Comparison of children with acute flaccid myelitis before and after 2014

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Abstract

Objective

To observe whether cases of acute flaccid myelitis (AFM) before and since August 1, 2014, had important differences and to further characterize patients with AFM regarding clinical, laboratory, imaging, and treatment findings.

Methods

All pediatric patients with AFM at our institution were reviewed. Demographic, clinical, and diagnostic data were collected through medical record review. Patients with onset before August 1, 2014, and after that date were compared and when applicable compared with Centers for Disease Control and Prevention data.

Results

Sixteen patients were included, 6 in the pre-2014 and 10 in the post-2014 group. The mean age in the pre-2014 group was 7.4 years and in the post-2014 group was 6.4 years. Initial symptoms were similar in both groups, as were functional and motor abilities at disease nadir and the most recent follow-up. Post-2014 patients had a higher mean CSF white blood cell count (57) and neutrophil count (30%) compared with pre-2014 patients (3.2 and 0.5%, respectively). Eighty percent of post-2014 patients had positive enterovirus/rhinovirus testing, with 57% of specimens positive for enterovirus D68 (EV-D68). On acute imaging, a triad of brainstem, cervical cord gray matter involvement, and ventral nerve root/cauda equina (CE) thickening/enhancement was found in 5 patients.

Conclusion

The groups had more similarities than differences but with a more inflammatory picture in the post-2014 patients. The constellation of cervical cord gray matter, brainstem, and nerve root/CE thickening should raise suspicion for AFM in the appropriate clinical setting. Most post-2014 patients had associated enterovirus infections, and over half tested for EV-D68 were positive. There was minimal clinical improvement in both groups despite various immunotherapies.

The term “acute flaccid myelitis” (AFM) was devised in 2014 to describe a distinct syndrome of rapid-onset flaccid paralysis with predominant involvement of spinal cord gray matter, often preceded by a respiratory or gastrointestinal illness, and typically with minimal recovery. The first cases were identified in California in 2012, coincident with an outbreak of enterovirus D68 (EV-D68) infections,¹ and there has since continued to be a temporal association between AFM cases and EV-D68 outbreaks. This led some to hypothesize an association

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between the 2 disease processes.² A case definition of AFM was developed by the Centers for Disease Control and Prevention (CDC) in 2014³: acute-onset focal limb weakness occurring on or after August 1, 2014, and MRI spinal cord lesions largely restricted to gray matter. The CDC began surveillance for AFM in August 2014, and as of March 2019, 558 cases have been confirmed in the United States.³

Our institution has collected data on children with apparent demyelinating disorders prospectively since 2000, including those with acute flaccid limb weakness. In this case series, we retrospectively examined the courses of patients who, besides presenting before 2014, fulfill the 2014 case definition for AFM and compared features of this population with children evaluated at our institution with AFM since 2014. We then compared our post-2014 population with CDC-reported cases regarding clinical course, diagnostic data, and outcomes.

Methods

Our pediatric neuroinflammatory database was queried for cases which fit the clinical criteria for AFM. Cases in which involved extremities developed hypertonia within one month of onset were excluded, whereas cases with sensory deficits or increased tone after one month from onset were included. Although sensory deficits and late development of hypertonia are atypical features of AFM, they are explained by the fact that both gray and white matter spinal cord tracts can be affected in some cases of AFM. Cases were divided into patients with onset before August 1, 2014 (“pre-2014 group”), and after August 1, 2014 (“post-2014 group”). Detailed demographic, clinical, laboratory, and neuroimaging data were collected on all patients. As a reference group, the cases which reported to the CDC between August 2014 and December 2014 (“CDC group”) were compared with the post-2014 group.⁴

Viral testing was performed in the University of Alabama at Birmingham (UAB) Virology Laboratory using reverse transcriptase real-time PCR. All neuroimaging studies were independently reviewed by a collaborating neuroradiologist. The modified Rankin Scale (mRS) was used to assess functional outcomes (0—no symptoms; 1—symptoms but no significant disability; 2—slight disability; 3—moderate disability, requiring some help but able to walk independently; 4—moderately severe disability, unable to walk or attend to needs independently; 5—severe disability, bedridden; and 6—dead). Extremity paralysis was evaluated in each patient individually at disease nadir and compared with weakness at the most recent follow-up.

Given our small sample size, descriptive statistical measures were used. Means with SDs or medians with ranges were used for continuous variables. For categorical variables, counts and percentages were used.

Standard protocol approvals, registrations, and patient consents

The institutional review board of the UAB approved the study protocol and authorized waiver of consent.

Data availability

Any data not published within this article are available at Children’s of Alabama. Deidentified patient-related data will be shared on request from any qualified investigator, maintaining anonymization of the individual patients.

Results

The pre-2014 group consisted of 6 patients with onset between 2007 and 2013, and the post-2014 group consisted of 10 patients with onset between August 2014 and September 2018. Both groups were similar regarding age, sex, and race/ethnicity (table 1).

Clinical presentation

Presenting symptoms are summarized in table 1. In both groups, most individuals first experienced neck or back pain and then reached their nadir within 24 hours of symptom onset. The prevalence of fever and prior infection were higher in the post-2014 group compared with the pre-2014 group, whereas prevalence of autonomic dysfunction, headache, and prior respiratory or gastrointestinal symptoms were similar between the groups. Overall, 3 patients required critical care admission for status asthmaticus shortly before developing weakness. At disease nadir, both groups had a similarly poor median mRS. The number and distribution of affected limbs were similar between the 2 groups (table e-1, links.lww.com/CPJ/A159).

Diagnostic findings

Diagnostic findings are summarized in table 2. All patients underwent lumbar puncture except 1 post-2014 patient, compared with 112 of 120 patients in the CDC group. Pleocytosis, defined as CSF white blood cell count (WBC) > 5 cells/mm,⁵ was considerably less common in the pre-2014 group compared with post-2014 and CDC groups. The median WBC count was substantially higher in post-2014 and CDC groups compared with the pre-2014 group as well. All groups had a lymphocytic predominance and normal median CSF protein. Nerve conduction studies were performed on a minority of patients (5 total), all with non-specific findings of lower motor neuron injury, consistent with the diagnosis of AFM.

Although there was a wide range of the number, type, and specimens of viral studies, all patients had at least 1 viral study performed. Given the previously described temporal and geographical association of AFM with enterovirus outbreaks,⁶ we focused on enterovirus studies. We included rhinovirus respiratory specimens because there are data suggesting that EV-D68 cross-reacts with human rhinovirus

Table 1 Patient characteristics/clinical presentation

	Pre-2014 group	Post-2014 group	CDC group
Total patients, n	6	10	120
Sex, female, n (%)	3 (50)	6 (60)	49 (41)
Age, y, median (range)	8 (0.9–12.9)	5.7 (2.8–17.5)	7.1 (0.4–20.8)
Age, y, mean $\pm$ SD	7.4 $\pm$ 4.5	6.4 $\pm$ 4.3	NA
Race/ethnicity, n (%)			
Caucasian	3 (50)	6 (60)	79 (83)
African-American	2 (33)	4 (40)	7 (7)
Latino	1 (17)	0	29 (33)
Weakness onset to nadir <24 h, n (%)	4 (67)	9 (90)	NA
Symptomatology, n (%)			
Headache	2 (33)	5 (50)	NA
Neck/back pain	5 (83)	9 (90)	NA
Cranial neuropathy	0	2 (20)	34 (28)
Encephalopathy	0	1 (10)	12 (11)
Seizure	0	0	5 (4)
Fever	3 (50)	10 (100)	74 (64)
Prior illness	4 (67)	10 (100)	NA
Upper respiratory	3 (75)	9 (90)	105 (90)
Gastrointestinal	1 (25)	1 (10)	NA
Status asthmaticus	1 (17)	2 (20)	NA
Autonomic dysfunction	3 (50)	5 (50)	NA
Extremities involved, n (%)			
Monoplegia	2 (33)	2 (20)	30
Hemiplegia/paraplegia	2 (33)	4 (40)	NA
Quadriplegia	2 (33)	4 (40)	30 (25)
mRS, nadir, median (range)	4 (3–5)	4.5 (3–5)	NA

mRS = modified Rankin Scale.

on respiratory molecular platforms.⁷ The pre-2014 patients were overall less likely to have had any enterovirus testing, with only 2 CSF specimens, both of which were negative. In the post-2014 group, all patients had a variety of enterovirus specimens tested, and 8 had a positive result in at least 1 specimen, most often respiratory or stool. Seven patients had specimens analyzed for EV-D68, 4 of which had at least 1 specimen subtyped to EV-D68.

Of 7 post-2014 CSF specimens tested for enterovirus, 1 patient had enterovirus isolated in the CSF, although EV-D68 subtyping was negative. This patient additionally had a respiratory specimen positive for rhinovirus and a stool specimen positive for enterovirus, which was subtyped to

EV-D68. This contrasts with the CDC data in which of 97 CSF specimens reported (all tested at external sites), only 2 were positive for enterovirus/rhinovirus. Of 55 CSF specimens tested at the CDC, only 1 was positive for EV-D68, which had >3,000 red blood cells/ μ L with no data on serum testing.

Imaging findings

We divided MRI scans into acute-phase MRI (<7 days of the onset of weakness), subacute-phase MRI (8–42 days), and chronic-phase MRI (>42 days) scans. There was a variety of acute, subacute, and chronic phase scans in all patients. Acute/subacute imaging characteristics are summarized in table e-2 (links.lww.com/CPJ/A159).

Table 2 Diagnostic findings

	Pre-2014 group (n = 6)	Post-2014 group (n = 10)	CDC group (n = 120)
Days from weakness onset to first LP, median (range)	3 (0–14)	2 (0–4)	2 (0–42)
LP ≤ 2 d from weakness onset, n/total (%)	3/6 (50)	8/9 (89)	NA
CSF WBC > 5, n/total (%)	1/6 (17)	8/9 (89)	91/112 (81)
CSF WBC, median (range)	1 (0–14)	68 (0–110)	44 (0–664)
CSF WBC, mean (SD)	3.2 (5.4)	57 (41)	NA
% lymphocytes, median (range)	89 (14–100)	59 (10–90)	74 (46–89)
% lymphocytes, mean (SD)	73 (40)	54 (33)	NA
% neutrophils, median (range)	0.5 (0–69)	30 (5–80)	8 (2–27)
% neutrophils, mean (SD)	17.5 (34)	35 (31)	NA
CSF protein, median (range)	27 (16–42)	38 (23–72)	43 (34–60)
CSF protein, mean (SD)	27 (9)	41 (16)	NA
Viral studies positive/tested, n (% positive)			
Any enterovirus/rhinovirus specimen	0/2	8/10 (80)	36/208 (17)
Enterovirus, respiratory	NA	4/10 (40)	24/56 (43)
Rhinovirus, respiratory	NA	4/8 (50)	24/56 (43)
Enterovirus, serum	NA	0/4	0/43
Enterovirus, CSF	0/2	1/7 (14)	1/55 (2)
Enterovirus, stool	NA	5/8 (63)	11/54 (20)
EV-D68 positive/tested, n (% positive)			
Any specimen	NA	4/7 (57)	12/35 (34)
Respiratory	NA	3/5 (60)	11/23 (48)
Serum	NA	0/4	NA
CSF	NA	0/2	1/1 (100)
Stool	NA	2/5 (40)	0/11
Nerve conduction studies	1	4	NA

EV-D68 = enterovirus D68.

Imaging findings in our patients showed some novel results. In acute scans, most patients had diffuse cord gray matter involvement (figure 1). Some patients had white matter involvement affecting the dorsal and/or lateral corticospinal tracts (figure e-1, links.lww.com/CPJ/A158). Brainstem findings involved pontine tegmentum and posterolateral medulla with signal abnormality continuing caudally to the cervical cord gray matter (figure 2). Ventral nerve root and/or cauda equina (CE) nerve root enhancement were seen in half of patients in both groups (figure e-2).

In the pre-2014 group, 2 patients had spinal cord white matter involvement on acute/subacute-phase imaging, one of which isolated to central gray matter and anterior horn cell

involvement on chronic-phase imaging. There were ventral cervical and/or CE nerve root thickening and enhancement noted in 4 patients, which correlated with deficits in 2 patients. Of the 5 patients who had subacute and/or chronic MRIs, neurologic deficits at the last follow-up correlated with MRI abnormalities in 3 patients.

In the post-2014 group, 4 patients had spinal cord white matter abnormalities on acute/subacute imaging. When patients had brainstem abnormalities, cervical cord lesions were contiguous with brainstem lesions. Five patients had CE nerve root thickening/enhancement in acute and subacute stages, which correlated with deficits in 4 patients. Similar to the pre-2014 group, the anterior horn myelomalacia became

Figure 1 Acute-phase axial T2 image. Image shows central cervical cord gray matter hyperintensity (arrow)

more isolated in chronic-phase imaging. Of the 8 patients with subacute and/or chronic MRIs, neurologic deficits at the most recent follow-up correlated with MRI abnormalities in 7 patients.

Management and outcomes

Management and outcome characteristics are summarized in table 3. All patients were treated with some form of immunomodulatory agent, including IV immune globulin (IVIG), high-dose IV steroids, or plasmapheresis. The CDC published recommendations for management of AFM in November 2014,⁸ which specifically discouraged the use of steroids or plasmapheresis but did not endorse or recommend against the use of IVIG. In response to these recommendations, the patients presenting after that date were less likely to be treated with plasmapheresis or steroids, although 4 of the 7 patients presenting after that time still received at least one of those therapies. Overall, the median number of treatment courses and time to first treatment were similar between the 2 groups. All post-2014 patients were treated with IVIG, compared with a third of pre-2014 patients. In addition, all pre-2014 patients received steroids, compared

with 60% of post-2014 patients. Plasmapheresis was used in a minority of patients in both groups. Treatment modalities were not provided for the CDC group.

The median hospital stay was considerably longer in post-2014 patients compared with pre-2014 patients. Only 1 patient in the pre-2014 group had an intensive care unit stay (3 days), compared with 60% of post-2014 patients with

All post-2014 patients were treated with IVIG, compared to a third of pre-2014 patients. Additionally, all pre-2014 patients received steroids, compared to 60% of post-2014 patients.

Figure 2 Acute-phase sagittal STIR image. Image shows diffuse hyperintensity in the pons medullary tegmentum (red arrows) in continuity with central cervical and thoracic cord hyperintensity (green arrows)

a median stay of 26 days. All patients who had intensive care unit stays required mechanical ventilation.

Functional and motor outcomes are summarized in table e-1 (links.lww.com/CPJ/A159). The median time to the most recent follow-up was 6.2 months in the pre-2014 group and 16.6 months in the post-2014 group. At the follow-up, the median mRS in both pre-2014 and post-2014 groups was 3.5, whereas the median mRS at disease nadir was 4 in the pre-2014 group and 4.5 in the post-2014 group. The median change in mRS between nadir and follow-up was 0 in both groups, and the mean change in mRS was 0.5 in the pre-2014 group and 0.6 in the post-2014 group. At the most recent follow-up, all patients had some degree of disability, and in both groups, half were somewhat impaired and half were completely dependent. There were no deaths in either group at the most recent follow-up. Both groups had a majority of patients with no functional improvement from their nadir. Overall, the range in extremity paralysis for each patient changed little from disease nadir to the most recent follow-up in both groups. Many patients had other persistent residual symptoms at the most recent follow-up, including home mechanical ventilation (2 post-2014 patients), bilevel positive airway pressure (1 post-2014 patient), neurogenic bladder requiring catheterization (1 pre-2014 and 2 post-

2014 patients), and neurogenic bowel requiring colostomy (1 post-2014 patient). One pre-2014 patient requiring mechanical ventilation was transferred to an out-of-state hospital 3 days after admission, with no further follow-up at our institution.

Discussion

We report on 16 cases of AFM at a single children's hospital between 2007 and 2018, divided by onset before August 1, 2014, and after that date. This date was chosen because it was included in the original CDC case definition of AFM in 2014.⁵ However, in June 2017, the Council of State and Territorial Epidemiologists case definition used by the CDC was updated to remove the date restriction.⁸ We believe the historical distinction of this date still carries relevance because the number of cases of AFM with temporal and geographical associations with enterovirus outbreaks was noticeably more prominent after this date.¹ However, as nationwide surveillance for AFM only began in 2014, there are limited cases in the literature of AFM associated with enterovirus before 2014.¹ This paucity of data makes it difficult to determine whether these earlier cases represent the same disease or whether a phenotypic or pathophysiologic change occurred in cases since 2014. This series both adds important information regarding the phenotype of AFM before 2014 and underscores similarities and differences between patients before and after 2014.

Our study highlights several contrasting features between the groups. Although most patients in both groups had associated symptoms of fever, prior infection, neck or back pain, and reached their clinical nadir within 24 hours of weakness onset, all these features were more prevalent in the post-2014 group. The 3 patients who presented with status asthmaticus shortly before developing weakness likely represent cases of Hopkins⁹ syndrome, a poorly understood syndrome first described in 1974 in which asthma exacerbations are associated with paralysis due to injury of spinal cord anterior horn cells. Both pre-2014 and post-2014 groups had a similarly poor median mRS and significant motor weakness at nadir.

Although both groups had CSF studies obtained relatively soon after weakness onset, there were some important differences between the groups. Nearly all post-2014 patients

Nearly all post-2014 patients had a robust pleocytosis, compared to only one patient in the pre-2014 group, implying a more inflammatory intrathecal process.

Table 3 Treatment and clinical course

	Pre-2014 group (6)	Post-2014 group (10)	CDC group (120)
Treatment			NA
Time from onset to first treatment, d, median (range)	2.5 (0–15)	1 (0–4)	
No. of treatments, median (range)	1.5 (1–4)	2 (2–3)	
No. of different treatment modalities, median (range)	1.5 (1–3)	2 (1–3)	
IVIG, n (%)	2 (33)	10 (100)	
Steroids, n (%)	6 (100)	6 (60)	
PLEX, n (%)	2 (33)	4 (40)	
Length of hospital stay, d, median (range)	7.5 (3–16)	27 (5–140)	NA
PICU stay, n (%)	1 (17)	6 (60)	58/112 (52)
Length of PICU stay, d, median (range)	3 (NA)	26 (4–40)	NA
Mechanical ventilation, n (%)	1 (17)	6 (60)	26/109 (20)
Time to the most recent follow-up, mo, median (range)	6.2 (0.1–136)	16.6 (1.4–51)	4.2
mRS at the follow-up, median (range)	3.5 (2–5)	3.5 (2–5)	NA
Change in mRS, nadir to follow-up, median (range)	0 (0–2)	0 (0–3)	NA
Change in mRS, nadir to follow-up, mean (SD)	0.5 (0.84)	0.6 (1.1)	NA
Function outcomes, n (%)			
Fully functional (mRS 0–1)	0	0	10 (18)
Somewhat impaired (mRS 2–3)	3 (50)	5 (50)	38 (68)
Complete dependence (mRS 4–5)	3 (50)	5 (50)	8 (14)
No improvement (Δ mRS = 0)	4 (67)	7 (70)	NA

IVIG = IV immune globulin; LP = lumbar puncture; mRS = modified Rankin Scale; NA = not applicable; PICU = pediatric intensive care unit; PLEX = plasmapheresis.

had a robust pleocytosis, compared with only 1 patient in the pre-2014 group, implying a more inflammatory intrathecal process. Comparing viral studies between the groups was limited in that a minority of pre-2014 patients had any enterovirus or rhinovirus testing; thus, our study cannot support an argument for or against the association of enterovirus with AFM in pre-2014 patients. In the post-2014 group, most patients had some form of positive enterovirus or rhinovirus specimen, including 1 CSF specimen. More than half of patients with samples tested for EV-D68 were positive. This supports previous studies showing a correlation between AFM and EV-D68 infection.^{2,4,10}

Our study describes 1 patient in the post-2014 group with enterovirus detected in the CSF and a stool specimen positive for EV-D68. Because there has been only 1 patient reported to the CDC with enterovirus isolated from the CSF, which was itself a questionable positive result with >3,000 red blood cells in the CSF, it has been difficult to ascertain the

relationship between AFM and EV-D68. Although there is biological plausibility and support from epidemiologic data to argue for a causal relationship between AFM and EV-D68, the paucity of enteroviral CSF specimens in AFM cases has confounded the association. There is a single pathologic specimen reported in 2011 from a fatal case of EV-D68 CNS infection in a 5-year-old with acute flaccid paralysis, which revealed neuronophagia of anterior horn motor nuclei.¹¹ Our patient adds support to the argument that EV-D68 is a causative agent in AFM.

On subacute scans, the cord involvement regarding both craniocaudal extent and degree of cross-sectional cord involvement showed improvement, which varied from a few vertebral levels to near-complete resolution of abnormalities. On chronic scans, not only did the longitudinal and cross-sectional involvement improve but also injury was mostly limited to anterior horn cells, described as a “snake eyes” appearance. Subacute/chronic MRI findings correlated with

residual neurologic deficits in most patients, although more frequently in post-2014 patients. However, if chronic imaging was obtained after a long gap (such as years), the abnormalities often became very subtle, which may lead to poor correlation of chronic MRI findings with permanent deficits.

There was substantial overlap in the acute/subacute imaging findings of the pre-2014 and post-2014 patients, which correlates with other case series.¹² The most recurring imaging features were cervical cord central gray matter involvement (seen in 15 patients), pontine tegmentum and posterolateral medulla signal abnormality (variably seen in 8 patients), and CE and ventral nerve root thickening and enhancement (seen in 8 patients). The triad of pontine tegmentum, central cord gray matter, and CE/ventral nerve root abnormalities, observed in 5 patients, has been previously described.¹² The presence of 2 of 3 of these findings (seen in 10 patients) could potentially be suggestive of the disease in the appropriate clinical setting.

The mRS was used to evaluate functional outcomes, and extremity paralysis was compared in each patient from nadir to follow-up. Although the mRS was originally developed for stroke outcomes, there is a precedent of using the mRS to measure disability in patients with acute flaccid paralysis^{13,14} because it covers functional outcomes with intuitive steps ranging from no symptoms to death. Because the primary symptom of AFM is motor weakness, we thought it important to specifically include motor outcomes as well. There was often resolution or dramatic improvement of weakness if extremities were minimally involved at disease nadir, but of extremities with severe or complete weakness at nadir, none had full return of strength at the most recent follow-up.

All patients were treated with some combination of high-dose IV steroids, IVIG, or plasmapheresis, with similar numbers of treatments; however, there were some noteworthy differences in treatment modalities between the 2 groups (table e-3, links.lww.com/CPJ/A159). All pre-2014 patients were treated with high-dose IV steroids and a third with IVIG and/or plasmapheresis. In the post-2014 group, all patients were treated with IVIG, with a majority also receiving either high-dose IV steroids and/or plasmapheresis. There was no correlation between treatment regimens and improvement in mRS or extremity strength. The differences in the use of IVIG and steroids between the groups could be explained by the presumed underlying pathophysiology. Because many pre-2014 patients were thought to have a flaccid variant of transverse myelitis, they were treated with high-dose IV steroids, the standard acute treatment for transverse myelitis. As the association with enterovirus became more evident in 2014, the concern that AFM was potentially an infectious process prompted IVIG to be used first line to avoid immunosuppression from steroids, in addition to the 2014 CDC recommendations advising against steroid and plasmapheresis use.¹⁵

Post-2014 patients had longer hospital stays and were more likely to require mechanical ventilation and intensive care compared with pre-2014 patients, implying a more severe clinical course. However, when comparing both functional and strength outcomes between the 2 groups, there were only negligible differences. All patients at the last follow-up were either somewhat impaired or completely dependent and had little functional improvement from their disease nadir. In addition, motor weakness did not improve considerably and in most cases remained relatively stable from disease nadir. This contrasts with the CDC data, in which 18% of patients were fully functional at the last follow-up, 68% were somewhat impaired, and 14% were completely dependent. This discrepancy could be explained by regional or geographic variation in disease severity, variability in clinician assessment, or differences in patient catchment.

Our study had several limitations. The small sample size, with further division of patients into pre-2014 and post-2014 groups, limits the generalizability of our results to larger populations and the ability to draw substantive conclusions. To somewhat offset this limitation, the clinical data from patients reported to the CDC between August and December 2014 were used for comparison with our post-2014 group when possible to substantiate whether our results were similar to those seen on a national level. Overall, our post-2014 group was similar to the CDC data except in outcomes, in which our patients generally had poorer results. Selection bias likely affected our data because we reported only on pediatric patients seen at our tertiary institution, potentially missing milder cases of AFM. Because the association with enterovirus was not well-known before 2014, enterovirus testing in the pre-2014 patients was limited, and no EV-D68 subtyping was performed. Although our data were collected prospectively, there were no systematic evaluations and treatments of patients, which should leave one to carefully interpret our findings. In particular, when patients were critically ill during their nadir, a detailed, formal motor examination was often limited. The correlation between treatments and outcomes was likely confounded by severity bias because more severely affected patients typically received more aggressive treatment.

Pre-2014 and post-2014 patients had many similarities including acute onset of weakness, associated prior infection and fever, poor response to treatment, and significant residual disability and persistent weakness. Notable differences in the post-2014 group include more prevalent fever, higher CSF WBC, and higher neutrophil count. The triad of pontine tegmentum, cervical cord gray matter, and nerve root enhancement abnormalities was seen in a minority of patients, with subacute/chronic abnormalities isolated to areas which correlate with neurologic deficits in most patients. Although most post-2014 patients had concomitant enterovirus infections, most of which were

TAKE-HOME POINTS

- Patients with AFM before and since 2014 were overall similar in clinical presentation and diagnostic characteristics, but post-2014 patients were typically more acutely ill.
- Most patients with AFM since 2014 had enterovirus isolated from respiratory or stool specimens, and more than half of those tested for EV-D68 were positive.
- Triad of cervical cord central gray matter, pontine tegmentum, and CE/nerve root abnormalities on acute MRI scans should raise suspicion for AFM in the appropriate clinical setting.
- Most patients with AFM both before and since 2014 had minimal improvement in both function and strength between disease nadir and the most recent follow-up despite various immunotherapy regimens.

EV-D68, this difference is inconclusive given the lack of testing in pre-2014 patients. Overall, the 2 groups appeared to have more in common than qualities that separate them. Although our small sample size is limiting, this series indicates that these 2 groups of patients likely represent the same disease process with some phenotypical variation. Our series includes 1 patient with enterovirus isolated in the CSF and EV-D68 in the stool. This is a rare finding in a disease process which has been well-known to correlate with EV-D68 respiratory infections, but with limited evidence of direct CNS penetration by the virus. This study adds guarded support to the argument that EV-D68 is a causative agent in AFM, although more sensitive molecular testing and pathologic specimens are still needed. The minimal response to immunotherapy in our patients regardless of the treatment regimen argues in favor of the position that AFM is more likely a directly infectious rather than an immune-mediated process. Finally, the overall minimal recovery both in functional and motor outcomes despite varied and aggressive acute treatments argues toward careful risk assessment when choosing immunotherapies in these patients.

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Appendix Authors

Name	Location	Contribution
Lydia Marcus, MD	University of Alabama at Birmingham, Birmingham	Designed and conceptualized study, reviewed medical records, analyzed the data, and drafted and revised manuscript
Sumit Singh, MD	University of Alabama at Birmingham, Birmingham	Reviewed neuroimaging and drafted and revised the manuscript
Jayne Ness, MD, PhD	University of Alabama at Birmingham, Birmingham	Designed and conceptualized the study and revised the manuscript

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