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Evaluation of Olfactory Disorders in Patients with Asthma

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ABSTRACT

Background: Olfactory dysfunction is a common but under-diagnosed complaint, and there is a lack of studies evaluating the direct correlation between asthma and olfactory disorders. Objectives: To evaluate the presence of olfactory disorders in patients with asthma.

Methods: Ninety-three patients with asthma aged ≥ 18 years were selected at the ProAR Clinic in Salvador, Brazil, between March 2019 and February 2020. All the patients underwent the University of Pennsylvania Smell Identification Test (UPSIT) and otorhinolaryngological/clinical evaluation. We analyzed the correlation between the classification of olfactory disorders and clinical variables of asthma.

Results: Among the 93 enrolled asthmatic patients (63 had moderate to severe asthma and 30 had mild asthma), 89 (95.7%) were diagnosed with olfactory disorders, and four (4.3 %) had normosmia. Individuals with moderate to severe hyposmia or anosmia were older (56.5 years), while individuals with normosmia or mild hyposmia were younger (49.4 years) (p=0.029).

Sixty-seven patients (72%) were diagnosed with chronic rhinosinusitis (CRS), but only 5.9% had nasal polyps. No statistically significant differences were found in the analysis of association between CRS and olfactory disorders. None of the patients with anosmia met the criteria for allergic rhinitis; however, all individuals with normosmia met the criteria for allergic rhinitis (p=0.035). We found that 86.9% of asthmatic patients with moderate to severe hyposmia or anosmia had used oral steroids in the previous year or injectable steroids in the last 6 months. Among individuals with normosmia or mild hyposmia, 64.5% had used oral or injectable corticosteroids during the same period (p=0.012). Fourteen patients in this study were not diagnosed with allergic rhinitis or CRS. The UPSIT demonstrated that all patients with no apparent nasal diseases had olfactory disorders.

Conclusion: Olfactory disorders are common in asthmatic patients.

Keywords: Asthma; Olfaction Disorders; Anosmia; Olfactometry; Chronic Rhinosinusitis; Rhinitis

INTRODUCTION

Asthma is a chronic inflammatory airway disease that is commonly associated with nasal illness [1,2]. The concept of a "single airway" is supported by the reports of studies on pathophysiological connections between nasal and bronchial diseases that involves systemic and neurogenic mechanisms in bronchial decompensations [3-5]. Communication among local sensory neurones, immune cells, and resident lung stromal cells has been described, leading to the exacerbation of symptoms of asthma [6].

Olfactory dysfunction is a common but under-diagnosed complaint in the global population, with an estimated prevalence of 1.5-25%. This variability is due to the variety of olfactory tests and the diversity of the populations studied [7]. CRS and allergic rhinitis are well established in the literature as causes of olfactory disorders [8]. Olfactory dysfunction resulting from CRS can be described as a combination of components: conductive, sensorineural, and even central [9]. The International Consensus Statement on Allergy and Rhinology with focus in Olfaction, published in April 2022, brought data that correlate the presence of inflammatory proteins in the mucus of the olfactory cleft of patients with CRS [10]. Although the association between olfactory disorders and nasosinusal ilnesses is well established, the direct correlation between asthma and olfactory disorders remains unclear [10].

In view of asthma being a multifactorial disease, various study centers around the world are bringing them together to validated bio-clinical phenotyping between asthma cohorts [11]. Recent study has been demonstrated remarkable similarities in major clinical characteristics of one Brazilian asthma cohort in comparison to an European severe asthma cohort, which supports that asthma presents status as a disease entity, despite heterogeneous phenotypes [12].

The correlation between CRS, chronic rhinitis, and olfactory disorders is well established in the literature; however, studies that explore the direct association between asthma and olfactory disorders are limited.

Thus, the main objective of this study was to evaluate the presence of olfactory disorders in patients with asthma, using the University of Pennsylvania Smell Test (UPSIT). We also aimed to correlate the presence and severity of olfactory disorders with the severity and control of asthma, to investigate the association between the presence and severity of olfactory disorders with blood eosinophilia and total IgE, and to assess the correlation between diagnosis and control of chronic rhinosinusitis (CRS) and the severity of olfactory disorders.

METHODS

Study Design and Population

This cross-sectional study was part of a cohort research project submitted and approved by the local ethics committee (Resolution No. 099/2009; amendment 2,383,699).

Ninety-three participants with asthma, aged ≥18 years, without distinction of sex, and agreed to participate in the study by signing an informed consent form were selected. The following were exclusion criteria: patients with impaired understanding and communication, pregnant women, participants who took part in clinical trials within the last 6 months, patients lost to follow-up in the last 6 months, and presence of acute upper airway infection.

Data Collection

To characterize the sample population, anthropometric measurements were noted, including weight, height, and body mass index (BMI). Participants were asked about their current and past smoking habits. We also evaluated

the participant's medical records regarding the use of inhaled corticosteroids in the last 3 months, nasal corticosteroids in the last 3 months, oral corticosteroids in the last 12 months, and injectable corticosteroids in the last 6 months.

Blood collection and evaluation of complete blood count were performed using cut-off points>150/µL and >300/µL to categorize the presence of eosinophils [15,16]. The atopic subjects were identifyed by the presence of specific IgE in the serum (≥0.70 KU/L) for at least one aeroallergen. The aeroallergens evaluated by solid-phase fluorescence immunoassay (ImmunoCAP™) (Thermo Fisher Scientific, Uppsala, Sweden) considering the cut-off of 0.70 KU/L., were: Dermatophagoides pteronyssinus, Blomia tropicalis, Aspergillus fumigatus, Dermatophagoides farinae, dog epithelium, Periplaneta americana, Penicillium notatum and domestic cockroach (Greer Laboratories, USA).

The diagnosis and classification of asthma were validated by two pulmonologists after reviewing clinical records and complementary evaluation. Patients for whom both auditors positively affirmed the diagnosis of asthma were included in the study and classified in terms of severity as mild, moderate, or severe asthma, respecting the diagnostic criteria of GINA 2014 [15].

Clinical asthma control was assessed by considering the month prior to the date of clinical assessment, which reflected the participant's response to treatment. The participants were then classified as controlled, partially controlled, or uncontrolled according to the same criteria as in GINA 2014 [15].

The Asthma Control Questionnaire (ACQ-6), whose score is a reliable indicator for assessing asthma control [17], was also applied.

To assess pulmonary function, patients underwent a spirometry test to determine forced expiratory volume in 1s (FEV1), forced vital capacity (FVC), FEV1/FVC, and Forced Expiratory Flow 25–75% (FEF25-75), before and 15 min after inhalation of 400 mcg of salbutamol, as recommended by the ATS/ERS, using a Koko® Spirometer (Ferraris Medical, USA).

During the otorhinolaryngologic evaluation, the criteria for chronic rhinosinusitis and nasosinusal symptom control were applied. The criteria used for the etiological definition and control of chronic rhinosinusitis (CRS) in asthmatic patients were those established by the EPOS 2012 (European Position Paper on Rhinosinusitis and Nasal Polyps), revised in 2020. For the clinical definition of the type of CRS, diagnostic confirmation was performed using nasal endoscopy along with evaluation of endoscopic signs of nasal polyps or mucopurulent drainage, obstruction, or middle meatus oedema, using the Lund Kennedy staging for nasosinusal polyposis [18,5]. After diagnosis of CRS, patients were classified according to the level of control achieved as controlled, uncontrolled, and partially controlled CRS [18,5].

The diagnosis of allergic rhinitis was based on the presence of cardinal symptoms (sneezing in clusters, nasal itching, clear and abundant coryza, and nasal obstruction) and detection of at least one specific IgE for elevated aeroallergens (>0.70 kUA/l) [19].

The UPSIT, which was administered to all the participants, consists of 40 odorants in odoriferous strips that are scratched with the tip of a pencil and positioned 1 cm from the nose. The patient indicated the described odour by choosing one of four options. The number of odours identified was used as the test result. With sex and age graphs,

it is possible to classify patients as having normosmia (normal sense of smell), mild hyposmia, severe hyposmia, and anosmia. Self-perception of smell and taste was investigated in all patients [20].

Statistical Analysis

Descriptive analysis was performed using mean values, standard deviations, and simple and relative frequencies, depending on the measurement level of each variable.

To identify differences in numerical variables between two distinct groups, the non-parametric Kruskal-Wallis test and the Mann-Whitney test were used. The chi-squared test or Fisher's exact test was used to test the association between two categorical variables. The significance level adopted for all the statistical tests was 5%.

The association between variables was verified using logistic regression analysis, which was measured by calculating the odds ratio (OR) and 95% confidence interval (95% CI).

The Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM Corporation, Armonk, NY, USA) was used for all analyses.

RESULTS

The study started with a sample of 94 patients with asthma; one patient was excluded due to a diagnosis of acute rhinosinusitis (ARS) on the day of the otorhinolaryngological evaluation. Among the 93 asthmatic patients that were included in the study, 86% (80 patients) were female. The average age of the participants was 54 years; most patients (69.9%) had no history of smoking, 63 patients had a diagnosis of moderate to severe asthma, and 30 patients had mild asthma (Table 1).

Table 1: Clinical characteristics of the study sample (93 patients with asthma).

Variables	**N(%)**
Age (years)	54,0 ± 13,7
Body Mass Index (BMI), kg/m2	30,3 ± 6,3
Female	80(86,0)
Current Smoking	2(2,1)
Moderate to Severe Asthma	63(67,7)
Controlled Asthma (GINA)*	53(59,5)
Controlled Asthma (ACQ)	46(49,5)
Chronic Rhinosinusitis	67(72,0)
Controlled Rhinosinusitis**	4(6,1)
Allergic Rhinitis***	42(53,2)
Smell disorders (UPSIT)	
Normosmia	4(4,3)
Mild hyposmia	28(30,1)
Moderate hyposmia	34(36,6)
Severe hyposmia	20(21,5)
Anosmia	7(7,5)

*N= 89 **N=66 ***N= 79

Using the GINA strategy to assess asthma control, 59.5%, 22.5 %, and 18% had controlled, partially controlled, and uncontrolled asthma, respectively. According to the validated ACQ questionnaire, 49.5% of the patients had controlled asthma, 23.7% had partially controlled asthma, and 26.8% had uncontrolled asthma (Table 1).

All patients were evaluated for CRS criteria, and 72% (67 individuals) met the diagnostic criteria for CRS (Table 1).

Sufficient information to define the diagnosis of allergic rhinitis was found in 79 patients; of these, 53.2% (42 patients) met the diagnostic criteria for allergic rhinitis (Table 1).

Considering the entire sample studied, 14 patients were not diagnosed with allergic rhinitis or CRS. Of these, all (100%) had olfactory disorders diagnosed through the UPSIT, with the following distribution: six patients had moderate hyposmia, five had severe hyposmia, and three had anosmia.

After performing the UPSIT, of the entire sample of 93 patients, 4 (4.3%) patients had no olfactory disorder (normosmia) and 89 (95.7%) were diagnosed with olfactory disorders (mild hyposmia, 30.1%; moderate hyposmia, 36.6%; severe hyposmia, 21.5%; and anosmia, 7.5%) (Table 1).

An assessment of olfactory disorders according to asthma severity allowed us to conclude that 95.2% of individuals with moderate to severe asthma in this study had olfactory disorders, and among individuals with mild asthma, the proportion of olfactory disorders was 96.7% (Figure 1).

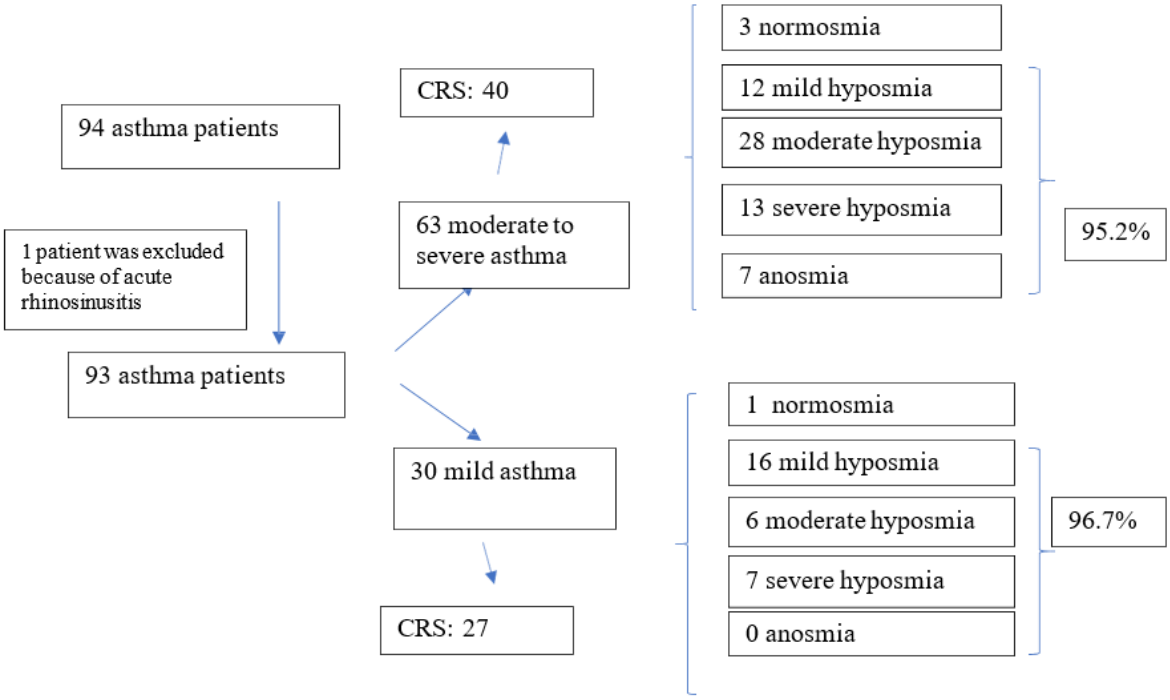

Figure 1: Flow chart showing the included patients and the distribution of olfactory disorders.

The correlation analysis between self-perception of olfactory disorder and the UPSIT olfactory test findings allowed us to conclude there is a direct correlation between the two (kappa=0.277; p=0.025). Correlation between the classification of olfactory disorders and clinical variables of asthma. An analysis of the association between olfactory diagnosis and clinical characteristics was performed using the UPSIT and by classifying the individual into one of the five categories already described (Table 2).

The mean age of patients with normosmia was 49.5 complete years, while that of patients with anosmia was 72.4 complete years (p=0.037). All participants with anosmia (seven patients) had severe asthma (p=0.005). No statistical significance was found in the analysis between asthma control and olfactory disorders, or between eosinophil levels and total IgE levels when correlated with the UPSIT findings (Table 2).

Table 2: Association between olfactory disorders and clinical asthma variables.

Variables	Normosmia	Mild Hyposmia	Moderate Hyposmia	Severe Hyposmia	Anosmia	p-value
	n = 4	n = 28	n=34	n=20	n=7	
Age#	49,5 ± 21,1	49,4 ± 12,5	53,9 ± 10,8	55,3 ± 12,4	72,4 ± 17,5	0,037#
FEV1 before BD absolute#	1,6 ± 0,5	2,1 ± 0,6	1,8 ± 0,6	1,8 ± 0,8	1,1 ± 0,5	0,007#
VEF1% before BD#	58,4 ± 12,5	79,9 ± 18,6	69,1 ± 19,3	69,6 ± 18,3	59,9 ± 16,3	0,053#
Total IgE#	211,1 ± 275,3	698,9 ± 1117,7	622,1 ± 981,3	398,4 ± 459,5	104,1 ± 64,1	0,405#
Female	4(100,0)	25(89,3)	28(82,4)	16(80,0)	7(100,0)	0,555*
Early Asthma Onset	3(75,0)	12(57,1)	14(51,9)	8(47,1)	1(14,3)	0,278*
Controlled Asthma (GINA)	2(50,0)	13(48,1)	23(71,9)	10(52,6)	5(71,4)	0,562*
Blood Eosinophils >150/µl	3(75,0)	19(70,4)	20(62,5)	8(50,0)	2(33,3)	0,392*
Moderate to Severe Asthma	3(75,0)	12(42,9)	28(82,4)	13(65,0)	7(100,0)	0,005*
CRS	3(75,0)	24(85,7)	23(67,6)	13(65,0)	4(57,1)	0,379*
Controlled	1(33,3)	2(8,3)	1(4,3)	-	-	0,126*
CRS Allergic Rhinitis	2(100,0)	14(58,3)	16(59,3)	10(52,6)	-	0,035*
Inhaled Corticosteroid Use Last 3 Months	1(25,0)	9(32,1)	14(41,2)	10(50,0)	2(28,6)	0,682*
Oral Corticosteroid Use Last 12 Months	-	2(7,1)	2(5,9)	2(10,0)	-	0,875*
Oral or Injectable Corticosteroid Use Nasal Corticosteroid Use last 3 Months	3(75,0)	17(63,0)	30(88,2)	16(80,0)	7(100,0)	0,094*
	2(50,0)	12(44,4)	16(47,1)	6(30,0)	5(71,4)	0,420*

*Chi square test **Fisher's exact test #Kruskal-Wallis test

All the patients were evaluated for CRS. Of these, 72% (67 subjects) met the diagnostic criteria for CRS, with the following distribution of olfactory disorders: 3 patients with normosmia, 24 patients with mild hyposmia, 23 patients with moderate hyposmia, 13 patients with severe hyposmia and 4 patients with anosmia. It was not possible to find a statistically significant difference between the subgroups allocated by olfactory dysfunction severity regarding to the presence of CRS (Table 2). Among the 67 patients who met the criteria for CRS, 4 (5.9%) had nasal polyposis diagnosed by nasal endoscopy and a diagnosis of moderate hyposmia.

None of the patients with anosmia (7) was considered to have allergic rhinitis. In contrast, all patients with normosmia (n = 2) had allergic rhinitis (p = 0.035).

Evaluation of the correlation between olfactory disorders grouped according to severity and clinical asthma variables the same clinical characteristics were analysed by comparing two large groups allocated according to olfactory disorder severity: the first group of patients with normosmia and mild hyposmia, and the second group of patients with moderate hyposmia, severe hyposmia, or anosmia.

Following the analysis by individual olfactory classification, in the subgroup analysis, the second group had a higher mean age (56.5 years), while individuals in the first group were younger, with a mean of 49.4 years (p = 0.029) (Table 3).

Table 3: Association between clustered olfactory disorders and clinical asthma variables.

Variables	Normosmia or Mild Hyposmia	Moderate, Severe Hyposmia or	p-value
	n=32	Anosmia n=61	
Age#	49,4 ± 13,3	56,5 ± 13,3	0,029#
FEV1 before BD absolute #	2,0 ± 0,6	1,7 ± 0,7	0,017#
FEV1% before BD #	76,9 ± 19,2	68,3 ± 18,6	0,051#
Total IgE#	610,2 ± 1029,2	513,4 ± 820,0	0,790#
Female	29(90,6)	51(83,6)	0,276**
Early Asthma Onset	15(60,0)	23(45,1)	0,222*
Controlled Asthma (GINA)	15(48,4)	38(65,5)	0,215*
Blood eosinophils >150/µl	22(71,0)	30(55,6)	0,160*
Moderate to Severe Asthma	15(46,9)	48(78,7)	0,002*
Controlled CRS	3(11,1)	1(2,6)	0,105*
Chronic Rhinosinusitis	27(84,4)	40(65,6)	0,055*
Allergic rhinitis			0,296*
No (n=37)	10(38,5)	27(50,9)	
Yes (n=42)	16(61,5)	26(49,1)	
Inhaled Corticosteroid Use Last 3 Months	10(31,3)	26(42,6)	0,285*
Oral Corticosteroid Use Last 12 Months	2(6,3)	4(6,6)	0,662**
Oral or Injectable	20(64,5)	53(86,9)	0,012*
Corticosteroid Use			
Nasal Corticosteroid Use Last 3 Months	14(45,2)	27(44,3)	0,935*

*Chi square test **Fisher's exact test # Mann-Whitney Test

Among individuals with moderate hyposmia, severe hyposmia, or anosmia, 78.7% had severe asthma, while 21.3% had mild-to-moderate asthma. In the group of individuals with normosmia and mild hyposmia, 53.1% had mild-to-moderate asthma and 46.9% had severe asthma (p=0.002) (Table 3).

In the evaluation of the use of oral steroids in the last year or injectable steroids in the last 6 months, 86.9% of patients with moderate hyposmia, severe hyposmia, or anosmia had used these medications. Among individuals with normosmia or mild hyposmia, 64.5% had used oral or injectable steroids during the same period (p=0.012) (Table 3).

The binary logistic regression model for olfactory disorders adjusted using the criteria for CRS, allergic rhinitis, and use of corticosteroids did not identify any of the variables as risk factors in the bivariate analysis (Table 4).

Table 4: Binary logistic regression model for olfactory disorders adjusted by the criteria of chronic rhinosinusitis, allergic rhinitis and use of corticosteroids.

Variables	Gross Odds (IC 95%)	Adjusted Odds (IC 95%)
Corticosteroid Use	1,72 (0,51 - 5,78)	3,38 (0,81 - 14,14)
Rhinosinusitis Criteria	0,51 (0,19 - 1,35)	0,59 (0,20 - 1,73)
Allergic Rhinitis Criteria	0,41 (0,16 - 1,07)	0,36 (0,13 - 1,02)

DISCUSSION

Our study found a higher proportion of olfactory disorders among patients with asthma. We evaluated 93 patients, of whom 63 had moderate to severe asthma, 30 had mild asthma, and 95.7% of asthmatic patients had olfactory disorders. A Korean study published in 2021 found a prevalence of olfactory dysfunction of 46.6% in patients with asthma, regardless of severity [10]. The higher proportion of patients with severe asthma may explain this finding.

The association between asthma and olfactory disorders was also proposed in a Japanese study published in 2020, which evaluated olfactory disorders in individuals with CRS with or without asthma, and demonstrated worse olfactory function in patients with chronic rhinosinusitis and asthma when compared to those with chronic rhinosinusitis only [13]. A study that evaluated 64 patients with severe asthma, and found a strong association between severe asthma and CRS (86%), in addition to a strong association between uncontrolled severe asthma and self-reported hyposmia (78%), independently of the presence of nasal polyps [14].

Patients with more severe asthma are expected to require more frequent use of systemic corticosteroids [12], which may explain the correlation found between the severity of olfactory disorders and the use of oral corticosteroids in the last year or injectable corticosteroids in the last 6 months. However, the present study did not find a significant correlation between olfactory disorders and asthma control.

The proportion of asthmatic patients with CRS was 72%. Among those patients with severe asthma, 63.5% had CRS. A previous study found that 53.4% of asthmatic patients had CRS, and revealed that 19.2% of asthmatic individuals had nasal polyps [10]. In 2015, another study found that 86% of patients with severe asthma had CRS.[14] Our study found no statistically significant correlation between the presence of criteria for CRS and olfactory disorders. We consider that the small sample size, associated with the fact that we found only four patients with CRS with nasal polyps diagnosed by nasal endoscopy, may explain this difference between our results and those of previous studies.

Our findings must be interpreted within the context of the limitations of this cross-sectional study. Some symptoms of asthma can overlap with those of CRS, such as coughing. In addition, it is necessary to recognise that there may be confounding variables in the understanding of CRS coexistence, which may have contributed to the high proportion of individuals diagnosed with CRS in this study.

Only 14 patients in this study were not diagnosed with allergic rhinitis or CRS; surprisingly, all patients had olfactory disorders that were diagnosed through the UPSIT. Recent studies have described the activation of sensory neurons in asthmatic patients by exogenous irritants or endogenous inflammatory mediators, resulting in the release of neuropeptides and activation of neuronal receptors that regulate inflammation, mucus production, vasodilation, and respiratory symptoms [6]. Such activations could explain the role of asthma in the pathophysiology of olfactory disorders independent of nasal factors associated with the known Th2 response.

Patients with more severe olfactory disorders, such as anosmia, did not meet the criteria for allergic rhinitis. In contrast, all patients with normosmia in this study met the criteria for allergic rhinitis. The absence of anosmia in individuals with allergic rhinitis is in agreement with the literature, which predicts milder, sometimes cyclic, olfactory disorders in patients with allergic rhinitis [7].

Older individuals had more severe olfactory disorders, which is in line with previously published data that associate olfactory dysfunctions with more advanced age [29].

This Study's strengths include the fact that we performed the UPSIT in all patients, which allowed diagnostic accuracy, as well as the possibility of studying patients belonging to a large asthma reference service with access to medication for free, the most diverse examinations and regular medical follow-up.

A limitation of the study is the imbalance in the distribution of the participants: 63 had moderate to severe asthma, while 30 had mild asthma. The higher number of individuals with moderate to severe asthma in the study was because the study was carried out in a highly specialised referral service. The non-randomness of the sample was because the patients in this study came from another study in progress; this factor along with the possibility of unmeasured confounding variables can be considered as limitations.

We believe that despite the limited number participants, the data generated in this study reflected real-world findings regarding the prevalence of these disorders in the general population of asthmatic patients, especially among those with moderate to severe asthma, which is a particularity of this observation.

Our results reinforce the importance of otorhinolaryngological evaluation of asthmatic patients for the investigation and follow-up of nasosinusal illness, while paying special attention to the investigation of olfactory disorders through olfactometry. Due to the scarcity of reports on this matter in the literature, olfactory disorders may not receive proper attention in patients with asthma and consequently compromise their quality of life. When olfactory disorders are properly diagnosed, it allows for the early establishment of assertive therapeutic strategies.

CONCLUSION

Olfactory disorders are common in asthma, and its reinforce the importance of otorhinolaryngological evaluation of these patients, especially with the use of olfactometry.

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