

Validation of a screening questionnaire for atopy with serum IgE tests in a population of pregnant Dutch women

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Summary

Background We have started a large birth cohort study in which pregnant women with and without atopy are differentially included. In view of the large number of subjects to be screened (12 000), a simple questionnaire was developed for the assessment of atopy in pregnant women.

Objective The objective of our study was to evaluate the efficacy of a questionnaire using serum IgE tests.

Methods During an antenatal visit to the midwife clinic, 175 expecting mothers completed a questionnaire and from each subject blood was obtained in which total and specific IgE against house dust mite, cat, dog, birch and grass was determined.

Results When atopy was defined as the presence of a positive test for IgE against at least one allergen, seven questions from the questionnaire had a sensitivity and specificity of 55.0% and 88.7%, respectively. With the use of the questionnaire it was possible to select about 50% of the subjects with specific IgE to one or more common inhalant allergens. The positive predictive value of the screening questions was 71.7%. Taking total IgE into account did not change these results.

Conclusion The screening questionnaire is an efficient tool for differential inclusion of subjects with and without atopy in epidemiological studies.

Keywords: allergies, atopy, questionnaire, sensitivity, specificity, specific IgE, total IgE, validation

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Introduction

There is growing evidence that the prevalence of inhalant allergy and asthma in childhood is increasing. Although data from The Netherlands are lacking, studies from other developed countries illustrate this [1–3]. The prevalence of asthmatic symptoms among children is considerable in The Netherlands. A recent nationwide survey among 4–12-year-old children found a prevalence of about 7% for ‘attacks of shortness of breath with wheezing in the past 12 months’ and of about 13% for ‘wheeze in the past 12 months’ [4].

Several studies [5,6] have shown that an important genetically predisposing factor for a child to develop

asthma or inhalant allergy, is a family history of atopic disease.

Few investigators have attempted to validate the use of screening questionnaires for inclusion of atopic subjects in population studies on inhalant allergy and/or asthma. Nielsen *et al.* [7] validated a questionnaire amongst almost 1600 subjects by using skin-prick tests with common allergens (birch, grass, mugwort, dog, cat, horse, house dust mite and moulds) as a reference. Odds Ratios between 1.5 and 12 were found for the different screening questions. Bergmann *et al.* [8] used a Phadiatop IgE-antibody test for common inhalant allergens as a reference amongst 793 women and 353 men and found a specificity of about 86% and a sensitivity around 60%. Both studies showed that selection of atopic subjects is possible, but that a substantial

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proportion of atopic subjects (about 40%) will not be selected using a screening questionnaire only. In both of these studies pregnant women were excluded.

We have started a large birth cohort study in which pregnant women with and without atopy are differentially included. The study is on Prevention and Incidence of Asthma and Mite Allergy (PIAMA), and it is a combined effort of our Department and the Sophia Hospital for Children of the Rotterdam Medical School (Professor H. J. Neijens and Professor J. C. de Jongste), the Beatrix Hospital for Children of the Groningen University Medical School (Dr J. Gerritsen), the Central Laboratory of the Red Cross Blood Transfusion Service (Professor R. C. Aalberse) and the National Institute of Public Health and the Environment (Dr H. A. Smit). In the study, 1200 children of atopic mothers, and 2500 children of non-atopic mothers will be followed from before birth until age 8. In view of the large number of subjects to be screened to include this number of subjects (12 000), a simple questionnaire was developed for the detection of atopy in pregnant women. The questionnaire was validated in a population of pregnant Dutch women using serum IgE tests as a reference.

Methods

Population

Midwives were asked to hand out a short screening questionnaire with questions on respiratory allergies and asthma to expectant mothers visiting their clinic from September 1995 until December 1995. Participating practices were located in Groningen and Ede, Arnhem and Tiel (all near Wageningen). At the same time, a venous blood sample was obtained from each subject. A total of 175 women participated in the study.

Questionnaire

The questionnaire (appendix 1) consisted of questions about allergy to house dust, house dust mite and pets and about a doctor's diagnosis of the allergy in question. Furthermore questions were asked about hay fever, asthma and eczema.

Blood samples and IgE determination

Blood was sampled in evacuated blood collecting tubes with clotting factor (Venoject; Terumo Europe NV, Leuven, Belgium). After a maximum of 60 h in the refrigerator the blood was centrifuged at 1000 g and the serum was stored at -20°C .

Total IgE concentrations were determined by enzyme immunoassay (EIA) as described by Doekes *et al.* [9] with two modifications: anti-IgE-coated microwell plates were

stored at -20°C before use, and the assay was calibrated with reference preparations for total IgE (200 and 50 kU/L) from Kabi-Pharmacia, Sweden (lot nr 69697). Each microtitre plate contained a serum control (pooled normal human serum — a mixture of sera from at least 200 healthy blood donors from several European countries (Precinorm^R; Boehringer, Mannheim, Germany) and blanks (PBTG: phosphate buffered saline containing 0.05% (v/v) Tween-20 and 0.5% (w/v) gelatin). IgE concentrations (U/mL) were determined by direct interpolation of the observed optical density at 492 nm (OD_{492}) on non-transformed calibration lines, provided that the OD_{492} values were in the range between the mean $+3$ SD of the reagent blank and an upper limit of 2.5.

Presence of allergen-specific IgE concentrations was also assessed by EIA as described by Doekes *et al.* [9]. Allergen-coated microwell plates were also stored at -20°C . Sera were tested for specific IgE against house dust mite (*Dermatophagoides pteronyssinus*, 10 mg/mL; lotnr 10.01; ALK Benelux, Houten, The Netherlands), cat (25 mg/mL; lot nr 15.02; Diephuis), dog (20 mg/mL; lot nr 15.01; ALK Benelux), grass pollen (a mix of rye and timothy, 10 mg/mL; lot nr 01.03 and 01.07; ALK Benelux) and birch pollen (*Betula verrucosa*, 25 mg/mL; lot nr 02.04; ALK Benelux). Allergens were prepared by diluting stock solutions of these allergens in phosphate buffered saline (PBS, pH 7.4). All sera were tested in duplicate. A serum was considered positive if the mean OD_{492} exceeded the OD_{492} of the corresponding reagent blank by 0.05.

Statistical analysis

Data were analysed using SAS version 6.04 for Personal Computers.

Results

Table 1 shows the prevalence of the reported answers to the questions in the questionnaire, the percentage of subjects with total IgE higher than 100 kU/L and the percentage of subjects with specific IgE-antibodies against the tested allergens. Of the 18 subjects who reported an allergy to house dust, 14 subjects also reported to be allergic to house dust mite. Subjects with specific antibodies against grass, birch and house dust mite were most common in this population. Of 29 subjects with IgE antibodies against birch, 20 also had IgE against grass. Of the 14 subjects with IgE against cat or dog, nine subjects also had IgE against house dust mite.

Table 2 shows the association between the different sets of questions used and the presence of specific and total IgE.

To validate reported allergies and/or symptoms with respect to specific serum IgE content, the sensitivity,

Table 1. Prevalence of reported allergies, symptoms, and elevated total and specific IgE in the study population ($n = 175$).

		Prevalence (%)
Questionnaire	House dust	10.3
	PD [@]	9.1
	House dust mite	9.1
	PD	8.6
	Pets	12.0
	PD	7.4
	Asthma	5.1
	PD	4.6
	Recent asthma attack	2.3
	Hay fever	20.7
	Eczema	43.4
Total IgE	> 100 kU/L	17.5
Specific IgE	Cat	8.0
	Grass	21.1
	Birch	16.6
	House dust mite	17.1
	Dog	2.9
	More than one test positive	34.3

[@] PD, = Physician diagnosed.

specificity, the percentage of IgE-positive subjects detected by the questionnaire, and the predictive value of a positive screening outcome (PV +) were calculated for different sets of questions from the questionnaire. Sensitivity is the fraction of IgE-positive subjects who are also found to be atopic by the questionnaire. Specificity is the fraction of IgE-negative subjects found to be nonatopic by the questionnaire. The predictive value of a positive screening outcome (PV +) was calculated as follows: $PV + = \text{number of atopic subjects correctly (i.e. IgE-positive) detected by the questionnaire} / \text{total number of atopic subjects detected by the questionnaire}$.

The eczema question was found to be very non-specific. Seventy-six subjects answered this question positively, of which only nine had elevated specific IgE against any of the tested allergens. The question on eczema was therefore excluded from all further analyses.

Table 3 shows the results of the analysis in which all questions except the question on eczema were combined. Subjects with at least one, respectively, at least two positive answers were regarded as atopic. As Table 3 shows, specific IgE (A) against one or more allergens was more clearly associated with positive answers in the questionnaire than total IgE higher than 100 kU/L (B).

There were four subjects who only had positive answers to one or more of the questions on asthma and it turned out that none of them had specific IgE to any of the allergens we tested. Analysis of this set of questions showed a higher specificity and predictive value of a positive screening outcome than the set with questions on asthma included.

Table 4 shows the difference between absorbance levels for the various specific allergens between subjects found to be atopic by the questionnaire and subjects not so identified by the questionnaire, among those with detectable quantities of specific IgE. The subjects who had reported one or more allergies generally had higher levels of specific IgE but the difference was statistically significant for grass only. The geometric mean of the total IgE level was 54 U/mL for atopic subjects (defined by the questionnaire) and 13 U/mL for non-atopic subjects. This difference in total IgE level was statistically significant ($t = -5.45$, $P < 0.0001$).

Discussion

We evaluated a simple screening questionnaire for the detection of atopy, to be used in a large population of pregnant women. We found that the questionnaire had a reasonable combination of sensitivity and specificity, using specific IgE measurements as a standard. A number of sets of questions were analysed. The questionnaire in which the eczema question as well as all questions on asthma were eliminated, resulted in the most favourable combination of

Table 2. Total and specific IgE in relation to the different sets of questions used.

Group	<i>n</i>	≥ 1 positive specific IgE – test	total IgE > 100 kU/L	specific or total IgE elevated
whole group	175	56 (32.0%)	30 (17.1%)	62 (35.4%)
≥ 1 positive answer all questions	94	40 (42.6%)	22 (23.4%)	43 (45.7%)
≥ 1 positive answer questions 1–10	48	33 (68.8%)	16 (33.3%)	33 (68.8%)
≥ 2 positive answers questions 1–10	30	22 (73.3%)	10 (33.3%)	22 (73.3%)
≥ 1 positive answer questions 1–6, 10	44	33 (75.0%)	16 (36.4%)	33 (75.0%)
≥ 2 positive answer questions 1–6, 10	26	22 (84.6%)	10 (38.5%)	22 (84.6%)

Table 3. Comparison of answers to questions in the questionnaire and the presence of elevated total and specific IgE for ≥ 1 or ≥ 2 positively answered questions. Question on eczema was eliminated.

Criterion used	Sensitivity (%)	Specificity (%)	PV + (%)	% selected
A				
≥ 1 positive answer	55.0	87.0	68.8	27.4
≥ 2 positive answers	36.7	93.0	73.3	17.1
B				
≥ 1 positive answer	53.3	77.4	33.3	27.4
≥ 2 positive answers	34.5	86.2	33.3	17.1
C				
≥ 1 positive answer	50.0	86.2	68.8	27.4
≥ 2 positive answers	33.3	92.7	73.3	17.1

A, Specific IgE against one or more of the allergens tested;

B, Total IgE > 100 kU/L;

C, A and/or B.

sensitivity, specificity and predictive value of a positive screening outcome. The requirement of having at least two positive answers reduced the percentage of subjects that were selected considerably. Using only one positive answer resulted in significantly more subjects who were 'positive', without seriously reducing the predictive value.

Bergmann *et al.* [8] validated a questionnaire concerning atopic family history with regard to Phadiatop test results. By using a combination of 20 questions, for women, a sensitivity of 64% and a specificity of 84% was found. The sensitivity we found by using a combination of seven questions was lower (51.7%) but the specificity was slightly higher (90.6%).

Nielsen *et al.* [7] did not include any questions about diagnoses in their survey, since symptoms of allergy would not necessarily cause the subject to consult a doctor and because the criteria for diagnosis might vary. In our survey, comparison of the entire questionnaire with a questionnaire in which all questions about a doctor's diagnosis were eliminated, showed no significant differences. We therefore conclude that in our population, it seemed to be necessary nor harmful to include such questions.

In a study among children, Murray *et al.* [10] evaluated the predictive values of various questions on allergic symptoms for detecting a positive skin test against mite, tree, grass, dogs and cats. Sensitivities ranged from 51 to 56%, specificities from 63 to 85%. The values in our study were slightly better, but it must be kept in mind that we looked at IgE positivity to any of the evaluated allergens, and that we did not evaluate the specific allergens separately.

Table 4. Absorbance of specific IgE (OD_{492}) against different allergens among subjects reacting positively to the ELISA for a certain allergen. The difference is shown between subjects with and without reported allergy for the corresponding allergen according to the questionnaire.

	No allergy reported			Allergy reported		
	n	Median	Range	n	Median	Range
cat	4	0.24	(0.13–0.54)	10	0.72	(0.14–2.81)
dog	2	0.19	(0.18–0.20)	3	0.15	(0.13–0.23)
grass	12	0.31	(0.11–5.00)	25	2.80	(0.12–5.00)**
birch	10	0.49	(0.17–0.91)	19	0.59	(0.17–5.00)
mite	13	0.17	(0.09–0.61)	17	0.18	(0.11–0.88)

** $P < 0.01$ (*t*-test)

When the difference between total IgE and specific IgE was considered, specific IgE was found to be more closely associated with the questions in the questionnaire than total IgE.

The level of total IgE was higher in subjects who were atopic according to the questionnaire than in non-atopic subjects, although some of the (questionnaire-defined) non-atopic subjects had high total IgE titres as well. About half of the subjects with detectable quantities of specific IgE against one or more of the tested allergens had one or more positive answers to the questions. The other half could not be distinguished from subjects without specific IgE by means of this questionnaire. The use of total IgE did not improve this. Among subjects with detectable quantities of specific IgE the subjects that were 'atopic' according to the questionnaire had higher specific IgE levels, especially total IgE, and IgE against cat and grass.

If the response to our questionnaire was biased in the sense that relatively more atopic women participated, this would have increased the precision of our study, as we would have had relatively more atopic women to study. We have no information to decide whether this has occurred, however.

Our results show that the screening questionnaire is not sensitive enough to detect a very high proportion of subjects with elevated specific IgE; however, most subjects without specific IgE were correctly classified as nonatopic by the questionnaire. Although use of this instrument in our epidemiological study inevitably leads to some misclassification, it is a more rapid and cost-effective method than IgE testing or the use of other objective means of measuring atopy in the population. By measuring IgE in only those subjects who are enrolled in the birth cohort study, we will be able to later assess the atopic status of the subjects more precisely.

Our conclusion is that the screening questionnaire provides an efficient tool for differential inclusion of subjects with and without atopy in epidemiological studies.

Appendix 1

Screening questionnaire for detection of atopy in pregnant women.

- (1) Are you allergic to house dust?
- (2) If so, has a physician diagnosed this allergy?
- (3) Are you allergic to house dust mite?
- (4) If so, has a physician diagnosed this allergy?
- (5) Are you allergic to pets?
- (6) If so, has a physician diagnosed this allergy?
- (7) Have you ever had asthma?
- (8) If so, has this been diagnosed by a physician?
- (9) Have you had an asthma attack in the past 12 months?
- (10) Do you have any kind of allergy to the nose, such as hay fever?
- (11) Have you ever had eczema or some other kind of skin allergy?

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