

POINT OF VIEW

Asthma in Latin America: where the asthma causative/protective hypotheses fail

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The current concepts on asthma causation and protection have been the subject of challenges and changes during the last years. Probably the most important are related with the findings of large, well-standardized epidemiological studies undertaken at global scale which have included children from several countries in different stages of development and with diverse ethnic and cultural backgrounds¹⁻³. These studies have provided information on largely ignored aspects related to asthma prevalence in low-resourced countries, and have shown that findings, conclusions and hypotheses based on studies from well-resourced countries are not globally applicable. Furthermore, they are widely insufficient to explain the peculiarities of the distribution pattern of asthma symptoms' prevalence in the world. The consistent lack of representation of low-resourced and culturally diverse populations in past epidemiologic studies on asthma in children has subtracted global validity to their results and has been probably an important impediment for advancing in the determination of the etiopathogenic bases of the disease. The inadequacy and partiality of this developed-countries'

approach, has been recently shown by worldwide large and inclusive studies which indicate that several "truths" regarding asthma-related epidemiologic issues are not consistent and are probably applicable only to the minority of asthmatic children. The International Study of Asthma and Allergies in Childhood (ISAAC), the largest epidemiological study ever performed at global-scale, has consistently demonstrated a remarkable variability of current asthma symptoms in the different countries and regions of the world, high prevalence in developing countries, lack of universal application of hypotheses on causation (low proportion of asthma attributable to atopy), and protection (high prevalence of asthma in children living in developing localities and low hygienic standards), and an erratic relationship between air pollution (smog) and prevalence of asthma symptoms (low asthma prevalence in centres with heavy air pollution).

In Latin America, a developing region where there was no regional comparative information of childhood asthma until the advent of ISAAC (13 years ago), it has been consistently found that several of its centres were among those with the highest prevalence of asthma symptoms in the world^{2,4,5}. The high prevalence of asthma in developing countries has been simplistically explained as that in such localities there is a different type of asthma, mainly determined by infections or viral respiratory diseases and where allergy or atopy plays a very minor role. The concept that asthma is non-atopic in developing countries, and atopic in developed ones, has commanded the notions on asthma causality, at least from a first world perspective for a long time. This would be supported by the theory that the lack of stimulation of the immune system by agents and fac-

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tors related to low socioeconomic status i.e. burden of respiratory infections, low hygiene with all its inherent aspects (parasites, endotoxins), among others, results in a shift toward immune responses driven by Th2 cells and mediators. The latter has been somehow supported by European studies on the protective effect against asthma of farm conditions of life which would be mainly determined by endotoxin exposure, however, in the USA it has been demonstrated that farm environment not only does not protect against asthma in children but it is a risk factor^{6,7}.

In order to contribute to the debate, it seems reasonable to look at the eventual protection of farm environment against asthma in the other way round; that means that individuals living under farm environmental conditions are less or not exposed to the same harmful agents present or associated with urban environmental and "modern" lifestyle. This weak or lack of exposure to urban harmful agents in a farm environment would fit well with the general impression that asthma is much more prevalent in cities than in rural localities. Altogether it would suggest that asthma is predominantly an urban disease, not just because of population concentration but mainly because of population exposure. However, the relationship of asthma prevalence with the different urban and rural environments existing in the distinct regions of the world is still deeply unknown. It is likely that the result of the balance between ecological exposures and ecological adaptation, inherent to each human setting, is ultimately responsible for the large difference in asthma prevalence, and possibly other asthma characteristics, observed in the world. The latter would be supported by the pattern of distribution of asthma prevalence in children found by recent global studies, which cannot be satisfactorily explained by current knowledge. Furthermore, it suggests that several hypotheses on asthma causation and protection could not be applicable worldwide or valid for diverse populations.

It was for the first time, and after the results of ISAAC phase I in Latin America, when we reported that factors supposedly protective for asthma, such as those related to low socioeconomic status and low hygienic conditions, seem not to play such a protective role⁴, suggesting that the hygiene hypothesis was not universally applicable. In opposition, those factors appear to increase the risk for asthma and suggest that environmental risk factors mainly related to low socioeconomic status of urban populations are major determinants for the prevalence of asthma symptoms at each locality. In fact, the high prevalence of asthma in children living under low hygiene conditions, high index of poverty, suffering from high

prevalence of gastrointestinal parasites infestation (mainly ascariasis), high rates of gastrointestinal and lower respiratory tract infections since early on in life, among others, are consistently present in some centres from developing countries that also have a high prevalence of asthma. Other studies from non-affluent regions of the world have reported similar findings^{8,9} in areas where these factors are usually present at a large scale but asthma-like symptoms and allergies prevalence is as high as found in children from well-resourced countries.

Parasite infestation mainly by *Ascaris lumbricoides*, is probably the most important representative of low hygiene, among the several other factors affecting populations living under extreme poverty. Although parasite infestation has been considered as protective for asthma, in Latin America *Ascaris lumbricoides* infection does not play that role. In a case-control study performed in children living in a shanty town and suffering from a high prevalence of current *Ascaris* infestation¹⁰, the prevalence of asthma symptoms in the *Ascaris*-infested group (60.5 %) was similar to that in non-infested children (58.6 %). This study, besides showing a non-protective effect of parasite on asthma prevalence, found a very high prevalence of current asthma symptoms in those without ascariasis (but living in extreme poverty), suggesting that all the other eventually protective factors, abundantly present in that population, were significant risks for a much higher prevalence of asthma. In rural China, it has been found that ascariasis in children aged 8-18 years was associated with an increased risk of childhood asthma, atopy and bronchial hyperresponsiveness to methacholine; the association of sensitization to common aeroallergens with increased asthma risk was also enhanced in those children infected with *Ascaris*, and importantly, such infestation was associated with an increased risk of asthma independent of sensitization to aeroallergens⁸. In those different unprivileged populations, there was no apparent protection against asthma or atopy in children infested by *Ascaris*, neither for those not infected but living under eventually "protective" low hygienic conditions. Recently¹¹, a study in Southern Brazil reported that *helminth* infestation was inversely associated to atopy (positive skin prick test to aeroallergens employed by ISAAC 2 protocol); in that study a high-load *Ascaris* infestation and atopy were asthma risk factors. These data suggest a complex relationship, between helminthic infestation and atopy, asthma symptoms and bronchial responsiveness that remains to be clarified.

Although the high asthma prevalence in Latin America has received relatively little attention, the findings in this region cast doubts not just upon even-

tual protective factors against asthma in children, as mentioned above, but also on the general validity of the predominant asthma etiological theories^{4,12}. The well-resourced countries' vision of asthma etiology, based on an allergen sensitization early in life which after the continuous exposure to allergens results in asthmatic airway inflammation (allergic disease), what would be mainly explained by the lack or weakness of Th1 effectors stimulation (hygiene hypothesis), can explain just a very minor part of asthma in children. As occurs with the hygiene hypothesis, the concept that childhood asthma is predominantly an allergic disease is becoming more and more difficult to accept, particularly from a worldwide vision (all the Worlds included) such as that provided by large-scale global studies¹⁻³. Actually, almost 10 years ago, it was reported that less than 50 % of asthma would be attributable to atopy¹³, showing also a significant variability in the sensitization rates. Most recently, ISAAC phase II, which included several centres in several different affluent and non-affluent countries, has found that the link between atopic sensitization and asthma symptoms differs strongly among populations with no correlations between prevalence rates of current wheeze and atopic sensitization¹⁴. The fraction of current wheeze attributable to atopic sensitization has been reported to range from 0 % in Ankara (Turkey) to 93.8 % in Guangzhou (China); it was also found that a mean of 41 % of current asthma symptoms can be attributable to atopy in all the affluent countries (combined)¹⁴. Surprisingly, the same was found with respect to flexural eczema, a condition conventionally thought to be strongly related to atopy; again ISAAC II found only a weak association between atopy and flexural eczema¹⁵ and no more than 28 % of flexural eczema would be attributable to atopy in affluent countries. Similarly, a lack of association between atopy and bronchial responsiveness has been recently reported in Chilean adolescents¹⁶ showing that bronchial responsiveness in children with and without current asthma symptoms can be enhanced without a concomitant increase in atopy.

On the other hand, there is increasing evidence that other non-atopic mechanisms are much more importantly related to asthma and they can result in a complete asthmatic response and clinical progression¹⁷. Even though allergen exposure can trigger asthma exacerbations, this is not the commonest cause. Both in adults and in children, the majority of asthma exacerbations are caused by respiratory virus infections¹⁸, and it is likely that viral respiratory infections by common respiratory virus, very early in life, may have an important role initiating the events that will finally result in the sequence of recurrent

bronchial obstruction (exacerbations), considered as the main characteristic of asthma.

The recent information on asthma prevalence in children from Latin America, and also other developing regions, suggests that the extended concepts that asthma is allergic in well-resourced countries and non-allergic in low-resourced ones, or that low hygiene conditions are protective for asthma elsewhere, can no longer be sustained under the current worldwide epidemiological knowledge and recent objective information. Those standardized studies demonstrate that the proportion of children whose asthma is attributable to atopy is remarkably low in developed and developing countries and that asthma prevalence in developing countries is at least as high (or as low) as in fully developed ones (which markedly differs in hygiene standards, among other aspects).

One of the most interesting findings from recent studies describing the prevalence of asthma in Latin America is its large and unexplained variability, with some centres in Mexico having some of the lowest prevalence in the world (together with Tibet) whilst some centres in Central America, Cuba, Brazil and Peru had some of the highest. The large variability of the prevalence of current asthma symptoms in Latin America, clearly independent from geographic, climate, cultural, ethnic or language aspects, as shown by ISAAC phase III results, is illustrative on how the inclusion of several centres in most of the countries can result in exceptionally high, or low, asthma prevalence within the same region. This suggests that differences in environmental (ecological) conditions are strongly related with the difference in prevalence and eventually with the clinical expressions of the disease.

The role of some environmental factors such as smog and tobacco on altering asthma prevalence in children of Latin America is largely unknown and paradoxical in the case of smog. The prevalence of asthma symptoms in big Latin American cities with well-know high levels of air pollution (smog) such as Mexico, Sao Paulo and Santiago were much lower (or similar) than places with significantly lesser atmospheric pollution. Regarding tobacco, we have recently found in a random sample of 4,738 adolescents who completed the ISAAC video questionnaire plus questions on tobacco smoking, that at least 27 % of current asthma symptoms in that sample were attributable to active tobacco consumption (population attributable risk)¹⁹.

The information available on asthma prevalence in childhood in Latin America undoubtedly indicates that asthma can no longer be considered as a minor health problem far behind respiratory infections as it

was in the past. This is the time when governments and health authorities in Latin America have the responsibility and the scientific bases to implement and support efficient national and regional asthma programs, in order to improve morbidity and mortality registration, develop asthma research, and modernise diagnosis and treatment strategies.

The present epidemiological evidence in Latin American certainly provides new insights on asthma in childhood that should motivate further investigations on its causes and eventual protective factors. Hopefully, such initiatives should take into account the evident lesson about the need to include true representative samples of the several diversities of children populations, if we want to gain universally valid information on these crucial aspects of asthma in childhood.

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