Adult case of acute flaccid paralysis with enterovirus D68 detected in the CSF

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Practical Implications

We describe a specific reverse transcriptase PCR protocol with an enhanced sensitivity and specificity to identify enterovirus D68 in CSF, a methodology that may contribute to the development of a vaccine or treatment for acute flaccid paralysis.

Although once considered rare, incidence of enterovirus D68 (EV-D68) infections has been increasing throughout the 21st century, and is connected to cases of acute flaccid paralysis (AFP),^{1,2} a condition for which there is no established treatment. We report a 28-year-old Japanese woman admitted to our hospital with distal muscular weakness after experiencing upper respiratory symptoms and subsequently diagnosed with AFP.

Case report

A 28-year-old Japanese woman with a history of atopic dermatitis initially presented with low-grade fever and symptoms of upper airway inflammation in September 2015. She was admitted to our hospital 1 week later, after experiencing distal muscular weakness predominantly in the right upper limb. She had no obvious cardiorespiratory or abdominal abnormalities. Flaccid paralysis of the right upper limb was observed, without loss of sensation and in the absence of cranial nerve abnormalities. Blood test values were as follows: white blood cell count, 7,500/ μ L (standard range: 3,600–8,000/ μ L); C-reactive protein levels, 0.2 mg/dL (standard range: <0.3 mg/dL); and creatine kinase levels, 48 IU/L (standard range: 62–287 IU/L). Analysis of CSF revealed a cell count of 59/ μ L (mononuclear leukocytes, 17/ μ L; polymorphonuclear leukocytes, 42/ μ L) and a protein level of 39 mg/dL. We did not detect herpes simplex virus, varicella-zoster virus, poliovirus, or enterovirus 71 in the CSF. Gray matter hyperintensities were observed on T2-weighted cervical MRI, primarily in the right anterior horn at levels C4–7 (figure). Suspecting AFP due to inflammation of the anterior spinal horn, we administered steroid pulse therapy consisting of 1,000 mg/d of methylprednisolone for 3 days. On the fifth day of hospitalization, flaccid paralysis appeared in her upper left limb as well. A second cervical MRI revealed bilateral hyperintensities in the anterior horn. During nerve conduction testing, the right median-ulnar nerves failed to conduct motor neuron action potentials, while severe amplitude reductions were observed in the left median-ulnar nerves. No abnormalities were observed in the lower limbs or sensory nerves. The patient subsequently underwent 2 courses of IV immunoglobulin therapy (400 mg/kg for 5 days). Symptoms of pneumonia appeared after admission, and subsequent hypoxemia was treated with noninvasive positive pressure ventilation for a total of 10 days. EV-D68 was not isolated from CSF, pharyngeal swab, or stool samples (taken 2, 16, and 30 days after admission), and it was not detected in standard genetic testing, e.g., 5'-UTR-PCR. However, it was successfully detected in CSF using an EV-D68-specific real-time reverse transcriptase PCR

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Figure T2-weighted cervical MRI

Gray matter hyperintensities were observed in T2-weighted cervical MRIs, primarily in the right anterior horn at levels C4–7 (arrows) (1.5 T; repetition time 2,500.0 milliseconds, echo time 120.0 milliseconds). B.a is C level 4; B.b is C level 5; B.c is C level 6; and B.d is C level 7.

(RT-PCR) assay.³ This finding led to our diagnosis of AFP due to EV-D68. Six months later, flaccid paralysis in her upper limbs had not improved.

DISCUSSION

Reports of children experiencing severe respiratory insufficiency accompanied by EV-D68 infection appeared in 2014, with AFP observed in some cases.^{1,2} In addition, multiple cases of AFP of unknown origin resembling polio-like paralysis have been reported in Japan since August 2015.⁴ The condition primarily affects children, and the condition is suspected to be connected to EV-D68. After 2014, EV-D68 had been detected in the upper airways in some cases of AFP with accompanying respiratory infection. However, detection of EV-D68 in the CSF was not reported in any of these cases. Before 2014, only 2 reports had described detection of EV-D68 in the CSF.^{5,6} The present case represents the first since 2014 in which it was detected in the CSF of patients experiencing flaccid paralysis accompanied by respiratory infection.

Enterovirus belongs to *Picornaviridae*, a family of viruses that also includes the poliovirus. The mechanism by which poliovirus causes flaccid paralysis depends on the migration of the virus to cells of the anterior horn via retrograde axonal transport. Cases in which EV-D68 has

been detected in the CSF typically present with lymphocyte infiltration into the anterior spinal cord with associated neuronophagia of motor neurons, pathologic findings that resemble those of paralytic poliomyelitis.⁵ AFP due to EV-D68 is thus expected to have a pathologic mechanism similar to that of poliovirus.

Although a 2015 study suggested that the antiviral drug pleconaril may be useful for the treatment of EV-D68,⁷ there is no established treatment for AFP caused by EV-D68 infection. Furthermore, patients sometimes experience serious sequelae, indicating the need to develop a targeted vaccine.

The EV-D68-specific RT-PCR assay used here is considered to be 100 times more sensitive than the EV-D68 RT-PCR assay released by the Centers for Disease Control and Prevention. Furthermore, it does not amplify other enteroviruses, has high specificity, and is highly effective.³ Cases of AFP of unknown origin should be diagnosed after performing EV-D68-specific RT-PCR to ensure accuracy for the benefit of both the patient and future research.

REFERENCES

1. Pastula DM, Aliabadi N, Haynes AK, et al. Acute neurologic illness of unknown etiology in children—Colorado, August–September 2014. *MMWR Morb Mortal Wkly Rep* 2014;2014:901–902.
2. Ayscue P, Haren KV, Sheriff H, et al. Acute flaccid paralysis with anterior myelitis—California, June 2012–June 2014. *MMWR Morb Mortal Wkly Rep* 2014;63:903–906.
3. Wylie TN, Wylie KM, Buller RS, Cannella M, Storch GA. Development and evaluation of an enterovirus D68 real-time reverse transcriptase PCR assay. *J Clin Microbiol* 2015;53:2641–2647.
4. The National Institute of Infectious Diseases (Japanese). Available at: <http://www.nih.go.jp/niid/ja/diseases/a/ev-d68.html>. Accessed March 2, 2016.
5. Kreuter JD, Barnes A, McCarthy JE, et al. A fatal central nervous system enterovirus 68 infection. *Arch Pathol Lab Med* 2011;135:793–796.
6. Khetsuriani N, Lamonte-Fowlkes A, Oberst S, Pallansch MA. Enterovirus surveillance—United States, 1970–2005. *MMWR Surveill Summ* 2006;55:1–20.
7. Liu Y, Sheng J, Fokine A, et al. Structure and inhibition of EV-D68, a virus that causes respiratory illness in children. *Science* 2015;347:71–74.

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AUTHOR CONTRIBUTIONS

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