

Variability of total serum immunoglobulin E levels from birth to the age of 10 years. A prospective evaluation in a large birth cohort (German Multicenter Allergy Study)

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Summary

Background Many environmental factors influence the concentration of total serum IgE (tIgE); however, tIgE synthesis is believed to be under strong genetic influence. Multiple genetic studies on tIgE regulation have been performed. For these population-based studies tIgE was commonly determined at one time-point, assuming that tIgE phenotypes (adjusted for age and gender) are stable over time.

Objective We assessed correlations of tIgE levels from birth to the age of 10 years in the birth cohort MAS (Multicenter Allergy Study; $n = 1314$).

Materials and methods We determined cord-blood IgE levels, total and specific IgE at the age of 1, 2, 3, 5, 6, 7, and 10 years. Spearman correlation coefficients were calculated for tIgE at different time-points. All analyses were performed in the entire cohort, adjusted for gender, as well as in non-atopic children only.

Results tIgE percentiles increased steadily from birth to the age of 10 years with higher values for boys than for girls at each time-point. tIgE values from birth to 3 years of age correlated poorly with tIgE levels at 10 years ($r < 0.5$). However, good correlations ($r > 0.8$) were observed for tIgE concentrations at 6, 7 and 10 years. The same results were observed when the analyses were limited to non-atopic children.

Conclusion In childhood, tIgE levels underlie remarkable variation over time even in the absence of atopy. For cross-sectional population-based genetic and epidemiologic studies, tIgE values of children <5 years should be interpreted with caution since these values correlate poorly with tIgE levels later in life.

Keywords allergy, children, cohort, IgE, percentile

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Introduction

Elevated total serum IgE (tIgE) levels are characteristic for atopic disease and are believed to be under strong genetic influence [1–4]. However, many environmental factors are known to influence IgE synthesis, which hamper genetic studies and may explain some of the controversial findings of linkage and candidate gene studies on tIgE levels reported to date (summarized in Ref. [5]).

For genetic and epidemiologic cross-sectional studies, total and specific IgE concentrations are mostly determined at one-time point in a given study population. For population-based studies tIgE is adjusted for age and gender, since tIgE values increase from birth to the age of 25–30 years and decline

thereafter, and higher values are observed in boys than in girls [6–10]. However, it is unclear whether tIgE values adjusted for age and gender are stable from infancy to adulthood. We aimed to assess the longitudinal course of tIgE levels during the first 10 years of life in a large birth cohort and analysed correlations between tIgE levels at eight prospective time-points. Total tIgE percentiles during the first 5 years of life have been described by our group previously [11].

Selection of extreme phenotypes is generally recommended for genetic studies of complex traits, since these are believed to be under strongest genetic influence [12]. Therefore, we also evaluated the stability of very high and very low tIgE phenotypes during the first 10 years of life.

Materials and methods

Study population

The MAS cohort has been described in detail previously [11, 13]. Of 7609 infants born in six obstetric departments of West

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Germany (Berlin, Munich, Mainz, Düsseldorf, Freiburg) between January and December 1990, 499 infants (38% of the MAS study population) were included based on a double-positive family history and/or cord-blood IgE values above 0.9 kU/L, 815 infants (62%) were selected at random from the remaining newborns. These children (n initially 1314) were followed from birth to the age of 10 years in order to identify risk factors for atopic disorders and to describe the natural course of atopy-associated traits. Study participation rate was 60.0% at the age of 10 years. Yearly visits included physical examinations, standardized interviews and detailed questionnaires on symptoms of allergic disease. The tIgE levels were determined in cord blood, total and specific IgE against common food and inhalant allergens (egg, milk, soy, wheat, cat, dust mite, grasses, birch) were analysed at the age of 1, 2, 3, 5, 6, 7, and 10 years (± 6 weeks; CAP-RAST-FEIA, Pharmacia, Uppsala, Sweden) in 40.0–61.0% of the total study population. Remaining serum was stored at -20°C . From 132 children, blood samples were collected at each time-point. Each year percentiles for tIgE were calculated for male and female study subjects (see also Ref. [11]). Very high and very low IgE phenotypes were defined for a specific time-point when tIgE levels were above the 90th percentile or below the 10th percentile, respectively. Since most IgE values at birth (cord blood) were below the detection limit [14], only a very high IgE phenotype could be defined at birth.

In a subset of samples with $>50\%$ change of percentiles between two time-points tIgE values were reanalysed from stored serum to confirm the high intraindividual variability.

Parasitic infections are rare in Germany; however, IgE values from children that had a documented helminthic infection ($n = 9$) were excluded from the analyses for values determined at the visit before and after infection.

For statistical analyses, Spearman Correlation Coefficients were calculated (SAS 8.02).

Results

The tIgE concentrations increased steadily from birth to the age of 10 years with higher values in boys than in girls (Fig 1a and b). The IgE percentiles were quite similar when only children with blood samples collected at each time-point ($n = 132$) were included in the analysis (data not shown).

Table 1 shows correlations between tIgE values at different time-points from birth (cord blood) to the age of 10 years. Cord-blood IgE correlated poorly with tIgE values at later time-points ($r < 0.3$). Also, tIgE levels determined before the age of 5 years did not correlate well with values at the age of 7 and 10 years ($r = 0.42$ – 0.68). Good correlations were observed between tIgE values at age 6, 7 and 10 years ($r \geq 0.8$).

To evaluate the stability of extreme tIgE phenotypes, only individuals with tIgE above the 90th and below the 10th percentile at respective time-points were analysed prospectively. Again, before the age of 5 years even these extreme phenotypes appeared to be transient in many cases. For example, only 53.6% of the children with tIgE levels above the 90th percentile at age 1 also expressed a very high tIgE phenotype at age 2.

Figures 2a–c show prospective individual tIgE courses (based on percentiles) in children with very high IgE levels at

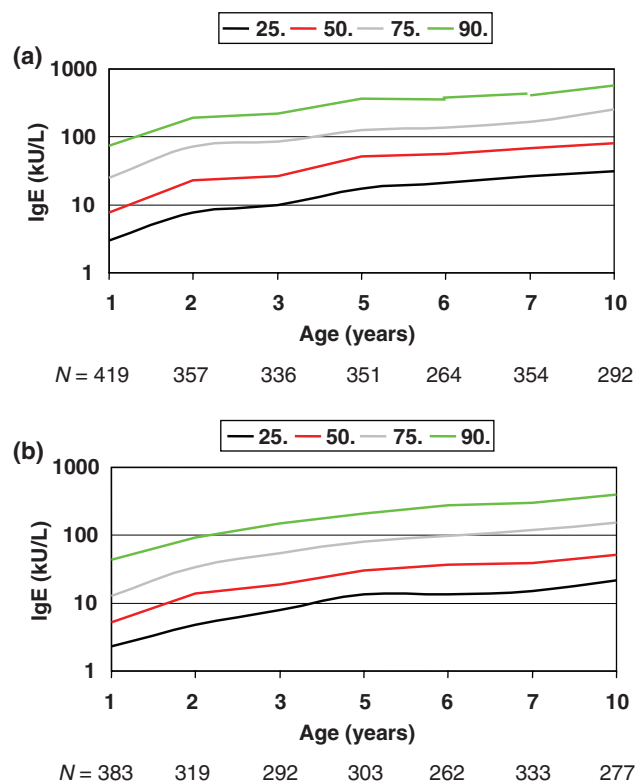


Fig. 1. (a) Percentiles for total IgE from 1 to 10 years of age (male). Percentiles were calculated based on all male children with available serum samples at respective time-points. (b) Percentiles for total IgE from 1 to 10 years of age (female). Percentiles were calculated based on all female children with available serum samples at respective time-points.

Table 1. Correlations between tIgE levels from birth (cord blood) to the age of 10 years

Age (years)	0	1	2	3	5	6	7	10
0	1.00	0.39	0.25	0.29	0.24	0.27	0.25	0.25
	1261	771	649	603	628	503	661	552
1		1.00	0.66	0.62	0.54	0.54	0.51	0.43
		802	541	486	494	388	519	438
2			1.00	0.74	0.65	0.59	0.57	0.42
			676	490	468	368	481	382
3				1.00	0.79	0.72	0.68	0.54
				628	442	368	455	361
5					1.00	0.89	0.85	0.71
					654	405	511	420
6						1.00	0.89	0.80
						526	439	338
7							1.00	0.85
							687	476
10								1.00
								579

Upper lanes indicate correlation coefficients, lower lanes the number of children with tIgE measurements at respective time-points. tIgE, total serum IgE.

birth (cord blood; Fig. 2a), at the age of 12 months (Fig. 2b) and at the age of 6 years (Fig. 2c) to the age of 10 years. Increased tIgE levels at birth (Fig. 2a) and 12 months (Fig. 2b) did not correlate well with very high IgE phenotypes at an

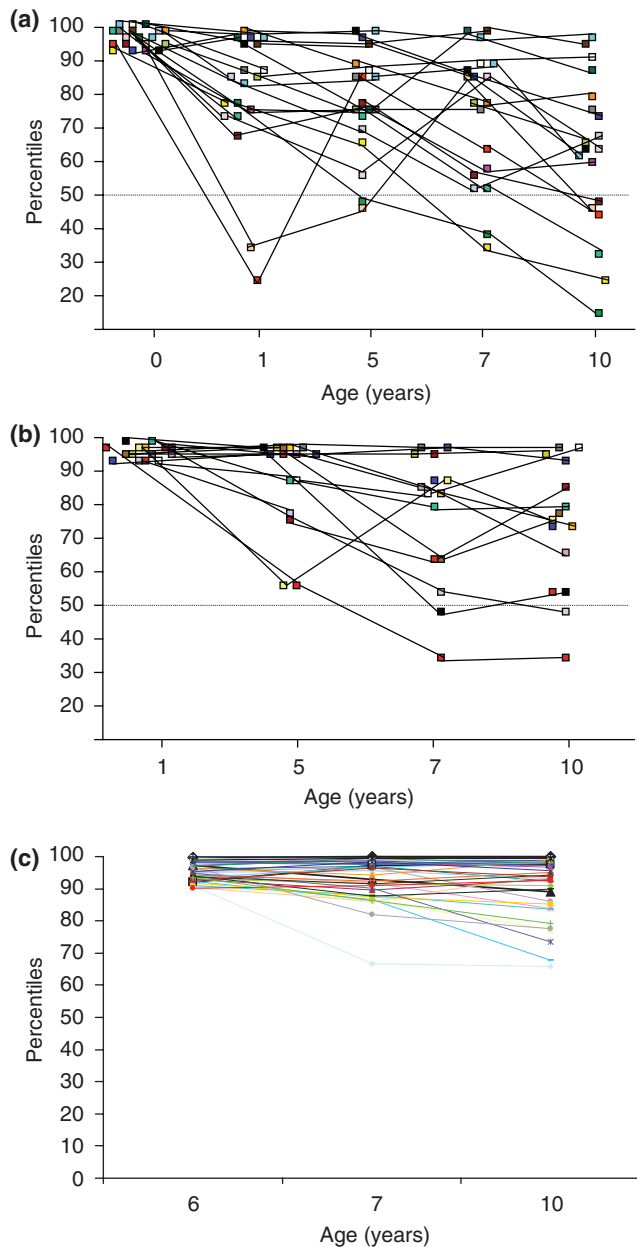


Fig. 2. (a) Longitudinal course of tIgE percentiles in children with cord-blood IgE > 0.9 kU/L and blood samples available for all time-points ($n = 19$). (b) Longitudinal course of tIgE percentiles in children with very high IgE (> 90th percentile) at 12 months and blood samples available for all time-points ($n = 15$). (c) Longitudinal course of tIgE percentiles in children with very high IgE (> 90th percentile) at 6 years.

older age. However, 83% of children with very high tIgE at the age of 6 years (Fig. 2c) remained above the 80th percentile at 7 and 10 years; the remaining children were all above the 65th Percentile at 7 and 10 years of age. Similar results were observed for very low IgE phenotypes (data not shown).

Since different levels of specific IgE may underlie the high degree of longitudinal intraindividual variability of tIgE, we performed the same analyses in non-sensitized children. All children with specific IgE (> 0.35 kU/L) against at least one out of nine common food and inhalant allergens (egg white, milk, soy, wheat, birch, grasses, house dust mite, cat and dog) were excluded from the analyses. As expected, tIgE levels and

Table 2. Correlations between tIgE levels from birth (cord blood) to the age of 10 years in non-atopic children only

Age (years)	0	1	2	3	5	6	7	10
0	1.00	0.35	0.20	0.32	0.24	0.18	0.23	0.28
	1261	591	470	431	393	290	384	315
1		1.00	0.59	0.51	0.39	0.44	0.40	0.34
		610	331	290	259	181	256	204
2			1.00	0.68	0.60	0.58	0.58	0.32
			486	289	235	169	218	175
3				1.00	0.75	0.68	0.63	0.46
				447	240	181	221	175
5					1.00	0.85	0.82	0.67
					411	197	252	196
6						1.00	0.84	0.76
						303	217	150
7							1.00	0.80
							399	230
10								1.00
								329

Upper lanes indicate correlation coefficients, lower lanes the number of children with tIgE measurements and no detectable specific IgE at respective time-points.

tIgE, total serum IgE.

respective percentiles were lower than in the total study population (data not shown). However, a similar degree of variability in young children was observed as previously in the total study population. Again, good correlations were observed between tIgE values at 6, 7, and 10 years (Table 2). Extreme IgE phenotypes (based on the 90th and 10th percentile of non-atopic children) were analysed prospectively. Extreme phenotypes during the first 3 years were mostly transient whereas children 6 years and older remained within the upper or lower 20th percentiles in more than 80% of cases, respectively (data not shown).

Discussion

In a large German birth cohort, we described the course of tIgE levels from birth to the age of 10 years. As expected, IgE levels increased from birth to the age of 10 years and were higher in males compared with females.

We observed a marked intraindividual longitudinal variability of tIgE in young children. tIgE values within the first 3 years of life correlated poorly with IgE values at the age of 7 and 10 years. Even extreme tIgE phenotypes (< 10th P./ > 90th P.) in young children did not remain stable over time in the majority of cases. However, tIgE levels in school age children (6, 7 and 10 years) correlated well. In this age group, very high and very low tIgE levels were also far more consistent.

Methodically, aspects with regard to IgE measurements cannot explain the marked variability observed in this longitudinal study since coefficients of variations within assay and between assay are 4–8% and 2–6%, respectively (Pharmacia, Uppsala, Sweden, CAP System, IgE FEIA, operator manual).

The poor correlations between total IgE levels could presumably be biased by varying participation rates at different

follow-up visits. Significant higher participation rates were observed in probands with a positive family history for atopy and a high level of parental education. Lower participation rates were seen for children with parental smoking. No differences were observed for children with one or more older siblings or between male and female participants. However, correlations between total IgE concentrations in pre-school-children were equally poor when children with detectable specific IgE levels were excluded from the analyses. Therefore, factors associated with an increased risk for atopy (positive family history, parental education) are unlikely to have a major effect on the data presented.

Also, the correlations did not improve at all after adjustment for sex or when male and female children were analysed separately (data not shown), indicating that gender-specific differences in total IgE values do not explain the poor correlations of total IgE concentrations within the first years of life.

Twin studies suggest that both cord-blood IgE and tIgE levels in older children and adults are under strong genetic control [1, 3, 15–17]. Jacobsen et al. [1] determined tIgE in mono- and dizygotic twin pairs at birth, and at the age of 6 and 9 years. Heritability accounted for 92% of cord-blood IgE levels and 78% of tIgE in 6- and 9-year old twins. However, no correlation was observed between cord blood IgE and tIgE levels later in childhood, which supports our present observations. The authors speculated that different genetic factors may determine tIgE levels at different time-points [1]. No other studies evaluated tIgE levels in mono- and dizygotic twins at different ages. In particular, no tIgE studies in pre-school twin pairs have been conducted to test whether the effect of genetic factors is less pronounced in early childhood. We assume that gaining immunologic competence against viral and bacterial antigens during the first years of life may – at least partly – explain the weak correlation of tIgE values at age 1–3 with values at age 7 and 10 years.

Since increased tIgE is characteristic of atopic disorders, many studies have been conducted to identify genes involved in IgE synthesis. Various variants in many candidate genes have been related to increased or decreased IgE levels (for review see Ref. [5]). Few studies could be confirmed in independent study populations. Those studies with highly significant results with regard to tIgE levels either included a very large number of study subjects [18] and/or selected (inbred) populations living in isolated areas [19] to minimize a confounding effect of environmental factors. These studies by Graves et al. [18] and Marsh et al. [19] suggest that different genetic factors regulate the synthesis of total (non-cognate) and specific (cognate) IgE synthesis. Strongest linkage on chromosome 5q and allelic associations (*IL-13* variant) were observed, when atopic individuals were excluded from the analyses. We therefore assessed the stability of tIgE phenotypes in children without sensitization to food or inhalant allergens at respective time-points. However, the same degree of variability in young children could be demonstrated.

We conclude that pre-schoolchildren should not be included in studies on the genetics of tIgE since these values (adjusted for age and gender) appear to correlate very poorly with those measured later in life.

Furthermore, this study supports previous reports suggesting that the determination of tIgE from cord blood or during the first years of life may not be helpful for the diagnosis or prediction of atopy [20–22].

The follow-up of the MAS-cohort will demonstrate whether tIgE percentiles remain constant in teenaged individuals.

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