Published in final edited form as:

Ann Neurol. 2016 September ; 80(3): 326–338. doi:10.1002/ana.24730.

Acute Flaccid Myelitis: A Clinical Review of US Cases 2012–2015

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Abstract

This review highlights clinical features of the increasing cases of acute flaccid paralysis associated with anterior myelitis noted in the United States from 2012 to 2015. Acute flaccid myelitis refers to acute flaccid limb weakness with spinal cord gray matter lesions on imaging or evidence of spinal cord motor neuron injury on electrodiagnostic testing. Although some individuals demonstrated improvement in motor weakness and functional deficits, most have residual weakness a year or more after onset. Epidemiological evidence and biological plausibility support an association between enterovirus D68 and the recent increase in acute flaccid myelitis cases in the United States.

From 2012 to 2015, increasing reports of a distinct syndrome of acute flaccid paralysis with anterior myelitis were noted in the United States, prompting increased surveillance.^{1,2} Previously, the terms “poliomyelitis” or ‘polio-like syndrome’ were used to refer to this

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Author Contributions

K.M. and S.R.D. conducted the literature search and wrote the first draft of the manuscript. K.M. and K.V.H. contributed images and figures. All authors (K.M., T.L.S., K.V.H., M.Y., C.A.G., K.L.T., and S.R.D.) provided expertise on their clinical experience with acute flaccid myelitis patients and significantly contributed to and critically reviewed the manuscript.

Potential Conflicts of Interest

Nothing to report.

clinical presentation. In order to avoid confusion with disease caused by poliovirus, the terms “acute flaccid paralysis with anterior myelitis” and eventually “acute flaccid myelitis” (AFM) were coined to refer to cases of acute flaccid weakness with spinal cord gray matter lesions on imaging or evidence of spinal cord motor neuron injury on electrodiagnostic testing.^{1,3} The term AFM will be used throughout this review for consistency.

This review focuses on clinical features of the recent increase in AFM cases in the United States from 2012 to 2015. In this review, we provide a detailed description of published AFM cohorts in the United States from California, Colorado, and Utah, as well as epidemiological data from the Centers for Disease Control and Prevention (CDC) nation-wide surveillance and international case reports. We review the epidemiology, clinical characteristics, diagnostic testing, and therapeutic recommendations for AFM. We highlight distinguishing features that can be used to differentiate AFM from other known neurological causes of paralysis and compare the recently reported AFM cases to other infectious acute flaccid paralysis syndromes. Last, we weigh the evidence for and against the association of the recent increase in cases of AFM with enterovirus D68 and suggest areas for future research.

Search Strategy and Selection Criteria

Primary references for this review were identified by searches of PubMed using the search terms “acute flaccid myelitis”, “acute flaccid paralysis”, “anterior myelitis”, “poliomyelitis”, and “polio-like” restricted to relevant articles published between January 1, 2012 and July 1, 2016 in the English language. All reports referring to cases of acute flaccid paralysis with spinal cord gray matter lesions on imaging or evidence of spinal cord motor neuron injury on electrodiagnostic testing in the United States were reviewed. Cases meeting criteria for other acute flaccid paralysis syndromes were excluded. We included reports from the CDC national investigation of limb weakness and interim considerations for clinical management.^{4,5}

Review

Case Series and Case Definitions

In the fall of 2012, the California Department of Public Health (CDPH) received three reports of cases of unexplained sudden paralysis; in 2 cases, poliovirus testing was requested. In response, the CDPH initiated enhanced state-wide surveillance in California for cases meeting a definition of acute-onset flaccid limb weakness with spinal gray matter lesion on magnetic resonance imaging (MRI) or electrodiagnostic studies consistent with anterior horn cell damage. From June 1, 2012 to July 31, 2015, 59 reported cases met the CDPH case definition.⁶

In August 2014, a cluster of children with a similar neurological syndrome presented to Children’s Hospital Colorado (CHCO) in Aurora, Colorado, in the midst of an outbreak of enterovirus D68 respiratory disease.² A case definition of any patient presenting to CHCO with acute-onset focal limb weakness and/or cranial nerve dysfunction associated with MRI findings of predominantly gray matter lesions in the spinal cord and/or brainstem was used

to identify children with this syndrome. From August to October of 2014, 12 children met the case definition.⁷

In response to the CDPH and CHCO reports, the CDC established a case definition for enhanced nationwide surveillance of AFM, which included individuals less than 21 years of age with acute flaccid limb weakness and MRI involvement of predominantly the gray matter of the spinal cord without identified etiology presenting after August 1, 2014. Between August and December of 2014, 120 children from 34 US states met the criteria.⁸ Ten children meeting the CDC AFM case definition and 1 additional child with cranial nerve dysfunction presenting to Primary Children's Hospital (PCH) in Utah during the 2014 enterovirus D68 outbreak were subsequently reported.¹⁰ Tables 1 and 2 summarize clinical characteristics of the CDPH, CHCO, and PCH cohorts of AFM described above, as well as nation-wide CDC epidemiological data. Of note, CDC nation-wide epidemiological data include 24 CDPH, 9 CHCO, and 10 PCH cases. Following reports of the public health investigation of AFM cases associated with enterovirus D68 in the United States, cases of acute flaccid paralysis associated with enterovirus D68 have been reported from Canada,^{11,12} France,¹³ Norway,¹⁴ and Great Britain^{15,16} (Supplementary Table).

Epidemiology

AFM predominantly affected older children (median age: 7.1 years) with a slight male predominance. Despite a wide age range (5 months–73 years) reported from CDPH surveillance (which did not include age restrictions in the case definition), only 9 patients (15%) were over 21 years of age.⁶ There were no identified ethnic or racial predispositions. The majority of affected patients were previously healthy, with asthma being the most commonly identified underlying illness.^{3,6–8,10} Six immunocompromised patients with AFM, including 2 with solid organ transplantation (cardiac, renal), 1 with chronic lymphocytic leukemia, 1 with acquired immune deficiency syndrome, 1 with diabetes mellitus type 1, and 1 on pharmacological immunosuppression with systemic lupus erythematosus, have been reported.^{6–8,17} Of 37 cases with vaccine status reported from the CDPH, CHCO, and PCH cohorts, 34 (92%) had received all recommended vaccines and 3 (8%) were unvaccinated because of personal belief exemptions.^{1,7,10} No common-source environmental exposures or common travel risk factors were identified.

Clinical Characteristics

A prodromal, often febrile, illness preceded the onset of neurological deficits in most patients by a median of 5 days (Fig 1).^{6–8,10} Respiratory symptoms of rhinorrhea, cough, or pharyngitis were most commonly reported, often with sick contacts in the household with similar symptoms.^{6–8} Gastrointestinal symptoms of vomiting or diarrhea were reported in 64% of patients from CDPH surveillance.⁶ Most patients reported clinical improvement in their preceding illness before return of fever accompanied by headaches, stiff neck, or pain in the neck, back, or affected limb around the time of neurological deficit onset.^{6,7}

Timing, quality, and pattern of limb weakness in AFM were consistent with acute lower motor neuron disease. Patients reported rapid progression from full strength to neurological nadir over a period of hours to a few days, with a median of 4 days in the PCH cohort.^{6,10}

Weakness was uniformly flaccid, in accord with the case definitions, and associated with decreased or absent reflexes.^{6–8} Severity of reported weakness ranged from complete paralysis (0/5 strength, Medical Research Council grade¹⁸) to mild weakness (4/5 strength).^{6,7} Distribution of affected limbs ranged from one to all four extremities and was typically asymmetric.^{6–8,10} Upper extremities were most commonly affected, with proximal muscle groups in the C5 to C6 distribution more profoundly affected than distal muscle groups in the C8 to T1 distribution.^{6–8,10} In the CHCO and PCH cohorts, sensation was intact in all patients.^{7,10} In contrast, CDC surveillance reported numbness in affected limbs in 24% of patients and CDPH surveillance reported that 44% of patients had sensory deficits: 31% with pain/temperature deficits and 22% with fine touch/vibration deficits.^{6,8}

Cranial nerve dysfunction often accompanied limb weakness, suggesting a tropism for motor neurons common to the anterior horn of the gray matter of the spinal cord and the cranial nerve motor nuclei of the brainstem. Though not included in the case definition, cranial nerve dysfunction was noted commonly among AFM cases from CDPH and CDC surveillance.^{6,8} In the CHCO and PCH clusters, 3 children had cranial nerve dysfunction without the associated limb weakness required to meet CDC AFM case definition.^{7,10} Hypophonia, dysarthria, and dysphagia consistent with CN IX and X dysfunction; diplopia attributed to cranial nerve VI dysfunction; and facial weakness attributed to cranial nerve VII dysfunction were most common.^{7,8} Seizures were reported in 4% of AFM cases from CDC surveillance. Altered mental status was absent in the CHCO cohort, but present in 22% of CDPH cases and 11% of CDC cases.^{6,8} Bowel or bladder dysfunction was present in 18% of the PCH and 51% of the CDPH cohorts, but absent in the CHCO cohort.^{6,10}

Diagnostic Studies

Most patients had a mild-to-moderate cerebrospinal fluid pleocytosis (median, 44 white blood cells [WBCs]/ μ l) on initial lumbar puncture, with lymphocytic predominance in the majority of cases.^{6–8,10} Cerebrospinal fluid (CSF) protein was mildly elevated (median, 43 mg/dL) at presentation in most cases.^{6–8} CSF glucose was normal in all except 3 reported CDC cases.^{6–8} Oligoclonal bands and anti-aquaporin 4 antibodies were negative in tested patients.^{6,7}

MRI of the brain and spinal cord demonstrated lesions suggestive of spinal motor neuron injury, which correlated with neurological deficits found on exam (Fig 2). Lesions were primarily nonenhancing with gadolinium contrast and were best observed on T2 and fluid-attenuated inversion recovery series.¹⁹ Within days of onset of neurological illness, poorly defined signal abnormality was found throughout the gray matter of the spinal cord in many cases, sometimes accompanied by cord edema.¹⁹ Over the following days to weeks of weakness, the signal abnormalities became more well defined within the anterior horn cell region.¹⁹ After weeks to months, most spinal cord lesions resolved and nerve root enhancement not initially present on early imaging became apparent in some cases.^{6,10,19} Spinal cord gray matter lesions were confluent and longitudinally extensive (median, 10–17 vertebral levels in the PCH and CHCO cohorts; 90% spanning at least three vertebral levels in the CDPH cohort).^{6,7} The cervical region (C2–C8) was most commonly affected,

followed by the upper thoracic region (T1–T3), though lesions from brainstem to conus medullaris were noted.^{6–8}

Brainstem lesions in the cranial nerve motor nuclei correlated with cranial nerve dysfunction on exam. Lesions were most common within the pons (specifically the dorsal pontine tegmentum and ventral pons), followed by the medulla, midbrain, and dentate nuclei of the cerebellum.¹⁹ Supratentorial lesions were absent in the CHCO and PCH cohorts, but found in 11% of CDC surveillance and 31% of the CDPH cohort, predominantly in the cortical and subcortical (thalamus, caudate) gray matter.^{6,8,10,19}

Electrodiagnostic studies demonstrated a motor neuropathy or neuronopathy with no sensory abnormalities on nerve conduction studies of affected limbs.^{6,7,20} Consistent with neuroimaging findings, electrophysiological changes were most commonly observed in the C5 to C7 levels in the upper extremity. Electromyographical changes were also observed in muscle groups and limbs that were clinically unaffected. Motor nerve conduction studies variably demonstrated reduced response amplitudes of compound muscle action potentials within the first 3 weeks and were consistently demonstrated after 3 weeks.⁶ Reduced recruitment of motor unit potentials were observed within the first week and persisted.⁶ Fibrillation potentials were not detected in the first week, but appeared in the following weeks and persisted.⁶ After the first 3 weeks, most patients with AFM had low response amplitudes of compound muscle action potentials, reduced recruitment of motor unit potentials, and fibrillation potentials, which persisted for months.⁶ In studies performed within a month of symptoms, low response amplitudes of compound muscle action potentials, severe ongoing denervation, and severe reduction in recruitment motor unit potentials appeared to be associated with a poor prognosis for recovery of muscle strength (unpublished observation). Electromyographic changes persisted over a year after onset in some cases.⁶

Management

Immunomodulatory and/or antiviral agents were administered to most AFM cases in the United States, though the retrospective nature of data from these cohorts does not allow systematic assessment of response to treatment. The majority of AFM patients received intravenous immune globulin (IVIG), many received high-dose intravenous steroids, several underwent plasmapheresis, and some received antiviral therapy (Table 3).^{6–8,10} No significant clinical improvement or deterioration was noted with any of these therapies.

In November 2014, the CDC drafted interim suggestions for management of children with AFM, based primarily on expert opinion.⁵ Because of the possibility of an active neuroinvasive infectious process without effective antiviral therapy, the CDC recommended reducing immunosuppression medications, when possible, and discouraged the use of steroids and plasmapheresis. However, there is incomplete understanding of the pathophysiology of AFM and no clinical trial data available to guide therapeutic recommendations. It remains uncertain whether AFM is an active infectious process or a postinfectious inflammatory process; therefore, the use of immunomodulatory therapies remains controversial. In cases of severe cord edema, judicious use of steroids may be necessary to limit additional cord injury.

Given the lack of a clear indication for efficacy in treatment of AFM, use of IVIG was not endorsed in the CDC interim recommendations. IVIG has been shown to help prevent poliovirus poliomyelitis when administered before exposure, but fails to prevent or impact severity of paralysis when administered after poliovirus infection in cases of preparalytic poliomyelitis.^{21–23} In agammaglobulinemic children, IVIG has efficacy in treatment of chronic enteroviral central nervous system (CNS) infections, suggesting a role for antibody-mediated immunity.²⁴ IVIG has also been shown to modulate systemic and CNS cytokine production in enterovirus A71 encephalitis, though effect on clinical outcomes has not been systematically evaluated.²⁵ In 2014, all commercially available preparations of IVIG tested contained high levels of neutralizing antibody against the circulating strains of enterovirus D68 in the United States.²⁶ It is the opinion of these authors that in the absence of alternative effective therapies, IVIG may be the safest available therapy with the potential for efficacy if given very early in the course of disease or in immunocompromised patients with enterovirus-associated AFM.

In the absence of a confirmed viral etiology and in vitro susceptibility of available antivirals at the time of publication of the CDC interim recommendations, there were insufficient data to recommend antiviral treatment.⁵ However, fluoxetine has since been confirmed to have in vitro antiviral activity against enterovirus D68 (including the 2014 outbreak strain) and other enteroviruses.^{27–29} A recent case report describes favorable response to fluoxetine in a patient with X-linked agammaglobulinemia and chronic enterovirus (coxsackie B virus) encephalitis.³⁰ Fluoxetine has been proposed as a potential therapeutic agent to be investigated in enterovirus-associated cases of AFM.³¹

Vigilant supportive care was identified by the CDC recommendations as the mainstay of AFM management. This includes mechanical ventilation in cases of impaired airway protection attributed to bulbar weakness or respiratory failure resulting from diaphragmatic paralysis, as well as feeding support in cases of loss of bulbar function. Physical and occupational rehabilitation therapies are recommended as soon as the patient is clinically stable in order to prevent atrophy and contractures and maximize functional outcomes. Rehabilitation needs of AFM patients can be extensive and may require inpatient and outpatient therapies at a dedicated center with multidisciplinary experience. Nerve or muscle transfers have been used for brachial plexus polio-like paralysis cases.³² These transfer procedures have been proposed as a possible therapeutic option in patients with no innervation of functional muscle groups, though no reports exist on the use of this procedure for AFM. Furthermore, the timing of when the procedure may be of highest yield and minimal risk is not known. Support for the psychological as well as physical effects of disability should be provided for those afflicted.

Course

Nearly all patients diagnosed during the acute phase of their illness were hospitalized. A significant proportion required invasive or noninvasive ventilatory support because of bulbar weakness and inability to protect the airway, or for respiratory failure attributed to paralysis of the respiratory musculature.^{6–8,10} Ventilated patients required prolonged intensive care unit stays, and some continued to be ventilator dependent at the time of hospital

discharge.^{6,7,10} The CDPH reported two deaths among their cohort, both in immunocompromised adults.⁶

Most patients developed significant muscle atrophy in the affected limbs in the weeks to months following onset of weakness.³³ Some patients experienced persistent pain for weeks to months after onset. Extent of recovery has varied greatly.⁶ Of 45 patients in the CDPH cohort with follow-up data available at a median of 9 months, complete recovery was noted in 7 (16%). All children in the PCH cohort showed improvement in neurological abnormalities, though 9 of 10 (90%) had residual motor deficits at last follow-up (median, 6 months).¹⁰ At 1-year follow-up in the CHCO cohort, minimal to no improvement in strength was observed in the most profoundly affected proximal muscle groups, whereas less-affected distal muscle groups and cranial nerve impairments were noted to improve or resolve.³⁴ Functional gains were noted with rehabilitation therapies involving recruitment of surrounding muscle groups, even in cases with no objective improvement in strength of affected muscles. Nationwide, only 3 (5%) of 56 AFM patients reported complete recovery of strength and 10 (18%) reported being fully functional at a median of 4.2 months after onset.⁸

Comparison With Known Neurological Entities

The combination of hypotonic weakness and radiographical or electrophysiological evidence of anterior horn cell disease are the most specific findings in AFM. Factors that help to clinically differentiate AFM from other neurological causes of limb paralysis, such as idiopathic transverse myelitis, acute inflammatory demyelinating polyneuropathy (Guillain Barré Syndrome), and acute disseminated encephalomyelitis, are presented in Tables 3 and 4. The pattern of tropism for spinal cord motor neurons in recent AFM cases in the United States is clinically, radiographically, and electrophysiologically similar to other infectious acute flaccid paralysis syndromes (such as poliovirus, enterovirus A71, enterovirus D70, West Nile virus, and Japanese encephalitis virus), suggesting a common pathophysiology.^{35–41} Indeed, these other infectious acute flaccid paralysis syndromes would all meet the current AFM case criteria. Hopkins' syndrome may be a historical clinical description of AFM. First described in 1972, Hopkins' syndrome is a rare disorder of children presenting with asymmetric flaccid limb weakness following an asthma-like acute respiratory illness with clinical features and imaging similar to recent AFM cases in the United States.^{42–44}

Etiological Investigations

Given that the vast majority of AFM cases had received the recommended schedule of vaccines and that wild-type or vaccine strain poliovirus was not identified in any AFM case in the United States, poliovirus is unlikely to have contributed to the increase in AFM cases in the United States. No infectious agents of clinical significance have been identified in the CSF of any of the 2012–2015 AFM cases in the United States, despite extensive microbiological investigations, including next-generation sequencing for novel pathogens, with the exception of enterovirus D68 identified in the CSF of 1 patient with a bloody lumbar puncture.^{8,9,45} A variety of nonenteroviral respiratory viruses was identified in respiratory specimens from individual cases, including a variety of rhinoviruses, respiratory

syncytial virus, influenza virus, parainfluenza virus, and adenovirus.^{6–8,10} Several nonpolio enteroviruses were identified in respiratory or stool specimens from AFM cases.^{3,6,7,46} Of these, enterovirus D68 was the most commonly identified infectious agent and the only virus identified in 2 cases.⁸ Five of 11 (45%) AFM cases at CHCO and 9 of 41 (22%) AFM cases from the CDPH with respiratory specimens tested were positive for enterovirus D68, whereas none of the PCH cases had enterovirus D68 identified.^{6,7,10} Of 17 nation-wide AFM cases reported to CDC with respiratory specimens collected within 7 days, 8 (47%) were positive for enterovirus D68.³

Epidemiological evidence supports an association between the 2014 outbreak of enterovirus D68 respiratory disease and the recent increase in cases of AFM in the United States. Before the 2014 nation-wide enterovirus D68 outbreak, only 26 cases of enterovirus D68 respiratory disease were reported to the CDC from 1970 to 2005, with increasing small clusters of enterovirus D68 respiratory disease from 2008 to 2010 in Europe, Asia, and the United States.^{47,48} Thus, the identification of enterovirus D68 in a small number of isolated cases of polio-like syndromes between 2008 and 2012 was considered unusual and suspicious.^{49,50} In 2014, the largest outbreak of enterovirus D68 respiratory disease ever described occurred in the United States with 1,153 confirmed infections and likely millions of milder cases that went untested.⁵¹ The increase in AFM cases at the CDPH, CHCO, and PCH that both temporally and geographically correlated with the 2014 enterovirus D68 respiratory outbreak further strengthened the association of enterovirus D68 with this polio-like syndrome.^{6,7,10} At CHCO, the number of AFM cases from August to October 2014 during the enterovirus D68 outbreak was 3 times higher than the maximum number of cases retrospectively identified in any 3-month period in the preceding 4 years.⁷ A case-control study at CHCO demonstrated that the adjusted odds of enterovirus D68 detection in the nasopharynx of AFM cases compared to outpatient controls tested for respiratory pathogens during the same time period was 4.5 to 10.3, suggesting this was not merely detection of baseline carriage rates during an outbreak.⁵² This association was unique to enterovirus D68 and was not found among other non-D68 enteroviruses circulating in Colorado during the 2014 outbreak. Ongoing CDPH surveillance from 2012 to 2015 likewise demonstrated that the incidence of AFM cases in California from August 2014 to January 2015 during the enterovirus D68 outbreak was significantly greater than those reported from June 2012 to July 2014 (0.16 vs 0.028 cases per 100,000 person-years; $p < 0.001$).⁶ All enterovirus D68 isolates from respiratory samples from the CDPH and CHCO AFM cases grouped into a single clade B1 strain, which emerged in 2010.⁴⁵

In addition to the epidemiological association, the similarity of enterovirus D68 and AFM to other enteroviruses and their associated acute flaccid paralysis syndromes lends biological plausibility to the potential of enterovirus D68 to cause neurological disease. Enterovirus D68 is a picornavirus in the enterovirus family, which contains polioviruses and enterovirus A71, the two most common viral causes of acute flaccid paralysis. Enterovirus D68 has been identified in the CSF of 2 patients with acute flaccid paralysis^{47,50} and, more recently, in the CSF of 2 patients with aseptic meningitis,⁵³ demonstrating the virus' neuroinvasive potential. Autopsy of a fatal case of acute flaccid paralysis in a 5-year-old boy with enterovirus D68 identified in CSF by reverse-transcriptase polymerase chain reaction

demonstrated neuronophagia and cytotoxic T-cell inflammation in motor nuclei of the anterior spinal cord.⁵⁰

The absence of enterovirus D68 in CSF and the lack of CNS tissue specimens from the 2012–2015 AFM cases complicate the ability to establish a causal relationship with AFM in these instances. Poliovirus and enterovirus A71 are infrequently detected in CSF from acute flaccid paralysis cases and more readily identified in stool, which may parallel the inability to detect enterovirus D68 in CSF in AFM cases with the virus more readily identified in respiratory specimens.^{54,55} Biological plausibility and a strong epidemiological association support that enterovirus D68 is a nonpolio enterovirus capable of causing AFM and may have contributed to the recent increase in AFM cases in the United States in 2014.

Investigation of the association between enterovirus D68 and AFM, as well as the role of other nonpolio enteroviruses and rhinoviruses in the etiology of AFM is ongoing.

Future Directions

Before 2015, the United States was one of only a few countries that did not conduct acute flaccid paralysis surveillance. In 2015, the US Council of State and Territorial Epidemiologists began voluntary surveillance for AFM using a standardized case definition of persons of any age with onset of acute focal limb weakness *and* either: (1) MRI with spinal cord lesion largely restricted to gray matter spanning one or more spinal segments (confirmed case) *or* (2) CSF pleocytosis of >5 WBCs/mm³ (probable case).⁵⁶ Clinicians are requested to report confirmed or probable cases, regardless of etiology, to their state or local health department and submit the following specimens from as early as possible in the course of illness: CSF, blood, respiratory swab or aspirate, and two stool specimens separated by 24 hours. The importance of the early collection of respiratory samples, in addition to CSF, serum, and stool specimens, has been highlighted by the recent US AFM cases associated with enterovirus D68. Enhanced surveillance of cases meeting AFM criteria, regardless of age, febrile prodrome, or identified etiology, will allow characterization of the epidemiology of the various causes of AFM in the US.

Given biological plausibility and epidemiological data supportive of an association between enterovirus D68 and AFM, further studies are needed to clarify this relationship. Assessing for intrathecal antibody production may provide an alternative method to evaluate for neuroinvasive infection in the absence of virus or viral nucleic acid in CSF. Animal models are needed to investigate the neurotropic potential of enterovirus D68, understand the pathophysiology, and identify potential therapeutic interventions. Establishing whether AFM is an active infectious or postinfectious inflammatory process will be critical to determining whether antiviral or immune modulating therapy will be most effective for treatment. Investigating host genetics and immune response may identify host factors predisposing to AFM. Closely following the long-term outcomes of those affected by AFM will provide better understanding of the course of this disease. Identifying prognostic factors, which predict recovery versus permanent damage, may help to inform decisions of rehabilitation therapies versus nerve or muscle transfer in individual cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Timeline of clinical features of acute flaccid myelitis cases in the United States 2012–2015.

CMAPs = compound muscle action potentials; CSF = cerebrospinal fluid; EMG = electromyography; GI = gastrointestinal; MUPs = motor unit potentials; NCV = nerve conduction velocity.

FIGURE 2.

Representative magnetic resonance imaging (MRI) images of the spinal cord in acute flaccid myelitis cases in the United States 2012–2015. MRI images from acute flaccid myelitis patients in the Children’s Hospital Colorado cohort. (A and B) Sagittal T2-weighted MRI sequences of the spinal cord demonstrate longitudinally extensive, hyperintense lesions. (C and D) Axial T2-weighted MRI sequences of the spinal cord demonstrate predominant involvement of the spinal cord gray matter.

TABLE 1

Clinical Presentation of Acute Flaccid Myelitis Cases in US Cohorts 2012–2015

Source	CDPH ^a	CHCO ^b	PCH ^c	CDC ^d
No. of cases	59	12	11	120
Demographics				
Sex (% male)	56	75	91	59
Median age (range) in years	9 (0.5–73.0)	11.5 (1–18)	9 (1–14)	7.1 (0.4–20.8)
Pre-existing conditions, %	25	33	0	21
• Asthma	19	25	0	10
• Immunocompromised	5	8	0	2
Prodromal illness, %	92	100	64	90
Fever	80	100	45	64
Respiratory symptoms	71	92	NR	81
Gastrointestinal symptoms	64	0	NR	NR
Neurological illness, %				
Headache	49	58	NR	NR
Stiff neck	34	83	NR	NR
Pain	69	67	NR	51
Altered mental status	22	0	NR	11
Neurological deficits, %				
Limb weakness	100	83	91	100
• Upper extremity weakness	73	75	64	77
• Lower extremity weakness	NR	42	36	66
• Asymmetric	NR	70	NR	47
Sensory involvement	44	0	0	21
Hyporeflexia	NR	80	NR	81
Cranial nerve dysfunction	27	83	18	28
Bowel or bladder dysfunction	51	0	18	NR

^aCDPH = California Department of Public Health. Case definition: acute flaccid myelitis (AFP) with magnetic resonance imaging (MRI) lesion in gray matter of spinal cord or electrodiagnostic evidence of spinal motor neuron damage in California June 2012–July 2015.

^bCHCO = Children's Hospital Colorado. Case definition: AFP and/or cranial nerve dysfunction with MRI lesions in the gray matter of the spinal cord or brainstem presenting to CHCO August 1, 2014–October 31, 2014.

^cPCH = Primary Children's Hospital. Case definition: AFP with MRI lesions in the spinal cord largely restricted to gray matter in patients <21 years presenting to PCH February 2014–January 2015.

^dCDC = Centers for Disease Control and Prevention. Case definition: AFP with MRI lesions in the spinal cord largely restricted to gray matter in patients <21 years in the United States August 1, 2014–December 31, 2014. Of note, CDC nation-wide epidemiological data include 24 CDPH, 9 CHCO, and 10 PCH cases.

NR = not reported.

TABLE 2

Diagnostic Findings, Treatment, and Course of Acute Flaccid Myelitis Cases in US Cohorts 2012–2015

Source	CDPH ^a	CHCO ^b	PCH ^c	CDC ^d
No. of cases	59	12	11	120
Laboratory findings, %				
CSF pleocytosis (median, range of WBCs/uL)	74 (41, 0–888)	91 (55, 1–309)	64 (36, 7–170)	81 (44, 0–664)
CSF protein >45mg/dl on first lumbar puncture (median, range)	48 (44, 10–286)	45 (44, 22–92)	NR	48 (43, 17–921)
Virus identified in CSF	0	0	0	2
Enterovirus D68 identified in respiratory specimen (no. positive/no. tested)	22 (9/41)	45 (5/11)	0 (0/8)	20 (11/56)
Non-D68 rhino-/enterovirus identified in respiratory specimen (no. positive/no. tested)	10 (4/41)	36 (4/11)	11 (1/9)	21 (12/56)
Imaging findings, %				
T2 gray matter lesions spanning multiple vertebral levels on spinal cord MRI	90 (>3 levels)	100 (>3 levels)	91 (>3 levels)	96 (>1 level)
Nerve root enhancement on spinal cord MRI	20	40	NR	34
Brainstem lesions on brain MRI	NR	75	36	35
Supratentorial lesions on brain MRI	31	0	0	11
Electrophysiological findings, %				
Motor findings in affected limb	100 (12/12)	100 (5/5)	NR	NR
Sensory findings in affected limb	NR	0	NR	NR
Treatment/course, %				
Intravenous immune globulin	73	75	82	73
Plasmapheresis	22	17	9	15
Intravenous steroids	71	42	55	54
Antivirals	3	17	0	NR
Response to treatment	None noted	None noted	NR	NR
Intubation/ventilatory support	34	25	9	20
Persistent motor deficits at last follow-up (no. with deficits/no. followed; median follow-up interval)	84 (38/45; 9 months)	75 (6/8; 12 months)	90 (9/10; 6 months)	95 (53/56; 4.2 months)

^aCDPH = California Department of Public Health. Case definition: acute flaccid myelitis (AFP) with magnetic resonance imaging (MRI) lesion in gray matter of spinal cord or electrodiagnostic evidence of spinal motor neuron damage in California June 2012–July 2015.

^bCHCO = Children's Hospital Colorado. Case definition: AFP and/or cranial nerve dysfunction with MRI lesions in the gray matter of the spinal cord or brainstem presenting to CHCO August 1, 2014–October 31, 2014.

^cPCH = Primary Children's Hospital. Case definition: AFP with MRI lesions in the spinal cord largely restricted to gray matter in patients <21 years presenting to PCH February 2014–January 2015.

^dCDC = Centers for Disease Control and Prevention. Case definition: AFP with MRI lesions in the spinal cord largely restricted to gray matter in patients <21 years in the United States August 1, 2014–December 31, 2014. Of note, CDC nation-wide epidemiological data include 24 CDPH, 9 CHCO, and 10 PCH cases.

CSF = cerebrospinal fluid; WBCs = white blood cells; NR = not reported.

Clinical Presentation of Acute Flaccid Myelitis Compared to Other Neurologic Syndromes With Acute Limb Weakness

TABLE 3

	Acute Flaccid Myelitis Cases in the United States 2012–2015	Idiopathic Transverse Myelitis	Acute Inflammatory Demyelinating Polyneuropathy	Acute Disseminated Encephalomyelitis
Prodrome	Preceding illness	Febrile respiratory or gastrointestinal illness common, median of 7 days previous	Respiratory, gastrointestinal, or systemic illness common	Febrile respiratory illness or vaccination common
	Associated symptoms at onset	Fever; meningial signs; limb/neck/back pain common	Dysesthesia and paresthesias; back pain	Fever; meningial signs; encephalopathy
Motor deficits	Progression	Progression over hours to days	Progression over hours to days	Progression of multifocal deficits over 4 to 7 days
	Distribution	Asymmetric; upper>lower limb	Symmetric or asymmetric; bilateral; below level of lesion	Commonly asymmetric
	Tone	Flaccid	Can be flaccid in acute phase, then spastic	Spastic
	Deep tendon reflexes	Decreased or absent	Can be decreased in acute phase, then increased	Increased
Associated deficits	Sensory deficits	Variably present in affected limb	Common, sensory level present	Common
	Autonomic deficits	Bowel and bladder dysfunction possible	Common, especially bowel or bladder dysfunction	Possible
	Cranial nerve deficits	Common, especially bulbar dysfunction, diplopia, facial weakness	Uncommon	Possible, especially optic neuritis

TABLE 4

Diagnostic Findings and Clinical Course of Acute Flaccid Myelitis Compared to Other Neurological Syndromes With Acute Limb Weakness

Diagnostic findings	CSF features	Acute Flaccid Myelitis Cases in the United States 2012–2015	Idiopathic Transverse Myelitis	Acute Inflammatory Demyelinating Polynuropathy	Acute Disseminated Encephalomyelitis
Imaging features	Imaging features	Mild pleocytosis; normal to mildly elevated protein	Lymphocytic pleocytosis in half; elevated protein	No pleocytosis; elevated protein	Lymphocytic pleocytosis; elevated protein
		Confluent, longitudinally extensive, nonenhancing lesions in gray matter of spinal cord; cranial nerve motor nuclei lesions in brainstem; nerve root enhancement later in course	Gadolinium-enhancing, often contiguous lesion involving multiple levels of the spinal cord; gray and white matter with associated edema	Normal brain and spinal cord imaging; nerve root and cauda equina enhancement common	Multiple poorly defined heterogeneous, bilateral, often asymmetric lesions in the deep white and gray matter; spinal cord involvement possible
EMG/NCS features	EMG/NCS features	Low response amplitude of CMAPs; reduced recruitment of MUPs; fibrillation potentials; no sensory findings	Abnormal somatosensory evoked potentials and motor evoked potentials	Slowed nerve conduction velocities reflecting segmental demyelination and absent H reflexes early in course; Motor units with denervation potentials common by 3 weeks; normal sensory potentials in acute motor axonal neuropathy variant	Typically none
Treatment/course	Response to treatment	No response noted to IVIG, steroids, PLEX	Response to high-dose IV steroids, second-line PLEX, IVIG	Response to IVIG, second-line PLEX	Response to high-dose IV steroids, second-line IVIG, or PLEX
	Course	Muscle atrophy in affected limbs; most with functional improvements, but residual limb weakness	Partial recovery in most over months to years; some degree of residual disability in most	Return of function over weeks to months with favorable outcome in most	Most improve with treatment though with incomplete recovery
	Recurrence risk	No recurrences have been reported to date	A subset will eventually develop a relapsing autoimmune condition (eg, MS, NMO).	Typically monophasic, although chronic, relapsing disease may develop in ~2% of individuals.	Monophasic in >80% of cases

CSF = cerebrospinal fluid; EMG = electromyography; NCV = nerve conduction velocity; CMAPs = compound muscle action potentials; MUPs = motor unit potentials; IVIG = intravenous immunoglobulin; PLEX = plasmapheresis; IV = intravenous; MS = multiple sclerosis; NMO = neuromyelitis optica.