and quality of life in chronic rhinosinusitis

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Abstract

Background—Cognitive dysfunction and its relationship to both pain and disease-specific quality of life (QOL) in chronic rhinosinusitis (CRS) have not been investigated previously. We sought to analyze the correlations of pain and disease-specific QOL with cognitive function in CRS.

Methods—Adults with CRS were prospectively enrolled in a cross-sectional study. Participants' cognitive function was assessed using the Cognitive Failures Questionnaire. Pain was characterized using the Short-Form McGill Pain Questionnaire (SF-MPQ) and the Brief Pain Inventory Short Form. Disease-specific QOL was ascertained using the Rhinosinusitis Disability Index (RSDI) and Sinonasal Outcome Test-22 (SNOT-22). Disease severity was assessed using nasal endoscopy and computed tomography. Bivariate correlations of pain and cognitive dysfunction, disease-specific QOL, and clinical measures of disease severity were ascertained.

Results—In patients with CRS (n=70) there was a significant correlation between cognitive dysfunction and pain severity scores ($R_s = 0.321$, $p < 0.01$). A similar correlation was identified with pain interference ($R_s = 0.317$, $p < 0.01$) and cognitive dysfunction scores. This is mirrored by a significant correlation between another measure of pain severity, the SF-MPQ and cognitive dysfunction ($R_s = 0.498$, $p < 0.01$). In patients with CRS there was a significant correlation between disease-specific QOL scores and cognitive function scores as measured by the SNOT-22 ($R_s = 0.395$, $p < 0.01$) and the RSDI ($R_s = 0.528$, $p < 0.01$).

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Conclusions—In patients with CRS increasing pain and worse QOL are associated with cognitive dysfunction. Possible mechanisms for this cognitive dysfunction include differential neural activation secondary to chronic pain and/or the sequela of a chronic inflammatory state.

MeSH Key Words

Sinusitis; rhinosinusitis; chronic disease; quality of life; rhinitis; cognition; chronic pain

Introduction

Chronic rhinosinusitis (CRS) is a highly prevalent disease that has substantial effects on overall well-being and disease-specific quality of life (QOL). Reduced QOL in patients with CRS is complex, however it is most likely influenced by an array of disease manifestations and symptomatology. These vary from the rhinologic symptoms of nasal discharge, nasal obstruction, and facial pain/pressure, to central behavioral dysfunction including fatigue, depression, reduced sleep, decreased social functioning, and anecdotally a poorly defined neurocognitive dysfunction.¹ This central behavioral dysfunction may be the etiology of the significant association of comorbid psychiatric disease including anxiety and depression in patients with CRS.²

To date there has never been an objective evaluation of the neurocognitive dysfunction described by patients with CRS, nor has there been an evaluation of symptoms such as facial pain as a possible etiology. One of the challenges in investigating neurocognitive impairment is in precisely defining this symptom. Patients frequently complain of “clouded thinking” or “poor memory” but are still able to carry on with independent activity. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) defines mild neurocognitive disorders as: evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition). These deficits must not be due to a underlying medical issue or delirium and must be noticeable by either the patient or a caregiver but not prevent completion of the activities of daily living.³

A large body of literature in pain management has demonstrated a degree of cognitive dysfunction associated with chronic pain. A recent meta-analysis, demonstrated a moderate, but significant decrease in verbal and non-verbal working memory, attention, and immediate auditory and visual memory secondary to increased pain.⁴ Furthermore, a meta-analysis from 2014 established that higher level decision making, termed executive functioning, in patients with chronic pain is significantly hampered.⁵

Allergic rhinitis has also been implicated in cognitive dysfunction. Patients, when exposed to their allergen, exhibit slower and less accurate responses on tests of cognitive function. The level of the cognitive dysfunction does not correlate well with measures of symptom severity in this population.^{6,7} This suggests that this may be secondary to an inflammatory milieu rather than the true rhinologic symptoms; however, this has never been further investigated.

Chronic inflammatory conditions have also been linked to cognitive dysfunction. This has been demonstrated in sarcoidosis, sickle cell anemia, obesity, and many other diseases.^{8–10} For example, in sarcoidosis, successfully treating the underlying inflammation decreases patients' cognitive impairment.⁸ Likewise, gastric bypass surgery was found to improve cognitive impairment in obese patients. This may be a secondary benefit to reducing patients' underlying inflammatory load.^{10,11}

Our primary objective was to characterize the neurocognitive dysfunction in patients with CRS. We hypothesize that the cognitive dysfunction symptoms noted by many patients with CRS may be related to severity of rhinologic symptoms, facial pain, or chronic inflammation seen in CRS.

Materials and Methods

Patient Population and Inclusion Criteria—Adult subjects (≥ 18 years of age) with a diagnosis of CRS using the 2007 Adult Sinusitis Guidelines were prospectively enrolled into an ongoing observational cohort investigation.¹ The site of enrollment was the Sinus and Skull Base clinic at the University of Utah (Salt Lake City, Utah), a tertiary referral center for the Intermountain West. The Institutional Review Board at the University of Utah approved the investigational protocol (IRB#: 00061810). Patients were required to complete all questionnaires in English. All patients had completed a 14-day course of broad spectrum or culture directed antibiotics and must have completed a 3-week course of topical steroids or a 5-day trial of oral corticosteroids prior to becoming eligible for enrollment. Participants were rarely prescribed these treatments at the time of enrollment. All participants were asked to complete an enrollment form which included demographic, social/medical history including: age, gender, household income, current tobacco use, alcohol use, depression physician diagnosis, asthma, allergies (both by history or testing), aspirin intolerance, cystic fibrosis, obstructive sleep apnea, history of headache disorder or facial pain, and previous sinus surgery.

Exclusion criteria—Patients determined to have recurrent acute rhinosinusitis or a diagnosis of ciliary disorder were excluded to minimize heterogeneity of the study population. Additionally, patients failing to complete the relevant pain, cognition, and QOL questionnaires were excluded. Patients unable to provide informed consent including those with diagnosed mental handicap were excluded. Patients with other medical conditions associated with pain including fibromyalgia or a primary headache disorder including migraine headache were excluded due to potential for pain symptoms not secondary to CRS. Patients with obstructive sleep apnea and depression were not excluded. Patients with allergy history were also not excluded.

Research Instruments—At enrollment patients were asked to complete the Cognitive Failures Questionnaire (CFQ), the Brief Pain Inventory-Short Form (BPI-SF), and the Short Form-McGill Pain Questionnaire (SF-MPQ) including the Present Pain Intensity (PPI). In addition, patients were asked to complete the Rhinosinusitis Disability Index (RSDI) and the Sinonasal Outcome Test-22 (SNOT-22).

Cognitive-Failures Questionnaire

The CFQ is a self-report questionnaire consisting of 25 events of cognitive failure in 3 domains: perception, memory, and motor function. Patients are asked to respond to a Likert-like scale rating the frequency with which the event has occurred in the last 6 months. The responses are never (0), very rarely (1), occasionally (2), quite often (3), and very often (4). The responses are totaled (Range: 0–100) with higher values indicative of worse perceived cognitive function. The questionnaire has been shown to be relatively independent of intelligence or education level.^{12,13}

The Brief Pain Inventory-Short Form

The BPI-SF was originally created to evaluate pain severity and interference with daily life in malignancy. This has since been validated in chronic, non-malignant pain, and is widely used in the literature.¹⁴ Further, we have recently shown this instrument to be useful in evaluating sinus-specific pain in CRS.¹⁵ The severity of sinus pain is indicated by asking respondents to indicate the intensity of their pain, on a scale of 0 (no pain) to 10 (pain as bad as you can imagine), when it was at its worst and best in the last 24 hours. Respondents are also asked to indicate, on the same scale, the average severity of their pain and the current severity of their pain. The mean of these four scales is then calculated (Range: 0–10). Sinus pain interference with daily life is then assessed by asking respondents to indicate how much their sinus pain interferes, on a scale of 0 (does not interfere) to 10 (completely interferes), with: general activity, mood, walking ability, normal work, relation with other people, sleep, and enjoyment of life. The mean of these interference measures (Range: 0–10) is then calculated and used as an indicator of sinus pain interference. Higher scores represent increased pain severity and interference.

Short Form-McGill Pain Questionnaire

The participants were then asked to complete the SF-MPQ. This consists of 15 sinus-related pain characteristics and patients are asked to rate each of these descriptors from 0 (none) to 3 (severe). The first 11 pain descriptors assess the “sensory” subdomain of sinus-related pain. The final 4 descriptors represent the “affective” subdomain of sinus-related pain. These responses are summed to indicate severity (sensory: 0–33, affective: 0–12, and overall: 0–45) and higher numbers indicate worse severity. Finally, respondents are asked to characterize the overall intensity of their sinus pain on a scale from 0 (no pain) to 5 (excruciating);¹⁵ this assessment which is part of the SF-MPQ can be separately reported as the PPI.¹⁶

Rhinosinusitis Disability Index

The RSDI is a 30-item list of statements relating to the physical, functional, and emotional. The respondent replies with a score of 0 (never) to 4 (always) on a Likert-like scale. The physical subdomain consists of 11 statements and responses are summed with a range of 0–44 with higher scores representing greater disability. The functional subdomain consists of 9 statements allowing for a range of 0–36 with higher scores representing greater disability. The emotional subdomain consists of 10 statements (Range 0–40) with higher scores

indicating greater disability. The subdomain scores can be summed to give an index of overall disability (Range: 0–120) with increased values indicating greater disability.¹⁷

Sinonasal Outcome Test-22

The SNOT-22 questionnaire consists of a list of 22 symptoms to which respondents are asked to rate the severity of the problem from 0 (No problem) to 5 (Problem as bad as it can be). The SNOT-22 has been organized into 5 discrete subdomains: rhinologic symptoms, extranasal rhinologic symptoms, ear/facial symptoms, psychological dysfunction, and sleep dysfunction.¹⁸ Responses relevant to each subdomain are summed to give scores indicative of the severity of the problems in each subdomain. The responses can also be summed to give an overall rating (Range: 0–110) of severity of the sinonasal symptoms. Higher values are indicative of worse disease-specific QOL.^{18,19}

Clinical Measures of Disease Severity—Patients included in the study underwent high-resolution computed tomography (CT) imaging with contiguous 1mm sections using a standardized protocol to best visualize the paranasal sinuses. The imaging was reviewed in both the coronal and sagittal plane by the enrolling physician and graded using the Lund-Mackay scoring system.²⁰ The degree of opacification of the bilateral maxillary, anterior and posterior ethmoid, sphenoid, and frontal sinuses is graded from 0 (normal) to 2 (complete opacification). The ostiomeatal complex is graded as 0 (patent) or 2 (opacified). The scores are then summed and a total score generated (Range 0–24) with higher values indicating greater opacification. In addition as part of the initial evaluation, the patient underwent nasal endoscopy using a rigid 30° endoscope. These exams were then scored by the enrolling physician using the Lund-Kennedy scoring system. This system quantifies the degree of: polypoid, discharge, edema, scarring, and crusting. Scores for each of these findings from 0 to 2 are generated bilaterally. The scores can be summed to produce an overall Lund-Kennedy score (Range: 0–20). Higher total scores indicate increased severity of endoscopic findings, correlating with severity of disease.²¹

Data Management, Sampling Size Estimations, and Statistical Analysis—Study data were collected using standardized research instruments. All participants were assigned a unique study identifier to ensure confidentiality. Data were manually entered into an electronic database (Microsoft Access; Microsoft Corp., Redmond, WA) by a trained research coordinator. SPSS (IBM Corp., Armonk, NY, Version 22) statistical software was used for data analysis. An estimated sample size was calculated for bivariate correlation coefficients (R) between two continuous outcome variables (Table 1). Calculations assumed 80% power (1-β error probability) and a 0.050 alpha level. This sample size estimate is for any two continuous variables and may not hold true when applied to specific study outcome measures if any assumptions are violated.

Simple descriptive statistics were calculated to summarize patient characteristics, such as age, gender, and other health conditions. Two-sided bivariate Pearson's (R_p) and Spearman's rank (R_s) correlations were used to determine the association between cognitive functioning and other disease severity and QOL measures, such as the RSDI and SNOT-22. Significant results were indicated by a p-value less than a 0.050 alpha level.

RESULTS

A total of 70 patients were enrolled and met inclusion criteria between August, 2013 and November, 2014. In this group 48.6% had allergy (n=34), 60% had prior sinus surgery (n=42), and 20% had a diagnosis of depression (n=14). The other demographic characteristics are outlined in Table 2. The average SNOT-22 score was 57.68 (standard deviation (SD) 19.05) and the average RSDI was 51.09 (SD 24.66) consistent with that seen in the average CRS study population.²² The mean Lund-Kennedy endoscopy score was 6.00 (SD 3.17) and the mean Lund-Mackay CT score was 12.77 (SD 6.65).

Patients with CRS demonstrated an average CFQ score of 40.53 (SD 18.14). There was no significant correlation with the CT and endoscopy scores (Table 3). A weak but significant correlation of scores on the pain questionnaires and CFQ scores was identified. The CFQ correlated positively with the BPI-SF pain severity score ($R_s=0.321$, $p=0.008$) and the BPI-SF pain interference score ($R_s=0.317$, $p=0.009$). Likewise, the CFQ correlated positively ($R_s=0.498$, $p<0.001$) with the total SF-MPQ and all of its subdomains (Table 4).

A bivariate analysis including the CFQ and SNOT-22 revealed a weak but significant positive correlation ($R_s=0.395$, $p=0.001$) between CFQ score and SNOT-22 total score and several of the subdomains in patients with CRS. An even stronger significant positive correlation was noted between the CFQ and the RSDI ($R_s=0.528$, $p<0.001$). This correlation extended to all the subdomains (physical, functional, emotional) (Table 5).

DISCUSSION

Cognitive dysfunction is a frequent complaint of patients with CRS. Our cohort demonstrated a significant positive correlation of cognitive dysfunction with disease-specific QOL scores and facial pain scores. In patients with CRS there was a significant positive correlation of SNOT-22 and RSDI scores with CFQ. However, when the SNOT-22 subdomains were analyzed the rhinologic symptoms did not demonstrate a significant correlation. The subdomains of ear/facial symptoms, psychological disturbance, and sleep were significant correlates. Psychiatric disturbance, sleep disturbance, or pain could be imparting an effect on the CFQ and are all candidates known to be comorbid in CRS.^{2,23} These factors were not controlled for and could help explain the low correlation coefficients as we may be detecting the down-stream effects of one of these factors or even the effects of a multifactorial etiology. In patients with allergic rhinitis, the level of cognitive dysfunction does not correlate well with symptom severity. Likewise, the subdomains of the SNOT-22 indicate that the rhinologic symptoms do not significantly associate with cognitive function. This suggests that pain or inflammation may play a large role in the modulation of cognitive function.

It is highly plausible that facial pain, which is highly prevalent in CRS,¹⁵ may be a driving factor that is modulating the cognitive dysfunction in CRS. Our results demonstrate significant correlations in patients with CRS between pain (in the form of the BPI-SF and SF-MPQ) and cognitive dysfunction. As mentioned, the correlation of pain and cognitive dysfunction is well known in the pain management literature. Animal models subjected to

chronic pain have demonstrated neural pathway plasticity that is posited as one potential etiology.²⁴ On functional magnetic resonance imaging pain processing is demonstrated as activation in the somatosensory cortical areas 1 and 2, the insular cortex, the thalamus, the prefrontal cortex and the anterior cingulate cortex (ACC). Furthermore, the ACC plays a critical role in executive functioning.²⁵ Patients with chronic pain, when observed performing an executive functioning task, show different central activation when compared to controls.^{25,26} Similar findings are echoed in other areas of the brain, with other imaging modalities, and with EEG.^{27–29}

The mechanism by which facial pain significantly correlates with both CFQ and QOL is unknown. Chronic inflammation may be an important and plausible factor that is contributing to both disease-specific QOL and pain leading to CFQ elevation. Clinical investigations demonstrated that patients with sarcoidosis with poor disease control had increased rate of cognitive failure that was thought to be associated with worse inflammation, as treatment with TNF- α inhibitors improved both their cognitive failure and disease severity.⁸ Further, patients with sickle cell anemia have been shown to have increased pro-inflammatory cytokines even between acute attacks. A recent study by Andreotti C. et. al., explored this population for cognitive dysfunction. A group of 25 pediatric patients with magnetic resonance imaging of the brain negative for cerebral infarcts was included. Assays demonstrated elevated levels of IL-4, IL-5, IL-8, and IL-13 compared to normative populations. A wide-range of cognitive measures was used to identify any cognitive dysfunction in this population. Overall, patients scored worse than their unaffected peers. Interestingly, there was found to be a negative correlation between cytokine levels and scores on the cognitive tests (indicating worse dysfunction with increasing inflammatory load).⁹ It is unknown if increasing levels of inflammatory mediators are associated with neuropsychiatric disability in CRS, although preliminary findings suggest that patients with CRS who report reduced sleep dysfunction also have corresponding increase in anti-somnogenic mediators.²³

Cognitive function in allergic rhinitis has been better explored than in CRS. The largest study, to date, compared patients with allergy to ragweed (n=234) to controls (n= 62) who were asked to complete testing measuring vigilance and cognition. Participants were randomized to a control group and to a group that was exposed to ragweed. Participants who were symptomatic at the time of testing (from ragweed exposure) scored worse on a broad battery of cognitive instruments. Interestingly, there was no correlation with the severity of the allergy symptoms that they experienced and the degree of cognitive dysfunction.⁷

Although this investigation did find significant correlations between cognitive function and pain measures, as well as cognitive function and QOL, the correlation coefficients were in the range of 0.317 to 0.528, indicating weak to moderate correlation. The relatively low strength of correlation suggests a possible multi-factorial mechanism. Neither pain nor any single symptom of CRS was found to be strongly associative in modulating cognitive function in this disease process. More likely, an underlying process like chronic inflammation modulates pain, QOL, cognitive function, and the other perturbations seen in CRS. There is substantial evidence of cognitive dysfunction in other inflammatory conditions and even evidence of correlation with cytokine level and improvement with anti-

inflammatory or immunomodulator treatment.^{8,9} This molecular testing and treatment response have not been demonstrated in CRS but would certainly be directions for future research. Furthermore, we did find associations with the sleep and psychological subdomains of the SNOT-22 and the CFQ. These, too, merit exploration in future research.

CONCLUSIONS

Patients with CRS demonstrate a significant positive correlation between the CFQ and pain surveys as well as a significant positive correlation between the CFQ and disease-specific QOL instruments. These findings may be mechanistically related to chronic inflammation, facial pain, psychiatric disturbance, sleep disturbance, or some other coexisting factor. Further research is needed to evaluate the roles of these factors and to elucidate mechanism.

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Table 1

Sample size estimations for correlation coefficients (R)

R ²	Effect Size (R)	Sample Size
0.100	0.316	73
0.104	0.322	70
0.105	0.324	69
0.150	0.387	47
0.200	0.447	34
0.250	0.500	26
0.300	0.547	21
0.350	0.591	17
0.400	0.632	14

R²; coefficient of determination

Table 2

Baseline Characteristics of Study Group, QOL scores, Clinical Measures of Disease Severity and Pain Scores.

Characteristics	CRS	
	Mean [SD]	N(%)
Age (years)	48.23 [15.38]	
Males		39 (55.7)
Females		31 (44.3)
Depression		14 (20.0)
Asthma		36 (51.4)
ASA sensitivity		10 (14.3)
Allergy		34 (48.6)
Tobacco smoking		5 (7.1)
Alcohol consumption		19 (27.1)
Prior sinus surgery		42 (60.0)
Obstructive Sleep Apnea		10 (14.3)
QOL Scores		
SNOT-22	57.68 [19.05]	
RSDI	51.09 [24.66]	
Clinical Measures		
Lund-Kennedy Endoscopy Score	6.00 [3.17]	
Lund-Mackay CT score	12.77 [6.65]	
Pain Scores		
BPI-SF pain severity	3.51 [1.95]	
BPI-SF pain interference	3.49 [2.67]	
Total SF-MPQ	12.43 [9.86]	
Sensory dimension	9.86 [7.58]	
Affective dimension	2.88 [2.62]	
PPI	14.54 [11.01]	
CFQ score	40.53 [18.14]	

Quality of Life (QOL), Chronic Rhinosinusitis (CRS), Standard Deviation (SD), Rhinosinusitis Disability Index (RSDI), Sinonasal Outcome Test-22 (SNOT-22), Computed Tomography Imaging (CT), Brief Pain Inventory-Short Form (BPI-SF), Short Form-McGill Pain Questionnaire (SF-MPQ), Present Pain Inventory (PPI), Cognitive Failures Questionnaire (CFQ)

Table 3

Bivariate Pearson's Correlation of Measures of Disease Severity and Cognitive Function

	Lund-Kennedy Endoscopy Score		Lund-Mackay CT Score	
	Rp	p-value	Rp	p-value
CFQ	−0.053	0.674	−0.095	0.442

Cognitive Failures Questionnaire (CFQ), Computed Tomography Imaging (CT)

Table 4

Bivariate Spearman's Correlation of Cognitive Function and Pain Scores

	Cognitive Failures Questionnaire	
	Rs	p-value
BPI-SF pain severity	0.321	0.008 *
BPI-SF pain interference	0.317	0.009 *
Total SF-MPQ	0.498	<0.001 *
Sensory dimension	0.422	0.001 *
Affective dimension	0.507	<0.001 *
PPI	0.509	<0.001 *

Chronic Rhinosinusitis (CRS), Standard Deviation (SD), Brief Pain Inventory-Short Form (BPI-SF), Short Form-McGill Pain Questionnaire (SF-MPQ), Present Pain Inventory (PPI),

* indicates significance at $p < 0.050$.

Table 5

Bivariate Spearman's Correlation of Quality of Life Measures and Cognitive Function

	Cognitive Failures Questionnaire	
	Rs	p-value
RSDI Total Score	0.528	<0.001*
Physical Subdomain	0.467	<0.001*
Functional Subdomain	0.364	0.002*
Emotional Subdomain	0.557	<0.001*
SNOT-22 Total Score	0.395	0.001*
Rhinologic Symptoms	0.127	0.307
Extra-nasal Rhinologic Symptoms	0.156	0.204
Ear/Facial Symptoms	0.441	<0.001*
Psychological dysfunction	0.472	<0.001*
Sleep dysfunction	0.316	0.009*

Chronic Rhinosinusitis (CRS), Rhinosinusitis Disability Index (RSDI), Sinonasal Outcome Test-22 (SNOT-22),

* indicates significance at $p < 0.050$.