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Clinical Letter

Cytokine Profile in a Patient With Enterovirus D68-Associated Acute Flaccid Myelitis

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Introduction

Acute flaccid myelitis (AFM) is an uncommon neurological disease with acute polio-like paralysis.[1] Spinal magnetic resonance imaging (MRI) in patients with AFM revealed longitudinal, anterior horn-specific lesions in spinal cord suggestive of anterior myelitis.[1] The frequent occurrence of patients with AFM coincided with enterovirus D68 (EV-D68) outbreaks during 2014 in the United States,[2] or during 2015[3] and 2018 in Japan. The identification of EV-D68 in respiratory specimens from patients with AFM worldwide further supports the association.[1] An experimental model showed paralysis occurred in neonatal mice after EV-D68 infection.[4] However, a causal relationship has not been proved in humans without direct virus isolation from affected tissues, infrequent detection in cerebrospinal fluid (CSF).[1]

Cytokine profiles in CSF suggest whether the inflammation in central nervous system is caused by viral direct invasion,[5] which has not been reported in AFM previously. Here we present a first report about EV-D68–associated AFM with inflammatory cytokine analysis.

Patient Description

This five-year-old Japanese girl with a history of bronchial asthma presented with difficulty in walk after symptoms of respiratory tract infection. She had headache and fever, and felt muscle weakness in a left leg the day before admission. On admission, she was alert, and her temperature was 38.7°C. She had no spontaneous activity in her lower extremities except for the right ankle and was unable to sit. Neurogenic bladder was present. She complained of pain and itching. Examination of CSF demonstrated 277 cells/mm^3, predominantly lymphocytes. Both protein and glucose concentrations were normal. Initial spinal MRI showed slight hyperintensity and enlargement of spinal cord at T11/12-T12/L1 level. Peripheral nerve conduction examination showed loss of the F wave. She was diagnosed with AFM. EV-D68 was detected in a nasopharyngeal sample, but remainders were negative. She was treated with intravenous immunoglobulin and methylprednisolone pulse therapy. The follow-up MRI revealed hyperintensity lesions in T2-weighted and short tau inversion recovery (fat-suppressed) image within spinal cord (Fig). In addition, gadolinium-enhanced images showed newly enhanced lesions in cauda equina. She was discharged on the day 24 without a neurogenic bladder. After

Informed consent was obtained from the parents of the patient. We were given approval to conduct this study by the institutional review board of Yamaguchi University Hospital (No. H30-161).

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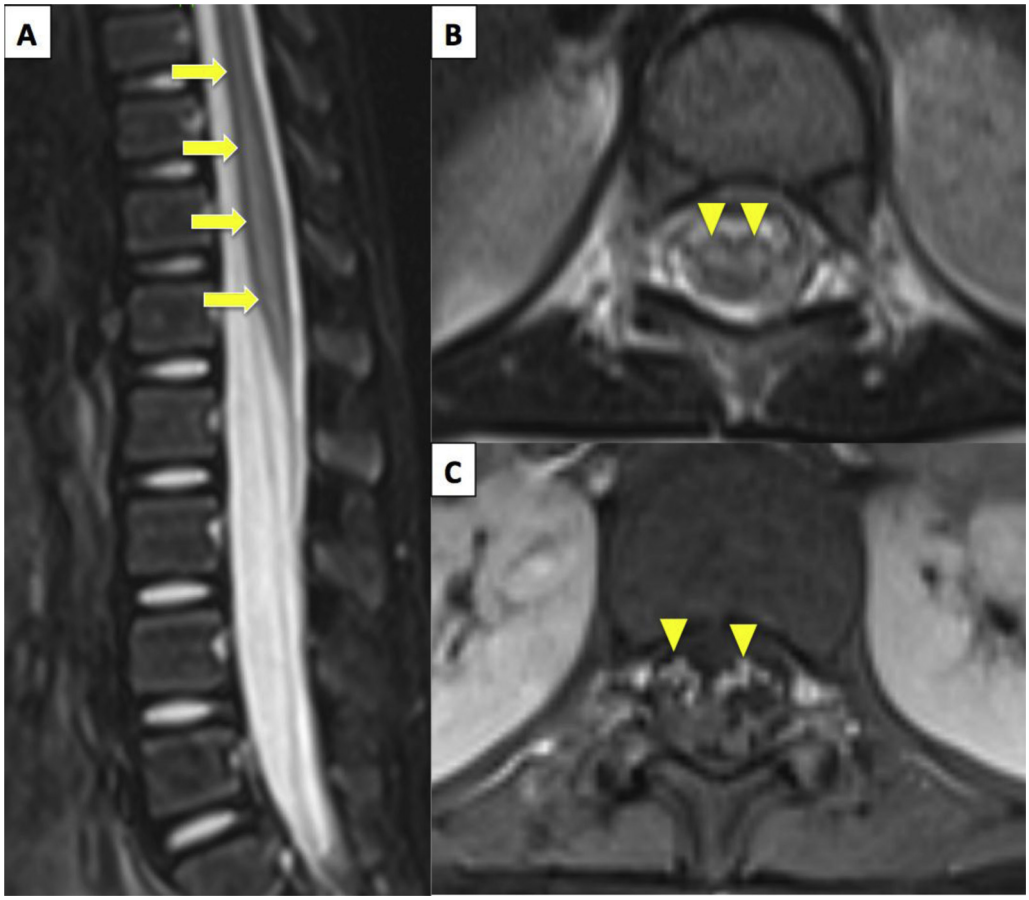

FIGURE. Magnetic resonance image findings on day 22. Sagittal (A) and axial (B) short tau inversion recovery (fat-suppressed) images show hyperintensity and swelling in spinal cord predominantly in anterior horn (arrows, arrowheads). Gadolinium-enhanced T1-weighted image (C) demonstrates enhanced lesions in bilateral anterior roots of cauda equine (arrowheads).

four months, she could sit without support and crawl, but the muscle contractions of her legs were hardly seen.

The serum and CSF cytokine levels, including interferon (IFN)-γ, tumor necrosis factor, interleukin (IL)-2, IL-4, IL-6, and IL-10, were measured by a human cytometric bead array kit (BD PharMingen, San Diego, CA, USA). Although serum cytokine levels were hardly increased, the CSF IL-6 and IFN-γ levels were markedly increased on day 2 of admission, but not others (Table).

Discussion

This report is the first to demonstrate cytokine profiles in EV-D68–associated AFM. EV-D68 was detected in a nasopharyngeal sample, but not CSF, similar to previous reports.[1] However, the CSF IL-6 and IFN-γ levels were markedly increased. IFN-γ plays an important role in host defense against viral infection. It has been reported that CSF IFN-γ levels were increased in central nervous system disorders with direct viral invasion, such as viral meningitis and encephalitis, but not in immune-mediated ones, such as acute disseminated encephalomyelitis.[5] In animal experiments, intramuscular and intracerebral injection of EV-D68 to neonatal mice induced AFM-like paralysis, and EV-D68 was detected from spinal cord.[4] Our findings suggest EV-D68–associated AFM may be caused by direct EV-D68 invasion to spinal cord even if virus was not detected in CSF. It is important for the treatment whether spinal dysfunction is due to direct viral invasion or secondary immune-mediated response. Further studies are necessary to investigate the pathophysiology of EV-D68–associated AFM.

TABLE.
Cytokine Profiles in Serum and CSF (day 2)

	IL-6 (pg/mL)	IL-10 (pg/mL)	IFN-γ (pg/mL)	TNF (pg/mL)	IL-2 (pg/mL)	IL-4 (pg/mL)
Serum (Reference range)	5.8 (<9.5)	10.5 (<6.8)	<7.1 (<21.1)	<2.8 (<3.9)	<2.6 (<3.9)	3.4 (<3.8)
CSF (Reference range)	1043.0 (<6.2)	11.4 (<2.8)	165.7 (<7.1)	<2.8 (<3.5)	3.1 (<2.6)	<2.6 (<6.6)

Abbreviations:
CSF = cerebrospinal fluid
IFN = interferon
IL = interleukin
TNF = tumor necrosis factor
Limit of detection (pg/mL): IL-6, 3.0; IL-10, 2.8; IFN-γ, 7.1; TNF, 2.8; IL-2, 2.6; IL-4, 2.6.

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