Incidence of viral infection of the respiratory tract in acute asthma patients treated in the emergency room*

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ABSTRACT

Objective: To evaluate the incidence of viral infection in patients with acute asthma treated in the emergency room. **Methods:** We conducted a cohort study of patients aged 12 and older presenting to the emergency room of the Hospital de Clínicas de Porto Alegre with acute asthma. Nasopharyngeal aspirate was collected, and antigens were detected through indirect immunofluorescence staining for respiratory syncytial virus, adenovirus and influenza, as well as for parainfluenza types 1, 2, 3 and 4. Data were collected regarding demographic characteristics, medical history, the attack that led to the current emergency room visit, and clinical outcomes. **Results:** From March to July of 2004, 49 patients were examined for viral infection of the respiratory tract. Respiratory viruses were identified in 6 patients (3 with adenovirus, 2 with influenza A, 1 with parainfluenza type 1). The mean age of the patients with viral infection of the respiratory tract was 61.7 ± 11.5 years, compared with 41.7 ± 20.9 years for the patients without such infection ($p = 0.027$). There were no other significant differences in clinical characteristics or outcomes. **Conclusion:** The incidence of viral infection of the respiratory tract in acute asthma patients 12 years and older treated in an emergency room was 12.2%, which confirms that viral infection is a significant precipitant of acute asthma for patients in this age bracket.

Keywords: Emergency Service, Hospital; Vírus diseases/prevention & control; Asthma; Respiratory tract infections; Influenza A virus, human

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INTRODUCTION

Asthma exacerbations are related to predisposing factors of various natures. Exposure to inhaled allergens, especially mould, pollen and dust mites, has received considerable well-deserved attention as a trigger for extrinsic asthma.[1] Other significant precipitating factors are: exercise, drug use, air pollution, weather changes and exposure to cold.[1-3] In addition, respiratory tract infections have also been correlated with asthma attacks.[2] It has recently been suggested that the significance of viral infections as an inducing factor for acute exacerbations of asthma has been underestimated, primarily due to limitations of the available diagnostic methodology used to identify respiratory viruses.[1,4-5]

In children, viral infections increase airway responsiveness and are responsible for 26% to 42% of acute asthma episodes.[6] In adults, the role of viral infections as a cause for asthma exacerbations has not yet been well defined.[7-8] In three recent studies, the frequency of identification of the respiratory virus related to asthma attacks ranged from 0% to 44%.[1,9]

Studies using new diagnostic techniques such as polymerase chain reaction have increased the frequency at which viral infections are identified in adults with asthma exacerbations.[10]

The incidence of respiratory viruses as inducing factors of acute asthma in patients treated in emergency rooms has not been studied in our milieu. Consequently, the elucidation of the role of the predisposing factors in severe acute asthma may contribute to optimizing the management of the prevention of this disease.[11-12]

The objective of this study was to evaluate the incidence of respiratory viruses in patients with acute asthma treated in the emergency room of the Hospital de Clínicas de Porto Alegre (Porto Alegre Hospital das Clínicas) in the city of Porto Alegre, Brazil, comparing the characteristics of patients presenting samples that test positive for respiratory viruses with those of patients presenting samples that test negative.

METHODS

This was a study of the incidence of respiratory viruses (respiratory syncytial virus, adenovirus and influenza, as well as parainfluenza types 1, 2, 3 and 4), with convenience samples, making the diagnosis based on positive results for viral antigens through indirect immunofluorescence assay (IFA) of nasopharyngeal fluid obtained from patients aged 12 and over with severe acute asthma and treated in the emergency room of the Porto Alegre Hospital das Clínicas.

Inclusion criteria were previous medical diagnosis of bronchial asthma; age 12 or above, and being for asthma-related symptoms indicating exacerbation of the disease (dyspnea, wheezing or cough). Exclusion criteria were chronic pulmonary disease, cardiac insufficiency and lack of written informed consent (from the patient or legal guardian).

Sample selection consisted of evaluation of patients who had been consecutively treated during a restricted period of availability for carrying out the IFA for identification of viruses. The research team visited the emergency room in the morning and in the afternoon looking for patients with acute asthma. Since the diagnostic test was not available in the evening, on weekends or on holidays, patients treated during these periods were not considered for inclusion.

Clinical evaluation was carried out by members of the research team and consisted of the completion of a standardized questionnaire. This questionnaire included questions regarding demographic data (gender, age, race, marital status, weight and height), clinical history (age when asthma was first diagnosed, number of previous visits to an emergency room within the past 30 days and in the past year, number of hospitalizations in intensive care units in their lifetime, number of intubation and mechanical ventilation episodes in their lifetime, medication in use, use of nebulization for bronchodilation treatment and history of smoking) and chronology/features of the current exacerbation (duration of the attack, subjective identification of the inducing factor for the attack, symptoms during the asthma attack and symptoms of flu in the family). Clinical findings upon admission were also recorded (axillary temperature, heart rate, respiratory frequency, pulmonary auscultation findings and oxygen saturation measured through digital pulse oximetry), as well as the outcomes after treating the asthma attack (hospitalization in an intensive care unit, hospitalization in an infirmary or being discharged from the emergency room). For the

identification of inducing factors for the attack, patients were first asked whether they could perceive any inducing event for the worsening of asthma. Subsequently, we tried to determine whether the triggering factor was a respiratory infection (flu, cold or sinusitis), an inhaled allergen (dust, mold, animal fur, pollen or other), exercise or a weather change.

Diagnostic evaluation for the identification of respiratory viruses involved the use of IFA of nasopharyngeal fluid, using viral antigens of respiratory syncytial virus, adenovirus and influenza, as well as of parainfluenza types 1, 2, 3 and 4. Nasopharyngeal fluid was collected using a urethral tube attached to a Bioject needle-free CO_2-powered injector (Bioject Medical Technologies, Portland, OR, USA). The tube was introduced through the nostril up to the nasopharynx, after which 20 cm of H_2O were aspirated and the secretion was obtained using a vacuum aspirator (Fanen). Samples were transported in a Styrofoam container with reusable ice packs (4°C) to the Instituto de Pesquisas Biológicas, Laboratório Central (Central Laboratory of the Institute of Biological Research).

In the laboratory, samples were transferred to a previously identified sterile centrifuge tube containing 2 mL of phosphate buffered saline. Samples were suspended for mucus dilution/cell release and then centrifuged at 1500 rpm at room temperature. Three slides were prepared from each sample under analysis. One was used for the triage of positive cases and one for the determination of the agent if the triage was positive. The third slide was stored in a freezer (-70°C) in case it became necessary to repeat the IFA. Sample material was distributed in seven circles, each approximately 0.05 cm in diameter, on each slide. This material was dried and fixed in acetone at 4°C for 10 minutes. For the staining of slides, 25 mL of specific monoclonal antibodies for each virus (anti-respiratory syncytial virus, anti-adenovirus, anti-influenza A and anti-influenza B, as well as anti-parainfluenza types 1, 2, 3 and 4) were introduced into each circle. We used the Respiratory Panel 1 Viral Screening & Identification Kit (Chemicon International, Temecula, CA, USA). Subsequently, the slides were incubated in a humid chamber at 37°C for 30 minutes, subjected to three 5-minute washes in phosphate buffered saline and dried with cool air. Subsequently, a drop of the specific conjugate was added, followed by incubation in a humid chamber at 37°C, rinsing and drying. Slides were prepared with buffered glycerol and read under fluorescence microscopy.

The data were entered into a Microsoft Excel, version 2000, database. Subsequently, the Statistical Package for the Social Sciences program, version 12.0 was used to process and analyze the data. Descriptive and comparative analyses between the group of patients whose samples tested positive for respiratory viruses and the group of those whose samples tested negative were carried out. We used Student's t-test for the analysis of continuous variables presenting normal distribution for independent samples. We used the Mann-Whitney U test for the analysis of continuous variables presenting abnormal distribution. We used the chi-square test for the analysis of categorical variables and, when necessary, Yates's correction or Fisher's exact test. The alpha was set at 0.05.

The Porto Alegre Hospital de Clínicas Ethics Committee and Research Committee approved the study. All participating patients or (for patients younger than 18) their legal guardians gave written informed consent.

RESULTS

From March to July 2004, 353 patients diagnosed with acute asthma were treated in the emergency room of the Porto Alegre Hospital de Clínicas. Of those 353 patients, 142 were evaluated for possible inclusion in the study, 52 of which were excluded because they were diagnosed with chronic pulmonary diseases, 11 because they were diagnosed with cardiac insufficiency and 24 because they declined to participate in the study. For the remaining 55 patients, clinical data and nasopharyngeal aspirate samples were collected. The aspirate samples from 6 patients were insufficient for the IFA, and the final sample therefore comprised 49 patients.

Of the 49 patients studied, 40 (81.6%) were female and 9 (18.4%) were male. In the study sample, 30 (61.2%) patients were Caucasian and 19 (38.7%) were non-Caucasian. Mean age of patients was 44.10 ± 20.93 years. Samples from 6 patients (12.2%) were positive for respiratory viruses. The viruses identified were adenovirus (3 cases), influenza A (2 cases) and parainfluenza type 1 (1 case).

TABLE 1

General characteristics of the patients studied

Variable	Total (n = 49)	Positive sample (n = 6)	Negative sample (n = 43)	p
Gender				0.302
Male	18.4%	4.1%	14.3%	
Female	81.6%	8.2%	73.5%	
Age (years)	44.1 ± 20.9	61.7 ± 11.5	41.7 ± 20.9	0.027
Race				0.262
Caucasian	61.2%	4.1%	57.1%	
Non-Caucasian	38.7%	8.2%	30.6%	
Marital status				0.398
Single	58.3%	10.4%	47.9%	
Married	35.4%	2.1%	33.3%	
Widow(er)	6.3%	0.0%	6.3%	
Weight (kg)	61.2 ± 17.6	73.2 ± 9.9	59.4 ± 17.9	0.074
Height (m)	1.58 ± 0.10	1.58 ± 0.11	1.58 ± 0.10	0.914

Categorical variables presented as %; continuous variables presented as mean ± standard deviation; chi-square test for categorical variables; Student's t-test for independent samples for quantitative variables

Table 1 shows the general characteristics of the patients in the study. A statistically significant difference was found for age. Patients presenting negative samples were younger (41.7 ± 20.9 years) than those presenting positive samples (61.7 ± 11.5 years) (p = 0.027). No statistically significant difference was found for any of the other variables shown.

Table 2 shows the analysis of data concerning patient history. There was no statistically significant difference (p > 0.05) between the two groups for the following variables: age at which asthma was diagnosed, previous visits to an emergency room (% of positive responses), number of visits to the emergency room in the past 30 days and in the past year, hospitalizations within the past year (% of positive responses), number of hospitalizations in the past year, admissions to an intensive care unit (% of positive responses), number of admissions to an intensive care unit, previous intubations (% of positive responses), number of previous intubations, history of smoking (% of positive responses), current

TABLE 2

Data regarding patient history

Variable	Positive sample (n = 6)	Negative sample (n = 43)	RR (95% CI)	p
Age at diagnosis (years)	24 (37.3)	12 (29)	-	0.251
Previous visits to ER (% of +)	50.0%	86.0%	0.23 (0.05 - 0.94)	0.067
Visits within the past 30 days	1 (0)	1 (0.25)	-	0.354
Visits within the past year	1.5 (4.8)	2 (6.5)	-	0.572
Hosp. within the past year (% of +)	16.7%	37.2%	0.38	0.650
Nº of hosp. within the past year	5 (0)	1 (1)	(0.05 - 2.97)	0.101
Admission to ICU (% of +)	16.7%	20.9%	0.78	1.000
Nº of admissions to ICU	1 (0)	2 (2.5)	(0.10 - 6.0)	0.350
Previous intubation (% of +)	16.7%	14.3%	1.17 (0.16 - 8.6)	1.000
Nº of intubations	1.5 (1.25)	1 (1)	-	0.866
Smoking history (% of +)	83.3%	37.2%	6.67 (0.84 - .89)	0.089
Present smoking (% of +)	16.7%	0.0%	9.6 (4.19 - 22.00)	0.245
Passive smoking (% of +)	33.3%	51.2%	0.52 (0.11 - 2.59)	0.702

RR: relative risk for positive identification of viruses; 95% CI: 95% confidence interval; ER: emergency room; % of +: % of positive responses; hosp.: hospitalizations; #: number; ICU: intensive care unit; Categorical variables presented as %; continuous variables presented as median (interquartile range) Mann-Whitney U test for quantitative variables; chi-square test for categorical variables

TABLE 3

Use of medications and nebulization by the patients studied

Variable	Positive sample (n = 6)	Negative sample (n = 43)	RR (95% CI)	p
Oral corticosteroids past month	66.7%	53.5%	1.63 (0.33 - 8.08)	0.865
Inhaled corticosteroids	50.0%)	44.2%	1.23 (0.27 - 5.49)	1.000
Long-acting beta-2 adrenergic agonists	33.3%	44.2%	0.67 (0.14 - 3.30)	0.950
Oral xanthine	16.7%	20.9%	0.78 (0.10 - 5.95)	1.000
Short-acting beta-2 adrenergic agonists	50.0%	72.1%	0.44 (0.10 - 1.94)	0.531
Inhaled ipratropium	50.0%	48.8%	1.04 (0.23 - 4.66)	1.000
Use of nebulization	50.0%	79.1%	0.32 (0.08 - 1.40)	0.296

RR: relative risk for positive identification of viruses; 95% CI: 95% confidence interval; Categorical variables presented as % of positive responses; Mann-Whitney U test for quantitative variables; chi-square test for categorical variables

TABLE 4

Data regarding the current attacks experienced by the patients studied

Variable	Positive sample (n = 6)	Negative sample (n = 43)	RR (95% CI)	p
Duration of attack (hours)	42 (43.5)	12 (44.0)		0.145
Identification of triggering factor				
Infection (% of +)	66.7%	32.6	3.44 (0.70 - 16.97)	0.241
Allergens (% of +)	0%	23.3%	1.18 (1.03 - 1.35)	0.433
Exercise (% of +)	0%	7.0%	1.15 (1.03 - 1.29)	1.000
Weather changes (% of +)	0%	39.5%	1.23 (1.04 - 1.45)	0.148
Attack/use of systemic corticosteroids (% of +)	66.7%	44.2%	2.26 (0.46 - 11.22)	0.550
Symptoms				
Headache (% of +)	66.7%	69.8%	0.88 (0.18 - 4.31)	1.000
Rhinorrhea (% of +)	50.0%	62.8%	0.63 (0.14 - 2.82)	0.877
Nasal congestion (% of +)	50.0%	60.5%	0.69 (0.16 - 3.08)	0.964
Sore throat (% of +)	50.0%	25.6%	2.4 (0.57 - 10.93)	0.448
Earache (% of +)	16.7%	20.9%	0.78 (0.10 - 5.95)	1.000
Dysphonia (% of +)	50.0%	37.2%	1.58 (0.36 - 7.03)	0.877
Myalgia (% of +)	83.3%	62.8	2.66 (0.34 - 20.94)	0.594
Cough (% of +)	100.0%	88.4%	0.86 (0.77 - 0.97)	0.872
Expectoration (% of +)	100.0%	81.4%	0.53 (0.10 - 2.78)	0.572
Fever at home (% of +)	83.3%	37.2%	6.67 (0.84- 52.89)	0.089
Flu symptoms in the family (% of +)	50.0%	58.1	0.75 (0.17 - 3.35)	1.000
Signs				
Axillary temperature 37.8°C (% of +)	40%	11.9%	3.81 (0.77 - 18.85)	0.316
HR (beats/min)	109.00 ± 8.3	109.5 ± 20.5		0.961
RF (breaths/min)	28.0 ± 3.5	26.2 ± 6.0		0.514
Wheezing (% of +)	100.0 %	93.0%	0.87 (0.78 - 0.97)	1.000
Rales (% of +)	0.0%	14.0%	0.53 (0.10 - 1.49)	0.755
Crackles (% of +)	16.7%	25.6	0.62 (0.08 - 4.77)	1.000
SpO_2 (%)	96.6 ± 2.2	94.7 ± 5.0		0.409

RR: relative risk for positive identification of viruses; 95% CI: 95% confidence interval; % of +: % of positive responses; HR: heart rate; RF: respiratory frequency; SpO2: oxygen saturation measured by digital pulse oximetry

Categorical variables presented as %; continuous variables presented as median (interquartile range) or as mean ± standard deviation Student's t-test for independent samples or Mann-Whitney U test for quantitative variables; Chi-square test for categorical variables

TABLE 5

Outcomes of the attacks experienced by the patients studied

Outcome	Positive sample (n = 6)	Negative sample (n = 43)	RR (95% CI)	p
Discharge from ER (%)	50.0%	76.7%	0.65 (0.29 - 1.48)	0.321
Hospitalization (%)	50.0%	23.3%		
Stay in ER (hours; mean ± SD)	4.67 ± 6.37	9.93 ± 11.34	-	0.440

RR: relative risk for positive identification of viruses; 95% CI: 95% confidence interval; ER: emergency room; SD: standard deviation; Chi-square test for categorical variables; Student's t-test for independent sampling of quantitative variables

smoking (% of positive responses) and passive smoking (% of positive responses).

Table 3 shows data concerning the use of medications (oral corticosteroids in the past month, inhaled corticosteroids, long-acting inhaled beta-2 adrenergic agonists, oral xanthine, short-acting beta 2-adrenergic agonists and inhaled ipratropium bromide) and the use of nebulization. There was no statistically significant difference ($p > 0.05$) for these variables between the two groups.

Table 4 shows the analysis of data concerning the present attack. Mean duration of the attack was 42 hours in the group presenting positive samples (interquartile range of 43.5 h) and 12 hours in the group presenting negative samples (interquartile range of 44 h) ($p = 0.145$). In the group presenting positive samples, 66.7% of the patients had the subjective impression that the asthma attack was triggered by a respiratory infection, whereas only 32.6% of the patients in the group presenting negative samples related the asthma attack to a respiratory infection ($p = 0.241$). In the group presenting positive samples, no patients related the triggering of the attack to being exposed to inhaled allergens, exercise or weather changes, whereas 23.3% of the patients in the group presenting negative samples related the attack to exposure to inhaled allergens ($p = 0.433$), 7% to exercise ($p = 1.00$) and 39.5% to weather changes ($p = 0.148$). In the group presenting positive samples, 66.7% of the patients were making use of oral corticosteroids at the moment of the attack, whereas, in the group presenting negative samples, 44.2% of the patients were using corticosteroids ($p = 0.550$). Comparing the two groups, we detected the following incidences of, respectively, symptoms and signs: headache (66.7% and 69.8%; $p = 1.000$), rhinorrhea (50% and 62.8%; $p = 0.877$), nasal congestion (50% and 60.5%; $p = 0.964$), sore throat (50% and 25.6%; $p = 0.448$), earache (16.7% and 20.9%; $p = 1.000$), dysphonia (50% and 37.2%; $p = 0.877$), myalgia (83.3% and 62.8%; $p = 0.549$), cough (100% and 88.4%; $p = 0.872$), expectoration (100% and 81.4%; $p = 0.572$), fever at home (83.3% and 37.2%; $p = 0.089$), symptoms of flu in the family (50% and 59.1%; $p = 1.000$) and axillary temperature = 37.8°C (40% and 11.9%; $p = 0.316$). There was no statistically significant difference between the two groups in terms of heart rate, respiratory frequency, wheezing, rales, crackles or oxygen saturation measured by digital pulse oximetry.

Table 5 shows the outcomes of the asthma attack. Comparing the group of patients presenting positive samples to that of those presenting negative samples, 50% and 76.7%, respectively, were discharged directly from the emergency room ($p = 0.321$); 50% and 23.3%, respectively, were hospitalized ($p = 0.321$); and the mean duration of the emergency room stay was 4.67 h and 9.93 h, respectively ($p = 0.440$).

DISCUSSION

In the present study, the incidence of respiratory viruses in patients with acute asthma treated in the emergency room was 12.2%. Of all clinical characteristics studied, only age was found to correlate with the identification of respiratory viruses, and patients presenting positive samples were, on average, older than those presenting negative samples.

The incidence found in the present study was similar to that found in other studies using the IFA technique as a diagnostic method. In those studies, the frequency of the identification of respiratory viruses ranged from 10% to 21%.[8,13]

Various factors might have contributed to

underestimating the identification of viruses in the present study. Principal among such factors is the very sensitivity of the IFA method. In addition, the duration of the viral profile might have interfered with the identification of viruses since the IFA technique is most efficient when carried within 24 to 48 hours after the onset of symptoms.[14] In our study, the median duration of symptoms of the asthma attacks was 12 hours, with an interquartile range of 44 hours. Therefore, the frequency found in the identification of the virus during the asthma attack depended directly on the methodology in use. Some techniques, such as viral isolation in cell culture, may increase the viral load and improve the sensitivity of the IFA test, but they are difficult to perform and are not available in our practice.[15-16] Furthermore, respiratory infections caused by other types of viruses, such as rhinoviruses and coronaviruses, were not considered in this study, and such viruses might have been triggering factors for the asthma attacks.[17-19] The identification of these viruses requires special techniques such as cell culture and polymerase chain reaction.[4] Studies using these new diagnostic techniques have shown an increase in the frequency of viral infections in adults with asthma exacerbations.[15-20] Therefore, the results in our study were limited by the technique used (IFA).

Despite its inherent flaws, the IFA technique it is a rapid and effective method for the detection of viruses. In addition, IFA is affordable and has proven useful for the diagnosis of respiratory infections in clinical practice. Nevertheless, further complementary studies, using polymerase chain reaction, are warranted.

The technical difficulty encountered in this study was the small amount of material collected from the nasopharyngeal aspirate, even after this procedure had been routinely carried out through both nostrils. This was illustrated by the fact that 6 of the 55 patient samples were considered insufficient for viral testing in the study.

It is important to highlight that, in the analysis of data concerning patient histories, the relative risk (RR) for positive identification of viruses related to a history of smoking and current smoking, although less than statistically significant ($p = 0.089$ and $p = 0.245$, respectively), was high (RR = 6.67 and RR = 9.6, respectively). This finding may express the deleterious effect of smoking, which predisposes patients to viral infections and asthma exacerbations.

The data presented in Table 4 concerning the present attack show that, although less than statistically significant ($p = 0.089$), the frequency of fever at home was higher (83.3%) among patients presenting positive samples than among those presenting negative samples (37.2%). In addition, 40% of the patients presenting positive samples had an axillary temperature equal to or greater than 37.8°C at admission, and this only happened to 11.9% of the patients presenting negative samples ($p = 0.316$). This finding may, together with the increase in the sample size, confirm the expression of fever as a clinical marker of an infectious process (in this case, of a viral infection). The fact that all patients presented high frequencies of symptoms consistent with viral infection (headache, rhinorrhea, nasal congestion, sore throat, earache, dysphonia and myalgia) also deserves attention. Furthermore, the subjective identification of respiratory infection (cold, flu or sinusitis) as a triggering factor for the attack did not differ between the two groups. Even if the method used to identify viral infection had underestimated the real incidence of respiratory viruses in this sample, the high frequency of these symptoms in the group presenting negative samples very likely provides evidence of the lack of specificity of these clinical parameters as indicators of viral respiratory infection. In contrast, although the difference between the two groups was less than statistically significant, 23.3% of the patients presenting negative samples identified exposure to inhaled allergens as the triggering factor for the attack, whereas none of the patients presenting positive samples associated their asthma attacks to such exposure.

The sample selection technique and the small sample size can be considered methodological limitations. The sample selection technique, known as convenience sampling,[21] made the execution of this clinical study possible within the constraints of our present reality. Volunteering and other selection biases were minimized through the strategy of consecutively including the people who sought treatment during the study period, and that the sample we obtained adequately represented the target population of the study. Regarding the small sample size, we should take into consideration

the fact that the present study was the first step in a broader study that will try to provide a better definition of the incidence of respiratory viruses in acute asthma, as well as to profile the seasonality of acute asthma and to identify potential correlations between identification of viruses and clinical characteristics.

In conclusion, the incidence of respiratory viruses in patients aged 12 and older presenting to the emergency room with acute asthma was 12.2%, which confirmed viral infections as a contributing factor in the triggering of asthma attacks, although it was found to be less frequent than in the pediatric age bracket. The only clinical characteristic correlated with the identification of respiratory viruses was age, and patients presenting samples that tested positive for these viruses were, on average, older than those who presented samples that tested negative.

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