Validação de um questionário de rastreio de asma alérgica em crianças de idade escolar – Comparação com a fracção de óxido nítrico no ar exalado e testes cutâneos por picada

Validity of a questionnaire in a school-based allergic asthma screening – Comparison with exhaled nitric oxide fraction and skin prick tests

Data de recepção / *Received in*: 19/11/2011
Data de aceitação / *Accepted for publication in*: 21/12/2011

Rev Port Imunoalergologia 2011; 19 (4): 215-221

Teresa Vieira[1], João Almeida Fonseca[1,2], Rui Silva[3], Linda Cruz[4], Ana Reis Ferreira[1], Ana Leblanc[1], André Moreira[1,2], Maria Graça Castel-Branco[1]

[1] Serviço de Imunoalergologia, Centro Hospitalar de São João, EPE, Porto
[2] Faculdade de Medicina da Universidade do Porto
[3] Unidade de Imunoalergologia, Centro Hospitalar de Trás-os-Montes e Alto Douro, EPE, Vila Real
[4] Serviço de Urgência, Centro Hospitalar de São João, EPE, Porto

RESUMO

Introdução: Em estudos populacionais para rastreio de asma alérgica em crianças são necessários instrumentos válidos e simples. **Objectivos:** Avaliação de questões do questionário ISAAC para rastreio de asma alérgica em crianças de idade escolar utilizando instrumentos simples e objectivos da prática clínica: fracção exalada de óxido nítrico (FeNO) e testes cutâneos por picada (TCP). **Métodos:** Estudo transversal de 173 crianças, dos 8 aos 12 anos, pertencentes a três escolas da área urbana do Porto. Autopreenchimento pelos pais de um questionário, incluindo questões do ISAAC. Nas escolas foram realizados TCP a aeroalergénios comuns e determinada a FeNO. Como marcador de asma alérgica foi definida a presença de TCP positivos e FeNO aumentado (≥25ppb). Para cinco questões foram calculadas sensibilidade, especificidade, valor preditivo positivo e valor preditivo negativo (IC a 95%). **Resultados:** A FeNO encontrou-se significativamente aumentada nas crianças com história de sibilância no passado (26,5 ± 24,9 *vs.* 16,6 ± 15,3; p=0,002), nas crianças com sibilância com o exercício nos últimos 12 meses (34,1 ± 28,2 *vs.* 18,9 ± 18,8; p=0,005), e nas que utilizaram medicação antiasmática nos últimos 12 meses (30,7 ± 23,6 *vs.* 19,4 ± 14,9; p=0,01). Todas as questões apresentaram baixa sensibilidade, desde 7% ("alguma vez teve asma no passado" e "diagnóstico médico de asma") a 64% ("alguma vez teve sibilância no passado"). A especificidade das questões variou entre 60% ("alguma vez teve sibilância no passado") e 90% ("diagnóstico médico de asma" e "uso de medicação antiasmática no último ano"). Todas as questões apresentaram valores preditivos negativos elevados. **Conclusões:** As questões analisadas apresentaram globalmente pouca capacidade na identificação de crianças atópicas com FeNO aumentado. A questão que no entanto se revelou mais útil para rastreio de asma alérgica em crianças foi "alguma vez teve sibilância no passado". Os questionários e medidas objectivas como a FeNO e TCP podem complementar-se no rastreio de asma alérgica em crianças.

Palavras-chave: Alergia, asma, questionário, rastreio, validação.

ABSTRACT

Background: *There is a need for simple, reliable tools to screen for childhood allergic asthma in populational-based studies.* ***Objectives:*** *To assess questions from the ISAAC questionnaire in a school-based allergic asthma screening using simple and objective daily practice tools: exhaled nitric oxide fraction (FeNO) and skin prick tests (SPT).* ***Methods:*** *Cross-sectional study of 173 schoolchildren aged 8 to 12, from 3 schools in the urban area of Porto. Children's parents completed a self-administered questionnaire adapted from ISAAC questionnaire. SPT to common aeroallergens and FeNO were performed at schools. A surrogate for allergic asthma was defined by both SPT positive and increased FeNO (≥25ppb). Sensitivity, specificity, positive predictive value and negative predictive value (CI at 95%), were calculated for 5 questions.* ***Results:*** *FeNO was significantly increased in children who reported wheezing at any time in the past (26.5 ± 24.9 vs. 16.6 ± 15.3; p=0.002), in children wheezing with exercise in the last 12 months (34.1 ± 28.2 vs. 18.9 ± 18.8; p=0.005) and using asthma medication in the last 12 months (30.7 ± 23.6 vs. 19.4 ± 14.9; p=0.01). The questions had low sensitivity, from 7% ("ever had asthma" and "physician diagnosis of asthma") to 64% ("ever had wheezing at any time in the past"). The specificity ranged between 60% ("ever had wheezing at any time in the past") and 90% ("physician diagnosis of asthma" and "asthma medication use in the previous year"). All questions had high negative predictive values.* ***Conclusions:*** *The analyzed questions had poor ability to identify atopic children with high FeNO values. However, the most useful question to screen for allergic asthmatic children was "ever had wheezing at any time in the past". Questionnaires and objective measures such as FeNO and SPT may complement each other for allergic asthma screening in children.*

Key-words: *Allergy, asthma, questionnaire, screening, validation.*

INTRODUCTION

In children, asthma is a particularly important public health problem[1] and the most relevant phenotype is allergic asthma. There is a need for simple, reliable tools to screen for childhood allergic asthma in populational-based studies. As a standard approach, lung function or airway hyperresponsiveness tests are difficult to perform on a large scale, require extensive resources and correlate poorly with clinical symptoms. Moreover, children's cooperation is difficult at early ages[2,3]. Despite the significantly higher diagnostic yield of eosinophils count in induced sputum compared to the standard approach, no clear advantages in technique, cooperation, cost and speed have been reported[4,5]. Recent guidelines from the American Thoracic Society provide clinicians with a practical approach to use exhaled nitric oxide fraction (FeNO) and to interpret the values in varying clinical settings[6]. FeNO emerges as an alternative tool with superior diagnostic accuracy in inhaled corticosteroids-naive patients, considering that is a non-invasive, quick and easy-to-perform biomarker of airways inflammation[4,5,6,7,8]. These advantages have been addressed for the diagnosis of asthma in school children[9,10,11].

To overcome some inconsistencies, a combined assessment of FeNO with other tools may improve its value[12]. Allergy testing provides important information, since atopy is the major risk factor for asthma[1] and it is an important determinant of FeNO levels[13,14,15]. Written questionnaires have been widely used as screening instruments. The International Study of Asthma and Allergies in Childhood (ISAAC) is one of the most used questionnaires and one which has been validated in several countries and settings[16]. The aim of this study was to assess questions from ISAAC questionnaire in a school-based allergic asthma screening using simple and objective daily practice tools: FeNO and skin prick tests (SPT).

METHODS

A cross-sectional study that included consecutive children aged 8 to 12, from 3 schools with different socioeconomic status in the urban area of Porto, Portugal, was conducted. Children with a history of allergic rhinitis or eczema were not excluded, considering that these are common co-morbidities in allergic asthma.

Children's parents completed a self-administered questionnaire, including 5 questions adapted from the ISAAC questionnaire, reporting allergic symptoms, asthma symptoms, physician diagnosis of asthma and asthma medication. At the schools, SPT were performed using disposable 1mm tip lancets to seven common aeroallergens in the area (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae,* cat epithelium, grass mix, olive, *Parietaria* and *Alternaria*, with histamine (10mg/mL) and saline solution as positive and negative control, respectively *(*Leti – Spain). Readings were taken at 15 minutes and a mean wheal diameter of 3mm or more greater than negative control was considered positive[17], with at least one positive SPT as a proxy of atopy. FeNO (NIOX® MINO, Aerocrine AB, Sweden) was also measured at schools during a single breath exhalation, according to the ERS/ATS guidelines and expressed as parts per billion (ppb)[18]. As a cutoff for increased FeNO we considered values ≥ 25ppb[8]. A surrogate for allergic asthma was defined by both positive SPT and increased FeNO. This group of children was compared with all the other participants.

We used standard methods to calculate proportions, means and standard deviations (SD) for the variables considered. A Student t test was employed to compare FeNO values between groups, with $p<0.05$ considered significant. For each of the five questions, sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), with confidence interval (CI 95%) were calculated. Statistical analysis was performed using the SPSS® version 17 statistical program.

This work is part of the upkids-project[19] which sets out to evaluate the association between diet, overweight and allergies in children and has already assessed the prevalence of aeroallergen sensitization and increased FeNO values in children of different socioeconomic backgrounds[20].

Prior to study, and to promote participation, meetings with teachers and children were held, explaining our objectives and the importance of asthma awareness. Letters were sent to the parents of all children who completed the study, informing them of their children's results.

The study was approved by the Hospital São João E.P.E. Ethics Committee (Porto, Portugal). The parents' written consent was given before answering the questionnaire and performing the tests.

RESULTS

Of the 418 children attending the three schools, 132 (31.6%) did not obtain parental consent, 29 (7.0%) were not present at schools on the days of the study or did not cooperate in performing SPT or FeNO, and 84 (20.0%) did not complete or return the questionnaires, and were therefore excluded. A total of 173 (41.4%) were included in the final analysis (51.4% girls, mean age ± SD of 9.3 ± 1.2 years).

Forty-one percent of children were atopic, 26% had increased FeNO and 21% had both an increased FeNO and atopy. Fifty-three percent of the atopic children had high FeNO compared to 8% in nonatopic children.

Twelve percent of the parents reported physician diagnosis of asthma and 15% asthma medication use in the previous year. FeNO was significantly increased in atopic children (mean ± SD ppb) (33.7 ± 26.8 vs 12.5 ± 7.5; p<0.001) and in children with positive answers, such as "ever had wheezing at any time in the past" (26.5 ± 24.9 vs 16.6 ± 15.3; p=0.002), "wheezing with exercise in the last 12 months" (34.1 ± 28.2 vs 18.9 ± 18.8; p=0.005), and "asthma medication use in the previous year" (30.7 ± 23.6 vs 19.4 ± 14.9; p=0.01) (Table 1).

Table 2 presents the Se, Sp, PPV and NPV of the five questions dealing with allergic asthma diagnosis, excluding children under inhaled corticosteroids. The questions had

Table 1. Results of the five questions of the upKids-questionnaire related to allergic asthma diagnosis according to the skin prick tests (SPT) and exhaled nitric oxide fraction (FeNO)

Questions†	SPT + (n)		FeNO ± SD*		
	FeNO<25*	FeNO ≥25*	All	SPT +	SPT -
Ever had wheezing at any time in the past					
Yes	14	27	26.5 ± 24.9[a]	39.0 ± 28.6[d]	12.9 ± 7.6
No	19	9	16.6 ± 15.4	26.1 ± 22.9	12.4 ± 7.5
Wheezing with exercise in the last 12 months					
Yes	1	7	34.1 ± 28.2[b]	50.8 ± 28.9[e]	15.0 ± 9.4
No	30	25	18.9 ± 18.8	30.0 ± 25.8	12.1 ± 6.4
Ever had asthma					
Yes	2	6	24.5 ± 16.8	33.3 ± 18.1	16.7 ± 11.4
No	28	28	20.6 ± 21.2	34.0 ± 28.2	12.0 ± 6.8
Physician diagnosis of asthma					
Yes	3	7	23.1 ± 18.7	34.6 ± 20.6	12.7 ± 8.2
No	29	29	20.7 ± 21.1	33.5 ± 28.0	12.4 ± 7.5
Asthma medication use in the previous year**					
Yes	27	24	30.7 ± 23.6[c]	38.9 ± 25.2	15.3 ± 8.1
No	5	12	19.4 ± 14.9	32.1 ± 27.4	12.2 ± 7.5

† – results for "unknown" answer not shown; * ppb; ** any of: inhaled or systemic corticosteroids, short or long β-2 agonists; [a] p=0.002; [b] p=0.005; [c] p=0.01; [d] p=0.051; [e] p=0.04

Table 2. Sensitivity, specificity, positive and negative predictive value of the five questions of the upKids-questionnaire related to allergic asthma diagnosis (%)

Questions	Se	Sp	PPV	NPV
Ever had wheezing at any time in the past	64.3	60.0	26.5	89.7
Wheezing with exercise in the last 12 months	17.9	87.7	38.4	85.1
Ever had asthma	7.1	86.9	16.7	82.5
Physician diagnosis of asthma	7.1	90.0	14.3	81.8
Asthma medication use in the previous year*	14.3	90.8	25.0	83.1

* any of: systemic corticosteroids, short or long β-2 agonists; Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value

low Se, from 7% ("ever had asthma" and "physician diagnosis of asthma") to 64% ("ever had wheezing at any time in the past") to identify atopic children with high FeNO values. The Sp ranged between 60% ("ever had wheezing at any time in the past") and 90% ("physician diagnosis of asthma" and "asthma medication use in the previous year"). All questions had high NPV. Computing a score with three questions ("ever had asthma","ever had wheezing at any time in the past" and "wheezing with exercise in the last 12 months") did not improve the discriminatory properties of these questions.

DISCUSSION

The most useful question to screen for allergic asthmatic children was "ever had wheezing at any time in the past", with a Se of 64% and a NPV of 90%. The other 4 questions also had high NPV, allowing allergic asthma to be ruled out. However, their Se was low, showing that the questions answered by the parents were insufficient to identify atopic children with high FeNO values. Other combinations of answers did not improve the assessment accuracy.

This study has, for the first time, evaluated screening questions for allergic asthma in Portuguese school-aged children.

We still do not have a gold standard tool for childhood asthma detection. Our validation analysis was based on objective diagnostic tests, increased FeNO plus positive SPT, as a proxy of allergic asthma phenotype. This phenotype is recognized as the most common in pediatric asthma, providing the rationale for the clinical use of FeNO. We used the same FeNO asthma range values of Pijnenburg MWH *et al*[8]. FeNO has been shown to distinguish children with probable asthma[9,11], despite some conflicting results[10,21] and variety in reference values. A comparison of the diagnostic yield of FeNO in school children to eosinophils count in induced sputum showed similar results and a significantly better accuracy against the standard approach spirometry. The Se, Sp, NPV and PPV for the best cutoff point of FeNO (19ppb) was 80%, 92%, 89% and 86%, respectively[11]. Another study using our FeNO cutoff showed a NPV and a PPV of 80% and 100%, respectively[22].

In our study, FeNO values were significantly increased in children who have had wheezing previously, wheezing with exercise and who used asthma medication in the previous year, recognized as indicators of probable asthma. The estimated prevalence of allergic asthma was around 21%, according to the established premise. A selection bias may have occurred as only children whose parents completed the questionnaire were included. Probably the impact of non-responders led to a slight increase in prevalence, since we have observed that atopic children were more motivated to complete

the study by answering the questionnaires[20]. Many other factors can affect FeNO values, such as atopy, allergic rhinitis, atopic eczema, respiratory infections, anti-inflammatory medication, age or height[12,15,21,22]. Children receiving anti-inflammatory medication such as inhaled corticosteroids were excluded from the questions' diagnostic ability analysis, but we verified that FeNO was significantly increased in the inhaled steroids-treated group than in children without medication (38.1± 19.7 vs.20.1±20.5ppb, p=0.007), raising questions about disease control or compliance, among others. In a subsample of 73 children, the prediction intervals of FeNO were calculated as a function of standing height, according to the proposed model by Malmberg *et al*[23], but the results did not improve considerably (data not shown). False-positive cases may result from the inclusion of children with a history of allergic rhinitis or eczema. Nevertheless, these cases were not excluded, because they are common manifestations in children with asthma and, if excluded, would significantly limit the contribution of FeNO as a screening tool.

Some studies have evaluated asthma screening questionnaires to be used in schools, compared to a physician diagnosis. Wolf *et al*[24], considering the clinical history, physical examination and spirometry without reversibility, found a Se of 65% and a Sp of 88% to the question "has your child ever had episodes of wheezing in the last 12 months", validating a simple five-question instrument, the Brief Pediatric Asthma Screen (BPAS). More recently, the same group updated their questionnaire and included additional questions to detect allergic rhinitis as well as asthma (BPAS+)[25]. The authors identified a simplest scoring of any 1 of 4 items for asthma (wheeze, persistent cough, night cough and response to change in air temperature) that yielded the best balance of Sp (74%) and Se (73%). A Spanish version of the asthma portion of the BPAS+ questionnaire has already been validated, achieving a Se and a Sp of 74% and 86%, respectively[26]. Thus, the BPAS+ questions had better results than the ISAAC-based questions used in this study.

Redline *et al*[27] observed that the presence of cough (sometimes or more times) and/or breathing problems (rarely or more times) yielded a Se of 80%, a Sp of 75%, a PPV of 50% and a NPV of 92%, when compared with a bronchodilator response and SPT, but not with inflammatory markers. With similar evaluation tools, the same authors carried out another study, showing that no single parents questions (from a total of 10) or specific combinations appeared to be clearly superior for asthma prediction[28].

In conclusion, the questions used to screen for childhood asthma seem to have insufficient sensitivity. The best questions for screening purposes are yet to be identified and probably will not be the same in different countries and settings. A multidimensional screening tool is required, with questionnaires and simple objective diagnostic tests complementing each other. Objective measures such as FeNO and SPT may be useful to help rule in allergic asthma in school-based screenings.

AGRADECIMENTOS

Os presentes autores gostariam de agradecer a Pedro Moreira e Patrícia Padrão (Faculdade de Ciências da Nutrição e Alimentação, Universidade do Porto), pela participação no desenho do questionário *upkids*, na leitura óptica dos questionários e no planeamento do estudo; aos Laboratórios Leti (Espanha), pelo fornecimento das lancetas e extratos para realização dos testes cutâneos por picada, e à Fundação Vítor Baía 99, pelo equipamento para determinação da fracção do óxido nítrico no ar exalado.

Declaração de apoios financeiros: João Almeida Fonseca recebeu honorários por palestras realizadas e uma bolsa de investigação da Aerocrine (Suécia), empresa manufactora dos aparelhos de medição da fracção do óxido nítrico no ar exalado. Sem outros conflitos a declarar.

Contacto/Contact:
Teresa Vieira
Serviço de Imunoalergologia, Centro Hospitalar de São João, EPE, Porto
te_vieira@yahoo.com.br

REFERENCES

1. Bacharier LB, Boner A, Carlsen KH, Eigenman PA, Frischer T, Gçtz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FER, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008; 63:5-24.
2. Liem JJ, Kozyrskyj AL, Cockroft DW, Becker AB. Diagnosing asthma in children: what is the role for methacholine bronchoprovocation testing? Pediatr Pulmonol 2008; 43(5):481-9.
3. Dundas I, Mckenzie S. Spirometry in the diagnosis of asthma in children. Curr Opin Pulm Med 2006; 12(1):28-33.
4. Fortuna AM, Feixas T, González M, Casan P. Diagnostic utility of inflammatory biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. Respir Med 2007;101(11):2416-21.
5. Garcia-Marcos L, Brand PL. The utility of sputum eosinophils and exhaled nitric oxide for monitoring asthma control with special attention to childhood asthma. Allergol Immunopathol 2010;38(1):41-6.
6. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, *et al*. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184(5):602-15.
7. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma – comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med 2004; 169:473-8.
8. Pijnenburg MWH, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. Clin Exp Allergy 2007; 38:246-59.
9. Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax 2003; 58:494-9.
10. Prasad A, Langford B, Stradling JR, Ho LP. Exhaled nitric oxide as a screening tool for asthma in school children. Respir Med 2006;100:167-73.
11. Sivan Y, Gadish T, Fireman E, Soferman R. The use of exhaled nitric oxide in the diagnosis of asthma in school children. J Pediatr 2009;155:211-16.
12. Lopes C, Fonseca J, Delgado L, Moreira A, Barros R, Moreira P, Castel-Branco MG. Assessing asthma control: questionnaires and exhaled nitric oxide provide complementary information. Eur Respir J 2008; 32(5):1419-20.
13. Jouaville LF, Annesi-Maesano I, Nguyen LT, Bocage AS, Bedu M, Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. Clin Exp Allergy 2003;33(11):1506-11.
14. van Amsterdam JG, Janssen NA, de Meer G, Fischer PH, Nierkens S, van Loveren H, Opperhuizen A, Steerenberg PA, Brunekreef B. The relationship between exhaled nitric oxide and allergic sensitization in a random sample of school children. Clin Exp Allergy 2003; 33(2):187-91.
15. Cibella F, Cuttitta G, La Grutta S, Passalacqua G, Viegi G. Factors that influence exhaled nitric oxide in Italian schoolchildren. Ann Allergy Asthma Immunol 2008;101(4):407-12.
16. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998; 12:315-35.
17. EAACI subcommittee on skin tests. Allergen standardization and skin tests. Allergy 1993;48:48-82.
18. Baraldi E, de Jongste JC. European Respiratory Society; American Thoracic Society. Measurement of exhaled nitric oxide in children, 2001. Eur Respir J 2002;20:223-37.
19. Bessa M, Valente H, Cordeiro T, Padrão P, Moreira A, Lopes C, Moreira P. Ingestão de alimentos fluidos e risco de excesso de peso em crianças. Acta Med Port 2008; 21:161-70.
20. Silva R, Cruz L, Vieira T, Leblanc A, Ferreira A, Fonseca J, Moreira A, Castel-Branco MG. Prevalence of aeroallergen sensitization and increased exhaled nitric oxide values in schoolchildren of different socioeconomic status. J Investig Allergol Clin Immunol 2010; 20(3):210-3.
21. Welsh L, Lercher P, Horak E. Exhaled nitric oxide: interactions between asthma, hayfever, and atopic dermatitis in school children. Pediatr Pulmonol 2007;42(8):693-8.
22. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MWH, Silkoff PE, Bisgaard H. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;115:1130-6.
23. Malmberg LP, Petäys T, Haahtela T, *et al*. Exhaled nitric oxide in healthy nonatopic school-age children: Determinants and height--adjusted reference values. Pediatr Pulmonol 2006;41:635-42.
24. Wolf RL, Berry CA, O'Connor T, Coover L. Validation of the brief pediatric asthma screen. Chest 1999;116(4 Suppl 1):224S-8S.
25. Wolf RL, Berry CA, Quinn K. Development and validation of a brief pediatric screen for asthma and allergies among children. Ann Allergy Asthma Immunol 2003;90(5):500-7.
26. Berry CA, Quinn K, Wolf R, Mosnaim G, Shalowitz M. Validation of the spanish and english versions of the asthma portion of the brief pediatric asthma screen plus among hispanics. Ann Allergy Asthma Immunol 2005;95:53-60.
27. Redline S, Larkin EK, Kercsmar C, Berger M, Siminoff LA. Development and validation of school-based asthma and allergy screening instruments for parents and students. Ann Allergy Asthma Immunol 2003;90(5):516-28.
28. Redline S, Gruchalla RS, Wolf RL, Yawn BP, Cartar L, Gan V, Nelson P, Wollan P. Development and validation of school-based asthma and allergy screening questionnaires in a 4-city study. Ann Allergy Asthma Immunol 2004; 93(1):36-48.

Validity of a questionnaire in a school-based allergic asthma screening – Comparison with exhaled nitric oxide fraction and skin prick tests

Validação de um questionário de rastreio de asma alérgica em crianças de idade escolar – Comparação com a fracção de óxido nítrico no ar exalado e testes cutâneos por picada

Data de recepção / *Received in*: 19/11/2011
Data de aceitação / *Accepted for publication in*: 21/12/2011

Rev Port Imunoalergologia 2011; 19 (4): 215-221

Teresa Vieira[1], João Almeida Fonseca[1,2], Rui Silva[3], Linda Cruz[4], Ana Reis Ferreira[1], Ana Leblanc[1], André Moreira[1,2], Maria Graça Castel-Branco[1]

[1] Serviço de Imunoalergologia, Centro Hospitalar de São João, EPE, Porto
[2] Faculdade de Medicina da Universidade do Porto
[3] Unidade de Imunoalergologia, Centro Hospitalar de Trás-os-Montes e Alto Douro, EPE, Vila Real
[4] Serviço de Urgência, Centro Hospitalar de São João, EPE, Porto

ABSTRACT

Background: There is a need for simple, reliable tools to screen for childhood allergic asthma in populational-based studies. **Objectives:** To assess questions from the ISAAC questionnaire in a school-based allergic asthma screening using simple and objective daily practice tools: exhaled nitric oxide fraction (FeNO) and skin prick tests (SPT). **Methods:** Cross-sectional study of 173 schoolchildren aged 8 to 12, from 3 schools in the urban area of Porto. Children's parents completed a self-administered questionnaire adapted from ISAAC questionnaire. SPT to common aeroallergens and FeNO were performed at schools. A surrogate for allergic asthma was defined by both SPT positive and increased FeNO (≥25ppb). Sensitivity, specificity, positive predictive value and negative predictive value (CI at 95%), were calculated for 5 questions. **Results:** FeNO was significantly increased in children who reported wheezing at any time in the past (26.5 ± 24.9 vs. 16.6 ± 15.3; p=0.002), in children wheezing with exercise in the last 12 months (34.1 ± 28.2 vs. 18.9 ± 18.8; p=0.005) and using asthma medication in the last 12 months (30.7 ± 23.6 vs. 19.4 ± 14.9; p=0.01). The questions had low sensitivity, from 7% ("ever had asthma" and "physician diagnosis of asthma") to 64% ("ever had wheezing at any time in the past"). The specificity ranged between 60% ("ever had wheezing at any time in the past") and 90% ("physician diagnosis of asthma" and "asthma medication use in the previous year"). All questions had high negative predictive values. **Conclusions:** The analyzed questions had poor ability to identify atopic children with high FeNO values. However, the most useful question to screen for allergic asthmatic children was "ever had wheezing at any time in the past". Questionnaires and objective measures such as FeNO and SPT may complement each other for allergic asthma screening in children.

Key-words: Allergy, asthma, questionnaire, screening, validation.

RESUMO

Introdução: *Em estudos populacionais para rastreio de asma alérgica em crianças são necessários instrumentos válidos e simples.* ***Objectivos:*** *Avaliação de questões do questionário ISAAC para rastreio de asma alérgica em crianças de idade escolar utilizando instrumentos simples e objectivos da prática clínica: fracção exalada de óxido nítrico (FeNO) e testes cutâneos por picada (TCP).* ***Métodos:*** *Estudo transversal de 173 crianças, dos 8 aos 12 anos, pertencentes a três escolas da área urbana do Porto. Autopreenchimento pelos pais de um questionário, incluindo questões do ISAAC. Nas escolas foram realizados TCP a aeroalergénios comuns e determinada a FeNO. Como marcador de asma alérgica foi definida a presença de TCP positivos e FeNO aumentado (≥25ppb). Para cinco questões foram calculadas sensibilidade, especificidade, valor preditivo positivo e valor preditivo negativo (IC a 95%).* ***Resultados:*** *A FeNO encontrou-se significativamente aumentada nas crianças com história de sibilância no passado (26,5 ± 24,9 vs. 16,6 ± 15.3; p=0,002), nas crianças com sibilância com o exercício nos últimos 12 meses (34,1 ± 28,2 vs. 18,9 ± 18,8; p=0,005), e nas que utilizaram medicação antiasmática nos últimos 12 meses (30,7 ± 23,6 vs. 19,4 ± 14,9; p=0,01). Todas as questões apresentaram baixa sensibilidade, desde 7% ("alguma vez teve asma no passado" e "diagnóstico médico de asma") a 64% ("alguma vez teve sibilância no passado"). A especificidade das questões variou entre 60% ("alguma vez teve sibilância no passado") e 90% ("diagnóstico médico de asma" e "uso de medicação antiasmática no último ano"). Todas as questões apresentaram valores preditivos negativos elevados.* ***Conclusões:*** *As questões analisadas apresentaram globalmente pouca capacidade na identificação de crianças atópicas com FeNO aumentado. A questão que no entanto se revelou mais útil para rastreio de asma alérgica em crianças foi "alguma vez teve sibilância no passado". Os questionários e medidas objectivas como a FeNO e TCP podem complementar-se no rastreio de asma alérgica em crianças.*

Palavras-chave: *Alergia, asma, questionário, rastreio, validação.*

INTRODUCTION

In children, asthma is a particularly important public health problem[1] and the most relevant phenotype is allergic asthma. There is a need for simple, reliable tools to screen for childhood allergic asthma in populational-based studies. As a standard approach, lung function or airway hyperresponsiveness tests are difficult to perform on a large scale, require extensive resources and correlate poorly with clinical symptoms. Moreover, children's cooperation is difficult at early ages[2,3]. Despite the significantly higher diagnostic yield of eosinophils count in induced sputum compared to the standard approach, no clear advantages in technique, cooperation, cost and speed have been reported[4,5]. Recent guidelines from the American Thoracic Society provide clinicians with a practical approach to use exhaled nitric oxide fraction (FeNO) and to interpret the values in varying clinical settings[6]. FeNO emerges as an alternative tool with superior diagnostic accuracy in inhaled corticosteroids-naive patients, considering that is a non-invasive, quick and easy-to-perform biomarker of airways inflammation[4,5,6,7,8]. These advantages have been addressed for the diagnosis of asthma in school children[9,10,11].

To overcome some inconsistencies, a combined assessment of FeNO with other tools may improve its value[12]. Allergy testing provides important information, since atopy is the major risk factor for asthma[1] and it is an important determinant of FeNO levels[13,14,15]. Written questionnaires have been widely used as screening instruments. The International Study of Asthma and Allergies in Childhood (ISAAC) is one of the most used questionnaires and one which has been validated in several countries and settings[16]. The aim of this study was to assess questions from ISAAC questionnaire in a school-based allergic asthma screening using simple and objective daily practice tools: FeNO and skin prick tests (SPT).

METHODS

A cross-sectional study that included consecutive children aged 8 to 12, from 3 schools with different socioeconomic status in the urban area of Porto, Portugal, was conducted. Children with a history of allergic rhinitis or eczema were not excluded, considering that these are common co-morbidities in allergic asthma.

Children's parents completed a self-administered questionnaire, including 5 questions adapted from the ISAAC questionnaire, reporting allergic symptoms, asthma symptoms, physician diagnosis of asthma and asthma medication. At the schools, SPT were performed using disposable 1mm tip lancets to seven common aeroallergens in the area (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae,* cat epithelium, grass mix, olive, *Parietaria* and *Alternaria*, with histamine (10mg/mL) and saline solution as positive and negative control, respectively *(*Leti – Spain). Readings were taken at 15 minutes and a mean wheal diameter of 3mm or more greater than negative control was considered positive[17], with at least one positive SPT as a proxy of atopy. FeNO (NIOX® MINO, Aerocrine AB, Sweden) was also measured at schools during a single breath exhalation, according to the ERS/ATS guidelines and expressed as parts per billion (ppb)[18]. As a cutoff for increased FeNO we considered values ≥ 25ppb[8]. A surrogate for allergic asthma was defined by both positive SPT and increased FeNO. This group of children was compared with all the other participants.

We used standard methods to calculate proportions, means and standard deviations (SD) for the variables considered. A Student t test was employed to compare FeNO values between groups, with $p<0.05$ considered significant. For each of the five questions, sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), with confidence interval (CI 95%) were calculated. Statistical analysis was performed using the SPSS® version 17 statistical program.

This work is part of the upkids-project[19] which sets out to evaluate the association between diet, overweight and allergies in children and has already assessed the prevalence of aeroallergen sensitization and increased FeNO values in children of different socioeconomic backgrounds[20].

Prior to study, and to promote participation, meetings with teachers and children were held, explaining our objectives and the importance of asthma awareness. Letters were sent to the parents of all children who completed the study, informing them of their children's results.

The study was approved by the Hospital São João E.P.E. Ethics Committee (Porto, Portugal). The parents' written consent was given before answering the questionnaire and performing the tests.

RESULTS

Of the 418 children attending the three schools, 132 (31.6%) did not obtain parental consent, 29 (7.0%) were not present at schools on the days of the study or did not cooperate in performing SPT or FeNO, and 84 (20.0%) did not complete or return the questionnaires, and were therefore excluded. A total of 173 (41.4%) were included in the final analysis (51.4% girls, mean age ± SD of 9.3 ± 1.2 years).

Forty-one percent of children were atopic, 26% had increased FeNO and 21% had both an increased FeNO and atopy. Fifty-three percent of the atopic children had high FeNO compared to 8% in nonatopic children.

Twelve percent of the parents reported physician diagnosis of asthma and 15% asthma medication use in the previous year. FeNO was significantly increased in atopic children (mean ± SD ppb) (33.7 ± 26.8 vs 12.5 ± 7.5; p<0.001) and in children with positive answers, such as "ever had wheezing at any time in the past" (26.5 ± 24.9 vs 16.6 ± 15.3; p=0.002), "wheezing with exercise in the last 12 months" (34.1 ± 28.2 vs 18.9 ± 18.8; p=0.005), and "asthma medication use in the previous year" (30.7 ± 23.6 vs 19.4 ± 14.9; p=0.01) (Table 1).

Table 2 presents the the Se, Sp, PPV and NPV of the five questions dealing with allergic asthma diagnosis, excluding children under inhaled corticosteroids. The ques-

Table 1. Results of the five questions of the upKids-questionnaire related to allergic asthma diagnosis according to the skin prick tests (SPT) and exhaled nitric oxide fraction (FeNO)

Questions†	SPT + (n)		FeNO ± SD*		
	FeNO<25*	FeNO ≥25*	All	SPT +	SPT -
Ever had wheezing at any time in the past					
Yes	14	27	26.5 ± 24.9[a]	39.0 ± 28.6[d]	12.9 ± 7.6
No	19	9	16.6 ± 15.4	26.1 ± 22.9	12.4 ± 7.5
Wheezing with exercise in the last 12 months					
Yes	1	7	34.1 ± 28.2[b]	50.8 ± 28.9[e]	15.0 ± 9.4
No	30	25	18.9 ± 18.8	30.0 ± 25.8	12.1 ± 6.4
Ever had asthma					
Yes	2	6	24.5 ± 16.8	33.3 ± 18.1	16.7 ± 11.4
No	28	28	20.6 ± 21.2	34.0 ± 28.2	12.0 ± 6.8
Physician diagnosis of asthma					
Yes	3	7	23.1 ± 18.7	34.6 ± 20.6	12.7 ± 8.2
No	29	29	20.7 ± 21.1	33.5 ± 28.0	12.4 ± 7.5
Asthma medication use in the previous year**					
Yes	27	24	30.7 ± 23.6[c]	38.9 ± 25.2	15.3 ± 8.1
No	5	12	19.4 ± 14.9	32.1 ± 27.4	12.2 ± 7.5

† – results for "unknown" answer not shown; * ppb; ** any of: inhaled or systemic corticosteroids, short or long β-2 agonists; [a] p=0.002; [b] p=0.005; [c] p=0.01; [d] p=0.051; [e] p=0.04

Table 2. Sensitivity, specificity, positive and negative predictive value of the five questions of the upKids-questionnaire related to allergic asthma diagnosis (%)

Questions	Se	Sp	PPV	NPV
Ever had wheezing at any time in the past	64.3	60.0	26.5	89.7
Wheezing with exercise in the last 12 months	17.9	87.7	38.4	85.1
Ever had asthma	7.1	86.9	16.7	82.5
Physician diagnosis of asthma	7.1	90.0	14.3	81.8
Asthma medication use in the previous year*	14.3	90.8	25.0	83.1

* any of: systemic corticosteroids, short or long β-2 agonists; Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value

tions had low Se, from 7% ("ever had asthma" and "physician diagnosis of asthma") to 64% ("ever had wheezing at any time in the past") to identify atopic children with high FeNO values. The Sp ranged between 60% ("ever had wheezing at any time in the past") and 90% ("physician diagnosis of asthma" and "asthma medication use in the previous year"). All questions had high NPV. Computing a score with three questions ("ever had asthma","ever had wheezing at any time in the past" and "wheezing with exercise in the last 12 months") did not improve the discriminatory properties of these questions.

DISCUSSION

The most useful question to screen for allergic asthmatic children was "ever had wheezing at any time in the past", with a Se of 64% and a NPV of 90%. The other 4 questions also had high NPV, allowing allergic asthma to be ruled out. However, their Se was low, showing that the questions answered by the parents were insufficient to identify atopic children with high FeNO values. Other combinations of answers did not improve the assessment accuracy.

This study has, for the first time, evaluated screening questions for allergic asthma in Portuguese school-aged children.

We still do not have a gold standard tool for childhood asthma detection. Our validation analysis was based on objective diagnostic tests, increased FeNO plus positive SPT, as a proxy of allergic asthma phenotype. This phenotype is recognized as the most common in pediatric asthma, providing the rationale for the clinical use of FeNO. We used the same FeNO asthma range values of Pijnenburg MWH *et al*[8]. FeNO has been shown to distinguish children with probable asthma[9,11], despite some conflicting results[10,21] and variety in reference values. A comparison of the diagnostic yield of FeNO in school children to eosinophils count in induced sputum showed similar results and a significantly better accuracy against the standard approach spirometry. The Se, Sp, NPV and PPV for the best cutoff point of FeNO (19ppb) was 80%, 92%, 89% and 86%, respectively[11]. Another study using our FeNO cutoff showed a NPV and a PPV of 80% and 100%, respectively[22].

In our study, FeNO values were significantly increased in children who have had wheezing previously, wheezing with exercise and who used asthma medication in the previous year, recognized as indicators of probable asthma. The estimated prevalence of allergic asthma was around 21%, according to the established premise. A selection bias may have occurred as only children whose parents completed the questionnaire were included. Probably the impact of non-responders led to a slight increase in prevalence, since we have observed that atopic children were more motivated to complete

the study by answering the questionnaires[20]. Many other factors can affect FeNO values, such as atopy, allergic rhinitis, atopic eczema, respiratory infections, anti-inflammatory medication, age or height[12,15,21,22]. Children receiving anti-inflammatory medication such as inhaled corticosteroids were excluded from the questions' diagnostic ability analysis, but we verified that FeNO was significantly increased in the inhaled steroids-treated group than in children without medication (38.1± 19.7 vs.20.1±20.5ppb, p=0.007), raising questions about disease control or compliance, among others. In a subsample of 73 children, the prediction intervals of FeNO were calculated as a function of standing height, according to the proposed model by Malmberg *et al*[23], but the results did not improve considerably (data not shown). False-positive cases may result from the inclusion of children with a history of allergic rhinitis or eczema. Nevertheless, these cases were not excluded, because they are common manifestations in children with asthma and, if excluded, would significantly limit the contribution of FeNO as a screening tool.

Some studies have evaluated asthma screening questionnaires to be used in schools, compared to a physician diagnosis. Wolf *et al*[24], considering the clinical history, physical examination and spirometry without reversibility, found a Se of 65% and a Sp of 88% to the question "has your child ever had episodes of wheezing in the last 12 months", validating a simple five-question instrument, the Brief Pediatric Asthma Screen (BPAS). More recently, the same group updated their questionnaire and included additional questions to detect allergic rhinitis as well as asthma (BPAS+)[25]. The authors identified a simplest scoring of any 1 of 4 items for asthma (wheeze, persistent cough, night cough and response to change in air temperature) that yielded the best balance of Sp (74%) and Se (73%). A Spanish version of the asthma portion of the BPAS+ questionnaire has already been validated, achieving a Se and a Sp of 74% and 86%, respectively[26]. Thus, the BPAS+ questions had better results than the ISAAC-based questions used in this study.

Redline *et al*[27] observed that the presence of cough (sometimes or more times) and/or breathing problems (rarely or more times) yielded a Se of 80%, a Sp of 75%, a PPV of 50% and a NPV of 92%, when compared with a bronchodilator response and SPT, but not with inflammatory markers. With similar evaluation tools, the same authors carried out another study, showing that no single parents questions (from a total of 10) or specific combinations appeared to be clearly superior for asthma prediction[28].

In conclusion, the questions used to screen for childhood asthma seem to have insufficient sensitivity. The best questions for screening purposes are yet to be identified and probably will not be the same in different countries and settings. A multidimensional screening tool is required, with questionnaires and simple objective diagnostic tests complementing each other. Objective measures such as FeNO and SPT may be useful to help rule in allergic asthma in school-based screenings.

AGRADECIMENTOS

Os presentes autores gostariam de agradecer a Pedro Moreira e Patrícia Padrão (Faculdade de Ciências da Nutrição e Alimentação, Universidade do Porto), pela participação no desenho do questionário *upkids*, na leitura óptica dos questionários e no planeamento do estudo; aos Laboratórios Leti (Espanha), pelo fornecimento das lancetas e extratos para realização dos testes cutâneos por picada, e à Fundação Vítor Baía 99, pelo equipamento para determinação da fracção do óxido nítrico no ar exalado.

Declaração de apoios financeiros: João Almeida Fonseca recebeu honorários por palestras realizadas e uma bolsa de investigação da Aerocrine (Suécia), empresa manufactora dos aparelhos de medição da fracção do óxido nítrico no ar exalado. Sem outros conflitos a declarar.

Contacto/Contact:
Teresa Vieira
Serviço de Imunoalergologia, Centro Hospitalar de São João, EPE, Porto
te_vieira@yahoo.com.br

REFERENCES

1. Bacharier LB, Boner A, Carlsen KH, Eigenman PA, Frischer T, Gçtz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FER, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008; 63:5-24.
2. Liem JJ, Kozyrskyj AL, Cockroft DW, Becker AB. Diagnosing asthma in children: what is the role for methacholine bronchoprovocation testing? Pediatr Pulmonol 2008; 43(5):481-9.
3. Dundas I, Mckenzie S. Spirometry in the diagnosis of asthma in children. Curr Opin Pulm Med 2006; 12(1):28-33.
4. Fortuna AM, Feixas T, González M, Casan P. Diagnostic utility of inflammatory biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. Respir Med 2007;101(11):2416-21.
5. Garcia-Marcos L, Brand PL. The utility of sputum eosinophils and exhaled nitric oxide for monitoring asthma control with special attention to childhood asthma. Allergol Immunopathol 2010;38(1):41-6.
6. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, *et al*. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184(5):602-15.
7. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma – comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med 2004; 169:473-8.
8. Pijnenburg MWH, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. Clin Exp Allergy 2007; 38:246-59.
9. Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax 2003; 58:494-9.
10. Prasad A, Langford B, Stradling JR, Ho LP. Exhaled nitric oxide as a screening tool for asthma in school children. Respir Med 2006;100:167-73.
11. Sivan Y, Gadish T, Fireman E, Soferman R. The use of exhaled nitric oxide in the diagnosis of asthma in school children. J Pediatr 2009;155:211-16.
12. Lopes C, Fonseca J, Delgado L, Moreira A, Barros R, Moreira P, Castel-Branco MG. Assessing asthma control: questionnaires and exhaled nitric oxide provide complementary information. Eur Respir J 2008; 32(5):1419-20.
13. Jouaville LF, Annesi-Maesano I, Nguyen LT, Bocage AS, Bedu M, Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. Clin Exp Allergy 2003;33(11):1506-11.
14. van Amsterdam JG, Janssen NA, de Meer G, Fischer PH, Nierkens S, van Loveren H, Opperhuizen A, Steerenberg PA, Brunekreef B. The relationship between exhaled nitric oxide and allergic sensitization in a random sample of school children. Clin Exp Allergy 2003; 33(2):187-91.
15. Cibella F, Cuttitta G, La Grutta S, Passalacqua G, Viegi G. Factors that influence exhaled nitric oxide in Italian schoolchildren. Ann Allergy Asthma Immunol 2008;101(4):407-12.
16. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998; 12:315-35.
17. EAACI subcommittee on skin tests. Allergen standardization and skin tests. Allergy 1993;48:48-82.
18. Baraldi E, de Jongste JC. European Respiratory Society; American Thoracic Society. Measurement of exhaled nitric oxide in children, 2001. Eur Respir J 2002;20:223-37.
19. Bessa M, Valente H, Cordeiro T, Padrão P, Moreira A, Lopes C, Moreira P. Ingestão de alimentos fluidos e risco de excesso de peso em crianças. Acta Med Port 2008; 21:161-70.
20. Silva R, Cruz L, Vieira T, Leblanc A, Ferreira A, Fonseca J, Moreira A, Castel-Branco MG. Prevalence of aeroallergen sensitization and increased exhaled nitric oxide values in schoolchildren of different socioeconomic status. J Investig Allergol Clin Immunol 2010; 20(3):210-3.
21. Welsh L, Lercher P, Horak E. Exhaled nitric oxide: interactions between asthma, hayfever, and atopic dermatitis in school children. Pediatr Pulmonol 2007;42(8):693-8.
22. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MWH, Silkoff PE, Bisgaard H. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;115:1130-6.
23. Malmberg LP, Petäys T, Haahtela T, *et al*. Exhaled nitric oxide in healthy nonatopic school-age children: Determinants and height--adjusted reference values. Pediatr Pulmonol 2006;41:635-42.
24. Wolf RL, Berry CA, O'Connor T, Coover L. Validation of the brief pediatric asthma screen. Chest 1999;116(4 Suppl 1):224S-8S.
25. Wolf RL, Berry CA, Quinn K. Development and validation of a brief pediatric screen for asthma and allergies among children. Ann Allergy Asthma Immunol 2003;90(5):500-7.
26. Berry CA, Quinn K, Wolf R, Mosnaim G, Shalowitz M. Validation of the spanish and english versions of the asthma portion of the brief pediatric asthma screen plus among hispanics. Ann Allergy Asthma Immunol 2005;95:53-60.
27. Redline S, Larkin EK, Kercsmar C, Berger M, Siminoff LA. Development and validation of school-based asthma and allergy screening instruments for parents and students. Ann Allergy Asthma Immunol 2003;90(5):516-28.
28. Redline S, Gruchalla RS, Wolf RL, Yawn BP, Cartar L, Gan V, Nelson P, Wollan P. Development and validation of school-based asthma and allergy screening questionnaires in a 4-city study. Ann Allergy Asthma Immunol 2004; 93(1):36-48.

PORTUGUESA