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Family Background of Respiratory Atopy: a Factor of Serum IgE Elevation in Atopic Dermatitis

MASAMI UEHARA

Department of Dermatology, Shiga University of Medical Science, Seta, Otsu 520-21, Japan

The incidence of family history of atopic diseases in patients with atopic dermatitis (AD) was dependent upon the number of family members. In AD patients whose family had four persons or less, the diagnostic value of atopic family history was considerably diminished. To investigate if personal or family history of atopic respiratory disease (ARD) are implicated in elevating serum IgE in AD, serum IgE values were analyzed in 200 AD patients who had a family of five or more. AD patients who had a personal or family history of ARD showed significantly higher serum IgE than AD patients who lacked both personal and family ARD history. Patients with only AD and very high serum IgE commonly had a family ARD history. Patients with severe AD and normal serum IgE mostly lacked personal and family ARD history. It appears that about 40% of total AD patients do not have predisposition for ARD. ***Key words: Heterogeneity of serum IgE; Family history of atopy; Atopic respiratory disease; Severity of dermatitis.***

Masami Uehara, Department of Dermatology, Shiga University of Medical Science, Seta, Otsu 520–21, Japan.

Although the elevation of serum IgE level in many patients with atopic dermatitis (AD) has been well established, the diagnostic value of elevated serum IgE for this condition is still obscure (1–3). The main reason for the obscurity seems to be the difficulty in explaining the fact that serum IgE levels are normal in 20% to 30% of patients with otherwise typical AD (4–6).

Various investigators (4–10) have demonstrated that severity of dermatitis and coexistence of respiratory atopic disease (ARD) are the important clinical factors which elevate serum IgE concentration in AD. However, all previous studies have confirmed that serum IgE levels are not elevated in some patients with severe AD, and that very high serum IgE values are often observed in patients with AD who do not have a personal history of ARD. These findings might suggest that some other factors are also implicated in elevating serum IgE in AD.

By examining influences of family background of ARD on serum IgE concentration in patients with AD, I previously reported that the presence of a family history of ARD plays an important role in serum IgE elevation in AD (11). The present paper summarizes the data on the relationship between family history of ARD and serum IgE levels in a large number of patients with AD.

Family history of atopy in recent years

Several decades ago, it was reported that approximately 70% of patients with AD had a family history of atopic diseases (12, 13). Therefore, atopic family history has been regarded as one of the major criteria in the diagnosis of AD (1, 14).

Unfortunately, the incessant decrease in the birth rate through the last decades has greatly lowered the incidence of family history of atopic diseases. Table 1 shows the relation between the number of family members and family history of atopy in 427 consecutive young adults (age: 15–30 years) with AD who visited our dermatological clinic during the last three years (1985–1987). The most prevalent family was that of four persons, i.e., parents and two children. In patients with AD who had such a small nuclear family, the incidence of atopic family history was only 53%. On the other hand, family history of atopy was

Table I. *Relationship between number of family members and incidence of atopic family history in 427 patients with atopic dermatitis (age: 15–30 years)*

No. of family members	No. of patients	Family history of atopic diseases +	–
3	48	15 (31%)	33 (69%)
4	251	134 (53%)	117 (47%)
5	101	76 (75%)	25 (25%)
6–7	27	21 (79%)	6 (21%)
Total	427	246 (58%)	181 (42%)

positive in more than 70% of patients with AD who had a family of five or more. Thus, it is clear that data on atopic family history has reliable diagnostic value only in those patients with AD who have a family of five persons or more.

Classification of patients with AD

To investigate whether presence of family ARD history implies a relationship to serum IgE level in AD, 200 consecutive young adults (age: 15–30 years) with AD, 100 mild cases and 100 severe cases, were selected. The present study examined only the patients with AD who had a family of five or more.

The degree of dermatitis was determined using the following criteria: *Mild:* localization of active skin lesions to two or three anatomical areas for at least 6 months prior to the present examination. *Severe:* involvement of 70% or more of the total body surface for at least 6 months before this study.

The 200 patients were classified into three groups: 1) those who had personal ARD history (98 cases), 2) those who did not have personal ARD history, but had a family history of ARD (40 cases), and 3) "pure" AD patients who had neither personal nor a family history of ARD (62 cases). The distribution of the three groups in mild AD cases was almost the same to that in severe AD cases (Table II).

Evaluation of serum IgE levels

Serum IgE concentrations were measured by the radio-immunosorbent assay (Pharmacia, Uppsala), and expressed in U/ml. Mikawa et al. (15) reported that the upper limit of serum IgE levels in normal Japanese adults is around 500 U/ml. In the present study serum IgE values greater than 500 U/ml were regarded as increased, and those greater than 2000 U/ml as very high.

Table II. *Classification of patients with atopic dermatitis (AD) by personal/family history of atopic respiratory disease (ARD)*

	Patients with AD who had a personal ARD history	Patients with only AD who had a family ARD history	"Pure" AD patients
Mild AD (100 cases)	49	21	30
Severe AD (100 cases)	50	18	32

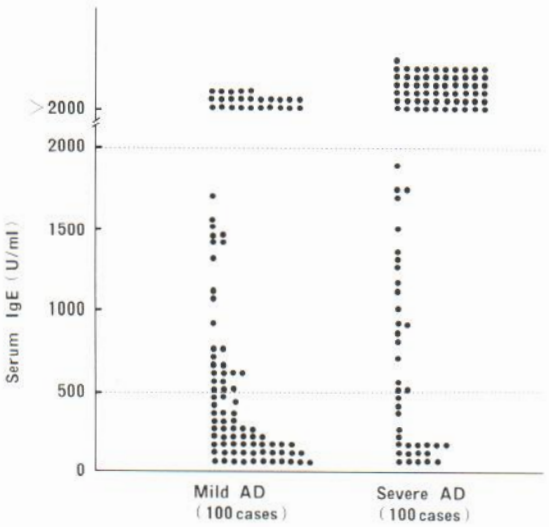

Fig. 1. Distribution of serum IgE values in 100 mild cases and 100 severe cases of atopic dermatitis.

Serum IgE levels in mild AD cases and severe AD cases

Fig. 1 shows the distribution of serum IgE values in the 100 mild cases and 100 severe cases of AD examined. The levels of serum IgE roughly correlated with the severity of dermatitis. However, a very high serum IgE value was observed in 25% (25/100) of the mild cases, while a normal or only moderately elevated serum IgE level (i.e., lower than 2000 U/ml) was seen in 39% (39/100) of the severe cases.

Serum IgE levels in AD patients having a personal ARD history

In the group of patients with AD who had a personal history of AD, serum IgE levels were elevated in the majority of mild cases, and in all of the severe cases (Fig. 2). A feature of this group was that very high serum IgE values were obtained in nearly all (47/49) of the severe cases, and in a considerable number (17/38) of the mild cases. Overall, there was a positive correlation between the levels of serum IgE and the severity of dermatitis.

Serum IgE levels in patients with "pure" AD

In the group of patients with "pure" AD who had neither a personal nor a family history of ARD, serum IgE levels again correlated with the severity of dermatitis (Fig. 3). But the severe cases of this group showed only a slight or moderate elevation of serum IgE. Thus, as can be seen from Figs. 2 and 3, there was a

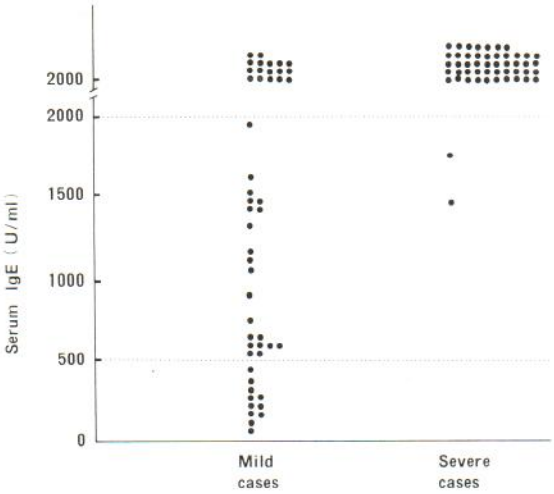

Fig. 2. Serum IgE levels in patients with atopic dermatitis who had a personal history of respiratory atopy.

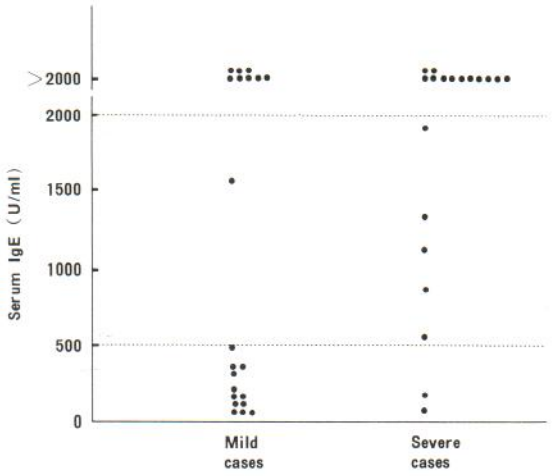

Fig. 4. Serum IgE levels in patients with only atopic dermatitis who had a family history of respiratory atopy.

striking difference in the magnitude of serum IgE elevation between patients with severe AD who had a personal history of ARD and severe cases of "pure" AD.

An important finding was that serum IgE levels were normal in 20 (63%) of the 32 severe cases in the "pure" AD group. It then became evident that most (20/22) of the patients with severe AD and a normal serum IgE value belonged to the "pure" AD group (Figs. 1 and 3).

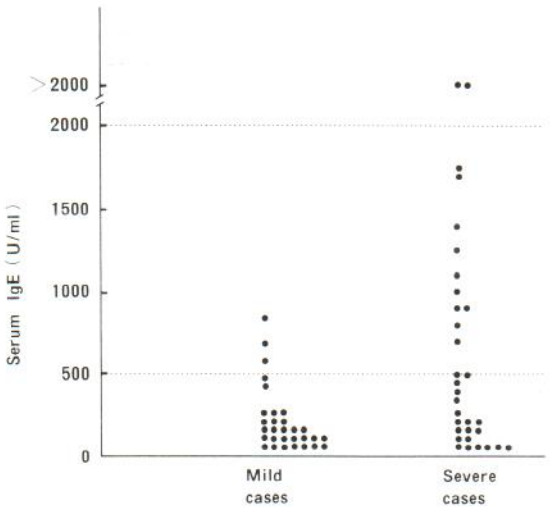

Fig. 3. Levels of serum IgE in patients with "pure" atopic dermatitis who had neither personal nor family history of respiratory atopy.

Serum IgE levels in AD patients having only a family history of ARD

In patients with AD who did not have a personal but had a family ARD history, serum IgE level and severity of dermatitis had a close correlation (Fig. 4). An interesting finding was that in contrast to the "pure"

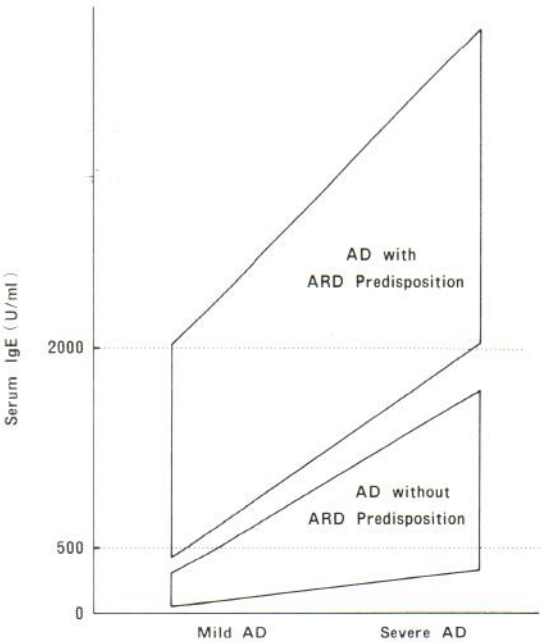

Fig. 5. A schematic presentation of the heterogeneous distribution of serum IgE values in patients with atopic dermatitis.

AD group, half (20/40) of the patients in this group showed very high serum IgE levels. Thus, it became clear that the great majority (20/22) of the patients with only AD and very high serum IgE value were those who had a family history of ARD (Figs. 3 and 4).

DISCUSSION

The present results confirm the findings of previous studies (4–10) that serum IgE levels in AD roughly parallel the severity of dermatitis.

By classifying patients with AD into three groups on basis of a personal or a family history of ARD, the present study further demonstrates that the magnitude of serum IgE elevation in AD is associated with both a personal and a family history of ARD. Serum IgE values were slightly or moderately elevated in severe cases of "pure" AD who had neither a personal nor a family history of ARD, while very high serum IgE levels were consistently seen in severe cases of AD who had a personal history of ARD. These findings suggest that AD *per se* can bring about only a moderate elevation of serum IgE, and that the serum IgE elevation induced by AD is greatly amplified in AD patients who have a personal history of ARD.

Very high serum IgE values were observed in many patients with severe AD who did not have a personal history of ARD, but had a family history of ARD. It is likely that the AD-induced serum IgE elevation is also amplified in AD patients who have subclinical ARD or predisposition for ARD. On the other hand, a normal or moderately elevated serum IgE occurred in some cases of severe AD who had only a family history of ARD. This suggests that the AD group with only family history of ARD includes some patients who do not have ARD predisposition. It is known that atopic diseases are inherited with incomplete penetrance (16, 17).

Thus, on basis of the serum IgE producing potential, patients with AD may be classified into two subgroups: 1) those with ARD predisposition who have an enhanced ability for production of IgE, and 2) those without ARD predisposition who do not have an enhanced IgE producing potential (Fig. 5).

Hanifin and Rajka (18) have stated that serum IgE level greater than 2000 U/ml adds considerable support to the diagnosis of AD. But the present results show that such very high serum IgE levels may occur exclusively in those patients with AD who have a personal or family history of ARD, i.e., predisposition for ARD. Furthermore, it became evident that in patients with severe AD, serum IgE level of 2000 U/ml is a value which clearly separates patients with ARD predisposition from patients without such predisposition.

Finally, the occurrence of very high serum IgE values in approximately 60% of severe AD patients in the present study suggests that the remaining 40% of the severe AD patients did not have ARD predisposition. Interestingly, the distribution of AD patients with a personal ARD history and those with only a family ARD history were almost the same in the severe AD group and the mild AD group, suggesting that prevalence of coexistent ARD predisposition in AD patients has no relation to the severity of the dermatitis. From both these sets of data, it may be concluded that AD patients without ARD predisposition comprise about 40% of the total AD patients in a Japanese population.

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