

Serum Immunoglobulin E Levels in Israeli-Ethiopian Children: Environment and Genetics

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Abstract

Background: Since 1984, several waves of Ethiopian immigrants have settled in Israel. On arrival they were found to be highly infected with intestinal parasites and to have increased serum immunoglobulin E and eosinophilia.

Objectives: To study serum IgE levels in Ethiopian children growing up in the environment of Israel.

Methods: We assessed four groups of children of Ethiopian origin: a) adolescents examined on their arrival to Israel (group 1, n=11); b) adolescents born in Ethiopia and living in Israel for more than 7 years (group 2, n=10); c) children of Ethiopian origin born in Israel, without a history of allergy or asthma (group 3, n=15); and d) asthmatic children of Ethiopian origin born in Israel (group 4, n=8). A thorough clinical interview and examination as well as laboratory work up (including serum IgE levels, stool parasites and absolute eosinophil count) were performed.

Results: Group 1 (11 newly arrived Ethiopian adolescents) had a mean eosinophil count of 688 cells/ml (0–1739) and a mean serum IgE of 1043 IU/ml (253–2932), $P < 0.0009$ as compared to group 2. Helminthic parasites were observed in 8/11 individuals; after 1 year of follow-up and anti-parasitic treatment, serum IgE levels did not change significantly. Group 2 (10 Ethiopian born adolescents living in Israel for on average 10 years, 7–15 years) had a normal leukocyte count, MEC 192 cells/ml (range 54–289), serum IgE 142 IU/ml (range 14–399 IU/ml) and no parasites in stool. Group 3 (15 Ethiopian children born in Israel) had a normal leukocyte count, MEC 128 cells/ml (0–324), serum IgE 55 IU/ml (7–189 IU/ml), similar to age-matched Israeli controls. In group 4 (8 Israeli born children of Ethiopian descent diagnosed with asthma), serum IgE showed significant elevation compared to Israeli age-matched asthmatic children ($P < 0.005$).

Conclusions: High levels of IgE found in Ethiopian children on arrival to Israel declined to Israeli control levels after several years of living in the new environment. Ethiopian children born in Israel had normal levels of IgE, suggesting that environment is the main factor affecting IgE levels in this population. Israeli born Ethiopian children with asthma had significantly increased serum IgE levels compared to asthmatics of Israeli origin. These findings suggest that both environmental and genetic factors determine the level of serum IgE in these children.

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Since 1984 Israel, already an amalgam of different ethnic backgrounds, received successive waves of Ethiopian immigrants fleeing the devastation of famine, disease and war in Africa. To date, approximately 60,000 Ethiopian Jews have settled into the Israeli western lifestyle and environment. On arrival, the overwhelming majority (75%–90%) was found to be infected with intestinal parasites [1–4], serum immunoglobulin E levels were extremely high [5,6], most had peripheral blood hyper-eosinophilia [5,6], and very few reported a history compatible with atopic disease [6,7]. The high serum IgE is thought to be a consequence of both parasite-specific and Th2-dependent parasite non-specific immune responses [8–13]. High IgE levels due to ectoparasite infestation usually decline after successful treatment of the infection [14], although the time frame for this reduction is variable.

The present study aimed to explore whether environmental or genetic factors are responsible for the elevated serum IgE found in young Ethiopian immigrants to Israel.

Patients and Methods

Patients

We assessed four groups of children of Ethiopian origin.

- **Group 1 (n=11):** Ethiopian adolescent immigrants, who arrived at the Ofra settlement with their families in 1998, were examined within 1–3 months of their arrival to Israel. This was part of a larger prospective study that included adults and children. Demographic data, environmental conditions and history of atopy-related complaints were recorded using two simply structured questionnaires translated into Amharic and filled out with the help of a trained health worker. Clinical status was described and a laboratory workup was done, including complete blood count, absolute eosinophil count, stool examination for parasites, and total serum IgE. Immediate-type hypersensitivity to common aeroallergens was assessed by skin prick test. All patients in this group were reexamined 1 year later after at least one treatment course for intestinal parasites.

Ig = immunoglobulin
MEC = mean eosinophil count

- **Group 2 (n=10):** Ethiopian adolescent “oldtimer” immigrants, living in Israel for more than 7 years, were examined on a routine visit to a pediatric primary care facility. Their medical records were reviewed and they were interviewed regarding history of allergic disease. They also underwent a thorough clinical evaluation and a laboratory workup including complete blood count, absolute eosinophil count, total IgE in serum, and stool examination for parasites.
- **Group 3 (n=15):** First-generation Israeli born children of Ethiopian descent were examined on a routine visit to a pediatric primary care facility. Their medical records were reviewed and the patients’ parents/guardians were interviewed regarding history of atopy. Clinical status and results of a laboratory workup, including complete blood count, absolute eosinophil count, total IgE in serum and stool examination for parasites, were recorded.
- **Group 4 (n=8):** First-generation Israeli born children of Ethiopian descent with a diagnosis of asthma were all siblings of patients in group 3. They underwent the same clinical and laboratory investigation performed by the same clinician.
- **Controls:** As normal values for IgE we used published data on serum IgE levels of healthy Israeli children at various ages [15]. For data on IgE levels in Israeli asthmatics we summarized 1 year of data from the pediatric asthma clinic at Kaplan Medical Center in Rehovot, Israel.

Methods

- **Skin prick tests:** Skin prick tests were carried out according to accepted recommendations using lancets for prick in the forearm of the patients and glycerinated standardized allergen extracts, including dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), feather mix, cat and dog epithelium, mold mix, pollens of grass mix, parietaria, weed mix, olive and cypress. Histamine (1 mg/ml) was used as a positive control and glycerinated saline solution as a negative control. All allergens used are standardized extracts manufactured by Bayer (Spokane, WA, USA).
- **Stool examination for parasites:** Determination of helminths in stool specimens was performed by quantification of parasite eggs in the stool. The stool samples were stored at 40°C

Table I. Mean and 95% confidence interval of peripheral blood eosinophils and serum IgE in Ethiopian children

Ethiopians	No. of patients	Blood eosiniphils	Serum IgE	Parasite infestation
Newly arrived (group 1)	11	688 (241–1136)	1044 (552–1536)	8 (73%)
One year later	11	786 (247–1325)	1356 (492–2220)	6 (54%)
“Oldtimers” (group 2)*	10	192 (125–256)	142 (46–238)	0
Israeli born (group 3)**	15	187 (112–282)	55 (32–78)	0
Israeli born with asthma (group 4)***	8	385 (42–728)	1455 (491–2419)	0

* Adolescents born in Ethiopia and living in Israel >7 years.
 ** First-generation Israeli born children of Ethiopian descent, without clinical evidence of atopic disease.
 *** First-generation Israeli born children of Ethiopian descent, with clinical evidence of asthma, and siblings of patients in group 3.

until examination within 7–14 days. Stool examinations and egg counts were performed according to Beaver et al. [16] and a modification of the Richie formalin-ether sedimentation method [17] Hookworm larval identification was done using an agar plate fecal culture method [18].

- **Serum total IgE level:** Measurements of total IgE were performed using a commercial assay (Abbott Laboratory’s Total IgE IMx System, USA). The lower detection limit of this system is approximately 0.048 IU/ml (0.1 ng/ml).

Statistical evaluation

Comparison of means was performed using a one-tailed ANOVA, SPSS for Windows, Version 11.5.

Results

Group 1 consisted of 11 new immigrant adolescent patients at the Ofra settlement clinic in 1998. The mean age of the 4 males and 7 females was 13.7 years (95% confidence interval 12.7–14.7). All were healthy by self-report and examination; none reported a history of allergic rhinitis, asthma or atopic dermatitis (atopy-related complaints), and none were taking medication. Stool examination revealed that 8 (73%) had single or multiple parasite species infestation. All patients had a normal white cell count and hemoglobin content. Values of absolute eosinophil count and serum IgE for all groups are shown in Table I. No significant difference was observed in mean serum IgE between the stool parasite-positive group and the parasite-negative patients. Skin prick tests for immediate-type hypersensitivity to common aero-allergens were all negative in this group on initial examination, while the histamine-positive control elicited a normal positive response. Follow-up of the same patients 1 year after arrival (group 1A) showed a decrease in parasite prevalence and a significant decrease in parasite load but no decrease in peripheral blood eosinophila and no decrease in serum IgE levels [Figure 1].

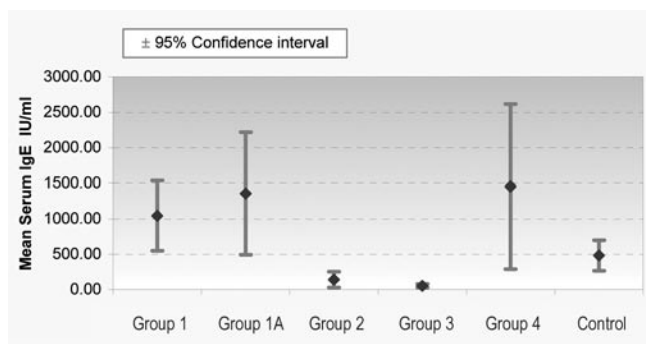


Figure 1. Comparison of mean serum IgE (95% confidence interval) in Ethiopian children.

Group 1 = newly arrived immigrants
 Group 1A = same patients after 1 year in Israel
 Group 2 (“oldtimers”) = adolescents born in Ethiopia and living in Israel >7 years
 Group 3 = first-generation Israeli born children of Ethiopian descent, without clinical evidence of atopic disease
 Group 4 = first-generation Israeli born children of Ethiopian descent, with clinical evidence of asthma, and siblings of patients in group 3.

Group 2 comprised 10 Ethiopian adolescent "oldtimer" immigrants examined at routine visits to a pediatric primary care facility during the period May 1998 to December 2000; the mean age of the 4 males and 6 females was 14.7 (95% CI 12.9–15.7). All were healthy by self-report, medical record review and physical examination, and none reported a history of atopy-related complaints or taking medication. All patients had a normal white cell count and hemoglobin content. All stools examined were negative for parasites. The results are detailed in Table 1 and Figure 1. As a group, total serum IgE was significantly reduced as compared to group 1.

In group 3 (15 children, first-generation Israelis of Ethiopian descent identified during routine visits to a pediatric primary care facility during the period May 1998 to December 2000), the mean age of the 5 males and 10 females was 6.4 (95% CI 4.1–8.7). All were healthy by parental report, medical record review and physical examination, and none reported a history of atopy-related complaints or taking medication. All patients had a normal white cell count and hemoglobin content. All stools examined were negative for parasites.

During the screening of patients in group 3 we identified eight asthmatic children in the same families, all of whom were born in Israel, and we performed a similar battery of tests for these patients. These eight patients constituted group 4 [Table 1]. All stools examined were negative for parasites. Mean serum IgE in this group was 1455 IU/ml (95% CI 491–2419). Analysis of variance demonstrated a significant difference ($P < 0.005$) in serum IgE between this group and an age-matched group of Israeli asthmatics [Figure 1].

Discussion

Metazoan intestinal parasites and plasmodium species are strong inductors of both parasite-specific and non-specific IgE. In newly arrived Ethiopian immigrants to Israel, high rates of parasite infestation and significant parasitic loads were repeatedly observed. After 1 year of living in Israel, despite a decrease in infestation rates and a decrease in parasitic load, mean serum IgE remained high. These results are consistent with previously published data from our group and from others. Our finding – that healthy adolescents born in Ethiopia and living in Israel for more than 7 years had IgE levels similar to age-matched Israeli controls [15] as well as to the observed normal serum IgE levels in Israeli born first-generation children of Ethiopian descent – is supportive of an environmental or parasite-associated effect. However, high levels of serum IgE found in Israeli born asthmatic children of Ethiopian descent, as compared to an age-matched cohort of Israeli asthmatics of Caucasian descent, support the conclusion that an additional mechanism, independent of parasite-induced immune deregulation, is also – at least partially – effective.

Theoretically, such mechanisms include the possibility of prenatal imprinting due to intrauterine exposure to maternal factors causing a Th2 skew [19–22]. Our group previously dem-

onstrated [23] that newborns of Ethiopian immigrant mothers with high serum IgE are born with relatively high cord blood IgE, directly proportionate to maternal values. Therefore, it is possible that the high serum IgE in asthmatics of Ethiopian origin is a first-generation effect of intrauterine "environmental" exposure.

Another possible contributing factor is a race-associated genetic mechanism; it was previously shown that IgE levels are higher in blacks than in Caucasians [24]. We hold that the racial attributed differences are not of themselves enough to explain the highly significant divergent results in this small sample of patients. Lastly, there may be as yet unidentified genetic factors that contribute in this population to increased IgE levels associated with atopy and asthma.

Conclusions

We have found that with time and parasite eradication, IgE levels in Ethiopian born adolescents declined to Israeli age-adjusted norms. Israeli-born healthy, non-atopic children of Ethiopian descent have IgE levels similar to those of their Israeli Caucasian peers. However, first-generation Israeli asthmatic children of Ethiopian descent had significantly higher IgE levels than Israeli asthmatics, even though they lived similarly in a "parasite-free" environment. Based on these results one could speculate that both genetic and environmental factors play mutually inclusive roles in the modulation of IgE production in this population.

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CI = confidence interval

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