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Acute flaccid paralysis in a child infected with enterovirus D68: A case report

A broad range of tests for viral, bacterial, and autoimmune causes was undertaken when a 9-year-old presented with polio-like symptoms.

ABSTRACT: Enterovirus D68 is increasingly being reported as a cause of severe respiratory illness across North America, with several children in Canada testing positive for this virus and experiencing concurrent polio-like symptoms. In one recent case in British Columbia, a 9-year-old patient presented with acute flaccid paralysis of his left arm following a respiratory illness and fever. Enterovirus D68 was eventually isolated in a nasopharyngeal specimen and the patient was treated with intravenous immunoglobulin. To date the patient has experienced only slight improvement in his left arm function. This case illustrates the importance of appropriate screening for polio and nonpolio enteroviruses. Clinicians faced with a case of acute flaccid paralysis should contact their regional health authority or the BC Centre for Disease Control for early guidance on how to collect specimens for testing. While there is no established treatment protocol for enterovirus D68 infection, we do know that hand washing and avoiding close contact with ill people can prevent transmission.

Enterovirus D68 (EV-D68) is increasingly being reported as a cause of severe respiratory illness across North America.[1] Members of the Picornaviridae family, enteroviruses (EVs) are nonenveloped, single-stranded RNA viruses that have traditionally been classified as polioviruses, coxsackieviruses A, coxsackieviruses B, and echoviruses E.[2] Recently, human enteroviruses have been subdivided into four species—enterovirus A, B, C, and D—of which there are more than 100 serotypes.[3]

Transmission of EVs is by the fecal-oral route, respiratory secretions, or close contact with infected people.[4] Peak EV transmission occurs in the summer and fall in temperate climates.[4] Nonpolio EV infections are largely asymptomatic, but can result in a range of diseases, including respiratory illnesses and central nervous system infections.[5] Specifically, nonpolio EVs have increasingly been reported in association with acute flaccid paralysis (AFP) in immunocompetent North American children.[5,6]

Like poliovirus, enterovirus A71 (EV-A71) and others are known to cause AFP, which results from inflammation and destruction of the anterior horn cells of the spinal cord.[7] AFP is nearly always asymmetric, affects proximal more than distal muscle groups, progresses over 2 to 3 days, and is associated with neck or back pain.[7] There is reduced muscle tone and weakness, but typically sensation is unaffected. EV-D68, which primarily causes respiratory infections, is another serotype that may cause AFP.[5,6,8] EV-D68 was first identified in California in 1962 and appears to be relatively uncommon.[9] However,

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because EV-D68 is not reportable in North America, the incidence of infection may be underestimated.[5] During an outbreak of EV-D68-related respiratory illness between 2008 and 2010 in Asia, Europe, and the United States,[9] a previously healthy 5-year-old presented with a fatal case of fever, pneumonia, and AFP.[10] In that case, examination of the cerebrospinal fluid (CSF) revealed aseptic meningitis, and EV-D68 was detected by PCR.[10] A second case of EV-D68 associated with AFP was then identified through nationwide surveillance.[11]

Between 2012 and 2014, 23 cases of AFP were identified in California with no definitive cause identified, although respiratory specimens for two of the children tested positive for EV-D68.[5] In September 2014, EV-D68 was detected in the respiratory specimens of several children with concurrent AFP in Canada and the US.[5,6] While the full spectrum of EV-D68 infections and any causal relationship with AFP have not been fully established, the medical community needs to be aware that acute flaccid paralysis can be associated with this enterovirus infection, as illustrated by a case of AFP in a child with EV-D68 infection in British Columbia.

Case data

A previously healthy, fully immunized 9-year-old boy presented to BC Children's Hospital with sudden-onset left arm weakness and inability to move his left arm in the morning. He had an upper respiratory illness that had begun 5 days earlier with fever, cough, rhinorrhea, and post-tussive emesis. He had had headaches for 2 days accompanied by neck and left shoulder pain. His history was significant for travel to the south Atlantic region of the US 1 month earlier. Family members had similar cold-like symptoms around the same time. There was no history of contact with sick individuals, insect bites, recent vaccination, toxin exposures, animal exposures, trauma, rash, visual disturbance, dysphagia, or bowel or bladder dysfunction. Earlier in childhood he had received four doses of inactivated poliovirus vaccine according to the schedule recommended in BC and had not traveled outside of North America, making poliovirus infection unlikely. His family history was negative for childhood cancer, immunodeficiency, or vascular disease.

Physical examination of the patient revealed a temperature of 38.3°C with a heart rate of 131, a respiratory rate of 12, oxygen saturation of 98%, and blood pressure of 128 mm Hg over 82 mm Hg. He appeared anxious but alert. While he had a full range of motion in his neck and back, and no evidence of meningmus, he did have tenderness along the cervical vertebrae. The results of a cranial nerve examination, including fundoscopy, were normal. He had normal right arm and bilateral leg strength. Other than slight left thumb abduction, he had no strength (0/5) in his left arm (deltoid, biceps, triceps, wrist, and intrinsic muscles). The left arm was hypotonic and areflexic. Sensation was difficult to assess, but was judged to be grossly normal to all modalities. The patient was slightly unsteady during the tandem gait test. The results from the remainder of his physical examination were normal, with no significant respiratory, cardiovascular, or skin findings.

Results from a complete blood count were normal, with the exception of a slightly elevated neutrophil count. Serum electrolytes, coagulation factors, liver enzymes, C-reactive protein, chest X-ray, and CT of the head without contrast revealed no abnormalities. CSF examination showed red blood cells in the CSF (117×10^6/L) and mild pleocytosis (88×10^6/L; neutrophils 41% and lymphocytes 44%), normal glucose, and elevated protein (0.5 g/L).

Intravenous vancomycin, cefotaxime, and acyclovir were started. An MRI of the spine revealed asymmetric, fusiform swelling of the cervical cord between the second cervical vertebra (C2) and the upper border of the first thoracic vertebra (T1), with left-sided predominance **Figure 1**. There was T2/FLAIR hyperintensity in the C2 to T1 region **Figure 2**. There was no distal intraspinal abnormality noted, and the brain appeared normal, other than for a single subtle hyperintense focus in the left posterior pons of uncertain significance.

Nucleic acid testing of a nasopharyngeal swab was positive for enterovirus, which was subsequently typed as EV-D68 by sequencing . The specimen was negative for rhinovirus, influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, adenovirus, coronavirus, and mycoplasma. CSF cultures were also negative and all antimicrobials were discontinued after 48 hours. Serology results were negative for herpes simplex virus (HSV) 1 and 2, syphilis, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Results were negative for *Mycoplasma pneumoniae* IgG antibodies, but positive for *M. pneumoniae* IgM antibodies. PCR testing of CSF was negative for enterovirus, HSV, CMV, EBV, and human herpes virus 6. There were no oligoclonal bands in the CSF and antibodies for neuromyelitis optica were negative.

One day after admission, the child developed mild weakness in his right shoulder and neck flexors (–4/5). Nerve conduction tests in the right arm and neck found no abnormalities, in contrast to studies of the left arm, which showed motor nerve conduction was absent despite normal sen-

sory nerve function. The child defervesced by day 2 of admission and his headaches decreased in intensity. He received two courses of intravenous immunoglobulin (IVIG) at 1 g/kg/d starting on day 3 of admission, which did not result in any improvement in motor function of the left arm.

Unfortunately, to date the patient has not recovered left arm motor function. This finding is similar to other cases of polio-like illness that have shown poor to no recovery of motor function despite aggressive initial treatments with pulse steroids, IVIG, plasma exchange, or all three.[8] At the patient's most recent follow-up appointment, 7 weeks after discharge, there was slight improvement of the left arm function with grade 3 extension, but the left arm continued to be hypotonic and areflexic. Subtle right arm and neck weakness had resolved.

Discussion

Since the eradication of wild-type poliovirus from most areas through successful vaccination programs, acute flaccid paralysis has become rare.[8] The last case of paralytic poliomyelitis in North America was in 1979.[5] Currently, wild-type poliovirus is only endemic in Afghanistan, Nigeria, and Pakistan, but there have been cases of transmission to other countries that previously were polio-free.[12] Vaccine-associated AFP can occur with the oral (live) poliovirus vaccine, which has not been used in North America since 2000.[5] Around the world, AFP now occurs at a rate of approximately 1 case per 100 000 children under age 15.[8]

The US Centers for Disease Control and Prevention (CDC) recommends testing for poliovirus in all cases of AFP of unknown cause or suspected viral origin.[5] For highest yield, CDC guidelines recommend collecting specimens within 14 days of symptom onset and before administration of IVIG.[5] Specimens include two stool samples collected more than 24 hours apart, CSF, acute-phase serum, and nasopharyngeal and throat swabs. Unfortunately, EVs can be difficult to isolate even when appropriate specimens are obtained during acute illness.

The differential diagnosis for acute flaccid paralysis in a child can include both upper and lower motor neuron pathologies, as both may present acutely with flaccid paralysis.[13] Upper motor neuron causes of AFP include stroke, postictal paresis, and spinal cord pathologies related to trauma, abscess, tumor/paraneoplastic syndromes, or inflammatory processes such as transverse myelitis.[13] Lower motor neuron causes include diseases that affect the anterior horn cells, peripheral nerve, neuromuscular junction, and muscle. Lower motor neuron disorders that cause AFP include infections (bacterial or viral), postinfectious autoimmune conditions (for example, Guillain Barré syndrome), brachial plexus injury/trauma, toxins (for example, botulinum), and neoplasms.[13] The potential viral causes of motor neuron disease include poliovirus, nonpolio EVs, flaviviruses (for example, West Nile virus, tick-borne encephalitis), HSV, and rabies.[3] Bacterial causes include *Borrelia burgdorferi*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, and *Mycoplasma pneumoniae*.[3]

From the broad range of tests for viruses, bacteria, and autoimmune conditions done for our patient, the only abnormalities found were CSF pleocytosis, EV-D68 in the nasopharynx, and *M. pneumoniae* IgM antibodies in the patient's blood. *M. pneumoniae* infection is associated with a number of uncommon central nervous system manifestations, such as transverse myelitis and acute disseminated encephalomyelitis, that primarily affect white matter.[14] To our knowledge, however, AFP is not a recognized complication of *M. pneumoniae* infection. Furthermore, *M. pneumoniae* serology is not specific for acute infection,[15] and the PCR assay of the nasopharyngeal specimen was negative for *mycoplasma*. We therefore conclude that it is unlikely

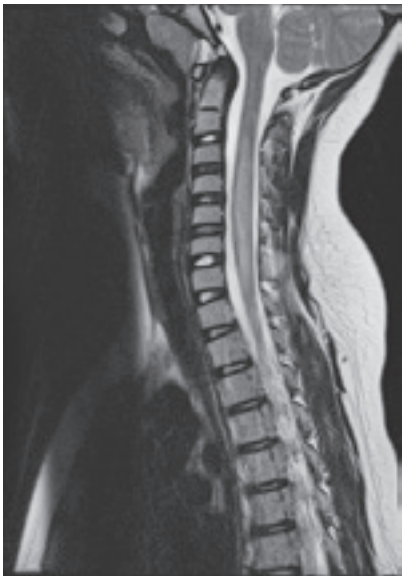

Figure 1. MRI T2-weighted coronal view of patient's spine showing asymmetric T2/FLAIR hyperintensity in cervical cord between C2 and T1, with left-sided predominance.

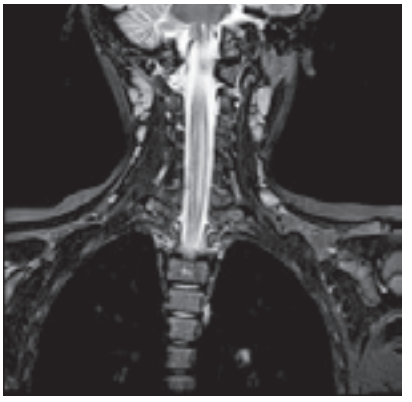

Figure 2. MRI T2-weighted sagittal view of cervicothoracic region revealing T2/FLAIR hyperintensity in the cervical cord between C2 and T1.

our patient's syndrome was attributable to *M. pneumoniae* infection.

It is not possible to prove that EV-D68 was the cause of acute flaccid paralysis in this case. Although detection of an enterovirus in the cerebrospinal fluid of a patient with AFP is definitive, PCR results are typically negative even in acute poliomyelitis.[8] Our patient's gender, age, and presentation resembled those of 23 AFP cases in California (June 2102 to June 2014), where males with a median age of 10 years were more frequently affected, and the patients had an upper respiratory illness less than 10 days prior to onset of AFP and there was CSF pleocytosis and an absence of sensory findings.[5] Similarly, there have been nine recent cases of AFP in Colorado presenting 3 to 16 days following the onset of a febrile respiratory illness.[6] Four of the patients were found to have EV-D68 in their nasopharyngeal specimens.

The lesson from this case for clinicians is that patients with AFP of uncertain cause must be screened appropriately for polio and nonpolio enteroviruses. In particular, EV testing should be considered when there is inflammation of the spinal cord that mostly involves gray matter, and there are polio-like symptoms (weakness with lack of sensory involvement). Most importantly, clinicians should remember that association does not prove causation, and thus more data are needed to confirm the relationship between EV-D68 and the neurological symptoms seen in some cases. The regional health authority and the BC Centre for Disease Control should be contacted early for guidance on collecting specimens when patients present with possible enterovirus infection. As yet there is no established treatment protocol. Preventive measures include hand washing and avoiding contact with ill people.

Summary

A recent case in British Columbia illustrates the importance of appropriate screening for polio and nonpolio enteroviruses. When a patient presented recently with acute flaccid paralysis of his left arm following a respiratory illness and fever, clinicians conducted a physical examination and collected samples for various laboratory investigations. Enterovirus D68 was eventually identified in a nasopharyngeal specimen and the patient was treated with intravenous immunoglobulin. Clinicians should be aware of the association between enterovirus infection and acute flaccid paralysis, and should contact their regional health authority or the BC Centre for Disease Control for early guidance on collecting specimens for testing.

Competing interests

None declared.

References

1. Owens B. Rare enterovirus continues to circulate in North America. Lancet 2014;384(9950):1250. Accessed 2 November 2014. http://dx.doi.org/10.1016/S0140-6736(14)61753-0.
2. Pallansch M, Roos R. Enteroviruses: Polioviruses, coxsackieviruses, echoviruses, and newer enteroviruses. In: Fields virology. 5th ed. Knipe D, Griffin D, Lamb R, et al. (eds). Philadelphia: Lippincott Williams & Wilkins; 2008.
3. Laxmivandana R, Yergolkar P, Gopalkrishna V, et al. Characterization of the nonpolio enterovirus infections associated with acute flaccid paralysis in South-Western India. PLoS One 2013;8:e61650.
4. Non-Polio Enterovirus Infection: Enterovirus D68-Centers for Disease Control and Prevention. Enterovirus D68. Accessed 3 November 2014. www.cdc.gov/non-polio-enterovirus/about/ev-d68.html.
5. Ayscue P, Haren K Van, Sheriff H, et al. Acute flaccid paralysis with anterior myelitis—California, June 2012-June 2014. MMWR Morb Mortal Wkly Rep 2014;63:903-906.
6. 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;63:901-902.
7. Solomon T, Lewthwaite P, Perera D, et al. Virology, epidemiology, pathogenesis, and control of enterovirus 71. Lancet Infect Dis 2010;10:778-790.
8. Rukovets O. News from the AAN annual meeting. Unexplained polio-like illness in California: What neurologists should know. Neurology Today 2014;14:58-59.
9. Centers for Disease Control and Prevention. Clusters of acute respiratory illness associated with human enterovirus 68—Asia, Europe, and United States, 2008-2010. MMWR Morb Mortal Wkly Rep 2011;60:1301-1304.
10. Kreuter JD, Barnes A, Mccarthy JE, et al. A fatal central nervous system enterovirus 68 infection Arch Pathol Lab Med 2011;135:793-796.
11. CDC Khetsuriani N, Lamonte-Fowlkes A, Oberst S, et al.; Centers for Disease Control and Prevention. Enterovirus surveilance—United States, 1970-2005. MMWR Surveill Summ 2006;55:1-20.
12. Moturi EK, Porter KA, Wassilak SGF, et al. Progress toward polio eradication—worldwide, 2013-2014. MMWR Morb Mortal Wkly Rep 2014;63:468-472.
13. Tsarouhas N, Decker JM. Weakness. In: Textbook of pediatric emergency medicine. 6th ed. Fleisher GR, Ludwig S (eds). Philadelphia: Lippincott Williams & Wilkins; 2010.
14. Narita M. Pathogenesis of neurologic manifestations of Mycoplasma pneumoniae infection. Pediatr Neurol 2009; 41:159-166.
15. Spuesens EB, Fraaij PL, Visser EG, et al. Carriage of Mycoplasma pneumoniae in the upper respiratory tract of symptomatic and asymptomatic children: An observational study. PLoS Med 2013; 10:e1001444. BCMJ