

Predictors of Airway Hyperresponsiveness in Symptomatic Children with Normal Spirometry and Suspicious of Possible Asthma

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Keywords

Airway hyperresponsiveness · Children · FEF₇₅ · Methacholine challenge · Nocturnal cough · Tree pollen allergy

Abstract

Background: Asthma diagnosis may be challenging particularly in patients with mild symptoms without an obstructive pattern in spirometry. Detection of airway hyperresponsiveness (AHR) by a positive methacholine challenge (MCC) is still an important diagnostic tool to confirm the presence of asthma with reasonable certainty. However, it is time consuming and could be exhausting for patients. We aimed to identify the predictive factors for AHR in children with respiratory symptoms without obstructive pattern in spirometry. **Methods:** Data from children who had undergone MCC were analyzed retrospectively. The demographic features of patients along with laboratory results were collected. **Results:** A total of 123 children with a median age of 10.5 years were enrolled. AHR was detected in 81 children (65.8%). The age of the children with AHR was significantly younger. The prevalences of aeroallergen sensitization, nocturnal cough, wheezing, and a baseline forced expiratory flow at 75% of vital capacity (FEF₇₅) <65% were significantly more frequent in children with AHR. Mul-

tivariate logistic regression analysis revealed age, ever wheezing, nocturnal cough, tree pollen allergy, and FEF₇₅ <65% as independent predictors of AHR. A weighted clinical risk score was developed (range, 0–75 points). At a cut-off point of 35, the presence of AHR is predicted with a specificity of 90.5% and a positive predictive value of 91.5%. **Conclusion:** In children suspected of having asthma, but without an obstructive pattern in the spirometry, combining independent predictors, which can be easily obtained in clinical practice, might be used to identify children with AHR.

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Introduction

Asthma is a chronic disease with a high prevalence which is characterized by chronic airway inflammation and variable expiratory airflow limitations. Apart from airway obstruction, the presence of airway hyperresponsiveness (AHR) is accepted as one of the important key factors in asthma pathogenesis [1]. However, AHR could be present in patients suffering from chronic obstructive

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pulmonary disease, cystic fibrosis, allergic rhinitis, and sometimes also in healthy patients [2].

One of the most common methods to identify and quantitate AHR is the direct methacholine challenge (MCC). De Baets et al. [3] described the MCC as the “gold standard” in asthma diagnosis. Nevertheless, the diagnostic power of MCC is still under discussion, but it is determined to be highly sensitive for diagnosis of a current asthma when admission symptoms are clinically persistent. Particularly in these patients, absence of AHR confirmed by negative MCC excludes current asthma with reasonable certainty [4, 5].

There is evidence that the MCC has a quite low specificity compared to indirect bronchoprovocation tests [6]. Thus, indirect tests are suggested as the best screening tool to detect asthma. However, in patients suffering from asthma-related symptoms without an obstructive pattern in spirometry and without a positive reaction to indirect bronchoprovocation, there is a diagnostic dilemma in reaching the correct diagnosis. Often, these children have repetitive medical visits without a final correct diagnosis and treatment. For these patients, the presence of AHR by a positive MCC is considered as the “gold standard” in being able to confirm the presence of asthma with reasonable certainty.

Although the MCC is accepted as a safe diagnostic tool, it is time consuming and could be exhausting for patients [7]. The aim of this study was to identify the predictive factors which allow for a reliable identification of patients with a high probability of AHR who would thus benefit from a validation by the MCC. This can prevent the mental stress and even other aggravating effects induced by the performance of the MCC in a pediatric population when it might not be necessary. Therefore, we have developed a prediction model combining factors that best predict AHR and can be easily obtained in practice. The diagnostic performance of this novel prediction model was also investigated.

Methods

Study Participants

We analyzed the data from children who had undergone the MCC at the Department of Pediatric Allergy at the Children's Hospital, University of Bonn, between January 2009 and December 2018. From an initial population of 939 children suspected of possible asthma, patients with an obstructive pattern in spirometry, that is, baseline forced expiratory volume in 1 s (FEV₁) and/or FEV₁/forced vital capacity (FVC) ratio <80% predicted, or with positive bronchodilator response (≥ 200 mL or $\geq 12\%$) reversibility in executed spirometry ($n = 712$), were not included. Furthermore,

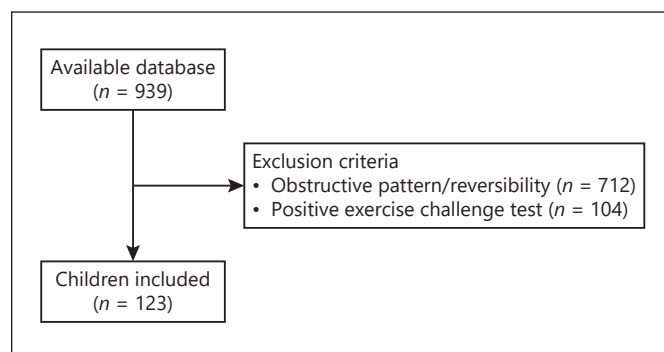


Fig. 1. Patient selection.

according to the established protocol in our department, children with primarily exercise-induced symptoms underwent exercise challenge testing before the MCC, and those children who had exercise-induced bronchoconstriction in the exercise challenge testing were also excluded ($n = 104$). Children were classified by a physician to be suspicious of possible asthma if at least one of the symptoms listed in the definitions were present. The data from 123 children were analyzed (Fig. 1).

Definitions

Admission symptoms were investigated at the patient's first visit by a standardized list of questions based on the International Study of Asthma and Allergies in Childhood (ISAAC) [8] using the German questionnaire developed by Duhme et al. [9]. Additional questions were used as have been previously described in detail elsewhere [10]. *Wheezing not associated with colds* was defined as a positive response to the question: “Has your child had wheezing or whistling in their chest in the past 12 months without a cold.” *Wheezing associated with colds* had the same definition as the clinical evidence of a viral cold [11]. *Ever had wheezing* was defined as a positive response to the question: “Has your child ever had wheezing or whistling in their chest at any time in the past” [8]. All symptoms were reported by the children and confirmed by the parents or by a physician. Children with at least one positive answer were declared as having asthma-like symptoms.

Skin Prick Tests

All children underwent skin prick testing to common aeroallergens for our region (ALK-Abelló, Hamburg, Germany) including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, and *Avena eliator*), grain pollen mix (*Secale cereale* and *Triticum aestivum*), weed pollen mix (*Artemisia vulgaris*, *Plantago lanceolata*, and *Ambrosia artemisiifolia*), tree pollen mix (*Alnus glutinosa*, *Corylus avellana*, *Betula verrucosa*, and *Quercus petraea*), molds (*Alternaria alternata* and *Aspergillus fumigatus*), and animal dander (cat and dog). Histamine (10 mg/mL of histamine phosphate) and 0.9% saline were used as positive and negative controls, respectively. Weal 3 mm greater than the negative control was considered a positive reaction.

Blood Eosinophil Counts and Serum Total Immunoglobulin E Levels

Blood eosinophil counts were determined by Coulter Counter (Beckman Coulter, Fullerton, CA, USA) leukocyte measurements. The serum total immunoglobulin E (IgE) level was measured with the ImmunoCAP system (Phadia AB, Uppsala, Sweden).

Bronchial Provocation Tests

To guarantee a meaningful performance of the challenge (MCC), following the accepted preparation guidelines [4, 12], patients had to discontinue taking short- or long-acting beta agonists, antihistamines, or corticosteroids/leukotriene receptor antagonists at least 24 h, 1 week, or 3 months, respectively, in advance. Testing was performed at least 3 months after the first submission. Furthermore, patients were requested not to smoke or eat a big meal 1 or 2 h, respectively, before starting challenge. Every patient was briefly informed about the course of the test procedure and got the opportunity to become familiar with body plethysmography. The administration of the MCC was largely automated according to the 1-concentration-4-step dosimeter protocol [13], which promises advantages in dosing accuracy and handling. In brief, spirometry was performed at baseline as a first step, followed by 4 steps, each with the inhalation of methacholine and subsequent spirometry 2 min after inhalation. With each step, the inhaled methacholine dose was raised, starting from 15 µg and increasing to a maximum of 720 µg. The exact dose inhaled at each step was determined by measuring the effective nebulization time at inspiration and referring it to the drug concentration and nebulizer power. The complete procedure was realized with the MasterScreen™ Body system (CareFusion, Höchberg, Germany) powered by the Sentry Suite software (Version 2.17.66, Hotfix Package 4) with automated control, providing a real-time visualization of the dose administration and breathing pattern. To optimize the inhalation process, patients could control their breathing themselves by a visual computer graphic imitating their breathing to attain an airflow of 0.5 L/s and to guarantee an inspiration time of 3 s during inhalation. The aerosol for inhalation was generated directly by the flow-triggered nebulization of a solution with a constant methacholine concentration (16 mg/mL isotonic saline [14]) through a mouthpiece of an APSpro jet-type nebulizer (240 mg/min performance; Medic Aid pro; Sidestream Care Fusion).

The current, as well as the cumulative, methacholine dose (PD20) which caused a decrease of FEV₁ by >20% was calculated by logarithmic interpolation. The end-of-test criterion was met if either FEV₁ decreased by >20% or the maximum cumulative methacholine dose of 960 µg had been inhaled. The result of the MCC was assessed as positive if PD20 was <960 µg. The latest versions of reference values for spirometry were used [15, 16].

Statistical Analysis

The median and interquartile range were computed for continuous parameters and counts and percentage for categorical variables. The continuous parameter FEF₇₅ was dichotomized using a cutoff of 65%. Group comparisons were carried out using the Mann-Whitney test and the χ^2 test as appropriate. Independent predictors of AHR, indicated by a positive MCC, were identified by multivariate logistic regression modeling entering parameters with $p < 0.05$ in a univariate analysis in a block. Odds ratios with their 95% confidence intervals and regression coefficients were computed. In order to create a weighted multivariate prediction

score, points were assigned to each of the elected predictors based on the respective regression coefficient multiplied by 10 and rounded up or down to the next integer number. An individual score value was calculated for each child by summing the weighted points of all the predictors. For each predictor, as well as for the multivariate score, sensitivity, specificity, a positive predictive value (PPV), and a negative predictive value (NPV) were determined at respective cutoff values, and receiver operating characteristics (ROC) curves were constructed. The SPSS software package 25 (IBM, Armonk, NY, USA) was used for all calculations. p values <0.05 were considered significant.

Results

The study population included 123 children (5–18 years) of which 64 (52%) were male. The MCC was positive in 81 (65.9%) children indicating the presence of AHR. In Table 1, the characteristics of the study population are summarized according to the presence of AHR. The median age of children with AHR was significantly younger at the time of diagnosis compared to those without AHR (9.7 vs. 12.3 years; $p = 0.001$). The prevalence of aeroallergen sensitization in the skin prick test was significantly higher in children with AHR when compared to those without AHR (35.7% vs. 58.0%; $p = 0.019$). Subclassification according to individual allergen groups revealed for AHR-positive children an elevated incidence of allergy to tree pollen (11.9% vs. 37.0%; $p = 0.003$), animal dander (9.5% vs. 27.2%; $p = 0.023$), and house dust allergy (21.4% vs. 44.4%; $p = 0.012$). For children with tree pollen allergy ($n = 35$), the result of MCC was independent of performing MCC during or after tree pollen season ($p = 0.752$).

With regard to admission symptoms, *nocturnal cough* (9.5% vs. 30.9%; $p = 0.008$), *wheezing not associated with colds* (4.8% vs. 22.2%; $p = 0.013$), and *wheezing associated with colds* (35.7% vs. 58.0%; $p = 0.019$) were observed significantly more frequently in AHR-positive children compared to children without AHR. Combining wheezing symptoms (*ever wheezing*) resulted in an improved significance (40.5% vs. 66.7%; $p = 0.005$), while significance was reduced for combinations of *nocturnal cough* with *exercise-induced cough*. However, *dyspnea* and *exercise-induced dyspnea*, even in combination with other parameters, did not reach significance. For the spirometry items, only a baseline forced expiratory flow at 75% of vital capacity (FEF₇₅) <65% was found significantly more frequently in AHR-positive children compared to the group without AHR (14.3% vs. 30.9%; $p = 0.045$). The diagnostic value of significant parameters in the univariate analysis is shown in Table 2.

Table 1. Comparison of demographic and laboratory data according to presence of AHR

	Study population (n = 123)	AHR positive (n = 81)	AHR negative (n = 42)	p value
Demographic data				
Male sex	64 (52.0)	42 (51.9)	22 (52.4)	0.96
Age at time of diagnosis, years	10.5 (8.0–13.0)	9.7 (7.1–12.0)	12.3 (9.7–14.0)	0.001
Family history of allergic disease	38 (30.9)	24 (29.6)	14 (33.3)	0.67
Family history of asthma	18 (14.6)	12 (14.8)	6 (14.3)	0.94
Family history of hay fever	25 (20.3)	13 (16.0)	12 (28.6)	0.10
Family history of eczema	6 (4.9)	4 (4.9)	2 (4.8)	0.97
Co-existence of 2 or more atopic diseases in family	10 (8.1)	4 (4.9)	6 (14.3)	0.07
Aeroallergen sensitization	62 (50.0)	47 (58.0)	15 (35.7)	0.019
Tree pollen	35 (28.5)	30 (37.0)	5 (11.9)	0.003
Grass pollen	48 (39.0)	36 (44.4)	12 (28.6)	0.09
Animal dander	26 (21.1)	22 (27.2)	4 (9.5)	0.023
Mold	7 (5.7)	5 (6.2)	2 (4.8)	0.75
House dust mite	45 (36.6)	36 (44.4)	9 (21.4)	0.012
Accompanying eczema	25 (20.3)	17 (21.0)	8 (19.0)	0.80
Accompanying allergic rhinitis/conjunctivitis	38 (30.9)	27 (33.3)	11 (26.2)	0.42
Pet ownership	51 (41.5)	36 (44.4)	15 (35.7)	0.35
Smoke exposition at home	13 (10.6)	10 (12.3)	3 (7.1)	0.37
Admission symptoms				
Daytime cough	67 (54.5)	49 (60.5)	18 (42.9)	0.06
Nocturnal cough	29 (23.6)	25 (30.9)	4 (9.5)	0.008
Exercise-induced cough	30 (24.4)	23 (28.4)	7 (16.7)	0.15
Co-existence of nocturnal and exercise-induced cough	12 (9.8)	11 (13.6)	1 (2.4)	0.047
Dyspnea	39 (31.7)	28 (34.6)	11 (26.2)	0.34
Exercise-induced dyspnea	60 (48.8)	36 (44.4)	24 (57.1)	0.18
Daytime cough and/or dyspnea	84 (68.3)	60 (74.1)	24 (57.1)	0.06
Exercise-induced cough and/or exercise-induced dyspnea	78 (63.4)	50 (61.7)	28 (66.7)	0.59
Ever wheezing	71 (57.7)	54 (66.7)	17 (40.5)	0.005
Wheezing not associated to colds	20 (16.3)	18 (22.2)	2 (4.8)	0.013
Wheezing associated to colds	62 (50.4)	47 (58.0)	15 (35.7)	0.019
Laboratory parameters^a				
Peripheral blood eosinophilia count >500/ μ L	19 (15.4)	18 (22.2)	1 (2.4)	0.002
Peripheral blood eosinophilia	4.0 (2.5–7.0)	5.6 (2.8–8.9)	2.8 (2.2–4.2)	0.004
Serum total IgE	123 (30–355)	150 (36–489)	77 (18–295)	0.07
Spirometry parameters, n (%)				
Baseline FEV ₁	100 (90–109)	100 (90–109)	101 (92–111)	0.49
Baseline FVC	93 (85–105)	93 (82–105)	93 (85–105)	0.84
Baseline FEV ₁ /FVC ratio	100 (89–112)	100 (89–111)	102 (89–117)	0.56
Baseline FEF ₂₅	87 (77–98)	87 (77–95)	89 (75–99)	0.70
Baseline FEF ₅₀	84 (75–98)	83 (74–97)	89 (80–104)	0.13
Baseline FEF ₇₅	78 (64–103)	77 (61–99)	86 (69–110)	0.08
Baseline FEF ₂₅ <65%	13 (10.6)	7 (8.6)	6 (14.3)	0.33
Baseline FEF ₅₀ <65%	12 (9.8)	10 (12.3)	2 (4.8)	0.18
Baseline FEF ₇₅ <65%	31 (25.2)	25 (30.9)	6 (14.3)	0.045

Data are presented as count (%) or median (interquartile range). AHR, airway hyperresponsiveness; IgE, immunoglobulin E; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF_{xx}, forced expiratory flow at XX percent of vital capacity. ^a Laboratory parameters were available in the study population (AHR+/AHR–) only from 80 (52/28), 93 (61/32), and 95 (62/33) children for peripheral blood eosinophilia count >500/ μ L, peripheral blood eosinophilia %, and serum total IgE, respectively.

A comparison of laboratory parameters reveals that the percentage of children with a blood eosinophilia count over 500/ μ L was significantly elevated in the AHR-positive group compared with children without AHR

(22.8% vs. 2.4%; $p = 0.002$; $N = 80$). Also, the median of the percentage of blood eosinophilia was significantly higher in AHR-positive children compared with the group without AHR (5.6% vs. 2.8%; $p = 0.004$; $N = 93$).

Table 2. Diagnostic performances of variables elected by univariate analyses

	Sensitivity, %	Specificity, %	NPV, %	PPV, %
Tree pollen allergy	37.0	88.1	42.0	85.7
Ever wheezing	66.7	59.5	48.1	76.1
Nocturnal cough	30.9	90.5	40.4	86.3
FEF ₇₅ <65%	30.9	85.7	39.1	80.6

FEF₇₅, forced expiratory flow at 75% of vital capacity; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Results of multivariate analysis

	Odds ratio	p value	Regression coefficient	Points in prediction score ^a
Age at time of diagnosis	0.83 (0.72–0.95)	0.008	–0.189	–2
Tree pollen allergy	4.16 (1.33–13.03)	0.014	1.425	14
Ever wheezing	2.87 (1.20–6.91)	0.018	1.056	11
Nocturnal cough	3.56 (1.02–12.42)	0.046	1.271	13
FEF ₇₅ <65%	3.08 (1.04–9.13)	0.043	1.123	11

Odds ratio is presented with 95% confidence interval. FEF₇₅, forced expiratory flow at 75% of vital capacity. ^a Points were calculated based on regression coefficients multiplied by a factor 10 and rounded off to the next integer number.

Table 4. Test characteristics of multivariate prediction score at various cutoff points

Cutoff point	Sensitivity, %	Specificity, %	NPV, %	PPV, %
>15	91.4	38.1	69.7	74.0
>25	80.2	66.7	63.6	82.3
>35	53.1	90.5	50.0	91.5
>45	24.7	97.6	40.2	95.2

NPV, negative predictive value; PPV, positive predictive value.

Multivariate logistic regression including age, *ever wheezing*, *nocturnal cough*, tree pollen allergy, and FEF₇₅ <65% confirmed that all parameters chosen are independent predictors of the occurrence of AHR. In Table 3, the results of multivariate analysis are summarized. Multivariate prediction score values, weighted as described in the Methods section, were calculated for each child as follows: individual score value = 14 × tree pollen allergy (yes = 1, no = 0) + 11 × ever wheezing (yes = 1, no = 0) + 13 × nocturnal cough (yes = 1, no = 0) + 11 × FEF₇₅ <65% (yes = 1, no = 0) – 2 × age (5–18 years) + 36. The last summand was added to get only positive score values ranging from 0 to 75 points. The individual score values calculated for our patients ranged from 3 to 61 with a median (interquartile range) of 32 (19–41). The risk of the occurrence

of AHR increased with the score value. In Table 4, the test characteristics of the multivariate score at various cutoff points are summarized. At a cutoff point of 35, the presence of AHR is predicted with a specificity of 90.5% and a PPV of 91.5%. At a cutoff point of 15, the sensitivity reaches >90%. The ROC curve displaying sensitivity and specificity of score with ascending cutoff points is shown in Figure 2. The area under the curve was 0.813.

Discussion

In the present study, we identified several factors associated with the occurrence of AHR in children. With 5 of these factors, we constructed a weighted multivariate

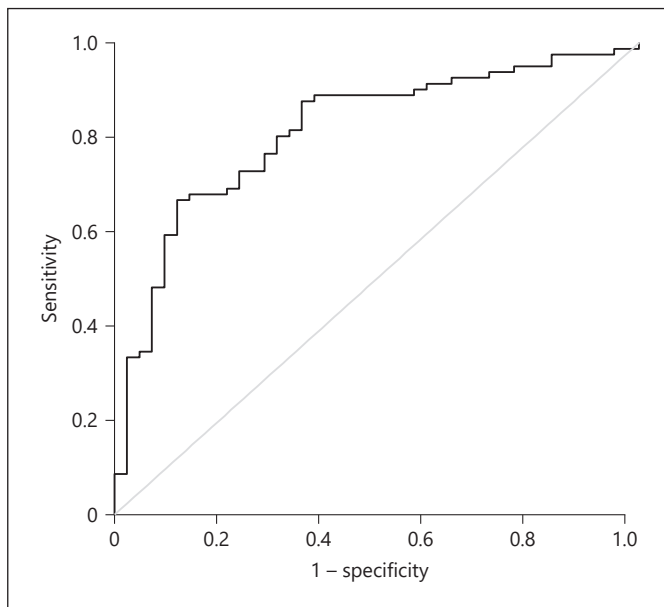


Fig. 2. Receiver operating characteristic curve of the multivariate prediction score for the presence of AHR. The area under the receiver operating characteristic curve was 0.813. AHR, airway hyperresponsiveness.

score to predict the presence of AHR in children suspected of having asthma but without an obstructive pattern in spirometry.

Association of Allergy, Atopic History, and Eosinophilia with AHR

Several studies have identified a personal history of having an allergy to various antigens as a risk factor for AHR [4, 17–19]. Tree pollen, especially, has been described as an important allergen in this context [20], while no association could be verified in relation to mold sensitization [20, 21]. In accordance with previous studies, we found an association of AHR with general skin test positivity as well as with sensitization to most aeroallergens, except mold, and where tree pollen sensitization reached the highest significance level. This high significance might be due to the specific local environment. The birch tree is widely spread in Germany and has emerged as a common allergen in children with allergic rhinitis and asthma [22].

In contrast, in an earlier study including children who were also without an obstructive pattern in spirometry, no significant relationship between personal allergy and the presence of AHR was detectable [10]. However, unlike the earlier study, in the present study, patients with

predominantly exercise-induced symptoms were excluded. The symptoms of the patients in our study group occurred mainly when they were at rest and were frequently triggered by allergens. Thus, it can be assumed that in the present study, there are more patients with allergies, supported by the higher percentage of sensitized children compared with the previous study (51.2% vs. 43.6%). Correspondingly, a stronger association between allergy and AHR can be expected. Especially in atopic patients, the MCC is accepted as a highly sensitive tool to detect AHR [23].

A family history of atopy has also been described by some authors as associated with AHR [24, 25], while others could not confirm such a relationship [26]. Although our data did not show a significant relationship of atopic family history with AHR, co-existence of 2 or more atopic diseases in the family nearly reached significance. In general, it is difficult to evaluate the influence of a genetic history because subjective measures might lead to overestimating the risk from family history. So, it can be assumed that parents suffering from respiratory symptoms would be more likely to recognize symptoms in their children and consult a physician [26, 27].

In accordance with the results of previous studies, we identified an association between high eosinophilia counts and AHR [10, 19, 28]. Unfortunately, our database of eosinophilia was incomplete, and therefore it was not included in the multivariate analysis.

Association of Asthma-Like Symptoms with AHR

Wheezing was identified in several studies as the most sensitive single symptom for asthma [17, 25] and was also included in many scores developed for the prediction of asthma [29]. An interrelation between wheezing associated with colds, AHR, and asthma has been reported [24, 30]. Likewise, several studies reported that nocturnal symptoms, and particularly nocturnal cough, are related to a decreased lung function as well as to a higher mortality of patients suffering from asthma [31].

Nocturnal cough is highly prevalent in adult patients with asthma [32], and a high frequency of nocturnal cough is shown to be significantly related to the presence of AHR [33]. While our findings confirm the importance of wheezing and nocturnal cough as predictors of AHR, Yavuz et al. [10] found that, in spite of a quite similar patient selection, there is neither a significant association of AHR with wheezing nor with nocturnal cough. They observed significance only for the co-existence of nocturnal and exercise-induced cough, a combination with reduced significance in our study.

Several studies have reported a negative association between AHR and dyspnea which might be due to a worse perception of breathlessness [10, 34]. The prevalence of dyspnea was also more frequent in children without AHR, however without reaching significance. Nevertheless, findings reported in the literature for single admission symptoms related to AHR and asthma seem to be inconsistent, probably due to a wide variability.

Association of Spirometry Findings with AHR

FEV₁ reflects mainly the functioning of the large and medium airways [35], whereas FEF represents the functioning of the medium-sized and small airways [35–37]. There are several studies observing the important role of FEV₁ in predicting AHR [17, 19, 38]. After excluding children with an obstructive pattern in spirometry, FEF becomes more important, and FEV₁ has been reported to lose its significance [10, 37]. Thus, FEF might have a possible role in the prediction of AHR, particularly in patients with a normal FEV₁ and FEV₁/FVC ratio [36, 37]. However, the predictive value of FEF for AHR is controversial. While some authors found a significant association of FEF values, especially of a forced mid-expiratory flow between 25% and 75% of vital capacity (FEF_{25–75%}), with AHR in patients with normal FEV₁ [36, 37, 39], others did not [40, 41]. This inconsistency may be due, at least, to the fact that some studies also included other diseases like cystic fibrosis [40, 41]. In our population, none of the spirometry variables recorded at baseline were significantly associated with AHR. However, after dichotomizing the FEF values at a cutoff of 65%, as proposed by others [36, 37], the role of FEF₇₅ <65% in predicting AHR became significant.

Association of Age with AHR

In this study, we found a negative association between age at time of diagnosis and presence of AHR. Also, in multivariate analysis, age remained a strong predictor of AHR. Our results were in accordance with several studies that report a relationship between age and AHR in children [19, 39, 42]. But, the relationship with age seems to be multifaceted. Obviously, pathophysiologic processes determining AHR alter with age [38] as well as with the duration of disease [43], and the predictive value of some variables changes depending on age [19]. An additional influence of age might be due to the considerable growth rate of children leading to the application of a larger dose in young children related to body size [39].

Prediction of AHR by a Multivariate Score

Admission symptoms related to AHR and asthma have a wide variability, and the diagnostic role of a single symptom is limited. The combination of single items can improve the power of prediction [10, 29]. We combined the 5 items, extracted by multivariate analysis as independent predictive factors, to construct a weighted multivariate score which reached an area under the curve >0.7 which is acceptable for a prognostic model [44]. In contrast to the previously established predictive scores like the asthma predictive index (API), we aimed for the diagnosis of current asthma and not for the prediction of the development of asthma in later life [29]. This algorithm could allow a reliable identification of those patients with an increased probability of AHR and where an extended diagnostic using MCC might be helpful. For this intent, a cutoff point of 15 with a sensitivity higher than 90% should be useful. This preselection might be helpful to prevent for some children the mental stress and even the exhaustion of such patients caused by the severe symptoms induced by the performance of the MCC.

Limitations

The comparability of our study population recruited from a specialized tertiary center for pediatric allergy is limited. We included only children with asthma-like symptoms and without obstructive pattern in spirometry. We also excluded patients with exercise-related leading symptoms. Due to these exclusion criteria, only patients with certain conditions could be recruited onto the study. In view of the high impact of tree pollen allergy – especially birch pollen – it could be difficult to use this score in other regions with different pollen profiles.

A potential weakness of our study, which is related to its retrospective design, seems to be the correct assessment of dyspnea, especially when the patient does not present dyspnea signs at the time of admission. However, our findings are extracted from a real-life setting, and it represents the routine diagnostic procedures. The large sample size is another strength of our study.

Conclusion

We identified tree pollen allergy, nocturnal cough, wheezing, a FEF₇₅ <65%, and a younger age as significant predictors of AHR. Combining these predictors in a weighted multivariate score improved the diagnostic value. This score might be used in children suspected of having asthma, but without an obstructive pattern in spirometry.

etry, to identify those who probably will show a positive response to the MCC as well as to substantiate the result of the MCC. Further studies are needed to confirm the predictive value of this score and the benefit in clinical practice.

Statement of Ethics

This consent protocol was reviewed and the need for written and informed consent was waived by the Ethics Committee of the Medical Faculty of Rheinischen Friedrich-Wilhelms-University, Bonn (April 18, 2019). This study complies with the guidelines for human studies, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

References

- Russell RJ, Brightling C. Pathogenesis of asthma: implications for precision medicine. *Clin Sci*. 2017;131(14):1723–35.
- Borak J, Lefkowitz RY. Bronchial hyperresponsiveness. *Occup Med*. 2016;66:95–105.
- De Baets F, Bodart E, Dramaix-Wilmet M, Van Daele S, de Bilderling G, Masset S, et al. Exercise-induced respiratory symptoms are poor predictors of bronchoconstriction. *Pediatr Pulmonol*. 2005;39:301–5.
- Cockcroft DW, Davis BE, Blais CM. Direct bronchoprovocation test methods: history 1945–2018. *Expert Rev Respir Med*. 2019;13:279–89.
- Sergeeva LI, Vonk J, Keurentjes JJ, van der Plas LH, Koornneef M, Vreugdenhil D. Histochemical analysis reveals organ-specific quantitative trait loci for enzyme activities in Arabidopsis. *Plant Physiol*. 2004;134:237–45.
- Cockcroft DW, Davis BE, Blais CM. Comparison of methacholine and mannitol challenges: importance of method of methacholine inhalation. *Allergy Asthma Clin Immunol*. 2020;16:14.
- Lévesque V, Poirier C, Dubé BP. Dose omission to shorten methacholine challenge testing: clinical consequences of the use of a 10% fall in FEV₁ threshold. *Allergy Asthma Clin Immunol*. 2018;14:88.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8:483–91.
- Duhme H, Weiland SK, Rudolph P, Wienke A, Kramer A, Keil U. Asthma and allergies among children in West and East Germany: a comparison between Munster and Greifswald using the ISAAC phase I protocol. *International Study of Asthma and Allergies in Childhood*. *Eur Respir J*. 1998;11:840–7.
- Yavuz ST, Civelek E, Tuncer A, Sahiner UM, Sekerel BE. Predictive factors for airway hyperresponsiveness in children with respiratory symptoms. *Ann Allergy Asthma Immunol*. 2011;106:365–70.
- Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008;32:1096–110.
- Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med*. 2019;200:e70–88.
- Merget R, Jörres RA, Heinze E, Haufs MG, Taeger D, Brüning T. Development of a 1-concentration-4-step dosimeter protocol for methacholine testing. *Respir Med*. 2009;103:607–13.
- Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report working party standardization of lung function tests, European Community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16:53–83.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European Community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16:5–40.
- Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324–43.
- Park JS, Choi YJ, Suh DI, Jung S, Kim YH, Lee SY, et al. Profiles and characteristics of bronchial responsiveness in general 7-year-old children. *Pediatr Pulmonol*. 2019;54:713–20.
- Tham EH, Lee AJ, Bever HV. Aeroallergen sensitization and allergic disease phenotypes in Asia. *Asian Pac J Allergy Immunol*. 2016;34:181–9.
- Lee E, Kim YH, Cho HJ, Yoon J, Jung S, Yang SI, et al. Clinical phenotypes of bronchial hyperresponsiveness in school-aged children. *Ann Allergy Asthma Immunol*. 2018;121:434–43.e2.
- Jo EJ, Eom JS, Mok J, Kim MH, Lee K, Kim KU, et al. Patterns of sensitization to aeroallergens and their effect on airway hyperresponsiveness in Busan, Korea. *Asian Pac J Allergy Immunol*. 2021;39(3):182–9.
- Vincent M, Corazza F, Chasseur C, Bladt S, Romano M, Huygen K, et al. Relationship between mold exposure, specific IgE sensitization, and clinical asthma: a case-control study. *Ann Allergy Asthma Immunol*. 2018;121:333–9.

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S.T. Yavuz and M. Reinsberg had primary responsibility for protocol development and analytic framework of the study, patient screening, enrollment, data entry, outcome assessment, and manuscript preparation. S. Siebert, C. Dreher, and T. Bogs participated in the patient screening, enrollment, and data entry and prepared the manuscript with S.T. Yavuz. R. Ganschow had contributed to protocol development, data analysis, and preparation and revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

- 22 Mosges R, Graute V, Christ H, Sieber HJ, Wahn U, Niggemann B. Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. *Pediatr Allergy Immunol*. 2010;21:1135–8.
- 23 Lee J, Song JU. Diagnostic comparison of methacholine and mannitol bronchial challenge tests for identifying bronchial hyperresponsiveness in asthma: a systematic review and meta-analysis. *J Asthma*. 2021;58:883–91.
- 24 Jung S, Suh DI, Lee SY, Yoon J, Cho HJ, Kim YH, et al. Prevalence, risk factors and cutoff values for bronchial hyperresponsiveness to provocholine in 7-year-old children. *Allergy Asthma Immunol Res*. 2018;10:466–77.
- 25 Fuchs O, Bahmer T, Rabe KF, von Mutius E. Asthma transition from childhood into adulthood. *Lancet Respir Med*. 2017;5:224–34.
- 26 Gray L, Peat JK, Belousova E, Xuan W, Woolcock AJ. Family patterns of asthma, atopy and airway hyperresponsiveness: an epidemiological study. *Clin Exp Allergy*. 2000;30:393–9.
- 27 Alharbi SA, Kobeisy SAN, AlKhater SA, Alharbi AS, Alqwaiee MM, Alotaibi FN, et al. Childhood asthma awareness in Saudi Arabia: five-year follow-up study. *J Asthma Allergy*. 2020;13:399–407.
- 28 Ciprandi G, Marseglia GL, Ricciardolo FLM, Tosca MA. Pragmatic markers in the management of asthma: a real-world-based approach. *Children*. 2020;7:48.
- 29 Castro-Rodriguez JA, Cifuentes L, Martinez FD. Predicting asthma using clinical indexes. *Front Pediatr*. 2019;7:320.
- 30 Jackson DJ, Gern JE, Lemanske RF Jr. Lessons learned from birth cohort studies conducted in diverse environments. *J Allergy Clin Immunol*. 2017;139:379–86.
- 31 Sutherland ER. Nocturnal asthma. *J Allergy Clin Immunol*. 2005;116(6):1179–87; quiz 1187.
- 32 Rassouli F, Tinschert P, Barata F, Steurer-Stey C, Fleisch E, Puhon MA, et al. Characteristics of asthma-related nocturnal cough: a potential new digital biomarker. *J Asthma Allergy*. 2020;13:649–57.
- 33 Fukuhara A, Saito J, Birring SS, Sato S, Uematsu M, Suzuki Y, et al. Clinical characteristics of cough frequency patterns in patients with and without asthma. *J Allergy Clin Immunol Pract*. 2020;8:654–61.
- 34 Ohwada A, Sato K. Heterogeneity of perception of symptoms in patients with asthma. *J Thorac Dis*. 2019;11:5218–27.
- 35 Francisco B, Ner Z, Ge B, Hewett J, König P. Sensitivity of different spirometric tests for detecting airway obstruction in childhood asthma. *J Asthma*. 2015;52:505–11.
- 36 Ciprandi G, Gallo F, Cirillo I. FEF25-75 and asthma in clinical practice. *Iran J Allergy Asthma Immunol*. 2018;17:295–7.
- 37 Malerba M, Radaeli A, Olivini A, Damiani G, Ragnoli B, Sorbello V, et al. Association of FEF25–75% impairment with bronchial hyperresponsiveness and airway inflammation in subjects with asthma-like symptoms. *Respiration*. 2016;91:206–14.
- 38 Hardaker KM, Downie SR, Kermode JA, Farah CS, Brown NJ, Berend N, et al. Predictors of airway hyperresponsiveness differ between old and young patients with asthma. *Chest*. 2011;139:1395–401.
- 39 Harmanci K, Bakirtas A, Turkas I. Factors affecting bronchial hyperreactivity in asthmatic children. *J Asthma*. 2008;45:730–4.
- 40 Lukic KZ, Coates AL. Does the FEF25-75 or the FEF75 have any value in assessing lung disease in children with cystic fibrosis or asthma? *Pediatr Pulmonol*. 2015;50:863–8.
- 41 Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making. *Eur Respir J*. 2014;43:1051–8.
- 42 Kim YH, Lee E, Cho HJ, Yang SI, Jung YH, Kim HY, et al. Association between menarche and increased bronchial hyper-responsiveness during puberty in female children and adolescents. *Pediatr Pulmonol*. 2016;51:1040–7.
- 43 Grönke L, Kannies F, Holz O, Jörres RA, Magnussen H. The relationship between airway hyper-responsiveness, markers of inflammation and lung function depends on the duration of the asthmatic disease. *Clin Exp Allergy*. 2002;32:57–63.
- 44 Caudri D, Wijga A, Schipper CMA, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. *J Allergy Clin Immunol*. 2009;124:903–10.e1–7.