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A 12-Year-Old Girl With Encephalopathy and Acute Flaccid Paralysis: A Neuropathological Correlation and Cohort Review



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Patient Presentation

This 12-year-old girl with a history of mild intermittent asthma presented with five days of fever to 104.2°F, which was initially without associated symptoms but was followed by acute onset headache, neck stiffness, and lethargy on the day of presentation. The patient was evaluated in the emergency department and underwent a lumbar puncture that revealed lymphocytic pleocytosis and increased protein concentrations in her cerebrospinal fluid (CSF) (Table 1). She was admitted to the inpatient ward for presumed viral meningitis and underwent empiric broad-spectrum antimicrobial treatment.

Her condition worsened over the next five days to include progressive encephalopathy associated with acutely developing tachycardia, tachypnea, tremor, and bowel incontinence, leading to endotracheal intubation for airway protection. She concurrently developed fulminant heart failure and required extracorporeal membrane oxygenation for ten days. Despite return of normal heart function and discontinuation of sedatives over the following week, she remained severely encephalopathic with flaccid paralysis and areflexia.

A brain magnetic resonance imaging (obtained two weeks after presentation) showed diffuse patchy T2 signal abnormalities throughout the brain and cerebellum involving both the gray and white matter, including the deep gray nuclei. The entire spinal cord was also affected,

with predominant involvement of the anterior cervical cord (Fig 1). Repeat CSF analysis showed persistent lymphocytic pleocytosis and increased protein concentrations. A broad evaluation for infection and markers of autoimmunity were nondiagnostic (Table 1).

Given the severity of her deficits and evidence of inflammation in her CSF, empirical immunomodulatory therapy was initiated with five cycles of plasmapheresis and 2 g/kg of intravenous immunoglobulin (IVIg) to treat a possible immune-mediated process. There was no appreciable short-term treatment response. Another magnetic resonance imaging (five weeks after presentation) revealed dramatic evolution of the signal abnormalities with the emergence of T1 signal voids throughout the neuraxis and profound brain and spinal cord atrophy (Fig 1). Electromyography and nerve conduction study showed diffusely small to absent compound muscle action potentials and normal sensory nerve action potentials. The patient then underwent a frontal lobe brain biopsy after which she received additional immunomodulatory therapy with methylprednisolone (5 g total), plasmapheresis (five cycles), and IVIg (2 g/kg).

Differential diagnosis

This girl presented with acute-onset meningoencephalitis, myocarditis, and generalized flaccid paralysis. The neurological localization suggested diffuse involvement of the both cerebral hemispheres (leading to encephalopathy) as well as the lower motor neurons (leading to flaccid paralysis), although flaccid paralysis may be secondary to severe encephalopathy alone in the acute phase. The presence of myocarditis further suggested a diffuse or multifocal process. Furthermore, the constellation of high

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TABLE 1.
Summary of Diagnostic Studies

CSF profile (at the onset of neurological symptoms)	191 total cells (per μL), 185 nucleated cells (5% neutrophils, 71% lymphocytes, 24% monocytes), glucose 65 mg/dL, protein 119.9 mg/dL
Repeat CSF profile (16 days after the onset of neurological symptoms)	97 total cells, 59 nucleated (1% neutrophils, 92% lymphocytes, 5% monocytes, 2% macrophages), glucose 82, protein 58.1
Infectious studies (not including routine bacterial, fungal, and AFB cultures) (all negative)	Brain tissue: PCR—enterovirus, JC virus, Ehrlichia, Bartonella, Mycoplasma, parechovirus, FilmArray, HSV, EBV, HHV-6, HHV-7, EV-D68 CSF: enterovirus, parechovirus, Toxoplasma, HSV, EBV, CMV, VZV, HHV-6, Mycoplasma, EV-D68. Antigen: Cryptococcus. Antibody: arboviruses, measles IgM (IgG positive), VDRL
Autoimmune markers (all negative)	Blood/serum: PCR—HIV, enterovirus, adenovirus, HSV, EBV, CMV, VZV, HHV-6, parvovirus, Ehrlichia, EV-D68. Antibodies: arboviruses, EBV, CMV, HIV, LCMV, mumps, Coxiella, RMSF, RPR. Antigen: HIV p24, Quantiferon
Imaging (16 days after the onset of neurological symptoms)—see Fig 1.	Nasopharyngeal: PCR—influenza, RSV, FilmArray, Mycoplasma, EV-D68 Stool: PCR—enterovirus, EV-D68
Imaging (36 days after the onset of neurological symptoms)—see Fig 1.	Oligoclonal bands (0), CSF and serum paraneoplastic panel, serum NMDA-R Ab, serum NMO IgG, ANA, ANCA, ENA, C3, C4, thyroglobulin Ab
Echocardiogram (6 days after the onset of neurological symptoms)	Diffuse and patchy diffusion-restriction and T2 hyperintensities throughout brain, brainstem, and whole spine (with anterior cervical cord predominance) and subtle leptomeningeal enhancement
EMG/NCS	Multifocal T1 hypointensities throughout brain, brainstem, and whole spine with profound brain and spine atrophy
Abbreviations:	Normal segmental anatomy, moderate dilatation of left ventricle, severe decreased systolic function of left ventricle, small pericardial effusion
AFB	Diffusely small to absent CMAPs, normal SNAPs
ANA	
ANCA	
CMAP	
CMV	
CSF	
EBV	
EMG/NCS	
ENA	
EV-D68	
HHV	
HIV	
HSV	
IgG	
JC	
LCMV	
NMDA	
NMO	
PCR	
RMSF	
RPR	
RSV	
SNAP	
VDRL	
VZV	

fever and CSF pleocytosis indicated either an infectious or a parainfectious, immune-mediated process.

Important considerations among infectious diseases included treatable neuroinvasive disease such as herpes simplex virus encephalitis and varicella zoster virus vasculitis, which prompted antiviral treatment with acyclovir initially.¹ Arboviral infections, such as West Nile virus, were a consideration given the presence of meningitis, encephalitis, and acute flaccid paralysis (AFP). Arboviral infections are also known to rarely cause myocarditis.^{2,3} Non-polio enterovirus (likewise, parechovirus) encephalitis was also a consideration, especially in light of concurrent myocarditis.⁴ The patient presented in the late summer of 2014 at the peak of the enterovirus D68 (EV-D68) respiratory outbreak when acute flaccid myelitis (AFM) became recognized as a clinical syndrome. She met the case definition for AFM that was later

announced in November 2014 by the Centers for Disease Control (CDC) along with two other patients, who presented with more typical features of AFM within a ten-day period. Table 2 summarizes AFM cases presenting to St. Louis Children's Hospital during and preceding the 2014 EV-D68 outbreak.⁵

Another consideration was acute disseminated encephalomyelitis (ADEM), but the prominence of persistent lower motor neuron signs and myocarditis was atypical.⁶ A variant of acute inflammatory demyelinating polyradiculoneuropathy, i.e., Miller-Fisher or Bickerstaff variant, was also considered.⁷ Evaluation of specific autoantibodies was nondiagnostic. Primary or secondary central nervous system vasculitis was also considered, which contributed to the decision to biopsy. Hopkins syndrome describes a polio-like syndrome occurring after an asthma

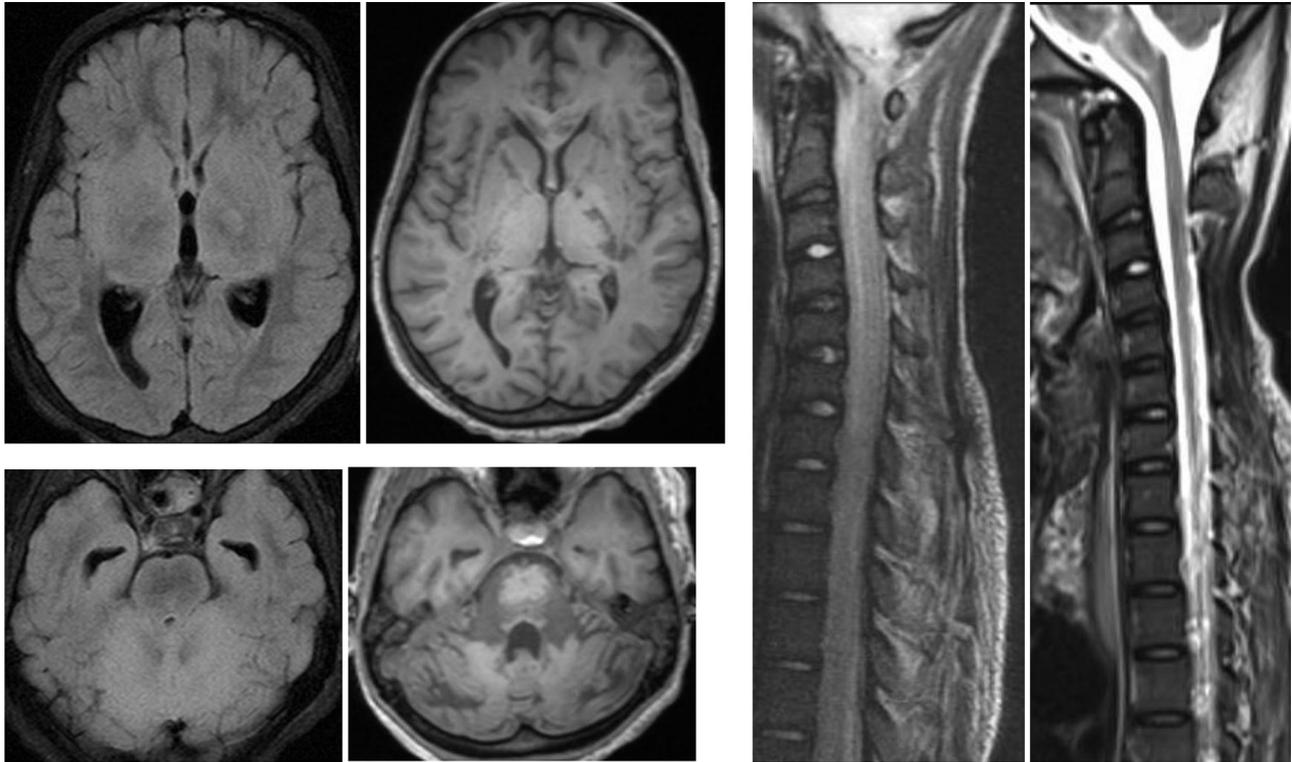
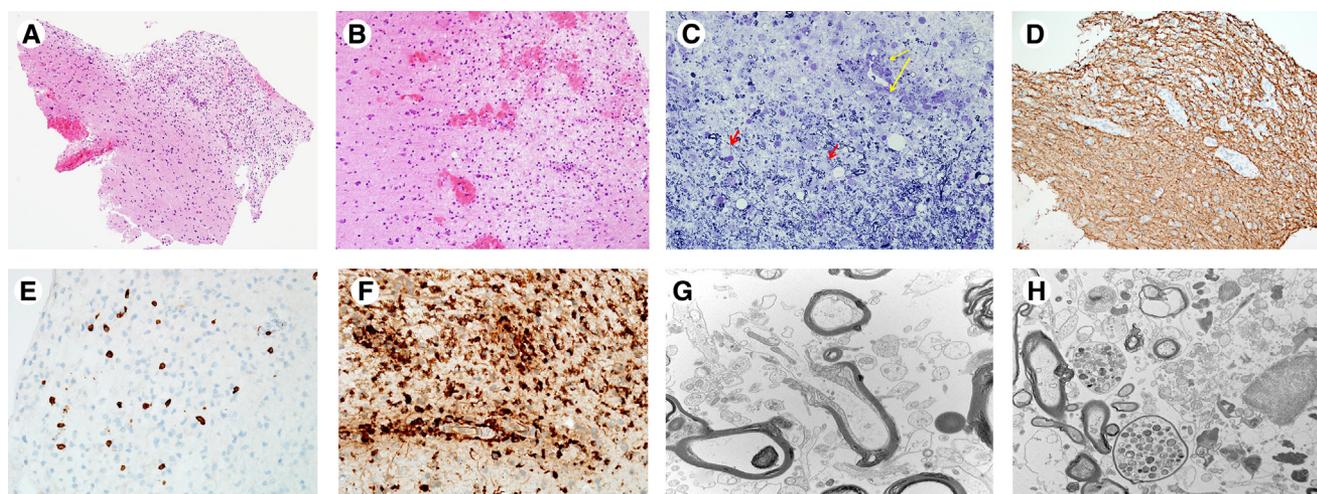


FIGURE 1. Evolution of the brain and cord imaging findings in Patient 6. The diffuse, patchy hyperintense lesions in the FLAIR sequence of the scan done at 16 days after presentation (left images, top and bottom) gives way to cerebral and cerebellar signal voids and atrophy in the adjacent T1 images from a scan done 20 days later. The diffuse T2 hyperintensity and subsequent atrophy are also apparent in the spinal cord (right two images).

TABLE 2. Demographics and Clinical Features of the Washington University/St. Louis Children’s Hospital Acute Flaccid Myelitis Cohort—Patient 6 is the Individual Described in Detail Earlier

Patient #	1	2	3	4	5	6
Age	15 years	14 years	22 months	15 months	7 years	12 years
Sex	F	F	M	M	F	F
Preceding illness	No	No	Yes, fever and URI 3 days prior	Yes, fever and URI 7 days prior	URI + sore throat at onset	Yes, fever for 5 days prior
Time to maximal severity	4 days	1 day	1 day	1 day	5 days	6 days
Other descriptors	Subacute back pain, then descending asymmetric bilateral weakness + neck/back/limb pain. Encephalopathy with respiratory failure	Descending asymmetric bilateral weakness + limb pain + bowel/bladder symptoms + sensory loss	Complete lower extremity paralysis, sparing left ankle	Isolated monoparesis + fever	Neck and shoulder pain with concurrent onset of bulbar and asymmetric proximal upper extremity weakness with mild lower extremity weakness	Meningitis then subacute encephalopathy, then flaccid paralysis
Non-neurological complications	Tracheostomy/ventilator dependent	None	None	None	G-tube dependent	Myocarditis requiring extracorporeal membrane oxygenation, tracheostomy/ventilator and gastrostomy dependence
Presented after August 2014	No (presented June 2012)	No (presented April 2014)	No (presented July 2014)	Yes	Yes	Yes

Abbreviation:
URI = Upper respiratory infection

**FIGURE 2.**

Histopathology and electron microscopy from frontal lobe biopsy. (A and B) Hematoxylin and eosin stain showing patchy perivascular loss of myelin (pink). (C) Plastic section showing perivascular loss of myelin (blue), “naked” axons and axonal spheroids (red arrows), and perivascular macrophages (yellow arrows). (D) Neurofilament stain shows relative axonal sparing. (E) CD3 stain (biopsy obtained after patient received steroids). (F) CD68 staining showing macrophage infiltration. (G and H) Electron microscopy showing demyelinated axons and axonal expansion with organelle accumulation amidst normal appearing axons with normal myelination. (The color version of this figure is available in the online edition.)

exacerbation, but our patient did not present with respiratory symptoms despite having a history of asthma.⁸

These considerations for immune-mediated processes were highly relevant given the existence of immunomodulatory therapies that may impact outcome in ways that are comparable with ADEM and acute inflammatory demyelinating polyradiculoneuropathy. However, the possibility that immunomodulation may lead to worsening infection was also an important consideration.

Pathology

A frontal lobe brain biopsy performed 39 days after presentation (following aggressive immunomodulatory therapy) showed inflammatory demyelination. Microglial proliferation and rod cell formation, as well as perivascular lymphocytic inflammation and focal macrophage infiltration, were present. There was patchy myelin loss with preserved and degenerating axons. No viral particles were seen on electron microscopy (Fig 2).

TABLE 3.

Treatment and Follow-Up of the Washington University/St. Louis Children's Hospital Acute Flaccid Myelitis Cohort

Patient #	1	2	3
IV steroids	Yes	Yes (7 days)	Yes (5 days)
IVIg	Yes	Yes (2 g/kg)	Yes (2 g/kg)
Plasmapheresis	Yes (12 cycles)	Yes (5 cycles)	No
Follow-Up description	At 3 years, 0/5 strength in arms, except 2-3/5 finger extension; proximal (2/5) greater than distal (4/5) lower extremity weakness	At 6 months, bowel/bladder symptoms resolved. At 10 months, minimal leg weakness, unimproved triceps weakness. At 9 months, underwent nerve transfer surgery from bilateral deltoids to triceps with modest improvement (2 to 3/5)	At 6 months, no significant improvement seen
MRS	4 at 44 months	2 at 21 months	4 at 6 months
Early WeeFIM	N/A	117 at 4 months	50 at 6 months
Recent WeeFIM	64 at 44 months	118 at 21 months	N/A

Abbreviations:

IVIg = Intravenous immunoglobulin

MRS = Modified Rankin scale

WeeFIM = Functional independence measure for children

Patient Outcome

The patient made functional gains for over a year after the acute phase of her illness. At the peak of symptom-severity during her 78-day stay in the intensive care unit, she had no appreciable brainstem function on examination (apnea test was not done). An electroencephalograph showed diffuse slowing but also clearly demonstrated state change and reactivity. At the time of her transfer to a long-term care facility, she was ventilator-dependent with only occasional spontaneous respiratory effort, had near-complete ophthalmoplegia, complete bulbar dysfunction, flaccid quadriplegia, and severe orthostatic hypotension.

At her nine-month follow-up visit, she had near-complete resolution of encephalopathy and had regained control of her extraocular movements. She had partial recovery of bulbar function and was able to speak with severe dysarthria and sip thick liquids to a limited extent. She also regained functional use of her dominant hand and was able to write with support and use a communication board.

By her 16-month follow-up visit, she demonstrated modest additional gains in hand function but continued to have orthostatic hypotension and only trace movements in her legs. Despite relatively significant recovery of function and an increase in her functional independence measure for children (WeeFIM) score from 18 (five months) to 46 (16 months), she remains tracheostomy- and ventilator-dependent and is fully dependent for all activities of daily living.⁹ She continues to receive limited oral feeding for pleasure, despite known silent aspiration that has led to bronchiectasis in her lower lungs.

Discussion

AFM describes a clinical syndrome consisting of acute onset focal limb weakness with evidence of spinal cord disease largely restricted to gray matter. This describes a broad clinical and etiologic spectrum of “poliomyelitis”

(*polio* referring to gray matter and *myelitis* referring to spinal cord inflammation) not specific to the poliovirus. AFM also fits into the larger category of acute flaccid paralysis (AFP), which is a heterogeneous clinical syndrome of variable localization and etiology that is not specific to spinal cord disease.¹⁰

Clusters of AFM in the United States during the summer of 2014 were geographically and temporally associated with an EV-D68–related respiratory outbreak.^{11–13} EV-D68 was found in the blood of one patient during the neurologically progressive phase of illness, and although EV-D68 was never found in the CSF in the two major case series in Colorado and California, it was the most common virus found in the nasopharyngeal and oropharyngeal samples (found in 12 of 25 patients). Other neurotropic enteroviruses known to be associated with AFP were not found via metagenomic deep sequencing in the Colorado and California cohorts, and phylogenetic analyses in the same cohorts showed an emergence of a distinct clade of EV-D68 that predominated the 2014 respiratory outbreak with speculation that polymorphisms present in this clade confer increased neurovirulence.^{11,12} Although these data are suggestive of a causal link between EV-D68 and AFM, no definitive etiology has been identified for the 120 cases from 34 states reported to the CDC between August 2014 and July 2015.¹⁴ Moreover, no neuropathologic correlate has been reported in known case series to further elucidate its pathogenesis.

Although an association between AFM and EV-D68 has been suggested by recent studies, the underlying pathogenesis—whether directly neuroinvasive or parainfectious/immune-mediated—remains unclear.^{11,12} The clinical course does not differentiate between either processes, as both disease processes can cause a monophasic illness, and delayed onset of neurological symptoms after a prodromal illness is seen both in neuroinvasive diseases (such as poliomyelitis) and in postinfectious diseases, such as ADEM or idiopathic transverse myelitis.^{7,15–21} CSF indices are similar between the two processes (lymphocytic pleocytosis with

TABLE 3
(continued)

4	5	6
No	Yes (5 days)	Yes (5 days)
Yes (2 g/kg)	Yes (2 g/kg)	Yes (4 g/kg)
No	Yes (10 cycles)	Yes (10 cycles)
At 1 month, walking again. At 1 year, not running yet with persistent mild weakness and atrophy in left leg	At 7 months, modest recovery of bilateral biceps function (antigravity) but no shoulder strength recovery. At 9 months, underwent nerve transfer surgery (expendable median nerve to biceps) with mildly improved bicep strength 9 months postoperation; another surgery at 10 months (ulnar nerve fascicle transfer to medial triceps) with unclear benefit 8 months postoperation. No longer requiring supplementary g-tube feeds	At 1 year, encephalopathy resolved, continued slow improvement with limited recovery of swallow function, minimum functional use of right hand and antigravity strength in other extremities; persistent ventilator/tracheostomy dependence. Continues to reside at long-term bridge hospital
1 at 16 months 59 at 1 month 105 at 16 months	3 at 19 months 93 at 5 months 105 at 19 months	5 at 16 months 18 at 5 months 46 at 16 months

normal to increased protein concentrations).^{6,7,15–21} Known neuroinvasive viruses such as poliovirus and enterovirus 70 and 71 have low CSF detection rates, and EV-D68 has been detected in the CSF in only two isolated cases of AFP and encephalitis outside the recent 2014 outbreak. Epstein-Barr virus has been detected in the CSF of one patient with AFM whose CSF showed the presence of 1500 red blood cells and thus complicating its interpretation because of contamination by peripheral blood.^{15–21} Neuroimaging findings in patients with EV-D68-associated AFM have been comparable with neuroinvasive disease related to poliovirus, enterovirus 71, or West Nile virus.²²

Our patient met the CDC case definition for AFM, but she had atypical features. First, she had severe encephalopathy, which has been reported on a small subset of patients in prior case series. Second, the patient developed fulminant myocarditis, which is a known complication of certain enteroviral infections (i.e., coxsackievirus B) but not reported in any of the case series from the EV-D68 outbreak or implicated in other neurotropic enteroviruses. These atypicalities put into question whether this patient was affected by the same process as the other patients meeting the AFM case definition. Aside from the temporal relationship to the EV-D68 outbreak, there is no supporting evidence that our patient's condition was related to EV-D68, including extensive testing with EV-D68-specific quantitative polymerase chain reaction.^{23,24} However, this is comparable with other reported AFM cohorts showing a temporal and geographic relationship to the 2014 EV-D68 outbreak but negative EV-D68 testing in most instances.^{11,12,25}

This child provides an unprecedented neuropathologic correlate to AFM. The inflammatory demyelination with relative axonal sparing is most compatible with the perivascular inflammatory demyelination seen in ADEM. Neutrophilic infiltrates and pericapillary “ball and ring” hemorrhages and hematomas seen in acute hemorrhagic leukoencephalitis were absent.²⁶ On the basis of this limited sample, the absence of viral particles on ultrastructure further suggests a parainfectious inflammatory process rather than direct neuroinvasive disease.

Immunomodulatory therapies such as corticosteroids, IVIg, interferon, and plasmapheresis for treatment of AFM remain controversial given the possibility of exacerbating an active infection and the lack of clinical data supporting their use. Current CDC guidelines do not recommend immunomodulatory therapy despite the significant morbidity associated with AFM, except for the consideration of corticosteroids for severe cord edema.²⁷ No antiviral drug is known to be effective against EV-D68 *in vivo*, although pocapavir has been used without discernable benefit.¹¹ An *in vitro* study has identified three candidate drugs with inhibitory activity at clinically achievable concentrations against representative strains of EV-D68 from the 2014 epidemic.²⁸ However, if AFM associated with EV-D68 is found to be a parainfectious inflammatory condition as opposed to a neuroinvasive process, antivirals may be of limited benefit if not given very early. Clinical equipoise is therefore maintained with regards to both immunomodulatory and antiviral therapy when considering both the limited evidence available and the severe disability caused by AFM.

Although supportive care and rehabilitative therapy are the mainstay of long-term management, peripheral nerve

surgery offers a novel approach to recovery for select patients. Two patients in our cohort at St. Louis Children's Hospital had peripheral nerve surgery, and although both pursued this intervention nine months after the onset of disease, the degree of muscle atrophy over time varied substantively to the point of forgoing surgery in some muscle groups in one of the patients. Appropriately timed electrodiagnostic studies may aid in early identification of completely denervated muscle that may be salvaged via nerve transfer. Absence of motor unit potentials coupled with the absence of compound muscle action potentials may identify areas of poor prognosis as in brachial plexus injuries.^{29,30}

Prognosis of AFM is generally poor. Sequelae have included the need for mechanical ventilation, persistent limb weakness (ranging broadly in distribution and severity), and bulbar weakness leading to gastrostomy and/or tracheostomy dependence. Determinants of good recovery have not been ascertained. Only a small subset of patients experience substantial recovery, with marginal motor recovery in most of the recent cohorts.^{11,12,25} We report similar findings in the St. Louis Children's Hospital cohort with sustained poor recovery demonstrated at longer follow-up time than previously reported (Tables 2 and 3—Patient 6 is described in detail in the patient description section).

Notably, two of our patients had relatively better recovery and also had distinct clinical features that suggested disease involvement of the central white matter. These were manifest by encephalopathy (correlating to findings compatible with ADEM on brain biopsy) in our patient described previously and bowel, bladder, and sensory disturbances in another patient. These findings are compatible with the relatively better prognosis in acute demyelinating disease such as ADEM and idiopathic transverse myelitis in contrast to the poor recovery associated with neuroinvasive disease directly affecting the alpha motor neuron.^{6,15,20,21,25} Thus recovery may be localization related, and clinically differentiating between deficits related to lower motor neuron injury and deficits related to white matter injury may be of prognostic value. Further characterization of existing cohorts with regards to their poliomyelopathic versus leukomyelopathic features may inform prognosis for future patients.

Final diagnosis

AFM—ADEM overlap syndrome.

Conclusions

We describe a child with atypical AFM with an unprecedented neuropathologic correlate that further elucidates its pathogenesis. Clinical equipoise is maintained with respect to the treatment of this disabling disease beyond supportive and rehabilitative care, which continues to be the mainstay of therapy. Determinants of prognosis for AFM may be localization related.

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