

TOTAL IgE, SPECIFIC IgE AND ASCARIS INFECTION AND THE EXPRESSION OF SKIN-TEST POSITIVITY AND ATOPIC DISEASES IN AFRICA

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ABSTRACT

Studies show rising rates of allergies and asthma in Africa, with increasing prevalence of allergic diseases in all communities, especially in rural and black African subjects. There is a complex interplay between environmental and genetic factors that affect the manifestation of allergies in Africa. The African setting is a wonderful 'natural experiment' where black African populations have co-evolved with parasites and micro-organisms, possibly leading to pro-allergic genetic potential, which has, however, been mitigated by continued exposure to factors in a traditional rural environment that downregulate manifestation of that potential. This complex situation leads to differences in presentation and diagnosis of allergy in Africa from those in First World settings. For example, rural to urban migration may lead to the lack of allergic family history in black African subjects, and parasite infestation may be an important factor in dictating total IgE levels, and may also have an effect on reducing skin reactivity.

Changes in the modern environment and lifestyle are associated with marked health effects.¹ Chronic non-communicable diseases have increased dramatically in both developed and developing regions and now provide one of the major global challenges of the 21st century. The dominant focus in non-communicable diseases is usually on 'the big four': cardiovascular disease, metabolic disease (obesity and type 2 diabetes), cancer, and chronic lung disease; allergic diseases are typically afforded less importance. This is despite allergies being the most common and earliest-onset of the non-communicable diseases with approximately 30-40% of the world's population being affected by one or more allergic conditions.²

RISING RATES OF ALLERGIES AND ASTHMA IN AFRICA

The ISAAC studies in South Africa confirm a rising prevalence of asthma, allergic rhinitis and eczema.³ The most data documenting this trend are on asthma prevalence. Epidemiological studies in South Africa in the 1970s reported very low rates of asthma in subjects of indigenous black African ethnicity,⁴ especially in rural settings.⁵ These subjects also demonstrated low rates of allergen sensitisation. Further studies in the 1990s and early 2000s, showed increasing prevalence rates of asthma in both urban and rural black African communities,^{6,7} and narrowing of the urban-rural gradient.⁸ In addition, an increased allergen sensitisation rate was noted in rural black Africans,⁹ with different patterns of sensitisation

in those with or without bronchial hyperresponsiveness⁸ (BHR). A recent study¹⁰ demonstrated rising trends in asthma and BHR in black Africans living in a peri-urban setting, and a strong association between both asthma and BHR with allergic sensitisation, with the highest rates of allergen sensitisation in subjects with BHR documented in an African setting and the widest difference in sensitisation rates between black African subjects with and without BHR.

GENETIC OR ENVIRONMENTAL FACTORS

Unanswered questions remain regarding the contribution of genetic and environmental factors on these changes and what effect these factors may have on the diagnosis of allergic diseases in the African setting.

In South Africa there is a marked discrepancy between asthma prevalence and mortality, with prevalence being higher in high socioeconomic groups and severity being worse in low socioeconomic groups.¹¹ Although this may partially be due to factors influencing access to care,^{12,13} and factors affecting questionnaire measures of asthma prevalence and severity,¹⁴⁻¹⁶ it is likely that environmental factors are also responsible in lower- and middle-income settings.¹⁷

The 'hygiene hypothesis'¹⁸ was proposed to explain the effect that crowding, and particularly sibship size, contributes to the expression of atopy in families. Von Mutius found strong influences of a farming environment on atopy¹⁹ and

developed the theory to relate the decreased risk of atopy to increased exposure to endotoxin,²⁰ and various bacteria²¹ and fungi²² and the diversity of micro-organism exposure.²² The 'old friends' hypothesis has developed this further and proposes that micro-organisms and macro-organisms such as helminths play a critical role in driving immunoregulation during critical phases of human development, and that diseases of the modern era, including multiple sclerosis, type 1 diabetes, and allergies, involve disrupted immunoregulatory circuits, reflecting reduced exposures to 'old friend' organisms with which humans co-evolved.²³ It is likely that similar factors are at play in rural South African environments, protecting subjects living there from manifesting with allergy, even should they have genetic potential to do so.

DEMOGRAPHIC SHIFTS

Because of the demographic shifts that have occurred in South Africa it is common that patients from peri-urban townships have parents who have migrated from rural areas. The parent and child may have the same genetic potential for allergy, but the parent was brought up in an environment where there were many protective factors and few pro-allergic factors and therefore does not manifest his/her genetic potential, whereas the offspring is exposed to an environment that promotes expression of the atopic diathesis. This may be responsible for the lack of a family history in many highly allergic black African subjects.²⁴

HOW DOES THIS AFFECT DIAGNOSIS OF ALLERGY IN AFRICA?

The protective rural environment is associated with a complex network of immune regulatory factors that result in findings of clinical relevance: skin-prick reactivity being higher in urban v. rural subjects, an inconsistent relationship between skin testing and IgE to the same allergen, and decreased utility of total IgE levels in correlating with atopy. While many environmental factors may be responsible for these, a major focus has been on the role of helminthic parasites.

TOTAL IgE LEVELS

While total IgE measurements are often used in clinical practice, total IgE is generally of limited value as a diagnostic test for atopic disease.²⁵ The level of total IgE is not useful to rule out sensitisation to common inhalant allergens but a high total IgE may indicate a high probability of sensitisation and may be useful to decide whether further investigation is warranted in patients with negative specific allergy tests to a panel of common inhalant allergens²⁶ such as the Phadiatop²⁷ test. There are genetic factors involved in IgE regulation as

well as strong effects of parasites on the induction of IgE. Many studies have shown that total IgE levels are higher in rural communities in Africa than their urban counterparts, and that these levels are, in turn, far higher than levels found in Caucasian populations in First World settings.²⁸ In black African subjects in a rural setting, there may be little or no difference in total IgE levels between asthmatics and controls.²⁹⁻³¹ Early research in South Africa³² found that IgE is much higher in black African and mixed-race subjects compared with Caucasians, and that the difference in total IgE levels between atopic and non-atopic subjects was significant in Caucasian subjects but not in black African and mixed-race subjects. A subsequent study³³ on cord blood IgE in black African, Caucasian and mixed-race subjects showed elevated cord blood IgE concentrations in black Africans independently of an atopic family history or maternal ascariasis (measured with *Ascaris* IgE). Early studies also documented urban-rural differences in total IgE levels among black African subjects elsewhere in Africa.^{30, 34}

Two studies have recently confirmed that African ancestry is a risk factor for asthma,³⁵ raised total IgE levels³⁵ and asthma exacerbations³⁶ in the USA. These studies attempted to control for confounders and argue towards a genetic reason for these differences. A meta-analysis of North American genome-wide association studies of asthma identified five susceptibility loci for asthma and elucidated different associations in populations of different ancestry.³⁷

A study performed in Cape Town attempted to elucidate the relationship between total IgE, atopy and *Ascaris* infection in black African teens.²⁸ The objective of this study was to determine total IgE levels in unselected urban black African high-school children and to correlate this with atopy and *Ascaris* sensitisation. Atopic status was assessed by means of specific allergen sensitisation (skin-prick tests (SPTs)) to 8 inhalant and 4 food allergens), self-reported asthma and BHR measured by methacholine challenge. *Ascaris* sensitisation was assessed by means of *Ascaris* IgE measured by ImmunoCAP.

In this study, total IgE was higher in atopic v. non-atopic subjects and correlated with the number of positive SPTs, self-reported asthma and BHR. Subjects without allergy or atopy had a median total IgE of 80-90 kU/l. In addition total IgE correlated with *Ascaris* IgE. There was a low incidence of subjects with raised *Ascaris* IgE, but in these subjects total IgE was raised well out of the 'normal' range. Raised IgE levels were most marked (median 1 019 kU/l) with class 2 *Ascaris* sensitisation, followed by class 1 *Ascaris* sensitisation and SPT reactivity (about 400 kU/l), followed

by a history of asthma (324.5 kU/l) and finally by BHR (214 kU/l). Subjects with no *Ascaris* sensitisation had median total IgE of 77.1 kU/l. Subjects without atopy/asthma had a total IgE of approximately 80-90 kU/l. Subjects with neither atopy nor *Ascaris* sensitisation had a median total IgE of 69.9 kU/l, similar to the levels seen in people of other genetic origins.

This suggests that total IgE levels in black Africans are not higher than those seen in other population groups on a constitutional or genetic basis, and are related (as in other populations) to both atopic status (skin tests, BHR, asthma) and parasite infestation. Previous studies that led us to believe there was a genetic basis to high IgE levels in black African subjects were probably flawed by being confounded by parasite infestation. There is no need for separate population-specific reference ranges. Blood *Ascaris* IgE measurement may be useful to exclude the impact of parasite infestation on total IgE levels without having to resort to IgG4 levels or direct stool collection.

PARASITE-RELATED IMMUNE MODULATION

The results of this study led us to wonder whether *Ascaris* is related not only to a raise in total IgE levels, but also to other measures of atopy. We investigated this relationship in the same cohort³⁸ and found that *Ascaris* sensitisation is associated with BHR. This association was dependent on the level of *Ascaris*-specific IgE in a dose-dependent fashion. For example, the prevalence of BHR increased by 75% for every level of *Ascaris* IgE class increase. Levels of *Ascaris* IgE were significantly higher in those with BHR compared to those without BHR.

In addition there was a dose-response relationship between increasing class of *Ascaris* IgE and sensitisation to one or more allergen, sensitisation to house-dust mites (HDM) and grass and number of positive SPTs.³⁸ The prevalence of subjects sensitised to at least one aeroallergen increased by 65% for every level of *Ascaris* IgE class increase, and *Ascaris* IgE class was strongly associated with total number of positive SPT for aeroallergens. The number of positive SPTs increased by 78% for every level of *Ascaris* IgE class increase. Any sensitisation to *Ascaris* was associated with more than double the prevalence of HDM sensitisation and almost four times the prevalence of grass sensitisation, and higher levels of *Ascaris* IgE were seen in those with HDM and grass sensitisation.

These findings may suggest that subjects in Africa with a genetic propensity to aeroallergen sensitisation also have upregulation of their defence system against parasitic infection.

There was, however, no association between *Ascaris* sensitisation and any of the atopic diseases (asthma, rhinitis and eczema).³⁸ This may suggest that other factors in the environment are more important than worm infestation in being protective against the development of allergic disease, despite the presence of allergen sensitisation.

A more complete study in Brazil³⁹ showed that the presence of serum anti-*Ascaris lumbricoides* IgE antibodies (but not active infection) was a risk factor for wheezing and atopy in preschool-aged Brazilian children, findings that are compatible with the theory that atopy is the primary factor whereby subjects with worm infection respond with an exaggerated IgE response and a resultant lowering of the worm burden or resolution of the infection. These studies may provide a clue as to the origin of the heightened tendency to allergy often seen in people of African and Indian extraction who live in industrialised countries.

The interactions between parasites and allergy can be postulated to occur at various levels. At the genetic level, evidence supports the hypothesis that relatively hostile ancestry conditions seen in tropical climates have caused genetic selection for strong pro-inflammatory T-helper 2 (Th2) immune responses that provide resistance to helminthic infections.^{40,41} On migrating to temperate regions, pronounced pro-inflammatory responses would have been less important and selected against as a result of increased mortality from overly vigorous responses to harmless environmental agents.⁴¹ This hypothesis is supported by the observation that pro-inflammatory alleles in several genes involved in inflammation are more prevalent in populations with long-term tropical ancestry than those with long-term residence in temperate regions, including variants associated with raised serum IgE levels.⁴²⁻⁴⁴ More recent reviews have identified common genes that confer protection against worm burden that are also the same genes involved in allergic asthma.^{45,46} Of these polymorphisms, the FcεR1-β polymorphism, which is the β chain of the high-affinity IgE receptor, has been shown to be more frequent in black South African asthmatics than white South African asthmatics.⁴⁷ In addition, when populations of tropical genetic origin relocate to a temperate region, they have a higher incidence of allergic inflammatory diseases than the local populations.⁴⁸⁻⁵⁰

In addition to these effects, exposure to parasites at certain critical stages of immune maturation may be postulated to alter the Th1/Th2 balance or induce regulatory T-cells. Finally parasitic infestation itself causes marked immune responses such as eosinophilia, increases in parasite

specific IgE,⁵¹ raised total IgE and raised parasite specific IgG4. The first two clearly favour the host but some immune responses may favour the parasite. Parasites are thought to have evolved the ability to generate polyclonal non-specific IgE in order to evade host immunity by saturating IgE receptors.⁵² This blocks the cross-linking of parasite specific IgE on mast cells and therefore prevents their degranulation. Hagel *et al.*⁵¹ found that in an area of high *Ascaris* prevalence very high total IgE was associated with an increased risk of reinfection after successful treatment. In another study,⁵³ her group found a negative correlation between total IgE and antigen specific IgE (including *Ascaris* IgE) as well as skin-test reactivity. In general, antiparasite IgE antibodies are low in children who are continually reinfected and high in adults who remain uninfected.⁵⁴

In Africa, there seems to be an inconsistent relationship between asthma (both self-reported and physician-diagnosed) and aeroallergen sensitisation, with subjects in urban areas demonstrating the relationship and subjects in rural areas demonstrating less association⁵⁵ or even total dissociation between aeroallergen sensitisation and allergic diseases.⁵⁶ There is, however, evidence that over time asthma in Africa is becoming 'more allergic' in nature.¹⁰

Worm infestation has been postulated as one of the factors responsible for the dissociation between symptoms and both allergy and atopic sensitisation, perhaps by non-specifically increasing IgE production⁵² with or without changing the predisposition to allergic diseases.

SKIN-PRICK REACTIVITY

As an additional effect of this non-specific IgE production, subjects may be protected from allergic diseases by blocking cross-linking of other allergen specific IgE.⁵⁷ Parasite-induced raised total IgE may cause negative skin tests and low allergic reactivity despite a high degree of sensitisation to those allergens. Hence, in the presence of parasite infection, the accuracy of assessing atopy with SPTs may be impaired. Many epidemiological studies have found that skin-prick reactivity is higher in urban than in rural subjects^{5,8,58} and others have shown impaired skin reactivity with parasite infestation.⁵⁹ This theory is supported by studies on antihelminthic treatment in which a drop in total IgE is accompanying by increased skin-prick reactivity to inhalant allergens.^{60,61}

Even without worm infestation, skin testing and specific IgE measurement are not interchangeable even in systems that use highly purified skin-test antigens.⁶² In a comparative study the amount of allergen that was required for a positive

skin-test result differed by up to a factor of 100 between patients with similar levels of specific IgE. High values of total IgE were accompanied by lower skin reactivity for allergen.

Another possible complication is recent data showing high IgE cross-reactivity between *Ascaris lumbricoides* and mite allergens such as tropomyosin and glutathione transferases.⁶³ This may have clinical importance in the evaluation of mite allergy in our setting and perhaps be a reason for some of the inconsistencies in epidemiological studies.

CONCLUSION

Allergy in Africa is an important public health problem.¹⁷ The African setting is a wonderful 'natural experiment' where black African populations have co-evolved with parasites and micro-organisms, possibly leading to pro-allergic genetic potential, which has, however, been mitigated by continued exposure to factors in a traditional rural environment that downregulate manifestation of that potential. This complex situation leads to differences in presentation and diagnosis of allergy in Africa from those in First World settings, such as the lack of allergic family history in black African subjects. Data suggest that parasite infestation is still the most important factor in dictating total IgE levels, and may also have an effect on reducing skin reactivity.

Declaration of conflict of interest

The author declares no conflict of interest.

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