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Acute flaccid myelitis: long-term outcomes recorded in the CAPTURE study compared with paediatric transverse myelitis

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ABSTRACT

Background Since 2014, the USA has documented three outbreaks of acute flaccid myelitis (AFM). Unique features and treatment responses of this myelitis variant have not been prospectively studied. This study prospectively measured outcomes in paediatric myelitis patients relative to treatments.

Methods This was a prospective, multicentre, non-randomised, observational cohort study. The study duration was 5 years and the length of follow-up was 1 year. This study collected data from children and families in North America. Patients were enrolled at academic centres with expertise in myelitis or online via a web portal. Paediatric patients diagnosed with myelitis were eligible for enrolment in the study within 6 months of onset of symptoms. Patients were characterised as transverse myelitis (TM) or the AFM variant based on clinical and radiographic findings.

Results The cohort of 90 patients included patients with AFM and TM. Of the 51 patients with AFM there was evidence of two clinically relevant patterns. This included a grey matter restricted form of AFM and a cohort with concomitant white matter that could explain lower extremity motor deficits in patients with lesions restricted to the cervical spine. The improvement in deficits with the use of corticosteroids was similar to what was observed in the TM cohort (p=0.97).

Conclusions Clinicians should consider on a case by case basis the approach to therapy for AFM patients. Prospective controlled studies of long-term outcomes would be useful in this growing patient population.

INTRODUCTION

Transverse myelitis (TM) has been classically described as an immune mediated condition causing demyelination within the spinal cord.[1] This term has caused confusion for clinicians, patients and researchers. Pathologically, any inflammation of the spinal cord (regardless of cause) can be called myelitis. When patients present with flaccid weakness in at least one limb and MRI changes predominate in the grey matter, patients are diagnosed with Acute Flaccid Myelitis (AFM). This subtype of myelitis has been increasingly recognised within the USA since 2014.[2] Significant data suggest an association between this condition and enteroviral infections, with over 500 confirmed cases among children since 2014.[3] The clinical and radiographic findings are quite similar to poliomyelitis caused by the poliovirus, with some distinct differences. Early in the course of these outbreaks the Center for Disease Control published treatment guidelines counselling clinicians to avoid corticosteroid and plasma exchange (PLEX) therapy due to a concern about worsening viral infections within the spinal cord (which have since been updated).[2] During this time, the Patient-Centered Outcomes Research Institute funded CAPTURE (Collaboration About Paediatric Transverse myelitis: Understand, Reveal, Educate) Study was prospectively enrolling paediatric myelitis patients into a study of treatment outcomes. While the CAPTURE study collected outcomes from traditional TM and AFM patients, this paper outlines novel findings relative to the AFM cohort. The CAPTURE database was analysed to determine if there was any positive or negative impact to the use of corticosteroids or PLEX in this unique patient population. The foundation of TM treatment has included corticosteroids and PLEX so the data from this cohort was used to place outcome data from the AFM patients into context.

METHODS

Seven enrolling centres were designated in the United States (Children's Health in Dallas, Texas; University of Colorado in Denver, Colorado; Toronto Sick Kids in

Toronto, Canada; Children's Hospital of Philadelphia in Philadelphia, Pennsylvania, Johns Hopkins Hospital in Baltimore, Maryland, Kennedy Krieger Institute in Baltimore, Maryland; Cincinnati Children's in Cincinnati, Ohio). Potential research participants were recruited by contacting the TM association, a patient advocacy organisation or by contacting an enrolling centre. Informed consent was obtained from parents of study participants and assent was obtained from participants 10 and older at an enrolling centre or by the central recruiting programme in Dallas, Texas, prior to the initiation of any study procedures.

Participants who were able to travel to an enrolling centre were entered into the 'in-person' cohort where they completed visits to obtain clinician-derived data. They also submitted patient-reported and parent-reported outcomes via electronic surveys at defined time points after symptom onset. Participants who were unable to travel were entered into the 'virtual' cohort in which they only submitted the electronic surveys. Subjects enrolled in the virtual cohort had imaging and medical records reviewed at the University of Texas Southwestern for case determination and classification. Study data were collected and managed using the REDCap (Research Electronic Data Capture) tools hosted at The University of Texas (UT) Southwestern.[4]

Study cohort

Participants were eligible for enrollment if they were diagnosed with myelitis, were between the ages of 0 and 17 at diagnosis, within 6 months of symptom onset, had access to the internet and had parents/guardians that were able to provide informed consent. Patients with diagnoses of systemic autoimmune conditions were excluded. If a patient had no flaccid weakness and predominantly white matter involvement, then they were classified as TM. Patients were classified as AFM if they had one or more flaccid limbs and predominantly grey matter changes on MRI. AFM patients were categorised as grey matter restricted if the T2 hyperintense signal change on MRI was only identified in anterior horns vs mixed grey and white matter if the T2 hyperintense signal change involved both grey and white matter.

Study period

The study initially launched in 2014 and continued through 2018. Patients were followed through the 1-year postonset time point.

Outcomes

For all patients enrolled, medical records and MRIs were examined to record date of onset; symptoms at onset; location of symptoms (right/left and upper/lower extremity); the presence of bowel and bladder symptoms; treatment(s) at onset; degree-of-improvement after each treatment; laboratory results; past illnesses, immunisations, family history and radiologic findings. Radiographic assessments and classifications were conducted centrally at UT Southwestern in a blinded fashion to the clinical data.

Longitudinal outcomes included patient and parent-reported outcomes and clinician-derived outcomes obtained within 30 days of symptom onset, 3 months postonset, 6 months postonset and 1-year postonset. Due to the inclusion criteria of the study allowing for patients who were at most 6 months postonset, many enrollees were missing data from the time of symptom onset or 3 months postonset.

The longitudinal patient-reported outcomes were collected via REDCap surveys distributed to patients and included the anger, anxiety, depression, fatigue, mobility, pain interference, peer relations, upper extremity function and paediatric quality of life PROMIS (Patient-Reported Outcomes Measurement Information System) forms.[5 6] Additionally, the PROMIS Parent Proxy forms were collected. The clinician derived data included 25-foot walk time, 6 min walk, Hauser Ambulation Index, FIM/WeeFIM (V.4.0). The FIM/WeeFIM (range 18–126) was the originally defined primary outcome while PROMIS scores were a secondary outcome. The PROMIS Paediatric and Parent Proxy short forms consist of questions resulting in a set of ordinal responses with lower scores equating to more severe symptoms. The PROMIS Paediatric and Parent Proxy forms included the following short forms: (1) emotional distress—anxiety (eight ordinal responses); (2) emotional distress—depressive symptoms (six ordinal responses); (3) fatigue (10 ordinal responses); (4) pain—interference (eight ordinal responses); (5) peer relationships (seven ordinal responses); (6) physical function—mobility (eight ordinal responses) and (7) physical function—upper extremity (eight ordinal responses). The PROMIS paediatric forms are only valid for patients 8 years of age and older and PROMIS Parent Proxy forms are only valid for patients between the ages of 5 and 17 years old.

The longitudinal clinician-derived data were collected for those subjects enrolled in the 'in-person' cohort and included 25-foot walk time, 6 min walk, Hauser Ambulation Index, WeeFIM (V.4.0).

If corticosteroids led to a worsening of the viral infection within the spinal cord, it would be expected that AFM patients who received corticosteroids would have a worse prognosis relative to AFM patients who did not receive corticosteroids and relative to TM patients who did receive corticosteroids.

Enterovirus testing

PCR testing was performed on cerebrospinal fluid (CSF), nasopharyngeal swab or stool specimens.

Missing data

Data were missing due to four causes: (1) participants enrolled 30 days after symptom onset or 30 days after 3 months postonset; (2) patients' failure to complete REDCap surveys within ±30 days of symptom onset, 3 months postonset, 6 months postonset and/or 1-year

postonset; (3) patients' failure to adhere to clinic visit schedule and (4) failure of clinicians to capture all relevant data during visits.

Statistical analysis

Demographic and clinical characteristics were compared between the 'in-person' and 'virtual' cohorts to determine if it was reasonable to pool the data from these two cohort. Categorical data were compared using two-tailed Fisher's exact tests and ordinal and continuous variables were compared using the Mann-Whitney U test.

After determining there was no evidence of differences between the 'in-person' and 'virtual' cohorts, the data were pooled for comparison of TM and AFM, as well as the subtypes of AFM. Two-tailed Fisher's exact tests were used to compare ORs between AFM and TM patient cohorts (or between grey matter isolated AFM and mixed-matter AFM). Ordinal logistics regression was used to compare the degree-of-improvement after initial treatment between AFM patients who received corticosteroids as their initial treatment versus those who received intravenous immunoglobulin as their initial treatment.

Significance was defined as $\alpha = 0.05$. Multiple testing adjustments were not used due to the exploratory nature of this analysis. However, it must be noted that because multiple testing adjustments were not performed, the reader must interpret all significant results with caution due to the inflation of a type I error and future efforts designed to answer defined hypotheses must be pursued to provide more definitive inferences. It should be noted that P_{25} denotes the 25th percentile and P_{75} denotes the 75th percentile. All data analyses were performed in R (V.3.6.1).

RESULTS

A total of 113 patients were initially enrolled in the CAPTURE study. Figure 1 provides a depiction of those patients excluded and included in the final analysis. There were 90 enrollees with analysable data (figure 1). Patients were excluded because of missing data relative to diagnosis (n=7), lack of follow-up (n=6) or alternate diagnoses (n=10). Fifty-one was classified as AFM and 39 as TM based on clinical and radiographic findings. The data stratified by cohort membership, diagnosis and AFM subtype are provided in online supplemental eTables 1 and 2.

Demographic and clinical data

Demographic and clinical data for the TM and AFM cohorts, as well as AFM stratified by MRI pattern are summarised in table 1. Based on the results in table 1, of the 36 TM patients and 49 AFM patients with data related to the presence (or absence) of a preceding illness, 63.9% of TM patients reported a preceding illness, while 81.6% of the AFM patients had an illness in the 90 days prior to symptom onset (OR 0.40, 95% CI 0.13 to 1.20, p=0.08), with 30 (60%) of them reporting a respiratory illness and 9 (18%) reporting a gastrointestinal/diarrhoeal illness. Forty-five (88.2%) of the AFM patients had no documented vaccinations within 90 days of onset.

AFM clinical data

At onset, more than half of AFM patients had weakness of the upper extremities, which was greater than the third of TM (38.5%) patients reporting upper extremity weakness at onset (OR=0.39, 95% CI 0.15 to 0.98, p=0.03). Of the AFM patients, 19 (38%) had upper extremity symptoms only, 12 (24%) had both upper and lower extremity

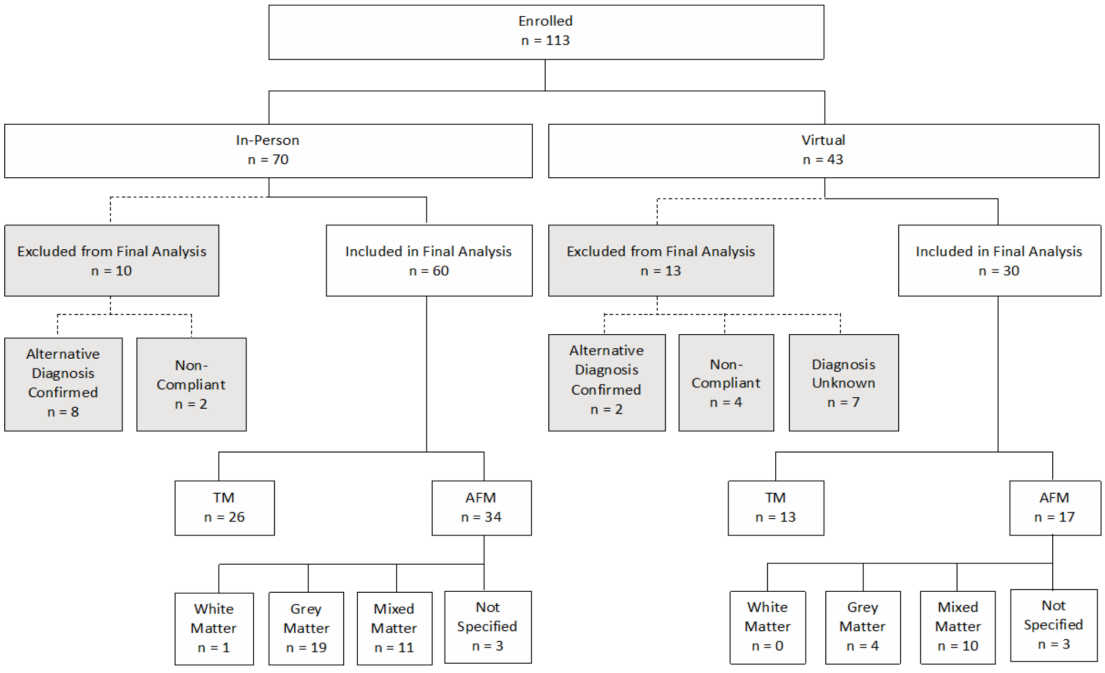


Figure 1 Enrolment diagram for the capture study. AFM, acute flaccid myelitis; TM, transverse myelitis.

Table 1 Demographic, symptoms at onset and laboratory results; cells without sample sizes denote results obtained from all patients in the given cohort

			AFM subtypes	
	TM	**AFM**	**Grey matter**	**Mixed matter**
N	39	51	23	21
Female	19 (48.7%)	17 (33.3%)	6 (26.1%)	8 (38.1%)
Median age at onset (range)	8.1 (0.3–17.9), n=38	5.4 (0.6–14.8), n=49	5.8 (1.1–14.2)	4.0 (0.9–14.8), n=20
Year of onset				
2014	7 (17.9%)	17 (34.0%), n=50	9 (39.1%)	8 (38.1%)
Spring	1	0	0	0
Summer	3	4	0	4
Fall	3	13	9	4
2015	10 (25.6%)	6 (12.0%), n=50	3 (13.0%)	3 (14.3%)
Winter*	1	3	0	3
Spring	3	1	1	0
Summer	4	1	1	0
Fall	2	1	1	0
2016	13 (38.5%)	27 (54.0%), n=50	11 (47.8%)	10 (47.6%)
Winter*	6	2	0	2
Spring	2	2	2	0
Summer	4	12	5	4
Fall	1	11	4	4
2017	9 (17.9%)	0, n=50	0	0
Winter*	4			
Spring	3			
Summer	1			
Fall	1			
Race				
Caucasian	34 (87.2%)	37 (72.6%)	16 (69.6%)	15 (71.4%)
African American	1 (2.6%)	4 (7.8%)	3 (13.0%)	1 (4.8%)
Asian	1 (2.6%)	4 (7.8%)	2 (8.7%)	2 (9.5%)
More than one race	1 (2.6%)	4 (7.8%)	0	3 (14.3%)
Preferred not to answer	2 (5.1%)	2 (3.9%)	2 (8.7%)	0
Ethnicity				
Hispanic or Latino	7 (18.4%), n=38	8 (15.7%)	3 (13.0%)	5 (23.8%)
Preferred not to answer	1 (2.6%), n=38	2 (3.9%)	2 (8,7%)	0
Illness within 3 months before onset	23 (63.9%), n=36	40 (81.6%), n=49	19 (82.6%)	16 (80.0%), n=20
Symptoms at onset				
Weakness	38 (97.4%)	48 (96.0%), n=50	22 (95.7%)	21 (100%)
Upper extremity only	6 (15.4%)	19 (38.0%), n=50	11 (47.8%)	7 (33.3%)
Lower extremity only	23 (59.0%)	17 (34.0%), n=50	7 (30.4%)	8 (38.1%)
Both upper and lower extremities	9 (23.1%)	12 (24.0%), n=50	4 (17.4%)	6 (28.6%)
Numbness	13 (33.3%)	15 (30.0%), n=50	6 (26.1%)	6 (28.6%)
Upper extremity only	0	3 (6.0%), n=50	2 (8.7%)	1 (4.8%)
Lower Eextremity only	11 (28.2%)	12 (24.0%), n=50	4 (17.4%)	5 (23.8%)
Both upper and lower extremities	2 (5.1%)	0, n=50	0	0

Continued

Table 1 Continued

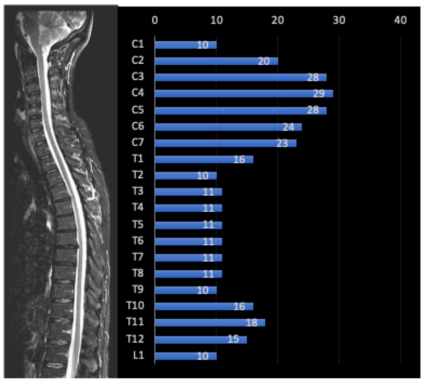
	TM	AFM	AFM subtypes	
			Grey matter	Mixed matter
Laboratory results				
CSF WBC				
Median (range)	3 (0–709), n=30	15 (0–287), n=43	15 (0–127), n=19	11 (0–287), n=18
CSF Protein				
Median (range)	47 (20–722), n=30	38 (18–596), n=41	48.5 (18–190), n=18	33 (20–203), n=17
Oligoclonal bands present	2 (7.1%), n=28	0, n=29	0, n=14	0, n=13
Enterovirus†				
Positive	3 (7.9%), n=38	18 (36.7%), n=49	12 (52.2%)	4 (19.1%)
Negative	6 (15.8%), n=38	6 (12.2%), n=49	3 (13.0%)	2 (9.5%)
Not tested	14 (36.8%), n=38	11 (22.44%), n=49	2 (8.7%)	8 (38.1%)
Negative (for tests available)‡	15 (39.5%), n=38	13 (26.5%), n=49	5 (21.7%)	7 (33.3%)
Not tested (for tests available)‡	0	1 (2.0%), n=49	1 (4.3%)	0

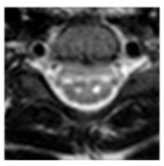
*Winter includes the previous year's December.
†Enterovirus testing was performed using CSF, nasopharyngeal or stool samples. A patient was classified as positive if they tested positive on at least one sample test, a patient was classified as negative if they tested negative on all tests, and a patient was classified as not tested if no samples were tested.
‡Includes those patients for whom certain samples were not tested or for whom data were not available for certain sample tests.
AFM, acute flaccid myelitis; CSF, cerebrospinal fluid; TM, transverse myelitis; WBC, white blood cell.

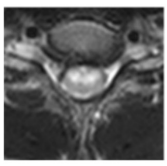
symptoms and 17 (34%) had lower extremity symptoms only. Fifteen (30%) AFM patients had sensory symptoms and 19 (38%) had bowel or bladder symptoms at onset (table 1).

Within the AFM patient population, CSF studies revealed a mean protein of 69.6 dg/mL (SD 96.5) and a mean white blood cell count of 37.4 white blood cells/mm^3 (SD 53.0). Oligoclonal bands were absent in all cases for which data were available (table 1).

MRI findings revealed 68% of AFM cases had a lesion that involved C4 compared with 43.2% of TM cases (OR 0.36, 95% CI 0.14 to 0.94), p=0.03). Review of axial imaging was possible in 45 AFM cases (six cases were not available for central review, but were classified as AFM based on their radiology report) and revealed two predominant patterns of cord involvement: lesions restricted to grey matter 23 (51.1%) and lesions that involved both the grey and white matter 21 (46.7%).(figure 2) (table 2) Of the 45 patients with axial imaging available for review, 40 (88.9%) had contiguous lesions and five had two separate lesions. Six of the 23 AFM (26.1%) patients with lesions restricted to grey matter had abnormalities restricted to the thoracic cord or lower, while this number was 6 of 21 (28.6%) among the patients with mixed involvement of both grey and white matter (table 1). For those patients with lesions restricted to the C3–C5 spinal segments, 93.5% had upper extremity weakness relative to the 31.6% of patients with lesions outside of the C3–C5 segments (OR 28.35, 95% CI 4.7 to 321.0), p<0.001).







Year	2014	2015	2016	2017	Total
Gray Matter Restricted	8	3	5	0	16
Gray/White Mixed	8	3	6	1	18

Figure 2 CAPTURE study AFM cohort MRI characteristics: two types identified. AFM, acute flaccid myelitis; CAPTURE, Collaboration About Paediatric Transverse myelitis: Understand, Reveal, Educate.

Table 2 MRI results by diagnosis; cells without sample sizes denote results obtained from all patients in the given cohort

			AFM subtypes	
	TM	**AFM**	**Grey matter**	**Mixed matter**
N	39	51	23	21
Mean months to MRI (SD)	1.1 (3.5), n=35	0.27 (0.92), n=48	0.4 (1.3), n=21	0.2 (0.4), n=20
Median months to MRI (range)	0 (–1 to 16), n=35	0 (0 to 6), n=48	0 (0 to 6), n=21	0 (0 to 1), n=20
Spinal Segment Where Lesion Present				
C1	9 (24.3%), n=37	12 (24%), n=50	7 (30.4%), n=23	3 (14.3%), n=21
C2	15 (40.5%), n=37	25 (50%), n=50	11 (47,8%), n=23	9 (42.9%), n=21
C3	19 (51.4%), n=37	33 (66%), n=50	15 (65.2%), n=23	14 (66.7%), n=21
C4	16 (43.2%), n=37	34 (68%), n=50	15 (65.2%), n=23	15 (71.4%), n=21
C5	19 (51.4%), n=37	33 (66%), n=50	15 (65.2%), n=23	14 (66.7%), n=21
C6	19 (51.4%), n=37	29 (58%), n=50	12 (52.2%), n=23	13 (61.9%), n=21
C7	20 (54.1%), n=37	28 (56%), n=50	11 (47.8%), n=23	14 (66.7%), n=21
C8	17 (45.6%), n=37	19 (38%), n=50	8 (34.8%), n=23	8 (38.1%), n=21
T1	18 (48.7%), n=37	20 (40%), n=50	7 (30.4%), n=23	9 (42.9%), n=21
T2	15 (40.5%), n=37	13 (26%), n=50	5 (21.7%), n=23	5 (23.8%), n=21
T3	16 (43.2%), n=37	11 (22%), n=50	5 (21.7%), n=23	4 (19.1%), n=21
T4	16 (43.2%), n=37	11 (22%), n=50	5 (21.7%), n=23	4 (19.1%), n=21
T5	13 (35.1%), n=37	12 (24%), n=50	5 (21.7%), n=23	5 (23.8%), n=21
T6	14 (37.8%), n=37	12 (24%), n=50	5 (21.7%), n=23	5 (23.8%), n=21
T7	11 (29.7%), n=37	12 (24%), n=50	5 (21.7%), n=23	5 (23.8%), n=21
T8	8 (21.6%), n=37	12 (24%), n=50	5 (21.7%), n=23	5 (23.8%), n=21
T9	9 (24.3%), n=37	10 (20%), n=50	5 (21.7%), n=23	2 (9.5%), n=21
T10	8 (21.6%), n=37	17 (34%), n=50	9 (39.1%), n=23	5 (23.8%), n=21
T11	8 (21.6%), n=37	19 (38%), n=50	11 (47.8%), n=23	5 (23.8%), n=21
T12	8 (21.6%), n=37	16 (32%), n=50	9 (39.1%), n=23	4 (19.1%), n=21
L1	4 (10.8%), n=37	10 (20%), n=50	6 (26.1%), n=23	2 (9.5%), n=21
L2	1 (2.7%), n=37	5 (10%), n=50	3 (13.0%), n=23	0, n=21
L3	1 (2.7%), n=37	3 (6%), n=50	2 (8.7%), n=23	0, n=21
L4	1 (2.7%), n=37	3 (6%), n=50	2 (8.7%), n=23	0, n=21
L5	1 (2.7%), n=37	3 (6%), n=50	2 (8.7%), n=23	0, n=21
Lesion matter involvement				
Grey matter				
Cervical	0, n=37	20 (44.4%), n=45	17 (73.9%), n=23	3 (14.3%), n=21
Thoracic	1 (2.7%), n=37	16 (35.6%), n=45	13 (56.5%), n=23	3 (14.3%), n=21
Lumbar	0, n=37	5 (11.1%), n=45	5 (21.7%), n=23	0, n=21
White matter				
Cervical	8 (21.6%), n=37	2 (4.4%), n=45	0, n=23	1 (4.8%), n=21
Thoracic	8 (21.6%), n=37	1 (2.2%), n=45	0, n=23	0, n=21
Lumbar	1 (2.7%), n=37	0, n=45	0, n=23	0, n=21
Mixed Matter				
Cervical	13 (32.4%), n=37	15 (33.3%), n=45	0, n=23	15 (71.4%), n=21
Thoracic	17 (45.6%), n=37	12 (26.7%), n=45	0, n=23	12 (57.1%), n=21
Lumbar	0, n=37	2 (4.4%), n=45	0, n=23	2 (9.5%), n=21

Lesion matter involvement denotes the number of patients whose lesions in the cervical, thoracic or lumbar segment of the spine occupied grey matter only, white matter only or grey and white matter (mixed matter).
AFM, acute flaccid myelitis; TM, transverse myelitis.

Table 3 Treatment history

			AFM subtypes	
	TM	AFM	Grey matter	Mixed matter
N	39	51	23	21
First treatment				
Corticosteroids	35 (90%)	35 (69%)	13 (57%)	19 (90%)
Median months from onset (P_{25}, P_{75})	0 (0, 0), n=31	0 (0, 0), n=31	0 (0, 0), n=12	0 (0, 0), n=16
Received one additional treatment	19 (54%)	15 (43%)	6 (46%)	6 (32%)
IVIG	6 (32%)	11 (73%)	4 (67%)	4 (67%)
PLEX	13 (68%)	4 (27%)	2 (33%)	2 (33%)
Received two additional treatments	8 (23%)	12 (34%)	3 (23 %)	9 (47%)
Corticosteroids → PLEX	2 (25%)	0	0	0
PLEX →PLEX	1 (12%)	0	0	0
IVIG →PLEX	1 (12%)	5 (42%)	2 (67%)	3 (33%)
PLEX →IVIG	4 (50%)	7 (58%)	1 (33 %)	6 (67%)
IVIG	3 (8%)	15 (29%)	10 (43%)	2 (10%)
Received one additional treatment	0	5 (33%)	3 (30%)	1 (50%)
IVIG	0	1 (20%)	1 (33%)	0
PLEX	0	1 (20%)	1 (33%)	0
Corticosteroids	0	3 (60%)	1 (33%)	1 (100%)
Received two additional treatments	3 (100%)	3 (20%)	1 (10%)	1 (50%)
Unknown → corticosteroids	1 (33%)	0	0	0
Corticosteroids →PLEX	2 (67%)	1 (33%)	0	1 (100%)
PLEX →IVIG	0	1 (33%)	1 (100%)	0
PLEX →corticosteroids	0	1 (33%)	0	0

AFM, acute flaccid myelitis; IVIG, intravenous immunoglobulin; PLEX, plasma exchange; TM, transverse myelitis.

Viral data

Fifty of the 51 AFM patients had data available relative to verifying the performance or lack of performance of enterovirus testing (one patient had missing data). PCR testing was performed on CSF, nasopharyngeal swab or stool specimens. Eleven of 50 AFM patients with recorded data indicated that no testing occurred. Of the 39 AFM patients who had a verifiable specimen tested for enteroviruses, 18 tested positive (46.2%). Seventeen of these positives were from nasopharyngeal swabs. Restricting to patients who had respiratory samples tested for enteroviruses, the percent positive among AFM patients was 51.5%. No patients had a positive CSF PCR for Enteroviruses (table 1). Of note, three TM patients tested positive for enteroviruses on swabs, but the significance is unknown.

Treatment data

Table 3 presents the treatment courses for all patients enrolled in the CAPTURE study. Treatment data were available for 51 AFM patients and 39 TM patients. From table 3, it can been seen that all patients received either intravenous immunoglobulin or corticosteroids as their initial treatment and no patients received PLEX as their initial treatment. Table 4 presents the parent/patient-recorded degree-of-improvement after initial treatment for TM and AFM patients. Based on the results of the ordinal regression model, there is no evidence that initial treatment with intravenous immunoglobulin resulted in greater improvement after initial treatment relative to initial treatment with corticosteroids ($\beta = -0.08$, SE=0.57, p=0.89). Of note, we are unable to quantify the impact of corticosteroids or intravenous immunoglobulin on patient outcomes as a 'no-treatment' comparator arm was not available in this study.

Patient-reported outcomess and parent-reported outcomes and clinician-derived outcomes

Due to the inability to adequately model and assess changes in patient-reported outcomes and parent-reported outcomes, as well as clinician-derived outcomes, descriptive statistics are presented in the supplementary material in online supplemental eTables 3–5.

DISCUSSION

The AFM variant of myelitis attracted significant attention in the USA during an outbreak in 2014 with subsequent outbreaks in 2016 and 2018.[7] These outbreaks have coincided with Enterovirus D68 circulation.[8–11] Of note, the cohort described in this manuscript is demographically similar to previously reported AFM cohorts within

Table 4 Degree of patient-reported qualitative improvement after initial treatment; cells without sample sizes denote results obtained from all patients in the given cohort

			AFM subtypes	
	TM	AFM	Grey matter	Mixed matter
N	39	51	23	21
Corticosteroids	35 (90%)	35 (69%)	13 (57%)	19 (90%)
No improvement	8 (24%), n=34	12 (34%)	4 (31%)	7 (37%)
Minimal improvement	12 (35%), n=34	13 (37%)	4 (31%)	8 (42%)
Some improvement	9 (26%), n=34	5 (14%)	2 (15%)	2 (11%)
Mostly recovered	5 (15%), n=34	4 (11%)	3 (23%)	1 (5%)
Fully recovered	0, n=34	1 (3%)	0	1 (5%)
IVIG	3 (8%)	15 (29%)	10 (43%)	2 (10%)
No improvement	1 (50%), n=2	6 (40%)	5 (50%)	1 (50%)
Minimal improvement	1 (50%), n=2	4 (27%)	2 (20%)	1 (50%)
Some improvement	0	3 (20%)	2 (20%)	0
Mostly recovered	0	2 (13%)	1 (10%)	0
Fully recovered	0	0	0	0

AFM, acute flaccid myelitis; IVIG, intravenous immunoglobulin; TM, transverse myelitis.

the USA.[12] Because the likely cause of AFM is the EVD68 virus, concerns relative to the use of corticosteroids in these patients have existed.[13] Data from this prospectively studied cohort suggests that corticosteroids may be safe in these patients and may be of benefit to AFM patients with white matter.

To date, reported outcomes have been retrospective while the CAPTURE study was initiated prior to the recognition of AFM outbreaks and was, hence, able to prospectively collect data on this important patient population. This paper presents the demographic, clinical, radiographic, laboratory and outcome data of this cohort. Fifty-three percent of AFM patients tested with the respiratory enterovirus/rhinovirus PCR were positive, but subtyping was not universally available. Radiographic data revealed two patterns of interest. First, there was a predilection for the cervical spinal cord with the majority of patients having involvement of the C3–C5 region. Twenty-four per cent of patients had both upper and lower extremity weakness at onset. Biologically, if pathological changes in the cord were restricted to the cervical cord, lower extremity weakness would have to occur as a result of damage to white matter based corticospinal tracts. Thus, MRIs were reviewed and classified as grey matter restricted vs mixed grey and white matter changes. Approximately half of patients had evidence of mixed grey and white matter pathology. There are several potential explanations for these two patterns on MRI. While there could be more than one viral aetiology for AFM, there could also be an evolution of MRI findings over time that was not captured in isolated clinical MRIs.

Epidemiologic and animal model data both support the theory that AFM is the result of a viral infection causing death of anterior horn motor neurons.[14] EVD68 is likely causative in the majority of cases.[12] The recognition of two radiographic patterns might suggest that some patients suffer weakness from viral mediated motor neuron cell death while other patients have concomitant damage to surrounding white matter tracts. This damage could result from the inflammatory response elicited by the viral infection. Initial recommendations from the CDC counselled against the use of corticosteroids or PLEX in AFM out of concern for potentiating an infectious aetiology and worsening outcomes. Furthermore, animal model data documented fatality among mice treated with corticosteroids.[14] Our data did not identify a unique risk to using corticosteroids in these patients and suggest that some patients may have experienced improvement. A controlled, randomised trial would be the ideal mechanism for quantifying risks and benefits, but due to the rarity and nature of this condition, such a trial would be difficult to execute.

LIMITATIONS

The CAPTURE study was not designed as a randomised control trial and was, therefore, at the mercy of patients' treating physician. This fact introduced considerable heterogeneity in the treatment regimen of patients making comparison of patient-reported, parent-reported and clinician-reported outcomes difficult. Furthermore, due to the inclusion criteria of the CAPTURE study allowing for patients to enrol up to 6 months after onset, considerable data were missing corresponding to onset and 3 months postonset. This restricted analysis of longitudinal outcome measures due to the absence of baseline severity, which is crucial to the analysis of improvement over time. Furthermore, missing data due to patients' lack of adherence and clinicians' failure to capture all necessary data resulted in the inability to adequately examine patients'

progression after follow-up. Regarding missing data due to adherence, there is the risk that the missingness is due to the impact of the disease and missing not at random. That is, if missing scores were obtained, they would have been lower (or higher) than those that were observed. Lastly, in dealing with a paediatric population, almost half of which is less than 5 years old, many paediatric outcome measures (PROMIS Parent Proxy and PROMIS Paediatric form) are not validated, resulting in substantial missing data. Finally, the design of the study did not allow us to routinely collect accurate baseline clinical data, preventing certain analyses about relative change over time, particularly during the early post-treatment patient experience. A early worsening of symptoms after initial treatment with corticosteroids or intravenous immunoglobulin would not be accurately captured in this data. Furthermore, given the small number of patients with in person data, clinician derived data could not be used to analyse for disparate outcomes among treatment groups. Despite these limitations, the CAPTURE study was able to collect the first prospective clinical, radiographic, laboratory and outcome dataset for AFM, which has become a new public health concern in the USA.

CONCLUSIONS

The CAPTURE study prospectively enrolled patients and identified two distinct MRI patterns of spinal cord involvement. The dataset also failed to identify a significant difference between subjects receiving corticosteroids and/or PLEX versus intravenous immunoglobulin only, but our data raise the question of using corticosteroids and/or PLEX in certain patient cohorts. Prospective studies need to be continued and expanded to develop validated treatment algorithms for this growing public health concern.

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REFERENCES

1 Beh SC, Greenberg BM, Frohman T, *et al*. Transverse myelitis. *Neurol Clin* 2013;31:79–138.
2 Division of Viral Diseases, National Centers for Immunization and Respiratory Diseases, CDC; Division of Vector-Borne Diseases, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Children's Hospital Colorado; Council of State and Territorial Epidemiologists. Notes from the field: acute flaccid myelitis among persons aged ≤21 years - United States, August 1-November 13, 2014. *MMWR Morb Mortal Wkly Rep* 2015;63:1243–4.
3 Messacar K, Tyler KL. Enterovirus D68-Associated acute flaccid myelitis: rising to the clinical and research challenges. *JAMA* 2019;321:831–2.
4 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
5 Kratz AL, Slavin MD, Mulcahey MJ, *et al*. An examination of the PROMIS(®) pediatric instruments to assess mobility in children with cerebral palsy. *Qual Life Res* 2013;22:2865–76.
6 Lai J-S, Stucky BD, Thissen D, *et al*. Development and psychometric properties of the PROMIS(®) pediatric fatigue item banks. *Qual Life Res* 2013;22:2417–27.
7 Messacar K, Abzug MJ, Dominguez SR. Acute flaccid myelitis surveillance: a signal through the noise. *Pediatrics* 2019;144. doi:10.1542/peds.2019-2492. [Epub ahead of print: 07 Oct 2019].

8 Messacar K, Asturias EJ, Hixon AM, *et al*. Enterovirus D68 and acute flaccid myelitis-evaluating the evidence for causality. *Lancet Infect Dis* 2018;18:e239–47.
9 Greninger AL, Naccache SN, Messacar K, *et al*. A novel outbreak enterovirus D68 strain associated with acute flaccid myelitis cases in the USA (2012-14): a retrospective cohort study. *Lancet Infect Dis* 2015;15:671–82.
10 Helfferich J, Knoester M, Van Leer-Buter CC, *et al*. Acute flaccid myelitis and enterovirus D68: lessons from the past and present. *Eur J Pediatr* 2019;178:1305–15.
11 Van Haren K, Ayscue P, Waubant E, *et al*. Acute flaccid myelitis of unknown etiology in California, 2012-2015. *JAMA* 2015;314:2663–71.
12 Ayers T, Lopez A, Lee A, *et al*. Acute flaccid myelitis in the United States: 2015-2017. *Pediatrics* 2019;144. doi:10.1542/peds.2019-1619. [Epub ahead of print: 07 Oct 2019].
13 Hopkins SE, Elrick MJ, Messacar K. Acute flaccid Myelitis-Keys to diagnosis, questions about treatment, and future directions. *JAMA Pediatr* 2019;173:117–8.
14 Hixon AM, Yu G, Leser JS, *et al*. A mouse model of paralytic myelitis caused by enterovirus D68. *PLoS Pathog* 2017;13:e1006199.