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Chronic rhinosinusitis and mood disturbance

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On behalf of the CRES Group

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SUMMARY

Background:

This study is part of the Chronic Rhinosinusitis Epidemiology Study (CRES). The overarching aim is to determine factors that influence the onset and severity of chronic rhinosinusitis (CRS). The aim of this analysis is to determine whether those with CRS are more likely to report psychiatric morbidity and in particular mood disturbance compared with healthy controls.

Methods:

CRES consists of a study-specific questionnaire regarding demographic and socioeconomic factors and past medical history as well as a nasal symptom score (SNOT-22) and SF-36 (QoL - quality of life tool). Both of these tools contain mental health or emotional well-being domains. Participants were specifically asked whether they had ever consulted with their General Practitioner for anxiety or depression. Questionnaires were distributed to patients with CRS attending ENT outpatient clinics at 30 centres

across the United Kingdom from 2007-2013. Controls were also recruited at these sites. Patients were divided into subgroups of CRS according to the absence/presence of polyps (CRSsNPs/CRSwNPs) or allergic fungal rhinosinusitis (AFRS).

Results:

Consultations with a family physician for depression or anxiety were higher amongst those with CRS than controls, but this was only significant for those with CRSsNPs. Odds ratio (OR) for CRSsNPs vs controls, 1.89, p=0.001; OR for CRSwNPs 1.40, p=0.078. Patients with CRS showed significantly higher mental health morbidity than controls across the mental health and emotional wellbeing domains of the SF-36 and SNOT-22. Mean difference in the mental health domain of SF-36 was 8.3 for CRSsNPs and 5.3 for CRSwNPs ($p<0.001$). For the emotional domain of SNOT-22, differences were 7.7 and 6.3 respectively ($p<0.001$).

Conclusions:

Depression and anxiety are significantly more common in patients with CRS compared to healthy controls, especially in those with CRSsNPs. This added mental health morbidity needs consideration when managing these patients in primary and secondary care settings.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common condition with a recent European study showing the prevalence of to be 10.9% across Europe which equates to 6.8 million Britons affected(Bachert, Van Bruaene et al. 2009). The recent European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS) (Fokkens, Lund et al. 2012), defines rhinosinusitis in adults as 'inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) ± facial

pain/pressure ± reduction or loss of smell and either endoscopic or CT findings of polyps, mucopus or mucosal oedema. Rhinosinusitis is considered 'chronic' if symptoms persist for > 12 weeks. CRS is currently subdivided into two main types – CRS with and without nasal polyps (CRSwNP and CRSsNP respectively), as exemplified by EPOS 2012 (Fokkens, Lund et al. 2012) to broad phenotypes, with allergic fungal rhinosinusitis (AFRS) as a distinct subtype of CRSwNP, which is particularly severe and difficult to treat.

Whilst diagnosis and treatment of CRS is largely based on nasal symptoms, it is known that CRS has a much wider effect on health. Consultations for CRS both in Primary Care and ENT tend to focus on the symptoms used to make a clinical diagnosis (Fokkens, Lund et al. 2012) rather than a more holistic evaluation of patient well-being including mental health (Galderisi, Heinz et al 2015). A previous study of 158 patients has suggested significant morbidity in CRS with quality of life scores worse than amongst those with other chronic diseases such as lower back pain (Gliklich and Metson 1995). Since CRS primarily affects those aged 40-60 years, the significant effect on an individual's functioning and productivity also has an impact in the workplace. CRS has been identified as one of the top ten most costly diseases for US employers (Goetzel, Hawkins et al. 2003). Qualitative interviews with patients with CRS have found that those affected describe low mood, poor sleep and even suicidal ideation (Erskine, Verkerk et al. 2015). EPOS states under the heading 'Research Needs' that studies are required to 'investigate the impact of psychological problems such as depression, stress exposure and anxiety' (Fokkens, Lund et al. 2012) .

The overarching aim of the CRS Epidemiology Study (CRES) was to identify differences in socio-economic variables between patients with CRS and healthy controls to aid better understanding of medical and non-medical factors contributing to the development or worsening of CRS. The purpose of this study is to consider the differences in psychiatric morbidity between those with different types of CRS and controls using several different self-reported measures of mental health and emotional well-being.

MATERIALS AND METHODS

Study Design and Setting

CRES was approved by the Oxford C Research Ethics Committee, sponsored by the University of East Anglia (UEA) and funded by the Anthony Long and Bernice Bibby Trusts. Following a pilot study of the questionnaire in 2006, the study commenced recruitment in ENT departments of the East Anglia region (East of England Deanery) of the UK in 2007. Following elevation to the National Institute of Health Research Clinical Research Network Portfolio in 2012, a total of 30 sites from around the UK (including Wales and Scotland) joined the study which ran between 2007 and 2013. The study specific questionnaire was anonymous and therefore consent was implied through participation. Participant information leaflets were provided.

Participants

Patients presenting to secondary care outpatient clinics and diagnosed with CRS by an ENT surgeon, as defined by the criteria laid out in the European Position Paper on Rhinosinusitis and Nasal Polyps (Fokkens, Lund et al. 2012) were invited to participate in the study regardless of symptom or disease severity or duration, and regardless of any prior interventions. Participants may therefore have been seen by ENT for the first time when they were recruited or they could have had treatment previously. Patients were classified by sub group of CRS (CRSsNPs, CRSwNPs or allergic fungal rhinosinusitis (AFRS) by a clinician prior to completion of the questionnaire using the EPOS definitions for with or without polyps (using endoscopic and/or radiological confirmation). Patients placed in the AFRS category met the Bent and Kuhn criteria (Bent and Kuhn 1994) or the St Paul's Sinus Centre modification of this (Philpott, Javer et al. 2011). Controls included family and friends of those attending ENT outpatient clinics and hospital staff who had no diagnosis of nose or sinus problems and had not been admitted to hospital in the previous 12 months.

Participants taking part in qualitative interviews were all recruited from one centre. Methodology and results of these studies are published elsewhere (Erskine, Notley et al. , Erskine, Verkerk et al. 2015)

Variables and data sources

The study questionnaire was designed with the input of the East of England Research Design Service and included study specific questions relating to socio-economic, environmental and medical co-morbid variables as well as the validated Short Form 36 Quality of Life (QoL) measure (SF-36) (18) measure and the Sino-Nasal Outcome Test questionnaire (SNOT-22)(19). In this analysis the mental health domain of SF-36 and the emotional domain for SNOT-22 were also used. SNOT-22 asks 22 symptoms of CRS, both nasal and non-nasal, these are scored from 0 to 5 for severity, so the total is out of 110. The emotional domain of SNOT-22 includes fatigue, reduced productivity, reduced concentration, frustration/restlessness/irritability, sadness and embarrassment. Participants were additionally asked whether they had consulted their GP for anxiety or depression.

Statistical analysis

The participant characteristics are described using mean and standard deviation for continuous measures and number and percentage for categorical variables. Both disease groups are compared to control in terms of proportion with any facial pain, anxiety, depression or anxiety and depression using logistic regression, using odds ratios to compare the disease groups to control. They were also compared using regression for Mental Health SF-36, SNOT-22 emotion, SF-36 total and SNOT-22 total, using the mean difference to compare the disease groups to control. Results were firstly unadjusted, then adjusted for age and sex. The mean difference was additionally adjusted for consultation for anxiety or depression.

RESULTS

A total of 1,470 participants were recruited as shown in table 1. The overall recruitment was 66% of those invited to participate. Information on reasons for non-participation is not available.

Table 1: Demographic information of CRS subgroups

1,464 participants included sufficient information to analyse consultations with anxiety and depression. All measures of mental well-being are shown in table 2.

Table 2: Mental well-being variables by CRS group

Differences between those with CRS and controls were found in rates of consultation with GP for anxiety and depression. Those with CRSsNPs reported significantly higher rates of consultation for both anxiety and depression than controls. Those with CRSwNP reported higher rates of consultation for depression, but this was not significant. Differences were found in total and mental health SF-36 score and total and emotional domain of SNOT-22 score, with those with CRS scoring more poorly than controls, and those with CRSsNPs scoring more poorly than those with CRSwNP in SF-36 and SNOT-22 overall and in both the mental health and emotional domains and in. Table 3 show odds ratios for these variables.

Table 3: Differences in psychiatric morbidity between subgroups

Those with CRSsNPs scored significantly more poorly than controls across all measures of mental and emotional health. Those with CRSwNPs scored more highly on the mental/emotional domains of SF-36 and SNOT-22**.**

Differences in scores for mental health and emotional domains as well as total SF-36 and SNOT-22 persist despite adjusting for consultation with GP for anxiety and depression (table 4).

Table 4: Differences in SF-36 and SNOT-22 after adjustment for gender, age and anxiety/depression

DISCUSSION

Key Results

All measures of anxiety and depression in this cohort were higher amongst those with CRSsNPs compared with controls. Mental health and emotional well-being measures were higher amongst those with CRSwNP than controls. Those with CRsNPs had scored more poorly than those with CRSwNPs. Differences in mental health and well-being persisted despite adjusting for consultation with GP for anxiety and depression.

Strengths and limitations

The study is self-reported, although there is no reason for any subgroup to over-report symptoms compared to any other.

A strength of the study is the ability to triangulate information about psychiatric morbidity from three sources; SF-36, SNOT-22 and GP consultation.

The study has focused on CRS patients in a secondary care setting, however it is recognised that the larger burden of CRS is seen in a primary care setting. We do not have data on disease severity according to objective measures such as the Lund Mackay score or endoscopic grading due to the anonymous self-reported nature of the study. These are known to be poor predictors of symptom severity(Hopkins, Browne et al. 2007) Participants were examined (via endoscopy) to establish subgroup prior to entry into the study but no further assessment of clinical disease was taken. We do not know whether those who have seen a GP for anxiety or depression have ongoing symptoms.

Interpretation

Any person with chronic disease is likely to score less favourably for mental health/ emotional well-being since they will often need to adjust their lifestyle, hopes and even employment to accommodate their illness (Turner and Kelly 2000); given that CRS does not give rise to a specific disability, the extent of the morbidity it is associated with may be overlooked by clinicians (Erskine, Notley et al. , Erskine, Verkerk et al. 2015), which in itself may lead to increased levels of distress. Previous smaller studies of 63 rhinitis patients and 143 CRS patients respectively have also found that such patients have increased levels of anxiety and depression (Ryden O, Andersson B et al. 2004, Wasan, Fernandez et al. 2007). The causal association is not well-understood; depression and anxiety may amplify symptoms of CRS or be the consequence of living with CRS, or it may be that the co-morbid anxiety and depression are epiphenomena. These results show that the psychological co-morbidity associated with CRS is significant. Such co-morbidities should be taken into account when managing patients. There is good evidence from other areas that appropriate treatment of co-morbid mental disorder is likely to improve outcomes of physical disorders (Moussavi, Chatterji et al. 2007).

Both state anxiety (defined as fear, tension, and increased arousal induced temporarily by specific situations perceived as threatening) and trait anxiety (a predisposition to stress and worry) have been found to be higher amongst those with both allergic rhinitis (IgE mediated) and vasomotor rhinitis (Vidian nerve hypersensitivity) than controls (Addolorato, Ancona et al. 1999) and could reflect autonomic nervous system (ANS) dysfunction. The nose has a rich and complex nerve supply which is experienced on a routine basis; rhinorrhoea in cold weather or when eating spicy foods. The ANS has a role in altering the nasal airway during postural change(Ko, Kuo et al. 2008) but the relevance of ANS dysfunction in the generation of nasal symptoms remains little studied. It has been evaluated in few previous series totalling fewer than 30 patients (Ishman, Martin et al. 2007). The main differences between patients and controls were that

sudomotor, cardiovagal and adrenergic subscores were all significantly more abnormal amongst patients than controls, as were overall ANS scores.

Personality traits, in particular 'type A' personality and anxiety are implicated in the development of cardiovascular disease, this may be explained by abnormal sympathetic nervous activity in response to stressors (Schroeder, Narkiewicz et al. 2000). Similar mechanisms may occur in the nasal airway, meaning that those who are more anxious already may be more likely to experience nasal symptoms such as congestion and rhinorrhoea. Fatigue is also a frequent concomitant symptom of ANS dysfunction and is regularly found in CRS patients. ANS dysfunction may therefore contribute to the several components of CRS symptom generation, including:

1. Predisposing factors - Personality and or other factors which set 'baseline' ANS activity in an individual
2. Precipitating factors – Responses to environmental triggers and state anxiety
3. Perpetuating factors – ANS dysfunction may feed into low mood, anxiety and fatigue

Stress and infections are independently associated with asthma development and exacerbation. There is evidence that stress hormones can alter immune processes, induce inflammation, and increase susceptibility to infection in those with asthma; T-Helper cells have particularly been implicated. Additionally, prolonged psychological stress is thought to predispose to respiratory infections in asthmatics (Trueba and Ritz 2013). CRS has a very complex aetiology, with bacteria, viruses, fungi, immune dysfunction, atopy and genetic predisposition all implicated; similar interactions with infection and stress may also apply.

The differences between those who have CRS with and without polyps are perhaps more complex to understand. Our results show that those without polyps are more likely to consult with their GP and also tend to score more poorly on the mental and emotional scales, as well as total SF-36 and SNOT-22. Clinically, those with nasal polyps and in particular those with AFRS (where nasal polyps are also present) are often considered to

have more severe disease with more obvious pathology. CRS is often considered to be a spectrum of disease from CRSsNP to AFRS. It could be logical to think therefore that patients with nasal polyps would experience more significant negative impact on their emotional well-being as a consequence of the physical manifestations of polyps, but this is not apparent in our data. Mental health scores in those with CRS have been found to correlate with *subjective* symptom scores (Nanayakkara, Igwe et al. 2013). Data from CRES found that when using total SNOT-22 scores, those with polyps scored more highly for nasal symptoms than those without (A cross sectional cohort study of Quality of life in CRS in the UK; a comparison between CRS subtypes, Rhinology journal – under review(Philpott, Erskine et al. 2016), although it is well known that measurements of individual objective parameters of disease such as peak nasal inspiratory flow rates or scoring the severity of CT scans (Lund Mackay score) do not correlate well with patients' own self-reported symptom scores (Hopkins, Browne et al. 2007). Our results find that emotional well-being is worse amongst those *without* nasal polyps. One explanation could be that patients with polyps may have an expectation that these can be removed facilitating a 'cure'. Some 'sinonasal' symptoms such as facial pain and headache have a vast possible aetiology and are well known to be associated with anxiety states; they are also found more frequently in patients with CRSsNPs than in those with polyps (found in our own study) (Durr, Desrosiers et al. 2001).

It has been suggested that certain clinical variables such as age, culture, expectations and mental and physical health may influence patient's reporting of their symptoms and consequently modify disease severity (Wilson and Cleary 1995). CRS patients with depression are known to report significantly worse pain and energy levels, and difficulty with daily activities when compared with a control group of CRS patients without depression (Brandsted and Sindwani 2007). Symptoms such as fatigue are also more likely to be reported in patients with depression. Studies have found dynamic changes in mu-opioid neurotransmission in response to an experimentally induced negative affective state which support a physiological basis for somatic amplification in patients with mood disturbance (Zubieta, Ketter et al. 2003, Wasan, Fernandez et al. 2007, Wasan, Fernandez et al. 2007). Pre-existing or concurrent psychiatric comorbidity may therefore affect

symptom reporting, with those with psychiatric co-morbidities known to report elevated symptom scores (Wasan, Fernandez et al. 2007). In our study, differences in mental health and well-being persisted, despite adjusting for consultation with GP for anxiety and depression, with those with CRS scoring significantly more poorly than controls. So even those with no diagnosis of depression or anxiety are still reporting decreased mental health and emotional well-being. This should be taken into consideration when managing patients with mood disturbance and CRS.

Clinically, the association between mood disturbance and CRS is important for many reasons. Depression or anxiety symptoms may decrease motivation to seek medical help or adhere to treatment plans (Turner and Kelly 2000). Many treatments for CRS involve nasal douching or application of nasal sprays or drops which can be time-consuming and inconvenient (Erskine, Notley et al.) and may be more challenging to stick to than simply taking a tablet. Oral steroids are frequently used in the management of nasal polyps and are known to affect mood in many ways; clinicians should be careful to discuss these mood-altering effects in those who may already have a mood disturbance. It may be necessary to screen those whose symptoms are particularly bothersome for anxiety or depression diagnoses, for example the Hospital Anxiety and Depression Score (HADS), to see whether such symptoms require treatment over and above management of nasal symptoms. Simply taking note of a patient's symptoms may be beneficial (Erskine, Notley et al. , Erskine, Verkerk et al. 2015). Other simpler measure such as writing down experiences have been found to bring about measurable physiological improvements in patients with comparable chronic conditions such as asthma (Smyth, Stone et al. 1999).

Conclusion

Our study has shown that those with CRS experience poorer mental well-being than healthy controls. Additionally, those with CRSsNPs score worse than those with polypoid disease. This is the largest UK study to show such a difference between these phenotypes, although anecdotally many clinicians have seen such a phenomenon in clinical practice. Our results should influence management strategies for patients with different nasal

pathologies by highlighting the importance of considering the non-nasal sequelae and associated symptoms of CRS particularly amongst those with CRSsNPs.

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AUTHORSHIP CONTRIBUTION
Please describe the individual contributions of each author to the paper.
Sally Erskine, Carl Philpott – Design of study, data collection, data analysis, writing of paper,
Claire Hopkins, Alasdair Robertson, Vishnu Sunkaraneni, Shahram Anari - data collection, data analysis, writing of paper,
Janet Wilson– analysis, writing of paper
Juilan Beezhold - analysis, writing of paper
Allan Clark – design, statistics, writing of paper

The CRES Group – Principle Investigators at sites across UK responsible for running of the study locally

CONFLICT OF INTEREST
No conflict of interest for any author identified

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Table 1: Demographic information of CRS subgroups

	Controls	**CRSsNP**	**CRSwNP**	**AFRS**
Participants	221	553	651	45
Females	143 (68.4%)	259 (53.1%)	185 (32.2%)	19 (43.2%)
Mean Age (s.d)	47.3 (14.9)	51.8 (15.3)	56.0 (14.6)	56.1 (12.7)
Range	19-82	18-84	17-102	20-76

Table 2: Mental well-being variables by CRS group

		Controls	***%***	***CRSsNP***	***%***	***CRSwNP/AFRS***	***%***
Total		***221***		***551***		***692***	
Consultation with GP	Anxiety	***35***	***15.84***	***128***	***23.23***	***112***	***16.21***
	Depression	***32***	***14.48***	***139***	***25.23***	***139***	***20.09***
	Anxiety or depression	***43***	***19.46***	***173***	***31.40***	***175***	***25.29***
Any facial pain		***28***	***13.86***	***363***	***70.90***	***388***	***57.82***
		Mean	*S.D*	*Mean*	*S.D*	*Mean*	*S.D*
Mental health SF-36		***77.91***	***14.99***	***69.58***	***19.82***	***72.65***	***18.23***
SNOT-22 (emotional domain)		***3.66***	***5.51***	***11.37***	***7.64***	***9.92***	***7.46***
SF-36 total		***80.75***	***15.12***	***65.92***	***21.41***	***69.28***	***19.62***
SNOT-22 total		***12.11***	***13.95***	***45.67***	***21.05***	***44.41***	***21.62***

Table 3: Differences in psychiatric morbidity between subgroups

	CRSsNP vs control				***CRSwNP vs control***			
	Unadjusted		***Age-sex adjusted***		***Unadjusted***		***Age-sex adjusted***	
	Odds ratio	***p-value***	***Odds ratio***	***p-value***	***Odds ratio***	***p-value***	***Odds ratio***	***p-value***
Anxiety	*1.61 (1.07,2.43)*	*0.024*	*1.83 (1.16,2.88)*	*0.009*	*1.03 (0.68,1.56)*	*0.896*	*1.38 (0.86,2.20)*	*0.183*
Depression	*1.99 (1.31,3.04)*	*0.001*	*2.25 (1.41,3.57)*	*0.001*	*1.48 (0.98,2.26)*	*0.064*	*2.03 (1.26,3.25)*	*0.003*
Anxiety or depression	*1.89 (1.30,2.77)*	*0.001*	*2.14 (1.41,3.24)*	*<0.001*	*1.40 (0.96,2.04)*	*0.078*	*1.88 (1.23,2.87)*	*0.004*
Any facial pain	*15.14 (9.73,23.56)*	*<0.001*	*27.36 (16.31,45.90)*	*<0.001*	*8.52 (5.56,13.06)*	*<0.001*	*18.46 (11.02,30.92)*	*<0.001*
	Mean difference	***p-value***	***Mean difference***	***p-value***	***Mean difference***	***p-value***		
Mental health	*-8.33 (-11.22,-*	*<0.001*	*-9.39 (-12.39,-*	*<0.001*	*-5.26 (-8.06,-*	*<0.001*	*-8.49 (-*	*<0.001*

SF-36	*5.44)*		*6.39)*		*2.46)*		*11.49,-5.48)*	
Snot22 (emotion)	*7.71 (6.53,8.89)*	*<0.001*	*8.28 (7.06,9.50)*	*<0.001*	*6.26 (5.12,7.40)*	*<0.001*	*7.50 (6.28,8.71)*	*<0.001*
SF-36	*-14.84 (-17.94,-11.74)*	*<0.001*	*-15.32 (-18.56,-12.08)*	*<0.001*	*-11.48 (-14.48,-8.48)*	*<0.001*	*-13.30 (-16.55,-10.05)*	*<0.001*
SNOT-22	*33.57 (30.21,36.92)*	*<0.001*	*35.99 (32.50,39.47)*	*<0.001*	*32.30 (29.07,35.54)*	*<0.001*	*36.81 (33.33,40.30)*	*<0.001*

Table 4: Differences in SF-36 and SNOT-22 after adjustment for gender, age and anxiety/depression

	CRSsNP vs control	***%***	***CRSwNP vs control***	***%***
	Mean difference	***p-value***	***Mean difference***	***p-value***
Mental health SF-36	-7.00 (-9.72,-4.28)	*<0.001*	-6.48 (-9.21,-3.76)	*<0.001*
Snot22 (emotion)	7.50 (6.34,8.66)	*<0.001*	6.86 (5.70,8.01)	*<0.001*
SF-36	-13.08 (-16.12,-10.05)	*<0.001*	-11.43 (-14.47,-8.40)	*<0.001*
SNOT-22	34.45 (31.05,37.86)	*<0.001*	35.51 (32.12,38.90)	*<0.001*