

Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children?

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The objective of this study was to evaluate the role of rhinitis (R) and atopic eczema (E) on asthma severity among asthmatic (A) schoolchildren identified by the International Study of Asthma and Allergies in Childhood written questionnaire (WQ). WQ was applied to parents of 6–7-yr-old schoolchildren (SC, $n = 3033$), and to adolescents (AD, 13–14 yr old, $n = 3487$), living in São Paulo, Brazil. An affirmative response to ‘has your child/have you had wheezing/whistling in the last year’ identified those with A, and an affirmative response to ‘the last 12 months has your child/have you had sneezing/runny/blocked nose when he/she you did not have a cold/flu?’ identified those with R. Subjects with an affirmative response to ‘has your child/have you had this itchy rash at any time in the past 12 months?’ were identified as having E. Subjects who had R associated with A were identified as AR and those with A associated with R and E as ARE. A who had at least two affirmative responses to questions for asthma severity: speech disturbance, more than four acute attacks, sleep disturbance, and wheezing with exercise were defined as having severe asthma. 22.1% AD and 24.3% SC were identified as A; 47.1% of those AD and 42.0% SC had AR and 10.0% of those AD and 12.8% of SC had ARE. Considering ARE, AR and A groups, speech disturbance during an acute episode of asthma was significantly higher among ARE AD (20.0% vs. 11.5% vs. 8.7%, $p < 0.05$), and ARE SC (22.1% vs. 13.9% vs. 10.5%, $p < 0.05$) in comparison with A. Likewise, more than four acute attacks in the last year was significantly higher among ARE AD (24.0% vs. 14.0% vs. 10.5%, $p < 0.05$) and ARE SC (32.6% vs. 19.4% vs. 12.8%, $p < 0.05$) as the frequency of sleep disturbance due to wheezing, for AD (61.3% vs. 42.0% vs. 38.4%, $p < 0.05$) and SC (77.9% vs. 67.3% vs. 58.4%, $p < 0.001$) and for ‘wheezing associated with exercise’ for AD (72.0% vs. 47.5% vs. 39.9%, $p < 0.001$) and SC (36.8% vs. 31.4% vs. 14.1%, $p < 0.001$). Prevalence of severe asthma was higher among ARE AD (57.3% vs. 31.9% vs. 27.0%, $p < 0.05$) and ARE SC (52.6% vs. 36.9% vs. 22.5%). In patients with A, the presence of R or E are risk factors for severe asthma, and both together (R and E) are a higher risk.

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Several epidemiological, etiological, anatomical and therapeutic similarities were reported between asthma and rhinitis. It has been hypothesized that asthma and allergic rhinitis are both manifestations of a single inflammatory process present

throughout the airway and that they represent a continuum of disease. Control of the inflammatory response associated with allergic rhinitis may help to reduce inflammation throughout the airway and improve control of asthma (1, 2).

Allergic rhinitis often precedes the onset of clinical asthma and is a risk factor for the development of asthma in children (3, 4) and adults (5). Several studies have pointed out that the prevalence of allergic rhinitis in asthmatic patients is 80–90%. Peroni et al. (4), in an epidemiological study applying the International Study of Asthma and Allergies in Childhood (ISAAC) protocol, observed in children aged 3–5 yr that the prevalence of asthma among those with rhinitis was three times higher than those without rhinitis. Guerra et al. (5), in a large longitudinal community population study, determined that rhinitis was an independent risk factor for adult-onset asthma between atopic and non-atopic subjects. Increase in healthcare costs and impairment of quality of life were observed in asthmatics with concomitant rhinitis (6).

The aim of this study was to evaluate the relationships between rhinitis and atopic eczema with more severe asthma in schoolchildren evaluated by the ISAAC(7).

Patients and methods

The self-applicable ISAAC written questionnaire was applied to parents of 6–7-yr-old schoolchildren (SC, $n = 3003$) and to adolescents (AD, 13–14 yr old, $n = 3487$) living in São Paulo, Brazil, during June–October 1999, under the supervision of the investigators I.C.C.N., G.F.W. and K.C.M. (7).

Subjects were selected among children who attended public and private schools in the southern area of the city of São Paulo, and they were from families of mid and low socioeconomic status. The population of São Paulo is composed of a mix of all Brazilian citizens and represents around 10% of the total population of Brazil. Information regarding the number of schools and students in the area was obtained from the city of São Paulo Secretary of Education's official records, and schools that had students in the age groups of 6–7 and 13–14 yr were selected for the study. Those schools that had both age periods were initially selected. After this they were drawn representing the same distribution of private and public schools observed in the area (as determined by the ISAAC protocol).

Twenty-seven schools comprising 4127 students in the age range of 6–7 yr were selected at random from the 167 schools in the area. Twenty-eight schools comprising 3600 students in the age range of 13–14 yr were randomly selected from the 124 schools in the area.

Collected data were entered into the database Epi-Info, provided by the ISAAC coordinators. The frequency of responses to each question was evaluated, according to range age. An affirmative response to 'has your child/have you had wheezing/whistling in the last year?' identified those with asthma (A), and an affirmative response to 'the last 12 months has your child/have you had sneezing/runny/blocked nose when he/she you did not have a cold/flu?' identified those with rhinitis (R). Subjects with an affirmative response to 'has your child/have you had this itchy rash at any time in the past 12 months?' were identified as having atopic eczema (E). Subjects who had R associated with A were identified as AR and those with A associated with R and E as ARE. The role of R and E as risk factors for more severe asthma were evaluated considering the following questions: more than four attacks in the last 12 months, speech disturbance in the last 12 months, sleep disturbance in the last 12 months, and wheezing with exercise in the last 12 months. Severe asthma was considered in those A who had affirmative responses to at least two questions for severe asthma. The data were analyzed with respect to age. For a final analysis both groups (CS and AD) were grouped.

Nonparametric tests (chi-square for trend, odds ratio, 95% confidence interval) were used for data analysis and $p < 0.05$ was considered significant.

Results

The prevalence of asthma was higher between those SC (404/904, 44.7%) and AD (439/1192, 36.8%) who had R than those had not (SC: 234/2129 or 11.0%; AD: 338/2295 or 14.5%). The same was observed with the students who had R plus E (SC: 95/163 or 58.3%; 75/166 or 45.2%) when compared with those without RE (305/1992 or 15.3%; AD: 304/2155 or 14.1%).

Prevalence of A was 24.3% for the SC and 22.1% for the AD. Considering A patients as a whole, 47.1% of SC and 42.0% of AD had AR and 12.8% of SC and 10.0% of AD had ARE. Questions regarding asthma severity, according to ISAAC protocol, were evaluated in A, AR and ARE groups (7). Speech disturbance during an acute episode of asthma was significantly higher among ARE AD (20.0% vs. 11.5% vs. 8.7%, for ARE, AR and A, respectively, $p < 0.05$) and ARE SC (22.1% vs. 13.9% vs. 10.5%, $p < 0.05$) in comparison with A. Higher proportion was observed among SC in comparison with AD. Likewise, more than four acute attacks in the last year was significantly higher among ARE AD

(24.0% vs. 14.0% vs. 10.5%, $p < 0.05$) and ARE SC (32.6% vs. 19.4% vs. 12.8%, $p < 0.05$) as well as the frequency of sleep disturbance due to wheezing, for ARE AD (61.3% vs. 42.0% vs. 38.4%, $p < 0.05$) and ARE SC (77.9% vs. 67.3% vs. 58.4%, $p < 0.001$). For both questions there were a higher proportion among SC. Wheezing associated with exercise was significantly higher for ARE AD (72.0% vs. 47.5% vs. 39.9%, $p < 0.001$) and ARE SC (36.8% vs. 31.4% vs. 14.1%, $p < 0.001$). In contrast, a higher proportion was observed among SC in comparison with AD. The prevalence of severe asthma was higher among ARE AD (57.3% vs. 31.9% vs. 27.0%, $p < 0.05$) and ARE SC (52.6% vs. 36.9% vs. 22.5%, $p < 0.05$). A slight increase in the prevalence was observed among SC in comparison with AD.

Analyzing SC and AD groups together we observed more severe asthma between ARE patients in comparison with those with AR and A. Risk of severe asthma was significantly higher when compared with A: ARE > AR (OR 2.3, 95%CI 1.7–3.3); ARE > A (OR 3.7 95%CI 2.6–5.2) and AR > A (OR 1.6 95%CI 1.2–2.0) (Table 1).

Discussion

The association or concomitance of asthma and rhinitis acquired great importance in the last years and has originated the ARIA initiative (2). The awareness of the magnitude of these two diseases in many regions of the world could allow a better way for the understanding of their interrelationships. Epidemiological studies have identified that the prevalence of allergic rhinitis is

up to three times higher than that of asthma. In Brazil, the ISAAC study showed that the mean prevalence of active asthma was 21.0%, and of rhinitis was 30.4%. For both conditions, about 50% have an association of rhinitis and asthma (8, 9).

In this study the prevalence of active asthma was 24.3% for the SC and 22.1% for the AD and was associated with rhinitis in 47.2% of the SC and in 42.0% of the AD. In approximately 10.0% of the patients there was an association of active asthma, rhinitis, and atopic eczema. These data differ from other authors who observed asthma prevalence 3.4 times higher among patients with rhinitis (3, 10).

An European multicentric study performed in patients with rhinitis documented higher frequency of asthma among those with perennial rhinitis independently from being or not atopic (11). Thus, the association between perennial rhinitis and asthma in non-atopic subjects with normal serum IgE levels is consistent with the hypothesis that rhinitis is an independent risk factor for asthma (5). In a previous study we evaluated the risk factors for asthma development among SC submitted to the ISAAC protocol and identified that the presence of nasal symptoms in the last year and a personal history of allergic rhinitis, were risk factors for asthma (12). Rusconi et al. (13), in a study of children aged 6–7 yr, observed a strong association between a personal history of eczema or of allergic rhinitis and late-onset persistent wheezing. The same was observed by Toren et al. (14) in patients with late-onset adult asthma. An objective estimate of this relationship can be demonstrated by the evaluation of non-specific

Table 1. Schoolchildren (6–7 and 13–14 yr old, $n = 6520$) with asthma alone (A) or asthma associated with rhinitis (AR) or asthma associated with rhinitis and atopic eczema (ARE) according to asthma symptoms related to severity

	A (%)	AR (%)	ARE (%)	Significant results*	OR (95% CI)
Number of children	667 (10.2)	673 (10.3)	170 (2.6)		
More than four attacks	77 (11.5)	111 (16.5)	82 (48.2)	ARE > AR ARE > A AR > A	4.7 (3.3–6.8) 7.1 (4.9–10.8) 1.5 (1.1–2.1)
Sleep disturbance	323 (48.4)	361 (53.6)	120 (70.6)	ARE > AR ARE > A	2.1 (1.4–2.0) 2.6 (1.8–3.7)
Speech disturbance	64 (9.6)	85 (12.6)	36 (21.2)	ARE > AR ARE > A	1.9 (1.2–2.9) 2.5 (1.6–4.0)
Wheezing with exercise	180 (27.0)	270 (40.1)	89 (52.6)	ARE > AR ARE > A AR > A	1.6 (1.2–2.3) 3.0 (2.1–4.2) 1.8 (1.4–2.3)
Severe asthma	165 (24.7)	230 (34.2)	93 (54.7)	ARE > AR ARE > A AR > A	2.3 (1.7–3.3) 3.7 (2.6–5.2) 1.6 (1.2–2.0)

*Chi-square for trend.

bronchial hyperresponsiveness (BHR). Patients with asthma associated with rhinitis have higher non-specific BHR to methacholine when compared with those with only asthma (15).

Other evidences that sustain the idea of a continuum are the results of the rhinitis treatment in patients with rhinitis associated with asthma: reduction of emergency department visits for acute attacks of asthma (16), attenuation of the exacerbation of BHR in asthmatic patients during the pollen season (17), and reduction in the increased BHR in allergic patients during the pollen season (18).

Eczema is frequently the first manifestation of atopic diathesis that occurs in genetically predisposed individuals. About 50% of the E patients develop asthma or allergic rhinitis in late infancy. A cohort study followed E children without asthma during 4 yr and at the end of this period, 45% of them manifested asthma-like symptoms and 35% of them were diagnosed as having asthma by a specialist (19). The early development of specific IgE to *Ascaris lumbricoides* and the maintenance of elevated levels of food-specific IgE were the main markers in these patients. In another study a positive history of atopic eczema and conjunctivitis were identified as risk factors for the development of asthma (20).

Eosinophilic infiltration is a cardinal feature of allergic inflammation and the eosinophil is considered as the principal inflammatory cell in asthma and allergic rhinitis. In patients with allergic diseases, allergen provocation can activate a systemic response that provokes inflammatory cell production by the bone marrow (21). After release and differentiation of progenitor cells, eosinophils, basophils, and mast cells are typically recruited to tissues in atopic individuals as a result of an expansion of hemopoietic compartments in the bone marrow that stimulates an increased turnover and traffic of mature eosinophils to the site of allergic inflammation (22). Recent studies that support the critical involvement of the bone marrow in the development of eosinophilic inflammation of the airways point out the systemic nature of these conditions and their potential for biologic intervention as manifestation. The association of the three allergic diseases would represent manifestations of a severe form of a systemic disease? Would a systemic treatment prevent or control these diseases?

The Early Treatment of Atopic Children study, a multicentric, double-blind placebo-controlled study, evaluated the preventive effect of cetirizine administered for 18 months on the onset of asthma in children with E. In the placebo group

50.4% developed asthma at a mean age of 27 months, and in those, 40% had a family history (father or mother) of asthma (23, 24). These data also reinforce the importance of E as a risk factor for asthma. The ISAAC protocol points out that more than four acute attacks of asthma, sleep disturbances, speech problems, and wheezing with exercise are markers of the severity of asthma (7). Thus, in order to apply a more restrictive definition of severe asthma we included those children with a positive answer to at least two of these questions (7).

In this study we also evaluated the possible interference of AR and AE in the prevalence of asthma. In both age periods we observed that the association of A to R and to E was accompanied by a higher risk of severe asthma. Table 1 summarizes all data after grouping both age periods and shows the higher ORs between the SC with ARE in comparison with A, and the intermediary OR between those with AR. These results allow us to conclude that the association of asthma and allergic diseases, as rhinitis and eczema is related to more severe asthma.

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