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Associations between atopic markers in asthma and intestinal helminth infections in Cuban schoolchildren

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Abstract

Total serum IgE (tIgE), allergen-specific IgE (sIgE), and skin prick test (SPT) are commonly used markers for atopy and atopic disease. The association between these measures and their relationship to clinical symptoms differs in affluent and non-affluent countries. We investigated the role of intestinal helminth infections in observed variations in atopic markers and asthma, and possible diagnostic and epidemiological consequences. A cross-sectional study was conducted in Cuban schoolchildren (n = 1285; 4–14 yrs). Atopy was determined by SPT, sIgE, and tIgE; asthma by International Study of Asthma and Allergies in Childhood questionnaire; and intestinal helminth infections by stool examination. Percentages of tIgE, sIgE, and SPT positives were 88.9%, 25.5%, and 16.5%, respectively. Asthma was found in 20.8%, and helminth infections in 20.9% of the children. All three atopic markers were significantly associated with each other and with asthma. Median tIgE levels were higher in helminth-infected than in uninfected children, irrespective of their status of atopy/asthma. Discordant results between SPT and sIgE were observed in 22.6% of the children. Among SPT positives, 41% were sIgE negative. The proportion of SPT negatives among sIgE positives was 74% in helminth-infected and 58.4% in uninfected children ($p < 0.05$). Helminth infections affected tIgE levels, reconfirming the limited value of tIgE for diagnosis of atopy and asthma in tropical areas. Higher frequencies of sIgE than positive SPTs were observed, especially in helminth-infected children. This corresponds with current hypothesis on the role of helminths in atopy. However, the observed proportion of sIgE negatives among children with positive SPT suggests that other mechanisms may also be involved.

Atopy is generally defined as a heritable predisposition to produce abnormal amount of IgE in response to contact with aeroallergens. Subsequently, one can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema (1). Commonly used markers for atopy and atopic disease are total serum IgE (tIgE), allergen-specific IgE (sIgE), and allergen skin prick test (SPT). These measures are often considered to be interchangeable, but there is increasing evidence that they can differ considerably, with important diagnostic and epidemiological implications.

Among the three indirect markers for atopic disease, SPT is usually considered to have the best efficiency to diagnose current respiratory allergic diseases; tIgE has a lower diagnostic value than SPT and sIgE (2–4). So far, study results have been inconsistent regarding the role of tIgE as a determinant of atopic disease, independent of SPT and circulating sIgE (3, 5–6). Moreover, tIgE is not only raised in allergic diseases, but also in parasite infections, questioning its usefulness in the evaluation of atopy/atopic disease in developing countries/tropical populations (7).

Apart from discrepancies between tIgE results and those with SPT and sIgE, discordant results between the latter two atopic markers have been reported as well. Generally, prevalences of atopy and atopic diseases are high among children in affluent countries, with comparable results for SPT and circulating IgE antibody determination (3, 8–10).

In non-affluent countries, however, there is less agreement between the two methods. Studies in tropical countries, with a high prevalence of parasitic infections in children, have shown high frequencies of circulating IgE antibodies, yet low prevalences of positive SPTs (11–13). This has been interpreted as a blocking effect of parasite-induced IgE antibodies (14). An alternative explanation is that there is a downregulation of skin reactivity in less affluent countries (10). This hypothesis was not unequivocally supported by a recent International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two study on international variations in associations of allergic markers in children. They reported high proportions of sIgE+/SPT− children in some affluent countries and even consistently higher proportions of sIgE−/SPT+ suggesting an enhanced SPT reactivity in non-affluent countries (3).

Here, we investigated the associations between circulating tIgE, sIgE, and SPT as atopic measures, in self-reported asthma and intestinal helminth infections in 4- to 14-yr-old schoolchildren in Cuba. Asthma rates in Cuba rival those found in developed nations with the highest prevalences (15, 16). Cuba is also – like many tropical countries – endemic for intestinal helminth infections (17). In this specific epidemiological context, we aimed at gaining more insight into the role of intestinal helminth infections in observed variations in atopic markers and asthma, and possible diagnostic and epidemiological consequences.

Materials and Methods

Study area and population

A cross-sectional study within school-aged children was performed between 2003 and 2004 in San Juan y Martínez (SJM), Pinar del Rio, a municipality in the west of Cuba and in Fomento, Sancti Spiritus, a municipality in the center of the island. Both municipalities are in rural mountainous areas, which are endemic for helminths (17). In San Juan y Martínez, 373 children from five primary schools and in Fomento 912 children from 14 primary schools were randomly selected and included in the study. Further details about study design and study group have been previously described by Wördemann et al. (17).

Written informed consent was obtained from the parents of each child. The study was approved by the ethical committees of the Institute of Tropical Medicine (ITM) in Antwerp (Belgium), the Pedro Kouri Institute of Tropical Medicine (IPK), and the National Institute for Hygiene, Epidemiology and Microbiology (INHEM) in Havana (Cuba).

ISAAC questionnaire

A parent or guardian of each child was interviewed by means of an extended version of the standard Spanish version of the ISAAC questionnaire (18). Asthma was defined according to the ISAAC definition of current asthma, that is, as an affirmative answer to the second ISAAC core question on current wheeze: 'Did your child wheeze in the last 12 months?' (18). Children with asthma were referred to a primary health care center for follow-up and treatment.

Skin prick testing

Skin prick testing was performed using extracts of two allergens that have been used worldwide by ISAAC, that is, house dust mite and cockroach (produced by ALK Abelló, Nieuwegein, the Netherlands). Both have been reported as major atopic sensitizers in developing countries (13, 20). Histamine (10 mg/ml) and allergen diluent were used as positive and negative controls, respectively. The extracts and controls were placed on the volar side of the left forearm using separate ALK lancets. Skin response was measured after 15 min, considering a wheal of 3 mm or larger in the absence of significant reactivity of the diluent control as a positive reaction. Atopy was defined as a positive SPT reaction (SPT+) to at least one of the applied allergens. Those taking regular short-acting antihistamines were asked to refrain from taking them for at least 72 h prior to skin prick testing.

IgE-testing

Ten milliliters of venous blood was collected from an antecubital vein from each child. Serum was separated and stored at −20°C in aliquots until use. Levels of tgE and sIgE to house dust mite (*Dermatophagoides pteronyssinus*) and cockroach (*Periplaneta americana*) were measured using the Phadia ImmunoCAP system (UniCAP, Pharmacia, Sweden) following the manufacturer's instruction. Results were expressed as kU/l. Values of sIgE equal and above 0.35 kU/l were considered positive (sIgE+) (UniCAP, Pharmacia, Sweden) (21). For tIgE, age-dependent cut-off levels (as defined by UniCAP) were used to define a positive reaction (4: ≥40; 5: ≥48; 6: ≥56; 7: ≥63; 8: ≥71; 9: ≥78; 10 yrs or older: ≥85 kU/l). For samples with a total IgE value exceeding the upper limit, a value of 5000 kU/l was assigned.

Detection of intestinal helminth infection

From each child, one fresh stool sample was collected. Two Kato Katz examinations (of 25 mg stool each) were performed according to standard procedures for the microscopic detection of parasite eggs of *Ascaris lumbricoides*, *Trichuris trichiura,* and/or hookworm (22). Other helminths such as *Strongyloides* and lymphatic filariosis were not considered, as these are very uncommon/not present in Cuba ((23) and (FA Nuñez, Personal communication)).

Statistical analysis

All analyses were conducted in SPSS for windows, version 19 (SPSS Inc., Chicago, IL, USA). Mann–Whitney and Kruskal–Wallis tests were used for comparing median levels of tIgE and sIgE between different groups. Pearson Chi-square tests were used to determine the mutual associations between tIgE, sIgE, and SPT and to assess their associations with the different helminth and asthma groups. Multivariable logistic

regression analysis was used to assess whether helminth infections and asthma were independently associated with tIgE. Outcomes of statistical tests were considered significant when p-values were smaller than 0.05.

Results

General characteristics

Response rates to tIgE, sIgE, SPT, ISAAC questionnaire and stool examination were 100% (1285/1285). Two hundred and sixty-eight children (20.9%) were helminth infected: 207 (16.1%) with one helminth species, 55 (4.3%) with two species, and 6 (0.5%) with the three different species (*A. lumbricoides*, *T. trichiura* and hookworm). Based on SPT, 212 (16.5%) children were positive, of whom 163 (67.9%) for one allergen and 49 (23.1%) for the two allergens. For sIgE, 328 (25.5%) children were positive, of whom 217 (66.2%) for one allergen and 111 (33.8%) for both allergens. The percentage of positives by tIgE determination was 88.9% (1142/1285). According to the ISAAC questionnaire, 20.8% (267/1285) of the children had asthma (Table 1). Table 2 gives an overview of the results for tIgE, sIgE, and SPT in asthmatic and non-asthmatic children (2a), and in those with and without helminth infections (2b), respectively.

Table 1 General characteristics and results for stool examination, tIgE, sIgE, skin prick test (SPT) determination, and international study of asthma and allergies in childhood questionnaire for the Cuban study population; epg, fecal egg counts; n, number of children

Number of children (n)	1285
Age	
Median (yr)	8
Range (yr)	4–14
Sex (% male)	51.2
Helminth infection	
Percentage positives (%)	
Any helminth	20.9
Ascaris lumbricoides	6.3
Trichuris trichiura	10.6
Hookworm	9.2
Median egg counts* (epg)	
A. lumbricoides	1600
T. trichiura	105
Hookworm	200
Range egg counts* (epg)	
A. lumbricoides	40–52 000
T. trichiura	20–2480
Hookworm	20–3920
Atopy	
Total IgE	
Percentage positives (%)	88.9
Median (kU/l)	369
Range (kU/l)	4.5–5000
Specific IgE	
Percentage positives (%)	25.5
Cockroach	12.8
House dust mite	21.3
Median (kU/l)	
Cockroach	0.03
House dust mite	0.08
Range (kU/l)	
Cockroach	0.0–20.7
House dust mite	0.0–100.0
SPT	
Percentage positives (%)	16.5
Cockroach	13.2
House dust mite	7.2
Asthma	
Percentage positives (%)	20.8

*Of positive children.

Total serum IgE, asthma, and helminth infections

Overall, a significant association between tIgE and SPT and sIgE respectively ($p < 0.05$) was observed. Median tIgE levels were lowest for children with sIgE−/SPT− (262 kU/l; range: 4.49–5000 kU/l), followed by sIgE−/SPT+ (343 kU/l; range: 16.5–3519 kU/l), sIgE+/SPT+ (986 kU/l; range: 23.1–5000 kU/l), and levels were highest for children with sIgE+/SPT− (1252 kU/l; range: 66.4–5000 kU/l) ($p < 0.05$). They significantly increased with increasing number of allergens found positive by SPT and by sIgE ($p < 0.05$) (data not shown).

Total IgE was significantly associated with asthma, even in children who were negative for SPT or sIgE ($p < 0.05$).

Equally, there was a significant association between tIgE and helminth infections ($p < 0.05$). Median tIgE levels did not increase with increasing number of helminth species or with infection intensity ($p > 0.05$) (data not shown).

Table 3 gives an overview of tIgE for all combinations of helminth infections, atopy, and asthma status. It shows that median tIgE levels were higher in helminth-positive children as compared to helminth-negative children, irrespective of their status of atopy/asthma, and *vice versa*. Indeed, multivariable analysis showed that helminth infection and asthma were independently associated with tIgE [$p < 0.05$; OR = 2.6 (95% CI 2.0–3.2) and 2.4 (95% CI 1.8–3.0), respectively].

SPT/sIgE, asthma, and helminth infections

Skin prick test and sIgE were significantly associated for each specific allergen ($p < 0.05$). One hundred and twenty-five children (9.7%) were SPT+/sIgE+, and 870 children (67.7%) were SPT−/sIgE−. Discordant results between SPT and IgE were observed in 290 (22.6%) children: 203 (15.8%) were SPT−/sIgE+ and 87 (6.8%) were SPT+/IgE−. Among children with positive sIgE, the percentages of children with negative SPT were 61.9% (203/328), while among SPT positive children, 41.0% (87/212) of the children was sIgE negative.

The percentage of SPT+/sIgE+ children was higher in asthmatic [19.1% (51/267)] than in non-asthmatic children [7.3% (74/1018) ($p < 0.05$)]. Nevertheless, a considerable

Table 2 Atopic markers for (a) asthmatic and non-asthmatic children (b) helminth-positive and helminth-negative children

	Asthma neg	Asthma pos	p-value
(a)			
Total IgE			
Percentage positives (%)	87.4	94.4	0.001
Median (kU/l)	345.0	486.0	0.002
Range (kU/l)	4.5–5000	19.7–5000	
Specific IgE			
Percentage positives (%)	22.2	38.2	0.000
Cockroach	11.5	18.0	0.005
House dust mite	18.3	33.0	0.000
Median (kU/l)			
Cockroach	0.02	0.05	0.000
House dust mite	0.07	0.1	0.000
Range (kU/l)			
Cockroach	0.0–20.7	0.0–10.1	
House dust mite	0.0–100.0	0.0–100.0	
SPT			
Percentage positives (%)	13.9	26.2	0.000
Cockroach	11.9	18.0	0.009
House dust mite	4.5	17.2	0.000
	Helminth neg	Helminth pos	p-value
(b)			
Total IgE			
Percentage positives (%)	87.3	94.8	0.001
Median (kU/l)	335.0	583.0	0.000
Range (kU/l)	4.5–5000	21.6–5000	
Specific IgE			
Percentage positives (%)	25.1	27.2	0.470
Cockroach	11.9	16.4	0.049
House dust mite	21.3	21.3	0.981
Median (kU/l)			
Cockroach	0.03	0.03	0.680
House dust mite	0.08	0.07	0.340
Range (kU/l)			
Cockroach	0.0–20.7	0.0–14.2	
House dust mite	0.0–100.0	0.0–100.0	
SPT			
Percentage positives (%)	16.9	14.9	0.436
Cockroach	13.2	13.1	0.960
House dust mite	7.4	6.3	0.560

SPT, skin prick test.

proportion of SPT−/sIgE− children was found among asthmatics as well [54.7% (146/267)]. The proportion of SPT−/sIgE+ children and SPT+/sIgE− children did not significantly differ between asthmatic and non-asthmatics ($p > 0.05$).

The proportion of SPT−/sIgE+ children was significantly higher in those with helminth infections [20.1% (54/268)] than in those without [14.7% (149/1017)] ($p < 0.05$), whereas the proportion of SPT+/sIgE− did not differ between helminth-infected children [7.8% (21/268) and those without infection (6.5% (66/1017)] (Table 4). Among children with positive sIgE, the proportion with negative SPT was 74% (54/73) in those with helminth infection and 58.4% (149/255) in those without ($p < 0.05$). Among children with positive SPT, the proportion with negative sIgE did not significantly differ between helminth positives [52.5% (21/40)] and helminth negatives [38.4% (66/172)] ($p > 0.05$). Allergen-specific analyses yielded similar trends, although not significant and more pronounced for house dust mite (data not shown).

Table 3 Median and range (kU/l) of tIgE for each helminth, atopy, and asthma subgroup within the Cuban study population.

	Total IgE		
	Median (kU/l)	Range (kU/l)	n
Helminth+/SPT+	815.0	85.6–5000	40
Helminth−/SPT+	621.5	16.5–5000	172
Helminth+/SPT−	547.5	21.6–5000	228
Helminth−/SPT−	299.0	4.5–5000	845
Helminth+/sIgE+	1524.0	143.0–5000	73
Helminth−/sIgE+	1027.0	23.1–5000	255
Helminth+/sIgE−	371.0	21.6–4254	195
Helminth−/sIgE−	245.0	4.5–5000	762
Helminth+/asthma+	735.0	51.0–3825	63
Helminth−/asthma+	435.0	19.7–5000	204
Helminth+/asthma−	567.0	21.6–5000	205
Helminth−/asthma−	323.0	4.5–5000	813

SPT, skin prick test.
n, number of children.

Table 4 Proportion of children with and without positive SPT and sIgE in helminth-infected and non-infected children

	Helminth−	Helminth+
SPT−/sIgE+ (%)	14.7 (149/1017)	20.1 (54/268)
SPT+/sIgE− (%)	6.5 (66/1017)	7.8 (21/268)
sIgE− among SPT+ (%)	38.4 (66/172)	52.5 (21/40)
SPT− among sIgE+ (%)	58.4 (149/255)	74.0 (54/73)

SPT, skin prick test.

Discussion

In this study, we investigated the associations between the atopic markers tIgE, sIgE, and SPT in asthma and intestinal helminth infections in Cuban schoolchildren. The prevalence of self-reported asthma was found to be 20.8%, which is in line with those found in various other Latin American countries as well as with some developed countries with the highest prevalence rates in the world (9, 15, 16, 24). Almost 21% of the study population was infected with one or more intestinal helminths. The percentage of children positive for IgE was 88.9%, while percentages of SPT and sIgE positives were remarkably lower (16.5% and 25.5%, respectively).

All three atopic markers were significantly associated with each other and with asthma ($p < 0.05$), even though large discrepancies were observed between the respective atopic

measures regarding the number of positives found. The latter is a well-known phenomenon in the diagnosis of atopic diseases and a matter of concern, as previously reported by our group (4). We found tIgE to be significantly associated with asthma, even in children who were negative for SPT or sIgE ($p < 0.05$). This has been found before (25) and explained by an allergic nature of asthma in 'non-atopic' persons or a non-causal association between asthma and tIgE, that is, co-inheritance (26, 27). However, studies are inconsistent regarding the role of tIgE as a determinant of atopic diseases (3, 5, 6). In a recent ISAAC Phase Two study on allergic markers, total IgE contributed only little to the risk of wheeze among children with no evidence of aeroallergic sensitization (3). More than 50% of the asthmatic children (based on ISAAC questionnaire) were negative for both SPT and sIgE. It has been found that asthma prevalence in Latin America is mainly non-atopic, whereas in developed countries its phenotype is rather atopic (24). Obviously, this has major consequences for the use of atopic markers to determine asthma prevalences. Up to now, the non-atopic phenotype is incompletely understood and still difficult to distinguish clinically (24).

Median tIgE levels in our Cuban study group were 369 kU/l (range: 4.49–5000 kU/l). These lie between the median IgE values of Caucasian and Black African groups and correspond with the mixed race group in a study by Levin et al. (7) on tIgE levels in populations with different genetic origin and area of residence. They are also in range with levels of tIgE among children in non-affluent countries, as reported by Weinmayr et al. (3).

In view of the well-known effect of helminth infection on tIgE, it was not surprising to find that not only allergic disease, but also helminth infection affected tIgE concentrations. A study on atopy, intestinal helminth infection, and tIgE in Gambian adults, however, failed to show such an association (28). According to the authors, this was partly related to the low intensity of helminth infections found (i.e. prevalence of 8.2% in a rural, and 17% in an urban area; no infection intensities were mentioned). Yet, we observed relatively low percentages of helminth positives (i.e. 20.9%) as well; thus, this explanation does not seem to hold here. It should be noted however that in both studies, some infections may have been missed because of a lack of sensitivity of the parasitological methods used (i.e. Kato Katz on one single stool sample in our study). Nyan et al. (28) measured tIgE levels in their Gambian non-atopic subjects, which were over twice those measured in non-atopic subjects living in industrialized countries, and suggested that there may still be some residual polyclonal IgE stimulation from prior helminth infections that could not be detected by parasitological stool examination. The authors concluded that measurement of worm-specific IgE might have given a better estimate of the overall burden of helminth infection.

In a recent study by Levin et al. (7), *Ascaris* infection was assessed by *Ascaris* sIgE levels in Black African high school-children. Early studies in South Africa revealed higher tIgE levels in Black Africans as compared to other ethnic groups (7, 28), maintaining the notion that they had a genetic propensity to raised IgE levels. By correlating tIgE levels with atopy, self-reported asthma and sensitization to *Ascaris* however, Levin et al. (7) found that helminth infection rather than genetic differences may be the determining factor of IgE levels in this population. This questions the need for ethnic group specific values in tIgE, as well as the validity of using tIgE estimation in helminth endemic areas. It should be noted, however, that this does not imply that genetic factors do not play a role in the regulation of tIgE levels as well. A recent study by Grant et al. (29) in Brazil indicated that genetic factors are likely to control tIgE levels even in the presence of helminth infection.

In the present study, SPT correlated well with sIgE. Nevertheless, discordant results were observed between sIgE and SPT. In affluent countries, the relationship between IgE and SPT reactivity to the same allergen has been reported to be strong whereas in less affluent countries these relationships become less strong, particularly as a function of living in an urban or rural area (3, 30). Indeed, various studies in developing countries have shown high frequencies of circulating IgE antibodies, yet low(er) prevalences of positive SPTs (3, 30). This has been explained by the 'mast cell saturation hypothesis'. This hypothesis states that polyclonal non-specific IgE levels induced by parasitic infections may saturate the receptors on the mast cells and consequently no reactivity will occur upon SPT (14). Alternatively, there may be a downregulation of skin reactivity in less affluent countries, possibly through helminth-induced IL-10 (10). In the present study, we could confirm a high proportion of SPT negatives among Cuban schoolchildren with positive sIgE (61.9%). Moreover, this proportion was significantly higher in helminth-infected children (74.0%) as compared to uninfected children (58.4%) ($p < 0.05$). These observations would support the above-mentioned hypothesis and the role of helminth infections herein.

While 61.9% of sIgE positive children were negative for SPT, 41% of SPT positive children had a negative sIgE. This would suggest an enhanced SPT reactivity, in contrast to the common patterns seen in developing countries. No significant difference in proportion of sIgE negatives among SPT positives was observed between helminth-infected as compared to uninfected children.

Similar discordant results were recently observed in an ISAAC Phase Two study on international variations in associations of allergic markers and diseases in children (3). The authors reported consistently higher proportions of sIgE-negative subjects among SPT positive children in non-affluent countries (37–61%) than in affluent countries (0–37%). Whereas less affluent countries had a higher proportion of SPT negatives among sIgE positive children (31–79%), they also found high proportions in some affluent countries, such as Spain and UK. As stated by the authors, these results do not unequivocally support the hypothesis of downregulation of SPT reactivity in less affluent countries.

Comparing our data with those of Weinmayr and colleagues (3), the pattern of discordance between SPT and sIgE results in Cuban children, particularly those with intestinal

helminth infections, corresponds best to their observations in non-affluent countries. It should be noted that the proportion of children with discordant results actually concerned only a limited percentage of the total (atopic) Cuban study population. In fact, 30.2% (125/415) of the atopic children and 77.4% of the total children population studied did not show discordant results of SPT and sIgE. The same can be argued for the children populations of the countries studied by Weinmayr et al. (3). Observed inter- and intra-country differences concerning discordance between sIgE and SPT results should therefore be interpreted with caution.

In summary, the atopic markers tIgE, sIgE, and SPT in Cuban schoolchildren were associated with each other and with asthma. Helminth infections affected tIgE levels, despite relatively low percentages of helminth positives in this population, reconfirming the limited value of tIgE for the diagnosis of atopy/asthma in tropical areas. Like in other non-affluent countries, higher frequencies of sIgE antibodies than positive SPTs were observed, especially in helminth-infected children. This would be in line with current hypothesis on the role of helminths in atopy. Apart from sIgE positives with negative SPT however, a considerable proportion of SPT-positive children had negative sIgE results, suggesting an enhanced SPT reactivity in these children. This phenomena has recently been observed in children from other affluent as well as non-affluent countries, suggesting other or additional mechanisms being of importance in the 'atopic march'.

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Authors contributions

KP, MBG, RJD, FAN, and LRR designed the research. MW, LMH, ARE, and RJD conducted the research. KV performed the statistical analysis. KV, KK, and KP interpreted the data. KV and KK drafted the manuscript. KV and KP had primary responsibility for the final content. All authors contributed to the critical revision and have approved the final version to be published.

Conflict of interest

The authors declare that they have no conflict of interest.

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