Feijen et al. World Allergy Organization Journal (2020) 13:100132
http://doi.org/10.1016/j.waojou.2020.100132

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Prevalence and triggers of self-reported nasal hyperreactivity in adults with asthma

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ABSTRACT

Background: Nasal hyperreactivity (NHR) is a common feature of various rhinitis subtypes and represents a novel phenotype of rhinitis. It is being reported in two-thirds of adult rhinitis patients irrespective of the atopic status. Data on the prevalence of NHR in patients with asthma are lacking, as well as the nature of evoking triggers.

Methods: Postal questionnaires were distributed to an unselected group of asthmatic patients in Leuven (Belgium, n = 190) and completed by 114 patients. In Mexico City (Mexico) and Brasov (Romania), respectively, 97 out of 110 and 80 out of 100 asthmatic patients attending the outpatient clinic completed the questionnaire. Non-asthmatic volunteers were recruited amongst university and hospital co-workers in Leuven (n = 53). The presence of self-reported NHR, the type of triggers evoking nasal and bronchial symptoms, medication use, self-reported allergy, and environmental factors were evaluated.

Results: Overall, 69% of asthma patients reported NHR, with 32% having more than 4 triggers evoking NHR. These triggers included mainly exposure to temperature and humidity changes, cigarette smoke, and strong odours. A higher prevalence of NHR was detected in allergic compared to non-allergic asthma patients (73% vs. 53% $p < 0.01$). The prevalence of NHR correlated with asthma severity, ranging from 63% (VAS $\leq$3) to 81% (VAS $\geq$7). BHR was found more frequently in patients with NHR compared to without NHR (89% vs. 53%, $p < 0.0001$).

Conclusion: NHR represents a clinical phenotype of upper airway disease affecting over two-thirds of asthma patients and correlates with asthma severity. Targeting NHR in patients with asthma is often overlooked and should be reinforced in the future to achieve better symptom control.

Keywords: Asthma, Nasal hyperreactivity, Bronchial hyperreactivity, Symptom severity, Atopy

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http://doi.org/10.1016/j.waojou.2020.100132

Received 8 November 2019; Received in revised from 15 May 2020; Accepted 17 May 2020
Online publication date xxx

INTRODUCTION

Asthma is a frequent co-morbidity of both rhinitis and chronic rhinosinusitis, both allergic and non-allergic.[1–4] Both bronchial (BHR) as well as nasal hyperreactivity (NHR) are cardinal features of asthma and rhinitis respectively. BHR is defined as a symptomatic response of the bronchi to a variety of physical, chemical, or environmental stimuli, resulting in wheezing, shortness of breath, coughing, and/or chest tightness.[1] The presence of BHR can be assessed by performing a bronchial provocation test with direct or indirect stimuli. Direct agents such as histamine and methacholine act directly on the airway smooth muscle cells, while indirect stimuli such as exercise, eucapnic hyperventilation, hypertonic saline, mannitol, and adenosine monophosphate induce bronchoconstriction by stimulating neuronal pathways or by stimulating the release of inflammatory mediators.[2,3]

Nasal hyperreactivity (NHR) is defined as increased sensitivity of the nasal mucosa to various non-specific stimuli, resulting in nasal symptoms such as obstruction, rhinorrhoea, itchy nose, and/or sneezing.[4] Known stimuli that are able to provoke NHR are strong odours, cigarette smoke, sudden changes in temperature, irritants, emotions, and/or physical exercise.[9,10] NHR is present in approximately two-thirds of rhinitis patients, with similar prevalence rates and provoking factors in allergic rhinitis (AR) and non-allergic rhinitis (NAR).[5,6] Although NHR is not routinely evaluated in clinical practice, several nasal provocation tests are described in literature to evaluate the presence of NHR.[4] In parallel with the histamine provocation test for BHR, a nasal histamine provocation test is described to diagnose NHR, but this test failed to prove a significant difference in increase of nasal resistance between patients with NAR and healthy controls.[7] An alternative nasal provocation test to diagnose NHR with high sensitivity (67%) and specificity (100%) is the cold dry air (CDA) provocation test. The latter consists of 15 min' exposure to a 25 l/min airflow of −10 °C and a relative humidity of <10%.[8,9] Superiority of nasal CDA exposure to nasal histamine provocation is proven in patients with non-allergic, non-infectious rhinitis, with a sensitivity for CDA of 87% and specificity of 71%.[9] In clinical practice, NHR can be diagnosed with a simple clinical history, with specific questions directed at the detection of nasal symptoms being induced by exposure to environmental triggers and/or stress factors.[5,10]

At present, NHR has not been evaluated in patients with asthma, nor are the triggers causing nasal symptoms evaluated. This study aims to document self-reported NHR in allergic and non-allergic asthma patients in 3 different geographical sites. Insight into this novel phenotype might lead to better therapeutic strategies to improve asthma symptom control.

MATERIALS AND METHODS

Study design

Patients, included in the 3 sites, had a physician-based diagnosis of asthma, with previous proof of reversibility of FEV1 $\geq$ 12% after inhalation of salbutamol and/or a positive histamine provocation test (PC20 $<$ 8 mg/ml). Healthy non-asthmatic volunteers were recruited amongst Belgian university and hospital co-workers (n = 53).

The questionnaires along with the informed consent document were sent by post in Belgium to a group of unselected patients recruited in a previous study.[11] This database consisted of 190 patients with asthma for which the home address was available. To reach an adequate response rate, non-responders were contacted twice by telephone. Responder bias was excluded by calling at least 15% of the non-responders and evaluating the presence of NHR. No significant difference in the prevalence of NHR was found between responders and non-responders in Leuven, making responder bias unlikely ($p = 0.325$; data not shown).

In Mexico and Romania, asthmatic patients were recruited amongst those attending the outpatient clinic of pulmonology and allergy.

Questionnaire

The survey was subdivided in 5 sections. The first section focused on the presence and severity of upper airway symptoms. Study participants were asked to score cardinal rhinitis and rhinosinusitis

symptoms, by indicating symptom severity on a 10 cm visual analogue scale (VAS).[16–18] Next, patients were asked for the presence of 1 or more non-specific factors provoking nasal symptoms, like sudden temperature changes, humidity changes, emotions/stress, cigarette smoke, strong odours, and physical exercise.[12] The second section focused on the presence and severity of lower airway symptoms, including the triggers for BHR. In Results, current asthma therapy, use of nasal sprays, and anti-allergic medication was interrogated. The fourth section was titled "environmental factors", and it contained questions regarding self-reported exposure to allergens in case of allergy, smoking, hobbies, and occupational environment. The last part of the survey asked for general demographic data. The presence of self-reported rhinitis and chronic rhinosinusitis was not assessed.

The original questionnaire was developed in Dutch. The Romanian and Spanish versions were forward and back translated. The full version of the survey can be found in the online supplement.

Definitions

VAS has been used previously as an easy measure to assess the severity of rhinitis as well as rhinosinusitis.[11–13] We used the following cut-off points for upper airway severity proposed by Hopkins et al.[14,15] Mild rhinosinusitis was defined as VAS $\leq$3 cm, moderate between 3 and 7 cm, and severe rhinosinusitis as VAS $\geq$7 cm.

NHR was defined as the presence of nasal symptoms such as sneezing, runny nose, nasal obstruction provoked by non-specific stimuli, including sudden changes in temperature, humidity changes, emotions or stress, cigarette smoke, strong odours, and/or physical exercise responsible for nasal symptoms.

Similar to the cut-off points used for upper airways, we defined mild asthma as VAS of total lower airway symptoms $\leq$3 cm, moderate asthma between 3 and 7 cm and severe asthma as VAS $\geq$7 cm. The SACRA study previously validated the use of the VAS as a predictor of GINA-defined asthma severity.[16]

BHR was defined as the presence of bronchial symptoms induced by non-specific stimuli, including sudden changes in temperature, humidity changes, emotions or stress, cigarette smoke, strong odours, and/or physical exercise.

The allergy status was determined based on the presence of self-reported allergies. Active smoking was defined as current smoke of at least 5 cigarettes a week.

Statistical analysis

Statistical analyses were performed with Graphpad Prism VI (Graphpad Software Inc., San Diego, USA). Normality was analyzed by D'Agostino-Pearson omnibus test. When normally distributed the T-test or ANOVA were used, otherwise the Mann–Whitney test or Kruskal-Wallis test were applied. To compare proportions, the Chi squared test was used. The significance level was set at $p < 0.05$. Multiple testing was preformed with Kruskal-Wallis test and post-hoc Dunn's multiple comparisons test.

RESULTS

Patient characteristics

The total number of included asthmatic patients was 291. They resulted from a response rate of 60%, 91%, and 80% in Belgium, Mexico, and Romania, respectively. Eighty-two percent of the included asthma patients had asthma symptoms for more than 5 years at the moment of inclusion. Control subjects ($n = 53$), without history of asthma symptoms, were recruited among the university and hospital staff in Leuven. Seventy-three percent of asthma patients suffered for more than 5 years of nasal symptoms. Subject characteristics are presented in Table 1.

No significant differences in age between the 4 cohorts were found ($p = 0.19$). A higher proportion of females was reported in the Mexican cohort compared to the other cohorts. Allergy was reported in 75%, 89%, and 65% of asthmatics in Belgium, Mexico, and Romania, respectively, compared to 28% in control subjects. The use of inhaled steroids was comparable between the 3 cohorts ($p = 0.66$), though a significant difference in nasal steroid usage was observed ($p < 0.0001$),

Subjects characteristics					
Country	ASTHMA PATENTS			CONTROLS	P value
	Belgium (n = 114)	Romania (n = 80)	Mexico (n = 97)	Belgium (n = 53)	
Age					
median (interquartile range)	47 (38–57)	49 (41–58)	47 (29–56)	47 (29–57)	0.19
mean (standard deviation)	47 (13)	49 (13)	44 (15)	44 (15)	
Gender (M/F)	56/58$^{\dagger\dagger\dagger *}$	37/43††	24/73	18/35	0.0014
Active smoking (%)	13 (11%)	9 (11%)	3 (3%)	2 (4%)	0.06
Respiratory allergy	86 (75%)$^{\dagger\dagger ***}$	52 (65%)$^{\dagger\dagger\dagger\dagger ****}$	86 (89%)***	15 (28%)	<0.0001
Nasal steroids use	48 (42%)$^{\#\#\dagger\dagger\dagger\dagger **}$	48 (60%)$^{\dagger\dagger\dagger ***}$	79 (81%)****	1 (0.5%)	<0.0001
Nasal Steroid + nasal antihistamine	0	9 (11%)	4 (4%)	NA	
Inhaled steroids use	88 (77%)	61 (76%)	79 (81%)	NA	
Inhaled and oral steroids use	3 (3%)	0	1 (1%)	NA	
Oral antihistamine	41 (36%)	21 (26%)	24 (25%)	4 (7%)	
Oral antileukotriene	14 (12%)	5 (6%)	15 (15%)	NA	
Oral antihistamine and antileukotriene	16 (14%)	5 (6%)	10 (10%)	NA	
No airway treatment	16 (14%)	16 (3%)	9 (9%)	NA	
VAS total lower airways					
median (interquartile range)	4 (2–6.3)$^{\#\#\# ***}$	2.2 (0.8–3.6) ****	2.6 (0.8–4.9) ****	0 (0–0)	<0.0001
mean (standard deviation)	4.1 (2.6)	2.3 (1.7)	3.2 (2.8)	0.1 (0.4)	
VAS total upper airways					
median (interquartile range)	4.6 (2–6.4)$^{\dagger\dagger **}$	2 (0.6–4.1)$^{\dagger\dagger\dagger ***}$	4.8 (1.5–6.5) ***	0 (0–0.2)	<0.0001
mean (standard deviation)	4.2 (2.8)	2.60 (2.4)	4.40 (2.9)	0.5 (1.3)	

Table 1. Patient and control characteristics, medication use and subjective report of upper and lower airways symptoms. Data were represented as median and 25–75% (interquartile range) percentile and mean and standard deviation, analyzed by Kruskal-Wallis test. We used chi-squared test to compare proportional groups. *Dunn's Multiple Comparison test was used as a post hoc test. *, ****, $p < 0.05$, $p < 0.0001$ respectively compared to controls. ††, †††, $p < 0.01$ and $p < 0.001$ respectively compared with the Mexican cohort. ##, ###, $p < 0.01$, $p < 0.001$ respectively compared to the Romanian cohort. VAS: visual analogue scale; NA: not applicable*

with the highest usage rate in Mexico (81%). The Belgian cohort had the highest VAS of overall lower airway symptoms, whereas VAS overall upper airway symptoms were equally high in Belgium and Mexico (Table 1). A small but significant correlation was found between VAS of upper and lower airway symptoms ($R^2 = 0.26$, $p < 0.0001$).

Self-reported nasal hyperreactivity

NHR was reported in 69% of patients with asthma versus 22% in the control population

($p < 0.0001$) (Fig. 1). The Romanian cohort had the lowest prevalence of NHR (53%), which was significantly different from the prevalence in Belgium (71%) and Mexico (78%). The most commonly reported provoking trigger of NHR was sudden change of temperature (75%), followed by humidity changes (53%) and cigarette smoke (53%). There were slight differences in the ranking of provoking triggers between the 3 cohorts. In the Belgian cohort, strong odours as provoking factor was rated in the second place, while the Romanian and Mexican patients reported this stimulus at the second-to-last place. One-third of asthmatics reported having 4 or more stimuli responsible for provoking upper airway symptoms.

We evaluated whether NHR correlated with increasing severity of upper airway symptoms as assessed by VAS. The prevalence of NHR was significantly higher in patients with severe upper airway symptoms (VAS $\geq$ 7; 78% presented NHR) compared to patients with mild sinonasal symptoms (VAS $\leq$ 3; 46% presented NHR) ($p = 0.0016$) (Fig. 1D).

A similar analysis was performed with the cut-off points recently proposed by Klimek et al for patients with allergic rhinitis who defined mild rhinitis as VAS <2 cm, moderate between 2 and 5 cm and severe rhinitis as VAS >5 cm.[17] This analysis confirmed the association between disease severity and NHR (Figure E1).

NHR was more prevalent in allergic asthma compared to non-allergic asthma (73% vs. 53%, $p < 0.01$) (Fig. 1E). Interestingly, patients using nasal steroids had a higher prevalence of NHR compared to patients who are not taking nasal steroids (74% vs. 59%; $p < 0.01$) (Figure E1). No significant difference in prevalence of NHR was found in relation to use of inhaled steroids ($p = 0.076$) or gender ($p = 0.71$).

Self-reported bronchial hyperreactivity

Next, we evaluated the presence of self-reported BHR. Seventy-eight percent of patients with asthma reported the presence of BHR (Fig. 2), with sudden temperature changes as the most common provoking stimulus (69%) followed by physical exercise (62%). Thirty-seven percent of patients had 4 or more stimuli responsible for evoking BHR. BHR was more present in patients with severe upper airways symptoms ((VAS $\geq$ 7; 93% presented BHR) compared to patients with mild sinonasal symptoms (VAS $\leq$ 3; 74% presented BHR) ($p = 0.01$) (Fig. 2D). There were no significant differences in BHR between allergic and non-

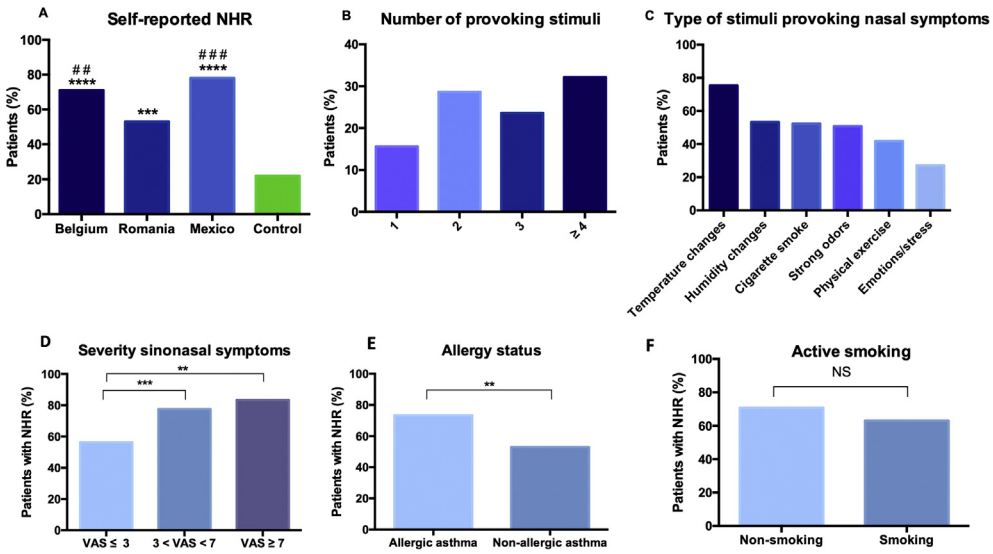

Fig. 1 NHR in asthma patients and control. (A) Percentage of patients with asthma reporting NHR. **(B)** Percentage of patients reporting how many triggers are provoking NHR. **(C)** Provoking stimuli displayed in order of frequency**. (D)** Percentage of self-reported NHR in mild (VAS $\leq$ 3), moderate (between 3 and 7 cm) and severe sinonasal disease (VAS $\geq$ 7). (**E**) Prevalence of NHR in allergic vs. non-allergic asthma. **(F)** Prevalence of NHR in non-smoking vs. smoking. ****; $p < 0.0001$, ****; $p < 0.0001$, ***; $p < 0.001$, **; $p < 0.01$ compared with control group. # # #; $p < 0.001$, # #; $p < 0.01$ compared with the Romanian cohort. NS; not significant

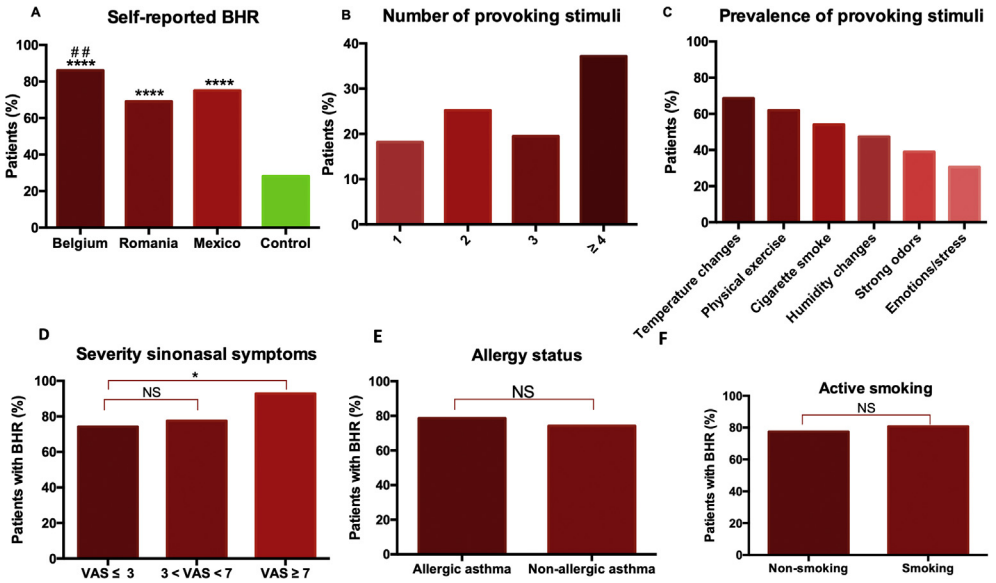

Fig. 2 BHR in asthmatic patients and controls. (A) Percentage of patients with asthma reporting BHR. **(B)** Percentage of patients reporting how many triggers are provoking BHR. **(C)** Provoking stimuli displayed in order of frequency**. (D)** Percentage of self-reported BHR in mild (VAS $\leq$ 3), moderate (between 3 and 7 cm) and severe sinonasal disease (VAS $\geq$ 7). (**E**) Prevalence of BHR in allergic vs. non-allergic asthma. **(F)** Prevalence of BHR in non-smoking vs. smoking. ****; $p < 0.0001$, *; $p < 0.05$ compared with control group. # #; $p < 0.01$ compared with the Romanian cohort. NS; not significant

allergic asthma ($p = 0{,}45$) (Fig. 2E) or smokers ($n = 27$) and non-smokers ($p = 0{,}69$) (Fig. 2F).

Correlation of NHR and BHR

We evaluated the presence of BHR in patients with or without NHR. BHR was detected in 89% of asthma patients with self-reported NHR, while only 53% of patients without self-reported NHR had BHR ($p < 0.0001$) (Fig. 3A).

NHR and asthma severity

Lastly, we evaluated whether NHR correlated with asthma control as assessed by VAS. The prevalence of NHR was significantly higher in patients with uncontrolled asthma (VAS $\geq$ 7; 81% presented NHR) compared to patients with mild symptoms (VAS $\leq$ 3; 63% presented NHR) ($p = 0.024$) (Fig. 3B).

DISCUSSION

In this multicentre questionnaire-based study, we investigated the prevalence of NHR in adults with asthma. We here demonstrate for the first time that NHR is present in up to 69% of patients with asthma. Considering the high prevalence of NHR in allergic and non-allergic rhinitis and the concept of united airway diseases, this finding is not completely unexpected.[18] Although the prevalence of NHR is similar in allergic and non-allergic rhinitis, we found a significant higher

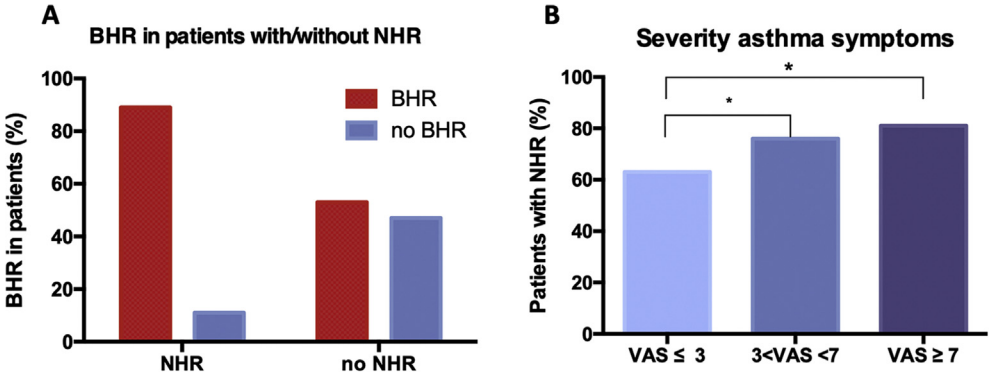

Fig. 3 Prevalence of BHR in patients with and without NHR. (A) Percentage of asthmatic patients with and without NHR reporting BHR. **(B)** Percentage of self-reported NHR in mild (VAS $\leq$3), moderate (between 3 and 7 cm) and severe asthma (VAS $\geq$ 7) *; $p < 0.05$

prevalence in asthma patients with self-reported respiratory allergies compared to patients without self-reported respiratory allergies,[5] suggestive of Type 2 cytokines being involved in NHR. Additional studies are needed to confirm this observation.

Sudden changes in temperature was found as the most common provoking stimulus of nasal as well as bronchial symptoms. Exposure to cold air has previously been associated with the induction of both upper and lower airway symptoms.[8,19] This has led to the development and validation of CDA provocation as a diagnostic test for NHR.[8,9] Interestingly, exercise was the second most important trigger of bronchial symptoms whereas this was only ranked fifth as a stimulus of nasal symptoms, most likely the result of a different breathing pattern, ie, shift from nose to mouth breathing, during exercise. This observation however confirms the role of exercise as an important driver of airway narrowing and bronchial symptoms.[20–22]

We might have underestimated the percentage of patients suffering from NHR as we applied the definition of NHR earlier proposed by Segboer et al, ie, induction of nasal symptoms upon exposure to external non-allergic triggers, which does not exclude those patients with aggravation of nasal symptoms by external triggers.

Patients in Romania showed the lowest prevalence of NHR (52%). This might be explained by the lower VAS of overall upper and lower airway symptoms as a reflection of better disease control. Given that we deal with two separate populations we cannot rule out other variables influencing the degree of NHR.

Almost all patients with NHR reported BHR, which is suggestive of similar pathophysiologic mechanisms underlying NHR and BHR. In addition, an association was demonstrated between the degree of upper and lower airway symptoms. This suggests that a common pathway leads to hyperreactivity of the unified respiratory mucosa in predisposed individuals. Indeed, our research group has previously demonstrated the involvement of Substance P and transient receptor potential (TRP) V channels in the development of NHR, which has also been reported in BHR and asthma.[23] Alternatively, upper airways disease is considered as an important trigger of bronchial symptoms via the blood stream and via nasobronchial neural pathways.[24] Here, the proportion of patients with severe upper airway symptoms was higher in highly symptomatic compared to lowly symptomatic asthmatics ($p < 0.0001$; Figure E2).

The prevalence of NHR significantly increased with increasing symptom severity reaching 80% for patients with the most severe airway symptoms. Suboptimal treatment for nose and sinuses is reflected by the fact that 40% of asthma patients had severe upper airway symptoms (data not shown and in Doulaptsi et al[25]). Treatments targeting NHR in patients with asthma might therefore be effective in reducing the burden of uncontrolled upper airway disease in these patients.

Of interest, we found that patients using nasal steroids had a higher prevalence of NHR compared to patients not using nasal steroids, whereas no association was found between the prevalence of BHR and inhaled steroid use. The association between NHR and nasal steroid use might be explained in two ways. Firstly, patients using nasal steroids might suffer from more severe nasal disease and therefore have a higher prevalence of NHR. This explanation is supported by the fact that a lower percent of patients with mild to moderate symptoms are on nasal steroids compared patients with severe symptoms (57 vs 67%, data not shown). Secondly, nasal steroids might not be effective in directly reducing NHR, as demonstrated by our group.[26] Corticosteroid treatment is typically targeting type 2 inflammatory responses. The pathophysiological mechanisms underlying NHR however go beyond type 2 inflammation and also involve neurogenic inflammation.[10,27]

Transient receptor potential (TRP) channels have been reported to be implicated in the development of NHR, as the overexpression of specific TRP channels like TRP A1 and V1 lead to an increased response to environmental triggers than in those with normal expression levels.[4] Additionally, dysfunction of the epithelial barrier might expose TRP channels of sensory nerves to more stimulation by exogenous triggers, hence contributing to NHR.[4] We previously showed that fluticasone propionate restores epithelial barrier

at tight junction level.[28] Interestingly, we recently demonstrated the effectiveness of a nasal spray containing both azelastine and fluticasone in reducing NHR in patients with house dust mite allergic rhinitis already after 4 w of treatment.[29] This might be explained by a combination of restoring epithelial barrier dysfunction and reducing TRP channel expression or activation on sensory nerves. The seemingly lack of effectiveness of the latter treatment on NHR in asthma needs to be explored further.

Several studies have shown a long-term reduction of nasal symptoms by repeated administration of capsaicin in patients with idiopathic rhinitis.[30,31] Capsaicin, found in chili peppers, is an irritant which is responsible for the burning sensation. The administration of capsaicin in the nasal mucosa results in a long-lasting decrease in sensitivity of nociceptors, such as TRPV1 and thereby reduces nasal symptoms.[10] Given the close link of NHR and TRP channel expression, capsaicin might be an attractive therapeutic option for all patients with NHR. We therefore propose that uncontrolled allergic rhinitis patients despite pharmacotherapy and with demonstrated NHR could be eligible patients for capsaicin treatment.

Despite the standardized protocol used in this study, some limitations were identified in this multi-center study: self-reported nature of the questionnaire-based study and lack of psychometric validation of the translated questionnaires.

In conclusion, we report here for the first time the presence of NHR in patients with asthma, which correlated with asthma severity. Novel insights into the impact of NHR on asthma control and BHR is warranted, as well as novel therapies targeting NHR, as it is not only present in patients with AR but also in patients with asthma.

Abbreviations

NHR: nasal hyperreactivity; BHR: bronchial hyperreactivity; VAS: visual analogue scale; AR: allergic rhinitis; FEV_1: forced expiratory volume in one second

Declaration of all sources of funding

P.W.H. and D.B are recipient of a senior researcher fellowship from the Fund of Scientific Research (FWO), Flanders, Belgium. B.S. holds a postdoctoral fellowship from FWO, Flanders, Belgium.

Authors' contributions

F.J., S.F.S., B.S. and P.W.H. designed the study, conducted the study, analyzed the data and wrote the manuscript. S.F.S., L.J.D and D.M.B, D.LL., M.GC., A.JC. and I.A. recruited patients for the study and contributed on the manuscript. W.F. and L.VG. revised the manuscript. All authors have critically reviewed the final version of the manuscript.

STUDY DESIGN

This multicentre observational study was conducted at University Hospitals of Leuven (Leuven, Belgium), Hospital Médica Sur (Mexico-City, Mexico), Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (Mexico City, Mexico) and Theramed Medical Center (Brasov, Romania) between May 2017–March 2018. Where applicable, the local ethical committees approved the study; all participants from Leuven and Brasov provided written informed consent.

Declaration of Competing Interest

All authors state they have no conflict of interest in relation to this study and the results described in the manuscript.

Acknowledgements

The authors would like to thank Ms. Leen Cools and Dr. Ina Callebaut for the help with sending out and collecting the questionnaires.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2020.100132.

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