Status Epilepticus: A Possible Association With Human Metapneumovirus Infection

Human metapneumovirus (hMPV) is a relatively recent addition to the multiplicity of viruses causing respiratory illness in infants and children. Although well described in its ability to cause respiratory illness, there is limited data detailing the association of hMPV with neurologic complications. In this report, we describe 2 toddlers with hMPV infection who presented in status epilepticus and went on to develop respiratory failure. Both patients fully recovered over 2 weeks and were discharged from the hospital with no sequelae. The association between hMPV infection and neurologic complications is increasingly being reported in the literature. Clinicians should be aware of these uncommon manifestations of a common respiratory pathogen and consider testing for hMPV when managing pediatric patients who present with unexplained status epilepticus or encephalitis. Pediatrics 2014;133:e747–e750

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ABBREVIATIONS:
- CSF—cerebrospinal fluid
- CXR—chest radiograph
- ED—emergency department
- hMPV—human metapneumovirus
- HSV—herpes simplex virus
- IV—intravenous
- PCR—polymerase chain reaction
- RSV—respiratory syncytial virus

Dr Webster drafted the initial manuscript and formatted the manuscript for presentation; Dr Gardner reviewed and revised the manuscript with specific attention to hospital course and case presentation data; Dr Dye reviewed and revised the manuscript with specific attention to the neurologic manifestations and data regarding seizures; and Dr Chima served as clinical mentor and critically reviewed and edited the manuscript. All authors approved the final manuscript as submitted.

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Human metapneumovirus (hMPV) is a paramyxovirus that belongs to the same family as respiratory syncytial virus (RSV) and parainfluenza. It causes both upper and lower respiratory tract infections and accounts for a substantial burden of respiratory disease among children, especially those aged <5 years. Recent data report an annual rate of hospitalization associated with hMPV to be 1 per 1000 children, which is similar to rates for influenza infection.\(^1\) In addition to respiratory disease, hMPV infection may have neurologic manifestations. However, in practice, clinicians may be unaware of this association.

In this case report, we describe two patients with hMPV infection who presented in status epilepticus and subsequently developed acute respiratory failure. A pertinent literature review of hMPV infections and associated neurologic manifestations is also presented (Supplemental Table 1).

**CASE REPORT 1**

A previously healthy 15-month-old term female presented to the emergency department (ED) in status epilepticus. Per parental report, after 2 days of mild rhinorrhea, the patient awoke in the night fussily but afibrile. They denied any ill contacts or recent travel. The parents described full body twitching, which was not suppressible, and eye deviation to the right. The patient was taken to the ED by emergency medical services, and treated with rectal diazepam followed by intravenous (IV) lorazepam, fosphenytoin, and finally phenobarbital, resulting in resolution of clinical seizure activity after an estimated 35 minutes. Concomitant with treatment, she underwent tracheal intubation for airway protection. Her physical examination was unremarkable, including the absence of fever. Imaging studies included a normal computed tomography scan of the head and a chest radiograph (CXR), which showed no abnormalities. Routine blood and cerebrospinal fluid (CSF) study results were normal. Results of blood, urine, respiratory, and CSF cultures, as well as viral polymerase chain reaction (PCR) assays for herpes simplex viruses (HSV) 1 and 2, were negative. Oligoclonal bands were not sent for analysis. A respiratory viral PCR panel was positive for hMPV. The patient was transferred to the PICU where she was placed on continuous video-EEG monitoring. EEG tracing reflected her being sedated; however, it was otherwise normal for age, and no further clinical or electrographic seizures were noted. She was extubated on hospital day 1 and quickly weaned to room air. After extubation, she was agitated and mildly encephalopathic without focal neurologic deficit and was transferred to a general pediatric floor. On hospital day 6, the patient developed tachypnea with increased respiratory secretions. A CXR showed perihilar, right upper lobe, and left lower lobe pneumonia with no pleural effusion or pneumothorax. She was transferred back to the PICU because of her respiratory distress. On hospital day 7, CXR demonstrated an interval development of pneumomediastinum, bilateral pneumothoraces, and worsening bibasilar opacities. She progressed to respiratory failure, requiring modest mechanical ventilatory support, including inhaled nitric oxide for hypoxemia. Results of additional blood, urine, and respiratory cultures were negative. No additional neuroimaging was required or obtained. She was successfully extubated on hospital day 12 and discharged from the hospital on hospital day 18. She returned for follow-up 1 month after discharge without residual sequelae, seizures, or medications.

**CASE REPORT 2**

An 18-month-old term female with a history of one previous simple febrile seizure presented with a fever and in status epilepticus. Her history was notable for decreased oral intake and subjective fever for a few hours before the onset of generalized tonic-clonic convulsions. The parents denied any ill contacts or recent travel. She was transported by emergency medical services to the ED; en route, the patient was treated with IV midazolam. She was febrile with ongoing seizure activity on arrival at the ED, where additional treatment with IV lorazepam followed by fosphenytoin resulted in resolution of clinical seizure activity, after an estimated 45 minutes. She underwent tracheal intubation for airway protection. The remainder of her review of systems and physical examination was unremarkable. EEG showed a retrocardiac opacity suggestive of atelectasis, and a computed tomography scan of the head showed no abnormality. She was admitted to the PICU and placed on continuous video-EEG monitoring. EEG tracing indicated a normal, asleep EEG for age, and no further clinical or electrographic seizures were noted. Results of routine blood and CSF studies were normal. Results of blood, urine, respiratory, and CSF cultures as well as viral PCR for HSV1 and HSV2 were negative. Oligoclonal bands were not sent for analysis. The patient was empirically treated with vancomycin, ceftriaxone, and acyclovir pending culture results. By hospital day 2, the tracheal aspirate grew *Moraxella catarrhalis*, and a respiratory viral PCR panel was positive for hMPV. Vancomycin and acyclovir were subsequently discontinued, and ceftriaxone was continued for 14 days. The patient developed worsening lung disease and hypoxemia over the subsequent days with diffuse bilateral infiltrates and pleural effusions. Respiratory support was escalated to high-frequency ventilation and inhaled nitric oxide from hospital days 4 to 7. Results of MRI and magnet resonance spectroscopy of the brain were normal.
The patient remained seizure free after the day of admission. Per a neurology consultation, the decision was made to continue fosphenytoin through extubation pending a more thorough neurologic examination off sedation. She was extubated on hospital day 14, transferred to a general pediatric floor on hospital day 17, and discharged from the hospital on hospital day 23. She required no scheduled medications upon discharge. Her postdischarge course and follow-up have been uneventful.

**DISCUSSION**

hMPV is a relatively recent addition to the multiplicity of microorganisms causing respiratory illness in infants and children. van den Hoogen et al² first demonstrated its presence in the respiratory secretions of children with lower respiratory tract disease; however, antibodies to hMPV were detected in archived serum samples as early as the 1950s. Virtually all children will show serologic evidence of infection with hMPV by 5 years of age, with a background incidence rate of ~5% to 15% in young children.³ It is second only to RSV as a cause of bronchiolitis. The incidence of hMPV infection is seasonal, with the highest incidence in the late winter months.³ ⁵ hMPV causes both upper and lower respiratory tract infections and has the potential to cause severe respiratory illness. Recent data from a multicenter study demonstrate substantial morbidity and higher-than-predicted mortality for critically ill children with hMPV infection.³⁴³⁵³⁷

Despite its predilection for the respiratory tract, hMPV has been reported in other body fluids such as blood, urine, and CSF and may involve other organ systems, specifically the central nervous system. There have been a handful of cases reported in the literature describing neurologic symptoms concomitantly with hMPV infection.⁸⁻¹¹ Notably, Sánchez Fernández et al⁹ described a 10-year-old girl with acute encephalitis in whom hMPV was detected in both respiratory secretions and CSF specimens. These authors speculated on an immune-mediated inflammatory mechanism for the observed changes (white matter changes in their case occurred after the virus could no longer be detected in the CSF specimen). Additional data from a retrospective study from Southern California detected hMPV in 5% of respiratory specimens obtained from children with respiratory illnesses. Seizures were reported in 6% of those patients, which was a significantly higher rate than in patients who tested positive for RSV. The same study also examined respiratory samples from 1474 children with encephalitis who took part in the California Encephalitis Project; 5 of these children tested positive for hMPV.⁹ Another prospective cohort study from Japan detected hMPV in clinical specimens (nasal scrapings, throat swabs, and sputum samples) from 141 children presenting to outpatient clinics with symptoms of respiratory tract infection. One child within this group developed encephalitis. In that same study, the authors performed further analysis of the serotype isolated in the patient with encephalitis and found it to be similar to 1 isolated from the brain and lung tissue of a toddler who succumbed to fatal encephalitis.⁸⁻¹¹ Hence, data from both of these studies demonstrate a possible association between hMPV infection and neurologic complications.

In our report, both children presented with significant neurologic manifestations without respiratory symptoms. After resolution of the seizures, both children went on to develop respiratory failure. In both cases, initial laboratory test results were normal and the presentation perplexing; however, we were cautiously reassured when they tested positive for hMPV, given the published literature demonstrating a possible association between hMPV and neurologic complications.

**CONCLUSIONS**

There seems to be limited but growing evidence that primary respiratory infections due to hMPV are more likely to have neurologic manifestations compared with infections with similar respiratory viruses. Clinicians should be aware of this association and consider testing for hMPV when managing pediatric patients who present with unexplained status epilepticus or encephalitis.

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