Hyperventilation syndrome in children with asthma

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Abstract

Background: Hyperventilation syndrome (HVS) may be associated with asthma. In the absence of a gold standard diagnosis for children, its impact on asthma has been rarely assessed. **Objective:** to assess the impact of HVS, diagnosed by a positive hyperventilation test (HVT), on the symptoms and lung function of children with asthma and determine the diagnostic value of the Nijmegen questionnaire in comparison to a HVT. **Methods:** Data from asthmatic children followed in the department of Pediatric Pulmonology of Necker Hospital and explored for HVS were retrospectively analyzed. HVS was diagnosed by a positive HVT. Asthma symptoms and lung function were assessed in children with or without a positive HVT. The sensitivity and specificity of the Nijmegen questionnaire were determined relative to the positivity of a HVT. **Results:** Data from 112 asthmatic children, median age 13.9 years [11.6–16], were analyzed. Twenty-eight children (25%) had mild or moderate asthma and 84 (75%) severe asthma. The HVT was performed on 108 children and was negative for 34 (31.5%) and positive for 74 (68.5%). The number of asthma exacerbations in the past 12 months, ACT score, and lung function did not differ between children with a positive HVT and a negative HVT. The Nijmegen questionnaire was administered to 103 children. With a threshold of 23, its sensitivity was 56.3% and specificity 56.3%. **Conclusion**: The symptoms and lung function of adolescents with asthma are not affected by the presence of HVS. The sensitivity and specificity of the Nijmegen questionnaire are low.

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ABSTRACT

Background: Hyperventilation syndrome (HVS) may be associated with asthma. In the absence of a gold standard diagnosis for children, its impact on asthma has been rarely assessed.

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Methods: Data from asthmatic children followed in the department of Pediatric Pulmonology of Necker Hospital and explored for HVS were retrospectively analyzed. HVS was diagnosed by a positive HVT. Asthma symptoms and lung function were assessed in children with or without a positive HVT. The sensitivity and specificity of the Nijmegen questionnaire were determined relative to the positivity of a HVT.

Results: Data from 112 asthmatic children, median age 13.9 years [11.6–16], were analyzed. Twenty-eight children (25%) had mild or moderate asthma and 84 (75%) severe asthma. The HVT was performed on 108 children and was negative for 34 (31.5%) and positive for 74 (68.5%). The number of asthma exacerbations in the past 12 months, ACT score, and lung function did not differ between children with a positive HVT and a negative HVT. The Nijmegen questionnaire was administered to 103 children. With a threshold of 23, its sensitivity was 56.3% and specificity 56.3%.

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INTRODUCTION

Hyperventilation syndrome (HVS) is characterized by a set of respiratory and extra-respiratory symptoms secondary to inappropriate hyperventilation in relation to metabolic demand, leading to acute or chronic symptoms [1–3]. These symptoms, varied and non-specific, can most often be partially or totally reproduced by voluntary hyperventilation [4–6]. However, there are no established diagnostic criteria. HVS is most often confirmed using the Nijmegen questionnaire, for which the positivity threshold is often considered to be 23 [7–12]. Positivity thresholds ranging from 17 to 25 have also been used to diagnose HVS[6,10,13]. The Nijmegen questionnaire has not been validated on children.

A number of authors have suggested that a positive hyperventilation test (HVT) could be the gold standard for the diagnosis of HVS[6,7,14]. The HVT makes it possible to reproduce the symptoms of hyperventilation by voluntary hyperventilation and evaluate the evolution of exhaled capnia according to the phase of the test[14–16]. It combines the evaluation of objective criteria: baseline $PETCO_2$ (partial pressure of CO_2 at the end of expiration before hyperventilation), time to return to baseline $PETCO_2$, low $PETCO_2$ (partial pressure of CO_2 at the end of expiration after hyperventilation) and subjective criteria (reproduction of symptoms). However, the criteria for HVT positivity are not standardized [14,16–21]. They most often consist of the reproduction of at least two symptoms of hyperventilation associated with a delay in the normalization of $PETCO_2$ or a severe drop in $PETCO_2$ after hyperventilation[14,18,21]. The specificity of the HVT was estimated to be between 60 and 66% in a study in which the gold standard for the diagnosis of HVS was a placebo test of hyperventilation with the administration of CO_2 concomitantly with hyperventilation [22]. The sensitivity of the HVT has been shown to be 91.8% and the specificity 90.7% for adults with severe asthma [6]. The value of the HVT is a subject of debate because HVS can be isocapnic, and some consider that only the regression of symptoms after respiratory recovery make it possible to diagnose HVS [11]. Nevertheless, the HVT allows the reproducible and objective evaluation of HVS by combining clinical and paraclinical criteria. HVS can be associated with asthma or be a differential diagnosis of asthma [1,2,4]. The prevalence of HVS is estimated to be between 5 and 26% among asthmatic children[9,23]. The validity and reproducibility of the Nijmegen questionnaire has not yet been fully established in this population.

Few studies have focused on HVS in asthmatic children. In a study of 760 adolescents, 120 of whom (15.8%) had asthma, the Nijmegen score was positive for 47 of the 760 adolescents (6.2%), of whom 31 (25.8%) were asthmatic [9]. In another study of 203 children with asthma, the Nijmegen score was positive in 5% of

cases, the asthma was controlled for 63% of the children, and 70% had non-severe asthma. None of these studies investigated the impact of HVS on asthma symptoms[23]. Finally, the diagnostic value of the Nijmegen questionnaire relative to the HVT has been little studied.

The objectives of this study were to evaluate: i) the impact of HVS on the asthma symptoms and lung function of asthmatic children diagnosed with a positive HVT and ii) the diagnostic value of the Nijmegen questionnaire compared to the HVT for the diagnosis of HVS in asthmatic children.

METHODS

Study population

The data of children followed for asthma in the Pediatric Pneumology and Allergology Department of the Necker-Enfants Malades Hospital between June 2013 and February 2021 who were tested for HVS were retrospectively analyzed. These children were identified using Dr Warehouse software[24], which allowed a search by keywords present in the computerized medical reports. The keywords or keyword combinations used to identify the patients were: "hyperventilation syndrome and asthma", "hyperventilation test and asthma", "Nijmegen and asthma", "hyperventilation test", " hyperventilation", "hyperventilation and asthma". Non-asthmatic patients and those for whom the lack of data did not allow a classification according to the GINA and an assessment of asthma control were excluded from the analysis.

Data collection

Data collected included demographic characteristics, atopic (atopic dermatitis, allergic rhinoconjunctivitis (ARC), IgE-mediated food allergies) and non-atopic (gastroesophageal reflux disease, clinical sleep apnea syndrome or confirmed by polygraphy) comorbidities, the pediatric asthma control test (ACT) score, the number of asthma exacerbations and severe asthma exacerbations (requiring hospital treatment and/or systemic corticosteroid therapy for 3 days or more), the number of days of taking oral corticosteroids for severe exacerbations, and the number of visits to the emergency room or emergency consultations for asthma exacerbations over the past 12 months. Children were categorized into frequent exacerbators ([?] 2 exacerbations per year in the last 12 months) and pauci-exacerbators[25]. The presence of sensitization to common pneumallergens (house dust mites, cat or dog dander, birch pollen, and grass pollen), defined by specific IgE > 0.1 kU/l or positive prick-tests, plasma eosinophilia, the plasma concentration of total IgE, and the lung function in the previous six months were also recorded.

Nijmegen score and hyperventilation Test

A Nijmegen score [?] 23 was considered positive.

The HVT was performed by a single operator and consisted of making the patient hyperventilate at a respiratory rate of 30 per min for a period of 3 min. The partial pressure of CO_2 at the end of expiration ($PETCO_2$) was measured continuously throughout the test using a capnograph. The basal $PETCO_2$ at the start of the test and the minimum $PETCO_2$ attained after the hyperventilation phase were measured. The symptoms reproduced were recorded after the hyperventilation phase (anxiety, paresthesia or tingling, dizziness, headache, visual blurring, chest tightness or pain, palpitations, ankylosis of the extremities or cold extremities, confusion, and cough). The duration of the return to the initial baseline $PETCO_2$ was then determined. The HVT was considered positive if at least two of the following three criteria were present:

- $PETCO_2$ at rest or after 5 min of recovery < 30 mmHg
- Time to return to the baseline $PETCO_2 > 3$ min
- Reproduction of more than two symptoms

A positive HVT confirmed the diagnosis of HVS.

Statistical analyses

Statistical analyses were performed using GraphPad Prism v.5.03 software (La Jolla, CA). Continuous variables are expressed as medians [25th-75th percentile]. Differences between the two groups were analyzed

using the Mann-Whitney non-parametric test. Correlations were assessed using the Spearman correlation test. A p value < 0.05 was considered significant.

Ethical aspects

The medical reports of the unit mention the possible use of patient medical data, in an anonymized manner, in the context of studies and their possible use in the absence of expressed non-objection. We did not receive any objection. Ethical approval was not necessary.

RESULTS

General characteristics of the included children

In total, 112 children were included (see flow chart in Figure 1). The characteristics of the selected children are summarized in Table 1. The population consisted of 59 girls (57.3%) and 53 boys (42.7%), with a median age of 13.9 years [11.6 -16]. Among them, 84 children (75%) had severe asthma (GINA 4 to 5) and 28 (25%) non-severe asthma (GINA 1 to 3).

The reason for carrying out the HVT was the presence of symptoms suggestive of HVS for 53 children (47.3%), the persistence of asthma symptoms despite good compliance with treatment for 21 (18.8%), and the systematic search for HVS in the context of the exploration of difficult-to-treat asthma for 38 (33.9%). The Nijmegen questionnaire was performed for 103 children (92%) and the median Nijmegen score was 23 [15-29].

Among the 112 children, 108 underwent a HVT (96.4%), for which the results are presented in Table 1.

The HVT was negative for 34 patients (31.5%) and positive for 74 (68.5%). The characteristics of children with a positive HVT and those with a negative HVT are presented in Table 2. The baseline PCO_2 at the start of the HVT was lower for children with a positive HVT than those with a negative test (35 mmHg [34-37] vs. 36 mmHg [35 -38], $p < 0.01$). The PCO_2attained after the hyperventilation phase was also lower for children with a positive HVT than those with a negative test (18 mmHg [17-20] vs 22.5 mmHg [19-26.5], $p < 0.01$). Finally, the time to return to baseline PCO_2 was longer for children with a positive HVT than those with a negative test (5 min [4-7] versus 1.5 min [1-2.1], $p < 0.01$). Symptoms reproduced during the HVT are presented in Figure 2. The most frequently reproduced symptoms among children with a positive HVT were dizziness for 58 children (78%), headaches for 49 (66%), and palpitations for 33 (45%).

Girls had a positive HVT more frequently than boys (59 girls (57.3%) vs 53 boys (42.7%), $p = 0.03$). Children with a positive HVT were older than those with a negative HVT (14.2 years [12.6-16.8] vs 12.7 years [9.3-14.7], $p < 0.01$). The frequency of perennial allergic rhinitis was higher among children with a positive HVT than those with a negative test (35 [47.3%] vs 14 [41.2%], $p = 0.04$). Children with a positive HVT had more IgE-mediated food allergies than those with a negative test (26 [35.1%] vs 2 [5.9%], $p < 0.01$).

Impact of HVS on asthma

The number of asthma exacerbations and severe exacerbations during the previous12 months and the ACT score did not differ between children with a positive HVT and those with a negative HVT (Table 2). However, ACT score results were available for only 47 children (42%). Similarly, the use of oral corticosteroid for asthma exacerbations or the number of visits to the emergency room for an asthma exacerbation during the last 12 months did not differ between children with a positive and those with a negative HVT. Lung function (pre-bronchodilator FEV1, reversibility, RV/TLC ratio) of patients with a positive HVT was identical to that of children with a negative test.

Sensitivity and specificity of the Nijmegen score

Among the 103 patients evaluated using the Nijmegen questionnaire, 54 (52.4%) had a score [?] 23. The Nijmegen score was higher in the group with a positive HVT than that with a negative HVT (23 [16-32] vs 20 [12-25.8], $p = 0.04$). The Nijmegen score correlated slightly with the HVT result ($r = 0.2$, $p = 0.03$).

The sensitivity of the Nijmegen score at the threshold of 23 was 56.3% and the specificity 56.3% compared to the HVT. The sensitivity and specificity of the Nijmegen score was also assessed for scores < 23. A Nijmegen score threshold < 23 improved sensitivity but reduced specificity (Table 3). The area under the ROC curve for the Nijmegen score was 0.63 [0.52-0.74] ($p = 0.04$) (Figure 3).

DISCUSSION

The aim of this study was to evaluate the impact of HVS on the asthma symptoms and lung function of asthmatic children and assess the diagnostic value of the Nijmegen score compared to the HVT for the diagnosis of HVS in this study population. Our results indicate that when HVS is defined by a positive HVT, the presence of HVS in children with severe asthma has no impact on asthma symptoms or lung function. The diagnostic value of the Nijmegen score compared to a positive HVT was low in this population.

Our results show that HVS predominates in adolescents, in particular when there are allergic comorbidities. This study confirms the female predominance described for HVS [9,12,26–28] and underscores the potential psychological impact of the association of several allergic diseases on HVS. Several studies have shown that patients with food allergies, perennial allergic rhinitis, or asthma show more anxiety or have higher depression scores[29,30]. Our results suggest that HVS may be related to the higher prevalence of anxiety disorders observed in the female population [31,32]. The presence of other allergic diseases, particularly among asthmatic teenagers, should therefore prompt the search for HVS.

In our study, asthmatic children with HVS confirmed by a HVT did not have more exacerbations or severe exacerbations than those without HVS, nor did they consume more oral corticosteroids. These results appear to contradict those of other studies [10,33]. Several factors may explain these differences. First, HVS in these studies was most often diagnosed from the Nijmegen score, whereas we diagnosed it based on the positivity of a HVT. Our results suggest that the specificity of the Nijmegen score is lower than that of the HVT. The risk of false positives is therefore possibly higher with the use of the Nijmegen score than the HVT. The use of the Nijmegen questionnaire with a threshold of 23 could therefore lead to an overestimation of the number of cases of HVS and bias analyses relating to the impact of HVS on asthma. In addition, most of the studies were carried out on adults, and excluded patients with severe asthma, whereas our population was essentially made up of adolescents with severe asthma. In our study, the high amount of missing data concerning ACT scores may have biased the analyses of asthma control. Although several studies have shown that the presence of HVS in asthmatic patients is associated with a decrease in the global ACT score, they did not find any impact on the various components of asthma control taken independently, in agreement with our results [8,13,34]. Our results also indicate that the presence of HVS diagnosed by the positivity of a HVT had no influence on lung function, and confirms the results reported in the literature[5,7,8]. This result was expected because HVS is not generally associated with the determinants of lung function, such as bronchial inflammation, bronchoconstriction, or remodeling.

The Nijmegen questionnaire is the most frequently used tool in HVS screening. Its main limitations are the absence of a gold standard test to assess its validity, the lack of data on its validity for asthmatic patients, and difficulties in understanding certain items, especially for younger children [26]. Certain items may be confused with symptoms related to asthma control (inability to breathe deeply, rapid breathing, shortness of breath), which could lead to an overestimation and the over-diagnosis of HVS [8,9]. The sensitivity and specificity of the Nijmegen questionnaire with a threshold of 23 were low in our study, making this score relatively noninformative for the identification of HVS, with a significant risk of false-positive children. Few studies have analyzed the value of this score in asthmatics. The sensitivity of the Nijmegen questionnaire with a threshold [?] 25 was estimated to be 71.7%, and the specificity 76.4% for 152 adults with severe asthma [6]. The performance of the questionnaire was compared to the presence of hypocapnia < 30 mmHg with a pH > 7.45 on arterial blood gases associated with the presence of HVS symptoms at rest or a positive HVT. This population was exclusively made up of adults and it is possible that the symptoms of HVS are better identified in this population than in children or adolescents. Two tests were used, one identifying patients with HVS symptoms at rest and the other patients with HVS symptoms during a hyperventilation phase. In another study of 162 asthmatic patients over the age of 17, the sensitivity of the Nijmegen Questionnaire

with a threshold [?] 23 was 23.6% and the specificity 98.1%. A threshold of 17 showed better performance, with a sensitivity of 92.7% and specificity of 91.6% [26]. In our study, the lower we made the threshold, the more the sensitivity increased, to the detriment of specificity. Using a lower threshold therefore appeared to be less useful for the diagnosis of HVS. The difference in the sensitivity and specificity of the aforementioned study compared to those of our study can be explained by the fact that the gold standard was based on the identification of symptoms of hyperventilation by the patient from a list, associated with predominant thoracic breathing. These symptoms were similar to those of the Nijmegen score, reducing the risk of patients being falsely identified as having HVS or being free of disease. Furthermore, the study did not include patients with severe asthma. No study has yet evaluated the performance of the Nijmegen score in children with asthma, in particular those with severe cases.

HVT is little used in practice, probably, at least in part, because it is not standardized or validated. Thus, the voluntary hyperventilation carried out during the test has a variable duration of 1 to 5 min, depending on the authors [6,16,22]. There are few studies describing the results of measurements taken during an HVT. In our study, there was a difference in the initial $PETCO_2$between children with positive and negative HVT, but the median value of the initial $PETCO_2$ was not < 35 mmHg. This is why certain authors consider that the measurement of baseline $PETCO_2$ in isolation is not a good diagnostic criterion for HVS because many patients with HVS do not show chronic hypocapnia[17,18,21,35]. One study evaluated the sensitivity and specificity of measuring baseline arterial capnia < 30 mmHg associated with a pH > 7.4. The sensitivity was 24.4% and the specificity 88.5% with respect to the HVT, suggesting that capnia measurement is not a good diagnostic test [6]. In our study, the value of the low $PETCO_2$ after the hyperventilation phase was lower in the positive HVT group, as in other studies [17,20,21]. The return time from the low $PETCO_2$ to the initial $PETCO_2$, which was longer for the HVT-positive group, was 5 min. The reported threshold value varies from 3 to 5 min, depending on the study[16–18,36–38]. All agree that the absence of a return to the initial $PETCO_2$ after a recovery phase of 3 to 5 min is an additional argument to confirm the positivity of the HVT. By combining $PETCO_2$ measurements with reproduced symptoms, the HVT makes it possible to objectively establish the diagnosis of HVS.

Our results indicate that the most frequently reproduced symptoms during the HVT are extra-respiratory symptoms: headache, dizziness, tingling sensations or paresthesia, and palpitations, in agreement with certain studies [11,14,39]. However, the symptoms reproduced vary according to the study. Several studies on adults found a predominance of respiratory symptoms (tachypnea, feeling of shallow breathing, feeling of chest tightness) [14,39]. We could not analyze the concordance between the symptoms described before the HVT and those that were reproduced. The concordance of the symptoms reproduced during the HVT and those of the Nijmegen score appear to be between 74 and 86%, depending on the study [14,17]. This means that the symptoms reproduced during the HVT are very close to those of HVS experienced by patients on a daily basis, reinforcing the interest of the HVT in the diagnosis of HVS.

In our study, the search for HVS was motivated by the presence of suggestive symptoms in 47% of cases; 54% of children with a positive HVT had suggestive symptoms versus 29% in the negative group. In the group with a negative HVT, we found a higher proportion of children who had had systematic screening for HVS as part of their severe asthma assessment. Our results therefore suggest that the HVT should be offered to adolescents with severe asthma when suggestive clinical signs are present, rather than routinely.

Our study had several limitations. Its unicentric and retrospective nature certainly induced a patient selection bias, and data were often missing. However, the analyzed population was well phenotyped and HVS was diagnosed based on the positivity of a HVT performed by a single operator. We had an over-representation of patients with severe asthma corresponding to GINA step 4 and 5. Our results cannot therefore be generalized to patients with non-severe asthma. In addition, there was a selection bias for patients presenting with uncontrolled asthma or symptoms suggestive of HVS on questioning, which may have led to an overestimation of the frequency of HVS. The ACT score had not been evaluated for many patients. However, it did not show any impact of HVS on the control of asthma. Some authors showed that respiratory rehabilitation of HVS can allow an improvement in the quality of life of patients as well as a reduction in anxiety scores[40,41].

The present study did not assess the impact of HVS rehabilitation and psychological care on asthma control. Despite its limitations, our study is one of the rare studies to focus on HVS in a pediatric population of asthmatics and to analyze the interest of the Nijmegen screening score and HVT in the diagnosis of HVS in children. Indeed, we had a large number of patients evaluated by the HVT and few studies have yet investigated its parameters.

In summary, HVS does not appear to have an impact on asthma symptoms or respiratory function for children with severe asthma. The Nijmegen questionnaire appears to show low sensitivity in this population. HVS is likely more common in asthmatic adolescents, children with allergic comorbidity, and, in particular, those with perennial allergic rhinitis. Further studies are needed to define a gold standard diagnosis of HVS and to measure its impact on asthma.

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FIGURES

Figure 1. Flow chart

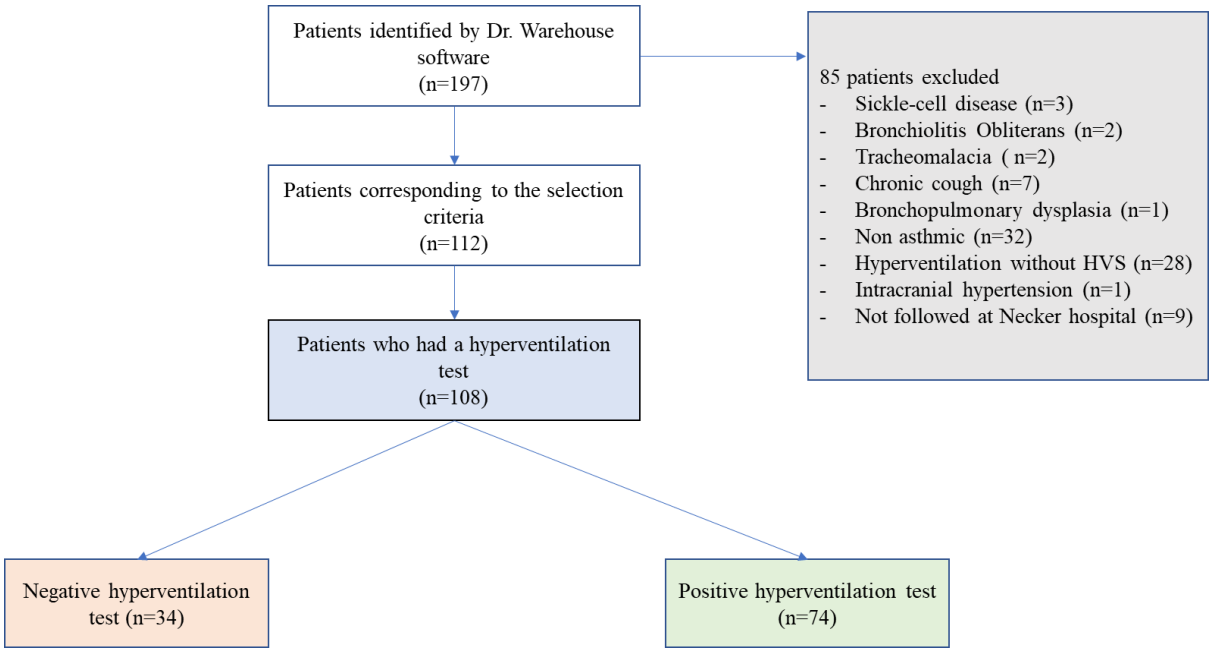

Figure 2. Symptoms reproduced in positive hyperventilation tests

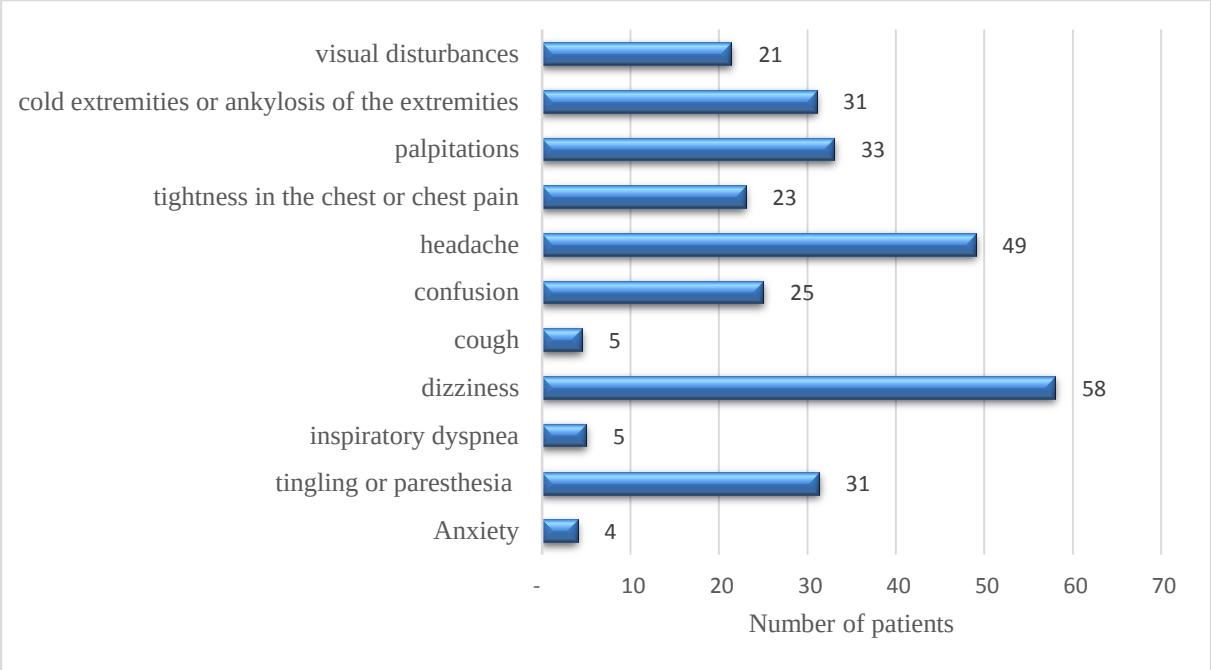

Figure 3. ROC curve for the Nijmegen score

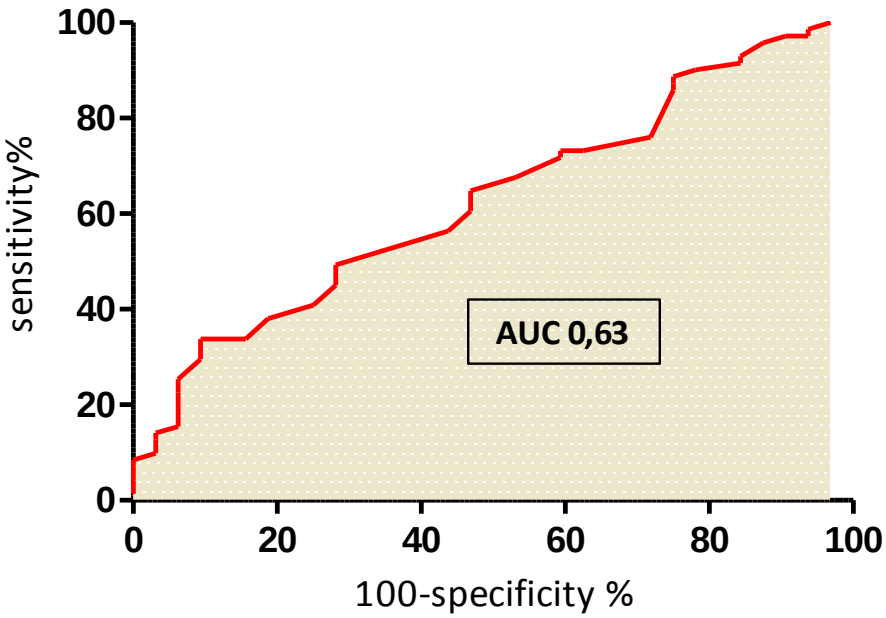

Table 1. General characteristics of the population

	Total (n = 112)	**Missing data (n (%))**
Sex M/F (n (%))	59/53 (57.3/42.7%)	-
Age (years)	13.9 [11.6-16]	-
BMI (kg/m^2)	20.7 [18-23.2]	4 (3.6%)
Family history of atopy (n (%))	68 (60.7%)	32 (28.6%)
History of prematurity	10 (8.9%)	57 (50.9%)
Atopic dermatitis (n (%))	30 (26.8%)	33 (29.5%)
Food allergies (n (%))	29 (25.9%)	37 (33%)
Allergic rhinoconjunctivitis (n (%))	90 (80.4%)	8 (7.1%)
Symptoms of gastroesophageal reflux (n (%))	38 (33.9%)	43 (38.4%)
Symptoms of OSAS (n (%))	16 (14.3%)	62 (55.4%)
Overweight or obese (n (%))	36 (32.1%)	4 (3.6%)
- **Obese (n (%))**	17 (15.2%)	
Eosinophils (/mm^3)	300 [200-600]	32 (28.6%)
Total IgE (kU/l)	277 [122.5-711]	40 (35.7%)
IgE Sensitivity		
- **Mites (n (%))**	68 (60.7%)	17 (15.2%)
- **Pollen (n (%))**	46 (41.1%)	23 (20.5%)
- **Birch (n (%))**	31 (27.7%)	23 (20.5%)
- **Cat or dog dander (n (%))**	40 (35.7%)	28 (25%)
Passive smoking (n (%))	26 (23.2%)	37 (33%)
Animals in the home (n (%))	35 (31.3%)	34 (30.4%)
Humidity or mold (n (%))	22 (19.6%)	36 (32.1%)
Pre-FEV1 (% of the theoretical value)	96 [82.5-105.8]	13 (11.6%)
FEV1/VC	91.6 [82.8 ; 97.4]	16 (14.3%)
Reversibility (%)	4.1 [0.7-8.4]	28 (25%)
RV/TLC	23 [17-27.4]	32 (28.6%)
FeNO (ppb)	24.3 [10.5-53.3]	72 (64.3%)
GINA		-
- **GINA 1-3 (n (%))**	28 (25%)	
- **GINA 4-5 (n (%))**	84 (75%)	
ICS dose (fluticasone equivalent in µg/d)	500 [37-500]	4 (3.6%)
Asthma control		
- **symptoms on exertion (n (%))**	79 (70.5%)	8 (7.1%)
- **daytime symptoms (n (%))**	49 (43.8%)	7 (6.3%)
- **nocturnal symptoms (n (%))**	40 (35.7%)	9 (8%)
- **number of days of Ventolin intake per week**	1 [1-7]	11 (9.8%)
Number of exacerbations per year	4 [1- 7]	13 (11.6%)

- **number of severe exacerbations**	2 [0-5]	9 (8%)
- **frequent exacerbators (n (%))**	70 (62.5%)	10 (8.9%)
- **number of days of corticosteroids**	6 [0-15]	19 (20%)
- **emergency room consultations**	0 [0-1.5]	15 (13.4%)
ACT score	13 [10-21]	65 (58%)
Asthma under control (n (%))	33 (29.5%)	5 (4.5%)
Reason for exploration		
- **evocative symptoms (n (%))**	53 (47.3%)	-
- **poor control; good observance (n (%))**	21 (18.8%)	
- **severe asthma (n (%))**	38 (33.9%)	
NIJMEGEN score	23 [15-29]	5 (4.5%)
Hyperventilation test (n (%))	108 (96.4%)	-
- **Baseline PCO_2 (mmHg)**	35 [34-37]	9 (8%)
- **Lowest PCO_2 (mmHg)**	19.5 [17-23]	8 (7.2%)
- **Time to return to baseline PCO_2 (min)**	4 [2-7]	4 (3.6%)

BMI: body-mass index, OSAS: obstructive sleep apnea syndrome, IgE: immunoglobulin E, FEV1: forced expiratory volume in the first second, VC: vital capacity, RV: residual volume, TLC: total lung capacity, ACT: asthma control test

Table 2. Comparison of the general characteristics of patients with a positive HVT and those with a negative HVT

Patients who had a HVT	HVT- (n = 34)	HVT+ (n = 74)	p
Sex M/F (n (%))	13/21 (38.2/61.8%)	45/29 (60.8/39.2%)	**0.03**
Age (years)	12.7 [9.3-14.7]	14.2 [12.6-16 .8]	**0.0003**
BMI (kg/m^2)	21 [16.4-23.2]	20.7 [18.3-23.3]	0.45
Overweight or obese (n (%))	11 (32.4%)	23 (31.1%)	0.81
Familial atopy (n (%))	24 (70.6%)	41 (55.4%)	0.23
Atopic dermatitis (n (%))	8 (23.5%)	22 (29.7%)	0.43
IgE-mediated food allergies (n (%))	2 (5.9%)	26 (35.1%)	**0.0004**
Allergic rhinoconjunctivitis (n (%))	27 (79.4%)	59 (79.7%)	0.75
- **Perennial**	14 (41.2%)	35 (47.3%)	**0.038**
- **Seasonal**	7 (20.1%)	27 (36.5%)	0.11
- **Persistent**	5 (14.7%)	23 (31.1%)	0.59
- **Moderate to severe**	9 (26.5%)	25 (33.8%)	0.65
Eosinophils ($/mm^3$)	400 [200-620]	300 [100-500]	0.37
Total IgE	499 [196-1077]	264 [99-634]	0.27
ICS (fluticasone equivalent in µg/d)	500 [500-500]	500 [319-500]	0.37

Pre-FEV1 (%)	96.1 [76-109.2]	95.4 [85.1-104]	0.72
Reversibility (%)	3.8 [0.1-8.4]	4 [1-7.8]	0.88
RV/TLC	22.2 [18.2-28.2]	23.2 [17-27.3]	0.83
GINA			
- **GINA 1- 3 (n (%))**	7 (20.6%)	18 (24.3%)	0.67
- **GINA 4- 5 (n (%))**	27 (79.4%)	56 (75.7%)	0.67
Number of exacerbations per year	4 [1.8-8.5]	4 [0.8-6.3]	0.51
- **frequent exacerbators (n (%))**	22 (64.7%)	46 (62.2%)	0.33
- **number of severe exacerbations**	3 [0-6]	2[0-4.5]	0.36
- **number of patients with severe exacerbations (n (%))**	21 (61.8%)	48 (64.9%)	0.97
	9.5 [0-24.3]	6 [0-15]	0.82
- **number of days of corticosteroids**	0 [0-2.3]	0 [0-1]	0.098
- **number of emergency room consultations**			
Asthma control			
- **symptoms on exertion (n (%))**	22 (64.7%)	53 (71.6%)	0.33
- **daytime symptoms (n (%))**	15 (44.1%)	31 (41.9%)	0.99
- **nocturnal symptoms (n (%))**	16 (47%)	22 (29.7%)	0.10
- **number of days of Ventolin intake per week**	0 [0-7]	1 [0-7]	0.67
ACT score	14 [10-22]	13 [10-20]	0.55
Asthma under control (n (%))	12 (35.3%)	21 (28.4%)	0.47
Reason for exploration			
- **suggestive symptoms (n (%))**	10 (29.4%)	40 (54.1%)	**0.018**
- **persistent symptoms; good observance (n (%))**	8 (23.5%)	13 (17.6%)	0.47
- **severe asthma (n (%))**	16 (47%)	21 (28.4%)	0.059
Nijmegen score	20 [12-25.8]	23 [16-32]	**0.04**
- **Nijmegen ≥ 23**	14 (41.2%)	40 (54.1%)	0.3
Baseline PCO_2 (mmHg)	36 [35-38]	35 [34-37]	**0.009**
Lowest PCO_2 (mmHg)	22.5 [19-26.5]	18 [17- 20]	**<0.0001**
Time to return to baseline PCO_2 (min)	1.5 [1-2.1]	5 [4-7]	**<0.0001**

BMI: body-mass index, OSAS: obstructive sleep apnea syndrome, IgE: immunoglobulin E, ISC: inhaled corticosteroids, FEV1: forced expiratory volume in the first second, VC: vital capacity, RV: residual volume, TLC: total lung capacity, ACT: asthma control test

Table 3. Sensitivity and specificity values according to the Nijmegen score threshold

Nijmegen score threshold	Sensitivity (%)	Specificity (%)
23	56.3	56.3
22	60.6	53.1
21	64.8	53.1
20	67.6	46.9
19	71.8	40.6
18	73.2	40.6
17	73.2	37.5