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Title: Prevalence and impact of nasal hyperreactivity in chronic rhinosinusitis

To the Editor:

Although bronchial hyperreactivity was first reported in 1859, it was only in 1960s that nasal hyperreactivity (NHR) emerged as a field of interest in medicine (1). NHR is defined as an overall hyperresponsiveness of the nasal mucosa to non-specific daily physical and/or chemical stimuli such as humidity, temperature changes, exercise, cigarette smoke, and perfumes (2). There is evidence for NHR being present in allergic (AR) and non-allergic rhinitis (non-AR) (3). The prevalence and pathophysiology of NHR in chronic rhinosinusitis (CRS), however, remains uncertain. CRS is a multifactorial disorder with different underlying pathophysiologic mechanisms contributing to disease development. Up to 20% of patients with CRS fail to achieve disease control, even after guideline-based treatment (4,5). Given that CRS and NHR may give rise to similar nasal symptoms, the presence of NHR in CRS has not yet been documented.

The aim of this study was to investigate the prevalence of self-reported NHR in patients with CRS with/without nasal polyps (CRRwNP and CRSsNP) and to determine the most common triggers.

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The study was conducted at the Department of Otorhinolaryngology, University Hospitals Leuven, Belgium, and the 1st Academic ENT Department of Aristotle University of Thessaloniki, Greece. Data were collected from a questionnaire completed by CRS patients who met the inclusion/exclusion criteria. A control group, not suffering from CRS, were recruited in Leuven. Detailed information on methodology is provided in the Online Supplement. The final study population consisted of 106 controls and 281 CRS patients. Demographics and population characteristics are depicted in **Supplementary Table E1**.

In Leuven, 200 out of 325 individuals (response rate 62%), who received a postal questionnaire, were included for analysis, whereas in Thessaloniki, 81 of the 92 questionnaires (response rate 88%) distributed among CRS patients were suitable for analysis. Self-reported NHR was reported in 64.8% of the studied population (Leuven 59.0% and Thessaloniki 79.0%, $p<0.001$) (**Table 1**), and was significantly higher compared to the control group (64.8% vs. 48.6%, $p=0.009$). Among patients with NHR, 49.4% had CRSwNP, 50.6% had CRSsNP, and approximately 91.8% reported to be under pharmaceutical treatment for CRS. Over half of patients with NHR (52.0%) were classified as uncontrolled based on their VAS-TNSS score, while 18.1% of patients, whose sinonasal disease was under control, reported symptoms consistent to NHR (**Table 2**).

We next explored which stimuli were provoking NHR, and found temperature changes as the most common NHR provoking stimuli (62.5%), followed by humidity (60.9%), odors, emotional stress and physical exercise (**Figure 1**). Up to 83.7% of the NHR group reported to have 1-3 triggers, while 13.6% reported four or more triggers. Additionally, we assessed the quantitative and qualitative characteristics of self-reported NHR provoking stimuli in CRSsNP and CRSwNP (**Supplementary Table E2**). Humidity changes and emotional stress were the major provoking stimuli in CRSsNP ($p=0.014$ and 0.026 respectively), while odors were reported as the major trigger in CRSwNP ($p=0.024$). No statistically significant difference was observed between the 2 subgroups regarding the number of provoking stimuli. Lastly, we evaluated whether treatment with intranasal steroids or other steroid regimen, duration of CRS disease (≤ 5 years and >5 years), or symptom severity correlated with NHR. We only found that quality of life, reflected by SNOT-22 was worse in patients reporting NHR compared to those without NHR ($p<0.05$). Allergy or asthma had no effect on the presence of NHR in CRS patients.

In routine clinical practice, NHR remains under-diagnosed and neglected due to lack of a simple diagnostic tool. Our group developed a protocol using cold dry air to measure NHR with a high sensitivity and specificity. However, this equipment is only available in few academic centers and is not used in daily practice (6). Nowadays, the diagnosis of NHR is based on the history of nasal symptoms induced by non-specific physical and/or chemicals stimuli (7). Interestingly, a higher prevalence of NHR was found in Thessaloniki compared to Leuven, which could be explained by the difference in the environment and climate. Furthermore, difference in recruitment strategy or study population (level of control, concomitant allergy/asthma) might also attribute to differences in NHR prevalence. Unexpectedly, a high prevalence of self-reported NHR was found in the control group. We believe this might be the result of the recruitment of controls, as the presence of CRS was the only exclusion criterium. Individuals with undiagnosed chronic rhinitis or CRS could be included as controls, and thus might explain the high prevalence of self-reported NHR. Overall, the most common trigger for provoking NHR was temperature changes, followed by humidity and odor exposure. Moreover, patients reporting NHR had a tendency for having higher SNOT-22 score, though without reaching statistical significance. When co-morbidities were excluded, a similar trend was still present. Additionally, 52% of patients with NHR were classified as uncontrolled, which is in line with the hypothesis that hyperreactivity is a possible feature of uncontrolled disease (4). Nonetheless, the pathophysiology of NHR is not fully elucidated. It is assumed that increased nasal epithelial permeability, dysbalanced autonomous nervous system with a predominance for parasympathetic innervation, decreased activation threshold of afferent sensory nerves to release neuromediators, and nasal vascular as well as glandular tissue alterations are possible underlying mechanisms, though needs further confirmation. Utilization of specific VAS–TNSS cut-off levels of control assessment was based on a previous study, where VAS scores of CRS symptoms were compared for different levels of control according to EPOS criteria (8). We recently demonstrated that VAS score for TNSS correlated with SNOT-22 and can accurately predict disease severity, level of control, and burden of disease in CRS (9).

Our study holds some limitations. Firstly, we did not objectively confirm the presence of NHR using CDA provocation, as this is only available in academic research centers. However, the history of self-reported NHR in relation to CDA-induced NHR has been reported by others (7) and

by ourselves (unpublished data). Therefore, a history of NHR is valid and user-friendly in daily practice. Secondly, the high prevalence of self-reported NHR in CRS might be biased since patients were recruited in academic referral centers and not in primary care facilities. Still, the prevalence of NHR corresponded well with the prevalence reported in AR and non-AR patients (2,3). Lastly, our study was performed on a relatively small sample size, but relevant to demonstrate NHR in CRS for the first time.

In this multi-institutional questionnaire survey, we report the presence of self-reported NHR in almost two third of CRS patients. NHR remains a neglected presenting symptom in CRS in daily practice and opens opportunities for further research on endotypes and phenotypes of CRS. The lack of a simple diagnostic tool, the limited data on the contribution of NHR to the disease severity, the limited insight into underlying pathophysiologic mechanisms of NHR in CRS and the impact of NHR on chronic rhinitis and rhinosinusitis, all underline the urgent need to invest into the unexplored role of NHR in the Rhinology field.

Figure legend

Figure 1. Type and frequency of NHR provoking stimuli in the total CRS population.

Abbreviations: * ; $p=0.026$, ** ; $p=0.005$

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Tables

Table 1. Prevalence of self-reported NHR by site, and in the total study population.

			Self-reported NHR			
			N (%)			
			Absent	Present	Don't know	p-value
Patients with CRS	Site	Center 1	63 (31.5%)	118 (59.0%)	19 (9.5%)	<0.001
		N= 200				
		Center 2	7 (8.6%)	64 (79.0%)	10 (12.3%)	
		N=81				
Patients with CRS	Total population		70 (24.9%)	182 (64.8%)	29 (10.3%)	0.009
	N= 281					
Control group	Center 1		42 (40%)	51 (48.6%)	12 (11.4%)	
	N=106					

Abbreviations: N; Number

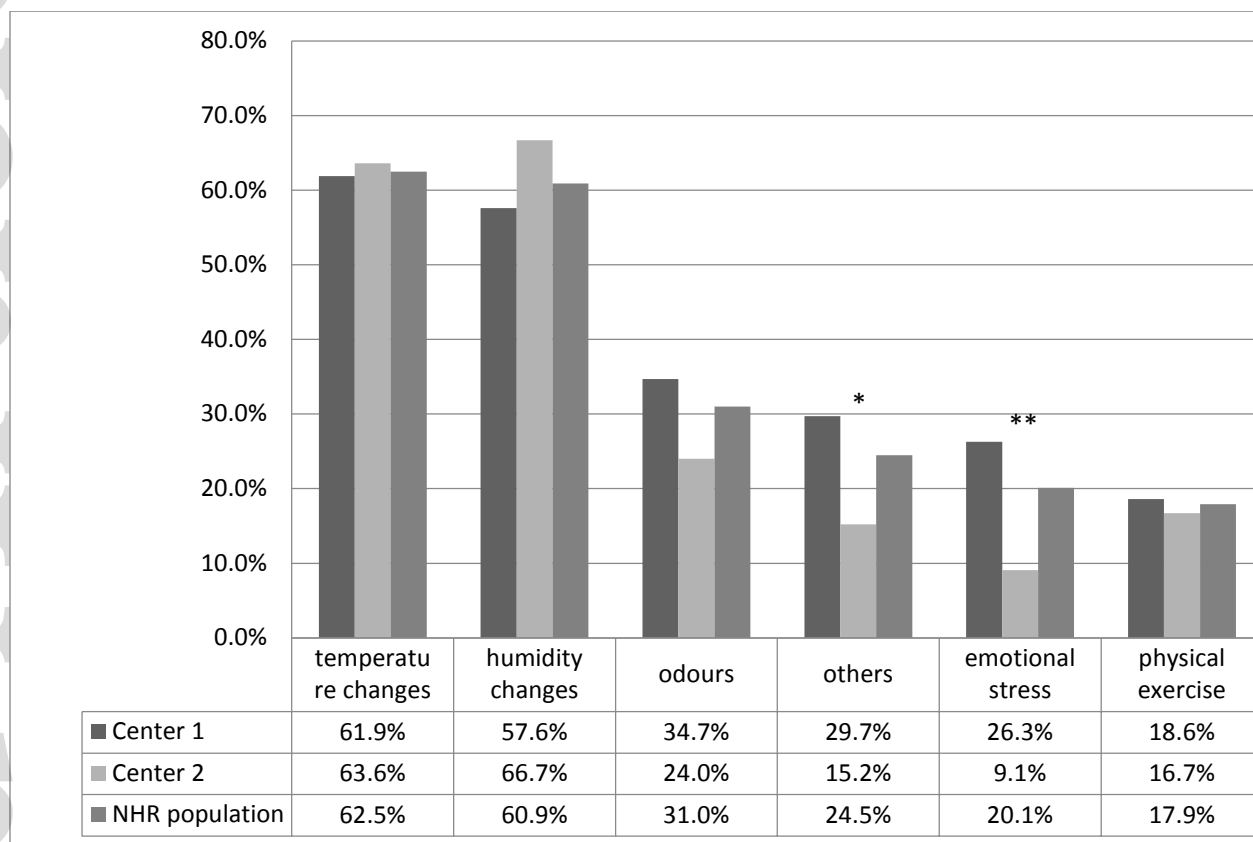
Table 2. Population demographic and clinical characteristics of patients with CRS and controls who reported nasal hyper-responsiveness.

Demographics						
Total	Center 1	Center 2	p-value ¹	Controls	p-value ²	

		N=182	N=118	N=64		N=51	
Gender; n (%)	Female	82 (45.3%)	48 (41%)	34 (53.1%)		34(66.7%)	
	Male	99 (54.7%)	69 (59%)	30 (46.9%)		17(33.3%)	0.004
Age (years); mean±SD		50.15±16.77	52.72±16.126	45.47±17.046	0.006	39.9 ± 16.4	<0.001
Surgery; n (%)	Yes	117 (64.3%)	103 (87.3%)	14(21.9%)	<0.001	NA	NA
Smoking; n (%)	Never	114 (63.3%)	77 (66.4%)	37 (57.8%)	0.073	43(86%)	0.035
	Current	31 (17.2%)	16 (13.8%)	15 (23.4%)		3(6%)	
	Ex-smoker	35 (19.4%)	23 (19.8%)	12 (18.8%)		4(8%)	
Current Treatment; n (%)	Yes	167 (91.8%)	107 (90.7%)	60 (93.8%)	0.472	NA	NA
Profession	Indoor	106 (65%)	78 (78.8%)	28 (43.8%)		42(85.7%)	0.067
	Outdoor	43 (26.4%)	11 (11.1%)	32 (50%)		7(14.3%)	
	Chemical	14 (8.6%)	10 (10.1%)	4 (6.3%)		0(0%)	
Clinical characteristics							
CRSSNP; n (%)		91 (50.6%)	53 (45.7%)	38 (59.4%)	0.079	NA	NA
CRSwNP; n (%)		89 (49.4%)	63 (54.3%)	26 (40.6%)		NA	NA
Co morbidities							
Asthma; n (%)		47 (26.1%)	32 (27.6%)	15 (23.4%)	0.544	3(5.9%)	0.003
Allergy; n (%)		83 (46.4%)	46 (40%)	37 (57.8%)	0.220	14(27.5%)	0.168
Level of control							
Controlled; n (%)		32 (18.1%)	27 (23.9%)	5 (7.8%)		NA	NA
Partially Controlled; n (%)		53 (29.9%)	44 (38.9%)	9 (14.1%)		NA	NA
Uncontrolled; n (%)		92 (52.0%)	42 (37.2%)	50 (78.1%)	<0.001	NA	NA

Abbreviations: N; Number, NA; Not Applicable

Figure 1. Type and frequency of NHR provoking stimuli in the total CRS population.



Abbreviations: * ; p=0.026, ** ; p=0.005

1 **Title: Prevalence and impact of nasal hyperreactivity in chronic rhinosinusitis**

2

3 **Online Supplementary file**

4

5 **Methods**

6 **Study design**

7 A questionnaire-based survey was conducted in 2 University Departments: the
8 Department of Otorhinolaryngology, Head and Neck Surgery of the University
9 Hospitals of Leuven in Belgium and the 1st Academic ENT Department of Aristotle
10 University of Thessaloniki (AUTH), AHEPA hospital in Greece.

11 In Leuven, subjects who visited the outpatient clinic and in whom CRS was diagnosed
12 between January and May 2016 were subtracted from the digital clinical files.
13 Evaluation of full medical records was performed by an ENT specialist to confirm the
14 diagnosis based on EP³OS defining criteria for CRS (symptoms, compatible
15 endoscopic findings and/or computed tomography abnormalities when imaging was
16 available). After screening of the patients' medical record, a questionnaire was sent
17 to 325 subjects who met the above criteria. Patients received a postal questionnaire
18 together with the study rationale, and an informed consent. Patients were asked to
19 fill out the questionnaire after signing the informed consent and to return all forms
20 by ordinary post. In order to reach a response rate of 60%, non-responders were
21 contacted by phone to communicate the importance of the study and encourage

22 them to fill out the documents. To exclude a possible selection bias, 20 randomly
23 selected non-responders were contacted by phone to repeat the questionnaire.

24 Furthermore, a control group of 106 subjects without a doctor-based diagnosis of
25 CRS were recruited at the University Hospitals Leuven. Participants were recruited by
26 a clinical-trial assistant and consisted of subjects working at the hospital and the
27 University of Leuven. The same questionnaire together with an informed consent
28 was handled over. Allergy and asthma was not considered a limitation for
29 participation in the control group.

30 In Thessaloniki, patients visiting the outpatient clinic were recruited. Study subjects
31 diagnosed with CRS based on EP³OS 2012 criteria were given the same questionnaire
32 translated into Greek language. Questionnaires were filled in upon patients' visit to
33 the outpatient clinic, instead of postal questionnaires.

34 In both centers, patients younger than 16 years, those with primary
35 immunodeficiency, ciliary dyskinesia, cystic fibrosis, malignant tumors, and/or
36 surgery for CRS within 6 months prior to the study were excluded from this study.
37 Patients with a previously documented diagnosis of psychiatric disorder were also
38 excluded from the study as their ability to give reliable information could be
39 disputed. Concomitant AR or bronchial asthma was not considered to be a limitation
40 for participation in the study. An informed consent was obtained from all
41 participants and the study was approved by the local institutional Medical Ethics
42 Committees.

43

Questionnaires

The questionnaire was subdivided in 4 parts. In part A; subjects were asked to give information about their CRS condition, current and past medication for CRS, medical and surgical history, and to provide answers on personal and demographic characteristics. In part B patients had to give information regarding their allergic status and/or asthma, and their current medication for these conditions while part C was dedicated to the presence and triggers of NHR. Patients were asked to evaluate if their nasal symptoms were worsening upon one or more triggers, i.e. changes in humidity or temperature, emotional stress, exercise, and chemical pollutants like perfumes and tobacco smoke, responsible for provoking NHR. Part D of the questionnaire was dedicated to assessing patients' Quality of Life (QoL) and severity of symptoms by using the SNOT-22 questionnaire and Visual Analogue Scale (VAS) scores. Patients were asked to draw a vertical line on a 10 cm scale from 0 to 10, according to how bothersome were specific sinonasal symptoms, and Total Nasal Symptom Score (TNSS) in the last month. Level of control was assessed by using the following cut-off points for TNSS: well controlled ($VAS \leq 2$), partly controlled ($VAS > 2$ and ≤ 5), uncontrolled ($VAS > 5$).

Statistical analysis

Descriptive statistics for baseline data are presented as counts (percentage (%)) for categorical variables and as mean (standard deviation (SD)) for normally distributed variables or as median (minimum-maximum) for continuous variables without a

normal distribution. Chi-square test or Fisher's exact test and T-test or Mann-Whitney U test were used to identify differences for qualitative or quantitative variables, respectively. A P-value of <0.05 was considered to indicate a statistically significant differences. Significant associations as given by Chi-square or Fisher's exact test were also evaluated with logistic regression analyses adjusted for center and other characteristics. Odds ratio (OR) and 95% confidence intervals (95%CI) are presented. Data management and statistical analyses were performed in IBM-SPSS Statistics software (version 23).

Multivariate analysis

No significant association was found between NHR in regard to presence of nasal polyps, treatment with intranasal steroids (INCS) or other steroid regimen, duration of CRS disease (≤ 5 years and >5 years), and VAS-TNSS score (data not shown). QoL reflected by means of SNOT-22 appeared to be worse in the NHR subgroup of CRS compared to CRS patients who did not report NHR with a borderline significant p-value ($p=0.08$). Similarly QoL was significantly worse in CRS patients compared to controls ($p<0.001$) and this finding remained significant even when we restricted analysis with cases and controls from Center 1 only ($p<0.001$) (data not shown). When co-morbidities (allergy, asthma) were excluded, a similar trend was still present. Among CRS patients with NHR, higher SNOT-22 score was observed in patients with concomitant allergy and asthma who scored VAS-TNSS ≥ 5 and had several surgeries (statistical analysis available upon request).

90 **Table E1.** Demographic and clinical characteristics of patients in the database study.

Demographics					
		Total CRS population N=281	Center 1 N=200	Center 2 N=81	P-value
Gender; n (%)	Female	120 (43%)	77 (38.1%)	43 (53.1%)	0.030
	Male	159 (57%)	121 (61.1%)	38 (46.9%)	
Age (years); mean±SD		50.13±1.030	52.45±16.453	46.62±17.692	0.013
Surgery; n (%)	Yes	186 (66.4%)	167 (83.9%)	19 (23.5%)	<0.001
Number of FESS median(min-max)		2(1-5)	2 (1-5)	1 (1-3)	0.552
Smoking; n (%)	No	177 (63.4%)	133 (67.2%)	44 (54.3%)	0.035
	Current	45 (16.1%)	25 (12.6%)	20 (24.7%)	
	Ex-smoker	57 (20.4%)	40 (20.2%)	17 (21%)	
Current Treatment; n (%)	Yes	251 (89.3%)	175 (87.5%)	76 (93.8%)	0.120
Profession	Indoor	171 (69.8%)	134 (81.7%)	37 (45.7%)	<0.001
	Outdoor	53 (21.6%)	16 (9.8%)	37 (45.7%)	
	Chemical	21 (8.6%)	14 (8.5%)	7 (8.6%)	
CRSsNP; n (%)		131 (47%)	86 (43.4%)	45 (55.6%)	0.066
CRSwNP n(%)		148 (53%)	112 (56.6%)	36 (44.4%)	
Asthma; n (%)		74 (26.5%)	58 (29.3%)	16 (19.8%)	0.101
Allergy; n (%)		113 (40.8%)	71 (36.2%)	42 (51.9%)	0.016
Controlled; n (%)		52 (19.1%)	45 (23.6%)	7 (8.6%)	<0.001
Partially Controlled; n (%)		82 (30.1%)	68 (35.6%)	14 (17.3%)	
Uncontrolled; n (%)		138 (50.7%)	78 (40.8%)	60 (74.1%)	

91

92 **Abbreviations:** n, N; number

93

Table E2. Number and type of NHR provoking stimuli in CRS patients with and without nasal polyps.

	CRSsNP n=91	CRSwNP n=89	CRSsNP vs CRSwNP
Number of NHR provoking stimuli per patient			
	N (%)	N (%)	P-value
0 trigger	1 (1.1%)	1 (1.1%)	NS
1-3 triggers	73 (80.2%)	80 (89.9%)	NS
≥4 triggers	17 (18.7%)	8 (9.0%)	NS
Types of NHR provoking stimuli			
	N (%)	N (%)	P-value
Temperature Changes	62 (68.1%)	52 (58.4%)	NS
Odours	21 (23.1%)	35 (39.6%)	0.024
Physical Exercise	13 (14.3%)	19 (21.3%)	NS
Emotional Stress	25 (27.5%)	12 (13.5%)	0.026
Humidity Changes	65 (71.4%)	47 (58.2%)	0.014
Others	25 (27.5%)	20 (22.5%)	NS

Abbreviations: N; Number, NS; Not Significant