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ORIGINAL ARTICLE

Comparison of acute flaccid myelitis and transverse myelitis in children and evaluation of diagnostic criteria

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Abstract

Background and purpose: Acute flaccid myelitis (AFM) and transverse myelitis (TM) are serious conditions that may be difficult to differentiate, especially at onset of disease. In this study, we compared clinical features of pediatric AFM and TM and evaluated current diagnostic criteria, aiming to improve early and accurate diagnosis.

Methods: Two cohorts of children with enterovirus D68-associated AFM and clinically diagnosed TM were compared regarding presenting clinical features, additional investigations, and outcome. Current diagnostic criteria for AFM and TM were applied to evaluate their specificity.

Results: Children with AFM ($n=21$) compared to those with TM ($n=36$) were younger (median 3 vs. 10 years), more often had a prodromal illness (100% vs. 39%), predominant proximal weakness (69% vs. 17%), and hyporeflexia (100% vs. 44%), and less often had sensory deficits (0% vs. 81%), bowel and/or bladder dysfunction (12% vs. 69%), and hyperreflexia (0% vs. 44%). On magnetic resonance imaging, brainstem involvement was more common in AFM (74% vs. 21%), whereas supratentorial abnormalities were only seen in TM (0% vs. 40%). When omitting the criterion of a sensory level, 11 of 15 (73%) children with AFM fulfilled the diagnostic criteria for TM. Of children with TM, four of 33 (12%) fulfilled the diagnostic criteria for probable/definite AFM.

Conclusions: Although there is considerable overlap between AFM and TM in children, we found important early differentiating clinical and diagnostic features. Meeting diagnostic criteria for AFM in children with TM and vice versa underlines the importance of thorough clinical examination and early and accurate diagnostic studies.

KEYWORDS
acute flaccid myelitis, acute flaccid paralysis, enterovirus D68, transverse myelitis

Members of the 2016 Enterovirus D68 Acute Flaccid Myelitis Working Group and the Dutch Study Group for Pediatric Multiple Sclerosis and Acute Disseminated Encephalomyelitis are listed in the Appendix.

INTRODUCTION

Both acute flaccid myelitis (AFM) and transverse myelitis (TM) are rare conditions, but with significant impact on individual patients. AFM is a poliolike disease characterized by acute flaccid limb weakness of presumed anterior horn origin, most commonly occurring in childhood [1, 2]. The pathophysiology is not completely clarified, but an association with specific viruses, in particular enterovirus D68 (EV-D68) and A71 (EV-A71) has been made [3–5]. According to the diagnostic criteria for AFM, as proposed by the international AFM Working Group in 2021, a definite diagnosis can be made based on the combination of acute flaccid paralysis (AFP), spinal cord gray matter abnormalities on magnetic resonance imaging (MRI), and pleocytosis in cerebrospinal fluid (CSF), in the absence of factors suggesting an alternative diagnosis [1].

TM is an immune-mediated condition of the spinal cord. The diagnosis is currently based on Transverse Myelitis Consortium Working Group (TMCWG) criteria [6]. These include (i) the presence of sensory, motor, and/or autonomic dysfunction attributable to the spinal cord; (ii) a clearly defined sensory level; and (iii) signs of inflammation of the spinal cord, indicated by CSF pleocytosis, an elevated IgG index, or gadolinium enhancement of the spinal cord on MRI. The presence of a sensory level is, however, often omitted in children [6–8]. Evidence of an associated systemic or infectious disease, as well as the presence of optic neuritis or brain MRI abnormalities suggestive of multiple sclerosis (MS), would exclude the diagnosis of idiopathic TM, but may lead to a diagnosis of disease-associated TM according to the TMCWG criteria.

Although early differentiation between AFM and TM is important, as there are significant differences with respect to treatment options and prognosis, this can be challenging, in particular at onset of disease [6, 8, 9]. This is especially true in children, for example, because of the difficulty of assessing sensory deficits on neurologic examination [9].

In this study, we aimed to find early differentiating clinical and diagnostic features between AFM and TM in children, by comparing two well-described cohorts of children with these conditions. Furthermore, we aimed to evaluate the specificity of diagnostic criteria for AFM and TM in these cohorts.

METHODS

Study cohorts

The AFM cohort comprised 21 pediatric cases (<18 years) from a previously described retrospectively collected cohort of 29 patients from Europe (adults and children) with AFM associated with EV-D68, diagnosed in 2015 or 2016 [2]. Part of this cohort was previously used for a comparison study between AFM and Guillain–Barré syndrome [10]. The diagnosis of AFM had been based on the presence of acute onset limb weakness, MRI abnormalities of the spinal cord, and/or CSF pleocytosis, fulfilling the Centers of Disease Control and Prevention (CDC) case definition from 2018 for probable or definite AFM [11]. Furthermore, EV-D68 had to be detected by polymerase chain reaction in a sample of any origin.

The TM cohort consisted of 36 children (<18 years old) with a clinical diagnosis of TM, selected from acquired demyelinating syndrome patients included in the Dutch nationwide prospective multicenter PROUD-kids study (Predicting the Outcome of a Demyelinating Event in Childhood) [12]. Some of these patients with TM were described previously [13]. Cases in which a diagnosis of AFM was considered by the treating physician were excluded. In line with the TMCWG criteria, children with TM in association with acute disseminated encephalomyelitis, as well as those with optic neuritis or supratentorial MRI abnormalities suggestive of MS at onset of disease, were excluded for the current study. Generally, these cases can easily be differentiated from idiopathic TM and they follow a different clinical course [13, 14].

Comparison studies

Both cohorts were compared with respect to demographic features, prodromal features, clinical characteristics at first presentation, and time course. Furthermore, a comparison of MRI features in spinal cord and brain, CSF abnormalities, and microbiology test results at onset of disease was made. Treatment type and outcome measures were compared. Outcome was reported in terms of ability to walk independently and recovery at final follow-up (full, partial, or no recovery). Results of electrophysiologic studies for the AFM patients and serum aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibody results tested by cell-based assay for the TM patients were reported if available.

Diagnostic criteria

The TMCWG criteria (Table S1) were applied to both cohorts. In the AFM group, the exclusion criterion of enterovirus-associated pathology of the nervous system was discarded [6]. Both the presence of a sensory level and criteria for proven inflammation are often omitted in children, as a sensory level may be difficult to assess and (repeated) CSF examinations are limitedly tolerated in children [7, 8]. Therefore, the whole set of criteria, and the criteria without a sensory level and/or without proven inflammation, were both applied.

The AFM criteria (Table S2), as proposed by the international AFM Working Group in 2021, were applied to both cohorts [15]. The criterion of decreased muscle tone in at least one of the weak limbs was not included, as this had not been recorded in both cohorts. Both (i) diagnostic features of AFM and (ii) factors suggestive for an alternative diagnosis were applied.

MRI examinations were reassessed if images were available; alternatively, the report of the radiologist was used. Terms such as "mostly affecting the gray matter," "presence of a central cord lesion," and "anterior myelitis" were deemed consistent with gray matter involvement on MRI.

Statistics

SPSS 23 was used for statistical analysis. Continuous data were presented as means and SD if normally distributed, and otherwise as medians and interquartile ranges (IQRs). Categorical data were presented as proportions. Continuous data of the two cohorts were compared with *t*-test if normally distributed and with Mann–Whitney *U* test if not normally distributed. Proportions were compared using the chi-squared or Fisher exact test. The Bonferroni correction was applied to correct for multiple comparisons. A two-sided *p*-value <0.05 was considered significant.

Standard protocol approvals, registrations, and patient consents

Studies from which data were used, were approved by the medical ethical review committee of the coordinating centers.

RESULTS

Demographic characteristics

The AFM cohort consisted of 21 children with AFM associated with EV-D68, and the TM cohort comprised 36 children with a clinical diagnosis of TM. Median age at onset of disease was 3 years (IQR = 2–5, full range = 8) for the AFM group versus 10 years (IQR = 5.5–15.6, full range = 17) for the children with TM ($p<0.001$; Table 1).

Most children with AFM presented between July and October of 2016 (16/21, 76%), whereas the month of presentation was more evenly distributed over the year in the TM group (no statistically significant difference). Of 13 TM patients diagnosed after July 2016, when the first AFM case in the Netherlands was reported, three were diagnosed in a period of increased EV-D68 circulation. These patients had significant sensory deficits and recovered completely at final follow-up, which argues against a diagnosis of AFM. Also, all TM patients were diagnosed at a tertiary center with expertise in the field of inflammatory conditions of the central nervous system, and most children in the TM cohort had a considerably long follow-up period, so we do assume that the diagnosis was made correctly.

Clinical presentation and course

A prodromal illness was more commonly seen in children with AFM, compared to children with TM (100% vs. 39%, $p<0.001$), and most often consisted of respiratory symptoms and/or fever in AFM patients (Table 1).

Limb weakness was commonly asymmetric in both AFM and TM (61% and 50%). Weakness in the legs was equally observed in both groups, whereas the arms were more often affected in AFM (90% vs. 33%, $p<0.001$). Furthermore, a different pattern of weakness was observed in which the legs were less often solitarily involved in AFM (10% vs. 56%, $p<0.001$), whereas both arms and legs were more often involved in AFM (75% vs. 44%, $p=0.002$). Proximal weakness was often more prominent in AFM (69% vs. 17%, $p=0.002$), whereas predominant distal weakness was only seen in TM (0% vs. 34%, $p=0.005$). Sensory deficits were only observed in children with TM (0% vs. 81%, $p<0.001$), and a sensory level was observed in 15 of 30 TM patients in whom details regarding a sensory level were recorded. Hyporeflexia at nadir was present in all patients with AFM and in almost half of TM patients (100% vs. 44%, $p<0.001$); hyperreflexia was not found in any patient with AFM, but in 44% of children with TM.

Autonomic dysfunction, most often presenting as bowel and/or bladder dysfunction, was noted in 20% of AFM patients and in 72% of TM patients ($p<0.001$). Cranial nerve dysfunction on the other hand was more commonly seen in AFM patients (50% vs. 14%, $p=0.005$; Table 1).

Time course, reflected in the time period between prodromal symptoms and onset of weakness (median = 6 vs. 12 days), and the time from onset of weakness to nadir (median = 3 vs. 4 days), did not significantly differ between both groups (Table 1). More children with AFM were treated with intravenous immunoglobulin (88% vs. 38%, $p<0.001$), whereas fewer were treated with steroids (61% vs. 89%, $p=0.02$). In both groups, one patient died because of respiratory failure. Relapses occurred in none of the AFM patients, but in four patients in the TM group. Most patients had residual deficits at final follow-up in both groups (95% and 81%), but the proportion of children walking independently was smaller in the AFM group (42% vs. 96%, $p<0.001$). Follow-up duration was however also significantly longer in the TM group (median = 30 months, IQR = 3–123 vs. median = 5 months, IQR = 2–12).

Additional diagnostic tests

Spinal cord MRI showed spinal abnormalities in 88% of AFM and 97% of TM patients. These lesions affected the spinal cord gray matter in all 10 AFM patients for whom these data were obtained, but also in 23 of 29 of TM patients (79%) for whom MRI assessment was possible (Table 2).

Enhancement of the spinal cord was seen in a similar percentage in AFM and TM patients (33% vs. 29%). Nerve root enhancement was only recorded in AFM patients and was seen in 24% of these patients. Longitudinally extensive lesions were often reported in both groups (88% vs. 79%).

In AFM patients, MRI of the brain more often showed brain stem abnormalities (74% vs. 21%, $p<0.001$). Nonspecific supratentorial abnormalities were not seen in AFM patients and in 13 of 32 TM patients (0% vs. 40%, $p<0.001$). Of these 13, two had MOG antibodies, one had AQP4 antibodies, and one was diagnosed with MS during follow-up, whereas nine had an idiopathic TM.

TABLE 1 Demography and clinical presentation of AFM and TM in children.

	AFM, $n=21$	TM, $n=36$	p
Demography			
Male:female (% male)	11:10 (52)	16:20 (44)	NS
Age, years, median (IQR, full range)	3 (2–5, 1–9)	10 (6–16, 1–18)	<0.001
Prodromal illness			
Prodrome, *n* (%)	21/21 (100)	14/36 (39)	<0.001
Time from prodrome to onset weakness, days, median (IQR, full range)[a]	6 (4–7,2–12)	12 (5–16, 1–18)	NS
Respiratory symptoms, *n* (%)	20/21 (95)	7/36 (19)	<0.001
Gastrointestinal symptoms, *n* (%)	7/21 (33)	4/36 (11)	NS
Fever, *n* (%)	18/19 (95)	7/35 (20)	<0.001
Time from onset weakness to nadir, days, median (IQR, full range)[b]	3 (2–5, 1–10)	4 (2–5, 1–20)	NS
Neurological symptoms, *n* (%)			
Limb weakness	20/20 (100)	32/36 (89)	NS
Weakness in arms	18/20 (90)	12/36 (33)	<0.001
Weakness in legs	17/20 (85)	31/36 (86)	NS
Weakness in arms only	3/20 (15)	1/36 (3)	NS
Weakness in legs only	2/20 (10)	20/36 (56)	<0.001
Weakness in arms and legs	15/20 (75)	11/36 (31)	0.002
Proximal > distal	11/16 (69)	5/29 (17)	<0.001
Distal > proximal	0/16 (0)	10/29 (34)	0.006
Asymmetric weakness	11/18 (61)	17/34 (50)	NS
Bilateral symptoms	17/20 (85)	34/35 (97)	NS
Sensory deficits	0/19 (0)	29/36 (81)	<0.001
Sensory level	0/19 (0)	15/30 (50)	<0.001
Areflexia/hyporeflexia at nadir	20/20 (100)	16/36 (44)	<0.001
Hyperreflexia in affected limbs at nadir	0/20 (0)	16/36 (44)	<0.001
Cranial nerve involvement	10/20 (50)	5/36 (14)	0.005
Autonomic dysfunction	4/20 (20)	26/36 (72)	<0.001
Bladder and/or bowel dysfunction	2/17 (12)	24/35 (69)	<0.001
Pain	6/19 (32)	19/36 (53)	NS
Encephalopathy	2/19 (11)	1/36 (3)	NS
Mechanical ventilation	13/21 (62)	1/29 (3)	<0.001
Treatment, *n* (%)			
Methylprednisolone	11/18 (61)	32/36 (89)	0.03
IVIG	16/18 (89)	10/36 (28)	<0.001
Plasmapheresis	5/18 (28)	4/36 (11)	NS
Follow-up			
Follow-up duration, months, median (IQR, full range)	5 (2–12, 1–48)	30 (15–55, 3–123)	<0.001
Complete recovery, *n* (%)	1/18 (5)	7/36 (19)	NS
Walking independently, *n* (%)	9/21 (42)	27/28 (96)	<0.001

Note: Data are presented as *n* (%) or median (IQR, full range). A p-value of >0.05 is noted as NS.

Abbreviations: AFM, acute flaccid myelitis; IQR, interquartile range; IVIG, intravenous immunoglobulin; NS, nonsignificant; TM, transverse myelitis.

[a]Median time between prodromal illness and onset of weakness based on 18 AFM patients and 36 TM patients.

[b]Median time between onset of weakness and nadir based on 17 AFM patients and 36 TM patients.

TABLE 2 Additional diagnostic test results in children with AFM and TM.

	AFM, $n=21$	TM, $n=36$	p
MRI			
Time from onset of weakness to MRI of spinal cord, days, median (IQR, full range)[a]	2 (2–2.3, 1–6)	4 (3–6, 1–50)	NS
Spinal cord lesion, *n* (%)	15/17 (88)	35/36 (97)	NS
Predominant gray matter involvement, *n* (%)	10/10 (100)	23/29 (79)	NS
Cervical involvement, *n* (%)	14/16 (88)	24/34 (71)	NS
Thoracic involvement, *n* (%)	8/16 (50)	25/34 (74)	NS
Lumbar involvement, *n* (%)	6/16 (38)	11/34 (32)	NS
Longitudinally extensive lesion, *n* (%)	14/16 (88)	26/33 (79)	NS
Spinal cord enhancement, *n* (%)	2/6 (33)	7/24 (29)	NS
Nerve root enhancement, *n* (%)	4/16 (25)	NR	np
Brainstem abnormalities, *n* (%)	14/19 (74)	6/29 (21)	<0.001
Supratentorial abnormalities, *n* (%)	0/19 (0)	13/32 (40)	<0.001
CSF			
LP performed, *n* (%)	18/21 (86)	34/36 (94)	NS
Time from onset of weakness to LP, days, median (IQR, full range)[b]	1 (1–2, 0–4)	4 (3–7, 1–27)	<0.001
Leukocyte number in CSF, median (IQR, full range)[c]	81 (25–141, 3–175)	13 (3–43,0–239)	NS
CSF pleocytosis, *n* (%)	14/15 (93)	19/34 (56)	NS
Protein concentration in CSF, g/L, median (IQR, full range)[d]	0.43 (0.31–0.58, 0.21–1.6)	0.29 (0.20–0.62, 0.17–1.17)	NS
Raised protein level, *n* (%)[e]	7/13 (54)	14/32 (44)	NS
IgG index abnormal, *n* (%)	NR	12/23 (52)	np
CSF oligoclonal bands, *n* (%)	NR	3/19 (16)	np
Antibodies, *n* (%)			
MOG antibodies	NR	3/23 (13)	np
AQP4 antibodies	NR	1/26 (4)	np
Virology abnormalities, *n* (%)			
CSF	0/15 (0)	0/28 (0)	NS
Respiratory material	18/19 (95)	1/6 (17)	np
Feces	6/17 (35)	2/5 (40)	np

Note: Data are presented as *n* (%) or median (IQR, full range). A *p*-value of >0.05 is noted as NS. Not all comparisons were performed, because of limited numbers; this is mentioned as np. Some items were not recorded in both patient groups, which is noted as NR.

Abbreviations: AFM, acute flaccid myelitis; AQP4, aquaporin-4; CSF, cerebrospinal fluid; IgG, immunoglobulin G; IQR, interquartile range; LP, lumbar puncture; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; np, not performed; NR, not recorded; NS, nonsignificant; TM, transverse myelitis.

[a]The median time between onset of weakness and MRI was available in 15 patients from the AFM cohort and in 36 patients from the TM cohort.

[b]The median time between onset of weakness and LP was available in 15 patients from the AFM cohort and in 33 patients from the TM cohort.

[c]The information on the number of leukocytes in CSF was available in 14 AFM patients and 33 TM patients.

[d]The information on protein concentration in CSF was available in 12 AFM patients and 33 TM patients.

[e]Raised protein was defined as a protein level >0.65 g/L for patients aged 1–3 months, >0.37 g/L for 3–6 months, >0.35 g/L for 6–12 months, >0.31 g/L for 1–10 years, and >0.49 g/L for 10–18 years.

Presence of such serum MOG and APQ4 antibodies was only recorded in TM patients. Of all tested patients, one patient had AQP4 antibodies (4%) and three patients showed positivity for MOG antibodies (13%; Table 2).

CSF investigations were performed in most AFM and TM patients (86% vs. 94%), but lumbar puncture was performed earlier after onset of weakness in AFM (1 vs. 4 days, $p<0.001$; Table 2). Numbers of patients with CSF pleocytosis were not significantly different between AFM and TM patients (93% vs. 56%).

Electromyography was performed in nine AFM patients and revealed abnormalities suggestive for axonal damage in eight. Virology testing was commonly performed in CSF in TM patients, whereas respiratory (16%) and fecal (14%) samples were tested in a limited number of patients.

Evaluation of clinical criteria

The TMCWG criteria were applied to both cohorts (Figure 1a, Table S1). None of the AFM patients fulfilled the complete set of TMCWG criteria for TM, because of the absence of a sensory level. When omitting the criterion of the presence of a clearly defined sensory level, 73% (11/15) of AFM patients in whom sufficient information was available fulfilled the criteria. If inflammation of the spinal cord was also not required, 83% (15/18) of patients fulfilled the criteria; in the remaining three patients, bilateral signs or symptoms attributable to spinal cord dysfunction, which is included in the TMWCG criteria, were not present.

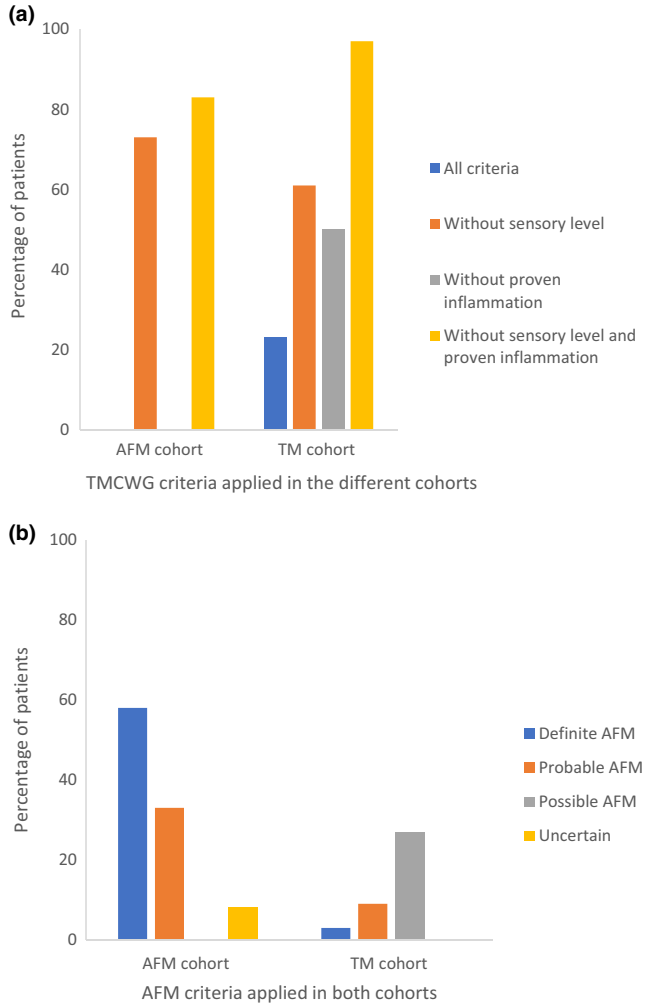

FIGURE 1 (a) Performance of the Transverse Myelitis Consortium Working Group (TMCWG) criteria. Percentage of patients fulfilling the complete set of TMCWG criteria for transverse myelitis (TM), and the criteria without the presence of a sensory level and/or proven inflammation, in both cohorts for patients from whom sufficient information was available. (b) Performance of the acute flaccid myelitis (AFM) criteria, showing percentage of patients fulfilling the AFM criteria in both cohorts for the patients for whom sufficient information was available for classification. Nineteen patients with TM had clear signs suggestive of an alternative diagnosis (not shown).

Of 30 children with TM with sufficient information available, seven (23%) fulfilled all TCWMG criteria. In 15 of the remaining 23 patients not fulfilling all criteria, no sensory level was found. In the other eight patients, no inflammation was demonstrated. When omitting the criterion of a sensory level, 61% (22/36) of TM patients fulfilled the criteria. In 13 of 14 patients not fulfilling the criteria, no inflammation was shown, whereas one patient did not have bilateral signs (Table S1). When omitting the criterion of proven inflammation, 50% (15/30) of TM patients fulfilled the criteria. The 15 patients not fulfilling the criteria did not have a sensory level. When omitting both the presence of a sensory level and proven inflammation, only one TM patient without bilateral signs did not fulfill the criteria.

The AFM criteria, as proposed by the international AFM Working Group were applied to both cohorts (Figure 1b; Table S2). Of the 33 patients with TM with sufficient information available, one (3%) fulfilled the criteria for definite, three (9%) for probable, and nine (27%) for possible AFM (Figure 1b).

Nineteen TM patients with a sensory level, with supratentorial MRI abnormalities, and/or with MOG or AQP4 antibodies were excluded, as these factors are noted to be suggestive for an alternative diagnosis in the AFM criteria [15]. One patient with a time interval from onset to nadir of 20 days was also not included in the classification (Table S2). Of the remaining 12 AFM patients who could be classified, seven (58%) fulfilled the criteria for definite and four (33%) for probable AFM. One patient (8%) was classified as uncertain, because no MRI was performed (Figure 1b).

DISCUSSION

This comparative study in two well-characterized pediatric cohorts of AFM and TM reveals both similarities and differentiating features between both disorders.

Both AFM and TM commonly present with acute onset limb weakness, which may be asymmetric, accompanied by pain and preceded by a prodromal illness. At onset of disease, hyporeflexia may be present in both conditions, including AFM and TM in the differential diagnosis of AFP. In both groups of patients, MRI of the spinal cord often reveals a longitudinally extensive lesion with significant gray matter involvement and CSF often shows pleocytosis (Figure 2). The similarities between both conditions are further underlined by the fulfillment of many of the diagnostic criteria for TM by AFM patients.

Besides described similarities, this study showed that upper extremity weakness is typical for AFM, as are predominance of proximal weakness, cranial nerve involvement, and brainstem abnormalities on MRI. On the other hand, the presence of a sensory level, bladder and/or bowel dysfunction, and hyperreflexia, probably explained by more diffuse spinal cord involvement, are more typical for TM. Furthermore, supratentorial abnormalities on MRI were only seen in TM.

The clinical characteristics and findings on ancillary investigations described in this study are similar to previously described

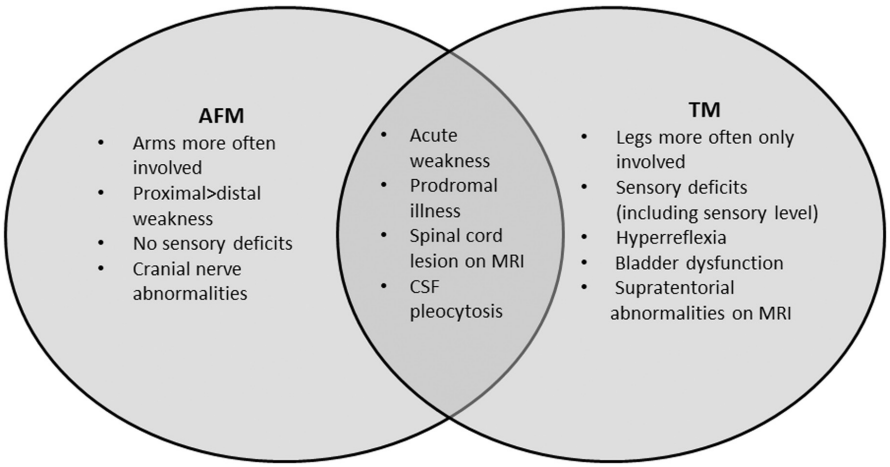

FIGURE 2 Overlapping and differentiating features between acute flaccid myelitis and transverse myelitis. Venn diagram illustrating differentiating and overlapping features between acute flaccid myelitis (AFM) and transverse myelitis (TM) in children. Features mentioned under both conditions are suggestive for either diagnosis, but must be used in a clinical context, as they are neither exclusive nor always present. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

cohorts of AFM and pediatric TM, supporting the representativeness of our findings [16–20]. Some studies have investigated the differences between AFM and TM. One prospective study, aiming to find differences in treatment outcome in pediatric myelitis patients, compared children with AFM and TM within their cohort [21]. Similar to our study, weakness more commonly affected upper extremities and CSF leukocyte numbers were higher in the AFM group. Sensory deficits were noted in 24% of AFM patients, which is higher compared to our study and previous studies [19, 21]. More detailed clinical information was not presented, impairing further comparison. Furthermore, diagnosis of AFM was based on the presence of flaccid weakness and gray matter abnormalities on MRI, regardless of enterovirus status, possibly leading to more heterogeneity within the AFM cohort [21]. A comparison study between children with restrictively defined AFM and children fulfilling the AFM criteria of the CDC, but with a possible alternative diagnosis, including four with TM, showed some findings similar to our study. This includes the differences in reflex pattern and sensory abnormalities [22].

Differentiation between AFM and TM is important for several reasons. First, there are therapeutic consequences, because the first-line treatment in children with TM consists of high-dose corticosteroids, whereas there are indications that steroid treatment may worsen outcome in AFM [8, 23]. Second, although residual deficits are common in both conditions, the motor outcome in TM is usually better than in AFM, which is also indicated by the number of children with TM who are ambulant at final follow-up in this study [8, 24]. An adequate diagnosis will help in counseling patients and their parents on the expected disease course. Third, especially for AFM, it is important to be aware of new clusters of cases to be able to relate these with outbreaks of associated enteroviruses for epidemiological purposes [25].

Children with TM may fulfill the clinical criteria for definite AFM. This underlines the need for thorough investigation, both clinically and with further diagnostic procedures, to search for factors suggestive of TM in a suspected AFM case [9]. These include the presence of sensory deficits and supratentorial abnormalities, mentioned in the diagnostic criteria and confirmed as differentiating factors in our study [1]. Evaluation of MRI abnormalities may also provide valuable information, with the caveat that MRI abnormalities may be subtle or absent in AFM, especially at onset of disease. Finally, we believe that timely and adequate virologic tests are important, as the finding of associated enteroviruses will strongly support the diagnosis of AFM.

The TMCWG criteria were developed in 2002 to create a set of uniform diagnostic criteria for TM [6]. These criteria were introduced before several important developments, in particular the discovery of AQP4 and MOG antibodies, and a new classification strategy has been proposed [26]. The TMCWG criteria are currently still in use and are believed to be applicable to children with suspected TM [8]. Importantly, the presence of a sensory level as a criterion, which would differentiate TM from AFM, is often omitted in childhood studies [7, 8]. The identification of a specific virus such as EV-D68 in suspected AFM cases would also lead to exclusion of idiopathic TM based on the criteria. However, as in many AFM cases no associated virus is isolated, possibly due to incomplete diagnostic testing or incongruence between the viral infection and onset of weakness, AFM cases may often fulfill the criteria for idiopathic TM. Conversely, the early identification of AQP4 or MOG antibodies would argue against an AFM diagnosis. Therefore, in children suspected of TM, a thorough clinical examination and complete diagnostic workup is important.

Our study has several limitations. First, the inclusion of patients was largely based on current diagnostic criteria, which may lead to circular reasoning. However, we do believe that this does not hinder the finding of differentiating features, which was the main purpose of this study. Second, sensory deficits are difficult to ascertain in young children. Although we do believe that these are less common in AFM patients, the younger age of the AFM cohort may have led to underreporting of sensory symptoms and overestimation of the differences found.

Third, the selection of children with EV-D68 impedes generalizability of the distinguishing features for AFM in association with other viruses, such as EV-A71 [5]. This does however improve the homogeneity of this group and provides more certainty of the diagnosis.

Fourth, the retrospective questionnaire-based nature by which cases were identified in the AFM cohort and the selection of EV-D68-positive cases may both have led to a bias toward more severe

cases. The similarity between the presented cohort and previous cohorts, however, supports the representativeness of the differentiating features found.

Fifth, certain tests may only be performed in selected patients in both cohorts, which may lead to confounding bias, inherent to the retrospective nature of this study. Finally, detailed information on the MRI results was not available from all children with AFM, so imaging characteristics could not be fully compared. This remains a topic for further research.

Patients were excluded from the TM cohort if, at onset of disease, signs of a disease-associated TM were present. As AQP4 and MOG antibody testing usually takes several weeks, and our aim was to find differentiating features at onset of TM presentation, we did not exclude the patients with a subsequent positive result for AQP4 or MOG antibodies, or the patients with MRI lesions suggestive of MS during follow-up. Therefore, some patients of the TM cohort were finally diagnosed with MS ($n=1$), AQP4-positive neuromyelitis optica spectrum disorder ($n=1$), and MOG antibody-associated disorder ($n=3$). Importantly, the differentiating features identified in this study and recommendations made in the discussion need validation in a prospective cohort.

In conclusion, we provide early distinguishing features between AFM and TM in childhood. Both disorders may, however, present similarly and fulfill clinical criteria of the other condition. Therefore, a careful clinical evaluation with timely and adequate diagnostic tests is important to help differentiate between AFM and TM and guide decisions on treatment.

AUTHOR CONTRIBUTIONS

Jelte Helfferich: Writing – original draft; formal analysis; methodology; conceptualization; data curation; investigation; visualization. **Arlette L. Bruijstens:** Writing – original draft; formal analysis; data curation; investigation; visualization. **Marjolein Knoester:** Investigation. **Oebele F Brouwer:** Supervision; methodology. **Rinze F. Neuteboom:** Supervision; funding acquisition; methodology; conceptualization.

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CONFLICT OF INTEREST STATEMENT

J.H., A.L.B., M.K., and O.F.B. have no conflicts of interest relevant to this study and no disclosures to report. R.F.N. has participated in trials by Sanofi and Novartis, and has received honoraria from Novartis and Zogenix.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article, within the limits of the General Data Protection Regulation.

DATA ACCESS AND RESPONSIBILITY

J.H. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet*. 2020;397:334-346. doi:10.1016/S0140-6736(20)32723-9
2. Knoester M, Helfferich J, Poelman R, et al. Twenty-nine cases of enterovirus-D68-associated acute flaccid myelitis in Europe 2016: a case series and epidemiologic overview. *Pediatr Infect Dis J*. 2019;38(1):16-21. doi:10.1097/INF.0000000000002188
3. 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-e247. doi:10.1016/S1473-3099(18)30094-X
4. Dyda A, Stelzer-Braid S, Adam D, Chughtai AA, MacIntyre CR. The association between acute flaccid myelitis (AFM) and enterovirus D68 (EV-D68)—what is the evidence for causation? *Euro Surveill*. 2018;23(3):17-00310. doi:10.2807/1560-7917.ES.2018.23.3.17-00310
5. Messacar K, Spence-Davizon E, Osborne C, et al. Clinical characteristics of enterovirus A71 neurological disease during an outbreak in children in Colorado, USA, in 2018: an observational cohort study. *Lancet Infect Dis*. 2020;20(2):230-239. doi:10.1016/S1473-3099(19)30632-2
6. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology*. 2002;59(4):499-505. doi:10.1212/WNL.60.4.730
7. Deiva K, Absoud M, Hemingway C, et al. Acute idiopathic transverse myelitis in children: early predictors of relapse and disability. *Neurology*. 2015;84(4):341-349. doi:10.1212/WNL.0000000000001179
8. Absoud M, Greenberg BM, Lim M, Lotze T, Thomas T, Deiva K. Pediatric transverse myelitis. *Neurology*. 2016;87(9 Suppl 2):S46-S52. doi:10.1212/WNL.0000000000002820
9. Theroux LM, Brenton JN. Acute transverse and flaccid myelitis in children. *Curr Treat Options Neurol*. 2019;21(12):64. doi:10.1007/s11940-019-0603-0
10. Helfferich J, Roodbol J, de Wit M-C, Brouwer OF, Jacobs BC. Acute flaccid myelitis and Guillain–Barré syndrome in children: a comparative study with evaluation of diagnostic criteria. *Eur J Neurol*. 2022;29(2):593-604. doi:10.1111/ene.15170
11. CDC. *Acute Flaccid Myelitis - Case Definitions*. 2021. Accessed August 16, 2022. https://ndc.services.cdc.gov/case-definitions/acute-flaccid-myelitis-2018/
12. Ketelslegers IA, Catsman-Berrevoets CE, Neuteboom RF, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. *J Neurol*. 2012;259(9):1929-1935. doi:10.1007/s00415-012-6441-6
13. Helfferich J, Bruijstens AL, Wong YYM, van Pelt ED, Boon M, Neuteboom RF. Prognostic factors for relapse and outcome in pediatric acute transverse myelitis. *Brain Dev*. 2021;43:626-636. doi:10.1016/j.braindev.2020.12.019
14. Yiu EM, Kornberg AJ, Ryan MM, Coleman LT, Mackay MT. Acute transverse myelitis and acute disseminated encephalomyelitis in childhood: spectrum or separate entities? *J Child Neurol*. 2009;24(3):287-296. doi:10.1177/0883073808323522

15. Murphy OC, Messacar K, Benson L, et al. Acute flaccid myelitis: cause, diagnosis, and management. *Lancet (London, England)*. 2021;397(10271):334-346. doi:10.1016/S0140-6736(20)32723-9
16. Meyer P, Leboucq N, Molinari N, et al. Partial acute transverse myelitis is a predictor of multiple sclerosis in children. *Mult Scler J*. 2014;20(11):1485-1493. doi:10.1177/1352458514526943
17. Pidcock FS, Salorio CF, Trovato M, Krishnan C, Kerr DA, Crawford TO. Acute transverse myelitis in childhood: center-based analysis of 47 cases. *Neurology*. 2007;68(18):1474-1480. doi:10.1212/01.wnl.0000260609.11357.6f
18. De Goede CGEL, Holmes EM, Pike MG. Acquired transverse myelopathy in children in the United Kingdom—a 2 year prospective study. *Eur J Paediatr Neurol*. 2010;14(6):479-487. doi:10.1016/j.ejpn.2009.12.002
19. Messacar K, Schreiner TL, Van HK, et al. Acute flaccid myelitis: a clinical review of US cases 2012–2015. *Ann Neurol*. 2016;80(3):326-338. doi:10.1002/ana.24730
20. Chong PF, Kira R, Mori H, et al. Clinical features of acute flaccid myelitis temporally associated with an enterovirus D68 outbreak: results of a nationwide survey of acute flaccid paralysis in Japan, August–December 2015. *Clin Infect Dis*. 2018;66(5):653-664. doi:10.1093/cid/cix860
21. Greenberg B, Plumb P, Cutter G, et al. Acute flaccid myelitis: long-term outcomes recorded in the CAPTURE study compared with paediatric transverse myelitis. *BMJ Neurol Open*. 2021;3(1):e000127. doi:10.1136/bmjno-2021-000127
22. Elrick MJ, Gordon-Lipkin E, Crawford TO, et al. Clinical subpopulations in a sample of North American children diagnosed with acute flaccid myelitis, 2012–2016. *JAMA Pediatr*. 2019;173(2):134-139. doi:10.1001/jamapediatrics.2018.4890
23. Hixon AM, Clarke P, Tyler KL. Evaluating treatment efficacy in a mouse model of enterovirus D68-associated paralytic myelitis. *J Infect Dis*. 2017;216(10):1245-1253. doi:10.1093/infdis/jix468
24. Martin JA, Messacar K, Yang ML, et al. Outcomes of Colorado children with acute flaccid myelitis at 1 year. *Neurology*. 2017;89(2):129-137. doi:10.1212/WNL.0000000000004081
25. Fischer TK, Simmonds P, Harvala H. The importance of enterovirus surveillance in a post-polio world. *Lancet Infect Dis*. 2022;22(1):e35-e40. doi:10.1016/S1473-3099(20)30852-5
26. Blackburn KM, Greenberg BM. Revisiting transverse myelitis: moving toward a new nomenclature. *Front Neurol*. 2020;11:519468. doi:10.3389/fneur.2020.519468

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A.

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