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Original Article

Evaluation of children diagnosed with a lower respiratory tract infection due to Human metapneumovirus

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ABSTRACT

Background. Human metapneumovirus (hMPV) is one of the leading causes of acute respiratory infections and bronchiolitis in infants. A history of prematurity and chronic diseases such as congenital heart disease or asthma/reactive airway disease (RAD) increases the risk of severe lower respiratory tract infection (LRTI) due to hMPV. In this cross-sectional study, we aimed to analyze the clinical outcome and risk factors for severe disease in children with LRTI due to hMPV.

Methods. The current cross-sectional study included children between 28 days and 18 years of age with the diagnosis of hMPV-associated LRTI hospitalizations, over two years from January 2016 to September 2018 in Health Science University Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. hMPV virus was detected by the multiplex polymerase chain test (PCR) (Commercial Multiplex Real-Time PCR: FTD Respiratory 21 plus, Fast Track Diagnostics, Luxembourg) from a nasopharyngeal swab. Patients who had positive results in multiplex PCR tests with other viral agents simultaneously were not included in the study. Data were retrospectively collected from the computerized hospital system.

Results. In this cross-sectional study, 62 patients who were hospitalized with the diagnosis of LRTI due to hMPV infection were included. Thirty-five (55.7%) of the patients were male. The median age was one year (2 months-15 years). Fifty-one (82.2%) patients were younger than two years. The median hospital length of stay was found to be 10 days (2-33 days) in patients with an underlying disease and 7,5 days (ranging from 2 to 20 days) in the patients without an underlying disease, this difference was significant (p=0.031).

Conclusions. Clinicians should consider hMPV as an important pathogen of LRTI even in healthy children, although we expect a poor course of disease in children with an underlying disease.

Key words: human metapneumovirus, lower respiratory tract infection, hospitalized, length of stay.

Human metapneumovirus (hMPV) is an enveloped, single-stranded, negative-sense RNA virus that was first discovered in 2001 and categorized in the genus Metapneumovirus of the family Paramyxoviridae.[1,2] The hMPV season occurs during the late winter and early spring months in temperate locations and overlaps with those of Respiratory Syncytial Virus (RSV) and influenza viruses.

hMPV causes acute respiratory tract illnesses, such as pneumonia, asthma exacerbations or croup in people of all ages and also it is one of the leading causes of bronchiolitis in infants.[2] The proportion of hMPV detected in nasopharyngeal samples from children with unexplained respiratory infections has varied from 1.5 to 25%.[1-3]

The clinical presentations in children with hMPV infection range from mild upper

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respiratory tract disease to severe bronchiolitis and pneumonia, similar to RSV infection, Moreover, very young hMPV-infected children may require hospitalization and mechanical ventilation.[1,3] A history of prematurity, chronic diseases such as congenital heart disease or neuromuscular disorders, and pulmonary diseases including asthma/reactive airway disease (RAD) increase the risk of severe lower respiratory tract infection (LRTI) due to hMPV.[4-8]

This study was conducted for evaluating the severity, length of hospital stay, and outcome of hMPV infections. We specifically aimed to analyze the clinical outcome and risk factors for severe disease in children with LRTI due to hMPV.

Material and Methods

The current cross-sectional study included children between 28 days and 18 years of age with the diagnosis of hMPV-associated LRTI hospitalizations, over two years from January 2016 to September 2018 in Health Science University Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital. This hospital is a referral center for pediatric patients in the Aegean Region of Turkey, with an annual 600.000 outpatients and approximately 24.000 hospitalizations in 2018. We evaluated a total of 102 hMPV cases during the study period.

Multiplex PCR for hMPV

Aspirate samples from each nostril and one nasopharyngeal swab were obtained in the supine position with the head positioned at the midline. Within a maximum period of 4 hours after collection, the samples were mixed and added to a Ringer lactate solution to a total of 4 mL. After homogenization, approximately 1 mL were separated into aliquots in cryotubes and stored at -80 °C. The DNA/ RNA was extracted from samples using an extraction kit (RTP DNA/RNA Virus Mini Kit, Stratec Molecular, Germany). The sensitivity and specificity were monitored by standard quality control for molecular diagnostics. The qualitative detection of 20 respiratory viruses including influenza [IF A, H1N1, and B], coronavirus [CoV 43, 63, 229, and HKU], parainfluenza [PI1, PI2, PI3, and PI4], human rhinovirus [HRV], respiratory syncytial virus [RSV A/B], human metapneumovirus [hMPV A/B], adenovirus [AdRV], enterovirus [EV], parechovirus, and human bocavirus [hBoV] were done by real-time multiplex PCR (FTD, Fast Track Diagnostics, Belgium).

A total of 102 patients were included in the initial analysis. Nine patients with missing data and 31 patients co-infected with other viral agents were excluded from the study. We included cases if they were hospitalized and had laboratory-confirmed h-MPV by PCR at presentation or during their hospital stay. All participants had an acute LRTI with symptoms of cough, shortness of breath, wheezing, or tachypnea plus consolidation recorded on a chest X-ray. Patient files were recorded from the computerized hospital system.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (version 22; SPSS, Chicago, IL, USA). Student's t-test was used to compare continuous parametric variables, the Mann-Whitney U test was used to compare continuous nonparametric variables, and $\chi 2$ or Fisher's exact tests were used for categorical variables when appropriate. A two-tailed p-value of < 0.05 was considered to be statistically significant.

Ethical approval was received for this research from Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital Ethics Committee. The patients or legal guardians of the participants provided signed informed consent forms for inclusion in the study.

Results

In this cross-sectional study, 62 patients who were hospitalized with the diagnosis of LRTI due to hMPV infection were included. Thirty-

five (55.7%) of the patients were male, and 27 (44.3%) were female. The median age was one year (ranging from 2 months to 15 years). Forty-one patients (66.1%) were younger than one year, and 51 (82.2%) patients were younger than two years.

Thirty patients (48.4%) had an associated underlying disease, and the most common one was allergic diseases (n=9, 30%) followed by neurological diseases including cerebral palsy (n=7, 23.3%), prematurity (n=5, 16.6%), congenital heart diseases (n=3, 10.0%), immunodeficiency (n=3, 10.0%), malignancies (n=2, 6.6%) and a genetic syndrome (Table I).

The median length of stay (LOS) of the patients was eight days (ranging from 2 to 33 days). The median length of stay was found to be ten days (ranging from 2 to 33 days) in patients with an underlying disease and 7.5 days (ranging from 2 to 20 days) in the patients without, this difference was statistically significant (p=0.031). The relationship between the LOS (measured by days) and age (measured by months) was investigated using the Spearman correlation coefficient. There was no significant correlation between the two variables (r = -.138, n = 62, p=0.283). The median length of stay was not significantly different between male and female patients (8 days, 3 to 33 days, vs 8 days, 2 to 17 days. p>0.05). A total of 12 (9.2%) patients required respiratory support, including 2 mechanical ventilation and intubation, 9 high-flow nasal cannulas (HFNC) and 1 continuous positive airway pressure (CPAP). Among these twelve patients who were transferred into the intensive care unit because of severe respiratory failure, nine patients (75%) had an underlying disease. The rate of patients requiring mechanical support (invasive and non-invasive support) within the patients with an underlying disease was significantly higher compared to the rate of mechanical support in the previously healthy group (p=0.04).

Table I. General features of patients.

Gender	n (%)
Female	27 (44.3)
Male	35 (55.7)
Years	n (%)
<1 year	41 (66.1)
<2 years	51 (82.2)
> 2 years	11 (17.7)
Underlying diseases	n (%)
Allergic diseases	9 (30)
Congenital heart disease	3 (10)
Median length of stay in the hospital	Day
Underlying diseases	10
No underlying diseases	8

Discussion

In our study, the absence of an underlying disease in approximately half of the patients showed that hMPV was a cause of severe pneumonia that required hospitalization even in healthy children. The other remarkable finding is that the duration of hospitalization was longer in patients with an underlying disease. In reviewing the literature, hMPV is a relatively newly recognized pathogen, but there are many studies on this subject. Since the initial description of hMPV in 2001, hMPV has been reported in many studies as a low respiratory tract infection pathogen in different countries around the world and the rate varies between 2.2 and 9%.[2,9-13]

Although hMPV can be seen at any age, including the adult age group, it is more common, especially before 5 years of age and has a more severe clinical course in this age group. According to the results of this study, the mean age of the patients was 1 year (2 months-15 years) and, a total of 51 (82.2%) patients were <2 years of age. In previous studies, the median age of the children ranged from 6 months to 3 years.[7-9,13-16] Heikkinen et al.[14] found that the incidence rates of hMPV decreased gradually with age.[14] Approximately 80% of cases were reported to be under 5 years of age.[14,17] However, the more intensive accumulation in age is present under 2 years of age which is supported by our findings.

The duration of hospitalization of patients varies, and having certain risk factors has an impact on this duration. Previous studies have shown that the median duration of LOS ranged from 3 days to 7 days.[7,8,11-13] Trenholme et al.[12] detected hMPV as a causative agent in 7% of the patients who were admitted to the hospital with a LRTI and hMPV was associated with increased LOS.[12] In this study, the duration of hospitalization was compared between the patients with and without an underlying disease. The LOS was longer in patients with an underlying disease compared to the patients without an underlying disease (median 10 vs 8 days, p = 0.046). This finding supports the information in the literature. Similarly, Han et al.[7] reported that the LOS of previously healthy patients was significantly shorter than those with risk factors.[7]

There are well-defined risk factors for hMPV, and these include asthma, prematurity, congenital heart disease. In these cases, the course of the disease is more severe. In the study by Pancham et al.[18], children with a history of prematurity had more severe hMPV disease regardless of age, ethnicity or asthma history.[18] Prematurity was identified as a risk factor for hospitalization due to hMPV infection in previous studies.[5-7,13,15,19] In our study, 30 patients (48.4%) had an associated underlying disease, and the most common one was allergic diseases (n=9, 30%) followed by cerebral palsy (n=7, 23.3%), prematurity (n=5 16.6%) and congenital heart diseases (n=3, 10.0%). The median LOS was found significantly higher in patients with an underlying disease (p=0.031). The other remarkable point, the rate of patients requiring mechanical support (invasive and non-invasive support) was significantly higher among the patients with an underlying disease, compared to the rate of mechanical support in the previously healthy group (p=0.04).

This study has limitations due to its retrospective design. First of all, data, including patients with hMPV and possible underlying disease, were collected retrospectively from the medical files, and microbiology laboratory. Secondly, our sample size, especially for the patients requiring respiratory support and follow up in the intensive care unit, was small. However, to the best of our knowledge, this is one of the few studies focusing on hMPV infections in children. Additionally, our data is largely consistent with the literature. Most of the patients in this study were under two years of age, and the duration of hospitalization increased in patients with an underlying disease.

In this study, we found that approximately half of the hospitalized patients with LTRI due to hMPV did not have an underlying disease. This finding indicates that hMPV is an important pathogen of LRTI also in healthy children. On the other hand, the duration of hospitalization was longer in patients with an underlying disease. Therefore, clinicians should consider hMPV as an important pathogen of LRTI even in healthy children, while we should expect a poorer course of the disease in children with an underlying disease.

Ethical approval

This study was approved by the Ethical Committee of Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research (approval number: 462; 2020/14-05, approval date: 08.10.2020).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NB, İD; data collection: EK, EB, İÇ, YS, FG, ÇÖE, ÖBS, HA, TÇ; analysis and interpretation of results: NB, İD, EK; draft manuscript preparation: EK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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