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ORIGINAL RESEARCH

Alternaria Sensitization and Allergy in Children and Adolescents: A Retrospective Diagnostic Study

Gözde Kabadayi, Jordis Trischler, Martin Hutter, Stefan Zielen, Katharina Blumchen, Johannes Schulze

Department of Pediatrics University Hospital, Division of Pneumology, Allergology, Infectious Diseases and Gastroenterology, Goethe University, Frankfurt, Germany

Correspondence: Gözde Kabadayi, Department of Pediatrics University Hospital, Division of Pneumology, Allergology, Infectious Diseases and Gastroenterology, Goethe University, Theodor-Stern-Kai 7, Frankfurt, 60590, Germany, Email goezde98@hotmail.com

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Purpose: *Alternaria alternata* (AA) grows on decaying material. Spores occur on hot and dry days in the summer and can trigger asthma and allergic rhinitis. Skin prick test (SPT-AA) and *Alternaria alternata*-specific IgE (AA-IgE) are used for diagnostic purposes, but their predictive value is unclear.

Patients and Methods: A retrospective analysis of electronic medical records to 2011–2021 was performed on symptoms, SPT-AA, AA-IgE, lung function, asthma therapy and bronchial provocation using *Alternaria alternata* extract (BP-AA).

Results: 149 children and adolescents (5–18 years) with Alternaria allergy were investigated. Between June and September, 86 Alternaria-sensitized patients had asthmatic symptoms and 113 had nasal symptoms (often outdoors or with mold exposure). SPT-AA and AA-IgE levels did not differ between the symptomatic and asymptomatic patients (SPT-AA, p= 0.23). A weak correlation was observed between the diagnostic tests in 49 patients with bronchial and/or nasal symptoms (r= 0.36, p= 0.01). Nineteen patients received provocation, 16 showed an early asthmatic response and 14 a late asthmatic response. Patients with BP-AA had a medium SPT-AA ≥7 mm or AA-IgE ≥16.8 kU/L. Both tests significantly correlate with PD20-AA (r= −0,49, p< 0.01 and r= 0.26, p< 0.01, respectively).

Conclusion: The Diagnosis of Alternaria allergy is still a challenge. The weak to moderate correlation between SPT-AA and AA-IgE seems to be allergen-specific. Typical medical history is a key diagnostic criterion. Allergy profiles and climate may play a role in the manifestation of symptoms. BP-AA help to establish threshold values for SPT-AA and AA-IgE. In unclear cases, nasal or bronchial provocation should be performed before immunotherapy.

Keywords: allergic asthma, allergic rhinitis, skin prick test, serum-specific IgE, bronchial allergen provocation

Introduction

The German Society for Pediatric Allergology and Environmental Medicine (GPAU) considers Alternaria allergy rare in Germany.[1] *Alternaria alternata* (AA) is a saprophytic fungus that occurs in nature mainly on decaying organic material, such as leaves, compost and silage, but also in stables where hay and straw are stored.[1] Alternaria spores are usually present in the air on hot and dry days during midsummer and late summer. Spore concentration depends on different geographical conditions and can vary locally depending on the weather, climate and year to year.[2] In a Europe-wide survey, the prevalence of a positive allergy test in adults was 3.3% with ranging from 0.2% to 14.4%. The highest prevalence was found in the United Kingdom, France (Montpellier), Germany (Hamburg) and Netherlands.[3] Alternaria allergy can lead to an asthmatic reaction with sudden respiratory distress in sensitized patients who are outdoor during sports.[1]

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Early and accurate diagnosis is clinically essential to prevent the development of asthma and severe exacerbations, enabling the early initiation of allergen-specific immunotherapy (AIT), especially in children predisposed to persistent respiratory disease.[4,5]

But owing to considerable variance, the detection of Alternaria allergy is a diagnostic challenge. The frequently performed skin prick test (SPT-AA) is very helpful because it is cheap and can be performed relatively quickly. However, the relation between allergic sensitization and symptoms is not always clear. Depending on the extent of the allergy, further diagnostics might be considered, such as determining the serum-specific IgE (AA-IgE) value and nasal or bronchial allergen provocations.

In a study Randriamanantany et al investigated the relationship between Alternaria sensitization, allergic rhinitis and asthma in 6726 children in six French cities. Of these, 2.8% (189) were sensitized to Alternaria, of which 28.6% (54) were monosensitized (0.8% of the total population). Alternaria sensitization was found to be strongly associated with rhinoconjunctivitis and allergic rhinitis. These symptoms also occur independently of asthma and are more pronounced in monosensitized children.[6] Two other studies[7,8] found an independent and significant association of Alternaria sensitization and asthma symptoms in children living in warm and dry regions (Australia and Arizona). In a Brazilian-Chilean study, no association was found between Alternaria sensitization and rhinoconjunctivitis when adjusted for sensitization to other allergens.[9] Another study[10] in a birth cohort of children did not show a statistically significant role of Alternaria as an independent risk factor for asthma or rhinitis.

Of 2942 patients examined in the study by Negrini et al in Italy, 306 (10.4%) had a positive SPT for Alternaria tenuis, of whom 37 were monosensitized. Fifty-four percent of the individuals had asthma, either with or without rhinoconjunctivitis, while 41% had rhinoconjunctivitis. While 60% had year-round symptoms, one-third had spring or fall symptoms, regardless of the environment. Children and adolescents were particularly affected. The authors concluded that a precise etiological diagnosis is rather empirical.[11]

In a Spanish study by Fernández et al, 74 patients aged 14–41 years who were sensitized to Alternaria underwent bronchial provocation with *Alternaria alternata* extract (BP-AA), because there was no clear association between Alternaria sensitization and allergic symptoms. In the Madrid region, most patients are additionally sensitized to grass pollen, which is present in the air at the same time as Alternaria spores in May and June. Due to the temporal overlap, BP-AA might differentiate between predominantly grass pollen and Alternaria allergy.[12] In this study it has been shown that the SPT-AA and the AA-IgE predicted a positive reaction in the BP-AA with a high degree of accuracy.[12] However, to date, no data are available to examine the value of individual diagnostic methods in children and adolescents.

In the past, AIT was generally not recommended for Alternaria allergy because the doctrine assumed that allergies to molds were rare and clinically less relevant.[1] However, in a single study with 45 children and adolescents, it was shown that AIT with a standardized *Alternaria alternata* extract significantly reduced hay fever and asthma symptoms.[13]

The presence of a matching clinical presentation with a positive SPT-AA or AA-IgE but also for other allergens in the same season (eg grass pollen and other molds such as Cladosporium) complicates reliable diagnosis. In such instances, BP-AA could help to distinguish between Alternaria allergy (positive tests + clinical symptoms) and Alternaria sensitization (positive test). However, there are concerns regarding the safety of BP-AA.

Using data collected over 10 years from the pediatric clinic of the University Hospital, the validity and accuracy of SPT-AA and AA-IgE were investigated in 448 children and adolescents diagnosed with Alternaria allergy to determine their suitability as predictive parameters for BP-AA to differentiate between sensitization and allergy.

Materials and Methods

Type and Characteristics of the Study

This work is based on a retrospective analysis in which all patients between the years 2011–2021 with the medical diagnosis "Alternaria allergy" or the international classification of diseases (ICD) "J30.3" (other allergic rhinopathy) or "B48.7" (mycoses caused by opportunistic pathogenic fungi) were filtered on the hospital information systems "ORBIS Dedalus Healthcare Systems Group" as well as "MediStar". After reviewing the files, all patients without an Alternaria allergy were eliminated. Records of children aged 5–18 with Alternaria allergy at the Department of Pediatrics of the

University Hospital were evaluated using Clinical Case Report Forms (CRF). Attention was paid to the clinical symptoms and tests performed to establish a diagnosis. The diagnosis in the clinic software was mainly attributed to positive SPT-AA results and medical history. The occurrence of sudden asthma symptoms on hot and dry days and nasal symptoms were investigated in more detail as part of their medical history. Asthma is defined as episodic symptoms such as shortness of breath, chest tightness, coughing and wheezing. These symptoms are caused by reversible bronchial obstruction due to chronic airway inflammation. Symptoms of rhinitis typically include a blocked or runny nose, nasal itching, tightness in the nose or sneezing and are an expression of an allergic inflammatory reaction of the nasal mucosa. The tests included SPT-AA and determination of AA-IgE and BP-AA. In addition, other criteria, such as age, weight, height, pulmonary function test results and prescribed medications were analyzed. The recommendation as well as the following implementation of an AIT against Alternaria was also part of the evaluation. The indication for AIT was mainly given by a positive BP-AA result. Therefore, we examined the safety of BP-AA in this age group.

This study was approved by the Ethics Committee of the Faculty of Medicine, Goethe University Frankfurt, c/o University Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany (number of ethics vote: 2022–871). A patient consent was not required by the IRB. According to the General Data Protection Regulation (GDPR), Federal Data Protection Act (BDSG), Section 27 (2) the right of access according to Article 15 of Regulation (EU) 2016/679 shall not apply if the data are necessary for purposes of scientific research and the provision of information would involve disproportionate effort. All procedures complied with data protection regulations and the Declaration of Helsinki.

Skin Prick Test

The allergens are applied as a standardized test solution (Alternaria, 5000 standardized biological units (SBU)/ mL, Allergopharma GmbH & Co. KG, Reinbek, Germany). If the resulting wheal size is equal to or greater than 3 mm, the SPT-AA is considered positive.

Serum-Specific Immunoglobulin E

The serum-specific immunoglobulin E can be determined by either the radio allergic sorbent test (RAST) or the fluorescence enzyme immunoassay (FEIA) (Thermo Fisher Scientific (Phadia AB), Uppsala, Sweden). An IgE concentration > 0.35 kU/L for *Alternaria alternata* is considered a positive result.

Bronchial Allergen Provocation

BP with an Alternaria allergen (Alternaria, 5000 SBU/mL, Allergopharma GmbH & Co. KG, Reinbek, Germany) was performed using the APS dosimeter technique (CareFusion). The provocation protocol was performed as described previously.[14]

The dose of inhaled allergen was doubled step by step, starting with five SBU: 5, 10, 20, 40, 80 and 160 SBU. This resulted in cumulative doses of 5, 15, 35, 75, 155 and 315 SBU. The individual provocation dose that caused a 20% drop in FEV_1 ($PD_{20}FEV_1$, Alternaria) in the early asthmatic response (EAR) was calculated using a logarithmic interpolation between the doses before and after the 20% drop in FEV_1. After BP-AA, patients received two to four puffs of salbutamol (0.1 mg) until FEV_1 returned to at least 90% of baseline. FEV_1 was measured for up to 10 hours after BP-AA. A decrease of $\geq$ 15% in FEV_1 was defined as a late asthmatic response (LAR) to Alternaria.

Statistical Analysis

GraphPad Prism 5.01 (GraphPad Software, La Jolla, CA, USA) and Microsoft Excel were used for statistical analyses. According to the Kolmogorov–Smirnov test, normally distributed data are expressed as the mean and standard deviation, whereas non-normally distributed data are expressed as the median and 25^{th} $^{-}75^{th}$ percentile. Student's *t*-test was used to test the difference between the responses of the two groups and the Mann–Whitney *U*-test was used to compare non-parametric groups. Correlations were calculated using the Spearman's rank correlation test. Statistical significance was set at $p \leq 0.05$.

Results

In this study, 448 children and adolescents diagnosed with Alternaria allergy or ICD code J30.3/B48.7 were screened. CRFs were designed to analyze patient data. Based on the inclusion and exclusion criteria, 20 patients were excluded because they were younger than five years and two because they were older than 18 years. Four patients had no SPT-AA or AA-IgE and 10 had negative allergy test results. A total of 149 patients were included in this analysis (Figure 1), 90% of whom originated from the Frankfurt area. The remaining 10% were recruited from locations within a 150-kilometer radius of Frankfurt. More detailed information on the gender, age, SPT-AA or AA-IgE and lung function parameters of these patients is presented in Table 1.

The files of 149 patients showed that 86 complained of asthmatic symptoms on hot and dry days (June to September). The occurrence of these symptoms (playground, meadow, forest, garden, camping in the field, countryside, bushes and shrubs) was only observed outdoors in 16 patients. Twelve children and adolescents reported exposure to mold in their medical histories. Playing with a moldy plant led to asthmatic symptoms in one patient, one patient developed asthmatic symptoms in an animal shelter, one on a farm, one at night with a tilted window (there were many old leaves on the roof of the house) and another after heavy rainfall in summer. Four had symptoms on vacation (Netherlands, Mallorca/Croatia, Poland and Serbia) and two had symptoms while swimming. Of the 86 children and adolescents with bronchial symptoms, 79 had SPT-AA and 42 had AA-IgE. Of the 63 patients who had no asthmatic symptoms but possibly nasal symptoms, 57 had SPT-AA and 25 had AA-IgE.

Rhinitis symptoms were also reported in 113 patients. Of these, 103 had SPT-AA and 49 had AA-IgE. Of the 36 children and adolescents without nasal symptoms but with possible bronchial symptoms, 33 had SPT-AA and 18 had AA-IgE.

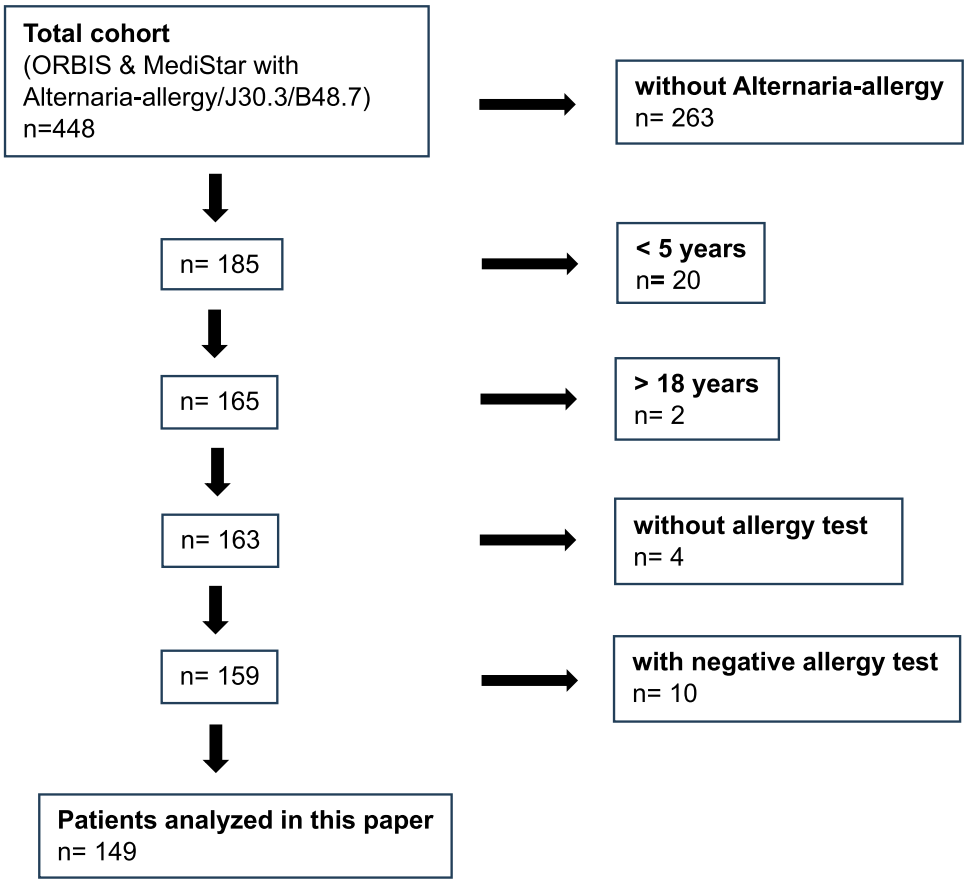

Figure 1 Flowchart for patient selection.

Table 1 Subject Characteristics

Subjects	n		
Male/Female	149		98/51
Age	149	yr; median, 25^{th} –75^{th} percentile	9.0, 7.0–11.0
Alternaria PRICK	136	mm; median, 25^{th} –75^{th} percentile	6.3, 5.0–7.0
Alternaria RAST	67	kU/L; median, 25^{th} –75^{th} percentile	15.6, 6.0–25.8
FEV_1	146	% predicted; mean ± SD	94.2 ± 16.7
FVC	147	% predicted; mean ± SD	91.7 ± 15.3

For bronchial and nasal symptoms, the SPT-AA or AA-IgE values were distributed approximately equally between the two patient groups, as shown in Figures 2 and 3. Statistical data on the SPT-AA/AA-IgE values in relation to the symptoms can be found in Table 2. Patients with bronchial and/or nasal symptoms (n= 134) did not differ significantly from those without (n=15)

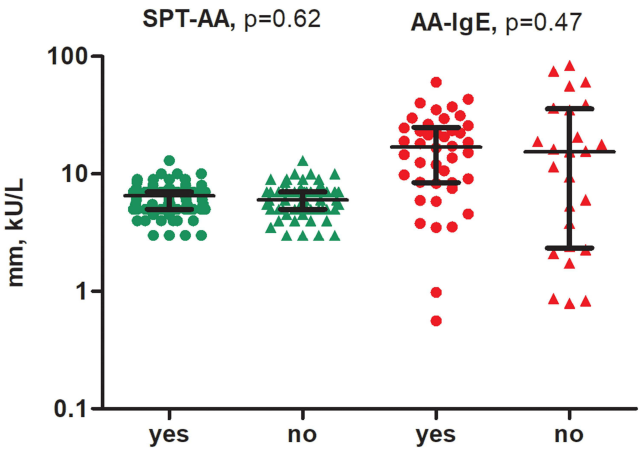

Figure 2 Association between bronchial symptoms and diagnostics: SPT-AA of patients with (yes) bronchial symptoms: median [25th-75th] 6.5 [5.0; 7.0]/without (no) bronchial symptoms: median [25th-75th] 6.0 [5.0; 7.0] and AA-IgE of patients with (yes) bronchial symptoms: median [25th-75th] 16.9 [8.4; 24.9])/without (no) bronchial symptoms: median [25th-75th] 15.4 [2.3; 35.8].

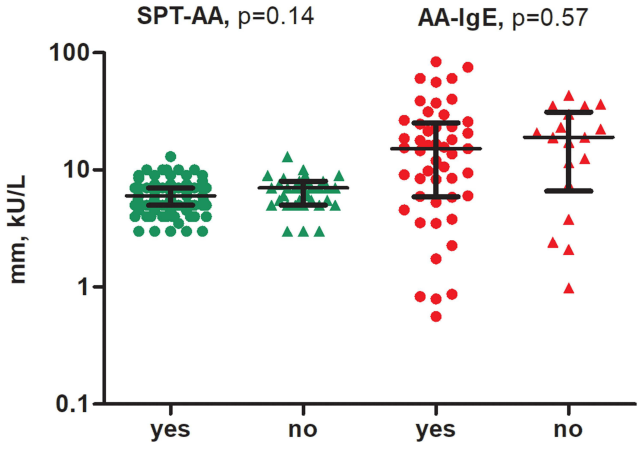

Figure 3 Association between nasal symptoms and diagnostics: SPT-AA of patients with (yes) nasal symptoms: median [25th-75th] 6.0 [5.0; 7.0]/without (no) nasal symptoms: median [25th-75th] 7.0 [5.0; 8.0] and AA-IgE of patients with (yes) nasal symptoms: median [25th-75th] 15.2 [5.9; 25.2])/without (no) nasal symptoms: median [25th-75th] 19.0 [6.6; 31.2].

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Table 2 PRICK/RAST Results of Patients ± Symptoms

	Bronchial Symptoms			Nasal Symptoms		
	+	–	p-value	+	-	p-value
Alternaria PRICK [mm; median, 25th –75th]	6.5, 5.0–7.0	6.0, 5.0–7.0	0.62	6.0, 5.0–7.0	7.0, 5.0–8.0	0.14
Alternaria RAST [kU/L; median, 25th –75th]	16.9, 8.4–24.9	15.4 2.3–35.8	0.47	15.2, 5.9–25.2	19.0, 6.6–31.2	0.57

(SPT-AA, p= 0.23). A total of 49 patients with bronchial and/or nasal symptoms underwent both, SPT-AA and AA-IgE testing. There was a weak correlation between the SPT and IgE values (r= 0.36, p= 0.01), as shown in Figure 4.

Of the 149 children and adolescents with positive SPT-AA and/or AA-IgE results, 28 were monosensitized, 50 had positive SPT and/or IgE results for mite allergy, 53 for animal dander and 50 for other molds (Cladosporium, Aspergillus, Candida and Helminthosporium). In addition, 21 had a positive SPT and/or IgE for grass pollen, 20 for birch pollen and 60 for both.

During the data analysis, 19 children and adolescents (six monosensitized) were challenged with Alternaria extract. Of these, 12 patients had EAR and LAR, four had EAR only, and two had LAR only (one monosensitized). One of the monosensitized patients had a weak EAR at 141.7 allergen units and no LAR.

We analyzed the indications for BP-AA. Of the 16 BP-AA-positive patients, 12 had typical asthmatic symptoms in the late summer (11 during exercise). One patient had typical symptoms after contact with a moldy plant and another patient had mold exposure at home. Two of the 16 patients had no typical symptoms of Alternaria allergy and therefore no anamnestic indication. Here, the performance of an Alternaria provocation test was justified only by the presence of a positive allergy test. The remaining three of the 19 provoked did not have a clear positive result. One patient reported that there were a lot of old leaves on the roof of the house and that he had to cough a lot at night whenever he slept with the window open. Another patient had a late summer cough with considerable impact and the last patient with borderline positive BP-AA did not report any typical symptoms of Alternaria allergy. Statistical data on allergy tests and PD20 are shown in Table 3. SPT-AA and AA-IgE levels were significantly correlated with PD20-AA levels (r= −0,49, p< 0.01 and r= 0.26, p< 0.01, respectively). ROC analysis could not be performed due to the low number of negative BP-AA.

Eleven of the 19 provoked patients received AIT (three monosensitized, of which one had a negative BP-AA). Four additional patients (one monosensitized) underwent AIT based on their medical history and allergy test results. In our cohort, subcutaneous AIT was performed using Novo-Helisen Depot (Allergopharma GmbH & Co. KG, Reinbek, Germany) and Tyrosin TU T.O.P. (Bencard Allergie GmbH, Munich, Germany). Most treatments were administered

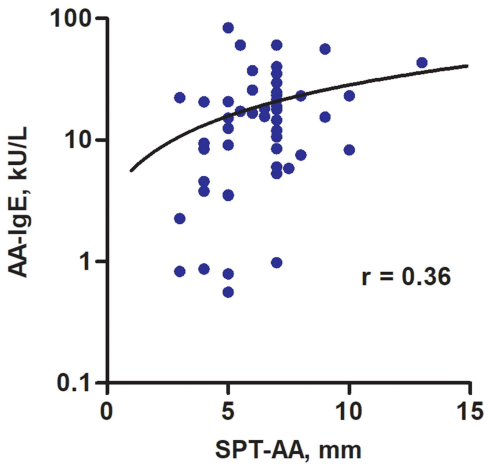

Figure 4 Correlation of SPT-AA/AA-IgE.

Table 3 PRICK/RAST/PD20 Alternaria of Patients with a Bronchial Provocation (AU; Allergen Units)

Subject	n	
Alternaria PRICK [median, 25th −75th percentile]	18	7.0 mm, 4.9–7.1
Alternaria RAST [mean ± SD]	13	16.8 kU/L, ± 9.3
PD20 Alternaria [median, 25th −75th percentile]	19	15.0, AU 7.0–75.0

outside the clinical setting, consequently, detailed retrospective data on treatment duration and outcomes were unavailable and AIT could not be analyzed in depth.

Asthma medication over the 10 years was as follows: Ninety-six patients received a short-acting beta-agonist (salbutamol) on demand. Twenty-four patients received an inhaled steroid (ICS), 84 combined with long-acting beta-agonists. In addition, 23 patients were prescribed the leukotriene antagonist, montelukast.

Discussion

The primary aim of this study was to investigate the significance of SPT-AA and AA-IgE levels and to perform ROC analyses to determine their suitability as predictive parameters for BP-AA. Of the 149 children and adolescents included in this study, only 19 received BP-AA. We could not perform a ROC analysis due to the low number of negative BP-AA. However, SPT-AA and AA-IgE levels significantly correlated with PD20-AA levels, indicating a close relationship. The results showed that the SPT-AA values were particularly associated with bronchial reactivity. Therefore, SPT-AA is useful for assessing the risk of bronchial reactivity to *Alternaria alternata*.

In the study by Fernández et al, ROC analysis showed for a CAP value of ≥ 1 kU/L a sensitivity of 91% and specificity of 72%, with an area under the ROC curve (AUC) of 0.859 for the prediction of a positive BP-AA. Patients with a CAP ≥ 18 kU/L had a positive predictive value and specificity of 100%. For a SPT-AA of ≥ 5 mm, the sensitivity was found to be 82% and the specificity was found to be 93% (AUC=0.957). A SPT-AA ≥ 8 mm had a positive predictive value and specificity of 100%. Negative SPT-AA had a very high predictive value for negative BP-AA results.[12]

In the work of Reijula et al 6 out of 7 patients with a clear history of rhinoconjunctivitis and a positive SPT (≥ 4 mm) for Alternaria or Cladosporium reacted positively in a conjunctival provocation test.[15]

In our study, almost all the patients who received BP-AA had a typical medical history and positive provocation. This shows that the preselection was precise and targeted. In patients with BP-AA, the median SPT-AA was 7 mm and the mean AA-IgE was 16.8 kU/L. These results were within the range of the Fernández cut-off values.[12] Therefore, we postulated cut-off values for children and adolescents with SPT-AA ≥ 8 mm and AA-IgE ≥ 18 kU/L.

Patients with a positive SPT for grass pollen were carefully examined, if the diagnostic results were conclusive, a specific AIT against grass pollen was initiated. Those affected by additional Alternaria sensitization were observed during the following season using a symptom diary. In Germany, grass pollen flights are most pronounced from May to July, depending on region and year.[16] Alternaria spore flight begins in July, reaches a peak in August and subsides again in September.[17]

Children and adolescents with bronchial/nasal symptoms were compared with those without symptoms in terms of SPT-AA and AA-IgE values. The lack of statistical significance of SPT and specific IgE levels shows that neither reliably differentiates between symptomatic and asymptomatic patients. Not all sensitized patients develop symptoms, therefore, the clinical relevance of positive test results should be questioned.

Although several studies, including ours, have not identified significant correlations,[9,10] other studies have demonstrated an association between Alternaria sensitization and bronchial as well as nasal symptoms.[6–8] Multiple factors likely contributed to these observations. One point to note is the different allergy profiles of our cohort. A total of 28 patients were monosensitized, 24 (86%) of whom had bronchial and/or nasal symptoms on hot dry days. Randriamanantany et al highlighted that monosensitization allows a precise assessment of the isolated effect of Alternaria, whereas polysensitization reflects a broader exposure to allergens. Therefore, the latter showed a higher prevalence and a stronger OR in this study.[6] Environmental factors may also have played an important role in this process. The study in the six French cities may have covered regions with higher exposure to Alternaria due to climatic conditions, making the effects of sensitization more pronounced.[6] The important role of climate in relation to airborne spore load and the associated sensitization was particularly evident in the study by Reijula et al. The cold climate of Finland provides suboptimal conditions for Alternaria growth, which is why Alternaria allergies are less clinically relevant in Finland than in warmer climates.[15]

In our data analysis, a random distribution of tests was observed. Sensitization only reflects immunological reactivity to Alternaria, without necessarily causing clinical symptoms. The manifestation of symptoms depends on additional factors such as allergen exposure, individual immune responses and allergy profiles. Symptoms most likely occur with sufficient spore exposure or low tolerance threshold. Individual cases, such as asthmatic symptoms after rain, at night with an open window or during holidays, show that exposure plays a key role and that individual anamnesis is very important in the interpretation of test results.

Forty-nine children and adolescents had bronchial and/or nasal symptoms and underwent both, SPT-AA and AA-IgE tests. A weak correlation was observed between the tests. Based on the data for mite and pollen allergies, a good correlation between SPT-AA and AA-IgE is expected.[18–21] Our results showed that the correlation between SPT and IgE levels for Alternaria allergens was more heterogeneous. For example, the study by Reijula et al showed no correlation between SPT-AA and AA-IgE levels ($r = 0.12$). Low levels of exposure to Alternaria in Finland may be associated with low IgE levels. In contrast, moderate correlation was observed for Cladosporium herbarum ($r = 0.47$).[15]

Valencia et al investigated the reliability of SPT and IgE for the diagnosis of Alternaria allergy. The correlation between these diagnostic tests was investigated in 33 patients. A correlation was observed ($r= 0.51$, $p < 0.05$). However, there was little correlation between the intensities of the test results. Highly positive SPT-AA results are generally not associated with highly positive AA-IgE results. Interestingly, AA-IgE was positive in four patients with negative SPT-AA.[22] In contrast to the above-mentioned studies, the study by Chambers et al showed a strong correlation between skin endpoint titration (SET) and RAST ($r = 0.653$) and a very strong correlation between SET and CAP ($r = 0.804$) for Alternaria tenuis.[21]

It seems to be an allergen-specific feature of Alternaria that the correlation between SPT and IgE is weak to moderate. The strong correlation reported by Chambers et al is an exception. However, in this work the SET method was used instead of SPT as the gold standard.[21] This underlines the need for a holistic assessment, consisting of symptoms and the two diagnostic tests, to gain a better understanding of the significance of sensitization to Alternaria.

In recent years, the diagnostic approach to *Alternaria alternata* allergy has evolved from the use of conventional extract-based methods toward the implementation of molecular tools. Traditional tests (SPT-AA and AA-IgE measurements) remain reliable and widely used in clinical practice.[23] However, extract-based testing may be affected by variability in fungal extracts and cross-reactivity with other mold species. To improve diagnostic precision, component-resolved diagnostics (CRD) have been introduced. The determination of IgE to the major allergen Alt a 1 enables the identification of true sensitization to *Alternaria alternata*, distinguishing it from cross-reactivity with other fungi.[23,24] More than 80–90% of Alternaria-sensitized patients show IgE reactivity to Alt a 1, confirming its relevance as a key diagnostic marker. Furthermore, Alt a 1 levels correlate more closely with clinical symptoms than total airborne spore counts, highlighting its value for assessing disease activity and exposure.[23]

A retrospective analysis involving serum samples from 255 children with positive SPT-AA demonstrated an excellent correlation between AA-IgE and Alt a 1 ($r = 0.943$, $p < 0.001$).[25] However, the proportion of positive results was slightly higher for AA-IgE compared to Alt a 1-IgE (84.7% vs 81.6%, ns). Based on these findings, the authors recommend the use of both SPT-AA and measurement of AA-IgE in patients with suspected Alternaria allergy.[23,25] Furthermore, Alt a 1

constitutes the principal component of AIT vaccines for Alternaria. Therefore, an assessment of Alt a 1 should be performed prior to initiating immunotherapy.[25]

In cases where standard systemic tests yield negative or inconclusive results, nasal provocation (NP) and the measurement of local nasal IgE can provide additional evidence for local allergic inflammation.[23]

Multiplex allergen assays such as ALEX^2 represent another modern diagnostic method. They allow the simultaneous determination of IgE antibodies against numerous allergen components, enabling a reliable distinction between mono- and polysensitized patients without cross-reactivities distorting the interpretation.[26]

The strict preselection in our work yielded positive results, with a high hit rate in BP-AA of 84% (16 out of 19). One limitation of this study is that children and adolescents with a possible Alternaria allergy were not provoked and therefore had no benefit from an AIT.

In the case of BP-AA, three children and adolescents were provoked only because of a clearly positive allergy test without a clear clinical diagnosis. Of these, BP-AA was borderline positive in one and clearly positive in two. This indicates that BP-AA may lead to overestimation in patients.

Another limitation of this study is the relatively small number of BP-AA, which could reduce its statistical power. Future prospective multicenter studies should confirm these retrospective results in pediatric populations.

An important issue is the frequent occurrence of severe LAR. Of the 19 children and adolescents provoked with *Alternaria alternata*, 14 showed a late reaction with cough and shortness of breath. Therefore, overnight inpatient stay is required after BP-AA. The indications for BP-AA in the diagnosis of Alternaria allergy should be critically reviewed and the results should always be evaluated in the context of the entire clinical situation.

Conclusion

In conclusion, the diagnosis of an Alternaria allergy is challenging. There was a weak correlation between symptoms and allergy tests, depending on allergen exposure. There was a weak-to-moderate correlation between the SPT and IgE levels. Both tests were significantly correlated with PD20-AA. In adult patients SPT-AA of $\geq$ 8 mm and AA-IgE $\geq$ 18 kU/L predicted a positive BP-AA.[12] In our study, almost all the patients with similar median and mean values for SPT-AA and AA-IgE had a positive provocation. A larger prospective study is necessary to confirm the cut-off values. Based on the current data we suggest a procedure analogous to the diagnostic and therapy algorithm for mite allergies[27] and the diagnostic and management algorithm for *Alternaria alternata* allergy as provided by Klain et al.[23] In cases where the patient's history is clear and there is a significant SPT-AA ($\geq$ 8 mm) and/or AA-IgE ($\geq$ 18 kU/L), we recommend specific AIT.[12,23,27] If SPT-AA or AA-IgE results are inconclusive, we recommend NP.[13,23,27] Only if the NP is negative a BP-AA should be performed in a specialized center, after careful consideration of the indication.[27]

Disclosure

Gözde Kabadayi, Dr Jordis Trischler, and Dr Johannes Schulze report no conflicts of interest in this work.

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