

Agreement of specific IgE and skin prick test in an unselected cohort of two-year-old children

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Abstract The objective of this study was to evaluate the agreement between specific IgE (sIgE) and skin prick test (SPT), and the possible association between total IgE concentration and allergy-related disorders, when performed in an unselected cohort of 353 two-year olds. Median total IgE was within the reference value for two-year-old children regardless of the presence or absence of allergy-related disorders. 18.7% of the children had one or more positive reactions to SPT and/or sIgE in a panel of 12 allergens. Agreement between SPT and sIgE was variable, being best for peanut and poorest for milk. Conclusion: In young children total IgE is of limited value when

evaluating allergy-related disorder. The lack of agreement among the positive tests of the sIgE and SPT for some allergens imply that these tests should not be used interchangeably, and both tests should probably be used complementarily when diagnosing atopic sensitization in small children.

Keywords Total IgE · Specific IgE · Skin prick test · Sensitization · Child · Atopic eczema · Allergic rhinoconjunctivitis · Asthma · Diagnostic agreement · Kappa

Introduction

In Trondheim, Norway, more than every fifth two-year-old child has been subject to allergy testing [23]. Allergen-specific tests like the skin prick test (SPT) and specific IgE (sIgE) immunoassays can establish whether the hypersensitivity is IgE-mediated, indicate causative allergens and are prerequisites for allergen-specific therapy [1, 9, 13]. Although several studies find good observed agreement between SPT and sIgE results, others have shown divergence [3, 5, 12, 14, 17]. Most of the previous studies have been performed in selected populations and several differences in the studies make it difficult to compare. Even so, in clinical praxis, SPT and sIgE are often used interchangeably [13].

In contrast to specific IgE tests, the clinical value of measuring the total IgE concentration is more questionable. Although a high total IgE concentration is associated with allergic asthma, there is considerable overlap between total IgE concentration in healthy persons and in patients with allergy-related disorders [4, 11, 15]. On the other hand, a low total IgE concentration has been proposed as a predictor for identifying nonsensitized patients [21].

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The objective of this study was to evaluate the agreement between sIgE and SPT and the possible association of total IgE concentration and allergy-related disorders, when used in an unselected birth cohort of two-year-old children.

Materials and methods

Study population

The Prevention of Allergy among Children in Trondheim (PACT) study is a large birth cohort intervention study aiming to reduce the incidence of allergy-related disorders among children. All who gave written informed consent to participate, and had undergone clinical examination in two substudies of the PACT study: the “Immunology and Microbial study in PACT” (IMPACT) and “The Probiotic study in PACT” (Pro-PACT), were included in this study. These studies are described in detail elsewhere [8, 22–24]. The study population inclusion is summarized in Fig. 1. Briefly, 720 women were recruited during pregnancy to participate in the IMPACT study. When their offspring reached 2 years of age, 441 children were still participating and invited to the 2 years clinical examination. Three hundred ninety children attended. Of some 1,200 invited pregnant women to the Pro-PACT study, 415 accepted the invitation. Two hundred seventy-eight attended the clinical examination at 2 years of age. The total study population thus consisted of 668 children.

Clinical interview and physical examination

A paediatrician or a dermatologist performed a structured clinical interview and examination. Atopic eczema was

diagnosed according to the UK working party’s criteria, and the severity was assessed in accordance with the Nottingham Eczema Severity Score (NESS) [10, 27]. Due to lack of diagnostic criteria for allergic rhinoconjunctivitis and asthma in two-year-old children, the physician used an 8-point visual analogue scale (VAS) to evaluate whether the child had any of the allergy-related disorders under investigation. A score of eight indicated that the physician was certain that the child had the respective disease. Presence of allergy-related disorders was assigned when a score of eight for either allergic rhinoconjunctivitis or asthma was given, or UK criteria for atopic eczema were fulfilled. VAS was also assigned for atopic eczema to further subdivide those who did not fulfil the UK criteria. A score of zero was categorized as “no symptoms or signs of allergy-related disorder”. An intermediate score between 0.1 and 7.9, and not fulfilling the UK criteria for atopic eczema, was grouped as “possible, but not clinically certain allergy-related disorder”.

Allergen-specific tests and total IgE

Allergen-specific IgE and the SPT were evaluated for 12 frequent sensitizing allergens in children in our geographic area. Food allergens: egg white (F1), milk (F2), fish (F3), peanut (F13), hazelnut (F17). Inhalant allergens: dog (E5), cat (E1), birch (T3), timothy (G6), mugwort (W6), *Cladysporium herbarum* (M2) (mould), *Dermatophagoides pteronyssinus* (D1) (mite). Serum samples were analyzed for total IgE and sIgE using the Immulite 2000 methodology (Siemens Healthcare Diagnostics, Deerfield, Ill.). The reference value for total IgE in two-year-old children, specified by the manufacturer, was 0–45 kU/L. The

Fig. 1 Study participants. Six hundred sixty-eight two-year-old children from an unselected population participated in the allergy study. The flowsheet show the distribution of study participants. Only one attempt of venepuncture was permitted that resulted in no or too small sample volume to analyze all the sIgE in 246 children. For an additional 70 children, SPT results were incomplete. Complete results for clinical examination, specific IgE (sIgE) and skin prick test (SPT) were available for 352 children, and all variables, including total IgE were available for 339 children

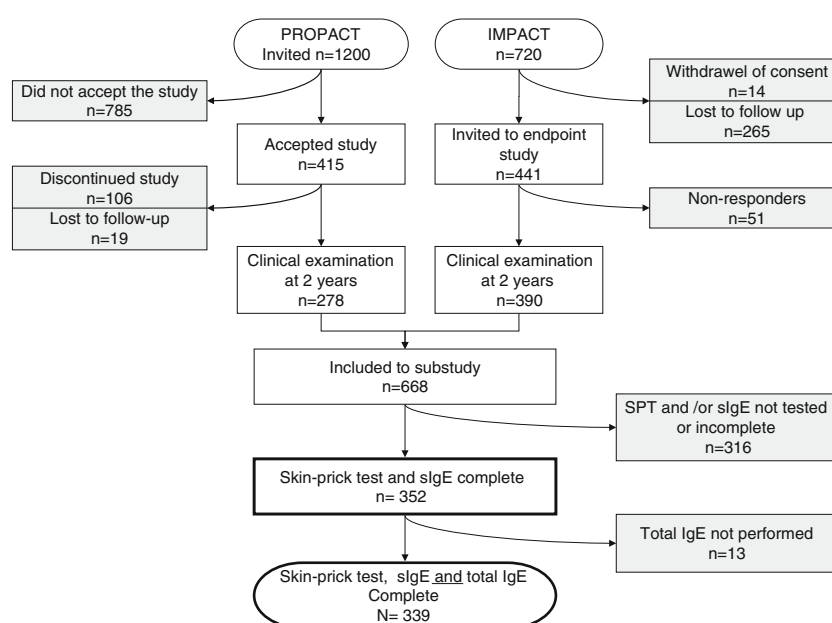


Table 1 Gender and allergy-related disorder in children with complete and not complete datasets. $N=668$

		Complete datasets $N=352$		Not complete datasets $N=316$	
			(95% CI)		(95% CI)
Mean age (months)		26.6	(26.1–26.6)	26.3	(26.3–26.8)
Gender	Boys (%)	48.3	(43.0–54.0)	50.6	(45.0–56.0)
	Girls (%)	51.7	(46.5–57.0)	49.4	(43.8–54.9)
Allergy-related disorder	Eczema (%)	19.9	(15.7–24.1)	17.4	(13.2–21.6)
	Asthma (%)	4.3	(2.1–6.4)	3.8	(1.7–5.9)
	Allergic rhinoconjunctivitis (%)	0.6	(–0.2–1.4)	0.9	(–0.1–2.0)

detection limit for sIgE tests was 0.1 kU/L. Concentrations of 0.35 kU/L or above were regarded as positive. SPT allergen extracts were purchased from Soluprick® (ALK-Abello, Copenhagen, Denmark) except for milk where undiluted fresh skimmed milk was used. Fresh skimmed milk for SPT was used as it is the routine method of milk SPT at the Paediatric Department, and the use of fresh food seems to give better responses [19]. For the other food allergens, fresh food was not implemented, thus commercial extracts were used.

Two experienced study assistants performed the SPTs. Parents were asked to cease antihistamine medication and to avoid steroid creams on forearms for their children 1 week prior to testing. The twelve allergens, two histamine controls (one on each arm) and one diluents–negative control (NaCl) were applied on the volar surface of both forearms, always starting with the right forearm. The tests were read after 15 min, and the sum of the longest diameter and the diameter perpendicular to its midpoint divided by two were recorded. In the presence of a positive control, a mean diameter at least 3 mm greater than the negative control was considered positive.

The child was considered sensitized if the SPT and/or the sIgE tests were positive for at least one allergen.

Ethics

The study was performed according to the Helsinki declaration. The Regional Committee for Medical Research

Ethics for Central Norway approved the study (Ref. 097–03). The study was granted license by the Norwegian Data Inspectorate to process personal health data, and one of the parents signed a written informed consent form. The Current Controlled Trials registration is ISRCTN28090297.

Statistics

Categorical data were analyzed using the Chi-square test, and continuous data were analyzed using the *t*-test or Mann–Whitney *U* tests. Agreement was given as observed agreement, proportional agreement of negative and positive tests, and kappa statistics were applied. The Spearman test was applied to evaluate correlation. All data were analyzed using the PC program package SPSS 15.0 (SPSS, Inc. Chicago, Ill.).

Results

Study population

Complete test results for SPT and sIgE were available for 352 children. In additional 13 children, all tests except for the total IgE concentration were completed; these children were excluded when evaluating variables related to the total IgE concentration, but otherwise included. There was no significant difference in the distribution of age, gender or

Table 2 Total IgE concentration and proportion of sensitized children according to allergy-related disorders in two-year-old children. $N=339$

Allergy-related disorder	n (%)	Sensitized		Total IgE, kU/L	
		n (%)	(95% CI of proportion)	Median	(95% CI)
No allergy-related disorder (VAS=0)	191 (56.3)	19 (9.9)	(6.0–14.6)	8.0	(6.1–9.0)
Possibly but not clinically certain allergy-related disorder (VAS=0.1–7.9)	77 (22.7)	19 (24.7)	(15.4–34.6)	13.0	(7.9–21.5)
Eczema (UK criteria)	70 (20.6)	24 (34.3)	(23.8–45.2)	11.1	(6.8–17.8)
Asthma (VAS=8)	15 (4.4)	4 (26.7)	(6.3–50.0)	27.7	(5.3–104.1)
Allergic rhinoconjunctivitis (VAS=8)	2 (0.6)	1	–	622.2	–

Table 3 Frequency of positive skin prick test (SPT) and specific IgE (sIgE) tests, and agreement of SPT and sIgE, for 12 allergens in two-year-old children. *N*=352

	sIgE+and SPT+	sIgE+and SPT−	sIgE−and SPT+	sIgE−and SPT−	Observed agreement	Proportional agreement of positive tests	Kappa	(95%CI)
Egg	10	30	0	312	0.91	0.40	0.37	(0.20–0.54)
Milk	2	15	1	334	0.95	0.20	0.19	(0.0–0.42)
Peanut	10	2	0	340	0.99	0.91	0.91	(0.78–1.0)
Hazel	5	2	3	342	0.99	0.67	0.66	(0.38–0.94)
Fish	1	3	0	348	0.99	0.40	0.4	(0.0–0.94)
Dog	5	7	0	340	0.98	0.59	0.54	(0.19–0.89)
Cat	3	5	0	344	0.99	0.55	0.58	(0.30–0.86)
Birch	6	9	0	337	0.97	0.57	0.56	(0.31–0.82)
Timothy	1	1	1	349	0.99	0.50	0.5	(0.0–1.0)
Mugwort	0	0	0	352	–	–	–	–
Mite	0	0	0	352	–	–	–	–
Mould	0	0	0	352	–	–	–	–

symptoms of allergy-related disorders between participants with complete and incomplete datasets (Table 1). The eczema severity was predominantly mild with NESS score below nine for 83% of those with complete datasets and 69% for those with incomplete. The difference was not significant.

Total IgE concentration and sensitization

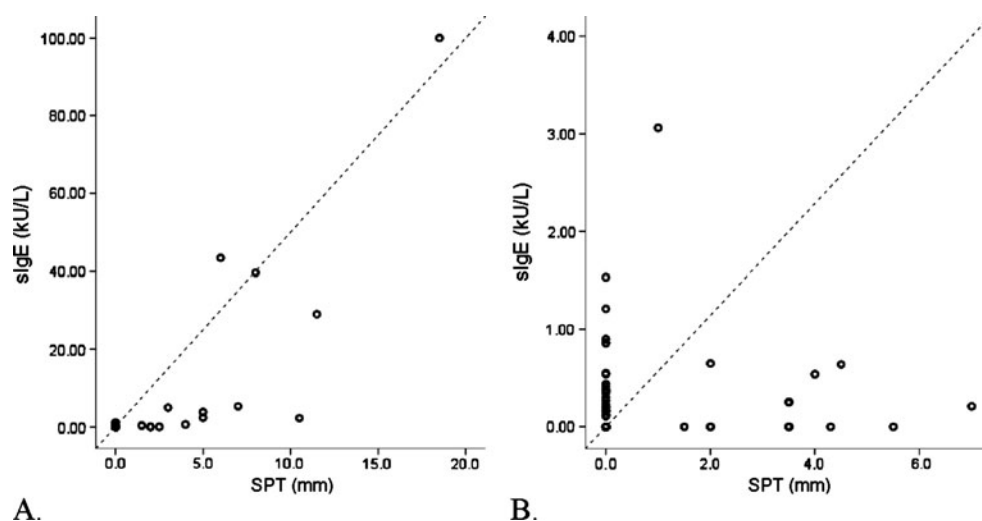
Total IgE concentration and frequency of sensitization according to symptoms of allergy-related disorders is presented in Table 2. Sixty-six children (18.7%) were sensitized (positive sIgE and/or SPT). Fifty-five children (15.6%) were sensitized against food allergens, 26 (7.4%) against inhalant allergens and 15 children (4.3%) against both food and inhalant allergens. The proportion of sensitized children (positive sIgE and/or SPT) increased

with higher concentrations of total IgE. Some 8.4% of the 178 children with total IgE concentrations below 10 kU/L, and 60.9% out of 23 children with concentrations above 100 kU/L were found to be sensitized.

Agreement between allergen-specific IgE and SPT

The agreement between sIgE and SPT is shown in Table 3. The proportional agreement of positive tests for sIgE and SPT varied among the 12 allergens. Using 0.70 kU/L as cutoff for sIgE increased the proportional agreement of positive tests when testing for dog and cat, but the proportional agreement was unchanged or even decreased for the other allergens (data not shown). The correlation between sIgE tests and SPT for peanut was good, but the remaining allergens displayed weaker correlation. Data for selected allergens are shown in Fig. 2.

Fig. 2 Correlation between SPT and sIgE for selected allergens: peanut and milk. The correlation was best for peanut (shown in **a**) and worst for milk (shown in **b**). Spearman's Rho respectively: -0.77 and 0.32



Discussion

This study showed a relatively poor association of total IgE with allergy-related disorders. Although the observed agreement of SPT and sIgE was good, and comparable with some other studies, the agreement among the positive test results was poor [3, 5, 7, 12, 17]. The median total IgE concentration was lower for eczema than for asthma. However, as severity scoring for asthma was not included in this study, it was not attainable to explore whether differences in severity could explain the difference in total IgE. Opposite many other studies, this is a study on an unselected population where lower total IgE and less severity of allergies may be expected [22]. As a consequence, the differences are less clear. The low total IgE levels in this study population are, however, relevant for family practitioners often meeting children with mild symptoms. This study may, therefore, be a supplement to other studies focusing on selected cohorts and more severe eczema.

A limitation to the study is that in 47% of the children, the analysis of either SP Tog sIgE was not complete, and they were, therefore, not included in the calculations. The main causes were refusals to have blood drawn, dry taps, and not enough amount of serum to complete all the analysis, as only one trial of venepuncture was permitted. However, as there was no significant difference in the clinical symptoms between the two groups, we consider the results valid. The prevalence of positive SPT and/or sIgE in our study was within the range published in other studies [16, 18]. We confirmed the dominating role of milk and egg sensitization, and eczema as the most common allergy-related manifestation at this age [25]. Ideally, sensitization to allergens should have been verified by double-blinded placebo-controlled challenge. This was, however, not within the scope of this study.

Our findings confirm that total IgE was more closely linked to atopy, than to clinical symptoms of allergy [20]. Total IgE was a poor screening test for sensitization as total IgE lower than 10 kU/L [21] did not preclude sensitization. A significant proportion of the population without allergy-related disorders was sensitized, underlining the point that positive results of SPT or sIgE only imply sensitization, and not necessarily clinical allergy [2, 6, 18].

There are several plausible explanations for the poor agreement between SPT and sIgE. It seems reasonable that the results of biologically different methods deviate from each other. However, the sources of allergen extracts differ for different producers and may cause divergent results. As a consequence a comparison is only valid for the methods used. Significant differences are shown among different sIgE immunoassays [19, 26, 28]. IgE analysis using other established methods may have shed some light on the cause

of this divergence; however, due to limited amounts of serum this was not possible. For SPT, although the commercial extracts have the advantage of comprehensive standardization, it may be that fresh foods may have resulted in more congruent results with sIgE [19]. However, performing SPT both with commercial extracts and fresh foods were not in the scope of this study.

Conclusion

In conclusion, the findings of this large study on an unselected population of two-year-old children confirms that total IgE is of limited value when evaluating allergy-related disorders in early childhood. The lack of agreement among the positive tests of the sIgE and SPT for some allergens, imply that these tests should not be used interchangeably. Instead, the tests should be used complementarily; if the first allergen-specific tests applied, SPT or sIgE, are inconsistent with clinical history, the test result should be confirmed by the alternative method. Both SPT and sIgE should be used when investigating the sensitization of young children.

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