Correlation of respiratory syncytial virus with risk factors related to recurrent wheezing in hospitalized infants.

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Abstract

Background: The respiratory diseases represent an important cause of morbidity and mortality in the pediatric age group, considered a public health problem and generate a great economic impact given the frequent use of the health system. The current study aims to verify the correlation of respiratory syncytial virus with the main risk factors associated with recurrent wheezing in hospitalized infants. Methods: Cross-sectional, descriptive and analytical study, carried out from May 2019 to May 2021, through the analysis of 681 electronic medical records in a secondary public hospital. The study included 105 infants aged less than 24 months, hospitalized for recurrent wheezing. The variables analyzed were subdivided into two groups according to the presence of the etiological agent: positive or negative for RSV. Results: Of the sample studied, 75.2% were RSV negative, with a predominance of males and an average age of 13 months. With respect to the risk factors analyzed, there was a higher incidence of prematurity (19.2%), heart disease (11.5%), family history of asthma (61.5%), and use of prophylaxis (73%) among those positive for RSV. Among positive for RSV, we observed greater use of mechanical ventilation (80%) and need for readmissions (65.4%), and a positive correlation was observed between the etiological agent and prematurity (p=0.009*), heart disease (p=0.026*), readmission (p=0.009*), and the use of mechanical pulmonary ventilation (p=0.007*). Conclusion: Faced with this prevalent public health pathology, there is a need to improve clinical care, with qualification and standardization of conduct by general pediatricians.

Introduction

The prevalence of atopic diseases, especially chronic respiratory diseases such as asthma and recurrent wheezing in childhood, has been increasing both in Brazil and worldwide. These diseases represent an important cause of morbidity and mortality in the pediatric age group, considered a public health problem, as they affect the quality of life of these patients, and generate a great economic impact given the frequent use of the health system.¹²³

Wheezing is a key warning sign in children in their early years and has been documented as a risk factor for asthma in childhood, adolescence, and adulthood²³⁴, considered more important when it becomes recurrent wheezing. In Latin America, approximately 100,000 children die in the first year of life as a result of acute respiratory infection and, in Brazil, around 35% of hospitalizations in infants in the first year of life are due to respiratory disease.⁵ Regardless of the cause, wheezing is a reason to seek medical attention in pediatric emergency services, especially in the first year of life.⁶⁷

The majority of studies point to a multifactorial etiology in the pathogenesis of wheezing in the first year of life, in addition to a close relationship with respiratory infections.⁸ However, there is still much controversy about how these various elements relate to each other.⁸ Approximately 90% of wheezing episodes in children
up to the third year of life are caused by viral respiratory infections, mainly Respiratory Syncytial Virus (RSV). \textsuperscript{4,9,10}

The impact that this condition has on quality of life and on the use of medical and hospital resources, as well as its high frequency worldwide, point to the need for better understanding of the epidemiology of wheezing in infants. \textsuperscript{2,11}

The current study aims to describe the clinical characteristics of the patients studied and to correlate the presence of Respiratory Syncytial Virus with the main risk factors associated with recurrent wheezing, and the main etiological agent of the pathology. The results can facilitate diagnosis, making it more accurate and earlier, so that better strategies can be developed in the prevention of this disease, providing better quality of life and a reduction in morbidity and mortality.

\textbf{Methods}

This is a cross-sectional, descriptive and analytical study, carried out from May 2019 to May 2021, in a university hospital in the south zone of the city of São Paulo. We selected, through the electronic records available in the MV SOUL system, all records with an ICD (International Classification of Diseases) of acute bronchitis (J20.9) in the period studied, totaling 681 cases. Exclusion criteria were patients over 2 years of age (376 patients), repeated patients (38), those not hospitalized (138), and patients with other ICDs incompatible with the disease under study (24). As inclusion criteria, all infants aged up to 24 months hospitalized for recurrent wheezing were included, totaling 105 patients.

The clinical characteristics were described taking into account sex, age in months, length of hospital stay (in days), and nutritional status, where those who, according to the Weight for Age (W/A) indicator of the Brazilian Society of Pediatrics\textsuperscript{13}, had a Z score $<-3$ or between -2 and -3 were considered malnourished. Prematurity was considered when born at less than 37 weeks of gestation\textsuperscript{14} (Brazilian Society of Pediatrics), being further divided into extremely premature, $<34$ weeks or late premature, between 34 and 37 weeks.\textsuperscript{15} The presence of breastfeeding was considered as yes when it occurred during hospitalization, whether exclusive or mixed, confirmed in the prescription of the Nutrition team that evaluated and monitored all hospitalized patients.

The presence or absence of congenital heart disease was considered when reported in the medical record or in the echocardiogram diagnosis. Allergic conditions were considered when noted in the history of anamnesis and in the medical records, related to atopic dermatitis, allergic rhinitis, drug allergies, and/or aeroallergens. The presence or absence of a family history of asthma in parents or siblings, when reported in the medical records, was also considered. The use of prophylactic medications (inhaled corticosteroids) and the need to remain in the Intensive Care Unit during hospitalization, with the use of mechanical pulmonary ventilation (MPV) or non-invasive ventilation (NIV) were also considered.

On patient admission, possible causes of wheezing, such as viral infections (RSV), or bacterial infections, such as pneumonia were investigated. All patients admitted to the service with recurrent wheezing and younger than 24 months were obligatorily investigated for RSV research, through immediate collection of nasopharyngeal aspirate in the Children’s Emergency Room. The patients were divided into two groups according to negativity or positivity for Respiratory Syncytial Virus prior to correlation of the variables.

The chi-square test or Fisher’s exact test and the independent t test were used to compare the positive and negative RSV groups. The Spearman Correlation was performed to verify possible correlations between risk factors and positive and negative RSV. The significance was fixed at 0.05 or 5\%. This work was approved by the Research Ethics Committees (CEP) of the Universidade Santo Amaro and Hospital Geral do Grajaú under opinions nos. 4,928,450 and 5,082,944, respectively.

\textbf{Results}

Of the 105 patients, 26 (24.8\%) were positive for Respiratory Syncytial Virus (RSV), and 79 (75.2\%) were negative. Regarding sex, there was a predominance of males in both positive (57.7\%) and negative (63.3\%)
RSV patients, but with no statistically significant relationship (p=0.7817). Considering age group, in both groups, positive or negative for RSV, a higher prevalence of infants between 13 and 24 months (p=0.8129) was observed, with the mean age between the positive and negative groups being quite similar, at around 13 months, with no statistical difference (p=0.850).

Table 1 shows that in terms of prematurity, there was no difference between the positive and negative RSV groups (p=0.904). However, when we divided the groups into extreme prematurity (< 34 weeks) and late prematurity (34 to 37 weeks), we found 100% of extremely preterm infants in the RSV positive group.

Regarding breastfeeding (BF), of the patients positive for the etiological agent, 23% were being breastfed, while among the negative patients, 19% were being breastfed. Of note, from the total number of patients analyzed in our study, only 20% were BF (Table 1).

With regard to heart disease (Table 1), there was no significant difference between the groups (p=0.4871), with a similar absolute number between them, but a higher percentage of positive results (11.5%). Among the positive RSV patients, there were two atrial septal defects and one Tetralogy of Fallot, while, among the negative RSV patients, there was one interatrial communication and three interatrial communication associated with persistent ductus arteriosus.

Furthermore, in Table 1, it can be seen that malnutrition was more present among patients negative for RSV (7.6%), and this difference was not statistically significant (p=0.8325). A higher percentage of pneumonia upon admission to hospital (6.3%) was also observed among the negative RSV, being considered pneumonia when the patient was admitted with this diagnosis, and was receiving antibiotic therapy, regardless of the criteria used. No cases of pneumonia were found among patients in the RSV positive group (p=0.433). The cases analyzed during the study with the diagnosis of pneumonia among the negative RSV did not have clinical, laboratory, or radiological criteria for pneumonia.

We found 6.3% of the infants in the RSV negative group with a positive history of allergic conditions (Table 1), and only 3.9% among the RSV positive patients, with no statistically significant difference (p=0.988). Infants with a positive family history for asthma occurred in a higher percentage in the group of positive RSV (61.5%), although without presenting a statistically significant difference (p=0.235). The group of positive RSV also showed a higher number of patients using prophylaxis (73%), although the negative patients also showed significant use of prophylactic medication, 60.7% (Table 1).

With regard to hospitalizations, the mean length of stay among children with positive RSV was 7.35 days and among children with negative RSV, 8.8 days (p=0.4837). Still with regard to hospitalizations, a significant drop was observed from 2019 to 2021, as shown in Graph 1.

Regarding the clinical outcomes, the patients had excellent prognoses in both groups, with no deaths occurring in the analyzed infants, with 96.1% discharged in the positive RSV group and 98.7% in the negative group. Few transfers were necessary in these groups, 3.9% among positive patients and 1.3% among negative patients.

The 105 patients were also analyzed regarding their severity and need for an Intensive Care Unit (ICU), with the use of additional oxygen therapy devices such as Non-Invasive Ventilation (NIV) or Mechanical Pulmonary Ventilation (MPV). Among RSV-positive patients, 19% (n=5) required the ICU, with mechanical pulmonary ventilation in 80% of cases and non-invasive ventilation in 20%. In the case of negative RSV patients, 19% (n=15) also required the ICU, with 47% needing MPV and 53% NIV.

Another variable analyzed in this study was the need for readmission and its recurrence. The number of readmissions was higher among positive RSV, with 65.4% (n=17) of cases, than among negative RSV, 15.2% (n=12) of cases, and most of the time it was considered a readmission (58.8%).

Table 3 shows the correlation between the risk factors and the positive and negative RSV groups, performed using the Spearman Correlation. There is a moderate correlation between prematurity and the positive RSV
group, with statistical significance (p=0.009*). Taking into account heart diseases, we found a positive correlation in both RSV+ (p=0.026*) and RSV- groups (p=0.002*). Non-invasive ventilation did not demonstrate a correlation with the evaluated groups, but the need for mechanical pulmonary ventilation was correlated with the RSV+ group (p=0.009*). A similar situation was found among readmissions, which were more frequent and correlated with the RSV+ group (p=0.007*). Malnutrition was a risk factor that showed a weak correlation, but with statistical significance within the group of patients negative for RSV (p=0.001*).

It is important to emphasize that the study was carried out during the Covid-19 pandemic and, as of April 2020, testing was started with Polymerase Chain Reaction (PCR) for Coronavirus in hospitalized patients with flu syndrome, initially only with symptoms for more than 3 days. RSV positive patients were excluded from the need for testing, regardless of symptoms. In this study, no positive patients for Covid-19 were identified.

Discussion

Approximately 90% of cases of recurrent wheezing are triggered by viral conditions, with RSV being the main etiological agent.\(^3,4,9,16\) In our study, we found a higher percentage of negative patients for RSV. One of the possible explanations for these data is that the study took place at the time of the emergence of the pandemic for Covid-19, where the important seasonality existing for the positivity of the main agent did not occur.

In the total population studied, 65 of the infants were male, regardless of whether they were positive or negative for RSV, which corresponded to a percentage of 62% against 38% of females. This fact is consistent with the literature and can be explained by an anatomical difference between the sexes in the first year of life, when boys have a smaller airway in relation to the lungs, and a forced airflow approximately 20% smaller than in girls, which is corrected after the first year of life by height.\(^4,17,18\)

According to Sousa, we define recurrent wheezing as those individuals who have a history of three or more episodes of wheezing within a six-month interval.\(^17,19\) This definition explains the possible reason for the inclusion of fewer patients from 0 to 6 months, when it is more common for them to have their first episodes of wheezing, and, consequently, a greater number of patients in the age groups of 7 to 12 months and 13 to 24 months, when there is more time for these episodes to occur. In addition, this age group has a greater probability of starting to attend daycare centers, which involves wider exposure to other children, with a greater number of acquired viral infections.

Regarding prematurity, several mechanisms have been suggested to explain the occurrence of recurrent wheezing in children with low birth weight and prematurity, such as reduced lung function during childhood, lung size or a higher incidence of viral infections in low birth weight children, immunological immaturity in the first months of life and exposure to allergens, in addition to bronchial hyperreactivity.\(^4,7,20,21\) Therefore, having a higher percentage of extremely premature infants in the positive RSV groups was expected, in accordance with the literature.

The role of diet, more especially food, during the first year of life, has been implicated in the development of asthma.\(^22\) Some studies report that exclusive breastfeeding for 4 months reduces the risk of asthma, and together with the late introduction of complementary foods, these factors promote a lower frequency of allergy to cow’s milk protein, atopic dermatitis, wheezing, and asthma.\(^8\)

We noticed that of the total number of patients analyzed in our sample, only 20% of them were BF, that is, 80% of our hospitalized patients were not BF, which we believe corroborates the literature, whereby breast milk is a protective factor for recurrent wheezing.\(^23\) For all children, BF reduces the risk of asthma and recurrent wheezing caused by viral infections. These protective effects increase with the duration of BF for at least 4 months, and protection seems to persist during the first decade of life.\(^6,21\)

When considering the analysis of hospitalizations in the period studied, this decrease is due to the period of the Covid-19 pandemic, in which the studied population was isolated, failing to attend schools and daycare centers, and being less exposed to the possibility of viral infections and other multifactorial events.\(^24\)
Regarding the use of additional oxygen therapy devices, the positive group showed greater expressiveness in the prevalence of invasive ventilation, which corroborates the literature reporting RSV positive patients as potentially more serious patients, the same was noted when analyzing readmissions, which were also predominant in the same group.\textsuperscript{25}

The findings showed that of the positive RSV patients, 73\% used prophylactic drugs. We do not know, in the absence of more concrete data, whether the correct doses were used, or whether the medications were used properly. At the same time, patients from the same group presented 65\% of readmissions, almost 60\% of them at least once.

This fact leads us to reflect that recurrent wheezing is a public health pathology and that it is necessary to improve the quality of pediatrician care for this pathology in hospital and outpatient clinics. Specialties, such as pulmonology, are not providing the necessary support for patients and do not exist in sufficient numbers to supply adequate care, so the patient either suspends or maintains the same medication, despite increasingly frequent crises, causing re-hospitalization and maintenance of a poor quality of life, with no improvement in the morbidity and mortality rates from this pathology.

Therefore, it is extremely necessary to improve the care these patients receive from the general pediatrician, as well as their qualification, in order to supply the follow-up of these individuals faced with this very prevalent pathology. Pediatricians could be qualified with an update on the treatment protocol for recurrent wheezing so that a uniform approach is performed for patients, as well as the creation of a medical record for admission to the inpatient unit, in order to improve the filling out of medical records, with better efficiency in the acquisition of essential information for the planning of strategies.

As a limitation of the study, we highlight the difficulty in carrying out data collection work through electronic medical records, the lack of information that should be included in a well-performed anamnesis, with a need for improvement in the quality of medical records and their proper completion. These missing factors can undoubtedly, make a difference in the results we want to evaluate.

In the current study, we concluded that there was an important correlation of risk factors for recurrent wheezing with positive RSV, such as prematurity, heart disease, invasive ventilation, and readmissions, with the need for qualification and standardization of conduct by the general pediatrician for clinical assistance faced with this prevalent public health pathology.

References


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