Incidence, Risk Factors and Outcomes Among Children With Acute Flaccid Myelitis: A Population-based Cohort Study in a California Health Network Between 2011 and 2016

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Background: Acute flaccid myelitis (AFM) is defined as an acute onset of limb weakness with longitudinal spinal gray matter lesions. Reporting bias and misdiagnosis confound epidemiologic studies of AFM. We mitigated these confounders by using a large data set to assess AFM incidence, risk factors and outcomes in a fixed population.

Methods: A retrospective cohort study was conducted within Kaiser Permanente Northern California population among children 1–18 years. Cases met radiographic and clinical criteria for AFM and were confirmed by two clinicians. Clinical and demographic data were assessed.

Results: A total of 28 patients met study criteria for AFM between January 1, 2011 and December 31, 2016, an overall rate of 1.46 per 100,000 person-years. Incidence increased from 0.30 to 1.43 cases/per 100,000 person-years between 2011 and 2016, respectively. Median age was 9 years. Risk factors included male sex, Asian ancestry and history of asthma, atopic dermatitis or head injury. Risk factors associated with poliomyelitis were absent. Prodromal illness was common; enterovirus was the most common pathogen detected (n = 5). Among the 27 patients with 12-month follow-up, most demonstrated some improvement, 11 (41.0%) had full recovery, but several had significant deficits with one death reported after the study period.

Conclusions: We employed a closed-population study to generate AFM incidence, risk and outcome data. Our findings support previous reports of male sex and atopy as risk factors. Interval increase in incidence, predisposing Asian ancestry and history of head injury were unique findings to this study. Overall prognosis was better than prior reports, but recovery was incomplete in several patients.

Key Words: AFM, Paralysis, risk factors, incidence

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Since 2012, there has been an increase in reports of pediatric paralysis described as acute flaccid myelitis (AFM), with a recent noticeable rise in 2016 and 2018.[1–3] AFM has been previously defined as a neurologic syndrome with an acute onset of flaccid limb weakness with associated longitudinal lesions of the spinal cord gray matter.[4] To date, estimates of AFM population incidence have relied primarily on passive reporting which is prone to underreporting and underrepresentation of demographic groups.[5] Although various enterovirus (EV) species, including EV-D68, have been isolated from a subset of AFM patients, they have typically been isolated from noncentral nervous system sites (eg, nasal swabs, stool), making a pathogenic link difficult to establish.[4] Nonetheless, AFM is often called a "polio-like" syndrome due to the many clinical, radiographic and demographic similarities with poliomyelitis.[2–4,6,7] Reports from poliomyelitis patients in the 1950s suggested antecedent intramuscular injections (eg, vaccines) and physical exertion during the prodromic illness as potential risk factors.[8,9] The goal of this study is to provide a comprehensive, population-based evaluation of AFM incidence data among pediatric patients in a large, community-based, fixed cohort comprising 1,052,632 patient-years, with retrospective analysis of potential risks factors and outcomes over a 5 year period.

MATERIALS AND METHODS

We conducted a retrospective cohort study of AFM cases within the Kaiser Permanente Northern California (KPNC) pediatric population. The study was approved by the Kaiser Foundation Institute and the University of California Berkeley Institutional Review Boards with waiver of informed consent. An AFM case was defined as a patient with acute onset of flaccid limb weakness and radiographic findings of spinal cord gray matter lesions spanning one or more vertebral segments. Cases were identified through a comprehensive electronic search of all KPNC members in Northern California 12 months to 18 years of age between January 1, 2011 and December 31, 2016 with spinal magnetic resonance images (MRIs) and at least one of the following diagnosis codes: paralysis/paresis, hemi paralysis/hemiparesis, ataxia, Guillain-Barre syndrome, transverse myelitis, demyelinating disease, neuromyelitis optica, multiple sclerosis, acute disseminated encephalomyelitis (ADEM), AFM or acute flaccid paralysis. All MRIs with such criteria were reviewed by a single study neuroradiologist (C.S.) who was blinded for AFM clinical characteristics. At minimum, all patients had sagittal T2, sagittal T1 and axial T2 sequences of the cervical and thoracic spine. After radiologic review, a second study clinician (M.K.) reviewed electronic medical records to assess for AFM clinical characteristics. Data elements of interest were either extracted from KPNC databases. The clinical case index date was defined as the first spinal MRI date. Patients were excluded a priori if they (1) were diagnosed with tethered cord or abnormal gluteal fold, (2) had less than 6-month continuous membership before index date or (3) had less than 1 month of membership post-index date.

Demographic information including age at AFM diagnosis, sex, race/ethnicity, residence location and socioeconomic status (SES) were collected. SES data were approximated by census data at block level with low SES defined as having a high probability of education lower than high school and/or household annual income less than $35,000.[10] Electronic medical record review was performed to identify preexisting health conditions, current medications (at the onset of AFM), recent immunizations (within 4 weeks before AFM diagnosis), site of immunization and recent trauma (including history/body site) within 6 months. Records were also evaluated for documentation of remote head trauma, defined as a clinical visit diagnosis of head injury, head trauma or concussion. Preexisting health conditions were determined by those currently or previously listed on patients' formal problem list or through searching diagnosis codes in an outpatient, inpatient or emergency department setting. Prodromal illnesses, extent of limb involvement and presence/absence of central nervous system deficits on clinical exam were documented. Laboratory data such as cerebrospinal fluid (CSF) white blood cell profiles (pleocytosis defined as >5 cells per μL) and protein counts (elevated protein defined as >25 mg/dL) and diagnostic testing were gathered.[11] Neurologic involvement was categorized as monoplegia if weakness was limited to 1 limb, polyplegia with 2 or 3 limbs and quadriplegia with 4-limb involvement of paralysis/weakness with or without respiratory compromise.

Information regarding recovery at discharge and 6 and 12 months postdischarge at a neurologist and/or physical medicine and rehabilitation specialist visit was collected. Recovery was classified into 3 categories based on Modified Rankin Scale[12]: none (no clinical recovery, Modified Rankin Scale of 5–6), partial (some recovery noted in weakness/extremity strength, respiratory or feeding function in comparison to previous exam, Modified Rankin Scale of 1–4) and full recovery (complete recovery to baseline and resolution of all neurological signs, Modified Rankin Scale of 0).[12]

We calculated the AFM annual incidence, followed by cases per quarter and month. We also examined resident geographic location without spatial analysis given small population size and difficulty with known AFM baseline incidence data. Binomial testing was used to compare the AFM cohort versus the KPNC pediatric population, age 12 months to 18 years with at least 1-year continuous membership during the 6-year period, for sex, race, SES, asthma, atopic dermatitis and remote history of head trauma. Bivariate analysis was used to estimate relative risk comparing the risk of nonrecovery at 3-time intervals between the presence or absence of certain clinical characteristics.

RESULTS

From January 1, 2011 to December 31, 2016, a total of 1,052,632 pediatric patient-years were captured in the KPNC database. From this cohort, we identified 302 individuals between 12 months and 18 years of age with one or more spinal MRI performed and had at least one supporting diagnosis; 272 patients were excluded due to the absence of a spinal lesion on MRI during review by study radiologist, followed by the exclusion of an additional 2 patients who did not meet clinical diagnosis of AFM (one patient with Guillain-Barre syndrome and one spinal cord trauma/transection patient). The final cohort meeting AFM criteria included 28 patients (Figure 1, Supplemental Digital Content 1, http://links.lww.com/INF/D457). The incidence rate fluctuated during the 6-year period with a 5-fold increase from 2011 with a crude rate of 0.30–1.43 per 100,000 person-years in 2016 (P = 0.05). There was a notable increase in cases in 2016 compared with the previous 5 years with the highest increase in 2016 quarter 4 with 5 cases in total (Fig. 1A). The highest number of cases was in September to December each year in comparison to other months (Fig. 1B). Resident locations were noted to be diverse throughout northern California.

Demographics

The median age of the 28 cases was 9 years and ranged from 2 to 17 years (Table 1). Compared with the KPNC population of comparable age, the AFM cohort had a significantly higher proportion of patients with Asian ancestry (35.7% vs. 19.0%, P = 0.02) and males (67.9% vs. 50.7%, P = 0.06; Table 2). The SES of the AFM cohort was comparable to KPNC population of comparable age.

Preexisting Conditions

Only one patient (3.6%) had a history of recent vaccination, and the body site of injection did not correlate with the location

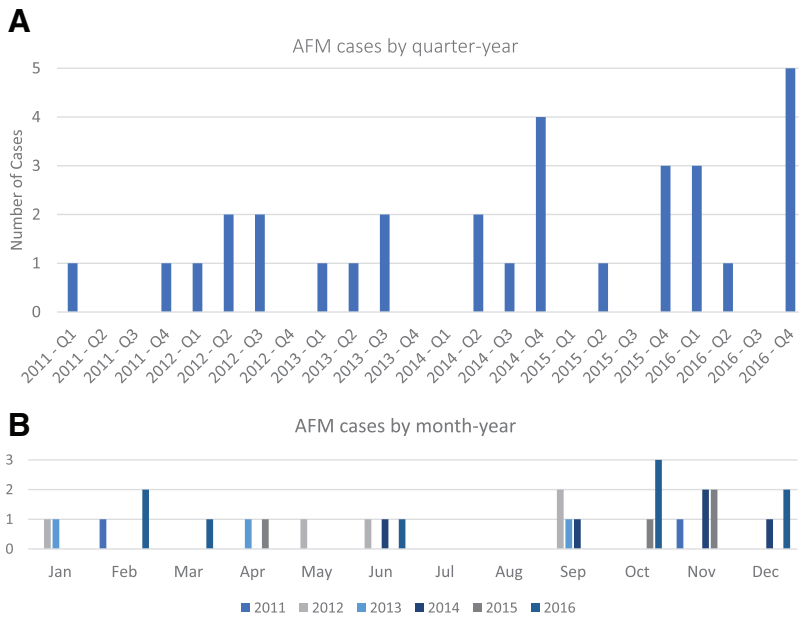

FIGURE 1. AFM by quarter-year (A) and seasonality (B). (A: Shaded area represents AFM case(s) from 2011 to 2016. quarter 1 (Q1) refers to January to March, quarter 2 (Q2) refers to April to June, quarter 3 (Q3) refers to July to September and quarter 4 (Q4) refers to October to December. B: Months are listed on *x*-axis with number of cases on *y*-axis and each year is represented in the key listed by color.

TABLE 1. Demographics and clinical characteristics of AFM cohort

Characteristics	Total (N = 28)	
Demographics		
Age		
Mean, SD	9.1	4.9
Median, (IQR)	9.0	(5.0, 14.5)
Range, (min, max)	15.0	(2.0, 17.0)
Male gender, N%	19	67.9
Race, N%		
White	12	42.9
Asian	10	35.7
Others	1	3.6
Unknown/not asked	5	17.9
Hispanic ethnicity, N%	8	28.6
Low SES,* N%	6	21.4
Medical history/preexisting conditions, N%		
Asthma	9	32.1
Atopic dermatitis	9	32.1
Autoimmune disease†	6	21.4
ADHD	3	10.7
Clinical presentation/coexisting features, N%		
Fever	23	82.1
On admission‡	8	34.8
Within 1 week prior‡	15	65.2
URI/Cough within 1 week	17	60.7
GI symptoms	10	35.8
Asthma exacerbation	2	7.1
Urinary retention§	8	28.6
Rash	8	28.6
Trauma within 6 months¶	4	14.3
Vaccine within 4 weeks	1	3.6
Head trauma/injury‖	7	25.0
Extent of involvement		
Monoplegia	5	17.9
Polyplegia	11	39.3
Quadriplegia	12	42.9
Discharge diagnosis		
Acute myelitis NOS	7	25.0
Other myelitis	3	10.7
Paralysis NOS	2	7.1
Infectious disease NOS	2	7.1
Post-infectious ADEM	2	7.1
Other individual diagnosis**	12	42.9

*Low SES was defined as having low education or low income based on the US Census and Geocode.

†Autoimmune diseases included diabetes type 1, psoriasis, multiple sclerosis, Bechet, neonatal onset multisystem inflammatory disease and ulcerative colitis.

‡Fever on admission and within 1 week prior calculated as out of the 23 patients who presented with fever.

§One patient had urinary tract infection diagnosis in setting of urinary retention.

¶Trauma was classified as extremity trauma within 6 months of AFM diagnosis though all trauma cases were within 4 months of diagnosis.

‖Head trauma/injury was defined as a historical encounter for head injury, trauma or concussion.

**Other remaining diagnoses were ADEM, enteroviral meningitis, Guillain-Barre syndrome, malaise and fatigue, myelitis unspecified, neuromyelitis optica, sepsis unspecified, skin sensation disturbance, unspecified viral encephalitis, vascular myelopathies, viral infection NOS and weakness.

ADHD, attention-deficient and hyperactivity disorder; GI, gastrointestinal; NOS, not otherwise specified.

of weakness/paralysis. Only 4 patients (14.3%) were noted to have extremity trauma within 4 months before AFM presentation, and the location of trauma did not correlate with the location of weakness/paralysis. A significant number of our AFM cohort (n = 7, 25.0%) had a prior encounter for head injury (average 2 years before AFM presentation) compared with the KPNC population (25.0% vs. 0.006%, $P < 0.001$; Table 2). Asthma (n = 9, 32.1%) and atopic dermatitis (n = 9, 32.1%) were the most common preexisting medical conditions among the AFM cases and both occurred more often in AFM patients compared with the KPNC population (asthma: 32.1% vs. 11.4%, $P < 0.001$; atopic dermatitis: 32.1% vs. 4.7%, $P < 0.001$). Six patients (21.4%) from the AFM cohort had some form of autoimmune disease (diabetes type 1, multiple sclerosis, Behcet disease, neonatal onset multisystem inflammatory disease and ulcerative colitis). Two patients (7.14%) were on oral steroids for a few days within 1 month before diagnosis of AFM.

TABLE 2. Binomial test comparing AFM cohort vs. KP population

	AFM Cohort		KP Population		*P*
	N	%	N	%	
Male gender	19	67.9	335,098	50.7	0.06
Race					
White	12	42.9	275,003	41.6	0.89
Asian	10	35.7	125,225	19.0	0.02
Others/unknown	6	3.6	204,518	31.0	0.28
Hispanic	8	28.6	188,129	28.5	0.99
Low SES*	6	21.4	137,540	20.8	0.94
Asthma*	9	32.1	75,017	11.4	<0.001
Head trauma/inj*	7	25.00	6,285	0.006	<0.001
Atopic dermatitis	9	32.14	31,334	4.7	<0.001

Head trauma/injury and atopic dermatitis are presented as cumulative incidence over 6-year period, as opposed to the average proportion of 2011–2016 for demographics and asthma cases, which remain relatively stable over time. These were chosen given ease of comparing to KPNC population. Asthma and atopic dermatitis are defined as the presence of diagnosis on problem list, head trauma/injury is defined as a clinical encounter for head trauma, injury or concussion.

Clinical Features

Most AFM patients had fever (n = 23, 82.1%), upper respiratory infection and cough (n = 17, 60.7%), and some (n = 10, 35.8%) had gastrointestinal symptoms at the time of admission or within 1 week of admission. The extent of limb involvement ranged from monoplegia, weakness in 1 limb (n = 5, 17.9%), to quadriplegia, 4-limb involvement with or without respiratory compromise (n = 12, 42.9%). Less than one-third of patients had symptoms that could be classified as supratentorial in origin on presentation (Table 1, Supplemental Digital Content 2, http://links.lww.com/INF/D456). The most common discharge diagnosis was acute myelitis not otherwise specified (n = 7, 25%) (Table 1)

Lab and MRI Results (Table 3)

Most AFM patients had CSF pleocytosis and elevated protein (Table 3). EV was isolated from 5 of 11 patients (45.5%) tested; all were from non-CSF samples and occurred September to December. All non-CSF samples that tested positive were collected 2–4 days after the onset of paralysis. Other infectious workup including viral and bacterial testing was also conducted on each patient without any notable results. Testing for neuromyelitis optica was done on 12 (42.9%) patients, and all were negative. Oligoclonal band testing was also performed on 12 (42.9%) but only positive on 1 patient who had a concurrent multiple sclerosis diagnosis.

As defined by our case definition, all 28 patients had at least one spinal MRI, and reports are summarized in Table 3. Overall, MRI consistently showed abnormal nonenhancing T2 hyperintensity within the spinal cord typically involving the central gray matter and specifically, often the anterior horn cells. Preference for the cervical and upper thoracic cord was noted. Over one-third of the cases (n = 12, 44.4%) had associated brain and/or brainstem involvement, and some patients exhibited cauda equina nerve root enhancement. Two patients had abnormalities on both spine and brain MRI. Many patients had repeat MRI studies at various time

TABLE 3. Lab and MRI results, treatment and LOS of AFM cohort

Lab Results		
CSF enterovirus samples tested, N (%)		
Positive	0	0.0
Negative	17	100.0
*Non-CSF enterovirus samples tested, N (%)		
Positive*	5	45.5
Negative	6	54.5
CSF white blood cell count (/μL)		
Mean, SD	59.5	92.5
Median, (IQR)	30.0	(2.0, 81.0)
CSF protein count (mg/dL)		
Mean, SD	46.7	47.2
Median, (IQR)	36	(26.0, 47.5)
Treatment, N (%)		
No treatment	1	3.6
Only steroid	4	14.3
Only IVIG	5	17.8
≥2 Treatments used†	18	64.3
Hospitalized information		
Hospitalized, N (%)	27	96.4
LOS, mean (SD)	21.2	27.4
PICU, N (%)	20	74.1
PICU LOS, mean (SD)	22.1	31.6
PICU LOS ≥50% of total LOS	13	65.0
MRI results‡, N (%)		
Cord§		
Central gray	28	100.0
Diffuse cord	15	53.6
Cervical	7	25.0
Thoracic	3	10.7
Conus lesion	4	14.3
>3 contiguous vertebral levels	24	85.7
Edema/swelling	19	67.9
Enhancement	10	35.7
Nerve root/cauda equina enhancement	5	17.9
Brain involvement	12	44.4
Brainstem	9	33.3
Cerebellum	1	3.7
Supratentorial white matter and cortex	6	22.2
Basal ganglia/thalami	3	11.1

*Non-CSF defined as from nasopharynx, pharynx, stool and serum, positive specimens were found to be enterovirus D68 (1), coxsackievirus type B3 (1), coxsackievirus type B4 (1) and nontypeable (2). Three patients tested positive from nasopharyngeal samples, one from a pharynx sample and one from a stool sample.

†≥2 Treatments used included IVIG, steroids, fluoxetine, and/or plasmapheresis

‡In brain imaging, N = 27 given one patient did not have brain imaging; Non-CSF, nasopharyngeal, pharynx and/or blood specimens.

§Categories of cord and brain involvements are not mutually exclusive).

MRI results are summarized for 28 for spine and 27 for brain.

intervals, and most often, MRI findings improved or resolved over time and correlated with clinical improvement.

Treatment, Length of Stay and Outcomes

Most patients received a combination of treatments (n = 18, 64.3%; Table 3). Most common treatments included intravenous immunoglobulin (IVIG) and steroids with more severe patients also receiving plasmapheresis and/or fluoxetine. No correlation was seen between treatment received, timing of treatment, order of treatment and recovery outcome. Almost all (n = 27, 96.4%) patients were hospitalized. The mean length of stay (LOS) was 21 days. Of those patients hospitalized in the pediatric intensive care unit (PICU; n = 20, 74.1%), the mean LOS was 22.1 days, with 13 patients having PICU LOS >50% of their total LOS. One patient was treated as an outpatient. This patient presented with bilateral lower extremity weakness and received 2 doses of IVIG in the outpatient setting with complete resolution of symptoms after 5 months.

TABLE 4. Recovery of AFM cohort at follow-up intervals

Improvement, N%	At Initial Hospital Discharge		Within 6 Months*		Within 12 Months*	
None (mRs 5–6)	4	14.3	0	0.0	0	0.0
Partial (mRs 1–4)	24	85.7	19	70.5	16	59.3
Full Recovery (mRs 0)	0	0.0	8	29.6	11	40.7

*One patient lost follow-up.
mRs, Modified Rankin Scale

The outcomes at 1 year of 27 patients are summarized in Table 4. One patient was lost to follow-up due to termination of membership 3 months after index date. Eleven patients (40.7%) had full recovery. Initial presentation did not predict recovery. For example, a 6-year-old patient who presented with right arm flaccid paralysis still had residual deficits at 1 year, while another patient, a 4-year-old patient who presented with quadriparesis had a normal neurologic exam at 1 year. Twelve months after AFM onset, 2 patients (7.40%) still required a tracheostomy, while 1 additional patient required tracheostomy placement because of episodes of recurrent respiratory compromise. Four patients (14.8%) had a gastrostomy tube at 12 months. No deaths were recorded in our cohort during the 12-month follow-up study period; however, we learned of one death from complications secondary to AFM that occurred less than 18 months after diagnosis. Bivariate analysis for relative risk estimation showed no significant findings between clinical characteristics at AFM onset and recovery at the 3 time intervals (data not shown).

DISCUSSION

Since 2012, there has been an increased interest and surveillance for AFM. The Centers for Disease Control along with other researchers have been collecting data on AFM patients. Van Haren et al[3] described the use of passive reporting to determine the minimum incidence of AFM in California from 2012 to 2015. This study noted the highest incidence during August 2014 to January 2015 with incidence of 0.16 cases per 100,000 person-years, also noted at the time of the US EV D68 outbreak. Limitations of this data set were underreporting and initiation of data collection only after a subtle increase in incidence prompted implementation of surveillance. A report by Sejvar et al[13] had similar limitations and extrapolating from a 5-month period of nationwide surveillance in 2014, reported the nationwide AFM incidence for individuals less than 21 years of age to be 0.32 cases per 100,000 population/year. These data also relied on passive reporting. Our study found a higher incidence (individuals between 1 and 18 years of age) of 0.75 cases per 100,000 population in 2014, 0.58 cases per 100,000 population in 2015 and an increase to 1.46 cases per 100,000 population in 2016. These higher proportions are likely to be more accurate than the previous data given reliance on passive reporting, which is at risk for underrecognition and underreporting. Our current cohort shares some overlapping patients with the Van Haren et al[3] cohort.

Our study also had some notable findings in comparison to other recent AFM studies in terms of demographic data. Similar to our findings, a male predominance has been reported by other investigators including cases from the California cohort, US cohort and Japan cohort.[2,3,6] Van Haren et al[3] reported 50 cases under 21 years old from 2012 to 2015 in California and noted a median age of 9 years, while a report of US cases 2012–2015 by Messacar et al[2] found a median age of 7.1 years. The median age of our cohort

was similar to the California cohort and US cohort but different from the median age identified in a Japanese cohort (median of 4.4 years) and the European cohort from Knoester et al[14] (median age 3.8 years).[6] Not yet reported in other studies, our study suggested an overrepresentation of AFM patients of Asian ancestry. The reason for the increase is unclear. It is possible that atopic dermatitis, an independent risk factor in our cohort, is highly prevalent among Asians and may be associated with a predisposition toward a pro-inflammatory Th17 immune polarization.[15] Asian ancestry is a well-characterized risk factor among cohorts of patients with Th17-associated neuroinflammatory disorders such as ADEM and neuromyelitis optica.[16–18] An additional study has shown a high seroprevalence of EV-D68 in an unaffected Chinese population, suggesting that underlying host and viral factors may affect neurovirulence.[19]

Our KPNC AFM cohort reinforces asthma as a significant probable risk factor; 32% of the AFM cohort had asthma compared with only 11% of similarly aged KPNC population. At least 2 prior cohorts have reported asthma as the most common preexisting medical condition.[20] Interestingly, a polio-like syndrome, also known as Hopkins syndrome, following asthma attacks has been described.[21] In these case reports, there is a striking similarity to the current AFM cases with anterior horn injury.[22] It is possible that asthma and atopic dermatitis are potential risk factors of AFM, and both are more common among children of Southeast Asian ancestry.[23] Additionally, over 20% of our AFM KPNC patients had a history of autoimmune disease, but we were unable to compare with the Kaiser baseline population given complexities in capturing all diagnosis codes for autoimmune disease or immunosuppressive medications. None of these patients were on immunosuppression in the preceding 6 months before diagnosis.

In terms of diagnostic testing, the results of our study were quite similar to other recent AFM studies where EVs were the most frequently detected pathogen but were not consistently identified and were rarely found in CSF.[2,3,6] As seen in our study, Knoester et al[14] reported that the majority of samples that were positive for EV were detected from respiratory samples. We also found that IVIG and steroids were the most commonly used treatments and did not see any correlation between timing of steroid or IVIG therapy or treatment type and outcome.

In comparison to other recent AFM case descriptions, we were able to obtain comprehensive follow-up data within the KPNC system (27 out of 28 patients had follow-up data available at 12 months).[2,3,6] In general, the outcomes were better than prior reports. Van Haren et al[3] noted that 38 out of 42 patients had persistent weakness at median follow-up of 9 months. Martin et al[24] noted that a majority of patients had persistent weakness after 1 year. Only 3 of 27 patients reported by Knoester et al[14], a European study including only AFM associated with EV-D68 in both pediatric and adult patients, had full clinical recovery. Forty percent (n = 11) of patients in our cohort made a full recovery. Patients who had partial improvement at 12 months varied in terms of extent of recovery, and some still had profound deficits such as ventilator dependency. The more favorable estimates of complete recovery may be the result of our capturing methods, which are less likely to manifest biases that favor more severe cases in reporting and follow-up. The difference may also be because the European study included only those AFM cases associated with EV-D68, while our study included AFM cases not specific to EV-D68. EV-D68 AFM may be more severe than AFM due to other EVs like EV-A71, which has had some reports of more favorable neurologic outcomes.[25] As for the biological mechanism for these somewhat unexpected recoveries, it is plausible that, in addition to the potential for permanent motor neuron injury, a portion of the acute motor deficits in some AFM patients may be due to transient tissue edema, inflammatory response and/or reversible cellular injury. Many patients with motor neuron injuries due to poliovirus and EV-A71 manifest similarly robust recoveries.[6,20,26]

Because the recent AFM cases have striking similarities to poliovirus, we examined some of the proposed risk factors of poliomyelitis. Young age, recent intramuscular injection, strenuous exercise and extremity trauma have been proposed to be associated with the development of paralysis in those infected with poliovirus.[8,26–28] The literature provides conflicting reports on SES as a risk factor for poliovirus.[29] We did not find any significant associations between these proposed risk factors and the onset of AFM in our KPNC AFM cohort.

We identified an unexpectedly high number of our AFM patients with a prior history of head trauma. Our evaluation was originally prompted based on previous reports suggesting an association between head trauma and multiple sclerosis.[30,31] It is plausible that trauma-induced disruption of the blood-brain barrier may induce a sustained disturbance in barrier integrity and neuroimmunity.[32] This may also explain the number of autoimmune cases that we identified given that both head injury and neuroinflammatory conditions could possibly predispose patients to AFM.

Our study had several limitations. It was a retrospective cohort study and AFM cases could have been missed due to misdiagnosis by treating physicians given that AFM is a rare entity. We sought to minimize misclassification by searching for other diagnoses that could have been given to AFM patients to rereview imaging and clinical presentations. We also attempted to limit bias by blinding the neuroradiologist to the patient's clinical history and MRI reports. Having only one study neuroradiologist for core inclusion criteria could have biased our results, given interobserver variations exist among neuroradiologists interpreting even apparent features of brain infection and inflammation.[33] However, the goal of neuroradiology review was to identify potential cases, which underwent another round of review searching for clinical characteristics. In addition, because MRI across KPNC uses standardized protocols, the image quality is relatively uniform. However, we could have underestimated cases because some AFM patients can have a normal MRI early in clinical course, while our study required an abnormal MRI.

Although the majority of our patients manifested persistent muscle weakness at 1-year follow-up, more than one-third mounted a full recovery. This variability in prognosis may reflect the pathogenic heterogeneity of the syndrome permitted by the current epidemiologic case definition. In keeping with this case definition, our inclusion criteria were agnostic to the presence, absence or species of infectious pathogens. And yet, even among a narrow set of AFM-associated viral pathogens, different species (eg, EV-A71 vs. EV-D68) may confer divergent clinical outcomes.[14,25] Future AFM investigations will benefit from improved clinical and/or laboratory markers to help account for clinical and pathogenic heterogeneity of affected individuals. These markers will ultimately be necessary to advance clinical care and therapeutics.

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