

Review article

IgE in neonates is not suitable for general allergy risk screening

Kjellman NIM. IgE in neonates is not suitable for general allergy risk screening.
Pediatr Allergy Immunol 1994; 5: 1–4. © Munksgaard 1994.

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Received August 30, 1993

Accepted August 30, 1993

The introduction of the radio-immuno-sorbent test (RIST) allowed the demonstration of a relationship between elevated levels of Immunoglobulin E (IgE) and allergic diseases and also made it possible to assess genetic and environmental effects on IgE production in healthy and allergic subjects (summarised in (1)). No correlation was found between IgE concentrations in cord blood and corresponding maternal serum samples.

In the beginning of the 1970s more sensitive methods for the determination of serum IgE concentrations became available, e.g. the paper disc radio-immunoassay (Phadebas IgE PRIST®) (2). The PRIST slightly underestimated the true values at low IgE concentrations (3). The finding that the risk for subsequent atopic disease in previously healthy infants and children was 6–10 times higher when the IgE concentration was in excess of the geometrical mean + 1 standard deviation (SD) (4) raised the possibility that it would be possible to identify, among healthy new-born babies, those with a genetically predetermined hyper-production of IgE and who were going to develop allergy/atopic disease within the next few years. A predictive capacity of high serum IgE concentrations was found also in new-born babies (5), supporting the notion of early screening for allergy risk babies.

To evaluate the predictive capacity of neonatal serum IgE determination we therefore started to collect all consecutive cord blood samples from deliveries in Linköping in December, 1974. It was possible to get cord blood IgE determinations with Phadebas IgE PRIST and a follow-up by questionnaire at 18

months of age from 1701 of 1884 (90.3%) live born babies in the community of Linköping (6). Clinical examination was performed in all children with suspected allergy/atopic disease and all subjects with a high neonatal IgE concentration. Unfortunately, no control group was investigated. Subsequently, 1654 of the cohort of 1701 babies (97%) took part in a follow-up by questionnaires up to 11 years of age (7–10). At this age, randomised samples were drawn from the groups with high and low neonatal IgE concentrations for clinical investigation and assessment of the reliability of our questionnaires. All children with asthma in the cohort have been subject to follow-up for 14 years (11). Our results confirmed that a high cord blood IgE level considerably increases the likelihood to develop atopic disease during infancy. This was also true for atopic disease developing at any age up to 11 years of age. Questionnaire data were reliable regarding current atopic disease but not for cumulative disease.

The cut-off was initially chosen at 1.3 kU/l as it represented the geometric mean + 2 standard deviations (SD) of children remaining healthy from birth to 18 months of age (5). The risk was about 10 times higher of developing atopic manifestations before 18 months of age for babies with an IgE above, compared with below, this cut-off level. In comparison, the risk was only doubled in children with a positive immediate family history of allergy. During the follow-up, the sensitivity and discriminatory power was found to be higher at a neonatal IgE concentration of 0.9 kU/l (10), which was also the cut-off of the PRIST used at that time, and approximately

corresponded to the geometric mean + 1 SD using an improved methodology for the IgE determinations (5). During the follow-up period, the sensitivity of a neonatal IgE screening with cut-off at 0.9 kU/l gradually fell to an unacceptable level at 11 years, when only every fourth child with allergic disease at any time was identified by an elevated cord blood IgE concentration (8).

The risk of developing any atopic manifestation up to 11 years of age was doubled in children with an elevated, compared with normal, neonatal IgE concentration, but the risk for bronchial asthma was increased by a factor 5–6 (8). Cord blood IgE determination was also of more help in finding those with several atopic diseases and with long-lasting problems than those with only one atopic manifestation and problems during a short period (12). The sensitivity of neonatal IgE screening to detect forthcoming asthma or multiple atopic manifestations was, however, too low to justify its use in a general screening (13). Neonatal IgE was, therefore, recommended as a means to select cases for clinical trials of allergy preventive measures, as about four of five children with an elevated cord blood IgE concentration and not subject to any prophylactic measures would develop at least one allergic manifestation up to 11 years of age (12).

The family history seemed slightly superior to neonatal IgE determination for screening up to age 11 (8). Only about half the group of children with an immediate family history of allergy did actually present allergic manifestations before 11 years of age, and many subjects developed allergic manifestations with no family history of allergy, showing that also a family history is a poor screening instrument.

New-born infants with a high cord blood IgE were likely to have higher IgE levels also at 18 months in comparison with those who had a low cord blood IgE concentration (6). There was however a poor correlation between neonatal IgE concentrations and those at 11 years of age (8). So, although an elevated neonatal IgE still had some predictive capacity when the children had reached 11 years of age, we had to realise, after a long and extensive study, that there seemed to be no rationale left for using neonatal IgE determination for general screening purposes (8).

Further confirmation of our initial hypothesis came already in 1975 from a group in California (14). They found higher IgE levels (as measured with a double antibody technique) during infancy in a group of children who later developed e.g. atopic eczema than among children who did not develop any atopic disease. A French group presented results of prediction based on cord blood IgE determination and maternal history of allergy (15, 16). They reported the cord blood test to be superior to the family history for predictive purposes. Many other

reports have been published since then, but, until recently, our cohort study was the largest. Most of the early published studies seemed to confirm that new-born babies with increased IgE concentrations were at considerably increased risk for early development of atopic disease (15, 17–19).

In recent years, several drawbacks of neonatal IgE determination have become apparent (20–30). The importance of the sampling technique has been highlighted. As many as 10% of samples may be contaminated with maternal blood (27, 28), unless precautions are taken to avoid this. Using our simple technique, i.e. free running of cord blood into a test tube after gentle wiping of the cord with a compress, contamination with maternal blood was detected by analysis of specific IgE (the same that had been found in corresponding maternal serum samples) in only about 2% of samples with an elevated cord blood IgE concentration.

Determination of IgA in cord serum has been advocated under the assumption that an elevated concentration proved contamination with maternal blood. However, it has later been demonstrated that there is also some foetal production of IgA (31). The wide-spread practice to exclude all sera with elevated IgA could therefore explain part of the lack of predictive capacity of elevated neonatal IgE concentrations in several later studies.

There is at present no ideal marker for contamination with maternal blood. Conversely to the results of some previous investigators (27, 28), there is probably no important difference between IgE concentrations in blood taken at 5 days of age and cord blood (Oldaeus et al., in preparation and (32)).

Much more is now known about factors other than contamination that may influence neonatal IgE concentrations. Certainly, genetic factors are one of the main determinants (20, 23, 33). There appears to be a slightly higher influence of maternal, compared with paternal, factors on the IgE concentration in a new-born baby. There may be some effect of ethnicity. Gestational age has little influence on IgE concentrations (26). Males have higher neonatal IgE concentrations than girls and season of birth may have some influence on the IgE level, not only in mothers but also in their new-born babies (20, 25, 26). Maternal intake of some drugs (progesterone, beta-blockers) seems to increase neonatal IgE concentrations (16, 34). Maternal smoking seems to affect cord blood IgE concentrations in accordance with a similar dose-response reported in adult smokers (35), i.e. increasing IgE concentrations are seen with the increasing number of cigarettes smoked up to a plateau level, and a further increase in the number of cigarettes achieves a reduction of IgE down to normal levels (Wahn, pers. comm.). This may explain some of the controversial results

presented, as the number of cigarettes actually smoked by the mother are usually not taken into account.

Many studies published in recent years, including some in cooperation with our group, have found "negative" results of neonatal IgE determination (22, 24, 27, 29, 30). A poor sensitivity and low positive predictive value of elevated cord blood IgE have been repeatedly demonstrated for the detection of children with any subsequent atopic disease. Some of the negative studies may have included too small groups (possible type II error). Some investigators used very wide definitions of atopy. Some papers show other flaws. An additional explanation for the poor predictive capacity of a high neonatal IgE concentration may be the institution of preventive measures, counteracting the genetic high risk factors. In essence, even well-performed recent studies have failed to support the concept of neonatal IgE determination as part of a general screening program.

In a large Danish study, when focusing on children with a clear-cut IgE-mediated disease as defined by both a typical history and an elevated serum IgE concentration at the time of diagnosis, it was confirmed that neonatal IgE determination is predictive of subsequent "allergic disease" (32, 36–38). When looking at the results, however, it is obvious that there are many false negative cases among the new-borns who later developed allergic disease, and a considerable proportion of those with a high IgE (now using 0.3 kU/l as cut-off) remained healthy. The study does, however, support the previous observation that a high neonatal IgE concentration is connected with later allergic disease. It confirmed that IgE determination in new-born babies is only suitable for selecting candidates for clinical trials of preventive measures.

So, in conclusion, we have to accept that total IgE determination at birth or later during the neonatal period is not suitable for general allergy risk screening. Papers published in the current issue of PAI support this standpoint. We will have to continue the search for tests or combinations of tests which allow early identification of babies at high risk for later allergy. These babies have to be identified before they have become sensitized, if preventive measures are to be considered in them.

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