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Is recurrent respiratory infection associated with allergic respiratory disease?

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ABSTRACT

Objective: Respiratory infections cause high morbidity and mortality worldwide. This study aims to estimate the relationship between allergic respiratory diseases with the occurrence of recurrent respiratory infection (RRI) in children and adolescents. **Methods:** The International Study of Asthma and Allergies in Childhood questionnaire and a questionnaire that provides data on the history of respiratory infections and the use of antibiotics were used to obtain data from patients. The relationship between the presence of asthma or allergic rhinitis and the occurrence of respiratory infections in childhood was analyzed. **Results:** We interviewed the caregivers of 531 children aged 0 to 15 years. The average age of participants was 7.43 years, with females accounting for 52.2%. This study found significant relationship between: presence of asthma or allergic rhinitis with RRI, with prevalence ratio (PR) of 2.47 (1.51–4.02) and 1.61 (1.34–1.93), respectively; respiratory allergies with use of antibiotics for respiratory problems, with PR of 5.32 (2.17–13.0) for asthma and of 1.64 (1.29–2.09) for allergic rhinitis; asthma and allergic rhinitis with diseases of the lower respiratory airways, with PR of 7.82 (4.63–13.21) and 1.65 (1.38–1.96), respectively. In contrast, no relationship between upper respiratory airway diseases and asthma and allergic rhinitis was observed, with PR of 0.71 (0.35–1.48) and 1.30 (0.87–1.95), respectively. **Conclusions:** RRI is associated with previous atopic diseases, and these conditions should be considered when treating children.

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Introduction

Respiratory infections are among the major causes of hospitalization and pediatric medical consultation, being directly associated with mortality in children. In addition, respiratory infections become a clinical challenge when they occur in a recurrent form due to difficulties in reaching precise diagnosis and adequate treatment (1,2).

Recurrent respiratory infection (RRI) is suggestive of a deficiency in the defense system or in the pulmonary pathways resulting from structural, functional, or environmental causes (3). RRI is more frequent in children aged 0 to 5 years and has a favorable evolution in most cases; in fact, RRI assists in the maturation of children's immune systems. However, in cases of higher severity, it may indicate the presence of a primary immunodeficiency (1,3).

Most cases of RRI in the first years of life are related to an overexposure to infectious agents or conditions, and not to immunological problems. For example, living in day care can be considered an aggravating factor for RRI for children under 5 years of age (3,4); also, wheezing in

RRI is more prevalent in developing countries, possibly due to low socioeconomic conditions. Among the risk factors for RRI are the attendance at day care, outdoor and indoor pollution, the mother smoking during pregnancy, passive smoking, breastfeeding for less than 3 months, cardiovascular diseases, congenital respiratory tract abnormalities, and chronic neurological diseases (3,5).

Epidemiological studies have investigated the occurrence of respiratory infections in atopic and nonatopic pediatric subjects and showed that viral respiratory infections in early life may increase the risk of a child to develop asthma later in childhood (6–8). On the other hand, few studies have analyzed the inverse association: the presence of allergic conditions such as asthma and allergic rhinitis as a risk factor for a patient having RRIs later in life (9,10). Therefore, in order to gather more information about allergic diseases and the risk of having RRI, we studied the occurrence of recurrent respiratory diseases in children and adolescents aged 0 to 15 and correlated with the existing allergic conditions (asthma and allergic rhinitis).

Methods

Study design

The work represents a cross-sectional study design. This study included children and adolescents aged 0 to 15 residing in the area covered by the Family Health Strategy units (ESF) of the municipality of Santo Ângelo, Brazil, assisted by the health system of the municipality.

The municipality of Santo Ângelo is located in the northwestern part of the state of Rio Grande do Sul, Southern Brazil, with an altitude of 285 m, 28°17'56"S, 54°15'46"W. According to the latest Census of the Brazilian Institute of Geography and Statistics (11), the population is estimated at 76,275 inhabitants, of whom approximately 9,821 inhabitants are in the 0–15 age group. The economy of the city is based mainly on the agricultural sector, having the provision of services as the second economic activity.

Selection of cases

Considering that the coverage of the health system in Santo Ângelo reaches only 40.75% of the population according to the data from the Brazilian Ministry of Health (12), there are approximately 4,002 inhabitants from 0 to 15 years old under ESFs coverage. Therefore, we performed the sample calculation for a population of 4,002 inhabitants, with a sample error of 5% and a confidence level of 99%, estimating a maximum percentage of respiratory infection events of 50%, resulting in 570 cases, of which 531 questionnaires were validated for the study. The data collection took place from March to June 2015; therefore, the data on respiratory problems refer to the year 2014.

The Family Health Strategy units (ESFs) are health teams distributed in a pre-established territory, especially in neighborhoods of greater social vulnerability; therefore, selection of individuals is based on area of occupancy and not necessarily on income. One ESF from each region (zones) of Santo Ângelo was chosen randomly: North, South, East, West, and Center. The questionnaires used in this study (see below) were applied with the help of all the community agents of each team. Each interviewer of the questionnaire carried out the application of 60 questionnaires in their area, using the strategy of toggling the houses visited for each three dwellings and skipping the houses that did not contain children.

All the completed questionnaires were included in this study, after obtaining the consent of parents and/or guardians. The study protocol was approved by the Ethics Committee of UFCSPA (Universidade Federal de Ciências da Saúde de Porto Alegre) and URI (Universidade

Regional Integrada), and by the National Ethics Committee (CAAE 14092513.5.0000.5354). The questionnaires were applied to parents and guardians of children and adolescents in all ESFs drawn for the study.

Questionnaire and definitions of respiratory infections

The data collection was performed through the application of two questionnaires. The first questionnaire followed the International Study of Asthma and Allergies in Childhood (ISAAC) protocol, developed by Asher et al. (13) and validated for the Portuguese language by Solé and Naspitz (14). The questionnaire included eight questions on asthma and nine questions on allergic rhinitis and was used to estimate the prevalence of asthma and rhinitis. A patient was considered asthmatic when answered “Yes” to the following questions: “Has your child had wheezing or whistling in the chest in the past 12 months?” and “Has your child ever had asthma?” Allergic rhinitis were estimated on the basis of positive answers to these questions: “In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when you (he/she) did not have a cold or the flu?” and “In the past 12 months, has this nose problem been accompanied by itchy watery eyes?” and “Has your child ever had hay fever?”

A second questionnaire prepared by the authors of this study was applied in order to establish the history of respiratory problems. The number of respiratory diseases in the last 12 months, the use of antibiotics and hospital admissions due to respiratory problems in the last 12 months, the occurrence of lower and upper respiratory infections, and a history of allergies were the main variables asked to the participants of the study (Table 1).

The outcomes were divided into lower and upper respiratory infections based on the following question: “How often did your child experience the following infections during the past 12 months?” The list of infections included pneumonia, acute bronchitis, otitis media, sinusitis, common cold, and tonsillitis. Respiratory infections were classified as lower respiratory tract infections (LRTI) including pneumonia, acute bronchitis; and upper respiratory tract infection (URTI) including common cold, tonsillitis, sinusitis, and otitis media.

Respiratory infections (RI) were reviewed in the medical records of patients in the ESFs to which each child belonged. Respiratory infection was considered either when laboratory diagnosis confirmed the presence of an infectious agent, or the patient presented two RI symptoms, or fever (axillary temperature greater and equal of 38°C) together with one symptom. The symptoms taken into consideration for diagnosis purposes

Table 1. Second questionnaire applied.

Questions	Answers
1. What respiratory problem has your child ever had in life?	() Common cold () Otitis media () Tonsillitis () Pneumonia () Sinusitis () Acute bronchitis
2. What respiratory problem has your child ever had in the last 12 months? How often did your child experience the following infections during the past 12 months?*	() Common cold () Otitis media () Tonsillitis () Pneumonia () Sinusitis () Acute bronchitis
3. In the past 12 months, how many times has your child taken antibiotics for respiratory problems prescribed by a doctor?	
4. In the past 12 months, how many times has your child been hospitalized due to respiratory problems?*	
5. Do the family members of the child have or have ever had asthma and/or allergic rhinitis? Who?	() Yes () No. () Father () Mother () Brother () Uncles () Grandparents

*Reviewed in the medical records of patients in the health unit.

were: mucopurulent rhinorrhea (stuffy and/or dripping nose), sore throat, cough (productive or dry), otalgia (earache), dyspnea, and mucopurulent secretion. These conditions were taken into account when present for at least 48 hours, in addition to the diagnosis that the doctor indicated in the medical record. Two investigators reviewed infection conditions, and a third party reviewed noncompliant cases. Finally, the case was considered as respiratory infection when two reviewers gave a positive indication.

Acute bronchitis was defined as acute onset cough of 2 to 14 days with or without sputum production in the absence of an underlying lung disease or focal chest signs and infiltrates on chest radiography. The reference standard to diagnose pneumonia is a new infiltrate on chest radiograph in the presence of recently acquired respiratory signs and symptoms. These include cough, increased sputum production, dyspnea, fever, and abnormal auscultatory findings (15). Unfortunately, in some cases, the physicians in primary care may not perform radiography and rely on the patient's history and physical examination. Of the 39 cases of pneumonia that occurred in the previous 12 months, 53.8% were diagnosed with the use of chest radiography.

Based on the data collected in this questionnaire, the RRI index was obtained according to Martino and

Ballotti (4), considering one of the following criteria: (a) six or more respiratory diseases per year; (b) at least one respiratory disease monthly (from April to August) involving only the upper airways; (c) three or more respiratory diseases per year involving the lower airways, such as pneumonia and bronchitis. Patients with health conditions such as cystic fibrosis, primary and secondary immunodeficiencies, airway malformations, and immobile cilia syndrome or primary ciliary dyskinesia were excluded from the study, as established by the Study Group in Immunology from the Italian Society of Pediatrics through epidemiological studies (4).

Statistical methods

Qualitative variables were described as absolute frequencies (N) and percentual frequencies (%). The association between asthma, allergic rhinitis, and occurrence of respiratory tract infections was verified by estimating prevalence ratio (PR) with 95% confidence intervals. The proportion analysis was performed using the chi-square test or Fischer's exact test. Data were analyzed using SPSS (version 17) for Windows (SPSS, Inc., Chicago, IL, USA), considering $p < 0.05$ as significant.

Results

Table 2 presents the characteristics of the study population according to age and gender. Females made up 52.2% of the population. Most subjects were in the age group 0 to 5 years (36.5%), followed by age groups 6–10 years (33.6%) and 11–15 years (29.9%), but there was no statistical significance between groups ($p = 0.250$).

Table 3 shows the clinical data obtained for the study population. The prevalence of asthma and allergic rhinitis based on the ISSAC questionnaire was 14.7% and 55.0%, respectively. The most frequent respiratory problem reported was common cold, affecting 91.9% of the studied population. Clinical conditions associated with URTI such as otitis media, tonsillitis, and sinusitis were also present (50.7%, 80.0%, and 24.1%, respectively). In addition, acute bronchitis and pneumonia, which are serious outcomes of LRTI were reported by 27.5% and 15.1% of the subjects, respectively.

Table 2. Characteristics of the study population.

Age (years)	Male N (%)	Female N (%)	Total N (%)	p -value	Population* (%)
0–5	102 (19.2)	92 (17.4)	194 (36.5)	0.251	1,164 (29.1)
6–10	80 (15.1)	98 (18.4)	178 (33.6)		1,292 (32.2)
11–15	72 (13.5)	87 (16.4)	159 (29.9)		1,546 (38.7)
Total	254 (47.8)	277 (52.2)	531 (100)		4,002 (100)

*Total population in health unit.

Table 3. Demographics and clinical characteristics of the study population.

Characteristic	Total (%) (n = 531)
Gender	
Female	277 (52.2)
Male	254 (47.8)
Age in years (media $\pm$ SD [†])	7.43 $\pm$ 4.41
Asthma [‡]	78 (14.7)
Allergic Rhinitis [‡]	292 (55.0)
Occurrence of respiratory diseases ever in life	
Common cold	488 (91.9%)
Otitis media	269 (50.7%)
Tonsillitis	425 (80.0%)
Pneumonia	80 (15.1%)
Sinusitis	128 (24.1%)
Acute bronchitis	146 (27.5%)

[†]SD: standard deviation. [‡]Data obtained based on the ISAAC questionnaire.

Results in Table 4 show the presence of asthma and allergic rhinitis in relation to RRI, the use of antibiotics in the previous 12 months, URTI and LRTI. With exception of URTI, which presented no significant association with asthma nor allergic rhinitis ($p = 0.371$ and $p = 0.166$, respectively), statistical significance was found for all other conditions ($p < 0.001$). For a patient with asthma, the PR of having RRI was 2.47 (95% CI: 1.51–4.02), of having LRTI was 7.82 (95% CI: 4.63–13.21), and the possibility of having used antibiotics in the previous year was 5.32 (95% CI: 2.17–13.0). The PR of a patient with allergic rhinitis having RRI was 1.61 (95% CI: 1.34–1.93), and the possibility of having used antibiotics in the previous 12 months was 1.64 (95% CI: 1.29–2.09).

Discussion

Atopic diseases are risk factors for the development of RRI in the upper and lower respiratory airways. A few studies have shown that respiratory infections are more common and last longer in patients with atopic disease than in

patients without atopic diseases. A study conducted with children aged 3 to 6 years showed that patients who have chronic allergies are more susceptible to severe respiratory infections (10). RRI was also shown to be associated with the development of allergic rhinitis (16) and asthma later during adult life (9). Another study, conducted in Finland showed that adults with asthma reported having a respiratory infection in the 12-month period preceding the asthma episode (17).

While RRI can predispose an individual to allergic conditions later in life, a reverse correlation should also be considered, in which rhinitis and asthma are two important conditions that could contribute to RRI, or even help predict if a patient will have RRI later in life (3). The present study showed that, in fact, patients with asthma and allergic rhinitis have an increased risk of having RRI. A previous study in Southern Brazil found an association of recurrent wheezing with acute respiratory infection and with the presence of rhinitis in children younger than 13 years (18).

The intense cold makes people more susceptible to infectious respiratory diseases (1,18,19). Autumn and winter are the seasons of highest incidence of respiratory infections, especially in children from large families who are more exposed to viruses at home and at daycare centers or schools (3). In addition, rapid changes in temperature that occur in areas of high thermal amplitude may also contribute to the onset of health problems, including those affecting the respiratory tract (20). Of note, during winter the temperatures in Santo Ângelo may vary between 2°C and 20°C in the same day (21). Therefore, climate in the region should be taken into account as a risk factor for RRI.

Childhood asthma is not one single disease, but rather a syndrome consisting of different disease entities with clinical features of wheezing. Several endotypes have

Table 4. Association between asthma and allergic rhinitis with clinical parameters.

Outcome	Asthma		PR (95% CI)	p-value*
	Yes (n = 61) N (%)	No (n = 470) N (%)		
RRI	38 (62.3)	175 (37.2)	2.47 (1.51–4.02)	<0.001
ATB	56 (91.8)	304 (64.7)	5.32 (2.17–13.0)	<0.001
LRTIs	44 (72.1)	88 (18.7)	7.82 (4.63–13.21)	<0.001
URTIs	54 (88.5)	432 (91.9)	0.71 (0.35–1.48)	0.371
Outcome	Allergic Rhinitis		PR (95% CI)	p-value*
	Yes (n = 241) N (%)	No (n = 290) N (%)		
RRI	125 (51.8)	88 (30.3)	1.61 (1.34–1.93)	<0.001
ATB	187 (77.6)	173 (59.7)	1.64 (1.29–2.09)	<0.001
LRTIs	85 (35.3)	47 (16.2)	1.65 (1.38–1.96)	<0.001
URTIs	225 (93.4)	261 (90.0)	1.30 (0.87–1.95)	0.166

Abbreviations: ATB: antibiotics use in the past 12 months; CI, confidence interval; LRTI, lower respiratory tract infection; N, number; URTI, upper respiratory tract infection; RRI, recurrent respiratory infection; PR, prevalence ratio. Comparisons were performed using the chi-square test or Fisher's exact test (*).

been described, generally characterized as a subtype of a condition with a distinct functional or pathobiological mechanism. Until now, mainly allergic asthma in childhood has been investigated immunologically in detail showing eosinophilic inflammation; however, a more T-helper (Th)17-shifted phenotype has been shown for neutrophilic asthma. Childhood asthma develops via innate and adaptive immune regulatory mechanisms, with interactions between the two. The common asthma paradigm describing dysregulation of several Th cells, with a Th2-cell predominance, innate immune cells also contribute to increased type 2 cytokine responses (22).

Allergic rhinitis and asthma are characterized by a common immune mechanism based on the induction of the Th2 lymphocyte pathway. As a consequence, individuals who have Th2 pathway induction reduce Th1 response. Some cytokines such as IFN- γ , typical of the Th1 response, are important for the control of infections; atopic patients have these cytokines reduced, which could be one of the reasons for allergic children to be more susceptible to respiratory infections (9,10).

Many viruses are involved in respiratory tract infections in asthmatic patients. Rhinovirus infections, which is very common in children, has been associated with higher infection in asthmatic than in nonasthmatic patients (7,8,23). Moreover, asthma has been considered as a risk factor for morbidity attributed to influenza and community-acquired pneumonia (7,24). During the 2009 influenza A H1N1 pandemic, asthmatic patients had almost twice as much pneumonia (50% vs. 27%) and required more intensive care than nonasthmatic patients (33% vs. 19%) (25). Another study demonstrated that the diagnosis of asthma at the age of 5 years was associated with recurrent and severe LRTI in the first two years of life (8). The risk of an asthmatic patient acquiring bacterial or viral pneumonia in the community is at least twice as high as in healthy people (26,27).

Viral infections associated with bacterial infections increase the severity of asthma (6,7). The microbiome in the upper respiratory tract of asthmatic patients is composed of a variety of potentially pathogenic bacteria, such as *Mycoplasma pneumoniae* (2) and *Streptococcus pneumoniae* (29), as well as viruses such as rhinovirus (30) and bocavirus (31).

There is a large body of literature supporting the association between viral infections and asthma, independent of age, phenotype, and asthma stage during which the viral infection occurs (32,33).

Increasing bacterial resistance to antimicrobial agents instigated interest in the preventive treatment for RRI. Symptoms of allergy and an infection caused by a virus do not require the use of antibiotics. In the present study, the use of antibiotics in the previous year in asthmatic

patients with RRI corresponds to 91.8%, and to 77.6% in patients with rhinitis and RRI. This data is very worrying, and for infections of this origin the recommended treatment could be based on immunostimulant methods, such as bacterial lysates (1,33). Prevention is also important, especially for recurrent infections of the lower respiratory tract, which can be done with vaccines against respiratory pathogens, such as type b *Haemophilus influenzae*, pertussis, pneumococcal and influenza (3). We are in agreement with those reported in the literature, indicating that in patients with asthma, viral infections are more frequently associated with asthma crisis, regardless of the phenotype, asthma duration, and natural history of the disease, but bacterial infections lead to an increase in inflammation and a worsening of the disease (33).

Treatment of patients with allergic rhinitis with immunotherapy can prevent the development of asthma and the sensitization of new allergens; therefore, the treatment offers persistent benefits, even after its discontinuation (34).

Validity and limitations of the study

This study included participants from the poorest neighborhoods in the region, who have limited access to healthcare and thus limited information about their health condition. Therefore, when asked if they have had asthma and/or allergic rhinitis, most of the cases only inform recent medical diagnosis of the pathology, and might ignore previous episodes if no medical assistance had been provided.

In the present study, we must consider that some occurrences registered as respiratory diseases have been manifestations of bronchial hyperreactivity or exacerbations of their allergic symptoms, as reported in similar studies (9,16). Besides that, events were counted considering a 12-month period reminder by questionnaires to the parents and/or guardians of the children, which pose a limitation to the study. Another limitation was that the study did not include the identification of pathogens involved in the respiratory infections, considering a possible change in the description of the pathology. Nevertheless, we believe that remembering that the child has had a serious respiratory infection is possible, especially pneumonia, acute bronchitis, although the exact diagnosis is more difficult to remember.

We highlight the limited laboratory resources available for the development of this study, a reason why no pathogen identification was possible, but this will be the subject of future investigations. Nevertheless, the information found is very relevant from the point of view of public health in the region studied.

Conclusions

RRI affecting the lower respiratory tract and the use of antibiotics are associated to asthma and allergic rhinitis in children.

Declaration of interest

The authors have no conflict of interest to declare. The authors alone are responsible for the content and writing of the paper.

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