

Allergic reactivity and socio-economic level in a tropical environment

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Summary

As some factors associated with the tropical environment can modify the expression of atopic disease, various indicators of allergic reactivity were compared between allergic and non-allergic subjects of different socio-economic level in Caracas, Venezuela (Lat. 10°N). The socio-economic levels considered were high (HSEL), medium-high (MSEL) or low (LSEL). As generally found in temperature climates, in the HSEL the total serum IgE levels of allergic patients were significantly greater than those of non-allergic individuals (geometric means of 274 *vs* 126 IU/ml, respectively), as were also the specific serum IgE antibody levels (55.6 *vs* 23.8% positive, respectively, for house dust). These results correlated closely with the skin-test reactivity of these subjects (60.3 *vs* 17.5% positive for house dust). In this group, the degree of intestinal helminthic infection was low (5.6% positive for *Ascaris*). In contrast, for the MSEL where the degree of parasitic infection was higher (13.0%), the total serum IgE levels were elevated in both allergic and non-allergic subjects (602 *vs* 363 IU/ml). Similarly, positivity for specific IgE antibody was high, and comparable between allergics and non-allergics of this group (61.5 *vs* 54.2%), as was also the case for skin-test reactivity (71.9 *vs* 60.4%). In the LSEL, parasitic infection was prevalent (47.6%), and the total serum IgE levels were markedly elevated, with little difference occurring between allergic and non-allergic individuals (2269 *vs* 1981 IU/ml). The positivity for specific IgE antibody was high, and effectively independent of the allergic state (75.6 *vs* 53.7%), but in contrast the skin test reactivity was relatively low (22.0 *vs* 9.8%). The lack of correlation between skin test and specific IgE results in this group appeared to have

two causes. Firstly, although the frequency of positivity in specific IgE was high, only low grade antibody activity was detected. Secondly, studies of skin reactivity indicated that some form of interference to target cell sensitization was occurring. The possible participation of helminth-induced polyclonally-increased IgE synthesis in the modification of allergic reactivity is discussed.

Introduction

It is well established that in temperate climates allergic patients tend to have elevated total serum IgE levels. These are primarily due to an enhanced synthesis of antibodies belonging to this isotype directed against environmental allergens [1, 2]. Such patients also exhibit strong cutaneous immediate hypersensitivity reactions to extracts of allergenic materials [3–5], which reflects, in part, the presence of this specific IgE antibody [6, 7].

The situation is, however, more complex in the tropical environment, as intestinal helminths are frequently endemic, and these can cause dramatic polyclonal stimulation of IgE synthesis [8–11]. This appears to influence the allergic reactivity of tropical populations in a manner that depends, at least to a certain extent, upon the intensity of helminthic infection. Thus, groups experiencing occasional helminthic infections can exhibit high prevalences of allergic disease [12, 13], whilst under conditions of intense infection the opposite seems to be the case [14–16].

The mechanisms involved in the modulation of allergic reactivity have yet to be clearly established [17–20], and the characteristics of tropical allergic patients still present considerable uncertainty.

In the present study, we evaluated allergic patients in the tropical environment of Caracas, Venezuela (Lat. 10°N), who belonged to three broadly defined socio-economic levels. As the degree of exposure to intestinal helminths was different between these groups, and changes that could be attributed to the effect of these parasites on IgE synthesis were observed, the results obtained can be suggested to reflect parasitic modulation of allergic reactivity.

Subjects and methods

Study population and socio-economic level

The socio-economic status of the groups under study was established by the evaluation of a number of factors, which included total income, place of living, type of housing, access to public services, family size and educational level.

The classification of socio-economic level was based upon the scale in official use in Venezuela (Centre for Biological Studies of Growth and Development of the Venezuelan Population: FUNDACREDESA). In this method, the relevant socio-economic indicators are assigned weighted point values, and scores are determined that define five groups, designated I–V (F. Mendez-Castellano, in press). Some selected features of these groups are illustrated in Table 1, and for the purposes of the present study, groups I and II were considered as HSEL, group III as MSEL, and IV and V as LSEL. The social and cultural characteristics of subjects of H or MSEL were generally comparable, with one of the most striking differences being the place of living; the

Table 1. Selected indicators of socio-economic level of family groups in the Venezuelan population*

Indicator	Socio-economic level†				
	I	II	III	IV	V
Gross monthly income (VEB)	> 30 000	8000–30 000	2400–8000	1000–2400	< 1000
Profession of head of family (%)					
Professional	84		14	0	0
Employee	16		78	18	1
Labourer	0		8	82	99
Mothers' educational level (%)					
Tertiary or advanced secondary	57		17	1	0
Partial secondary or advanced primary	43		82	93	48
Partial primary or illiterate	0		1	6	52
Academic achievement activity encouraged (%)‡	71		41	40	27
Sanitary facilities of home (%)					
Good–adequate	99		74	27	1
Deficient–greatly deficient	1		26	73	99
Shared sleeping facilities (%) §	9		36	48	72
% of Venezuelan population in each group	6		14	42	38

* Figures adapted from H. Mendez-Castellano, 'Aproximacion a la Salud de la Venezuela del Siglo XXI', Cuadernos Lagoven, Serie Siglo XXI, Caracas, 1985.

† Graffar scale adapted to Venezuela by FUNDACREDESA, Caracas.

‡ For boys.

§ Percentage of homes in which sleeping facilities of husband and wife are shared by other family members.

MSEL generally originated from areas of greater population density. The LSEL was studied in poorly serviced marginal areas of Caracas, using facilities kindly made available by Dr I. Perez-Schael (Instituto de Biomedicina).

Clinical history and patient selection

The allergic status of the subjects was determined by direct interrogation, conducted by a specialist medical practitioner, following a previously used protocol [13] that was adapted as necessary to the level of education and medical awareness of the study group. Individuals were classified as allergic if they had unmistakably suffered symptoms of allergic rhinitis and/or asthma repetitively over the preceding 3–5 year period. Non-allergic subjects were defined as those who denied any clinical history of allergic disease and who presented no abnormality upon physical examination.

The majority of the allergic patients were drawn from the allergy clinic of the Instituto de Biomedicina, and the non-allergics from a pool of normal subjects evaluated as part of a wider study of the Venezuelan population [13, 20]. The data relating to these subjects were stored as a computerized data-base, and the study groups were formed by the generation of age–sex matched pairs between the allergic and non-allergic individuals. The only other selection criterion applied was the completeness of data available. Absolute age–sex matching was not achieved in the HSEL, but ages were matched to within 2 years. The composition of the study groups

was as follows: LSEL; forty-one pairs, 51.2% male, 15.9 ± 10.7 years; MSEL: ninety-six pairs, 46.9% male, 17.1 ± 11.5 years; HSEL: sixty-three pairs: non-allergics: 52.4% male, 18.1 ± 10.1 years; allergics: 49.2% male, 19.7 ± 10.9 years.

Skin testing

Skin-prick tests [4] were performed with extracts prepared from mixed local house dusts, two species of *Dermatophagoides*, five common moulds, six types of insects, epithelia from eight animal species, the material collected by continuous suction air sampling ('aeroallergens') and *Ascaris lumbricoides* [13, 20].

Cutaneous sensitivity to histamine was evaluated by prick testing with a 1% w/v solution, and the biochemical or immunological function of the skin mast cells was determined by similar testing with either 5% codeine phosphate solution or 1 mg/ml goat anti-IgE Fc, respectively. Prausnitz-Kustner (P-K) tests were performed by the intradermal injection of 50 μ l of a human serum pool that contained high levels of specific IgE antibody (> level 4, Phadebas® RAST scale, Pharmacia, Sweden). This pool was negative for hepatitis viral antigen and anti-HIV antibodies, and had been centrifuged at $100\,000 \times g$ for 5 hr. Twenty-four hours after sensitization the cutaneous sites were challenged by a prick test with the appropriate allergenic extract. In this study the P-K tests were performed with *Dermatophagoides* allergen in subjects who were not reactive to this material, as preliminary trials revealed that the use of a common allergen best revealed the existence of interference with mast cell sensitization.

In all skin tests, positive reactions were taken as immediate weal diameters of ≥ 3 mm.

Total and specific serum IgE levels

The paper-disc technique of Ceska and Lundkvist [21] for the measurement of total serum IgE was used, and also adapted to the determination of specific IgE antibody [22]. While these tests were developed in our laboratory, they were standardized against the commercial 'Phadebas' test (Pharmacia, Sweden).

The positivity of the tests for specific IgE was taken either as ≥ 0.35 PRU/ml (level 1) or ≥ 0.7 PRU/ml (level 2), according to the 'Phadebas' scale.

Table 2. Infection by *Ascaris*, and total serum IgE levels, in allergic or non-allergic subjects of different socio-economic levels

	HSEL		MSEL		LSEL	
	Non-al. (63)	Al. (63)	Non-al. (96)	Al. (96)	Non-al. (41)	Al. (41)
<i>Ascaris</i> infection (%)	6.3	4.8	13.5	12.5	53.7	41.5
Geometric mean (± 1 s.d.) IgE level. IU/ml.	126 (399)	274 (1963)	363 (1479)	602 (1862)	1981 (11040)	2269 (12618)

Table 3. Skin test positivity (%) in allergic or non-allergic subjects of different socio-economic levels

	HSEL		MSEL		LSEL	
	Non-al. (63)	Al. (63)	Non-al. (96)	Al. (96)	Non-al. (41)	Al. (41)
House dust	17.5	60.3	60.4	71.9	9.8	22.0
<i>Dermatophagoides</i>	15.9	54.0	40.6	49.0	4.9	7.3
Moulds	7.9	27.0	22.9	20.8	7.3	7.3
Insects	7.9	30.2	20.8	25.0	9.8	26.8
Epithelia	9.5	22.2	12.5	7.3	4.9	4.9
Aeroallergens	7.9	23.8	22.9	22.9	4.9	7.3
<i>Ascaris</i>	6.3	6.3	29.2	38.5	63.4	63.4
Histamine	100.0*	96.4†	95.8	95.8	97.6	97.6
Codeine	91.4*	100.0†	85.4	96.9	78.0	92.7
Anti-IgE	85.7*	92.9†	88.5	89.6	90.2	87.8
P-K‡	100.0	83.3	100.0	100.0	40.9	45.0

* Only thirty-five cases tested.

† Only twenty-eight cases tested.

‡ Number of cases tested in P-K in order across row: 20, 18, 49, 28, 22, 40.

Faeces examination

Serially collected faeces samples were examined for the presence of eggs of intestinal helminths, after ZnSO₄ flotation when necessary [23]. As *Ascaris* was the most common helminth detected in the study population [13, 20], only the frequency of occurrence of this parasite is presented in the results section.

Statistical analysis

The total IgE levels were logarithmically transformed, and the mean +1 s.d. calculated. The means were compared by Student's *t*-test.

For the other tests, the proportions positive of the different groups were compared, using the raw data, by the χ^2 test.

Results

Parasitic infection and total IgE levels

In Table 2 it can be seen that infection by *Ascaris* was uncommon in the HSEL, moderately frequent in the MSEL, and prevalent in the LSEL. No statistically significant differences in the positivity for the parasite were noted between allergic and non-allergic subjects in any group.

The total serum IgE levels increased from relatively low values in the HSEL through to high concentrations in the LSEL, and whilst being generally higher in the allergic than the non-allergic subjects, this difference was statistically significant only in the MSEL and HSEL ($P < 0.001$).

Table 4. Positivity (%) for specific IgE antibody in allergic or non-allergic subjects of different socio-economic levels

	HSEL		MSEL		LSEL	
	Non-al. (63)	Al. (63)	Non-al. (96)	Al. (96)	Non-al. (41)	Al. (41)
<i>> level 1</i>						
House dust	23.8	55.6	54.2	61.5	53.7	75.6
Moulds	11.1	36.5	24.0	31.3	22.0	53.7
Insects	6.3	41.3	35.4	40.6	39.0	65.9
<i>Ascaris</i>	4.8	7.9	58.3	68.8	75.6	82.9
<i>> level 2</i>						
House dust	12.7	50.8	43.8	47.9	31.7	24.4
Moulds	6.3	27.0	8.3	27.1	9.8	7.3
Insects	6.3	30.2	11.5	16.7	14.6	12.2
<i>Ascaris</i>	3.2	4.8	16.7	21.9	56.1	41.5

Skin test positivity

The results of skin-prick testing (Table 3) demonstrate that allergic subjects of the HSEL were highly reactive toward extracts of common environmental inhalant allergens, and were significantly more so than their non-allergic counterparts ($P < 0.01$). The cutaneous reactivity of allergic individuals of the MSEL was also high but in this group the non-allergics were comparably responsive to the environmental allergens tested. In the LSEL the overall cutaneous positivity was low, and in general the allergic and non-allergic subjects showed similar reactivity.

The cutaneous positivity to *Ascaris* extract was low in the HSEL, moderate in the MSEL and high in the LSEL, but showed no relation with the allergic state.

The skin reactivity toward histamine, codeine and anti-IgE was comparable between the different study groups, but significantly lower positivity in P-K tests was found in the LSEL ($P < 0.01$). No differences related to the allergic state were demonstrated in these tests.

Specific IgE levels

In Table 4 it can be seen that a high proportion of the allergic subjects of HSEL had significant levels of serum IgE antibody against common inhalant allergens, and that non-allergics showed clearly lower positivity ($P < 0.01$). This was effectively the case whether levels of ≥ 0.35 (level 1) or ≥ 0.7 (level 2) PRU/ml were taken as positive. A generally good agreement between the results of skin testing and the presence of specific IgE antibody was observed in this group.

In the MSEL, as was found for skin testing, positivity for specific IgE was high in both allergic and non-allergic subjects. In the LSEL, in contrast to the skin test results, significant levels of IgE antibody were detected in relatively high proportions of the subjects, when values ≥ 0.35 PRU/ml (level 1) were taken as positive. Similarly to the MSEL, the positivity for specific IgE was not greatly different between allergic or non-allergic subjects of LSEL. When the limit was raised to ≥ 0.7 PRU/ml (level 2) the proportion positive was significantly reduced ($P < 0.01$). In fact, when allergic subjects

were considered, a much greater difference was found between the proportions positive against house dust at level 1 or 2 in the LSEL (75.6 vs 24.4%; $\chi^2 = 21.5$) compared to the HSEL (55.6 vs 50.8%; $\chi^2 = 0.29$).

Discussion

Allergic individuals are generally considered to demonstrate a number of particular characteristics that are closely related to their clinical condition. These include high immediate hypersensitivity skin reactivity to offending environmental allergens [3–5], significant serum levels of specific IgE antibody against these allergens, and elevated total serum levels of this immunoglobulin [1, 2]. Indeed, we found that allergic subjects in the tropical situation, and belonging to the high socio-economic level, were highly reactive to allergenic materials in their environment, and were significantly more so than their non-allergic counterparts. This was demonstrated both by skin testing and the measurement of specific IgE. The allergic group also had significantly elevated total IgE levels compared to the non-allergics. Less than 10% of the HSEL showed evidence of parasitic infection, either by examination of serially-collected faeces samples or by skin-test positivity to *Ascaris* extract. The latter does not provide a precise indication of actual infection, as not all exposed individuals develop cutaneous sensitivity, and the reactivity of responding subjects can persist for long periods after the apparent elimination of the parasite [24, 25]. However, skin reactivity to *Ascaris* extract does allow an estimation of the general degree of exposure of the population.

When subjects of medium to high socio-economic level were considered, less than 20% were found to be harbouring *Ascaris*. The observation that almost 40% of the group exhibited positive skin tests to the parasite extract does, however, suggest that contact with intestinal helminths is common in this socio-economic level. This was possibly the cause of their generally higher levels of total serum IgE, as such parasites can cause polyclonal stimulation of the synthesis of this immunoglobulin [8–11]. From the social and cultural point of view, the subjects of HSEL and MSEL were relatively comparable, perhaps the most striking difference being their degree of exposure to intestinal helminths. In this respect, the importance of the effect of mild parasitic infection on IgE synthesis was indicated by the finding that even the non-allergic subjects of MSEL demonstrated a high degree of positivity for specific IgE antibody against environmental allergens, and showed a correspondingly high cutaneous reactivity to extracts of these. This strengthens the concept that while the basic component of allergic reactions is IgE-mediated, allergen-stimulated, mast cell degranulation, the development of a disease process requires the intervention of a more complex series of factors. It is, however, important to note that the prevalence of allergic conditions in this socio-economic level is high [13].

In the LSEL, both the frequency of intestinal helminthiasis and the total IgE levels were elevated. In this group, the difference in total serum IgE levels between allergic and non-allergic subjects was not statistically significant, as was also the case for specific IgE. In these subjects of LSEL, a clear dissociation was found between the results of skin testing and specific IgE measurement. Whereas the positivity to environmental inhalant allergens was high for specific IgE antibody, the skin test reactivity to these was relatively low. We identified two factors that could contribute to this situation. The first is that whilst the total IgE levels were high, the response to a given allergen was relatively weak. Thus, when the threshold considered as positive for specific IgE was raised from 0.35 to 0.7 PRU/ml, a significantly lower proportion of the

LSEL were classified as positive. This effect was far less evident in the HSEL, in which the exposure to intestinal helminths was low. It appears, therefore, that in the LSEL, whilst the overall positivity for specific IgE is high, the activity of the antibody being detected was only of low grade.

It may be postulated that under conditions of intense helminthic infection the stimulation of IgE synthesis is widely polyclonal, and that the effect on each individual antibody specificity is relatively small.

The second factor that could possibly bear relation to the low cutaneous reactivity of the LSEL is reflected by the depressed positivity of P-K tests in this group. Various studies have suggested that the high levels of polyclonal IgE induced by parasitic infection may competitively inhibit the capacity of IgE antibody of a given specificity to sensitize the target cells [17, 26–30]. We showed that the cutaneous sensitivity of the LSEL to histamine was not altered, and that the basic integrity of the mast cells was maintained, as judged by reactivity to codeine and anti-IgE. The inhibition of passive sensitization suggests that the binding of IgE to mast cells is indeed less efficient in the LSEL. This socio-economic level does, in fact, demonstrate a significantly lower prevalence of allergic disease, compared to the MSEL or HSEL [13, 20].

The results of this study suggest, therefore, that factors related to the socio-economic level of tropical populations can influence the allergic reactivity of the group, and that intestinal helminthic infection could be an important factor in this effect.

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