

Original article

Diagnostic values of combination of free running asthma screening test and total serum allergen IgE level in children with asthma

Chen Xin, Li Yong and Zeng Meiying

Keywords: children asthma; free running asthma screening test; total serum allergen IgE level; combination; diagnostic value

Background A free running asthma screening test is usually used for screening exercise-induced bronchoconstriction. The total serum allergen IgE level can reveal the patient's atopy characteristics. Our study is to evaluate the diagnostic values of the combination of the two tests in asthmatic children and compare this new diagnostic method with the International Study of Asthma and Allergies in Childhood (ISSAC) questionnaires and the bronchial provocation test, which are popular diagnostic tool for pediatric asthma.

Methods A total of 773 school children were recruited in this study. The children's asthma was diagnosed by means of a combination of the free running asthma screening test and total serum allergen IgE level. The new diagnostic method value was assessed using receiver operating characteristic (ROC) curves and compared with other diagnostic tools such as ISSAC questionnaires and the bronchial provocation test.

Results The AUC of this new diagnostic method was higher than 0.9. When the cut-off value of total serum allergen IgE level was ≥ 47 KU/L, the sensitivity and the specificity were 71.4% and 85.1%, respectively, which were better than those of either the ISSAC questionnaires or bronchial provocation test.

Conclusion The combination of the free running asthma screening test and total serum allergen IgE level may be an effective diagnostic tool for children's asthma.

Chin Med J 2014;127 (5): 873-877

When a large scale survey for the incidence of children's asthma is conducted, questionnaires are usually employed, as they are easy to use. However, the results of questionnaires are mainly based on the subjective feelings of the respondents, and some asthma patients are not diagnosed in time,¹ which leads to under treatment. To improve the early diagnostic accuracy of children's asthma, i.e. to improve the sensitivity of the diagnostic methods, specialized methods such as the bronchial provocation test (BPT) are usually needed. Because these methods require professional devices and enough space, and are time-consuming, they are not suitable for large scale epidemiologic surveys. In our previous study on the incidence of exercise-induced bronchoconstriction (EIB) among children,² we occasionally found that the combination of the free running asthma screening test and total serum allergen IgE level can be used to diagnose children's asthma. The aim of this study was to investigate the diagnostic value of this new method for detecting children asthma and comparing it with other diagnostic tools such as the International Study of Asthma and Allergies in Childhood (ISSAC) questionnaire and bronchial provocation test.

METHODS

Participants

A total of 789 students were recruited from two schools in Beijing, China. Informed consents were obtained from

all the participants themselves, their parents and teachers before joining the study.

Study design and protocol

Surveys of the incidence of children's asthma by means of the ISSAC phase I questionnaires³

The core of the questionnaire survey of the internationally popular ISSAC phase I questionnaires was used (Written Questionnaire, WQ), the ISAAC WQ includes the following six questions: WQ 1. Have you ever had wheezing or whistling in the chest at any time in the past? (wheeze ever); WQ 2. Have you had wheezing or whistling in the chest in the last 12 months? (current wheeze); WQ 3. In the last 12 months, has your chest sounded wheezy during or after exercise? (wheezing after exercise); WQ 4. In the last 12 months, how often, on average, has your sleep been disturbed due to wheezing? (nocturnal wheeze); WQ 5. In the last 12 months, have you had a dry cough at night, apart from a cough associated with a cold or chest infection? (nocturnal cough); WQ 6. In the last 12 months,

DOI: 10.3760/cma.j.issn.0366-6999.20132576

Department of Senior Officials Health Care (Chen X), Department of Respiratory Medicine (Li Y), Department of Clinical Laboratory (Zeng MY), China-Japan Friendship Hospital, Beijing 100029, China
Correspondence to: Chen Xin, Department of Senior Officials Health Care, China-Japan Friendship Hospital, Beijing 100029, China (Tel: and Fax: 86-10-84205614. Email: chenxin7169@sohu.com)

This study was supported by a grant from Specific Funding for Research Projects on Chronic Respiratory Diseases, Clinical Medicine Division of Chinese Medical Association (No. 08020710149).

has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths? (severe wheeze). First, the participants finished the questionnaires independently in the classroom. Then, the uniformly trained surveyors answered a variety of questions raised by the participants but did not provide any cue interpretations. The responded rate was calculated as the number of participants with asthma symptoms divided by the total investigated participants. The ISSAC questionnaires survey was conducted for all the investigated children indoor. The incidence of asthma was calculated based on the surveyed results.

Survey of the incidence of children's asthma by combination of free running asthma screening test and total serum allergen IgE level

After the ISSAC questionnaire survey was finished, the free running asthma screening test (FRAST) was performed for all the participants in an outdoor environment. The environmental temperature was 10°C–15°C and the environmental humidity was 10%–20%. Before the FRAST started, all the participating children were measured for peak expiratory flow (PEF) three times, and the maximal data was recorded. After PEF data was recorded, the running test was performed without any warming up activities. The running test was carried out at competition speed. The male participants ran 1000 meters and female participants ran 800 meters. PEF measurement was conducted at 0, 5, 10, 15, 20, 25 and 30 minutes after exercise ended. When the PEF data decreased by 15% or more as compared to before FRAST, the FRAST results were regarded as positive. For the participants with positive FRAST results, their blood samples were drawn for measurement of total serum allergen IgE levels. The IgE levels were measured with the Unicap100 CAP allergen test system (Sweden) according to the standard protocol. Total serum allergen IgE levels less than 60 KU/L were regarded the normal levels. In order to avoid interference from intestinal parasite infection with total serum allergen IgE levels, all the participants whose total serum allergen IgE levels were higher than 60 KU/L were examined for the presence of parasite eggs in their excrement.

Survey of the incidence of children's asthma by using the standard asthma diagnostic method

For all the participating children whose total serum allergen IgE levels were higher than 60 KU/L or whose FRAST results were positive, they were investigated in detail using the diagnostic criteria of the *Guidelines of the Diagnosis and Treatment for Children's Asthma*.⁴ Those participants who showed typical clinical symptoms were diagnosed as having asthma. Those participants who did not show typical clinical symptoms of asthma were further measured by the bronchial provocation test (BPT). The BPT was conducted with Astograph Bronchial Provocation Test equipment (CHEST Ltd, Japan). Those participants who had a wheezing history and/or had positive BPT results were diagnosed as having asthma.

Statistical analysis

SPSS10.0 (SPSS Inc., USA) was used to perform statistical analysis. The measured data of the total serum allergen IgE levels were used as the critical points, the corresponding sensitivity at each critical point was used as the vertical (y) axis and the 1–specificity as the horizontal (x) axis, and the ROC curve was plotted. The areas under the curve (AUC) for different critical points, the sensitivity, the specificity and the positive likelihood ratio were calculated and compared. The point located at the left upper corner when the corresponding AUC reached maximal value was selected as the optimal cut-off value.

RESULTS

General information

A total of 789 students (11 to 13 year old) were recruited to participate in this study. According to inquiry results, 24 children (14 females and 10 males) had past case histories of wheezing and allergic rhinitis, with symptoms that occurred intermittently, and medicines that were not regularly taken. Sixty-five children (36 females and 29 males) had case histories of suspected allergic rhinitis. Considering the safety and the accuracy of the study data, six children with persistent wheezing symptoms and 10 children with case histories of respiratory tract infection within the last two weeks were excluded from this study. Thus, 773 children actually participated in this study (Table 1).

ISSAC questionnaires

Among 773 children, 19 children indicated they had wheezing symptoms within the past two years. The incidence of asthma was 2.5% (19/773).

Combination of free running asthma screening test (FRAST) and total serum allergen IgE level

Seventy-two children had a positive FRAST result, accounting for 9.3% of the total tested children (72/773). Among these 72 children, there were 13 children whose total serum allergen IgE level was higher than 60 KU/L, accounting for 1.7% of the total tested children (13/773). There were no eggs from intestinal parasites detected in excrement from these 13 children. Based on these data, the incidence of asthma was 1.7% (13/773).

Standard diagnostic method

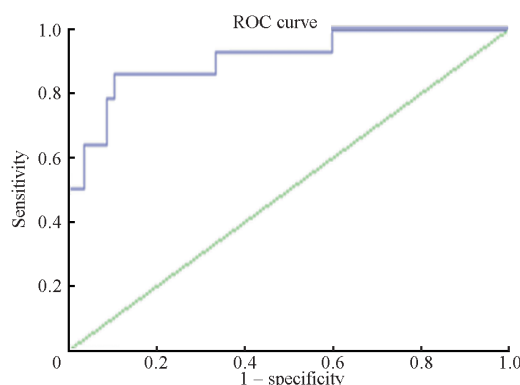
Among 81 children who were identified from a positive FRAST result and ISSAC result, 14 children were diagnosed with asthma according to their wheezing history

Table 1. The primary characteristics of the investigated children (n=773)

Primary characteristics	Results
Age (range) (Years)	12 ± 1(10–13)
Sex: male (female)	389 (384)
Children who had case history of wheezing and allergic rhinitis: male (female)	10 (14)
Children who had case history of suspected allergic rhinitis: male (female)	29 (36)

Table 2. The sensitivity and specificity of different boundary values of total serum IgE levels

Boundary value of total serum allergen IgE level (KU/L)	Sensitivity (%)	Specificity (%)
30.2	92.9	64.9
35.6	85.7	78.9
41.4	85.7	82.5
46.8	85.7	89.5
56.4	71.4	91.2
62.4	64.3	93.0

**Figure 1.** The ROC curve for asthma diagnostic values of combination of FRAST and total serum allergen IgE level.

and bronchial provocation test result, the incidence of asthma was 1.8% (14/773).

Comparison between combination of FRAST and total serum allergen IgE level with ISSAC questionnaires

The data shown in Table 2 and Figure 1 indicated that the AUC of the ROC curve from the combination of FARST and total serum allergen IgE level in the diagnosis of children with asthma was 0.909. The difference was statistically significant as compared to the value of 0.5 ($P < 0.001$). With this method, the accuracy in diagnosis of children's asthma was relatively high (AUC > 0.9). According to the statistic result, at the cutoff point of 46.750, the value of the corresponding correct diagnostic co-efficiency was maximal: the Youden co-efficiency was 0.742 (0.857–0.105) and the corresponding values for sensitivity and specificity were 85.7% and 89.5%, respectively. The value of the total serum allergen IgE levels may be the best diagnostic boundary point.

DISCUSSION

The diagnosis of children's asthma is mainly dependent on the typical symptoms, for those patients without typical symptoms, the bronchial provocation test is the objective criteria. However, the bronchial provocation test requires precision equipment, trained operators and enough space, and is relatively difficult to apply in epidemiological studies. So the questionnaires are usually used for epidemiological investigation of children's asthma⁵ because of simplicity and convenience. ISSAC is a unique worldwide epidemiological academic organization established in 1991. The purpose of ISSAC is to promote the cross sectional study and international cooperation on epidemiology and

pathogenesis of such allergic diseases as asthma, rhinitis and eczema in youngsters. ISAAC questionnaires are the standardized questionnaires that are applied to assess the international and inter-regional differences in the morbidity rate of asthma and other allergic diseases among different countries and regions. The sensitivity and specificity of ISSAC questionnaires have been confirmed.⁶ ISSAC have developed simple instruments that are suitable to be applied in an epidemiologic survey in a large scale of population study, and have been widely used around the world.⁷⁻⁹ The ISAAC study design comprises three phases. Phase I is a compulsory core study designed to assess the prevalence and severity of asthma and allergic disease in defined populations. Phase II was developed to investigate possible etiological factors. Phase III provides summarized information on the main findings of the study, regional tables and figures related to the prevalence and severity of current symptoms of asthma, rhinoconjunctivitis and eczema in the main regions of the world. The ISSAC Phase I questionnaire was used to assess the prevalence of children's asthma in our study.

Currently, ISSAC questionnaires are commonly recommended for epidemiologic survey of children's asthma.¹⁰ However, parts of the studies have pointed out the limitations of this method. A study in 1996¹¹ demonstrated that with ISSCA questionnaires for diagnosis of children's asthma, the sensitivity was 0.85 (0.73 to 0.93) and the specificity was 0.81 (0.76 to 0.86), which was superior to the bronchial provocation test whose sensitivity was only 0.54. But, when ISSAC questionnaires were used in association with the bronchial provocation test for diagnosis of children asthma, the specificity was 0.94 although the sensitivity was only 0.47, which was quite low. Another study conducted in 2003¹² indicated that ISSAC questionnaires solely applied for diagnosing children's asthma were not good enough; their sensitivity was 64% but its specificity was only 11%. It was suggested that it was better to apply ISSAC questionnaires after the participant's allergic disease has been confirmed. The ISSAC questionnaires are of two types: written questionnaires (WQ) and audiovisual questionnaires (AVQ); WQ are used in the majority of studies, including ours. According to a report, parent-reported ISAAC WQ may underestimate the prevalence of children's asthma compared with the AVQ.¹³ All these results indicate that ISSAC questionnaires, especially the widely used ISAAC WQ is unsatisfactory.

Exercise-induced bronchoconstriction (EIB) is a temporary reduction of pulmonary ventilation function after a vigorous exercise in children with asthma. The patients usually have oppression in the chest, hard breathing and even cough after vigorous exercise.⁴ The EIB incidence accounts for as much as 40% to 90% of the total asthma in children and is frequently related to the patient's vigorous activity.¹⁴ Currently, the exercise challenge test is the most commonly diagnostic method for EIB.¹⁵ The exercise challenge test can be classified into indoor type and field type; the indoor

Table 3. The sensitivity and specificity of various methods in diagnosis of children asthma²¹

Diagnostic methods for children's asthma	Sensitivity	Specificity	Youden's co-efficiency
Questionnaires	0.66–0.80	0.87–0.98	0.63–0.75
Bronchial provocation test	0.47	0.97	0.44
FRAST	0.35	0.97	0.32
Combination of questionnaires and bronchial provocation test	0.25–0.38	0.99	0.24–0.37

type needs a complicated procedure and equipment and shows a high percentage of negative results.^{2,16} The field type,¹⁷ FRAST, does not require specific space or devices and can be used in a large scale epidemic survey. Previous studies^{18,19} indicated that FRAST had a good correlation with both ISSAC questionnaires and bronchial provocation test for asthma diagnosis. FRAST is fit for diagnosis of children's asthma with a sensitivity of 58%–77% and a specificity of 60%–77%. The pulmonary functional criterion used for FRAST is forced expiratory volume (FEV₁) and its stability is better than that of PEF.²⁰

However, due to the limitation of equipment for FEV₁ in our study, we used PEF instead of FEV₁ as the pulmonary functional criterion. In our previous study,² we found that many children who had positive FRAST results lacked atopy characteristics and typical asthma symptoms. In order to assure the diagnostic accuracy of FRAST, we tried to combine an atopy factor, which was quantified by total serum allergen IgE level, with FRAST. Compared with ISSAC questionnaires, combination of FRAST and the total serum allergen IgE level have a similar degree of operational complexity and specificity (99.75% vs. 98.9%), and a slightly higher sensitivity (78.6% vs. 71.4%). However, this combination method also requires specific equipment.

Comparisons of several methods used for diagnosis of children's asthma²¹ (Table 3) indicated that questionnaires, the bronchial provocation test, FRAST, and even a combination of questionnaires and FRAST have been used, but none of these have satisfactory sensitivity. This means that some children may not be diagnosed and treated in time. Our new method has an obvious advantage over others methods in the sensitivity. The combination of the free running asthma screening test and total serum allergen IgE level may provide a new diagnostic method for determining asthma in children. The value of this diagnostic method needs to be verified through a much larger scale clinical study.

Acknowledgements: The participants in this study came from two schools for migrant workers' children in Beijing: Xingzhi middle school and Zhenhua school. The authors would like to thank all of the students, parents, teachers and directors of school for their active cooperation and help.

REFERENCES

- Janssens T, Verleden G, De Peuter S, Petersen S, Van den Bergh O. Predicting asthma treatment outcome at diagnosis: the role of symptom perception during a histamine challenge test. *J Asthma* 2012; 49: 230-236.
- Chen X, Zeng MY, Li Y, Lin JT. A study on the correlation between exercise-induced bronchoconstriction and atopy (in Chinese). *Chin J Tuberc Respir Dis* 2012; 35: 167-170.
- Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483-491.
- The Pediatrics Group of Chinese Medical Association, the Editorial Board of *Zhonghua Er Ke Za Zhi*. Guideline for the diagnosis and optimal management of asthma in children (in Chinese). *Chin J Pediatr* 2008; 46: 745-753.
- Global strategy for asthma management and prevention. (updated 2009). (Accessed April, 2009 at <http://www.ginasthma.org/documents/I>).
- Wandalsen NF, Gonzalez C, Wandalsen G, Solé D. Evaluation of criteria for the diagnosis of asthma using an epidemiological questionnaire. *J Bras Pneumol* 2009; 35: 199-205.
- Chen YZ, National Cooperation Group on Childhood Asthma. A nationwide survey in China on prevalence of asthma in urban children (in Chinese). *Chin J Pediatr* 2003; 41: 123-127.
- Liu CH, Shao MJ, Wang Q, Sha L, Li S, Luo YQ, et al. Epidemiological survey of children asthma prevalence in Beijing urban area (in Chinese). *Natl Med J China* 2013; 93: 574-578.
- Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. ISAAC Phase Three Study Group. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis. *Allergol Immunopathol (Madr)* 2013; 41: 73-85.
- Lukrafka JL, Fuchs SC, Moreira LB, Picon RV, Fischer GB, Fuchs FD. Performance of the ISAAC questionnaire to establish the prevalence of asthma in adolescents: a population-based study. *J Asthma* 2010; 47: 166-169.
- Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996; 25: 609-616.
- Gruchalla RS, Gan V, Roy L, Bokovoy J, McDermott S, Lawrence G, et al. Results of an inner-city school-based asthma and allergy screening pilot study: a combined approach using written questionnaires and step testing. *Ann Allergy Asthma Immunol* 2003; 90: 491-499.
- Kim MH, Kwon JW, Kim HB, Song Y, Yu J, Kim WK, et al. Parent-reported ISAAC written questionnaire may underestimate the prevalence of asthma in children aged 10-12 years. *Pediatr Pulmonol* 2012; 47: 36-43.
- Milgrom H, Taussig LM. Keeping children with exercise induced asthma active. *Pediatrics* 1999; 104: e38.
- Carlsen KH, Engh G, Mørk M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000; 94: 750-755.
- Garcia SS, Rodriguez Del Rio P, Escudero C, Ibañez MD. Asthma diagnosis and treatment - 1010. Lung function tests in exercise-induced asthma among pediatric population. *World*

- Allergy Organ J 2013; 6 Suppl 1: 10.
17. Vacek L. Incidence of exercise induced asthma in high school population in British Columbia. Allergy Asthma Proc 1997; 18: 89-91.
 18. Ponsonby AL, Couper D, Dwyer T, Carmichael A, Wood-Baker R. Exercise-induced bronchial hyperresponsiveness and parental ISAAC questionnaire responses. Eur Respir J 1996; 9: 1356-1362.
 19. Haby MM, Anderson SD, Peat JK, Mellis CM, Toelle BG, Woolcock AJ. An exercise challenge protocol for epidemiological studies of asthma in children: comparison with histamine challenge. Eur Respir J 1994; 7: 43-49.
 20. Strachan DP. Repeatability of ventilatory function measurements in a population survey of 7 year old children. Thorax 1989; 44: 474-479.
 21. Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. Thorax 2002; 57: 120-126.

(Received November 12, 2013)

Edited by Chen Limin