

The Prevalence of Parasite Infestation and House Dust Mite Sensitization in Gabonese Schoolchildren

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Key Words

Atopy · Skin test reactivity · Malaria · Helminth · Schistosomiasis · Filariasis · IgE · Africa

Abstract

Background: Allergic diseases seem less prevalent in communities in less developed parts of the world, where parasite infections are highly prevalent. Altogether not much is known about the association between chronic infections with tissue and blood-dwelling parasites and atopy. **Methods:** In an area in Gabon endemic for blood and tissue parasites, 520 schoolchildren were parasitologically examined and skin prick-tested for a set of common environmental aeroallergens. Levels of allergen-specific IgE and polyclonal IgE were measured. **Results:** In schoolchildren schistosome and filarial infections increased with age, whereas malaria was more prevalent in younger children. In contrast to allergen sensitization that increased with age, skin test reactivity tended to decline. The number of children with mite-specific IgE antibodies (47%) by far exceeded the number responding to skin prick testing (11%). Mite sensitization was found to be the highest in children infected with schistosomes and/or filariae whereas skin test reactivity

was lowest. The multiple logistic regression showed that the risk of a positive skin test was 8-fold higher with increasing levels of mite-specific IgE but was reduced by 72% when infected with blood stage helminths. **Conclusions:** Chronic blood and tissue parasite infections that are often capable of modulating immune responses in the host are negatively associated with skin test reactivity in a sensitized population.

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Introduction

The hypothesis that the rise in allergy in developed countries might be associated with the simultaneous reduction of infectious diseases [1] has led to an increased interest in studying allergic diseases in tropical settings. Studies performed in areas where infectious diseases are still highly prevalent indicated that the prevalence of allergy in such less-developed parts of the world is indeed lower than in western societies. For example, in different African countries the prevalence of self-reported asthma, allergic rhinoconjunctivitis as well as atopic eczema was less than 5% [2–4], which is clearly lower than that reported in the west [2]. Additionally, the prevalence of

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allergic disorders in developing countries is higher in urban than in rural settings, indicating that the development of allergy is associated with a more western lifestyle [3]. Few studies performed in tropical settings have produced data supporting the hypothesis that infectious diseases and atopy are negatively associated. In Guinea-Bissau individuals vaccinated against measles were at a higher risk of becoming atopic than subjects who had had a history of measles infection [5] and in Venezuela children treated against infections with intestinal helminths became more atopic over time [6]. To improve our understanding of how atopy might be associated with infectious diseases, a more diverse range of pathogens needs to be studied [7]. Blood stage helminths as well as malarial parasites might be of particular interest as these infections are chronic in nature and are associated with profound immunomodulation in the host [8–11]. Helminths causing schistosomiasis and filariasis are capable of surviving for many years in their human host despite living in a close encounter with the immune system. There is evidence that the immune responsiveness is downregulated during these infections, on the one hand enabling parasites to survive and on the other restricting the extent of damage to the host [8, 12, 13]. Moreover, malarial parasites have a strong modulating effect on the immune system of the infected host, resulting in a spectrum of clinical manifestations [9–11].

In an area in Gabon where *Schistosoma haematobium*, filarial parasites (*Loa loa* and *Mansonella perstans*) as well as malarial parasites (mainly *Plasmodium falciparum*) are endemic, we have initiated a study to understand the parasitological and immunological associations with atopy [14]. Here we report in detail the epidemiological associations between chronic blood and tissue parasite infections, IgE antibodies and the outcome of skin test reactivity to environmental allergens.

Materials and Methods

Study Area and Population

The study was conducted in Lambarene, which is situated on the equator in a typical Central African rain forest area at the river Ogooué in Gabon. Temperature oscillates around 27°C and there is rainfall throughout the year with considerably less rain in June, July and August. Lambarene is the fourth largest town of Gabon and has two hospitals: a state hospital and the Albert Schweitzer hospital. During a meeting at school parents and teachers were informed about the study, after which parents were invited to give permission for the participation of their children. Children of parents who had not attended the meeting, but who also wanted their children to participate after having heard of the study by other parents or teachers

were included after the researchers had been contacted by the parents. During February 1999 and May 1999 a total of 520 schoolchildren were included in this study, 254 boys and 266 girls, aged between 5 and 15 years (mean age = 8.8 years).

The participants were questioned by local health workers concerning their respiratory function based on modified questionnaires from ISAAC studies. Questionnaires also included questions on lifestyle variables such as the type of material of the house they lived in, whether cooking was done with gas, and whether a main water supply was available.

The children were examined by medical doctors for skin disorders on arms, legs, face and/or back, which could be attributed to allergy. They were screened for parasitic infections and skin prick-tested for common aeroallergens. A small volume of blood obtained initially by finger prick was screened for malarial parasites and microfilariae, and was also collected onto filter paper for measuring the levels of total IgE antibodies. Further analyses for determining levels of allergen-specific antibodies were performed on venous blood. Individuals who were found positive for malarial infections or who were symptomatic were subsequently treated with sulfadoxine/pyrimethamine. Finally, part of the children (n = 69) were tested for exercise-induced bronchohyperresponsiveness. Briefly, peak expiratory flows were measured before and after an exercise of 10 min running, using a portable computerized spirometer. A child was considered to be hyperresponsive if after exercise the peak expiratory flow had fallen more than 15%.

The study was approved by the Ethics Committee of the International Foundation of the Albert Schweitzer Hospital in Lambarene, Gabon. Written informed consent was obtained from parents of the children participating in the study.

Parasitological Diagnostics

In this area *P. falciparum* is hyperendemic and responsible for more than 90% of all malarial infections together with some *Plasmodium malariae* and *Plasmodium ovale* infections [15]. *S. haematobium* is focally highly endemic and the nonpathogenic *Schistosoma intercalatum* is sporadically reported, whereas *Schistosoma mansoni* is not prevalent in this area. The filariae species that are prevalent are mainly *L. loa* and *M. perstans*.

Infection with *S. haematobium* was determined by passing 10 ml of urine through a filter with 10-µm pore size and staining the eggs with a solution of ninhydrin (Merck, Germany). Infection with filariae and/or malarial parasites was determined by the staining of thick blood smears with Giemsa at pH 7.2. The prevalence of intestinal helminths such as *Ascaris lumbricoides* and/or *Trichuris trichiura* was determined in a subset of 66 children by using the Kato-Katz method [16]. Of this random sample 65% was infected with *Trichuris* [mean load of 90 eggs (1–925)/50 mg feces] and 55% with *Ascaris* [mean load of 1,208 eggs (1–6,370)/50 mg feces]. 74% of the children were positive for at least one of these intestinal helminths, i.e. *Ascaris* and/or *Trichuris*.

Skin Prick Testing

Skin test reactivity for aeroallergens was tested with extracts of *Dermatophagoides pteronyssinus*, *Dactylis glomerata* grass pollen, cat dander and dog dander preparations (HAL Allergen Laboratories, The Netherlands). Histamine chloride (10 mg/ml) was used as the positive control, and allergen diluent as the negative control (HAL Allergen Laboratories). Skin prick tests (SPT) were done on the volar side of the child's lower arm, using separate 25-gauge needles.

The longest diameter (D1) and the diameter perpendicular to it (D2) of the wheal were measured after 15 min. An SPT was considered positive when $D1 + D2/2$ was at least 3 mm [17]. Erythema was not used in the interpretation of skin tests because of the difficulty to record this in deeply pigmented skins. The same investigator performed all SPT.

Total IgE Antibodies

Total antibodies were measured in an enzyme-linked immunosorbent assay (ELISA) on blood samples collected onto filter paper as described before [18]. Briefly, blood drops obtained by finger prick were absorbed on discs of Whatman No. 3 filter paper (Merck, Germany). In Leiden, The Netherlands, a 1-cm-diameter circle was punched out of the filter paper and was eluted overnight at 4°C with 250 µl of assay buffer [phosphate buffer saline (PBS) containing 5% fetal calf serum and 0.05% Tween 20]. Blood spots of 1 cm in diameter that penetrated to the reverse side of the paper corresponded to a volume of 12.5 µl of serum. Therefore, after elution the dilution of serum was assumed to be 1/20.

Total IgE antibodies in the eluates were measured by ELISA. Maxisorp plates (Nunc, Roskilde, Denmark) were coated overnight at 4°C with rabbit anti-human IgE (Dako; 1:1,000) in 0.1 M bicarbonate buffer, and blocked with PBS/2% bovine serum albumin (BSA) at room temperature. After washing with PBS, 100 µl of the blood filter eluate (this is a final dilution of 1:20) as well as a 1:10 dilution of the eluate (1:200 serum dilution) were added to the wells. As a reference the WHO standard of human serum IgE (National Institute for Biological Standards and Control, Hertfordshire, UK) was used, applying a 9-fold serial dilution (1:2), starting at a concentration of 50 IU/ml. Plates were incubated for 1 h at room temperature, and after washing goat anti-human IgE-biotinylated antibody (1:1,000; Vector, Burlingame, Calif., USA) was added and incubated for 1 h, followed by an incubation with streptavidin-alkaline phosphatase conjugate (1:3,000; Dako, Glostrup, Denmark) for 2 h at room temperature. Finally 100 µl 1 mg/ml *p*-nitrophenylphosphate (pNPP) (Boehringer Mannheim, Germany) in 0.1 M diethanolamine (DEA) buffer was added and after 20 min the reaction was stopped by adding 100 µl 3 M NaOH. Absorbencies were measured at 405 nm.

Based on the frequency distribution curve of total IgE levels within the population, a threshold level of 1,000 IU/ml was used to distinguish between moderate and high levels of total IgE.

Allergen-Specific IgE

Serum levels of mite-, dog- and cat-specific IgE antibodies were determined by radioallergosorbent test (RAST) as described previously [19]. Briefly, serum (50 µl) was incubated overnight with 1.5 mg of Sepharose-coupled allergen in a final volume of 300 µl PBS, 3% BSA, 0.1% Tween 20. After washing away nonbound serum components, radiolabeled sheep antibodies (CLB, Amsterdam, The Netherlands), directed to human IgE, were added. After overnight incubation and washing, bound radioactivity was measured. Results were expressed as international units per milliliter. Calculation was performed by means of a standard curve that was obtained by RAST with a dilution series of a chimeric monoclonal IgE antibody against the major house dust mite allergen Der p 2 and Sepharose-coupled mite extract [20]. 1 IU is 2.4 ng IgE.

The detection limit of the assay was 0.30 IU/ml, and to individuals in whom no specific IgE could be detected by RAST a value of half the detection limit was given (0.15 IU/ml). Subjects were consid-

ered sensitized when concentrations of specific IgE of more than 1.0 IU/ml were measured.

Allergen Source

D. pteronyssinus mites (Commonwealth Serum Laboratories, Melbourne, Australia) were extracted in PBS (2% w/v), 0.1% Tween 20 for 4 h. After filtration, 5 ml extract was coupled to 1 g cyanogen bromide (CNBr)-activated Sepharose 4B (Pharmacia, Sweden). Commercial dog and cat dander (HAL Laboratories, The Netherlands) was coupled to CNBr-activated Sepharose in concentrations of 4 mg allergen/1 g of Sepharose.

Presence of Allergen in Dust Samples

In the study area in Gabon dust samples were collected from 11 households by vacuum cleaning with a specialized top filter (ALK-Abello, The Netherlands). Samples were stored at -20°C until being transported to the Netherlands. From each sample 3.5 mg was added to a volume of 5 ml PBS/0.5% Tween/0.2% NaN₃ and extracted overnight at room temperature. After centrifuging supernatants were collected and concentrations of the mite allergen Der p 1, the cat allergen Fel d 1 and of the dog allergen Can f 1 were determined by competitive RIA [21]. Levels of the mite allergen Der p 2 were measured by indirect RAST [22], whereas grass pollen allergen Dac g 1 and mite allergens Blo t 5 and Der f 1 (Indoor Biotechnologies, Cardiff, UK) were determined by ELISA, according to the manufacturer's instructions. Levels of Blo t 5 could not be quantified because of problems with the standard.

Statistical Analysis

Prevalence rates were calculated and compared for different groups using Pearson χ^2 tests. Antibody levels were not normally distributed and analysis was therefore performed on log-transformed data that better approached a normal distribution. Correlations were determined by measuring the Spearman correlation coefficient. Using the Mann-Whitney test levels of IgE antibodies between different groups were compared. The distribution of skin test reactivity to mite in relation to independent variables of interest was first studied in a 'univariate regression model' adjusted for indicated possible confounders. Subsequently, the independent effect of the variables found to be significantly associated with the outcome in the 'univariate' model was studied using multiple logistic regression, while adjusting for the same confounding variables. Odds ratios (OR) < 1 indicate a negative association between the variable and the outcome, whereas an OR > 1 is indicative of a positive association. In the regression models log-transformed data of IgE antibodies were used.

Outcomes of statistical tests were considered significant when two-tailed *p* values were smaller than 0.05.

Results

Allergic Disease and Socioeconomic Factors

Based on questionnaires 23 children (4.5%) reported respiratory problems. In 14 children the problem was exercise-induced and 3 reported problems when in proximity of a dog and/or a cat. No hospitalization due to

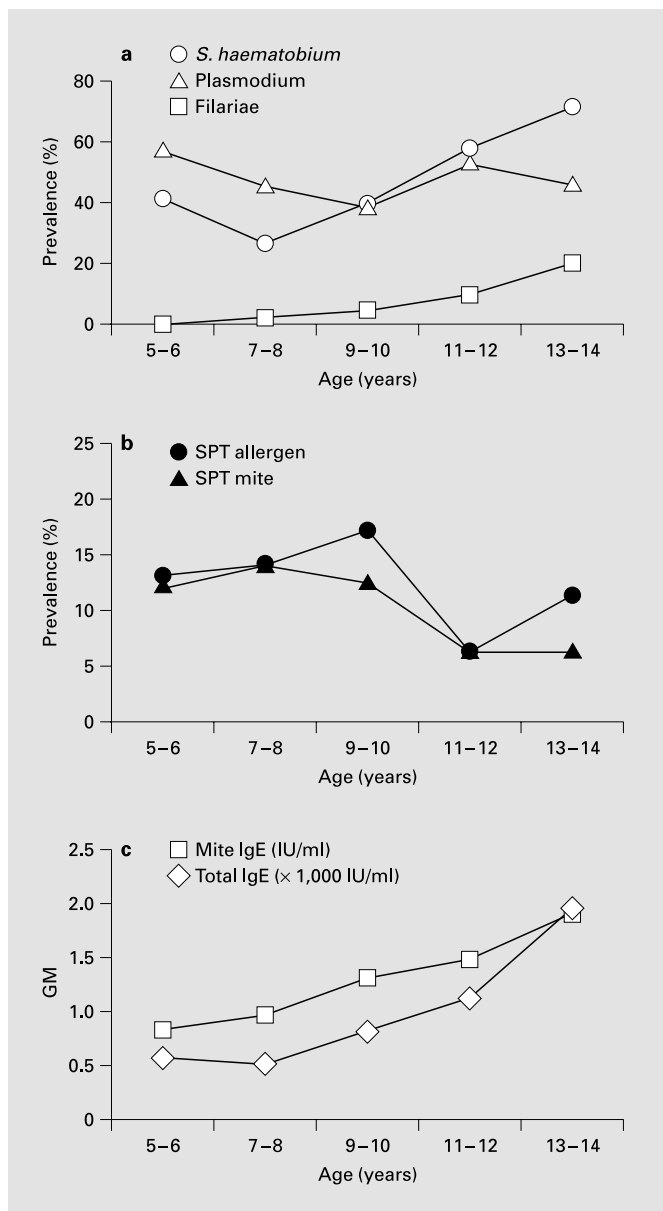


Fig. 1. Age curves in Gabonese children aged 5–6 years ($n = 92$), 7–8 years ($n = 174$), 9–10 years ($n = 130$), 11–12 years ($n = 77$) and 13–14 years ($n = 47$) for infections with schistosomes, *Plasmodium* and filariae (a), skin test reactivity to cat, dog, grass and/or mite, and to mite allergen only (b) and levels of mite-specific IgE and total IgE (c).

breathing problems nor any cases of a family history of asthma were reported. No symptoms that could be classified as allergic rhinitis were documented. Of the total study population a subgroup of 69 children was tested for exercise-induced bronchohyperresponsiveness and two (3%) were found to be hyperresponsive. The children

were examined for abnormalities of the skin on arms, legs and face that might be related to allergy. The only skin disorders found concerned mycosis scapula (6%), scabies (4%), pityriasis versicolor (8%) and heat rash (12%).

With respect to socioeconomic factors, 54% of the children lived in brick houses, 64% of the children belonged to households that cooked with gas, and 98% of the houses did not have a main water supply.

Parasite Infections

Of the 520 schoolchildren screened 215 subjects were found positive for malarial parasites in thick blood smears. These were mainly infections with *P. falciparum*, and only in a few cases were infections with *P. malariae* or *P. ovale* seen. Based on presence of eggs in urine 39% of the children were found to be infected with the blood-dwelling helminth *S. haematobium*, whereas only 6% of the children had blood samples positive for microfilariae of *L. loa* and/or *M. perstans*. As illustrated in figure 1a prevalence of urinary schistosomiasis increased with age in schoolchildren. Significantly more infections were detected in children aged 11–12 and 13–14 years compared to those in the younger age groups ($p < 0.05$). In accordance filarial infections increased with age and were significantly higher in the oldest age group compared to children 5–6, 7–8 and 9–10 years of age ($p < 0.05$). Malaria infections were highest in the youngest age group, but differences between age groups did not reach statistical significance.

Skin Test Reactivity

SPT were performed for the common aeroallergens cat and dog dander, grass pollen and house dust mite. Skin prick reactivity was predominantly found against mite allergens (table 1). All children showed a positive response to the histamine control, with a mean wheal size of 5.15 mm (minimum = 3.00 mm, maximum = 8.50 mm). The prevalence of skin test reactivity tended to become lower in the older age groups (fig. 1b), but differences between age groups did not reach statistical significance.

Allergen-Specific and Total IgE Antibodies

In contrast to mite-specific IgE antibodies, serum levels of both cat- and dog-specific IgE were low (table 1). Indeed in dust samples collected from houses the mite allergen Der p 1 [geometric mean (GM) = 459.30 ng/g dust, SEM = 1.33] and the tropical mite allergen Blo t 5 (concentrations unknown, see Material and Methods) were detected. In the samples hardly any cat allergen Fel d 1 (GM = 0.58 ng/g dust, SEM = 1.14), dog allergen Can

f 1 (GM = 0.58 ng/g dust, SEM = 1.24) and mite allergen Der p 2 (GM = 2.86 ng/g dust, SEM = 1.14) were found, whereas neither the grass pollen allergen Dac g 1 nor the mite allergen Der f 1 was detectable.

Sensitization to house dust mite determined by serum levels of specific IgE was higher than skin test reactivity found against mite: 47% of the children had mite-specific IgE antibodies of more than 1.0 IU/ml, whereas only 11% of the children responded to mite in skin prick testing (table 1). In these mite IgE-positive children levels of mite-specific IgE ranged between 1.00 and 181.97 IU/ml [GM = 3.56 IU/ml, geometric standard error of the mean (GSEM) = 1.10]. As shown in figure 1c levels of mite-specific IgE increased with age ($\rho = 0.202$, $p < 0.001$). Sensitization was found to be significantly higher in children aged 11–12 and 13–14 years than in those in the age groups of 5–6, 7–8 and 9–10 years ($p < 0.05$).

In the total study group levels of polyclonal IgE varied between 17 and 32,888 IU/ml (GM = 727 IU/ml, GSEM = 1.1). In 24% of the children levels of total IgE were less than 250 IU/ml, in 34% levels were found to be between 250 and 1,000 IU/ml, whereas in 42% of the children levels were higher than 1,000 IU/ml. Levels of total IgE increased with age ($\rho = 0.270$, $p < 0.001$) as illustrated in figure 1c.

Skin Test Positivity and IgE Antibodies according to Parasite Infections

The children were divided into four subgroups: those that were negative for all tested parasites ('not infected'); children that were only positive for malarial parasites ('Plasmodium only'); children that were positive for one of the helminths, i.e. positive for schistosome and/or filarial infections ('helminths only'), and children that were doubly positive for Plasmodium as well as for one of the helminths ('Plasmodium and helminths').

Since most skin test responses were to mite and only very few to other allergens tested, we concentrated on mite reactivity. In tables 2 and 3 the prevalence of skin test reactivity to mite, sensitization to mite (>1.0 IU/ml) and total IgE ($>1,000$ IU/ml) are given for the indicated subgroups, as well as the mean levels of total IgE and mite-specific IgE. In table 3 the p values are given for comparisons between the subgroups. Compared to noninfected children skin test reactivity to mite was lower in children infected with helminths and/or Plasmodium. However, sensitization to mite and having high levels of total IgE ($>1,000$ IU/ml) were significantly higher in children infected with blood stage helminths than in children without infection or infected with malarial parasites only (ta-

Table 1. Number of children in the total population of 520 Gabonese schoolchildren with a positive skin test result to aeroallergens indicated (wheal size >3 mm) and with serum levels of allergen-specific IgE >1.0 IU/ml

	SPT positive (n = 520)	Specific IgE >1.0 IU/ml (n = 520)	GM of specific IgE IU/ml
House dust mite	58	246	0.89 (0.30–2.67)
Cat dander	12	8	0.26 (0.18–0.36)
Dog dander	1	7	0.26 (0.17–0.36)
Grass pollen	4	ND	ND
At least one of the allergens	69	248	

In the last column GM and interquartile ranges in parentheses for levels of specific IgE are given (n = 520). ND = Not determined.

bles 2, 3). Similar results were found for the continuous data on IgE antibodies.

Determinants of Skin Test Reactivity

Logistic regression was performed for determining the contributions of the variables total IgE, specific IgE and helminth infections to the outcome of a positive skin test to mite. Associations of these independent variables with skin test reactivity were adjusted for age, sex, breathing problems, the availability of gas and the material houses were built with. As shown in table 4 the probability of a positive skin test was over 8-fold higher with higher levels of mite IgE and decreased independently by 72% when a child was infected with helminths.

In the univariate model total IgE and Plasmodium infection were not associated with skin test reactivity. However, as total IgE and mite-specific IgE are positively correlated, the effect of total IgE on skin test reactivity was studied in a multiple model including all variables, in this manner adjusting for the positive correlation between total and mite-specific IgE. The results showed a negative association between total IgE and skin test reactivity [OR = 0.50; 95% confidence interval (CI) = 0.26–0.97; $p = 0.041$]. The effect of helminth infections on skin test reactivity, however, remained stronger in this model (OR = 0.32; 95% CI = 0.14–0.77; $p = 0.011$) than the effect of total IgE. When restricting the multiple analysis to the subgroup of mite-sensitized children, i.e. those being at risk of a positive skin test, helminth infections

Table 2. Prevalence of skin test reactivity to mite, sensitization to mite (mite-specific IgE >1.0 IU/ml) and high total IgE (>1,000 IU/ml) for 520 study children subdivided into four subgroups based on being helminth and/or Plasmodium infected

	Not infected (n = 195)	Plasmodium only (n = 118)	Helminths only (n = 103)	Plasmodium and helminths (n = 104)
SPT mite-positive, %	17	12	8	3
Mite-sensitized (>1.0 IU/ml), %	39	40	55	53
Total IgE >1,000 IU/ml, %	30	37	51	56
GM mite IgE, IU/ml	0.99 (0.030–2.28)	0.97 (0.30–2.40)	1.46 (0.64–2.82)	1.37 (0.30–3.44)
GM total IgE, IU/ml	461 (167–1,169)	619 (240–2,349)	1,098 (427–2,981)	1,231 (384–3,545)

Helminth infection is present if the patient is positive for schistosome and/or filarial infections. GM and inter-quartile ranges in parentheses for levels of total and mite-specific IgE are given for each subgroup.

Table 3. P-values for comparing prevalences (Pearson χ^2 and levels of total and specific IgE (Mann-Whitney test) as given in table 2 between all subgroups

	p value for SPT mite	p value for mite IgE >1.0 IU/ml	p value for IgE total >1,000 IU/ml	p value for levels of mite IgE	p value for levels of total IgE
NI vs. Plasm.	0.173	0.858	0.197	0.865	0.062
NI vs. Helm.	0.033	0.010	0.001	0.003	<0.001
NI vs. Plasm. + Helm.	<0.001	0.03	<0.001	0.009	<0.001
Helm. vs. Plasm.	0.407	0.006	0.055	0.012	0.011
Helm. vs. Plasm. + Helm.	0.117	0.717	0.492	0.829	0.502
Plasm. vs. Plasm. + Helm.	0.019	0.073	0.007	0.026	0.001

NI = Not infected; Plasm. = Plasmodium-infected; Helm. = helminth-infected; Plasm. + Helm. = Plasmodium and helminth-infected.

Table 4. Univariate ('crude') and multiple ('adjusted') logistic regression for measuring the association of the independent variables 'levels of mite-specific IgE' (log-transformed; IU/ml), 'levels of polyclonal IgE antibodies (log-transformed; IU/ml)', 'Plasmodium infection' and 'helminth infection' with skin test reactivity to mite

	Crude			Adjusted		
	OR	95% CI	p value	OR	95% CI	p value
Mite-specific IgE	8.21	4.54–14.83	<0.001	8.47	4.61–15.57	<0.001
Total IgE	1.31	0.78–2.20	0.305			
Plasmodium	0.72	0.40–1.31	0.283			
Helminths	0.38	0.17–0.81	0.012	0.28	0.12–0.66	0.003

For levels of mite-specific and total IgE log-transformed data were used. Both models were adjusted for confounding by 'age', 'sex', 'breathing problems', 'house material' and 'cooking with gas'. In the multiple logistic regression only the independent variables that were found to be significantly associated in the univariate model were studied.

remained significantly negatively associated with a positive skin test result (OR = 0.28; 95% CI = 0.11–0.75; $p = 0.011$), whereas levels of mite-specific IgE remained a significant risk factor for skin test positivity (OR = 13.01; 95% CI = 4.35–38.94; $p < 0.001$). The effect of total IgE was no longer significant (OR = 0.45; 95% CI = 0.19–1.07; $p = 0.071$).

Discussion

The prevalence of skin test reactivity to aeroallergens in Gabonese children was found to be 13%, which is comparable to percentages presented by other studies in less-developed parts of the world [3, 5], but which is considerably lower than in westernized societies where approximately a quarter of the children is estimated to be atopic [2]. In our study population positive skin test results were predominantly found against house dust mite allergens. This is in accordance with other studies performed in Africa, where sensitization was reported to be mainly to house dust mite and to a much lesser extent to other aeroallergens such as cat dander, dog dander or grass pollens [3–5, 23]. Indeed, our analysis of local dust samples revealed the presence of mite allergens whereas neither dog, cat, nor grass pollen allergens were detectable.

In industrialized countries atopic persons, defined by having allergen-specific IgE antibodies, generally respond positively to a SPT [17]. It is therefore remarkable that in our population where almost half of the children had mite-specific IgE antibodies, only 11% were reactive to house dust mite in skin prick testing. The percentage of children found positive for mite IgE is similar to that reported in other studies performed in tropical settings [24, 25].

In our study population we found infections with schistosomes and filariae to increase with age, whereas malarial infections were the highest in the younger children. Parallel with the age-prevalence curves of these helminths, sensitization to mite and the production of high levels of total IgE increased with age. In contrast to IgE responses, skin test reactivity to mite declined with age. Indeed children who were infected with *S. haematobium* and/or filariae were found to be significantly more sensitized to mite and to be significantly less skin test-responsive to mite than children that were not infected. Plasmodium infections appeared to have an additional negative effect on skin test reactivity in helminth-infected children (8% in helminth-infected children vs. 3% in children infected with both helminths and Plasmodium).

The higher production of IgE antibodies in helminth-infected children might be well explained by the general expansion of IgE-producing B cells [26]. The question of whether the high degree of mite sensitization in our study population without concordant skin test reactivity might be explained by binding of nonspecific IgE in the RAST is unlikely, since IgE levels to mite could be fully inhibited by preincubation of sera with mite extract (unpubl. data). Helminth parasites and house dust mite are known to have several structures in common such as glutathione S-transferase, paramyosin and tropomyosin [27]. We are currently investigating whether any significant degree of cross-reactivity between house dust mite and helminths occurs in our population, but preliminary data indicate that this is not likely (unpubl. data).

Whereas sensitization to house dust mite was higher in children infected with helminths, skin test reactivity was lower. In the total study population as well as when analysis was restricted to children with mite-specific IgE, higher levels of mite-specific IgE were associated with a 8- to 13-fold increased risk of responding to skin testing, whilst chronic infections with helminths reduced this risk by 72%. It has been argued that the high levels of total IgE in helminth-infected subjects may compete with allergen-specific IgE in occupying mast cell Fc_ϵ receptors, thereby blocking hypersensitivity reactions [25, 28, 29]. However, total IgE does not play a prominent role in the strong negative association between helminth infections and skin test reactivity, as indicated by multiple logistic regression. Other factors related to infections that might be associated with preventing skin test reactivity have to be considered.

Most studies investigating the 'hygiene hypothesis' [1] address infections that induce a Th1-like response [5, 7, 30]. Since atopy and allergic disorders are characterized by a skewing of the immune response towards Th2, it has been suggested that suffering from Th1-inducing infections early in life would modulate the immune response and lower the risk of developing atopy-related Th2 responses [31, 32]. However, since helminth infections are characterized by skewing of the T helper response towards Th2 [33], this proposed Th1/Th2 paradigm might explain the increased levels of specific IgE to environmental allergens, but not the decreased skin test reactivity. It, therefore, appears important to look beyond the Th1/Th2 balance and to identify the mechanism(s) that lead to reduced atopy in children with chronic parasite infections. Of interest is that infections with blood stage helminths result in immunomodulation of the hosts' immune responses: to guarantee their long-term survival, the

worms induce a state of immune hyporesponsiveness in the infected host [12, 13]. It was recently shown that higher levels of parasite-induced IL-10 are associated with a reduced risk of a positive skin test to aeroallergens [14]. Further characterization of the mechanisms behind the negative association between chronic infections and atopy may have an important bearing on the management of allergic diseases.

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