Occupational exposure influences control of disease in patients with chronic rhinosinusitis*

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Abstract

Background: Chronic rhinosinusitis (CRS) is a frequent condition that is treated by endoscopic sinus surgery (ESS) when medical treatment fails. Irritating or sensitizing airborne agents can contribute to uncontrolled CRS. A prior study showed a linear correlation between occupational exposure and the number of ESS.

Methods: In this cross-sectional study we tested the hypothesis that occupational exposure is a risk for undergoing ESS. We sent questionnaires enquiring occupational exposure in patients with CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP). An expert assessed blindly the reported work exposures to inhaled agents. The relationship between occupational exposure on undergoing ESS was analysed.

Results: Among all patients who underwent ESS (n=343), 30% reported a relevant occupational exposure, which is significantly higher than the 4.8% found among CRS patients that underwent no prior sinus surgery (n=21). Besides occupational exposure, self-reported doctor-diagnosed asthma were independent variables contributing to the chance of undergoing ESS.

Conclusion: In our study we confirm occupational exposure as a risk factor for uncontrolled CRS, if defined by undergoing ESS. In CRS patients with uncontrolled symptoms, despite maximal conservative therapy, the clinician should explore the possible contribution of occupational exposure.

Key words: occupational medicine, occupational exposure, paranasal sinus disease, control of disease, precision medicine

Introduction

At the entry of the airway, the nasal mucosa is continuously exposed to a variety of airborne substances. These include the common aeroallergens that cause allergic rhinitis in atopic individuals, but also airborne pollutants and irritants and all of these can be encountered at the work floor as occupational exposures. The airways are the primary contact site for a variety of work-related dusts, gases, fumes and vapours. Depending on the amount inhaled and their physical-chemical properties, these agents can cause irritation, corrosive changes, and/or sensitization of the respiratory mucosa[1-3], not only posing as a risk factor for malignancies in specific cases, but more generally contributing to occupational airway disease, like rhinitis, rhinosinusitis and asthma[4, 5].

Chronic rhinosinusitis (CRS) is defined as an inflammation of the mucosa of the nose and the paranasal sinuses characterised by two or more symptoms, lasting more than 12 weeks, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) supplemented with facial pain/pressure and/or reduction or loss of smell. The symptoms need to be confirmed by either endoscopic abnormalities and/or computed tomography (CT) changes(6). Management of CRS is focused on achieving and maintaining clinical control of symptoms, which can be defined as a disease state in which a patient has no symptoms, or they do not affect quality of life (QoL)[6]. Ideally, prophylactic measures would exist

to prevent a chronic disorder like CRS[7]. Precision medicine aims to tailor prevention and management of disease in the individual patient in order to optimise outcomes and minimise costs[8-11]. It is estimated that currently at least 40% of CRS patients remain uncontrolled despite treatment[12]. These difficult-to-treat CRS-patients should be analysed for several factors that can cause lack of control; these can be related to either the disease, diagnosis, therapy, or patient. One of these factors, might be an (unrecognised) occupational exposure[13]. A well-known example is the increased prevalence of CRS in firefighters that had been exposed in the 9/11 World Trade Centre collapse in 2001. In this cohort a higher prevalence of non-resolving upper airway inflammation responding poorly to medical management was found, ultimately treated with surgery even years later. In the whole cohort of rescue and recovery workers a continued increasing cumulative incidence of 'asthma' and 'sinusitis' was found up to 9 years after exposure, compared to pre-exposure[14, 15].
Occupational agents can be classified as high molecular weight (HMW) compounds (>5kDa) —such as flour or animal antigens— or low molecular weight (LMW) compounds (<5kDa). The LMW compounds are again subdivided into two groups, depending on their sensitization capacity; LMW sensitizers, such as isocyanates, persulphate salts and acid anhydrides, lead to airway inflammation after the latency phase of immunologic sensitization, whereas LMW irritants, such as chlorine, ammonia or ozone, cause an immediate airway injury and inflammation through nonallergic pathways[16].
An earlier study on the impact of occupational exposure, suggested a linear correlation between the reporting of occupational exposure and number of Endoscopic Sinus Surgery (ESS) procedures in patients with CRS needed to control disease. This suggests that occupational exposure can be considered a risk factor for the occurrence of rhinosinusitis and its recurrence after surgery[5]. This means ESS, or multiple ESS, reflects uncontrolled CRS. The aim of this study is to confirm these findings in a second population and to test the hypothesis that work-related exposures are related to the risk of undergoing ESS.

Materials and methods

Study population

In this cross-sectional study we selected patients who had visited our tertiary referral rhinologic clinic, initially diagnosed with CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP), according to EPOS[6]. Patients were excluded if they were younger than 18 years or diagnosed with localized disease such as sinusitis from dental origin, fungal balls, and benign and malignant neoplasms, or those with underlying pathology such as primary ciliary dyskinesia, cystic fibrosis or immune deficiencies. We collected data on previous ESS, allergy to common aeroallergens, asthma and NSAIDs-exacerbated respiratory disease (N-ERD)[17] from medical files.
The study was approved by the local ethics committee of the Amsterdam University Medical Centers, location AMC (W13_152 # 13.17.0195).

Questionnaires

An extensive questionnaire (based on and modified from 'the occupational history form' proposed by Bernstein and also used by Hox et al.) was sent by mail to the screened patient population[5, 18]. This questionnaire enquires about rhinologic, pulmonary and general medical history, smoking, and current occupation, including specification of tasks.
Questions included occupational and recreational exposures, duration of exposures, type of agents (including an extensive list to choose from), and sinonasal symptoms.
Furthermore, subjects filled out the RSOM-31 to measure current rhinologic symptoms[19]. The RSOM-31 is a 31- item rhinosinusitis-specific questionnaire which contains 7 subscales: nasal, eye, sleep, ear, general, practical and emotional. Patients score their symptoms on a 6-item scale (0-5; *0) Not present/ no problem, 1) Very mild problem, 2) Mild or slight problem, 3) Moderate problem, 4) Severe problem, 5) Problem is "as bad as it can be"*, with a score ranging from 0 to 155. This questionnaire is the precursor of the widely used SNOT-22[20]. We included RSOM-31 scores of patients that answered at least 50% of the items (≥16 items), to reliably calculate a mean score[20].

Analysis of questionnaire responses

All returned questionnaires were analysed for relevant occupational exposure, independently and blindly by a physician specialised in occupational medicine (SRo). Occupational agents were categorized as being HMW sensitizers, LMW sensitizers or LMW irritants.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 26. Differences in characteristics were calculated through χ^2 test, One-way ANOVA test or Independent-samples Kruskal-Wallis Test, depending on whether categorical or numerical data were tested. A p-value below 0.05 was regarded statistically significant.
Additionally, we conducted a multivariate regression analysis to determine the best set of independent predictors for undergoing ESS. First, we made a pre-selection of possible predictors by univariate regression analysis.
Based on the total number of patients with no surgery (n=21), we could report on only 2 possible predictors. Possible predictors with a Wald-p value <0.10 were included in a multivariate logistic regression analysis.
To obtain a model for predicting individual risk for ESS in a CRS population that can be used in daily practice, we applied a backward selection (significance level to stay in the model: $p \leq 0.05$

Table 1. Patient characteristics.

		Total	nESS					
			0	1	2	3	≥4	p-value
	n	364	21	80	74	64	125	
	%	100	5,8	22	20	18	34	
Diagnosis (CRSwNP)	n	225	11	46	43	49	76	0,1
	%	62	52	58	58	77	61	
Age	Median	56	63	57	57	51	57	0,1
	IQR	19	20	17	17	23	16	
Gender (male)	n	205	12	41	40	35	77	0,7
	%	55	57	51	54	55	62	
Smoking	Yes (n)	36	3	10	7	2	14	0,3
	%	9,9	14	13	9,5	3,1	11	
	No (n)	203	10	46	44	43	60	
	%	56	48	58	60	67	48	
	Former (n)	125	8	24	23	19	51	
	%	34	38	30	31	30	41	
Allergy to common aeroallergens	n	128	7	28	24	27	42	0,7
	%	35	33	35	32	43	34	
Asthma	n	176	8	32	36	35	65	0,3
	%	49	38	40	49	56	52	
N-ERD	n	61	2	8	9	16	26	0,05
	%	17	10	10	13	26	21	
RSOM-31	μ (0-5)	346	1,13	1,55	1,57	1,80	1,83	0,05
	SD		0,90	1,08	1,14	1,04	1,09	

Total = Total study population; nESS = number of previous ESS; CRSwNP = Chronic rhinosinusitis with nasal polyps; IQR = Inter quartile range; N-ERD – NSAIDs = Exacerbated Respiratory Disease; RSOM-31 = RhinoSinusitis Outcome Measurement; μ = mean; SD = Standard deviation.

and based on likelihood-ratio test ($p \leq 0.10$) and Nagelkerke R^2) to reduce the number of predictors.

Results

Patient characteristics

Of the invited 877 patients with chronic rhinosinusitis with and without nasal polyps, 410 responded (46% response rate). 38 patients returned the questionnaire empty and 8 were excluded because they met exclusion criteria.

Of the patients that responded, 62% (n=225) were diagnosed with CRSwNP. 5.8% had undergone no surgery (n=21), 22% had undergone one surgery (n=80), 20% (n=74) two surgeries, 18% (n=64) three surgeries and 34% (n=125) four or more sinus surgeries. General patient characteristics are listed in Table 1. Patients that had undergone ESS only showed a trend of higher prevalence of N-ERD (p=0.05) and a higher RSOM-31 score (p=0.05).

There were no significant differences between responders and non-responders for diagnosis or items like age, gender, smoking, allergy, asthma or N-ERD.

Occupational exposure

Among all patients who underwent ESS (n=343), 30% reported a relevant occupational exposure, which is significantly higher than the 4.8% found among CRS patients that underwent no prior sinus surgery (n=21)(χ^2=6.30, p=0.04) (Figure 1). No significant difference was seen between patient groups with regards to exposures related to leisure activities (9.9% in ESS group vs. 14% in non-surgical group), including swimming in chlorinated pools (12% in ESS group vs. 14% in non-surgical group). The most frequently reported occupational agents are listed in Table 2. 70% of patients that had a relevant occupational exposure, were exposed to irritants, 37% to LMW sensitizers and 23% exposure to HMW sensitizers. Prevalence of exposure to irritants, LMW sensitizers and HMW sensitizers are shown in Figure 2; we found a higher prevalence in patients that underwent ESS (irritants χ^2= 5.51, p=0.018; LMW sensitizers χ^2= 2.67, p=0.102, HWM sensitizers χ^2= 0.12, p=0.728).

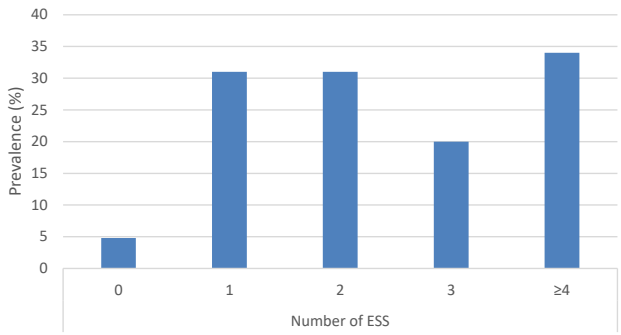

Figure 1. Prevalence of relevant occupational exposure. nFESS=0: 4,8% (n=1); nFESS=1: 31% (n=25); nFESS=2: 31% (n=23); nFESS=3: 20% (n=13); nFESS≥4: 34% (n=43).

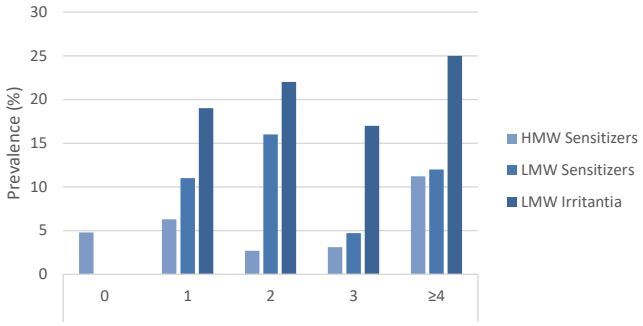

Figure 2. Prevalence of exposure to specific categories.

Table 2. Most frequently reported occupational agents.

Substance	Occupation	Frequency reported
Solvents (e.g., thinner, acetone, white spirit)	Painters, engineers, mechanics, …	35
Cleaning products and disinfectants (incl. bleach)	Cleaners, caretakers, housewives, nurses, …	34
Reactive chemicals (e.g., di-isocyanates, acrylates, epoxy resins)	(Spray) painters, car body repair, dentists, insulation worker	31
Welding fumes and metal dust	Mechanic, motor/car maintenance, metal workers, …	14
Combustion engine exhaust	Motor/car maintenance, drivers, …	13
Medication	Health care / pharmacy	12
Ammonia	Carpenters, mechanics, …	10
Flour	Baker, Farmer, …	9
Flowers	Floriculture, flower shop, …	9
Inorganic dust	Builders, warehousemen, …	8
Latex	Health care, dentist, nurse, …	6
Animals	Farmer, laboratory, …	4
Cement	Builders	4

Several potential prognostic factors were significantly associated with having at least one ESS, in the univariate analysis.

- Self-reported doctor-diagnosed asthma (OR: 2; 95% CI: 0.93 – 5.70)
- Occupational exposure (OR: 8.7; 95% CI: 1.15 – 65.71)

This was also the case in the prediction model (Table 3); the multivariable regression analysis on having had at least one ESS.

In this prediction model, variables like 'age', 'CRSwNP', 'allergy to common aeroallergens', 'smoking' or 'N-ERD' did not have a significant additional contribution to the chance of having had at least one ESS.

Current rhinologic symptoms

RSOM-31

Of the 364 patients analysed for occupational exposure, 95% (n=346) had answered at least 16 items on the RSOM-31 questionnaire. Mean scores (0-5) for RSOM-31 were 1,13 in patients that never underwent FESS, ascending from 1,55 (1 FESS), to 1,57 (2 FESS), to 1,80 (3 FESS) to 1,83 (≥4 FESS), suggesting that more uncontrolled disease was found in the group with more prior ESS. However, the one-way ANOVA test was not significant (p=0.05).

Discussion

The aim of this study was to confirm the previously suggested relationship between occupational exposure and the difficulty to control CRS, as measured by need and number of sinus surgeries. In this retrospective questionnaire-based study in a single tertiary centre CRS population, we confirmed that occupational exposure is a risk factor for ESS. In addition to self-reported occupational exposure, only self-reported doctor-diagnosed asthma was detected as a second independent variable contributing to the chance of undergoing ESS.

Previously, Hox et al. also reported an increasing prevalence of occupational exposure, in groups with increasing number of

Table 3. Prediction model (multivariable regression model) on having had at least one ESS.

							95% C.I.for EXP(B)	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Self-reported doctor diagnosed Asthma	0,809	0,466	3,009	1	0,083	2,246	0,900	5,602
Occupational exposure	2,145	1,032	4,315	1	0,038	8,541	1,129	64,617
Constant	2,093	,298	49,389	1	0,000	8,111		

Note: R^2=0,31 (Cox-Snell), 0,87 (Nagelkerke). Model $\chi^2(2)$=11,5

ESS[5], we could not confirm this finding. This different finding might be explained by the remarkable characteristics of the subjects with nESS=3. In these patients we found a relatively higher prevalence of CRSwNP, a lower age, less smokers, a higher prevalence of allergy to common aeroallergens, asthma and N-ERD, but a lower prevalence of occupational exposure, compared to the nESS=2 and nESS≥4 patients.

The difference in patient populations, as we serve as a tertiary referral rhinosinusitis clinic and in general see patients that were treated by other otorhinolaryngologists before, might cause selection bias, with relatively more patients with uncontrolled CRS, or possibly more risk factors contributing to uncontrolled CRS. This also means that the indications for previous surgery were set by other otorhinolaryngologists which could have led to an overrepresentation of the number of ESS procedures, and, therefore an overrepresentation of patients with uncontrolled CRS. Hox et al. included CRS patients planned for ESS, investigating a population sample with uncontrolled symptoms at inclusion. In our cross-sectional study we also included patients with controlled and partially controlled symptoms. Hox et al. also included patients with recurrent acute rhinosinusitis (ARS), we cannot compare this part of the study population. Also, Hox et al. included a control group of patients undergoing vocal cord surgery, where they found a prevalence of 12% of occupational exposure. We did not include a non-CRS control group, so we cannot compare. We included 21 patients that did not have prior ESS at the time they were included in our study. This small non-ESS part of the population might give an unbalanced view on prevalence of occupational exposure in CRS patients that were not treated with ESS before. Main reasons for not having undergone prior surgery were: successful medical therapy, indication for primary ESS at our first consultation, or a relative contra-indication for ESS; underlying disease or medication unfavourable for ESS (e.g. anticoagulants and heart failure).

Furthermore, the results from our tertiary referral centre study population might not be translated 1:1 to primary or secondary care CRS patients. However, lessons learnt in tertiary care might be applicable to any uncontrolled CRS patient; awareness of occupational exposure is relevant throughout the entire care system.

We used the same questionnaire as modified from Bernstein[18], so as to have the same occupational agents identified and have a similar scoring on possible relevant exposure. In our study we had one assessor of the occupational exposure (SRo), who was trained in the same clinic by the experts that scored the occupational exposure in the study by Hox, so we assumed a reliable comparable assessment of possible relevant occupational agents. Nevertheless, exposure misclassification is possible when using exposure assessments by experts.

For inclusion we set no maximum age of 65 years, risking recall bias for retired patients. Evaluation of relevant exposure is based on occupation and an extensive list of possible agents to choose from. We argued that retired patients could still recall their type of job and possible agents they were exposed to and the possible effects on CRS probably do not have an age limit. A similar analysis on our data with only patients between 18 and 65 years still has 'relevant occupational exposure' as a significant risk factor for undergoing ESS (data not shown). However, it should be noted that self-reported exposure may both over- and underestimate the actual exposure, especially if there has been a long delay between the exposure and the self-report. Patients who have developed symptoms may also be more prone to report exposure; this remains a limitation in self-reporting occupational exposure.

In our cross-sectional design, we sent a postal questionnaire to a selected set of CRS patients that had visited our rhinology practice. Due to the fact that we included patients from visits spread over several years, we did not attempt another postal or telephone reminder. We had a 46% response rate, which is a common response rate in mail surveys.

To evaluate current symptoms in our study population, we added the RSOM-31 to the occupational exposure questionnaire. The mean scores between 1.14 and 1.83 might imply that these patients still suffer from partially controlled CRS[12] as proposed by van der Veen in a Real-life study on uncontrolled CRS. For this comparison we transformed the RSOM-31 items to the SNOT-22 items, patients score 1.18 – 1.90 mean SNOT-22 score.

The cornerstone in managing occupational airway disease is prevention of its development by appropriate occupational hygiene. Early symptoms or sensitizations can be picked up by

means of questionnaires, skin prick tests for specific agents, and increased awareness for onset of nasal symptoms[21]. Once occupational work-related upper airway symptoms are established, avoidance of or reduction in exposure to the suspected causal agent is the key feature of the treatment strategy, with in ultimo relocation of the patient to another job without exposure. When adequate reduction in exposure is impossible or insufficient, rhinitis or rhinosinusitis should be treated according to the guidelines for non-occupational upper airway disease, including topical steroids and nasal rinsing and subsequent clinical evaluation of therapy compliance[6, 22]. This should include asking how patients rinse their nose (type of device, technique, medication, frequency, etc.).

Other studies on occupational exposure and CRS are mainly large-population epidemiologic studies, missing otorhinolaryngologists-based diagnosis of CRS[23-27]. They use questionnaire-based diagnosis of CRS in large population samples and mainly support the relationship between CRS and occupational exposure on a macro level. These results can be very useful in macro-economic and social policy making, however there is increased uncertainty on the actual CRS diagnosis.

The cross-sectional design of our study is well suited for investigating prevalences, however, we experienced several limitations. Our tertiary-care referral CRS population would be eminently suitable for investigating factors contributing to uncontrolled CRS. On the other hand, in several variables we measured unexpected prevalences; for example, lower prevalence of CRSwNP in nESS≥4 compared to nESS=3 (61% and 77% resp.), non-significant increase of prevalence of N-ERD with increased number of ESS and no relation with smoking, which is not in line with literature.

Despite the fact that our study cannot show a significant linear correlation between prevalence of occupational exposure and increased number of ESS, this study does confirm occupational exposure as a risk factor for CRS. For the clinician this yields a potential preventable factor in the complex aetiology of CRS and asthma. Recent papers by Feary et al. and Tarlo et al. on occupational exposures in asthma highlighted the importance of identifying occupational exposure by (primary) health care practitioners, to minimize the risk of long-term impairment from occupational asthma[28, 29].

Conclusion

In our study we confirm occupational exposure as a risk factor for uncontrolled CRS, defined by the need for ESS. In CRS patients with uncontrolled symptoms, despite maximal conservative therapy, the clinician should explore the possible contribution of occupational exposure.

Authorship contribution

DDdL: study design, questionnaire design, data collection, data analysis, analysis of questionnaires, literature search, writing manuscript. SRo: data analysis, analysis of questionnaires, writing manuscript. MC: study design, data collection, data interpretation, writing manuscript. PH: data interpretation, correcting manuscript. VH: data interpretation, correcting manuscript. WF: study design, data collection, data interpretation, writing manuscript. SRe: data interpretation, writing manuscript.

Conflict of interest

All authors declare that there are no conflicts of interest.

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