Survey of Immunoglobulin Levels in Atopic Families*

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SUMMARY **One hundred and ninety-six members (including both those affected by atopy and those not affected by it) of 39 atopic families, were assessed for immunoglobulin levels. There were no gross abnormalities in immunoglobulin G and M levels. Immunoglobulin E levels were high in 72 per cent of the whole population under study, especially in the patients affected by clinical atopy. Immunolobulin A levels were below normal mean values for age in 73 per cent of all family members regardless of their clinical picture (affected by atopy or healthy). The relationship of IgA levels and age were assessed and compared for members of atopic families and the non-atopic healthy control population. Control immunoglobulin levels from non-atopic individuals were obtained both from the literature and from the local population.**

ASIAN PACIFIC J ALLERG IMMUN 1984; 2 : 181-185.

Atopy is an inherited condition, as has been known for centuries; the mode of inheritance is believed to be polygenic.[1] The role played by environmental factors in the clinical expression of this inherited disease is emphasised by all authors;[2] however, many family studies have provided evidence of high heritability of IgE levels.[3] Measurements of the levels of other immunoglobulins –A, G and M– in atopic diseases show no gross abnormalities, although IgA deficiencies (transient or permanent) have been found in association with high IgE levels and clinical atopy.[4]

In the study presented here, we refer to immunoglobulin levels in a group of atopic families, all family members of which were investigated. The genetic pattern of IgE levels in these families was reported earlier.[5] In this paper we mainly study immunoglobulin A, G and M levels.

PATIENTS AND METHODS

One hundred and ninety-six individuals (parents and children) belonging to 39 atopic families were investigated. Ninety of them were clinically healthy and 106 affected by clinical atopy: asthma and eczema in nine of them, asthma and rhinitis in 16, asthma (only) in 39 and hay fever in 42 (Table 1). The clinical diagnosis was based on family history, case history, symptoms, physical examination, positive prick tests, high eosinophil counts, high IgE levels and good response to anti-allergic treatments. The reagents for prick tests were purchased from Hollister-Stier (U.S.A.). The extracts were 1:20 w/v for pollens, 1:50 w/v for dust mites and 1:10 w/v for moulds, in a solution of 50% glycerine as preservative, 0.5% sodium chloride and 0.27% sodium bicarbonate. Any wheal reaction 5 mm larger than the control was considered positive.

Immunoglobulin E levels were determined by Phadebas Prist technique and immunoglobulin A, G and M levels by immunodiffusion on Meloy plates. As mean normal values (N) and standard deviations (S.D.) for IgE, we used those given by Kjellmann[6] for individuals up to 14 years of age and those given by Barbee *et al* for individuals over 14 years[7] of age.

As mean normal values (N) and standard deviations (SD) for IgA,

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Table 1 Clinical picture of studied population: 39 atopic families

Diagnosis		No. of subjects
Healthy		90
Atopic	Asthma and eczema	9
	Asthma and rhinitis	16
	Asthma (only)	39
	Hay fever	42
	Total	106
Over all		196

G and M, we used those given by Stites.[8] A group of 177 healthy non-atopic, age-matched individuals who had no family history of atopy was assessed in our laboratory for immunoglobulin levels. The values obtained validated the international A, G and M normal values used for reference.

Statistical analysis

Log transformation was applied to all immunoglobulin levels obtained. Regression analysis was used to compare IgA values of healthy and atopic individuals in different age groups. A student T-test was used to assess the significance of differences between healthy and atopic individuals within the adult population.

RESULTS

The levels of IgG and IgM were evenly distributed around the mean normal values. IgE levels (histogram, Fig. 1) were above mean normal values (N) in 142 (72%) of the cases. Thirty-one of them (16%) were between N and N + 1 S.D., 27 (14%) between N + 1 S.D. and N + 2 S.D., and in 84 (42%) of the cases IgE values were above the N + 2 S.D. Elevated IgE levels appear in those family members who are affected by atopy, especially at a young age.

There is an overlap in the distribution of IgA levels (histogram, Fig. 2) of healthy and affected by atopy family members over all ages. In 144 (73%) of the cases IgA levels were below the mean normal (N) values for age. Fifty-six (28%) of them were between the N and N -1S.D., 71 (36%) between the N -1 S.D. and N -2 S.D. and in 17 (9%) of the cases IgA levels were below N -2 S.D. IgA values were particularly lower than normally expected in the age group between 11 and 30 years. Low IgA levels do not appear associated with the clinical status (healthy or affected by atopy).

Plots of standard IgA levels by age of the non-atopic population up to 20 years (Fig. 3) showed a steady increase of values with age, especially below the age of 10. Among members of atopic families (Figs. 4 and 5) there was a "knee effect" at the age of 10; a broken regression was fitted to this data. The regression line up to 10 years is $\log \text{IgA} = \underset{(26.3)}{3.723} + \underset{(4.7)}{0.123} \times \text{age}$ and above 10 years is $\log \text{IgA} = \underset{(17.0)}{5.033}$. All three coefficients were significantly non-zero (P value < 0.001) with the T-statistical values shown in parenthesis. IgA levels of members of atopic families over 20 years of age (Table 2) were significantly lower (P value < 0.001) than those of the control population (normal, non atopic individuals, not belonging to atopic families).

IgA levels of parents and children were compared within each one of the studied families (Table 3). The important results of this comparison are that in two families in whom IgA levels of both parents were over N -1 S.D.; the levels of three of their children were under N -2 S.D.; of five, between N -1 S.D. and N -2 S.D.; and of 12, over N -1 S.D. In eight families the IgA level of one parent was over N -1 S.D. and of the other under N -2 S.D.; IgA levels of three of their children were under N -2 S.D.; of 16 of them between N -1 S.D. and N -2 S.D.; and of 10, over N -1 S.D. In two families IgA levels of both parents were under N -2

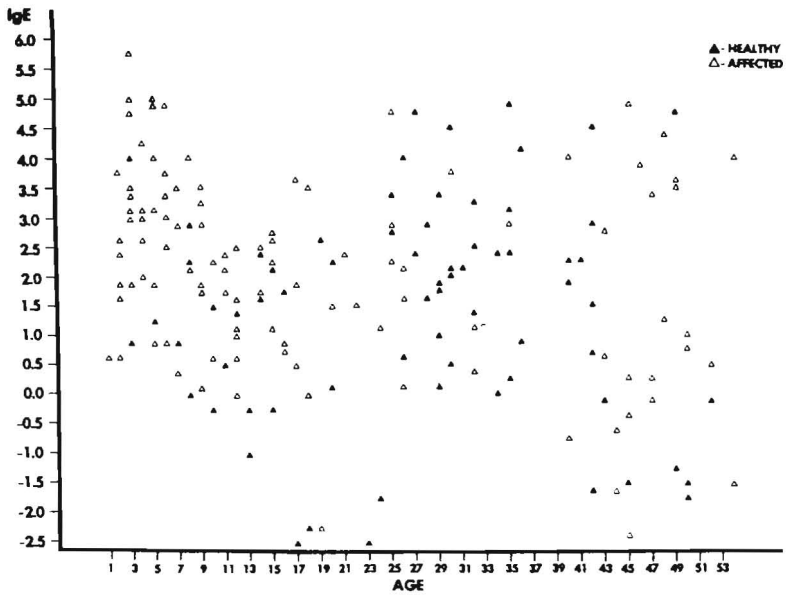

Fig. 1 IgE levels of whole population studied, standardised by age.

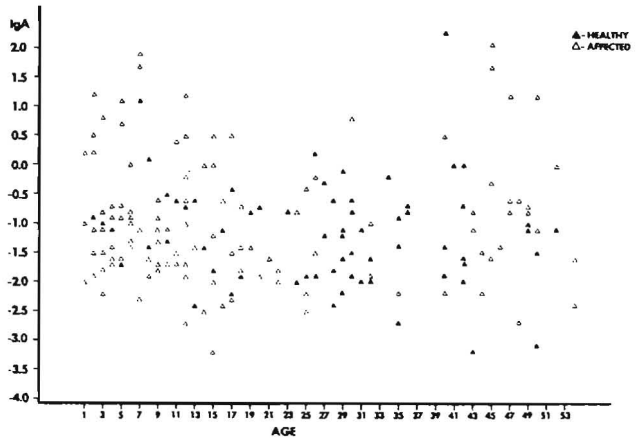

Fig. 2 Same for IgA levels.

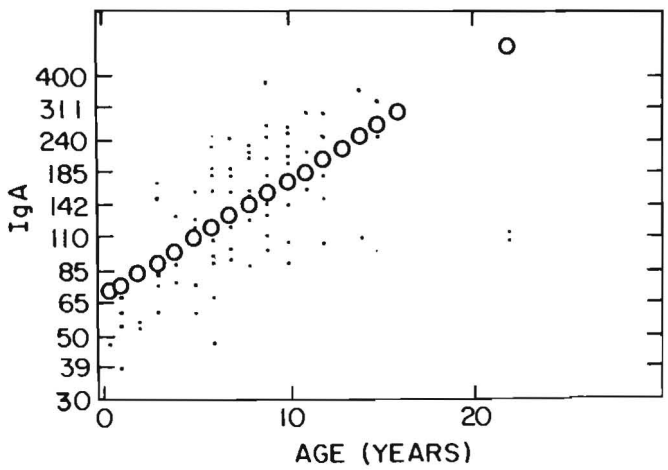

Fig. 3 Regression line of IgA levels (on log scale) of non-atopic control population up to 20 years of age (on background of individual values).

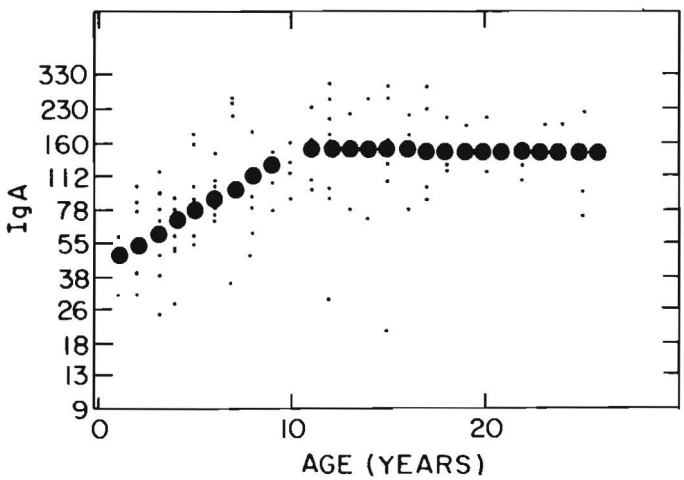

Fig. 4 Regression line of IgA values (on log scale) of members of atopic families up to 20 years of age (on background of individual values).

S.D.; IgA levels of two of their children were under N -2 S.D. and of two over N -1S.D.

DISCUSSION

Immunoglobulin E is now well established as the leading immunoglobulin for the diagnosis of an atopic background. However, abnormal values of other immunoglobulin classes have been found in cases of atopy.[9] Specifically, IgA levels are often low or even absent when atopy and high IgE levels are present.[10,12-14] Conley *et al*[15] described 11 IgA deficient patients with symptoms of autoimmune or atopic disease. Their IgA-bearing lymphocytes bore only small amounts of IgA in patchy distribution, similar to IgA-B cells from the newborn. They found that IgA-B cells from IgA-deficient patients were of an immature phenotype. Genetic factors in selective IgA deficiencies are mentioned by Amman[16] and reported by others.[17,18] Sloper *et al*[19] described low counts of IgA-producing plasma cells in the jejunal biopsies of children with atopic first-degree relatives.

Our results show an overall decrease in IgA levels over the population of atopic families studied with no difference between clinically healthy and atopic individuals. This decrease is not dramatic, and we certainly cannot consider it a classic deficiency. It is merely, as Soothill calls it,[20] "a low function within or near the normal range."

As shown in Figure 6, in members of atopic families there is a trend towards slow maturation of IgA levels which are less than N -1 S.D. until the age of 20 years. As can be seen from Table 2, in families with two normal IgA parents, 60 per cent of children have values that are normal and only 40 per cent have values less than N -1 S.D., whereas in families in which only one parent has a normal IgA value and the other an IgA value of less than N -1 S.D., 35 per cent of the children have normal IgA values and 65 per cent

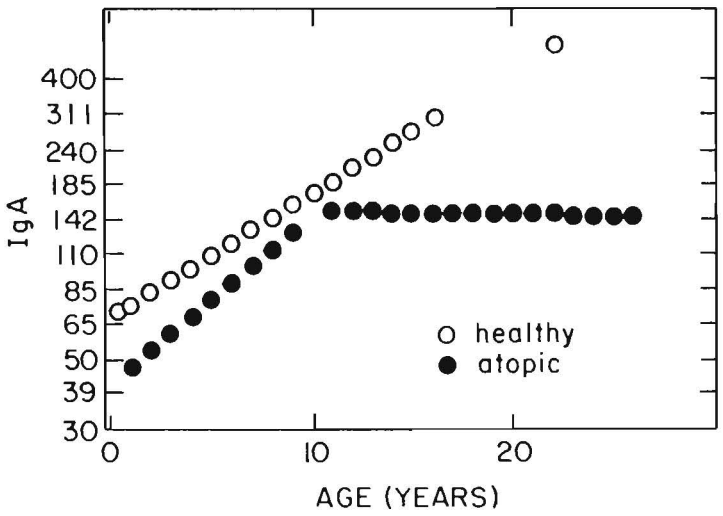

Fig. 5 Comparison between regression lines of IgA levels (on log scale) of non-atopic individuals and members of atopic families: note "knee effect" in the members of atopic families.

Table 2 Log IgA values for individuals over 20 years of age

Atopic families	No. of cases	Minimum	Maximum	Mean	S.D.
Members	78	3.21	6.07	5.07	.52
Non-atopic controls	68	4.700	5.91	5.53	.34

less than N -1 S.D. These findings were not indicative of dominant or codominant modes of inheritance.

In the 39 atopic families presented here, it seems that a low IgA levels is familial, possibly genetically determined by a polygenic mode of inheritance. Lower IgA levels were not predictive of clinical atopy within these families; however, because they appear as part of their familial "background", an inherited trait of low- and slow-maturing IgA globulin production might be an important factor in the pathogenesis of atopy.

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Table 3 Heritability of IgA levels within the 39 families studied

No. of families	IgA levels of parents	IgA levels of children			No. of children
		< N -2 S.D.	< N -1 S.D. and > N -2 S.D.	> N -1 S.D.	
5	Both >N – 1 S.D.	3	5	12	20
14	One >N – 1 S.D. N – 1 S.D. > One >N – 2 S.D.	4	21	14	39
8	One >N – 1 S.D. One <N – 2 S.D.	3	16	10	29
3	N – 1 S.D. >One >N – 2 S.D. One <N – 2 S.D.	1	4	2	7
7	N – 1 S.D. > Both >N – 2 S.D.	2	12	8	22
2	Both <N – 2 S.D.	2		2	4
(39)		(15)	(58)	(48)	(121)

N = mean normal value for age

Figures in parenthesis depict total numbers

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