Human Metapneumovirus in the Cerebrospinal Fluid of a Patient With Acute Encephalitis

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Objective: To report, to our knowledge, the first case of detection of human metapneumovirus in the cerebrospinal fluid of a patient during acute encephalitis.

Design: Case report.

Setting: University hospital.

Patient: A 10-year-old girl with acute encephalitis.

Results: Human metapneumovirus was detected in cerebrospinal fluid and nasal-wash specimens during the initial phase of mild encephalitis. Abrupt clinical deterioration was associated with the presence of multiple areas of demyelination and cortical abnormalities. Demyelinated areas improved after immunomodulatory therapy, but cortical lesions spread in both hemispheres. Surprisingly, clinical worsening occurred when the virus became undetectable in cerebrospinal fluid.

Conclusions: The detection of human metapneumovirus in cerebrospinal fluid strongly suggests its causative role in acute encephalitis. The evolution of the clinical and radiological features provided insight into the pathogenesis of human metapneumovirus encephalitis.


THE SPECIFIC ETIOLOGY OF AS many as 32% to 75% of acute encephalitis cases remains unknown even after a thorough etiological workup.1,2 The human metapneumovirus (hMPV) was discovered in 2001,3 and it has been established as a common pathogen of the respiratory tract.4,6 Human metapneumovirus has been proposed as an etiological agent of encephalitis because it has been isolated from the respiratory tract during the acute phase of several cases of encephalitis4,7,8 and in postmortem lung and brain tissue of a patient with a fatal encephalitis.9 To our knowledge, we report the first case of acute encephalitis in which hMPV was detected in cerebrospinal fluid (CSF). Additionally, we report the evolution of the clinical and neuroimaging features.

REPORT OF A CASE

A previously healthy 10-year-old girl presented with a runny nose and headache. After 4 days, she suffered a low-grade fever (38°C) and intense headache and was found unconscious in bed with vomit in her mouth, hypertonia of the mandibular muscles, and unreactive pupils. When assessed by emergency services personnel, she had a Glasgow Coma Scale (GCS) score of 8 points. She was intubated and brought to the hospital. A progressive improvement of clinical condition during transportation prompted extubation.

At hospital admission, her level of consciousness had improved (GCS score, 11 points) and the findings from the rest of the physical examination were normal. The results of blood analysis were unremarkable, urine toxicology screening was negative, and cranial computed tomography was normal. Analysis of CSF demonstrated the following: proteins, 0.03 g/dL (to convert to grams per liter, multiply by 10.0); glucose, 0.083 g/dL (to convert to millimoles per liter, multiply by 55.5); red blood cells, 3/µL; and white blood cells, 52/µL (with a differential cell count of 55% neutrophils and 45% lymphocytes). Combination intravenous treatment of acyclovir sodium, 10 mg/kg/8 h; cefotaxime sodium, 50 mg/kg/6 h; and vancomycin hydrochloride, 10 mg/kg/6 h, was started. Polymerase chain reaction (PCR) results were negative for herpes virus and enterovirus and positive for hMPV in CSF and...
nasal-wash specimens. The detailed description of the detection technique can be found in the eTable (http://www.archneurol.com). Cerebrospinal fluid culture yielded no organisms. Consequently, in the fourth day of admission, treatment with antibiotics and acyclovir was discontinued.

During the first days of admission, she was febrile and had a fluctuating level of consciousness with alternating episodes of agitation and sleepiness. Five days after admission, her clinical condition severely deteriorated, prompting intubation and admission into the intensive care unit. Clonic seizures affecting the left limbs were recorded and eventually controlled with a combination of valproate sodium and levetiracetam. A second CSF analysis demonstrated the following: proteins, 0.08 g/dL; glucose, 0.07 g/dL; red blood cells, 0/µL; white blood cells, 80/µL; IgG, 70 g/dL (reference range, 20-40 g/dL) (to convert to grams per liter, multiply by 0.01); oligoclonal bands, negative; albumin, 0.05 g/dL (reference range, 0.01-0.02 g/dL) (to convert to grams per liter, multiply by 10); neopterin, 342 nmol/L (reference range, 11-45 nmol/L); and biopterin, 25 nmol/L (reference range, 10-36 nmol/L). Polymerase chain reaction results for herpes virus 1 and 2, enterovirus, and metapneumovirus were negative. Noncontrast brain magnetic resonance imaging (MRI) analysis demonstrated the following: proteins, 0.08 g/dL; glucose, 0.07 g/dL; red blood cells, 0/µL; white blood cells, 80/µL; IgG, 70 g/dL (reference range, 20-40 g/dL) (to convert to grams per liter, multiply by 0.01); oligoclonal bands, negative; albumin, 0.05 g/dL (reference range, 0.01-0.02 g/dL) (to convert to grams per liter, multiply by 10); neopterin, 342 nmol/L (reference range, 11-45 nmol/L); and biopterin, 25 nmol/L (reference range, 10-36 nmol/L). Polymerase chain reaction results for herpes virus 1 and 2, enterovirus, and metapneumovirus were negative. Noncontrast brain magnetic resonance imaging (MRI) detected multiple (>20) well-defined, subcentimetric, T2- and T2-weighted, fluid-attenuated inversion recovery hyperintense lesions scattered throughout the subcortical, deep white matter, and left external capsule. Cortical thickening and increased signal intensity in the anterior pole of the right temporal lobe and posterolaterally in the left occipital lobe were also noted. Neither the white matter nor the cortical lesions showed restricted diffusion (Figure 1).

These MRI findings were suggestive of acute encephalitis with a concomitant acute demyelinating process, so intravenous immunoglobulin (2 g/kg for 3 days) followed by methylprednisolone (20 mg/kg for 3 days) and a tapering corticosteroid treatment with oral prednisone during 1 month were administered. Due to poor clinical response, plasmapheresis was performed on admission day 9. This treatment protocol was associated with a progressive improvement of her clinical condition, and she was extubated and transferred to the inpatient unit 18 days after admission.

At inpatient unit arrival, the patient could not speak or swallow and needed feeding by a nasogastric tube. Neurological examination disclosed general hypotonia and weakness with pyramidal signs predominating in her right limbs. Contrast-enhanced brain and spine MRI at this time of evolution showed that cortical thickening and abnormal signal intensities, previously limited to the temporal and occipital cortex, had spread to the frontal, parietal, and temporal lobes. These cortical lesions showed no enhancement but a markedly restricted diffusion, with low apparent diffusion coefficient values. Resolution of the previously seen white matter lesions was also noted (Figure 2). The spine MRI was normal. A rapid clinical improvement was noted in the following days. She was weaned from levetiracetam, valproate, and predni-
sone and was discharged home 35 days after hospital admission. At that moment, she was able to construct simple sentences, and motor impairment was restricted to mild signs of right hemiparesis.

Four months later, she was attending mainstream school without motor deficits. The neuropsychological assessment showed mild difficulties on social abilities and inappropriate and infantile behavior. She had recovered her previous abilities with written and oral language, and her learning and memory were normal, but she still had severe attention and executive deficits. Follow-up brain MRI showed widening of the frontoparietal sulci and marked cortical thinning, with predominance in the frontal, parietal, and temporal lobes (Figure 3).

![Figure 3. Magnetic resonance imaging 4 months after hospital discharge exhibits cortical atrophy (A and B) and gliotic changes (C). FLAIR indicates fluid-attenuated inversion recovery.](image)

Table. Patients With Neurologic Symptoms and Concomitant hMPV Infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Peiris et al, 2003&lt;sup&gt;10&lt;/sup&gt;</th>
<th>Kaida et al, 2006&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Hata et al, 2007&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Arnold et al, 2009 (Group 1)&lt;sup&gt;7&lt;/sup&gt;</th>
<th>Arnold et al, 2009 (Group 2)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Schildgen et al, 2005&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Present Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sex/age</td>
<td>NP</td>
<td>M/11 mo</td>
<td>F/6 mo</td>
<td>F/3 y</td>
<td>F/14 mo</td>
<td>M/14 mo</td>
<td>F/10 y</td>
</tr>
<tr>
<td>Samples tested for hMPV</td>
<td>Respiratory: positive</td>
<td>Respiratory: positive</td>
<td>Respiratory: positive</td>
<td>Respiratory: positive</td>
<td>Respiratory: positive</td>
<td>Postmortem brain and lung tissues: positive</td>
<td>Respiratory: positive</td>
</tr>
<tr>
<td>for hMPV</td>
<td>Urinary: positive</td>
<td>Urinary: positive</td>
<td>Urinary: positive</td>
<td>Urinary: positive</td>
<td>Urinary: positive</td>
<td>CSF: negative</td>
<td>CSF: positive</td>
</tr>
<tr>
<td>Neurologic presentation</td>
<td>Encephalitis</td>
<td>Encephalitis</td>
<td>Encephalitis</td>
<td>Encephalitis</td>
<td>Encephalitis</td>
<td>CSF: negative</td>
<td>CSF: positive</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>CT: Low-density areas in the WM</td>
<td>Normal (AD: 3)</td>
<td>Abnormal MRI in 2 (AD: 4): cerebral edema: multiple areas of increased signal throughout the WM without contrast enhancement</td>
<td>MRI: Multifocal lesions with high signal intensity. CT: multiple hypodense lesions</td>
<td>CT (admission): normal. MRI (5 d): multiple WM and cortical lesions MRI (18 d): spread of cortical lesions and resolution of WM lesions MRI (4 mo): postinflammatory cortical atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>NP</td>
<td>NP</td>
<td>Died 10 d after onset</td>
<td>NP</td>
<td>NP</td>
<td>Died during the episode</td>
<td>Attention and executive deficits</td>
</tr>
</tbody>
</table>

Abbreviations: AD, number of patients with available data; CSF, cerebrospinal fluid; CT, computed tomography; hMPV, human metapneumovirus; MRI, magnetic resonance imaging; NP, not provided; WM, white matter.
Human metapneumovirus is a well-established cause of respiratory tract infection in children and adults, and a growing body of literature is providing indirect evidence of its etiological role in encephalitis. In patients with hMPV respiratory tract infection, the prevalence of central nervous system symptoms is unusually high. In many cases of encephalitis of unknown etiology, hMPV has been simultaneously detected in the respiratory tract, and in a fatal case of encephalitis, PCR for hMPV was positive in postmortem lung and brain tissues. Together, these data strongly suggest that hMPV may be an etiological agent of encephalitis. However, as hMPV is found in respiratory tract samples from 12% to 20% of patients with respiratory tract infections and from 4% of asymptomatic individuals during the winter season, it can be argued that encephalitis and hMPV respiratory tract infection coexist but are not etiologically related. Our case report supports the hypothesis that hMPV may be a pathogenic agent in acute encephalitis because we have demonstrated the presence of hMPV in both nasal-wash and CSF specimens during the first stages of acute encephalitis.

The evolution of the neuroimaging findings provides some insight into the pathogenesis of metapneumovirus infection in the development of encephalitis. On the first MRI, the presence of multiple well-defined white matter lesions on top of several regions of abnormal cortical signal intensity suggests an acute demyelinating complication, even though no restricted diffusion was noted. The improvement of symptoms and the resolution of white matter lesions after immunomodulatory therapy highly support this suspicion. White matter involvement has been described in cases of suspected hMPV encephalitis, and multiple subcortical white matter lesions have also been described in encephalitis caused by the Nipah virus of the Paramyxoviridae family, although these lesions presented restricted diffusion in most of the cases and persisted for at least 1 month, suggesting a probable different pathogenesis.

In herpetic viral encephalitis, white matter lesions were considered an immune-mediated process and a warning sign of an immune-mediated worsening. In our patient, the neuroimaging findings worsened with severe brain swelling and cortical restricted diffusion with low apparent diffusion coefficient when the virus was already undetectable in the CSF. A similar delayed MRI worsening was previously described in herpes simplex encephalitis. The hypothesis that the main pathogenic factor in hMPV encephalitis is the reactive inflammatory process and the initial infection has only a trigger role is supported by the lack of detection of the virus in the CSF and the rarity of pleocytosis in previous cases of suspected hMPV encephalitis. The evolution of our patient, who had a severe clinical and radiological worsening after the virus became undetectable in the CSF, would add to this hypothesis.

In summary, the interest of our case lies in (1) the detection of hMPV in the CSF of a patient with acute encephalitis for the first time, and (2) it suggests that reactive inflammation may be more important than viral infection in the pathogenesis of hMPV encephalitis.