Rhinovirus and metapneumovirus in patients with severe acute respiratory infection

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ABSTRACT

Introduction. Viruses are the main etiologic agents involved in severe acute respiratory tract infections; a viral diagnosis is not established in a high percentage of cases.

Objective. To describe the frequency of rhinovirus and metapneumovirus in pediatric patients with severe acute respiratory infection and negative results for typical viruses by immunofluorescence and molecular biology at a sentinel unit of Mar del Plata.

Population and methods. This was a descriptive, cross-sectional study. The presence of rhinovirus and metapneumovirus was assessed by molecular biology in 163 cases negative for respiratory panel by referral surveillance techniques throughout 2015.

Results. Rhinovirus was detected in 51.5% of cases, metapneumovirus in 9.8%, and coinfection with rhinovirus and metapneumovirus in 6.1%. Results were negative for both viruses in 32.5%.

Conclusions. The selection of samples without a viral diagnosis allowed us to identify rhinovirus and metapneumovirus as causative agents of severe acute respiratory infections in children and assess their impact on child morbidity and mortality and on our health care system.

Key words: rhinovirus; metapneumovirus; respiratory tract infections; epidemiological surveillance; molecular biology.

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INTRODUCTION

Severe acute respiratory infections (SARI) are the main reason for consultation and hospitalization in pediatrics. Viruses are the most frequent etiological agents; in Argentina, according to the epidemiological surveillance protocol, respiratory syncytial virus (RSV), influenza A and B (FluA, FluB), parainfluenza (PI), and adenovirus (ADV) are tested by immunofluorescence (IF); influenza results are confirmed by molecular methods. Every year, the Sentinel Unit for the Surveillance of SARI (SU-SARI) of Hospital Interzonal Especializado Materno Infantil (HIEMI) of Mar del Plata reports hundreds of cases, but no viral diagnosis is made in a significant percentage of them. Antibiotic prescription in these patients is common, and it has an impact on bacterial resistance and costs.

In recent years, rhinovirus (RV) and metapneumovirus (MPV) have been increasingly reported as causative agents of SARI; however, they are not included in the laboratory surveillance protocol; therefore, their implication in the morbidity and mortality of the pediatric population of Mar del Plata remains unknown.

OBJECTIVE

To describe the frequency of RV and MPV in pediatric patients with SARI, with no comorbidities, and with negative results for typical viruses by immunofluorescence and molecular biology.

POPULATION AND METHODS

A descriptive, cross-sectional study was conducted at the National Epidemiology Institute Dr. Juan H. Jara in Mar del Plata between January 1st and December 31st, 2015.

Study population: hospitalized children younger than 16 years, with no comorbidities, selected by the SU-SARI of Mar del Plata who met the definition of SARI case: presence of signs and symptoms such as cough and/or tachypnea and/or wheezing and/or respiratory distress and/or positive signs on auscultation, with or without systemic symptoms (fever, headache) and/or diagnosis of pneumonia, bronchiolitis, bronchitis, or flu syndrome and negative bacteriological cultures on admission.

Biological samples: swabs, nasopharyngeal aspirates, or bronchoalveolar lavage, according to the protocols established by the National Ministry of Health and the World Health Organization (WHO). During 2015, samples with negative results for RSV, AD, FluA, FluB, and PI by IF, and undetectable results for FluA and FluB by molecular biology, according to the protocol established by the national reference laboratory, were included in the study.

RV detection: real-time reverse transcription-polymerase chain reaction (RT-PCR) assay by amplifying a 207 base pair fragment of the 5’ non-coding region. MPV detection: endpoint RT-PCR of a 248 base pair region of the nucleocapsid.

Variables

Dependent variables RV and MPV detection. Independent variables obtained from the SU-SARI’s clinical-epidemiological card: signs and symptoms, age, sex, length of stay (days), complications, and antibiotic use.

Ethical considerations: This study was approved by the Ethics and Research Committee of HIEMI. No informed consent was required because the samples and data were collected from the national surveillance system, whose reporting is mandatory.

Statistical analysis: The total frequency of RV and MPV was expressed as proportion. Univariate, bivariate, and multivariate analyses were performed.

Descriptive statistics were calculated for demographic and clinical variables: median values were estimated for continuous variables; absolute frequencies, proportions, and their 95% confidence intervals (CIs), for categorical variables. Associations between variables were established using the χ² test or Fisher’s exact test, as applicable. The association between variables and RV and MPV infection was estimated by calculating the OR. Support software: Epi Info 7 and Epidat 4.1.

RESULTS

During 2015, 30.3% (n = 163) of pediatric respiratory samples collected by the HIEMI’s SU-SARI from Mar del Plata were negative for viruses studied based on SARI surveillance. These patients had no comorbidities.

Over 163 samples studied, 110 were positive for RV, MPV or both; 84 (51.5%, 95% CI: 43.6–59.4) for RV; 16 (9.8%, 95% CI: 5.7–15.5) for MPV, and 10 (6.1%, 95% CI: 3.0–11.0) showed RV-MPV coinfection. Only 53 were negative for RV and MPV.
Patients’ median age was 6 months (14 days to 6 years). Children younger than 2 years were the most affected (Figure 1).

No statistically significant differences were found in terms of age when comparing the positive and negative subgroups of RV and MPV results ($p = 0.76$ and $0.51$, respectively).

The median length of stay was 4 days (1 to 43 days).

The presence of fever, cough, chest wall retraction, tachypnea, diarrhea, abdominal pain, respiratory failure, food refusal, cyanosis, and vomiting was assessed. No statistically significant differences were observed between the presence of these symptoms and RV detection ($p > 0.05$). However, children positive for MPV showed an association with the presence of chest wall retraction, abdominal pain, and respiratory failure ($p = 0.037$, $0.025$, and $0.017$ respectively). No positive association with the symptoms assessed was observed either in children with coinfection ($p > 0.05$).

With the exception of a patient with pertussis-like syndrome and positive for RV who died, patients with RV and MPV infection were recovered.

The seasonality of RV and MPV in our study period coincides with the peaks of circulation of other viruses reported by the SU-SARI (Figure 2).

Antibiotics were administered to 15% of patients with RV or MPV, during hospitalization.

**Figure 1. Number of cases of rhinovirus and metapneumovirus by age group in the Sentinel Unit for SARI surveillance**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total</th>
<th>ND</th>
<th>≥ 5 years</th>
<th>2-5 years</th>
<th>≥ 29 days &lt; 2 years</th>
<th>≤ 28 days</th>
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</thead>
<tbody>
<tr>
<td>MPV</td>
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<tr>
<td>RV</td>
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</tbody>
</table>

ND: no data; RV: rhinovirus; MPV: metapneumovirus; SARI: severe acute respiratory infection.

Source: SU-SARI of HIEMI. Laboratory of Virology. INE Dr. Juan H. Jara - ANLIS. Mar del Plata. Argentina. 2015.

**Figure 2. Seasonality of total rhinovirus and metapneumovirus cases**

RV: rhinovirus; MPV: metapneumovirus.

Source: Laboratory of Virology. INE Dr. Juan H. Jara - ANLIS. Mar del Plata. Argentina. 2015.
DISCUSSION

Our study describes the frequency of RV and MPV in pediatric patients with no comorbidities and negative results for common microorganisms and respiratory virus panel performed according to the epidemiological surveillance protocol for respiratory viruses, observed at a SU-SARI. This protocol includes the study of usual viruses by IF and influenza by molecular biology.1,2,6,7

Annually, 60-70% of cases observed by the SU-SARI of Mar del Plata were positive for at least one of the viruses included in the surveillance protocol. By incorporating RV and MPV into the Ministry’s viral surveillance protocol, the result yielded an improvement to 91%.

In recent years, RV and MPV have been increasingly reported as the leading cause of lower respiratory tract infection and hospitalization.3–5

Some authors, such as Maffey AF et al., have described the presence of RV in a higher proportion than influenza and even RSV.10,11 According to the bibliography, depending on the studied population and the laboratory approach implemented, viruses positivity ranges varies between 17% and 44% for RV and 1.5% and 10% for MPV.5,8–14

In our study, the percentage observed was higher for RV (51.5%), but similar for MPV (9.8%). If all SU-SARI patients were included, these values could have been higher, due to coinfections with usual viruses. We decided not analyze, we did not analyze coinfections because of other viruses presence would make it difficult to demonstrate the causative association of RV and/or MPV infection with SARI.

In this study we found a statistically significant association among MPV infection and the presence of chest wall retraction and respiratory failure. We also reported a death associated with RV with no other apparent cause. Patients with RV-MPV coinfection did not show worse clinical severity than those infected with a single virus.

According to the definition of risk group for SARI, most commonly affected patients were those under 2 years old.1

Seasonality of RV and MPV coincides with the peaks of other respiratory viruses circulation, confirming their contribution to the burden of disease in notified SARI.

Other authors have also studied RV and MPV in pediatric populations without underlying conditions.3–5,12–14

The detection of RV and MPV by molecular biology allowed us to confirm that, in our pediatric population, they are associated not only with mild respiratory symptoms, but also with SARI.

This is the first study conducted in healthy children which, having ruled out other infectious agents, attempted to demonstrate the impact of RV and MPV as causative agents of SARI in the SU of Mar del Plata.

CONCLUSIONS

The introduction of RT-PCR allowed us to identify RV in 51.5% of cases, MPV in 9.85% of cases, and RV-MPV coinfection in 6.1 % of cases in healthy pediatric patients with SARI who had negative results for common microorganisms and respiratory viruses included in the epidemiological surveillance panel.

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