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Sensitization profile in differential diagnosis: Allergic asthma *vs.* chronic (nonspecific) cough syndrome

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Background: In the subgroup of children with chronic cough, distinguishing children with allergic asthma from those with non-specific respiratory symptoms is difficult. We have focused on determination of diagnostic efficiency of serum total IgE, sIgE, and skin prick test in differentiation of asthmatic children from children with nonspecific respiratory symptoms.

Material/Methods: A total of 131 children with median age of 7.5 years were enrolled in study and divided into 2 groups; children with allergic asthma (N=71) and children with chronic cough (N=60). Participants underwent the standard allergological examination, including skin prick test and measurement of total IgE, and following 3 allergen-specific IgE antibodies against aeroallergens: *Dermatophagoides pteronyssinus*, *Ambrosia artemisiifolia,* and *Phleum pratense*.

Results: The percentage of patients with elevated level of total and sIgE was higher in children with allergic asthma than in children with chronic cough syndrome (P=0.0001). In children with asthma, sIgE had a better diagnostic value than total IgE. The best diagnostic efficiency of cut-off values for sIgE was shown for Der p sIgE. Skin prick test to all allergens had 78.82% sensitivity and 91.3% specificity in differentiating the 2 tested groups. The highest sensitivity and specificity in skin prick test was proved for *Dermatophagoides pteronyssinus*.

Conclusions: The sensitization profile consisting of total IgE, sIgE levels, and SPT clearly distinguishes children with allergic asthma from children with chronic nonspecific cough, but still with overlap. Therefore, diagnosis should always be confirmed by a thorough allergy investigation.

Key words: asthma • chronic cough • total IgE level • allergen-specific IgE level • diagnostic efficiency

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Background

Among the many different symptoms encountered in every day practice, cough is the most common symptom in children visiting the pediatrician. Chronic nonspecific cough is defined as a nonproductive cough in the absence of identifiable respiratory disease or known cause persisting for more than 3 to 8 weeks [1,2].

The usual symptom of asthma is chronic coughing [3]. As is well known, atopy and allergic sensitization play important roles in asthma. Routine diagnostic tests, such as total serum IgE determination, allergen-specific serum IgE determination, and skin prick test, can help significantly in diagnosing allergic asthma and distinguishing it from other respiratory diseases as well as from chronic nonspecific cough syndrome [1].

Although sensitization is a major risk factor for asthma development [4], the role of sensitization remains poorly understood and thus is continuously debated in scientific literature [5–7]. The importance of total serum IgE levels in diagnosis of asthma has been verified throughout a number of studies. Asthmatic children have an elevated level of total serum IgE levels [8–10]. It is also reported that asthma below certain levels of total IgE does not exist [10,11]. In addition, increased levels of total serum IgE at birth and in early life have been associated with an increased risk for the development of persistent asthma later in life [12].

While total serum IgE determination is one of the key methods to reveal atopy, the determination of allergen-specific IgE (sIgE) to environmental allergens has diagnostic and therapeutic importance; reveals the patient's sensitization to a certain allergen and enables monitoring of the success of specific immunotherapy (SIT) [13]. Among specific allergens, high sensitization rate have been reported for the house dust mites *Der p* (*Dermatophagoides pteronyssinus*) and *Der f* (*Dermatophagoides farinae*) [14–16]. Early sensitization and levels of sIgE to perennial respiratory allergens have likewise been associated with increased risk of childhood asthma [17,18]. Yunginger et al. similarly reported that mite sensitization early in infancy (measured by sIgE levels) accounts for an up to 19.7-fold increased risk for allergic asthma [19,20]. Arshad et al. also found house dust mite sensitization to be the most important risk for allergic asthma [21]. Kovac et al. have shown that asthmatic children with higher asthma severity have a higher serum concentration of both total IgE and specific IgE to *Der p* [15,22].

The atopy can also be defined by positive result to skin prick test (SPT) to a standard panel of allergens [23–25]. Investigating the association of skin test reactivity, total serum IgE levels, and peripheral blood eosinophilia with asthma, Khadadah et al. found SPT to be the most effective measure of atopy [26].

Tschopp et al. proved SPT has the best positive predictive value and best efficiency in diagnosing respiratory atopic diseases [27]. Comparing SPT to total serum IgE levels, Fajraoui et al. found that the 2 tests agree in 80% of cases [28].

Because chronic cough is one of the most common presentations of allergic asthma in children and being sensitized does not automatically include diagnosis of asthma, differentiation between allergic asthma and chronic (nonspecific) cough syndrome remains a relevant clinical problem. Even though allergic diseases and diagnostic methods have been investigated during recent years, conclusive guidelines on how to distinguish allergic asthma from chronic (nonspecific) cough in the population of children have not been available.

The aim of this study was to determine the diagnostic value of sensitization profile (including serum total, sIgE determination, and SPT) in children with persistent respiratory symptoms to differentiate between children with allergic asthma and children with chronic (nonspecific) cough.

Matherial and Methods

Study subjects

This study is an analysis of data collected from patients at Children's Hospital Srebrnjak, Department of Allergology and Pulmonology, Zagreb, Croatia, during a 6-month period. A total of 131 children, aged 1–15 years, were included in the study. There were 89 males (67.94%), and 32 females (32.06%). Informed consent was obtained from parents of all participants. The study was approved by the Ethics Committee of Children's Hospital Srebrnjak.

All of the patients included in the study experienced respiratory symptoms and were sent to our Department for further diagnosis. Participants underwent the standard allergological examination, including SPT to the standard set of inhalatory allergens common for the region, lung function tests, and *in vitro* diagnostic tests. Participants were tested for total IgE and 3 allergen-specific IgE antibodies against the most prevalent aeroallergens in children in continental region in Croatia: hose dust mites (*Dermatophagoides pteronyssinus)*, common ragweed (*Ambrosia artemisifoliae*), and timothy grass (*Phleum pratense*) pollen.

Study participants were divided into 2 groups:

1. Children with clearly diagnosed allergic asthma, ie, having at least 3 episodes of wheezing and/or a positive bronchodilatation test (NIH GINA 2009); N=71, age 2–15 years, $\bar{\chi}$=8 years, 49 (69.01%) males.

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2. Children with chronic cough, ie, having less than 3 episodes of wheezing, with persistent cough lasting for more than 6 weeks; N=60, age 1-14 years, $\bar{\chi}$=7 years, 40 (66.67%) males.

Total serum IgE concentration was determined by fluoroimmunochemical method (Abbot, USA) using an automatic analyzer IMx (Abbot, USA). For data comparison, 95% central range was used and serum IgE concentration was compared to in-house reference values [29].

The sIgE to 3 allergens – *Der p* (*Dermatophagoides pteronyssinus)*, *Phl p* (timothy grass pollen), and *Amb a* (short ragweed) – were determined by ImmunoCAP (Pharmacia, Uppsala, Sweden). Analysis was performed using a UniCAP 100 analyzer (Pharmacia, Uppsala, Sweden).

The SPT was performed with standardized allergens produced by Allergopharma, comprising the standard set of inhalatory allergens common for Croatia.

Statistical analysis

Data distribution was assessed by the test of proportion difference and Pearson χ^2 test. P<0.05 was considered statistically significant. Total and specific IgE concentration showed asymmetric distribution and were presented by range and median, and the statistical significance of the difference between the 2 groups was tested using the Wilcoxon test. The diagnostic efficiency of total IgE and sIgE determination – sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) – were estimated for the groups of patients with allergic asthma and chronic cough. Receiver operating characteristic (ROC) curve analysis was performed using STATISTICA for Windows, version 6.0 (StatSoft, Inc., Tulsa, OK, USA).

Results

The 2 tested groups differed in median total IgE. Median total IgE in the group of children with allergic asthma was significantly higher than in the group of children with chronic cough (495.0 kIU/L in the allergic asthma group; 59.0 kIU/L in the chronic cough group, P<0.05; Table 1)

The percentage of patients with elevated concentration of total and specific IgE was higher in children with allergic asthma than in children with chronic cough (*P*<0.0001; Table 2).

Comparing the number of patients with elevated total and sIgE level between the 2 groups, we found an elevated total IgE level in 97.2% of children with allergic asthma, whereas elevated IgE level was found in 31.7% children with chronic cough. Level of sIgE was elevated in 100% of children with allergic asthma and in 21.7% children with nonspecific cough (χ^2=116.258; df=2; *P*=0.0000, ** χ^2=129.741; df=2; *P*=0.0000)

Comparing levels of sIgE in sensitized children, we discovered that children sensitized to *Der p* had a higher concentration of sIgE than children sensitized to Phl p and Amb a (*P*<0.05) (Table 3).

We established that at a cut-off value of 116.6 kIU/L of total IgE had 96.8% sensitivity and 77.8% specificity in differentiating allergic asthma and chronic cough. When comparing sIgE to *Der p* in the group of children with allergic asthma and those in group with chronic cough, we found 89% sensitivity and 97% specificity (Table 4).

Table 1. Concentration of total IgE in children with allergic asthma, children with chronic cough, and healthy children.

Total IgE (kIU/L)	Allergic asthma (N=71)	Chronic cough (N=60)
Range	43.0–2453.8	5.0–1000.0
Median	495.0	59.0

Allergic asthma: chronic cough, *P*<0.05.

Table 2. Elevated serum concentration of total IgE and sIgE in children with allergic asthma and children with chronic cough.

	Total IgE	Specific IgE
Patients	Total IgE1 *	sIgE2 **
Allergic asthma (N=71)	69 (97.2%)	71 (100%)
Chronic cough (N=60)	19 (31.7%)	13 (21.7%)

* χ^2=116.258; df=2; *P*=0.0000, ** χ^2=129.741; df=2; *P*=0.0000.
[1] No. of patients with elevated total IgE concentration compared to in-house reference values (Dodig 2006) *.
[2] No. of patients with sIgE[2] concentration above cut-off value (>0.35 kIU/L) regardless of the allergen**.

Table 3. sIgE concentrations in children with allergic asthma and children with chronic cough.

Specific IgE (kIUA/L)	Der p	Amb a	Phl p
Range	0.44–0.93	1.1–471.0	0.35–96.1
AM ±SD	206.6±214.3	97.7±168.1	18.9±28.5
Median	94.4	21.1	6.4

AM – arithmetic mean; SD – standard deviation; Der p: Amb a *P*<0.05; Der p: Phl p *P*<0.05.

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Table 4. ROC curve analysis for the concentration of total and different serum sIgE in children with allergic asthma and children with chronic cough.

	Specific IgE			Total IgE
	Allergic asthma/chronic cough (N=71/60)			Allergic asthma/chronic cough (N=71/60)
	Der p	Amb a	Phl p	
AUC	0.933	0.679	0.739	0.927
Cut-off	0.35 kIU/L	0.39 kIU/L	0.35 kIU/L	116.6kIU/L
Sensitivity	89.0%	56.0%	60.5%	96.8%
Specificity	97.0%	80.5%	81.3%	77.8%
PPV		84.5%		78.4%
NPV		100.0%		95.4%

AUC – Area under the ROC curve; Sensitivity – probability that specific IgE will be positive when allergic asthma is present (true positive rate); Specificity – probability that specific IgE will be negative when allergic asthma is not present (true negative rate). PPV – positive predictive value, probability that disease is present when total/specific IgE is positive; NPV – negative predictive value, probability that disease is not present when total/specific IgE is negative.

The best diagnostic value of cut-off values for sIgE was found for *Der p* between children with allergic asthma and children with chronic cough (Table 4).

Discussion

The sensitization profile can be defined by total and specific IgE determination in serum and skin prick test to common inhalatory allergens. Data on exact diagnostic efficiency (a combined measure of sensitivity and specificity) of serum total and sIgE determination and clinical relevance of IgE level determination in differentiating children with asthma and non-specific respiratory symptoms differ from study to study.

This study showed that total IgE, and particularly sIgE, clearly distinguishes children with allergic asthma from children with nonspecific respiratory symptoms. This confirms the reports of other groups, who found that IgE testing improved the predictive accuracy and patient differentiation [30–33].

The differences in total IgE concentration between the 2 groups (children diagnosed with asthma and children with chronic cough) were confirmed by the values of IgE concentration ($P<0.05$) and ROC curve analysis. Cut-off values of total IgE concentration (116.6 kIU/L asthma *vs.* chronic cough) were determined with excellent diagnostic efficiency. Regarding literature variations of referent values for total IgE concentration, the variation is due to different populations included in the studies and the applications of different immunochemical methods for IgE determination [11,28,29,34–39].

Another important diagnostic procedure in estimating sensitization of children is the measure of IgE to specific allergens in blood. Results of our study show that children sensitized to the perennial allergen *Der p* showed a higher concentration of sIgE than in children sensitized to *Amb a* and *Phl p*, which are present only during the blooming season. It is believed that because house dust mites are the most widespread perennial inhalatory allergens, a greater exposure to *Der p* in comparison with other allergens results in higher sIgE concentration [40].

The concentration of sIgE is not a static variable. Variations between normal and elevated IgE in the same individual may occur, depending on the age, the exposure to the specific allergen, and disease development [13]. Diagnostic efficiency of sIgE to pollen allergens could therefore be influenced by the period during which blood was sampled (during or before *vs.* after the blooming season). It was also confirmed that exposure and sensitization to certain allergens strongly depend on the region and climate [21]. The allergens tested in this study are the most common inhalatory allergens in Croatia [41].

Sensitization to aeroallergens in correlation to asthma development is currently a world-wide scientific focus. Sensitization is most commonly defined by a positive skin prick test result, along with sIgE in serum. Being sensitized does not imply the diagnosis of allergic asthma or any other atopic disease [42,43]. In 2001, Crimi et al. showed that in a population of children proven to be sensitized, a third of them were without any allergic symptoms.

It is also important to emphasize the correlation between sensitization, especially to the most common aeroallergens, and asthma

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Table 5. ROC curve analysis for a positive SPT for *Dermatophagoides pteronyssinus*, *Ambrosia artemisifoliae,* and *Phleum pratense* in children with allergic asthma and children with chronic cough.

Parameter	Der p		Amb a		Phl p	
	Estimate	95% CIs	Estimate	95% CIs	Estimate	95% CIs
Sensitivity	83.61%	72.39, 90.84	66.67%	46.71, 82.03	66.67%	48.78, 80.77
Specificity	71.43%	59.95, 80.68	48.6%	39.34, 57.95	49.5%	39.95, 59.09
Positive Predictive Value	71.83%	60.46, 80.96	22.54%	14.37, 33.52	28.17%	19.04, 39.54
Negative Predictive Value	83.33%	71.97, 90.69	86.67%	75.83, 93.09	83.33%	71.97, 90.69
Diagnostic Accuracy	77.1%	69.19, 83.46	51.91%	43.42, 60.29	53.44%	44.92, 61.76
Likelihood ratio of a Positive Test	2.926	2.633–3.252	1.297	1.177–1.429	1.32	1.21–1.441
Likelihood ratio of a Negative Test	0.2295	0.1857–0.2836	0.6859	0.5159–0.912	0.6733	0.5318–0.8525
Diagnostic Odds	12.75	5.431–29.93	1.891	0.7464–4.79	1.961	0.8352–4.603
Cohen's kappa (Unweighted)	0.5446	0.3754–0.7139	0.08675	–0.0386–0.2121	0.1092	–0.02792–0.2464

in children [44]. In 2010 Craig used SPT to define sensitization and concluded that about 95% of patients with mild asthma were sensitized, as well as the 90% of those with severe asthma [45].

Craig et al. showed that 81% of children with asthma were polysensitized to at least 3 aeroallergens [46].

One of the most frequent sensitizations in children with asthma is to the house dust mite. As in Croatia, in many other countries around the world this sensitization is the most common among asthmatic children [47–49]. In Florida, 89.6% of asthmatic children had positive sIgE to house dust mites, along with 81.9% of Chinese asthmatic children and children in Zimbabwe [50–52].

Many studies have observed that deteriorating asthma can be related to increased exposure to allergens, particularly allergens from house dust mites, cockroaches, cats, rodents, mold, or pollen [53,54].

Sensitization profile also correlates with asthma severity and chance of asthma remission during childhood. ISAAC, the international study of childhood asthma and allergies, showed that remission of asthma is 10% yearly and was inversely correlated to sensitization. Carroll et al. confirmed that increasing atopic sensitization (estimated by SPT and total IgE level) is associated with increased disease severity in children with asthma [23]. Furthermore, elevated level total serum IgE has also been linked to risk of hospital admission [24,55,56]. In contrast, Jedrychowski et al. related reversibility of asthma with lung function growth [57].

Table 6. ROC curve analysis for a positive SPT to 1 or more of all tested allergens in children with allergic asthma and children with chronic cough.

Parameter	Overall data for SPT	
	Estimate	Lower–Upper 95% CIs
Sensitivity	78.82%	68.99, 86.16
Specificity	91.3%	79.68, 96.57
Positive Predictive Value	94.37%	86.39, 97.79
Negative Predictive Value	70%	57.49, 80.1
Diagnostic Accuracy	83.21%	75.88, 88.64
Likelihood ratio of a Positive Test	9.065	5.51–14.91
Likelihood ratio of a Negative Test	0.2319	0.2071–0.2598
Diagnostic Odds	39.08	12.37–123.4
Cohen's kappa (Unweighted)	0.6555	0.4884–0.8226

There are a number of factors that can influence sensitization, such as location of residence, sex, and ethnicity. With lower prevalence of sensitization, female sex and residence in a rural environment were proven to be connected [58–60].

A great number of studies have investigated risk factors for allergen sensitization and asthma development. Sporic et al. described a significant relationship between early life exposure

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to dust mite allergen and asthma at the age of 11 years [61]. Nevertheless, most other studies could not reproduce these results. Studies that are still ongoing, such as the Prevention and Incidence of Asthma and Mite Allergy study (PIAMA), the Manchester Asthma and Allergy Study (MAAS), and the Childhood Asthma Prevention study, are expected to reveal new information about asthma prevention through prevention of sensitization to specific aeroallergens.

In conclusion, it is important to emphasize that for a confirmed diagnosis of allergic asthma, determination of serum IgE should always be supplemented with a thorough allergy investigation, including a detailed medical history (especially concerning allergen exposure), the presence of other possible immediate hypersensitivity diseases, skin tests, challenges, examinations for eosinophilia in blood and mucous membrane secretions, and in some cases with excluding the GER as a possible risk for asthma development [62].

The results of our study show that determination of total IgE and sIgE is a good method for differentiating asthmatic children from those with nonspecific chronic cough. sIgE determination in children with clinical asthma symptoms had a better diagnostic value than total IgE determination. The best diagnostic value of cut-off values for sIgE was shown for *Der p*. In our study, SPT was shown to have lower efficacy (78.82% sensitivity, 91.3% specificity) in distinguishing asthmatic children from children with non-specific chronic cough in comparison with levels of sIgE.

Conclusions

Although the differentiation between children with non-specific respiratory problems and children with asthma can be difficult, sensitization profile (total and specific IgE levels and SPT) facilitates achieving diagnosis. After analyzing 131 patient aged 1–15 years, we conclude that total IgE, and particularly sIgE, clearly distinguish children with allergic asthma from children with nonspecific chronic cough. The final diagnosis should, however, always be confirmed by a thorough allergy investigation.

Considering the results of our study, as well as the results of other studies of sensitization profile and its correlation to asthma, we conclude that standardized procedures such as SPT, total IgE level, and sIgE should be performed in patients presenting with chronic cough, while it significantly correlates with asthma and can lead the physician to the final diagnosis of asthma *vs.* nonspecific cough.

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