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Case Report

Severe human parechovirus type 3 myocarditis and encephalitis in an adolescent with hypogammaglobulinemia

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SUMMARY

Human parechovirus (HPeV) belongs to the *Picornaviridae* family of RNA viruses. HPeV infections can be asymptomatic, lead to mild respiratory and/or gastrointestinal symptoms, or less frequently cause severe diseases such as sepsis, meningitis, encephalitis, and myocarditis. Severe neurological HPeV infections occur most commonly in infants and neonates. There are currently 16 recognized types of HPeV. HPeV type 3 (HPeV3) has been the predominant type associated with severe central nervous system disease in neonates and newborns since its discovery in 1999. Although HPeV-related infections have been reported in adults, symptomatic HPeV3 infections in adolescents and adults are uncommon. A case of severe HPeV3 myocarditis and encephalitis in an adolescent is described.

1. Introduction

Human parechovirus (HPeV), first isolated in 1956, is a positive-sense, single-stranded RNA virus of the family *Picornaviridae* and one of three species in the genus *Parechovirus*. There are currently 16 known HPeV types, which can cause a variety of diseases. Whereas HPeV3 is known to cause serious infections in neonates and infants, including sepsis, meningitis, and encephalitis, severe HPeV3 central nervous system (CNS) infections in adolescents and adults are rare.[1] A case of severe HPeV3 myocarditis and encephalitis in an adolescent that is of epidemiological significance is reported below.

2. Case report

A 16-year-old female with a history of systemic lupus erythematosus (SLE) diagnosed at age 10 years, presented to the hospital with chest pain and dyspnea. The previous diagnosis of SLE was supported by positive antibodies (ANA, Smith/RNP, and double-stranded DNA) and clinical arthritis, and biopsy-confirmed class IV lupus nephritis. The patient also had prolonged hypogammaglobulinemia secondary to rituximab. A chest X-ray revealed cardiomegaly and a small right-sided pleural effusion. Echocardiography indicated the presence of biventricular dysfunction and a systolic ejection fraction of 13%. A cardiac biopsy showed active myocarditis (Figure 1A). The myocardial tissue tested negative for parvovirus B19 and herpes simplex virus, but positive for HPeV using a real-time reverse-transcription PCR (RT-PCR) assay that detects all known members of the genus *Parechovirus*.[2] In situ hybridization demonstrated HPeV in cardiac myocytes (Figure 1B). The patient received intravenous immunoglobulin (IVIG) therapy (two doses of 37.5 g and two doses of 40 g) over a period of 3 weeks. During the subsequent 2 months, she regained normal cardiac function and was discharged.

One year later, the patient presented with a subacute onset of dizziness, unsteady gait, declining academic performance, fatigue,

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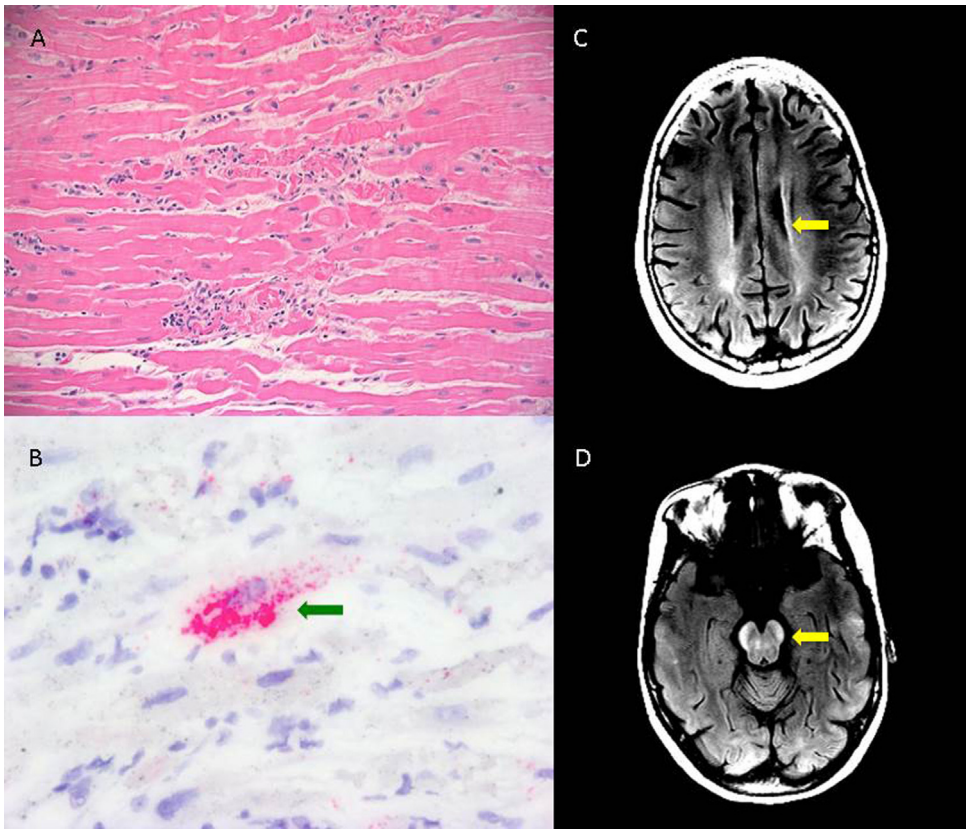

Figure 1. Hematoxylin and eosin staining of the heart showing active myocarditis (A). In situ stain for human parechovirus demonstrating the presence of viral RNA within cardiomyocytes (arrow) (B). MRI showing abnormal bilateral hyperintense signals (arrows) on T2/FLAIR sequences in periventricular white matter (C), and cerebral peduncles (D).

and daily frontal headaches. She was followed as an outpatient for 5 months. When her symptoms progressed to include slowed speech, difficulty performing executive functions, truncal ataxia, and a positive Romberg sign, the patient was admitted to the regional children's hospital. The differential diagnosis for her neurological symptoms was broad. Lupus cerebritis and demyelinating disease were ruled out clinically. Cerebrospinal fluid (CSF) examination demonstrated normal glucose and protein levels with no pleocytosis, and testing was negative for viral pathogens, including adenovirus, astrovirus, norovirus, rotavirus, sapovirus, enterovirus, parvovirus B19, herpes simplex virus, varicella zoster virus, Epstein–Barr virus, JC virus, and West Nile virus. CSF bacterial cultures were also negative. Liver function tests showed a mild elevation in alkaline phosphatase and alanine aminotransferase levels, which were not significant enough to cause hepatic encephalopathy. A serum sample tested positive for HPeV by PCR during week 4 of the hospital admission. The CSF sample from the first day of admission was tested retrospectively for HPeV and was positive, as was a stool sample.

During the first 6 weeks of this admission, the patient's presenting symptoms persisted, and she developed an intention tremor and head tremor. Next, she developed persistent urinary and fecal incontinence. During week 7, the patient developed difficulty swallowing and left-sided neglect. IVIG was administered 4 times (4.3 g, 17.2 g, 17.2 g, and 30.1 g) during weeks 8 and 9, while serum HPeV status was monitored until resolution of viremia. A repeat lumbar puncture was performed, and the CSF tested negative for HPeV. However, the patient continued to worsen clinically, becoming progressively weaker from weeks 8 to 12.

After week 12 of admission, the patient was transferred to our hospital. At the time of transfer, the patient could not move any of her extremities and had bilateral ophthalmoplegia. A brain MRI showed T2/FLAIR signal abnormalities in the periventricular white matter and brainstem (Figures 1C and 1D). The patient was admitted to the neurology intensive care unit and started on high-dose methylprednisolone 1 g intravenously every 6 h. Evaluation by rheumatology concluded her state was not consistent with lupus cerebritis. A paraneoplastic syndrome antibody panel and angiotensin-converting enzyme level were within normal limits. Her neurologic examination improved over the course of 2 weeks. Steroid therapy was changed to prednisone 40 mg/day, tapered to 20 mg/day, and she was discharged to an acute care facility.

Two months following discharge, the patient was re-admitted to the hospital for further neurological evaluation and IVIG treatment. On examination, she was quadriparetic with upper motor neuron examination findings. An echocardiogram showed an ejection fraction of 18%. Brain MRI demonstrated interval progression of the abnormal changes predominantly involving the corticospinal tracts. Analysis of CSF obtained during this admission was positive for HPeV. Complete VP1 gene sequencing (GenBank accession number **KP772256**) of this sample identified the virus as HPeV3, and the VP1 protein sequence was found to contain five unique amino acid substitutions that differ from recent (2009–2014) consensus HPeV3 protein sequences found in GenBank or sequenced at the US Centers for Disease Control and Prevention since 2009.[3] During this admission the patient received a 7-day course (15 g/24 h) of IVIG for a total of 105 g. The patient's motor strength was noted to improve, but her cardiac function did not improve; an echocardiogram prior to discharge demonstrated the ejection fraction was still low (18%). The patient was discharged to an acute care facility where she remained for 7 months and demonstrated gradual improvement in motor function. She has

been at home for 1 month under her mother's care, undergoes physical rehabilitation twice a week, and continues to improve.

3. Discussion

After enterovirus, HPeV is considered the second most common cause of viral meningitis in young children.[4] While not common in adults, severe HPeV infections have been reported in a 35-year-old with an influenza-like illness and a 78-year-old who died of pneumonia.[5,6] Additionally, an outbreak of HPeV1-related acute flaccid paralysis in Jamaica affected six patients of ages 1–27 years.[7] An outbreak of epidemic myalgia among adults (ages 25–66 years) in Japan was shown to be HPeV3-associated in 14 patients.[8] Infections with HPeV including HPeV3 have been described in adults, but HPeV3 infections occur mostly in children under 2 months of age.[9] Of all the HPeV types, HPeV3 has the strongest association with severe neurological illness. Cardiomyopathy and suspected HPeV1 myocarditis has been reported in a 5-month-old boy; however, no case of HPeV3 myocarditis has been documented prior to this report.[10]

The CSF findings, abnormalities on brain MRI, and clinical features in this adolescent with HPeV3 encephalitis are similar to those described in infants and neonates with HPeV3 encephalitis. CSF from this patient showed normal protein and glucose levels with no pleocytosis. Verboon-Maciolek et al. reported CSF pleocytosis in only one of 10 neonatal cases of HPeV3 encephalitis, and all 10 cases showed normal CSF protein and glucose levels.[11] Verboon-Maciolek et al. also reported seizures in nine of 10 infants with HPeV infection. While this patient did not have continuous electroencephalography (EEG) monitoring, episodes of seizure activity were observed.

Most picornaviral infections are controlled through humoral immunity. It is not surprising, therefore, that a patient with hypogammaglobulinemia such as this patient would be particularly susceptible to a severe HPeV3 infection. This patient's improvement after IVIG therapy confirms the utility of this intervention. The demonstration of HPeV RNA in the cytoplasm of cardiomyocytes suggests direct infection of these cells resulting in myocarditis. The resultant cardiac myocyte injury could be caused directly as a consequence of viral replication, indirectly via a cell-mediated immune response, or both. Whereas the myocarditis may represent a degree of cellular immune response, this patient's deficiency of humoral immunity promoted the establishment of a chronic HPeV3 infection with eventual spread to the CNS. The mechanisms of HPeV3-mediated cellular injury in the CNS, however, are currently unknown. Additionally, the high number of five unique amino acid substitutions identified in the VP1 protein of this virus compared to other contemporary HPeV3 strains may be explained by persistence of the virus and prolonged viral replication in this patient over at least 2 years. The clinical significance of these genetic changes on the behavior of this virus is not known, but could include altered sensitivity to IVIG therapy and changes in tissue tropism.

Serious HPeV3-related diseases, including encephalitis and myocarditis, may be more common than currently documented since this virus is not routinely tested for after infancy. This patient was identified as having HPeV primarily because she was initially hospitalized at a children's hospital that routinely screens for HPeV in cases of encephalitis. The differential diagnoses for both encephalitis and myocarditis, especially in immunocompromised patients, regardless of age, should be expanded to include HPeV3 infection. While therapy is extremely limited for HPeV3 infections, identification of these infections would allow for the option to initiate IVIG therapy. Additionally, establishing routine testing for HPeV in adolescent and adult patients with encephalitis and/or myocarditis will provide critical data regarding the true epidemiology of this emerging infection.

Conflict of interest: None.

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