

Total and specific IgE (RAST) in atopic twins

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Summary

Fifty sets of twins (thirty monozygotic [MZ] and twenty dizygotic [DZ]), of whom at least one twin had a history of atopy, were investigated by means of skin tests, RAST and IgE determinations. The concordance of atopies for MZ was, with 56.7%, significantly higher as compared with the DZ with 20%. The mean values of the log serum IgE level differences for MZ and DZ sets of twins was not statistically significant but the percentage distribution of the log serum IgE level differences showed a closer correlation of the IgE levels among MZ. The MZ sets do not show a better concordance in the specific reagin production, as measured by RAST or skin tests, than the DZ sets. These findings seemed to indicate that although the tendency to IgE production is genetically determined its specificity is governed mainly by environmental influences.

Introduction

Since Coca & Cooke (1923) and Wise & Sulzberger (1933) the clinical concept of 'atopy' has been taken to mean a group of diseases of immediate hypersensitivity including allergic rhinitis (hay fever), bronchial asthma and atopic dermatitis (atopic eczema in children), which must be regarded genetically as a unit (Schnyder, 1960). Atopic diseases can occur in combination or consecutively in the same person; they are familial and can replace one another in the same family. As the atopic diseases have a sufficient number of characters of their own, the term 'atopy', although questioned by Spector & Farr (1976), should be retained (Austen, 1978).

As a result of extensive statistical population surveys and observations of families, and especially twins, the atopies are now included among diseases for which there is an hereditary predisposition. Phenocopies, i.e. cases which are not predestined by heredity, must, according to Schnyder (1970) on the basis of genetic-statistical calculations, be very rare if, indeed, they exist at all. According to present knowledge it

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is most likely that atopy can be ascribed to multifactorial inheritance (additive polygeny) with a threshold values effect (Vogel, 1970). Consequently, a given atopic disease (phenotype) results from an unfavourable combination of several genes, together with the action of various environmental factors: the disease then become manifest when a certain threshold, which can be completely variable, is passed.

As many questions regarding the genetics of the atopy still call for clarification, it is important to separate out as many as possible of the basic associated immunological and non-immunological factors (e.g. neuro-vegetative, circulatory, sebotropic and skin-functional) and to determine their inter-relationship (Voigtlander, 1977). Considering the immunopathology, reagin formation is very important, even if this type of reaction is by no means confined to patients with atopic disease. The introduction of radio-immuno-assays such as RIST, PRIST and RAST for the measurement of the total and specific serum IgE levels marked not only a turning point in the routine diagnosis of atopic allergy but also has been valuable to research in this field. We report an investigation carried out on fifty sets of twins (thirty monozygotic [MZ] and twenty dizygotic [DZ]) of whom at least one twin had a manifest atopy, similar to that reported by the Hamburger working group (Bazaraal, Orgel & Hamburger, 1971; Bazaraal & Hamburger, 1972; Hamburger, Orgel & Bazaraal, 1973).

Material and methods

Patients

Seventeen sets of twins came from the group examined by Schnyder in 1960 (for details see Baumann, 1976), while thirty sets were covered by Fries (1980), in connection with a questionnaire circulated to 1106 twins who were members of the Swiss Twins Association. The diagnosis of atopy was based on clinical symptoms or a history of rhinitis (R) including rhinitis pollinosa (hay fever) (RP), bronchial asthma (BA) and atopic dermatitis (AD).

IgE determinations

The serum IgE (RIST) and RAST assays were carried out in accordance with the details given by the manufacturers (Phadebas, Pharmacia Diagnostics AB, Uppsala, Sweden).

Skin tests

Skin tests (prick tests and, where negative, intracutaneous tests) were carried out with aqueous allergen extracts made by Stallergènes Lab., Licence Hollister-Stier (test concentration 1:10³ w/v).

The following eight environmental allergens were routinely examined by the skin test and RAST: house dust (Hollister-Stier), house dust mite (*Dermatophagoides pteronyssinus*), Timothy grass, birch and hazel pollen, as well as the hair and epithelia of dogs, cats and horses.

Statistical evaluation

The statistical evaluation was made with the help of the advice and programmes of the Biostatistics Centre of the Medical Faculty, University of Zurich. Since the serum IgE level in the normal population does not have a normal distribution, values expressed as logarithms to the base 10 were employed ($= \log$).

Results

Percentage concordance of the atopies

Table 1 shows the percentages concordance for MZ and DZ twins as regards the presence or absence of an atopic condition. Concordance is significantly higher (56.7%) for the MZ as compared with the DZ. The relationships exactly correspond to the data given in the literature (Table 2). According to Schnyder (1970) the considerably larger MZ percentage concordance is an absolute proof that the atopies are hereditary.

Table 1. Percentage concordance of atopies in MZ and DZ twins

Atopies (rhinitis, asthma, atopic dermatitis)	MZ sets (n=30)		DZ sets (n=20)	
	Concordant	Discordant	Concordant	Discordant
	17	13	4	16
Percentage concordance	56.7	43.3	20	80

$$\chi^2 = 6.62; 5\% < P < 1\%.$$

Table 2. Concordance of atopy in twins (Schnyder, 1970)

Authors	MZ (n=144)		DZ (n=400)	
	Concordant	Discordant	Concordant	Discordant
Spaich-Ostertag (1936)	6	6	2	16
Harvald-Hauge (1956)	10	10	4	40
Rajka (1960)	3	2	6	3
Schnyder (1960)	6	6	1	22
Teodori (1962)	53	37	134	159
Niermann (1967)	5	0	3	10
Total	83	61	150	250
Percentage concordance	57.6	42.4	37.5	62.5

$$\chi^2 = 17.54; P \ll 1.$$

Serum IgE level

Figure 1 shows the distribution and mean values ($\pm s$) of the log serum level differences for monozygotic and dizygotic sets of twins. These titre differences in the two groups are not statistically significant ($t = 1.648$; $P > 5\%$).

Using the data of Bazaral, Orgel & Hamburger (1971) and Hamburger, Orgel & Bazaral (1973), Fig. 2 shows the percentage distribution of the log serum IgE level differences for the MZ and DZ sets. Hamburger *et al.* (1973) divided the log IgE differences of 595 randomized pairs of adults into three groups, namely into differences of less than 0.30 (32% of the sets), of 0.30 to 0.60 (25%) and of more than 0.60 (43%).

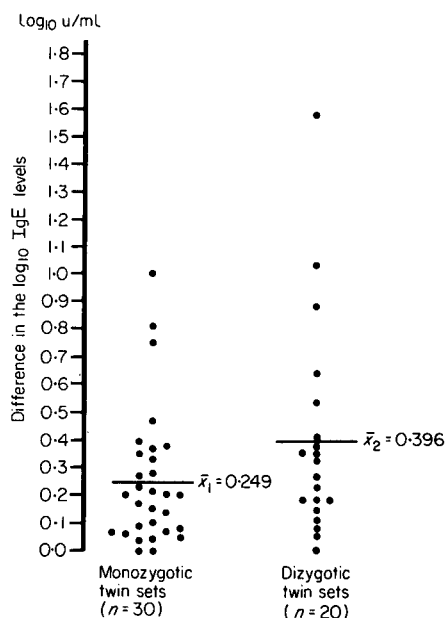


Fig. 1. Distribution and mean values ($\bar{x}_1$ and $\bar{x}_2$) of the log serum IgE levels for the MZ and DZ sets ($s_1 = \pm 0.242$; $s_2 = \pm 0.396$).

The value 0 would signify identical IgE levels; increasingly larger values show an increasingly greater difference in the IgE levels. Thus, according to their investigations the difference in 81% of the serum tests on one and the same individual, examined at intervals of between 0.5 and 5.5 years, was less than 0.3; no one gave a value of more than 0.6. Consequently the 'intra-individual' serum IgE level moves within significantly narrower limits than the 'inter-individual' level. In their sets of twins there was a significantly closer correlation of the IgE levels among MZ as compared with DZ. Thus our findings agree very well with theirs.

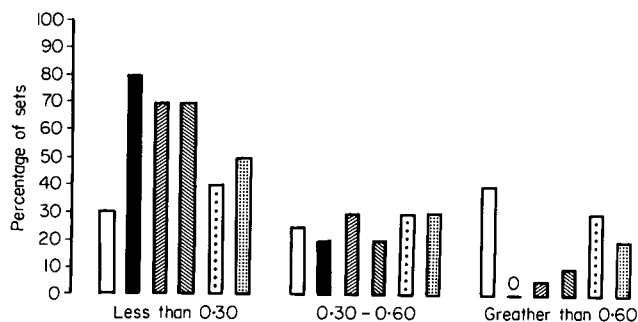


Fig. 2. Percentage distribution of the difference in the log IgE levels. □, Random sets ($n=595$)*; ■, single individual sets at 0.5–5.5 yr interval ($n=31$)*; ▨, monozygotic twin sets ($n=64$)*; ▩, monozygotic twin sets (Wüthrich) ($n=30$)*; ▪, dizygotic twin sets ($n=52$)*; ▫, dizygotic twin pairs (Wüthrich) ($n=20$).

* Data from Bazara, Orgel & Hamburger (1971).

Table 3. General concordance (+/+ , -/-) or discordance (+/-) of reagin formation (RAST), in general, in MZ and DZ

	MZ (n = 30)	DZ (n = 20)
Concordant	22	10
Discordant	8	10
Percentage concordance	73	50

$$\chi^2 = 2.84; P > 5\%.$$

Table 4. Percentage concordance in MZ and DZ of reagin formation when at least one allergen is RAST positive (as from Class 1) in one partner

	MZ (n = 20)	DZ (n = 13)
Concordant	12	3
Discordant	8	10
Percentage concordance	60	23

$$\chi^2 = 4.33; 5\% > P > 1\%.$$

RAST assays

It was of interest to determine whether there are significant differences in the ability to form specific reagins, as measured by the RAST method, between MZ and DZ. As can be seen from Table 3, this is not the case. On the other hand, when only those pairs of twins are considered in which at least one allergen is RAST positive in one partner, then MZ show a significant concordance (Table 4). If, however, the specific type of reaction is considered more closely (Table 5), then the concordance in the MZ sets is no

Table 5. Concordance or discordance in MZ and DZ as regards specific reagin formation (eight allergens in RAST)

Allergens	MZ (n = 30)		DZ (n = 20)		Significance
	Concordant (+/+)	Discordant	Concordant (+/+)	Discordant	
House dust	28 (2)	2	18 (0)	2	n.s.
House dust mite	25 (2)	5	16 (0)	4	n.s.
Timothy grass	25 (11)*	5	12 (2)*	8	n.s.
Birch pollen	26 (2)	4	16 (0)	4	n.s.
Hazel pollen	24 (1)	6	16 (1)	4	n.s.
Dog dander	29 (1)	1	19 (0)	1	n.s.
Cat dander	27 (2)	3	17 (0)	3	n.s.
Horse dander	28 (0)	2	20 (0)	0	n.s.

* $P < 5\%$.

better than in the DZ sets. The exception occurs with the Timothy grass allergen if only the RAST-positive sets are considered.

Results of the skin test compared with the RAST

Skin tests were carried out with 34 MZ (i.e. 17 sets) and 10 DZ. When the skin tests were negative there were no positive RAST findings. Out of 116 positive skin tests the RAST was also positive in fifty-two cases with the corresponding allergen, giving a correlation of 44.8%. The skin tests can thus indicate a specific sensitization which escapes detection by the RAST, since it is known that the RAST measures only an 'excess' of specific IgE, i.e. only freely circulating reagins which are not bound to mast cells or blood basophiles (Wüthrich & Kopper, 1974).

Discussion

On average, atopic persons have higher serum IgE levels than non-atopic individuals, the levels increasing in the following order: atopic cases with perennial allergic rhinitis, with rhinitis pollinosa and with 'extrinsic' asthma, while there is an extremely marked increase with atopic dermatitis (Wüthrich & Kopper, 1974; Wüthrich, 1978; Wüthrich & Fuchs, 1980).

In a non-selected population the serum IgE level distribution curve shows three peaks, with low (*ca* 75%), intermediate (23%) and high values (2%). This distribution follows the Hardy-Weinberg law for two alleles at a simple gene locus and corresponds to the frequency for atopic and non-atopic alleles given by Wiener, Zieve & Fries (1936) on the basis of clinical investigations. According to this model, a gene with two different alleles (AA-Aa-aa), with partial penetrance in the case of heterozygotes, must be assumed for the inheritance of the IgE level (Bazaraal *et al.*, 1971; Oprea, Krause & Stockberg, 1972; Oprea, 1979). Following IgE assays with 108 sets of twins (56 MZ and 46 DZ) Hamburger *et al.* (1973) and Bazaraal *et al.* (1971) also concluded that the serum IgE level is 84% genetically determined and that other factors, including the environment, account for only 16%. However, even if it is now established that IgE formation is genetically determined the factors governing the nature and intensity of specific antibody formation still call for study. Investigation of twins makes it possible to decide whether this characteristic is hereditary and to what extent environmental factors are responsible for its development.

MZ have the same hereditary factors and represent genotypically uniform material. Differences between MZ are therefore paratypical and are caused by the environment. On the contrary DZ behave like siblings. Hereditary characteristics are more often concordant in MZ than in DZ. In the case of characteristics which are neither purely hereditary nor purely environmental the twins method is of great importance. The greater the influence of hereditary factors in 'predispositional' diseases, the more frequently the characteristic shows concordance in MZ (Schnyder, 1960; Wendt, 1964).

The number of twins investigated for allergy is not very large. Schnyder (1960) found that only 35% of skin test positive MZ showed an identical test spectrum while the majority (65%) of the DZ sets examined were sensitized to different allergens. These findings seemed to indicate that although the tendency to reagin formation is genetically fixed its specificity is governed mainly by exogenous influences. It has now been shown by means of the RAST method that this is correct. A significant concordance between the MZ was found solely for reagin formation against Timothy

grass pollen antigen when only those sets were considered one at least of whom gave a corresponding positive RAST. Identification of histocompatibility-linked *Ir* genes in animals and IgE in man have revolutionized genetic studies of human atopic allergies (Marsh & Bias, 1978). As demonstrated with inbred mice and also proved with persons allergic to ragweed pollen, it is probable that the coupling of immune-response genes is with a given HLA-haplotype (Levine, 1973; Marsh, Bias & Hsu, 1973; Marsh, Bias & Ishizaka, 1974). This type of approach is, however, still in its infancy (Marsh & Bias, 1978), and further epidemiological and immunological studies are needed.

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