

Asthma in Latin America: the dawn of a new epidemic

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**Current Opinion in Allergy and Clinical
Immunology** 2008, 8:378–383

Purpose of review

Asthma is a heterogeneous disease with high morbidity worldwide. Unlike the low prevalence of asthma and allergy found in many developing countries, especially in rural settings, its prevalence in Latin America is high. In these sites, nonatopic asthma seems to be the most common phenotype observed among school-age children. Therefore, it seems that asthma in Latin America has some particular characteristics that will be presented and discussed in this article.

Recent findings

The prevalence of asthma-like symptoms in childhood is high in many populations studied in Latin America with similar frequencies to those reported in more developed countries. However, the mechanisms and risk factors associated with nonatopic asthma, which is the most prevalent phenotype in this region, have been scarcely studied.

Summary

The better understanding of asthma phenotypes that prevail in Latin America and the investigation of determining factor studies may help establish new diagnostic and therapeutic approaches. These findings should affect public health policies for this new asthma epidemic through the combination of the atopic and nonatopic phenotypes. We hope that this article sheds some new light into these important and most relevant questions.

Keywords

asthma, atopy, children, Latin America, nonatopic

Curr Opin Allergy Clin Immunol 8:378–383
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1528-4050

Introduction

Asthma is the most common chronic disease in childhood with high prevalence in many industrialized countries [1,2*]. Recent study [3] has demonstrated that, in contrast, many developing countries have low prevalence rates of atopic asthma. However, interestingly, overall asthma prevalence in Latin America has been shown to be higher than expected [4]. This apparent discrepancy of disease expression in the context of the current hygiene hypothesis paradigm has been only partially understood. The present review summarizes the characteristics of asthma in Latin America, discussing the most recently published epidemiological studies and raising hypotheses for the distinct phenotypes of asthma seen in this region.

Prevalence of global asthma

Atopic asthma has been widely studied over the last decades. Asthma in school-age children from developed countries is often associated with an atopic phenotype, characterized by increased bronchial responsiveness, peripheral blood eosinophilia, increased allergen-specific IgE

levels and positive allergen skin prick tests (SPTs) [5–7]. Mechanisms of this predominantly allergic disease phenotype, its epidemic course in the previous decades, and investigations on medical treatments have been the main focus of research in affluent countries. On the contrary, there are few studies on asthma burden and mechanisms of disease available from developing countries.

The International Study of Asthma and Allergies in Childhood (ISAAC) has been one of the most important initiatives advancing towards a better understanding of asthma worldwide. ISAAC phase I has studied school-aged children from 56 countries (in 155 centers). The first important ISAAC finding was that the prevalence of asthma and asthma-related symptoms vary significantly between and within countries. The highest prevalences found were from well developed, English-speaking countries. Countries from Eastern Europe and Asia had the lowest prevalence of asthma symptoms. The highest prevalence was about 20 times higher than the country with the lower prevalence (range 1.6–36.8%) [3].

Interestingly, other studies have shown that these prevalence differences may be found even in populations with

similar genetic backgrounds, yet from different settings that are rural and urban communities. In Africa, when compared with an urban population, children living in rural areas had less significant SPT responses. Moreover, exercise-induced bronchospasm was more closely associated with atopy in children living in urban areas [8]. Likewise, in Germany, the prevalence of asthma was lower in children in Dresden and Leipzig (former East Germany) when compared with Munich (former West Germany). Exposure of infants living in farms with stables and the consumption of farm milk was associated with both lower frequencies of asthma later in life (1 vs. 11%) and atopic sensitization (12 vs. 29%) [9,10]. These findings suggest that the effect observed among asthmatics living in nonaffluent communities should be equivalent to what happens in rural settings, indicating that these environments have protective factors for the development of allergy.

Among nonaffluent countries, with some exceptions, lower prevalence of asthma symptoms have been reported in the ISAAC database [3]. This finding may be in line with the concept of the 'hygiene hypothesis', in which a lower risk of asthma and allergy development may be associated with early life exposures to a high burden of infections (bacteria, viruses and parasites) [11]. On the basis of this hypothesis, a strong Th1-immune stimulation by microbial exposition and its products in early childhood may inhibit skewing towards Th2 immunity in atopic predisposed children [12,13]. Consequently, other asthma phenotypes may emerge in settings of nonaffluent populations. A fact that has been noticed is that the impact of hygiene may be mostly associated with markers of atopy instead of asthmalike symptoms.

A recent analysis [14^{••}] comparing data of well developed with less affluent countries has shown that prevalence rates of wheeze attributable to skin test reactivity correlated strongly with the Gross National Income (GNI) in the studied countries. In addition, the strength of the association between current wheeze and skin test reactivity assessed by odds ratio (OR) increased in parallel with GNI. A main conclusion that can be drawn from these valuable findings is that asthma is a multifaceted disease in which a strong interaction between genetics and the environment has a significant influence in the distinct asthma clinical outcomes. This evidence suggests that in populations in which there is higher social development, the increased prevalence of asthma symptoms will be more closely associated with atopy, whereas this may not be as significant among socially deprived populations.

Recent reliable data have showed that many Latin American countries present increased asthma prevalence in children [3,4]. As noted above, this finding seems paradoxical. Although some countries in Latin America

are defined as 'transitional economies', most populations are still at the level of nonaffluent societies, suffering from the overall burden of crowded urban settings in developing countries. Therefore, the next sections of this review will focus on the most recent data on prevalence of asthma in Latin America and the few hypotheses based on the distribution of clinical phenotypes.

Asthma prevalence in Latin America

Unlike many developing countries from other continents, asthma is highly prevalent in most cities in Latin America. On the basis of the ISAAC data, countries such as Brazil, Uruguay, Paraguay and Peru have showed that asthma prevalence rates range from 18 to 27% [3,4]. These numbers are very high when compared with those reported in other nonaffluent populations around the world, and can be compared with the highest prevalence rates in developed countries. Moreover, Pearce *et al.* [15^{••}], in phase III of ISAAC study, have shown that asthma prevalence in Latin America is still on the rise (+0.32% per year).

Regarding mortality of asthma in Latin America, this is not a negligible public health problem. Neffen *et al.* [16], during the 1980s, have found that mortality rates from bronchial asthma are significant in most of Latin American countries studied. The highest death rates (per 100 000) were found in Uruguay and Mexico (5.63), and the lowest in Paraguay (0.8) and Colombia (1.35). In many countries (Chile, Argentina, and Paraguay), deaths from asthma occurred predominantly in the home environment.

Other studies, independent of ISAAC Steering Committee database, with adequate methods applied, are in consonance with these findings of high prevalence of asthma. Chatkin *et al.* [17] have found a prevalence of 21% of current wheeze in 4–5-year-old children in Southern Brazil. Penny *et al.* [18] when surveying childhood asthma in socially deprived areas of Lima, Peru, where very low asthma prevalence would be expected due to the impact of poor hygiene, observed that the prevalence of asthma at any time since birth was close to 21%. These findings more than justify new approaches to better understand obstructive airway disease in childhood in this part of the world, considering its high prevalence and the burden for these communities.

Given the consistent significant variability of asthma in different populations around the world, it should be stressed that in Latin America it could not be different. Latin America also has regions with low prevalence of asthma such as shown in the cities of Cuernavaca, Mexico, and Punta Arenas in Chile (6.6 and 6.8%, respectively) [4]. This finding is in agreement with the

concept that asthma is a very heterogeneous illness that comprises very complex genetic and environmental relationships. However, in Latin America, 14 out of 17 (82%) centers reported in ISSAC study showed prevalence rates of wheeze in the last 12 months above 15% [4]. This observation denotes that we need to better understand asthma in this part of the world.

Risk factors and phenotypes of asthma in Latin America

Many urban populations in Latin America present high prevalence of asthma symptoms in childhood. In addition to that, and in contrast to developed countries, asthma in these populations is less significantly associated with atopy. Moreover, a nonatopic phenotype has been described as the most common presentation of childhood asthma in these regions [18,19[•]]. There is no consensus on why this may occur, but one possible explanation is that the role of crowding in poor urban environments as well as the early introduction of nursery care for children before the age of 2 may facilitate this early and aggressive milieu with respiratory viruses and other environmental factors.

The prevalence of atopy in different cities in Latin America ranges between 13 and 89% [14^{••},20[•],21]. In a study by our own group in an urban setting in Southern Brazil [19[•]], we have recently demonstrated that current wheeze is highly prevalent (26%) in children at the age of 10 years, but the vast majority (70%) with active asthma were nonatopic. Pearce *et al.* [22] have raised the issue of the role of nonatopic asthma being underestimated in many population studies. In the Isle of Wight birth cohort study [23], 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 years. In two populations of Peru and Chile, asthma symptoms were also not associated with atopy in schoolchildren from a deprived and low-income urban area [18,20[•]]. It should be emphasized though that one cannot underestimate the importance of atopy as the most significant risk factor associated with both persistent and severe disease, but its distribution among different populations, particularly in some developing countries, seems to be variable, according to genetics and its interaction with the environment.

Questions have been raised as to which environmental factors might be responsible for the high prevalence of asthma and asthma-related symptoms among poorer populations of Latin America, once the allergic pathway may not be its major driving force. Longitudinal studies [24,25] following children from birth and school-age children to adulthood have convincingly shown that distinct wheezing phenotypes exist in children. The

interaction between genetic susceptibilities and early-life environmental exposures play a key role in determining the distribution of these wheezing phenotypes in different populations worldwide.

A few important risk factors for asthma in nonaffluent populations have been identified. Viral infections, helminth expositions, passive smoking and smoking during pregnancy have been described as risk factors associated with asthma in these children.

Respiratory viral infections, particularly due to respiratory syncytial virus (RSV), which is commonly associated with acute bronchiolitis in the first 2 years of life have been associated with asthma later in life in developing countries [25,26]. The relationship between viral respiratory infections and asthma is mediated by specific factors of the viruses in combination with the genetic predisposition of the hosts [27,28]. More recently, rhinovirus, the most prevalent agent responsible for upper and milder lower respiratory illnesses has also been associated with the development of asthma in children and adults [29]. In Latin America, we have recently shown that, in children from a poor urban community in Southern Brazil, a history of bronchiolitis in early life was the major independent risk factor for asthma at the age of 10 years. Children who had an event of bronchiolitis in the first 2 years of life were 18 times more likely to present asthma than those who did not [19[•]]. In an other study from Southern Brazil [17], bronchiolitis in early life was highly associated with current asthma in 4–5-year-old children. These data suggest that the role of early life impact from viruses seems to be by far the most significant risk factor associated with asthma in Latin America.

Another consistent finding is that parasites may influence the development of allergy in many ways. Parasitic infections are very common among disadvantaged populations. A number of studies [30–33] have reported that helminth infections are associated with decreased prevalence of atopy (positive SPTs) and asthma. On the contrary, some studies [19[•],34] have showed that helminth infections may be positively associated with asthma. Although paradoxical, these findings have been partially explained by epidemiological and experimental studies.

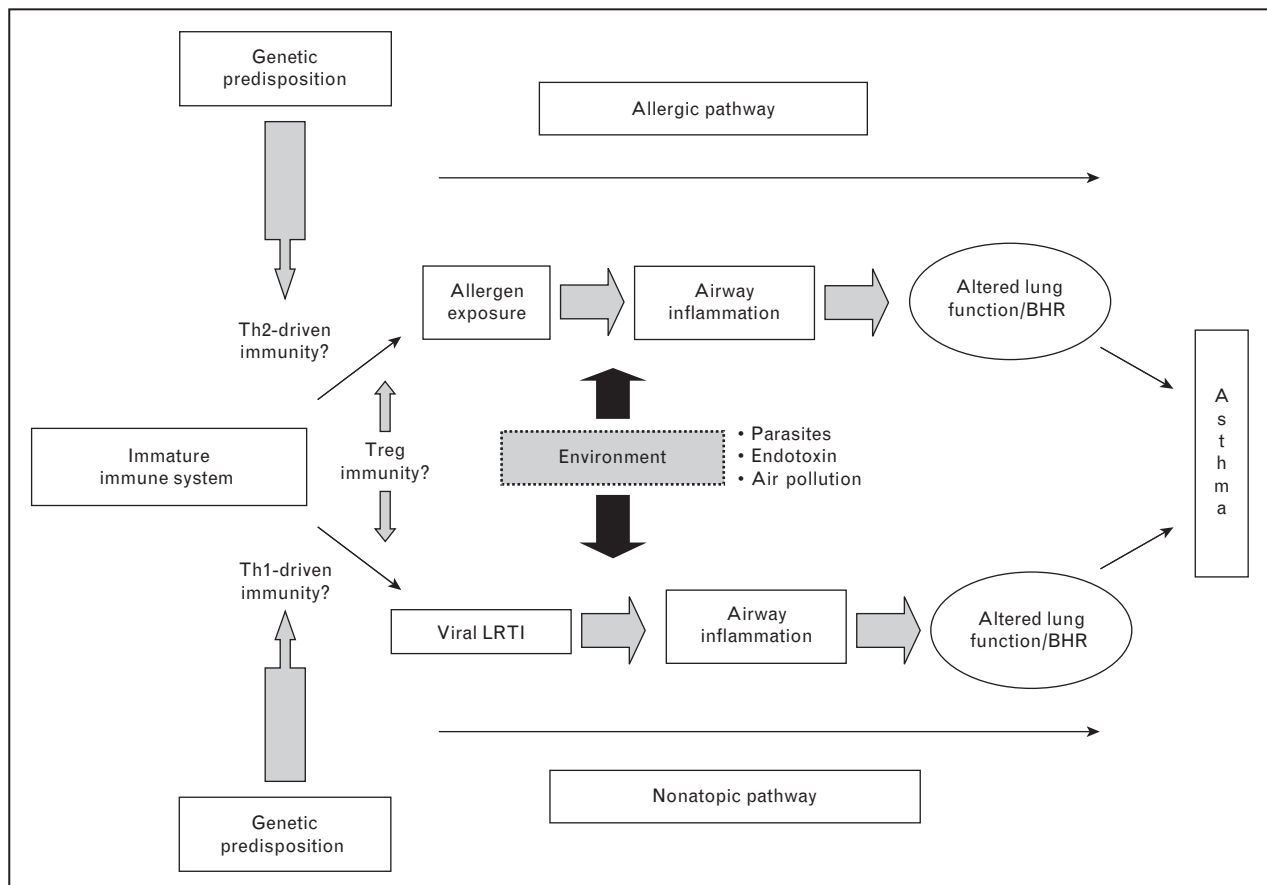
The protective effect by intestinal parasites on asthma development suggests that the inverse relation with atopy may not be influenced specifically by Th1 and Th2 imbalance. Instead of Th1 vs. Th2 stimulus, a strong regulatory T cell [through IL-10 and transforming growth factor beta (TGF- β) production] triggered by helminthes may play a key role in Th2-mediated allergic diseases [35,36]. Inversely to many of the findings of allergy being protected by parasite expositions, there are data pointing into the direction of helminthes being inducers of

asthma-like symptoms in children, possibly associated particularly with their lung life cycle [37]. Respiratory effects of some helminth infestations on the airways may be related to their passage through the lungs during part of their life cycle, resulting in bronchial inflammation. We have shown that children who had both bronchiolitis early in life and were positive for intestinal parasites had an OR for asthma that was greater than 50 [19*]. In an experimental model, Negrao-Correa *et al.* [38] have elegantly demonstrated that rats infected by helminthes with lung cycle (*Strongyloides stercoralis*) have increased bronchial hyperresponsiveness and lung inflammation. Therefore, some helminthes may suppress atopic inflammation in the airways and systemically, whereas at the same time others may increase the risk for asthma-like symptoms. A protective effect of helminth infection on asthma and allergies could also be related to either high infective load or chronic infection rather than simply owing to episodic presence of helminthes. These findings require further studies to be better understood.

As mentioned above, genetic susceptibility also contributes significantly to the development of asthma. It is also not clear whether the results of genetic studies from European and North American populations could be easily transferred to Latin American populations. In Latin America, there is a lack of studies on genetics of asthma. The authors argue that these types of studies are important to determine the role of specific polymorphisms on the expression of asthma in different populations from this region.

It is important to stress that although asthma and allergies are often closely associated in more urban and developed communities, they do not represent a single entity. There is certainly a difference between the mechanisms of disease and related risk factors from atopic and nonatopic asthma, although these 'diseases' may overlap. To the present, the nonatopic phenotype (mechanisms of disease, risk factors and long-term prognosis) is incompletely understood and still difficult to distinguish clinically. In Fig. 1, the authors illustrate a proposed

Figure 1 Model of causes and mechanisms of asthma in children



The nonatopic pathway may be especially significant among Latin American children. The mechanisms proposed for the development of airway diseases in these children are based on direct and indirect evidences that allow the authors to raise hypotheses. It should be stressed that both pathways may overlap on clinical level (atopic and nonatopic phenotype). BHR, bronchial hyperresponsiveness; LRTI, lower respiratory tract infection; Th1, T helper 1; Th2, T helper 2; Treg, T-regulatory cells.

model for causes of childhood asthma in Latin America. This model is not specific for children living in Latin America, but it does stress the fact that the pathway leading to nonatopic asthma may be significantly dependent on the role of acute viral infections in early life in these populations. Both the atopic and the nonatopic pathways should not be understood as independent mechanisms. The association of different environmental stimuli (especially respiratory viruses) with the genetic predisposition to atopy is probably the most significant combination of risk factors leading to persistent and more severe asthma.

Most of the populations studied in Latin America within the ISAAC framework are of low socioeconomic levels and most of them are exposed to high load of intestinal helminthes and viral infections. Paradoxically, these factors may either inhibit or stimulate allergic and airway diseases in this setting. Latin American populations have migrated intensely in the past 3–4 decades into large urban settlements. These large movements have important implications in health patterns and diseases. The high prevalence of asthma observed in Latin America may be related to these demographic changes. Intuitively, one would expect that rates for asthma among populations living under poor socioeconomic conditions would be low, especially given the conceptual framework of the hygiene hypothesis. In these urban settings, the role of crowding and the environment (indoor and outdoor pollution) are significantly associated with respiratory diseases in children. The impact of these variables on lung development and atopic immune response are key factors to be studied in Latin American populations.

The main conclusion that can be drawn from the recent studies in Latin America is that although prevalence of disease is high, its current most frequent clinical phenotype seems to be nonatopic. Even though this phenotype seems to be associated with a milder/attenuated form of disease, it presents a heavy burden to health systems in these countries. Most important is the fact that with the overall improvement in quality of life in many countries in Latin America, the numbers of children with atopic asthma should also be on the rise. Although these advances are not systematic and do not occur evenly we can foresee in the next decades that both phenotypes will coexist in highly prevalent forms.

Future studies among Latin American children with asthma should aim at better description of clinical phenotypes, detection of risk factors, and determination of genetic pattern. Ideally, these studies should be longitudinal and powered to study the decisive early life events leading to asthma.

Conclusion

In conclusion, asthma is highly prevalent in Latin America and seems to be mostly nonatopic. The phenotypes and genetic characteristics are yet poorly understood in these populations. We may be witnessing a new rise of asthma, especially in large urban settlements, probably due to the overlap of nonatopic and atopic phenotypes that follow better sanitary conditions in some of these communities.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 489).

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