

Serum IgG, IgA, IgM, and IgE levels and allergy in Filipino children in the United States

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The serum levels of IgE, IgG, IgA, and IgM of 27 American-born Filipino children 5 to 17 years of age were measured and found to be significantly higher than those of a control group of 24 Caucasian children of similar age distribution and attending the same general pediatric clinics. The geometric mean of serum IgE of the Filipinos was 227 U. per milliliter and of the Caucasians, 69 U. per milliliter ($p < 0.01$). The geometric means of other serum immunoglobulin levels of the Filipinos by comparison with the Caucasians were: IgG, 1,303 and 1,010 mg. per 100 ml. ($p < 0.01$); IgA, 195 and 120 mg. per 100 ml. ($p < 0.001$); and IgM, 141 and 92 mg. per 100 ml. ($p < 0.02$), respectively. The incidence of atopic disease was higher in the Filipino study group (48 per cent) than in the Caucasian control group (25 per cent); eczema was especially prevalent in the Filipino group. Elevated serum IgE levels were associated with atopic disease in both racial groups; however, there was no correlation between serum level of IgG, IgA, or IgM and atopy.

The level of IgE in serum is frequently elevated in individuals with allergic disease.¹⁻³ Serum IgE levels,⁴⁻⁵ as well as the probability of developing allergic disease,⁶⁻⁸ are largely under genetic control, although the mode of inheritance of these traits and their interrelationship has not been established.

In the absence of extraordinary antigenic stimulation, the serum IgE level of an individual remains relatively constant.^{5, 9} However, markedly elevated IgE levels occur in some, but not all, humans in association with a variety of helminth infestations.¹⁰⁻¹⁵ It is possible that racial groups differ in the extent to which IgE levels are increased, since very high IgE levels are noted most commonly in populations that are not of European descent. Although this difference may simply be a result of increased exposure to helminths, in the Ethiopian¹⁰ and Filipino¹² populations specifically, the IgE levels of healthy individuals as well are elevated relative to the IgE levels in populations of European descent. The differences in IgE levels between healthy non-European individuals resident in their native countries and healthy individuals of European descent resident in Europe or North America may result wholly from non-genetic factors such as undiagnosed or prior helminth infestation in the non-European control population. Alternatively, these differences may be due

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TABLE 1. Immunoglobulin levels, race, age, presenting complaint, and allergic status of study patients, listed in rank order of serum IgE levels

Rank order	Race	Serum IgE (U./ml.)	Atopic disease	Serum IgG (mg./100 ml.)	Serum IgA (mg./100 ml.)	Serum IgM (mg./100 ml.)	Presenting complaint	Age (yr.)
1	F.*	21,000†	Eczema	1,391	164	157	URI**	9
2	F.	2,530†	Eczema	1,470	164	147	Spondylosis	13
3	C.‡	1,378	Asthma	1,051	164	136	Vomiting	10
4	F.	880†	Eczema	1,051	22	181	Carbuncle	17
5	C.	671	○	1,051	213	83	Abdominal pain	11
6	F.	580†	Eczema	1,739	236	231	URI	14
7	F.	540†	Eczema	2,056	390	157	URI	6
8	C.	527	Asthma	1,176	291	78	URI, diarrhea	16
9	F.	500†	○	1,470	213	136	URI	11
10	F.	410†	○	1,315	113	136	Checkup	12
11	F.	385†	Eczema	1,243	164	136	Eczema	13
12	F.	325	Eczema	1,315	291	160	Contact rash	14
13	F.	310	Hay fever	1,315	202	136	URI	8
14	C.	302	Asthma	1,389	121	136	Asthma	8
15	F.	290†	Asthma	1,470	224	231	Eye check	16
16	F.	250	○	1,739	276	157	URI	13
17	F.	227†	○	1,112	213	103	URI	13
§18	F.	225	○	994	120	96	Checkup	12
19	C.	215	○	1,112	140	136	Sore throat	17
20	C.	213	Asthma	675	74	45	Sore throat	15
21	C.	193	Hay fever	940	120	111	Influenza	11
22	F.	187	○	1,176	182	157	Rash on leg	15
23	F.	182	Eczema	1,243	192	195	Checkup	7
24	F.	166	○	1,243	164	72	URI	5
25	F.	166	○	1,315	173	89	Rash on face	14

*Filipino.

**Upper respiratory tract infection.

†Stool examined for ova and parasites.

‡Caucasian.

§Median serum IgE levels for Filipinos.

¶Median serum IgE levels for Caucasians.

at least in part to genetic factors. Racial genetic differences resulting in elevated IgE levels may also explain the high frequency of atopic eczema observed among infants of Chinese descent in the United States¹⁶ and among children of West Indian descent in England.¹⁷

In order to evaluate the possibility that racial groups differ in serum IgE levels as a result of genetic factors, we compared American-born children of Filipino descent and an otherwise similar group of American-born children of European descent. The Filipino as well as the Caucasian populations studied consisted of dependents of United States Army personnel and shared a similar standard of living and access to medical care. Filipinos, rather than another racial group, were selected for this study because of this opportunity to compare individuals who were of similar socioeconomic status and because we and our colleagues had observed a high incidence of atopy in Filipinos.

MATERIALS AND METHODS

Study population

The study population consisted of 27 patients of bilateral Filipino descent 5 to 17 years of age and 24 Caucasian control patients with a similar age distribution attending pediatric

TABLE I. Cont'd

Rank order	Race	Serum IgE (U./ml.)	Atopic disease	Serum IgG (mg./100 ml.)	Serum IgA (mg./100 ml.)	Serum IgM (mg./100 ml.)	Presenting complaint	Age (yr.)
26	F.	154	Eczema	1,315	164	89	Eczema	15
27	F.	142	Asthma	1,470	213	157	URI	5
28	C.	138	○	753	48	96	Checkup	10
29	C.	126	Asthma	1,391	133	244	Checkup	12
30	F.	115	Hay fever	1,112	156	136	Checkup	16
31	F.	106	○	940	224	157	Checkup	10
32	F.	105	○	1,112	213	78	Checkup	7
33	C.	88	○	639	63	103	Checkup	6
34	C.	75	○	855	205	136	Contact rash	8
35	C.	60	○	1,051	173	195	URI	5
36	F.	54	○	1,051	182	300	Injury	13
37	C.	53	○	1,051	182	83	Cough	9
38	C.	48	○	940	173	111	Impetigo	9
39	C.	47	○	1,470	133	169	URI	16
40	C.	46	○	2,105	291	200	Jaw swelling	11
41	F.	45	○	1,644	133	246	URI	8
42	C.	31	○	796	78	119	Abdominal pain	16
43	C.	27	○	1,710	82	136	Headache	17
44	C.	23	○	713	173	136	URI	15
45	F.	22	○	1,391	306	89	Sore throat	9
46	C.	15	○	631	58	54	Poison oak	12
47	C.	12	○	1,209	146	96	Injury	10
48	C.	11	○	1,112	60	147	Injury	9
49	C.	9	○	889	82	54	Sore throat	6
50	C.	8	○	751	61	103	Cyst-knee	15
51	F.	7	○	1,112	182	111	Checkup	5

clinics, other than the allergy or dermatology clinics, at Letterman General Hospital, San Francisco. Parental consent to take a venous blood sample for a clinical study was obtained; allergy was not mentioned in order to avoid biased selection of patients with a special interest in allergic disease. Patients were questioned regarding the duration of residence in the United States and duration and location of residence overseas; any who reported residence elsewhere than in the United States or northern Europe were excluded from the study in order to minimize the probability of including individuals with elevated serum IgE levels due to previous helminth infestation.

Filipino patients with serum IgE levels above 200 U. per milliliter were asked to return to the clinics with two stool samples; a brief allergy history was then taken. The allergy history of all subjects was obtained from the hospital records; in every case in which a positive allergy history was obtained by interview it was confirmed by the hospital records. No bias favoring a diagnosis of allergy was therefore introduced by interviewing only selected patients.

Measurement of serum immunoglobulin levels

IgE levels were measured using a radioimmunoassay previously described.¹⁸ All experimental and standard sera were assayed in duplicate; the intraclass correlation coefficient of random normal samples assayed twice (where each assay was the average of duplicate determinations) was 0.996, indicating a high degree of reproducibility relative to the range of normal variation of IgE levels. IgE levels are expressed as units relative to World Health Organization IgE Standard 68-341 (one unit has been reported to contain 2.2 to 2.4 ng. IgE).^{9, 18, 20}

Serum IgG, IgA, and IgM levels were measured using radial immunodiffusion plates purchased from Meloy Laboratories, Springfield, Virginia. Levels are expressed as milligrams per 100 ml., relative to Meloy Laboratories standard serum Lot D701-5-1, to which both

TABLE II. Immunoglobulin data and statistical analyses

	Race	n	Mean $\pm$ S.D. Log ₁₀	Geometric mean	p
IgE	F.†	27	2.356 $\pm$ 0.636†	227.1 U./ml.	< 0.01*
	C.‡	24	1.839 $\pm$ 0.613	69.0 U./ml.	
IgG	F.	27	3.115 $\pm$ 0.079	1,303.2 mg./100 ml.	< 0.01
	C.	24	3.005 $\pm$ 0.135	1,010.4 mg./100 ml.	
IgA	F.	27	2.291 $\pm$ 0.120	195.2 mg./100 ml.	< 0.001
	C.	24	2.078 $\pm$ 0.228	119.6 mg./100 ml.	
IgM	F.	27	2.148 $\pm$ 0.156	140.6 mg./100 ml.	< 0.02
	C.	24	1.966 $\pm$ 0.336	92.4 mg./100 ml.	

*Calculated by Mann-Whitney U test; other significance levels determined by t test.

†Filipinos.

milligrams per 100 ml. values and International Unit values have been assigned by the manufacturer. These values for IgG are 1,710 mg. per 100 ml. and 208 I.U. per milliliter; for IgA, 291 mg. per 100 ml. and 191 I.U. per milliliter; and for IgM, 153 mg. per 100 ml. and 219 I.U. per milliliter.

Stool examination

Two stool samples were obtained from each patient tested. Portions of each sample were examined both after concentration by the ZnSO₄ centrifugal flotation method²¹ and after concentration by the sodium sulfate-acid-triton-ether sedimentation method.²² Ten random stool samples from Tijuana, Baja California, Mexico, an area in which helminthiasis is endemic, were examined concurrently, and 9 of these 10 individuals were found to be infested with one or more species of helminth parasites and protozoa. These samples thus provided a positive control series for the methods used.

Statistical analyses

All computations were done on the log₁₀ of the immunoglobulin concentration, since the log₁₀ of serum levels of IgG, IgA, and IgM have Gaussian distributions.²³ For statistical analyses of immunoglobulin levels not involving IgE, the t test for differences between independent means and Pearson's correlation coefficient were used. For calculations in which IgE levels were a variable, the Mann-Whitney U test for differences of medians or Spearman's

	n	Mean $\pm$ S.D. Log ₁₀	Geometric mean	p
Atopic F.	13	2.683 $\pm$ 0.612	481.5 U./ml.	
Nonatopic F.	14	2.053 $\pm$ 0.509	113.1 U./ml.	
Nonatopic C.	18	1.615 $\pm$ 0.506	41.2 U./ml.	
Atopic C.	6	2.509 $\pm$ 0.372	322.8 U./ml.	
Atopic F.	13	3.139 $\pm$ 0.076	1,377.2 mg./100 ml.	
Nonatopic F.	14	3.093 $\pm$ 0.079	1,237.4 mg./100 ml.	
Nonatopic C.	18	2.996 $\pm$ 0.142	990.8 mg./100 ml.	
Atopic C.	6	3.030 $\pm$ 0.119	1,071.5 mg./100 ml.	
Atopic F.	13	2.315 $\pm$ 0.115	206.2 mg./100 ml.	
Nonatopic F.	14	2.268 $\pm$ 0.124	185.4 mg./100 ml.	
Nonatopic C.	18	2.058 $\pm$ 0.240	114.3 mg./100 ml.	
Atopic C.	6	2.139 $\pm$ 0.196	137.7 mg./100 ml.	
Atopic F.	13	2.199 $\pm$ 0.109	158.1 mg./100 ml.	
Nonatopic F.	14	2.101 $\pm$ 0.181	126.2 mg./100 ml.	
Nonatopic C.	18	1.996 $\pm$ 0.287	99.1 mg./100 ml.	
Atopic C.	6	1.874 $\pm$ 0.476	74.1 mg./100 ml.	

†Log₁₀ rounded off to nearest 0.001.

§Caucasians.

rank-order correlation coefficient were used, since, in larger samples, the serum IgE levels and the log₁₀ of serum IgE levels have a multimodal^{3, 5, 18} rather than a Gaussian distribution.

RESULTS

The experimental data consisting of serum IgE, IgG, IgA, and IgM concentrations, atopic disease, presenting complaint, and age for Filipinos and for Caucasian controls are shown in Table I. The two groups were well matched for age (Filipinos: mean, 11.11 yr., S.D., 3.48; Caucasians: mean, 11.42 yr., S.D. 3.71) and were attending the clinics for a variety of reasons. Acute infections of the throat or respiratory tract constituted the most frequent presenting complaint and accounted for 41 per cent and 37.5 per cent of clinic visits by Filipinos and Caucasians, respectively.

Although the presenting conditions represented a normal spectrum of complaints, the history revealed a significant difference ($p < 0.05$)* in the incidence of atopic disease in the Filipino group (48 per cent) by comparison with the Caucasian group (25 per cent). Eczema is especially prevalent in the Filipino

*Single tailed test of the significance of two proportions, normal approximation to the binomial.

group and constitutes 69 per cent of the atopic disease in this group. One subject with eczema had, in addition, minimal asthma (rank order No. 8) and another (rank order No. 11), mild allergic rhinitis. All seven patients with eczema who were interviewed had had the condition since infancy; 5 of these (71 per cent) had a positive history of atopic disease in the immediate family. This is consistent with a previous report of positive family histories in about 60 per cent of cases.²⁴ No case of eczema was detected in the Caucasian control group, which is consistent with an incidence of 3 per cent to 11 per cent previously reported in young Caucasian children.^{16, 25}

Summarized serum immunoglobulin data and statistical analyses are presented in Table II. Serum IgE levels in the Filipino group are significantly higher than those of the Caucasian group and are, predictably, significantly higher in both Filipino and Caucasian atopic patients than in nonatopic patients of the same racial group. The difference in IgE concentration between atopic Filipinos and atopic Caucasians is not statistically significant. The elevated serum IgE levels observed in the Filipino group are consistent with the high incidence of atopic disease and are not a consequence of helminth infestation; all stool samples examined were negative for ova and parasites.

Additionally, the serum concentrations of IgG, IgA, and IgM are significantly elevated in the Filipino group as a whole relative to those of the Caucasian control group. Of special interest is the possibility that the increased concentrations of these immunoglobulins are secondary to atopic disease or eczema. However, the differences between atopic and nonatopic subjects and between eczematous and nonatopic subjects are not significantly different for IgG, IgA, or IgM within a racial group. Moreover, the serum concentrations of IgG, IgA, and IgM of atopic and nonatopic Filipinos are higher than those of atopic and nonatopic Caucasians, respectively (although in the case of IgM, the difference between nonatopic Filipinos and nonatopic Caucasians is not statistically significant). There is, therefore, no evidence that the elevated serum levels of IgG, IgA, and IgM observed in the Filipinos are specifically associated with atopic disease.

No significant correlation is observed between elevation of serum IgE level and elevation of serum concentration of IgG, IgA, and IgM within each racial group. However, a positive correlation was found between IgG and IgA concentrations in the Caucasian group as a whole ($r = 0.51$, $p < 0.02$) and between IgG and IgA concentrations in the atopic Filipino group ($r = 0.61$, $p < 0.05$). An association between the serum IgG and IgA level has been reported previously.²⁶ We are not able to ascribe any biologic significance to these correlations.

There is no significant correlation between age and serum concentration of the immunoglobulins assayed. The rate of change of immunoglobulin concentration in the age group studied is expected to be small.^{27, 28}

DISCUSSION

The serum immunoglobulin levels, most notably the serum IgE levels, as well as the frequency of atopy, were much higher in the Filipino group by com-

parison to the Caucasian group in this study. The Caucasian group studied would appear to be similar to the Caucasian population in general; the slightly higher geometric mean (69 vs. 40 U. per milliliter in adult Caucasian veterans)⁵ and somewhat higher frequency of allergic disease (25 per cent vs. 16.7 per cent found in a study of college students)⁸ may result from statistical fluctuation or from the fact that the group studied did not consist of unselected individuals, but instead consisted largely of sick children whose presenting complaints included atopic disease. The levels of IgG, IgA, and IgM found for the Caucasians were directly comparable to those found in other studies.^{27, 28} The extent to which the Filipino group studied corresponds to the Filipino population in general is not known, although the selection of sick patients rather than random individuals would result in some bias toward a higher apparent frequency of high IgE levels and allergic disease. We are not aware of any factors that would differentially select for atopy or elevated immunoglobulin levels in the Filipino group studied as opposed to the Caucasian group. Although we cannot exclude the possibility that unrecognized subtle cultural effects may account for the results obtained, we regard this as unlikely, especially since the Filipino children interviewed appeared to be well integrated into the general community. Helminthiasis has been excluded as a possible cause of elevated IgE levels in the Filipino patients both by stool examination and by the exclusion of patients who have resided in areas of endemic helminthiasis. In view of the considerations above, we interpret the differences in immunoglobulin levels and frequency of atopy to be the result of genetic differences between the two racial groups.

Twin studies^{4, 5} have shown that serum IgE levels are largely determined by genetic factors in Caucasians and, although the mode of inheritance is not established, it seems likely that a small number of loci are involved. With the exception of patients with helminthiasis or IgE myeloma, the Filipino patient with a serum IgE level of 21,000 U. per milliliter and another Filipino previously reported to have a serum IgE level of 22,000 U. per milliliter¹⁵ constitute two of the three IgE levels greater than 5,000 U. per milliliter observed in the approximately 1,500 serum IgE levels measured in this laboratory. It is possible that these two individuals represent the homozygous condition of a gene that, because of its low frequency in Caucasian populations, occurs almost exclusively as the heterozygote in populations of European descent. The lack of a significant difference between serum IgE levels in atopic Filipinos and atopic Caucasians indicates that elevated serum IgE levels are associated with allergic disease in both groups; the significant elevation of serum IgE levels of non-atopic Filipinos relative to nonatopic Caucasians may result from the fact that elevated IgE levels, which occur much more commonly in the Filipinos, are not invariably associated with allergy.

Serum levels of IgG, IgA, and IgM are also significantly higher in the Filipinos than in the Caucasians in this study. The serum level of IgG has previously been shown to be elevated in Negroes by comparison to Caucasians living within the same geographic area.²⁸⁻³⁰ This appears to be unrelated to social class^{26, 30} and has been attributed to genetic differences between the

two races. Twin studies^{31, 32} have shown that within the Caucasian population, a significant proportion of the variance of serum IgG, IgA, and IgM levels is the result of genetic effects, and, since the levels of these immunoglobulins in normal Caucasians overlap the levels observed in Filipinos, it is reasonable to assume that the differences in levels observed between Caucasians and Filipinos represent differences in gene frequencies rather than qualitative genetic differences.

Unusual gene frequencies for traits that are selectively neutral may occur in isolated populations simply as a result of genetic drift, and this mechanism may be responsible for the elevated IgE levels observed in Filipinos. However, the genes that determine elevated serum IgE levels, which are associated with increased morbidity and mortality from atopic disease, would presumably be selected against in the absence of compensating factors. Two possible compensating factors, contingent upon endemic helminthiasis, may be considered. The occurrence of protective reagin-mediated immunity to helminthiasis has been suggested on the basis of animal experiments³³ and an observation in humans¹³; this would constitute a selective advantage for IgE production. Another possibility is the speculation, based on indirect evidence,¹⁵ that helminthiasis should reduce the likelihood of allergic disease, which would cause genes for IgE production to be selectively neutral in areas of endemic helminthiasis.

The hypothesis that helminthiasis reduces the likelihood of allergic disease may be relevant as well to the observation of greatly increased incidence of atopic eczema among the children of Chinese or West Indian immigrants to the United States and to England, respectively, relative to the incidence of eczema in their parents' country of origin, in which the frequency of helminthiasis may be expected to be very high. This hypothesis does not preclude the possibility that differences of diet, climate, or other as yet unidentified environmental variables constitute etiologic factors that determine the manifestation of atopic disease in genetically predisposed individuals.

In view of the evidence that genetic factors affect both serum immunoglobulin levels and allergic disease, it is important that appropriate control groups be selected in immunologic studies of populations that are racially heterogeneous.

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Select the ONE best answer for the following question from the Allergy Foundation of America Self-Assessment Program:

Question 1. Which of the following statements about allergy to mold is correct?

- (A) The air is never free from fungus spores, but their numbers are fewest when the ground is covered with snow
- (B) Persons allergic to inhaled fungi usually have gastrointestinal symptoms when they ingest foods containing fungi
- (C) Sampling of mold populations by indoor culturing is valuable because there is little variation between indoor and outdoor species of fungi
- (D) Foam rubber in bedding and furniture is safe from contamination because foam rubber contains few nutrients that foster growth of molds
- (E) Persons allergic to *Penicillium* mold react adversely to penicillin

The correct answer and bibliographic reference will be found on page 244 of this Journal.