ASTHMA IN LATIN AMERICA: THE ROLE OF NONATOPIC PHENOTYPE

Renato T. Stein, M.D., Ph.D.

Introduction
Asthma in school-age children from developed countries is commonly associated with an atopic phenotype, including bronchial hyperresponsiveness, peripheral blood eosinophilia, increased allergen-specific immunoglobulin (Ig)E levels and positive allergen skin-prick tests (SPT). The well publicized ISAAC data has demonstrated that asthma and asthma-related symptoms are highly prevalent among many of the less-privileged communities in Latin America. {Mallol, 2000 #4} Penny and collaborators when surveying childhood asthma in socially deprived areas of Lima, Peru made the interesting observation that asthma and respiratory symptoms were highly prevalent at that setting but it was not associated with allergy.{4}

A recent analysis comparing data of well developed with less affluent countries has shown a significant discrepancy of the relation between markers of allergy and symptoms of asthma in these communities. {5} Prevalence rates of wheeze attributable to skin test reactivity correlated strongly with the Gross National Income (GNI) of the studied countries. In addition, the strength of the association between current wheeze and skin test reactivity, assessed by odds ratios, increased with GNI. A main conclusion that can be drawn from these findings is that asthma is a multifaceted disease where a strong interaction between genetics and the environment has a significant influence in the distinct asthma clinical outcomes. The idea becomes clear that in communities where there is good social development the high prevalence of asthma symptoms will be strongly associated with atopy while this is may not be so among socially deprived communities environments.

The overall risk for children from affluent countries to present a positive skin test are seemingly at odds with the so-called hygiene hypothesis, and suggest that the relationship between asthma and the atopic phenotype is less clear in children from developing countries. Data from Africa show that the association of asthma with atopy is stronger in children living in urban rather than rural settings. {6}

Parasitic infections are common among disadvantaged populations in Africa and Latin America. Recent data from these areas have shown an inverse association between helminth infections and allergy, and probably an attenuation of asthma-related symptoms. {7,8} As part of the ISAAC-Phase II data set one can observe that prevalence of asthma, asthma-related symptoms, and positive skin tests present are rather low among children living in a rural area in Ecuador. {5} Cooper and his Ecuadorian collaborators have also shown that there is a significant and strong inverse relation between intestinal infection with geohelmiths and allergen skin test reactivity in this heavily parasitized population. {9}

These findings of low asthma prevalence in Ecuador are in sharp contrast with the high frequency of asthma and asthma-related symptoms in most large urban settings surveyed by the ISAAC consortium in Latin America. {3} There is a clear difference between the findings of asthma and asthma-symptoms and those of atopy. The finding
of lower levels of atopy among poorer communities from the region seems quite consistent. Many but not all of the populations studied in Latin America within the ISAAC framework are of low socio-economic levels and for some of these children high-load intestinal helminth infections may be major inhibitors of the allergic pathway, or alternatively, may act as surrogate markers for other common “aggressive” environmental agents acting in the same allergy-protection direction. Inversely to the findings of allergy, there are quite consistent references pointing into the direction of helminthes being inducers of asthma-like symptoms.7,10

Asthma and the Environment
This raises the question as to which environmental factors might be responsible for the high prevalence of asthma and asthma-related symptoms among poorer populations of Latin America, 3 once the allergic pathway may not be a key factor. Some authors11,12 have suggested that the role of atopy in childhood asthma has been overestimated, even in Western countries. The fact that wheeze and asthma-like symptoms are frequently associated with atopy does not imply that these two phenomena are related in the individual child. Longitudinal studies following children from birth and school age children to adulthood have convincingly shown that distinct wheezing phenotypes exist in children. 13,14 The interaction between genetic susceptibilities and early-life environmental exposures plays a key role in determining the distribution of these wheeze phenotypes in different populations. This is particularly important in relation to early-life infections, especially those due to respiratory viruses, and their profound impact on the recurrence of wheezing during the first decade of life. 15,16

Virus and Asthma
The relation between viral respiratory infections and asthma is mediated by both specific factors of the viruses and by a genetic predisposition for some groups of individuals.17,18 RSV is the agent most frequently involved with moderate and severe clinical pictures in the first two years of life and closely associate with asthma later in life. 14,19 More recently Rhinovirus (RV), the most prevalent agent responsible for upper and milder lower respiratory illnesses, has been associated with the development of asthma in children and adults.15 Still, the association between severe bronchiolitis in infancy and asthma is not specifically related to RSV infection. A prospective study from Norway where infants admitted for severe bronchiolitis were followed showed that in comparison with a control group, these children were at a much greater risk for recurrent wheeze and lower lung function parameters at age 7 years, independent of the viral agent involved.19 These and other data suggest that there are innate host factors predisposing the outcomes of recurrent wheeze or asthma.

Conclusions
Pearce et al.20 have raised the issue of the role of nonatopic asthma being underestimated in many population studies. In the Isle of Wight, UK birth cohort study, for instance, the prevalence of atopic and nonatopic wheeze was similar, with atopic wheezing being more frequently associated with a diagnosis of asthma and treatment for asthma, whereas nonatopic wheeze was more closely associated with recurrent chest infections before the age of 2 yrs.12

In the study by our own group,10 the vast majority of wheeze and active asthma at the age of 10 yrs was nonatopic. In this population there is a potential impact of helminth infections attenuating the response to allergy skin tests. A similar finding has been
observed in a large rural population in China. The respiratory effects of Ascaris on the airways may be related to its passage through the lungs during part of its life cycle and its high allergenicity. Helminths may suppress atopic inflammation in the airways, while, at the same time increasing the risk of nonatopic wheeze. A protective effect of helminth infection on asthma and allergies may be related to either infective load or frequency of infection rather than simply to the presence of helminths.

Interestingly, apart from this “attenuating” effect of intestinal helminth infestation on markers of allergy, there was an independent direct effect of the parasites on symptoms of asthma. Furthermore, new data from our group suggest that helminth infection is associated with increased bronchial responsiveness, indicating that other factors, apart from atopy, are related both to asthma possibly via other inflammatory mechanisms.

References:


