INFECTION AND ATOPIC DISEASE BURDEN IN AFRICAN COUNTRIES: KEY TO SOLVING THE ‘HYGIENE HYPOTHESIS’?

Charles C Obihara, MD, PhD
Department of Paediatrics, St Elisabeth Hospital, Tilburg, The Netherlands

ABSTRACT
While most African countries are experiencing an epidemic rise in chronic infectious diseases, such as tuberculosis, malaria, HIV and parasites, industrialised, westernised countries are experiencing an epidemic rise in atopic and auto-immune diseases. One of the most popular explanations for this increase is the so-called ‘hygiene hypothesis’, which suggests that a decrease or altered exposure to microbes in the environment, as a result of improved sanitation and personal hygiene, smaller family sizes, shorter duration of breastfeeding, immunisations and lack of serious childhood infections, results in alteration of the immunoregulation. It has been demonstrated in animal studies that some infections may modulate the expression of the immune system, resulting in the suppression of allergic inflammation. This is achieved through the priming of regulatory T-cell activity, and these cells may be responsible for the protection of populations with chronic infectious diseases against atopic disease. If the specific molecules involved in the immunomodulatory and protective defence mechanisms of the host against these infectious agents were to be defined or isolated, they could be manipulated in such a manner as to warrant application for the development of both novel therapeutic and prophylactic strategies against atopic disease. African countries, with both a high burden of chronic and persistent infection and an increasing burden of atopic diseases may form an ideal ‘nature’s own laboratory’ to investigate the hygiene hypothesis.

INTRODUCTION
During the last few decades, the prevalence of atopic disease has increased globally, not only in industrialised countries, but also in less industrialised countries, especially in urban centres with a westernised lifestyle. The hygiene hypothesis suggests that a relationship exists between improved hygiene and an increase in atopic disease prevalence. It is clear that this relationship may be more complex than initially assumed. It may be under the influence of different factors, such as genetic variability, time of exposure, amount and length of exposure, type of infection, and the prevalence of environmental allergens.

An underlying mechanism for the hygiene hypothesis is that lack of microbial stimulation leads to either an inappropriate T-helper (Th) type immune response or inappropriate Th-cell regulatory mechanisms. There is evidence that the critical period for the establishment of the Th-cell balance is early childhood, when the Th2-skewed human immune system gradually becomes less Th2-skewed in non-atopic individuals, but not in atopic individuals. Among the infectious agents which have been inversely linked to atopic disease prevalence are measles in Guinea-Bissau, hepatitis A in Italian recruits and BCG-vaccination in schoolchildren from Japan. However, most of these initial findings have not been reproduced in other settings. Animal and experimental studies have consistently identified mycobacteria and parasitic infection as potential candidates in the hygiene hypothesis, by demonstrating that infection with these organisms or exposure to their products leads to regulatory mechanisms which restored the immune homeostasis. In contrast, the epidemiological relationship between infection and atopic disease in humans is still unclear and controversial. Most of these studies have been conducted in western populations with a low burden of infection. It has been suggested that inhibition of atopic inflammation in the presence of chronic infections, such as Mycobacterium tuberculosis and parasitic infection, probably occurs through the stimulation of regulatory and anti-inflammatory networks. In this paper we review the published papers from the African region on the relationship between mycobacterial and parasitic infection, and atopic disease. In addition, we discuss, based on the most recent publications, the implication of these findings for countries in Africa, where chronic infections with mycobacteria and parasites are highly prevalent.

INFECTION AND ALLERGIC DISEASE IN AFRICA
Recent insight into the hygiene hypothesis of atopic disease suggests that the protective effect of chronic infections, such as that caused by M. tuberculosis and parasites, on atopic disease would logically be more evident in populations with a high burden of these infections (such as in many non-affluent, mainly rural areas in African countries, where exposure to these chronic infections is more likely to be intense and persistent) than in populations with a low infectious burden (as in most industrialised countries and in some affluent urban areas in Africa with a westernised lifestyle, where exposure is more likely to be sporadic and intermittent). Although the epidemiological relationship between atopic disease and mycobacterial and parasitic infection has been reviewed recently, this relationship has not been evaluated in African countries, which carry the highest global burden of both mycobacterial and parasitic infection. Table I summarises the characteristics and findings of studies on the relationship between mycobacterial and parasitic exposure and atopic disease in different populations in Africa.
Table I. Characteristics and findings of studies on the relationship between mycobacterial and parasitic exposure or infection and atopic disease in different populations in Africa

<table>
<thead>
<tr>
<th>Type of infectious agent studied</th>
<th>Reference</th>
<th>Country</th>
<th>Year of publication</th>
<th>Study type</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>Inverse relationship?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacteria</td>
<td>Aaby et al.(^{25})</td>
<td>Guinea-Bissau</td>
<td>2000</td>
<td>Cross-sectional</td>
<td>271 (400)</td>
<td>3-14</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Ota et al.(^{20})</td>
<td>The Gambia</td>
<td>2003</td>
<td>Cross-sectional</td>
<td>507</td>
<td>8-12</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Obihara et al.(^{26})</td>
<td>S. Africa</td>
<td>2005</td>
<td>Cross-sectional</td>
<td>337</td>
<td>6-14</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Obihara et al.(^{27})</td>
<td>S. Africa</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>841</td>
<td>6-14</td>
<td>Yes</td>
</tr>
<tr>
<td>Parasitic infection</td>
<td>Van den Biggelaar et al.(^{31})</td>
<td>Gabon</td>
<td>2000</td>
<td>Cross-sectional/nested case-control</td>
<td>520/132*</td>
<td>5-14</td>
<td>Yes</td>
</tr>
<tr>
<td>Schistosoma haematobium</td>
<td>Scrivener et al.(^{18})</td>
<td>Ethiopia</td>
<td>2001</td>
<td>Nested case-control</td>
<td>572</td>
<td>≥16</td>
<td>Yes</td>
</tr>
<tr>
<td>T. trichiura/hookworm</td>
<td>Nyan et al.(^{19})</td>
<td>The Gambia</td>
<td>2001</td>
<td>Cross-sectional</td>
<td>429</td>
<td>15-34</td>
<td>Yes</td>
</tr>
<tr>
<td>Any intestinal parasite</td>
<td>Dagoye et al.(^{20})</td>
<td>Ethiopia</td>
<td>2003</td>
<td>Cross-sectional</td>
<td>563-856(^{1})</td>
<td>1-4</td>
<td>No</td>
</tr>
<tr>
<td>T. trichiura/A. lumbricoides/hookworm</td>
<td>Van den Biggelaar et al.(^{15})</td>
<td>Gabon</td>
<td>2004</td>
<td>RCT</td>
<td>341</td>
<td>5-13</td>
<td>Yes</td>
</tr>
<tr>
<td>A. lumbricoides</td>
<td>Obihara et al.(^{22})</td>
<td>S. Africa</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>359</td>
<td>6-14</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BCG – bacille Calmette-Guérin; MTB – Mycobacterium tuberculosis; RCT – randomised controlled trial; S. Africa – South Africa.

* 132 children out of 520 included in the nested control trial.
† Unclear the number of persons included in the analysis.
those without. The difference in finding was attrib-
uted (ORadj 0.5; 95% CI 0.3-0.9). This effect was dose-
conducted in Gabonese children. Van den Biggelaar
African setting is derived from the intervention study
between intestinal parasite infection and atopy in an
Ethiopia, Dagoye
naire-reported atopic disease symptoms (OR adj 0.43;
of children infected with
children with elevated
specific-IgE than in
Ascaris eggs) due to peri-
duced with elevated A. lumbricoides specific-IgE than in
those without. The difference in finding was attrib-
uted to the intermittent parasite infectious burden (low
median number of A. lumbricoides eggs) due to peri-
odic anthelminthic prophylaxis given to schoolchildren
from the area. Surprisingly it was observed that M.
tuberculosis co-infection modified the expression of
atopy in the children. In children without M. tubercu-
losis co-infection...
these anti-inflammatory mediators, which normally function to contain excessive immune effector responses of the host. These regulatory mechanisms might be beneficial to the host by maintaining a balance between effector and memory responses, but with low inflammatory response that causes minimal damage to the host. 

One practical positive ‘spin-off’ of this effect would be the suppression of allergic inflammation in populations exposed to a very high chronic infectious burden. This suggests that the protective effect of infections on atopic disease would logically be more evident in populations with a high and persistent burden of these infections (such as those living in rural and non-affluent urban areas of Africa, where exposure to these chronic infections is more likely to be intense and persistent) than in populations with a low burden (as in most industrialised countries and westernised, affluent, mainly urban areas in Africa, where exposure is more likely to be sporadic and intermittent).

**FACTORS POSSIBLY INFLUENCING HETEROGENEITY IN STUDY RESULTS IN AFRICAN POPULATIONS**

Among the important factors which may explain the heterogeneity in study results on this topic from the African region, next to differences in the study population, design and methodology (Table I), are differences in type, definition, amount and persistence of exposure to infection in the populations studied, and the lack of uniformity in the definition of atopy. One of the reasons for studying the relationship between infections and atopic disease is not only to understand the mechanism involved, but also to utilise it for future prevention and/or treatment of atopic disease. It is logical to assume that to solve the riddle of the hygiene hypothesis, studies need to be carried out in populations with both a high burden of chronic infections and a high prevalence of environmental allergens, as in some African regions. These studies would have to be multicentre, prospective cohort and interventional in design, in order to study effectively the urban-rural, genetic and interregional differences.

Type of infectious agent. The species of microbe or parasite may be very important in determining the degree of immune activation strong enough to induce suppression of atopic inflammation. For instance, there are suggestions that BCG immunisation evokes a weaker and shorter immune stimulation and memory, and is therefore not able to mimic the persistent immune stimulation provided by frequent exposure to wild-type M. tuberculosis. To support this are studies showing that M. bovis BCG is a poorer inducer of IL-12 than natural M. tuberculosis infection. Moreover, M. tuberculosis infection is associated with a larger TST size than M. bovis BCG or environmental mycobacteria. Although in African children neonatal BCG immunisation caused a transient TST reactivity, this became weak or even non-reactive at 5 years of age. Moreover, while some of the studies on the relationship between A. lumbricoides and atopic disease observed an inverse relationship, none of the studies in Africa which studied the relationship between T. trichiura infection and atopic disease observed a relationship. This seems to suggest either a weaker immune modulatory effect or a different mechanism of immunoregulation.

Amount of infection. There are indications that triggering the innate immune system through endotoxin exposure and the derived effect (increased or decreased atopic inflammation) may not only depend on the exposure but also on the amount of endotoxin. This has been shown in children from farming environ...
Prospective intervention studies are needed to confirm these findings.

Discrepancy in the definition of atopy, Lack of uniformity in the definition of atopy makes it difficult to compare results of studies carried out in African countries. This may also account for some of the heterogeneity of study results from the continent. While some studies defined atopy as questionnaire-reported symptoms or positive SPT or elevated serum specific IgE to common environmental allergens, others used both definitions. The use of the recently accepted World Allergy Organization (WAO) definition of atopy, as clinical allergic symptoms in combination with a positive SPT and/or an elevated serum IgE antibody level, makes it possible for future studies to define atopy more uniformly.

CONCLUSION

The results of epidemiological studies in African populations on the relationship between chronic infection such as that caused by mycobacteria and parasites are as inconclusive as those in other parts of the world. Part of this inconclusiveness may be attributed to differences in study design, population and methodology. However, it is not unthinkable that other environmental factors such as the type, amount and persistence of infection, prevalence of environmental allergens and sensitivity of allergy tests in the African populations may equally be of influence. Last but not least is the lack of uniformity in the definition of atopy used in the different studies. Despite the above-mentioned shortcomings of the present epidemiological studies on the relation of infection and atopic disease, the high prevalence of chronic infections and the rising incidence of atopic disorders due to westernisation in some communities in the African region, indicate that these communities form an ideal epidemiological platform to investigate the possible protective effect of infection on the development of atopy.

REFERENCES


