

Acute Transverse Myelitis Caused by Echovirus 11 in a Pediatric Patient: Case Report and Review of the Current Literature

Heidi L. Moline, MD¹, Peter I. Karachunski, MD^{1,2}, Anna Strain, PhD³,
 Jayne Griffith, MA, MPH³, Cynthia Kenyon, MPH³, and Mark R. Schleiss, MD¹

Abstract

A 12-year-old boy presented with acute flaccid weakness of the right upper extremity and was found to have acute flaccid myelitis with transverse myelitis involving the cervical cord (C1-T1). An interdisciplinary team-based approach was undertaken, including input from a generalist, an infectious diseases physician, and a pediatric neurologist. Consultation was sought from the Minnesota Department of Health to investigate for a potential etiology and source of the responsible infection. Evaluation for an infectious etiology demonstrated infection with human echovirus 11. The patient recovered with some disability. Echovirus 11 is among the more common etiologies of acute flaccid myelitis and should be considered in the differential diagnosis of this increasingly recognized pediatric infection.

Keywords

encephalitis, epidemiology, magnetic resonance imaging, MRI, pediatric, enterovirus, acute flaccid myelitis, viral meningoencephalitis

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Non-polio enteroviruses can cause a variety of central nervous system infections, including meningoencephalitis, aseptic meningitis, and acute myelitis. Human echovirus 11 frequently causes aseptic meningitis and the clinical syndrome of hand, foot, and mouth disease. Echovirus 11 is increasingly recognized globally as an emerging cause of acute flaccid myelitis in children. The authors present the case of a 12-year-old male with acute flaccid myelitis. Evaluation demonstrated evidence for echovirus 11 infection. The authors review the literature describing the association of echovirus 11 with acute flaccid myelitis.

Case Report

History and Presentation

In September 2014, a 12-year-old boy presented to the University of Minnesota Masonic Children's Hospital emergency department with a recent history of neck pain and progressive weakness of his right arm. His symptoms began 1 week prior to admission when he woke from sleep with neck stiffness. The following day, he experienced nausea with

emesis and was noted to have an oral temperature of 38.6°C. Neck stiffness worsened over the next few days with new-onset intermittent headaches. Upon initial presentation to the emergency department, weakness was noted and he had difficulty turning his head to the left, keeping it upright and raising his right arm. He did not have sensory changes. No other neurological deficits were noted. He had no rash, upper respiratory infection symptoms, joint swelling, sore throat, cough, abdominal pain, or dysuria. In the 6 months prior to the onset of

¹ Department of Pediatrics, University of Minnesota Masonic Children's Hospital, University of Minnesota Medical School, Minneapolis, MN, USA

² Department of Neurology, University of Minnesota Medical School, Minneapolis, MN, USA

³ Epidemiology and Control Division, Infectious Diseases, Minnesota Department of Health, Saint Paul, MN, USA

Corresponding Author:

Mark R. Schleiss, MD, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, University of Minnesota Medical School, 2450 Riverside Ave, Minneapolis, MN 55454, USA.

Email: schleiss@umn.edu



illness, he had been camping in Central Minnesota and had traveled to the United States Virgin Islands and the Amazon rainforest in Ecuador. There was no history of a prior tick bite.

Physical Examination and Evaluation

At the time of hospital admission, vital signs were normal but neurological examination was significant for absent muscle stretch reflexes in his right upper extremity. He had profound weakness in the proximal muscles and milder weakness in the distal muscles of the right upper extremity. Notably, he had less than antigravity strength in shoulder abduction, elbow flexion, and elbow extension and reduced strength ranging 3 to 4 on the Medical Research Council scale for muscle strength in the forearm and intrinsic hand muscles.¹ He had severe weakness in his right sternocleidomastoid muscle resulting in the head drop and tilt to the right. Because of weakness, he used his stronger left hand to turn his head to the left. He had no sensory deficit, long corticospinal tracts signs, or sphincter dysfunction. A complete metabolic profile, an erythrocyte sedimentation rate, and a C-reactive protein were normal. A complete blood count and differential leukocyte count demonstrated that his white blood cell count was normal at $8.2 \times 10^3/\mu\text{L}$. His hemoglobin concentration was 16.1 g/dL, and the lactate dehydrogenase was slightly elevated at 205 U/L. Radiographic studies of the cervical spine were normal. Cerebrospinal fluid (CSF) examination demonstrated a lymphocytic pleocytosis with a white blood cell count of 71/ μL . Magnetic resonance imaging (MRI) findings on the day of admission demonstrated abnormal cervical spinal cord signal, with hyperintensity extending from C1 level to the C7-T1 level, with associated cord expansion noted in sagittal T2-weighted images. Predominant involvement of the gray matter in the spinal cord was also noted in the axial T2-weighted image. These findings were diagnostic for transverse myelitis involving the C1-T1 segments with cord edema and preferential involvement of the gray matter (Figure 1A and B).

Hospital Course, Treatment, and Outcome

In light of these findings, the patient was commenced on acyclovir for possible herpes simplex virus infection and ceftriaxone for possible Lyme disease. He was also treated with high-dose methylprednisolone, 10 mg/kg/d, for a 5-day course. A second MRI, 4 days after admission, showed significant improvement in the hyperintensity of T2 signal and edema (Figure 1C and D). Additional MRI of thoracic spine revealed mild T2 hyperintense signal in the mid and lower thoracic cord, which was prominent in the central location extending from approximately T7 to L1. These findings had no clinical correlate. The patient's motor deficit remained restricted to only his right upper extremity. He was discharged 5 days after admission with recommendations for intensive outpatient physical therapy.

After discharge, he experienced progressive improvement in his right arm function. Upon evaluation 22 months after the

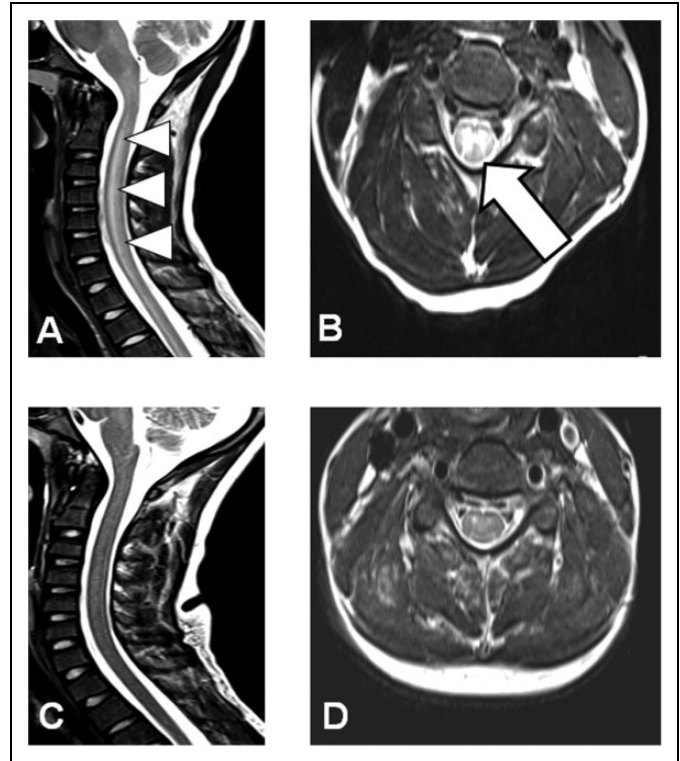


Figure 1. The patient's cervical magnetic resonance imaging (MRI) at admission. There was demonstration of an abnormal cervical spinal cord signal, with hyperintensity (arrowheads) extending from C1 level to C7-T1 level with associated cord expansion as seen in sagittal T2-weighted image (A). Predominant involvement of the gray matter in the spinal cord is also noted (arrow) in the axial T2-weighted image (B). A repeat MRI obtained 4 days after admission demonstrated remarkable evolution and notable improvement, with reduction in cord edema and progression toward resolution of the abnormal T2 signal (panels C and D).

onset of acute flaccid myelitis, he achieved good functional recovery but had significant residual weakness and atrophy, mainly limited to upper cervical segments C1-C5 on the right side evidenced by residual atrophy and weakness in the sternocleidomastoid, trapezius, and muscles innervated by the C5 segment including the deltoid, supraspinatus, infraspinatus, and to a lesser degree the biceps brachii. He recovered completely from deficits in elbow flexion and extension and regained normal strength in distal muscles.

The patient underwent an extensive laboratory investigation to identify an etiology for his acute flaccid myelitis, including HSV1/2 polymerase chain reaction (PCR) and serology, mycoplasma serologies, *neuromyelitis optica* IgG, dsDNA abs, arbovirus IgG/IgM serologies, varicella zoster virus PCR, a respiratory viral panel, antinuclear antibody screen, PPD, CMV, EBV, HHV6, human immunodeficiency virus, California encephalitis IgG, West Nile virus, Lyme IgG/IgM assays of cerebrospinal fluid and serum, and lymphocytic choriomeningitis virus serologies. These tests were all negative. A viral stool culture was, however, positive for enterovirus and preliminarily subtyped at the Minnesota Department of Health as

echovirus 11. The sample was sent to the Centers for Disease Control and Prevention (CDC) for additional testing, which confirmed that the virus was echovirus 11.

Discussion

Acute flaccid myelitis cases are characterized by acute flaccid limb weakness with evidence on imaging studies of spinal cord gray matter lesions or spinal cord motor neuron injury on electrodiagnostic testing.² Although some individuals demonstrate improvement in motor weakness and functional deficits, most have residual weakness a year or more after onset. As wild-type poliovirus has been reduced to a handful of countries, acute flaccid paralysis in children is increasingly attributed to other members of the enterovirus family.³ A large number of non-polio enteroviruses, including coxsackie A/B, echoviruses, and enteroviruses D68 and 71, have been associated with limb paralysis in children in the setting of acute flaccid myelitis. It has also been postulated that a novel enterovirus, such as enterovirus C105, may be responsible for some cases, although this requires additional investigation.⁴ During the fall of 2014, there was a notable increase in acute flaccid myelitis cases among children, which correlated with increased recognition of infections caused by enterovirus D68. In an investigation of 59 cases of acute flaccid myelitis in California,⁵ enterovirus D68 was isolated from respiratory secretions, serum samples, or stool specimens in 9 patients, although no patient had this virus identified in cerebrospinal fluid. In a nationwide surveillance study conducted by the CDC from 2014 to 2016, 120 acute flaccid myelitis cases (reported from 34 states) were examined. Most patients experienced respiratory symptoms and/or fever before the onset of limb weakness. Although enterovirus D68 was isolated from 20% of cases, only 1 child had confirmed central nervous system infection.⁶ Thus, the 2014 to 2016 outbreak in acute flaccid myelitis remains incompletely characterized.

The patient described in this case report had echovirus 11 infection as the likely etiology of his acute flaccid myelitis. Echovirus 11, a member of the *Enterovirus B* species group of the *Picornaviridae*, is commonly encountered in clinical practice and was reported in 1 review to be the most prevalent enterovirus in the United States from 1970 to 1983.⁷ Viruses within the enterovirus family preferentially target the motor neurons in the cranial nerve nuclei and anterior horns of the spinal cord, causing acute paralysis with sensory sparing—as was seen in the patient described in this report. Symptoms typically peak between 10 days and 4 weeks from symptom onset, with variable resolution. Echovirus 11 is commonly associated with hand, foot, and mouth disease⁸ and with congenital and perinatal infections, some of which are life-threatening depending upon the timing of maternal acquisition.^{9–11} Hand, foot, and mouth disease, meningoencephalitis, and in some cases, paralytic disease have also been described secondary to echovirus 11 infections occurring outside of the neonatal period.^{12–14}

Review of the literature supports a major role for echovirus 11 as an etiology of acute flaccid myelitis. Echovirus 11 is commonly isolated in viral stool cultures obtained from patients with acute flaccid myelitis.^{15–17} In a comparative study of fecal isolates from patients with acute flaccid myelitis, echovirus 11 was second only to coxsackie B virus among patients found to be shedding virus.¹⁵ The molecular basis of echovirus 11 pathogenesis is not understood. Echovirus 11 appears to be highly prone to recombination with other members of the *Enterovirus B* species group,¹⁸ which could contribute to emergence of more pathogenic disease-causing viral variants. The echovirus 11 VP1 protein also lacks the arginyl-glycyl-aspartic acid motif at the carboxyl terminus that serves as a critical component of the ligand for the cellular receptor used by related *Picornaviridae*, including coxsackieviruses.¹⁹ What role, if any, this molecular difference plays in pathogenesis is unknown.

Treatment of acute flaccid myelitis is limited to mitigation of inflammation, typically through the use of glucocorticosteroids and supportive care. Intravenous immunoglobulin has been employed as a therapy for acute flaccid myelitis. It is not clear whether the hypothesized benefit of intravenous immunoglobulin is related to neutralization of the causative virus, or through an immunomodulatory function. Commercial lots of intravenous immunoglobulin in the United States contain substantial neutralizing antibody titers to echovirus 11.²⁰ The experimental antiviral agent, pleconaril, has activity against many echoviruses in vitro, including echovirus 11,⁷ but antiviral resistance has also been observed,^{21,22} and the drug is not yet licensed for clinical use.

Conclusion

In summary, the patient described in this report met the CDC case definition for acute flaccid myelitis with acute onset of focal limb weakness, and an MRI demonstrating a spinal cord lesion largely restricted to gray matter, spanning the entire cervical and thoracic spine. There was a remarkable clinico-imaging dissociation in this patient, with relatively restricted clinical involvement as described above in spite of widespread changes detected by MRI. Care of the pediatric patient with acute flaccid myelitis often requires a multidisciplinary approach, including an infectious diseases physician, neurologist, physical, occupational, and speech therapists, and an orthotist in many cases. In addition, consultation with state health departments can be valuable in the investigation of infectious etiology and possible outbreaks.

Author Contributions

HLM drafted the manuscript. PIK, AS, JG, CK, and MRS critically revised the manuscript. All authors reviewed and approved the final submission.

Declaration of Conflicting Interests

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Ethical Approval

This case is presented with the express permission and authorization of the patient's family, in compliance with University of Minnesota Institutional Review Board policy.

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