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Immunoglobulin E in the sera of infants and children

by

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The serum IgE level has been studied from birth up to 14 years of age. The mean serum IgE concentration was found to be correlated with age. Parallel measurements in cord blood and maternal blood yielded a mean of 25 I.U./ml (range, 0—90 I.U.) for the former and one of 124 I.U./ml (range, 50-600) I.U.) for the latter. The normal IgE level ranged from 20 to 100 I.U./ml in infants and from 100 to 200 I.U./ml in children, but even values of 400 to 600 I.U. did not necessarily reflect a pathological condition. In the majority of patients with eczema, urticaria and spastic bronchitis, high IgE levels were measured. The highest individual and mean values were obtained in children harbouring intestinal helminths, though a normal IgE level also occurred in such patients. In coeliac disease the values were within normal limits.

Long before the protective mechanism of the human organism against antigenic substances had become known, the presence in the blood of some special substance has been assumed to be responsible for the often fatal hypersensitivity reactions [37]. Still, thorough studies of the immune substance have begun less than a decade ago [4, 5, 23, 25, 26] and IgE was the class of human immunoglobulin recognized last.

Studies of IgE have been made difficult by its low concentration in serum, its short half-life and the fact that its demonstration calls for very sensitive procedures. Owing to these difficulties, estimation of IgE has not become a routine and there are few data on IgE levels in infancy and childhood, and especially in the neonatal period [1, 3, 7, 8, 27, 39]. An attempt has therefore been made to clarify

1. the development of the serum IgE level in children;
2. the relation between maternal and fetal serum IgE levels;
3. the pathognomic value of the serum IgE titre in allergic conditions; and
4. the effect on IgE production of a decrease in local immune response (diminution or deficiency of IgA).

Material and Method

The patient material consisted of 80 healthy and 64 allergic infants and children. In 16 neonates, the cord blood was studied parallel with maternal blood. The time interval between blood sampling

and the measurements was as short as possible, since after prolonged storage erroneously low values are obtained [32]. In some cases, however, storage for a few days could not be avoided.

The IgE level of sera taken on an empty stomach was determined by the Phadebas kit (Pharmacia, Sweden). The serum samples and the standards were incubated with ^{125}I-IgE and anti-IgE antibody bound to Sephadex. After the reaction the bound antigen-antibody complex and the unbound fractions were separated by repeated washing and centrifugation, and the activity of the bound fraction was measured. The IgE concentration was estimated on the basis of a curve plotted from the different IgE standards of known concentration contained in the kit.

Results

Fig. 1. shows the IgE levels in the sera of healthy children. In cord blood the mean IgE content amounted to 25 I.U. The level shows a gradual elevation with age through a marked increase occurs only at the age of 6 to 8 years. After this time the IgE levels are similar as those measured in adults. In all age groups the physiological values range between wide limits. The mean IgE level was found to range from 20 to 100 I.U./ml in infancy and from 100 to 200 I.U./ml in childhood but values as high as

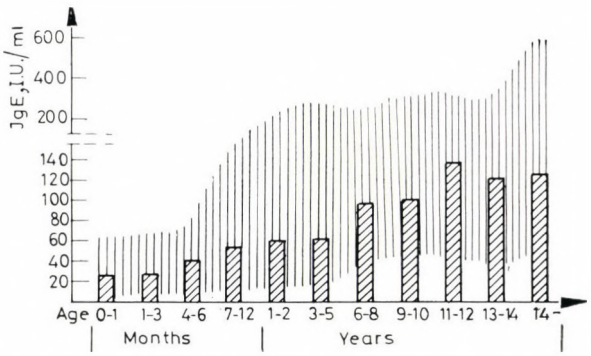

Fig. 1. Serum IgE levels in healthy children. Black column = mean value; lined area = limits

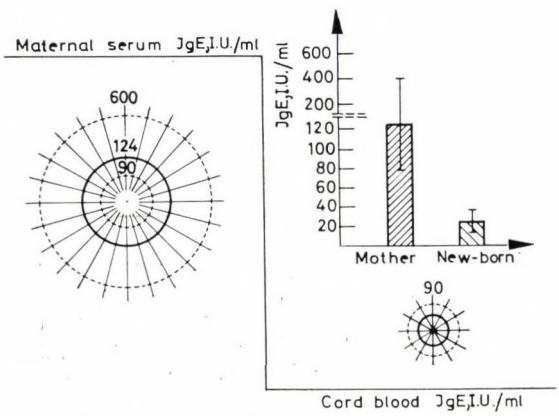

Fig. 2. Serum IgE values in 16 cord blood and maternal blood samples. Means ± S.D.

400 to 600 I.U./ml may occur in healthy children.

Fig. 2. shows the values for 16 neonates and their mothers. Despite the wide scattering, there was a marked difference between the two IgE levels; the maternal value fluctuated between 50 and 600 I.U./ml (mean, 124 I.U.) and the neonatal value ranged from 0 to 90 I.U./ml (mean, 25 I.U.). This showed clearly that the fetal IgE level is independent of the maternal one.

Individual serum IgE values measured in the acute phase of some untreated allergic diseases are shown in Fig. 3. The data seem to indicate that in the acute phase of certain diseases the serum IgE concentration may considerably exceed the upper limit of the normal level. This was the case with eczema, urticaria, seborrhoic dermatitis, spastic bronchitis and helminthiasis, although in some of these patients normal concentrations were measured. On the other

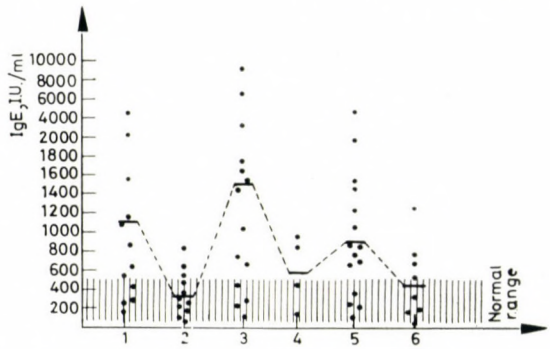

Fig. 3. Individual IgE values for allergic patients. 1. eczema-urticaria; 2. coeliac disease; 3. helminthiasis; 4. Schönlein-Henoch purpura; 5. spastic bronchitis; 6. subglottic acute laryngitis

Table I

Serum IgE levels in IgA deficient patients

Disease	No. of cases	IgA				IgE	
		Serum		Duodenal fluid		n	e
		d	a	d	a		
Helminthiasis	14	8	2	10	4	5	11
Coeliac disease	11	3	1	8	2	8	3
Other diseases due to malabsorption	7	4	–	7	–	5	2

a = absence
d = decreased
n = normal
e = elevated

hand, while in these diseases values of 1000 I.U. and higher are not rare, in other conditions likewise due to an allergic mechanism, e.g. coeliac disease, Schönlein—Henoch purpura and subglottic laryngitis, the elevation is moderate. In view of the small number of patients, a concentration characteristic of the majority of cases cannot be given, only the arithmetic means are shown in order to illustrate the tendency.

In Table I the serum IgE values for infants and children suffering from malabsorption are shown. In their serum and/or duodenal fluid the IgE concentration was low, or even absent. The serum IgE level showed great differences. In 80% of the helminthic infestations the IgE level was elevated, while in coeliac disease and other absorption disturbances the IgA/IgE ratio was less than 1:3.

Discussion

Since the clinical importance of IgE as a reagin consists in evoking a hypersensitivity reaction, its absence does not yet mean a pathological condition. Its study may, however, offer a certain help in the diagnosis of allergic and atopic diseases and in evaluation of the effect of the therapy applied. Apart from allergic processes, other diseases of the immune system may also influence the serum IgE concentration. In maturation disorders of the immune system, sex-linked agammaglobulinaemia, isolated IgA-deficiency, plasmocytoma, Waldenström macroglobulinaemia, paraproteinaemic myeloma, mucoviscidosis, rheumatoid arthritis, chronic nephritis, infectious mononucleosis, etc., the serum IgE level is very low or, on the contrary, remarkably high. Thus, a knowledge of normal values for healthy neonates, infants and children is indispensable not only in the diagnosis of allergic diseases, but also of several other diseases of the immune system. Moreover, similarly to the immunoglobulins having protective antibody properties, it may help to estimate the maturation and reactivity of the immune system.

IgE production starts at birth with a mean level of 25 I.U. and increases gradually until 10-14 years of age, when the mean adult level of about 200 I.U./ml is attained.

As to the IgE demonstrable in cord blood, its maternal origin seems to be contradicted by the following considerations.

a) As far as we know, of the immunoglobulins only IgG passes across the placenta in a notable amount.

b) The IgE concentration in fetal serum is independent of the maternal level [27, 41].

c) In contrast to IgG which is undoubtedly of maternal origin, the serum IgE titre increases after birth without any temporary decline. Considering its short half-life, this indicates that IgE is produced by the infant itself.

If the reagin present in the serum of the neonate is a protein formed independently of the mother, the question arises of the nature and site

of the stimulating allergen. The fetus is known to be capable of forming protective antibodies but *in utero* antibody production only takes place in response to some bacterial, viral or helminthic antigenic effect. The immune response to these stimuli may manifest itself in IgE production since this protein has been shown to represent the first immunoglobulin in the immune reaction [17]. Passage into the fetus of allergens inducing a specific IgE reagin production may also be assumed. The allergen may find its way through the materno-fetal blood circulation and the amniotic fluid, this being in connection with the fetal gastrointestinal tract which is certainly permeable for proteins.

The presence of IgE in the serum of the newborn may play a role in milk allergy. As discussed earlier [34] the reagin involved in the hypersensitivity reaction to cow's milk may be both IgE and IgG [14, 15, 22]. As in such cases the serum IgE level is low, this may be misleading as to the nature of the disease. Another question is whether in allergic diseases the IgE level is always elevated. The amount of circulating reagin depends on the quality of the allergen, on the site and duration of its effect, and also on the patient's age. For this and other reasons the level of the circulating reagin does not reflect truly the severity of the allergic reaction of the intreated patient in the acute phase of the disease. Even patients with atopic allergic disease may have normal IgE concentrations. In such cases it would be helpful to know the tissular event as the allergic reaction results from the binding to the specific antigen of reagin fixed to the corresponding tissue cells. At the same time the lack of increase in the IgE level may be due to the fact that the nutritive antibodies produced are reagins belonging to the IgG class [13-15, 22, 31]. Indeed, in gliadin-sensitive coeliac disease, the IgE concentration is normal or low [18, 33]. Though in the acute phase of atopic allergic diseases several thousand units of IgE are measured [11, 16, 20, 29, 35, 36, 42], the highest values are usually encountered in helminthic infections [2, 19, 28, 38]. The wide variation of the IgE level from normal to 9000 U of our patients with ascariasis or enterobiasis seems to support the observation that the reagin may remain normal in spite of the infestation. Though a number of parasites possess protein substances eliciting IgE-reagin production, the reaction might occur only in subjects whose HL = A system had been genetically coded for it [17]. Persistent urticaria in helminthic infections may be a manifestation of considerable reagin production. Thus, only an increased IgE level should be considered of diagnostic value; the serum IgE concentration seems to be more useful in estimating the effect of anti-allergic treatment [36].

IgE can be demonstrated not only in serum but also in other body fluids and secretions [6, 9, 20, 24, 43]. It is still not clear whether there exists

a local IgE system independent of the serum, as is the case with IgA. The facts that in a unit area of the mucosa of atopic patients there are more IgE producing cells than in healthy subjects, and that the concentration of IgE in the urine or colostrum of such patients exceeds the serum IgE level seem to point to the existence of a local IgE system [1]. Therefore, the relation between isolated IgA-deficiency and IgE-reagin production deserves attention. When Buckley and Dees [10] had found a correlation between IgA-deficiency and the frequency of antibodies to milk and Kaufman and Hobbs [30] had noted IgA deficiency in 5% of allergic patients, the importance of a decrease or lack of secretory IgA arose and we have shown that a deficiency of serum and/or secretory IgA was frequent in patients harbouring intestinal helminths [12]. There are, however, differences in the correlation between the lack or decrease of IgA and the production of IgE, depending on the nature of the disease. In coeliac disease IgE production is usually normal, the reagin being mainly of the IgG class [13, 31]. In other conditions associated with malabsorption the lack of a protective effect due to IgA deficiency allows an immediate connection between IgE producing cells and the antigen, and IgE production is enhanced [1, 40]. In agreement with Soothill's view [40], it may be assumed that the transient lack of IgA is compensated by IgE production in the mucosa. This leads to an allergic reaction but still exerts a protective effect against the antigens. Whatever the underlying mechanism, the present observations seem to point to a correlation between local IgA deficiency and enhanced IgE production.

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