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Pediatric acute flaccid myelitis: Evaluation of diagnostic criteria and differentiation from other causes of acute flaccid paralysis

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ABSTRACT

Background: Acute flaccid paralysis (AFP) is characterized by rapidly progressive limb weakness with low muscle tone. It has a broad differential diagnosis, which includes acute flaccid myelitis (AFM), a rare polio-like condition that mainly affects young children. Differentiation between AFM and other causes of AFP may be difficult, particularly at onset of disease. Here, we evaluate the diagnostic criteria for AFM and compare AFM to other causes of acute weakness in children, aiming to identify differentiating clinical and diagnostic features.

Methods: The diagnostic criteria for AFM were applied to a cohort of children with acute onset of limb weakness. An initial classification based on positive diagnostic criteria was compared to the final classification, based on application of features suggestive for an alternative diagnosis and discussion with expert neurologists. Cases classified as definite, probable, or possible AFM or uncertain, were compared to cases with an alternative diagnosis.

Results: Of 141 patients, seven out of nine patients initially classified as definite AFM, retained this label after further classification. For probable AFM, this was 3/11, for possible AFM 3/14 and for uncertain 11/43. Patients initially classified as probable or possible AFM were most commonly diagnosed with transverse myelitis (16/25). If the initial classification was uncertain, Guillain-Barré syndrome was the most common diagnosis (31/43). Clinical and diagnostic features not included in the diagnostic criteria, were often used for the final classification.

Conclusion: The current diagnostic criteria for AFM usually perform well, but additional features are sometimes required to distinguish AFM from other conditions.

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1. Introduction

Acute flaccid myelitis (AFM) is characterized by rapidly progressive flaccid weakness of the limbs, caused by damage of anterior horn cells in the spinal cord. Young children are mostly affected [1–3]. According to current diagnostic criteria, MRI abnormalities in the grey matter of the spinal cord and pleocytosis in cerebrospinal fluid (CSF) are required to make a definite diagnosis of AFM [4].

In typical cases, limb weakness develops over several days and is preceded by a respiratory illness. While limb weakness is required for the diagnosis, respiratory and cranial muscles are also frequently involved [1,5]. Recovery is often incomplete with severe residual deficits being common in affected patients [6].

Different viruses may cause AFM, probably by invasion of the anterior horn cells [2,3]. Poliomyelitis, caused by poliovirus, may fulfill the clinical criteria for AFM and was the most common cause before the implementation of effective vaccination strategies [7]. However, since 2014 cases have frequently been associated with non-polio enteroviruses, in particular enterovirus D68 (EV-D68) and A71 (EV-A71) [5, 8–10].

AFM is included in the broad differential diagnosis of acute flaccid paralysis (AFP), which covers other disorders of peripheral motor neurons and innervated muscles, including Guillain-Barré syndrome (GBS), toxic neuropathy or myopathy and botulism. However, central motor neuron disorders may also present with flaccid limb weakness, especially in the acute phase. These include transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), spinal cord ischemia and acute spinal cord compression [11]. Similarly to AFM, GBS as well as TM and ADEM may be preceded by a prodromal illness [12]. Also, in both TM and ADEM longitudinally extensive lesions of the spinal cord on MRI and CSF pleocytosis are commonly found [13,14]. Because of this clinical and diagnostic overlap between AFM and GBS, TM and ADEM, differentiation of these disorders may be particularly difficult, especially early in the disease course [12,15–17].

In a child with AFP, it is important to consider AFM early in the disease course. This enables the performance of early and proper investigations, which are required to confirm the diagnosis of AFM. Also, associated viruses are best identified early in the disease course, if appropriate sampling is performed [4]. Furthermore, patients with AFM may show rapid clinical deterioration, urging clinical monitoring [17, 18]. Lastly, in the mouse model of AFM, early administration of immunoglobulin improved outcome, and administration of monoclonal antibodies against specific strains of EV-D68 was effective in inhibiting progression of muscle weakness even several days after onset [19,20]. Also, in this mouse model, treatment with steroids was associated with deterioration of weakness [19]. While these findings need confirmation, these studies suggest that early treatment with immunoglobulin may be beneficial, whereas steroids may have negative effects. An early diagnosis will be required to investigate the effects of treatment in children with AFM.

To test the clinical usefulness of the present diagnostic criteria for AFM, we evaluated their application in a real-world cohort of children with acute onset limb weakness. By doing this, we aimed to identify both clinical and diagnostic features suggestive for AFM, or indicative for an alternative diagnosis.

2. Methods

2.1. Study population

The study population consists of a cohort of children with acute onset weakness, diagnosed between January 2014 and December 2019, previously used to estimate the incidence of AFM in children (<18 years) in the Netherlands [21]. These children had been identified by searching electronic health care data systems of ten hospitals in The Netherlands for specific diagnostic codes (ICD and DBC), related to acute weakness and/or infection. Children without weakness or with a clear diagnosis other than AFM, such as a genetic disease (e.g., spinal muscular atrophy) or structural abnormalities (e.g., traumatic spinal cord injury, malignancy, or congenital abnormalities) had been excluded [21]. Only children of whom sufficient data was available to apply the current AFM classification, were included in this study.

2.2. Application of diagnostic criteria

The current diagnostic criteria for AFM had been used in the previously described study to classify cases [4,21].(Table 1) In this study we further describe and analyze the previously performed classification process and the dilemmas encountered during this exercise.

First, an initial classification was made by merely applying the 'positive criteria' - acute flaccid limb weakness, abnormalities of the spinal cord grey matter on MRI, and pleocytosis in CSF - leading to a subdivision of five categories: (1) definite AFM, (2) probable AFM, (3) possible AFM, (4) uncertain or (5) no AFM (Fig. 1 step 1).

Hereafter, features mentioned in the diagnostic criteria as suggestive for an alternative diagnosis, shown in Table 1, were applied to consider exclusion of applicable patients [4]. (Fig. 1 step 2).

Third, cases in which there was a dilemma on the final classification, were discussed with two expert clinical neurologists (BCJ, OFB).

These three steps led to the final classification, in which patients could either retain or loose the label from the initial classification (definite AFM, probable AFM etc.). If the label from the initial classification was lost, the original diagnosis, as made by the treating clinician, was used for comparison.

The clinical features and diagnostic test results leading to the final classification were described. It was also described if clinical data was

Table 1
Diagnostic criteria for AFM (adapted from Murphy et al.[4]).

Diagnostic criteria for AFM classification				
Diagnostic items	Definite AFM	Probable AFM	Possible AFM	Uncertain
Acute onset of limb weakness (period from onset to nadir: hours to 10 days)	P	P	P	P
Prodromal fever or illness	P/A	P/A	P/A	P
Weakness involving one or more limbs, neck, face, or cranial nerves	P	P	P	P
Decreased muscle tone in at least one weak limb	P	P	P/A	P
Decreased or absent deep tendon reflexes in at least one weak limb	P	P	P/A	P
MRI: spinal cord lesion with predominant grey matter involvement, with or without nerve root enhancement	P	P	P	NP
CSF pleocytosis (white cell count> 5 cells/L)	P	A or NP	P/A or NP	P/A or NP
Factors that might suggest an alternative diagnosis:				
1. Encephalopathy that cannot be explained by fever, illness, respiratory distress, metabolic abnormalities or medications 2. Presence of sensory deficits on examination 3. Presence of lesions in the supratentorial white matter or cortex 4. Absence of CSF pleocytosis 5. Positive serum aquaporin-4 would exclude AFM 6. Positive serum MOG-antibody, which would suggest MOG-antibody associated disease [6]				

Permission for reproduction was obtained. AFM: acute flaccid myelitis; P: diagnostic item is **present**; P/A: presence of this diagnostic item is supportive but not required; A: diagnostic item is **absent**; NP test was **not performed**; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; MOG: myelin oligodendrocyte glycoprotein.

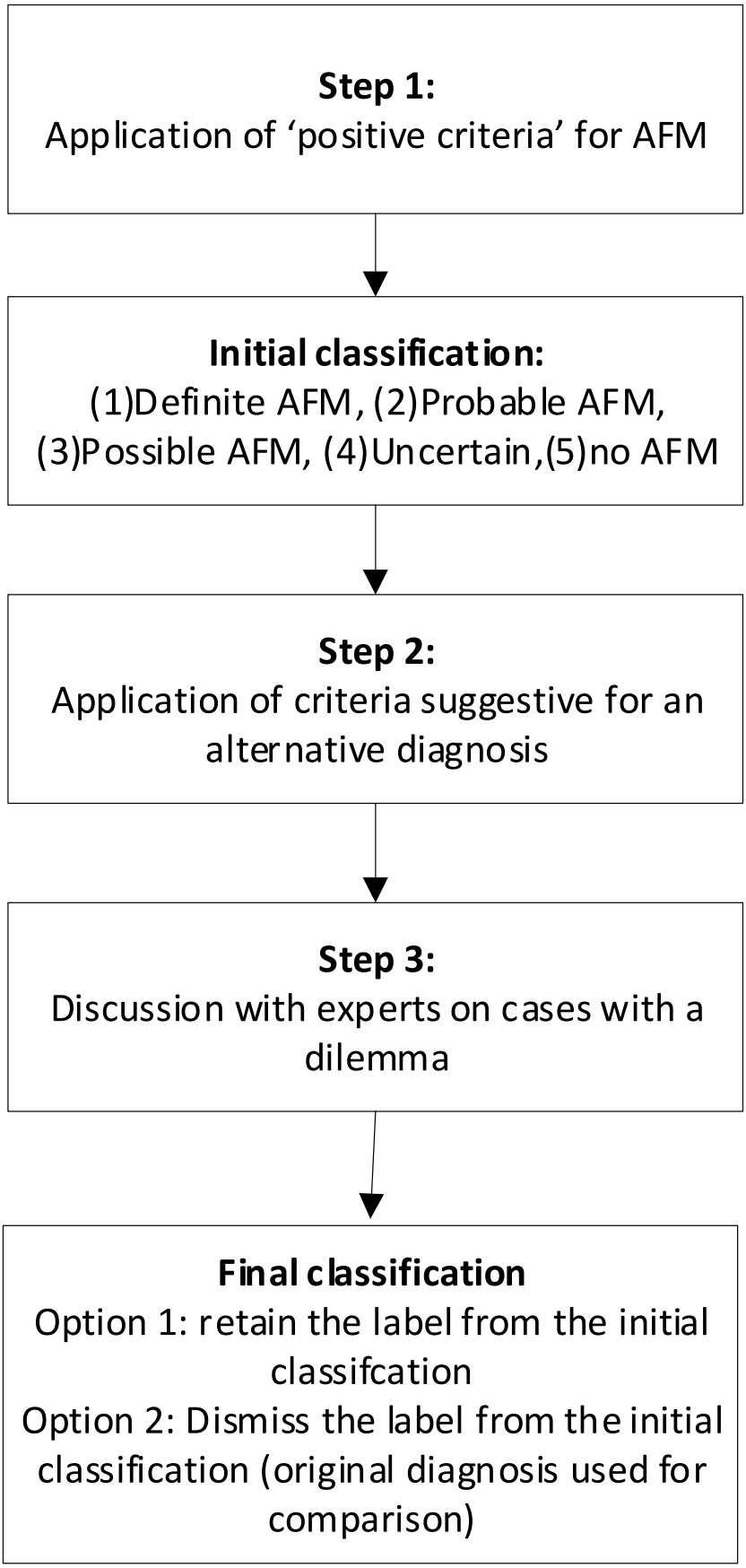

Fig. 1. Flow chart showing the different steps which were taken to arrive at the initial and final classification.

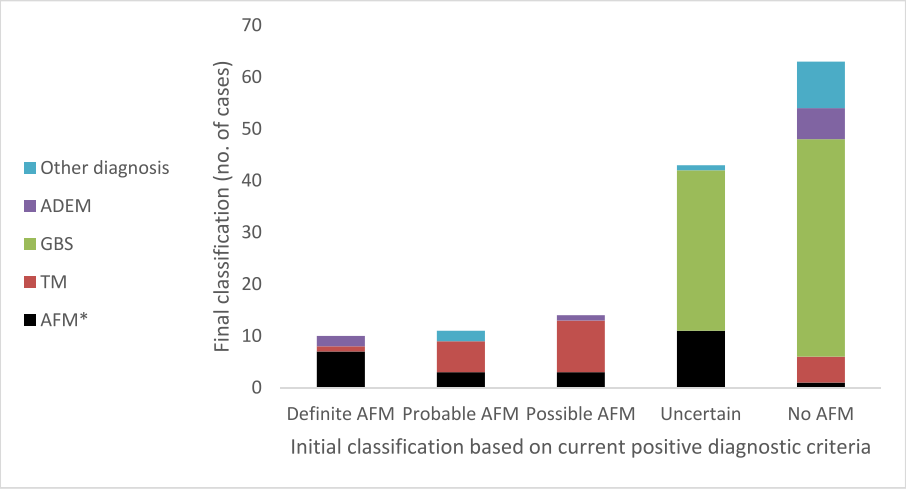

Fig. 2. The initial classification based on the 'positive diagnostic criteria' for AFM [4] is compared to the final classification. *AFM includes all cases which retained the label from the initial classification, except for the 'no AFM'- category that contained one case finally classified as AFM. AFM: acute flaccid myelitis, TM: transverse myelitis, GBS: Guillain-Barré syndrome, ADEM: acute disseminated encephalomyelitis.

not available, or if tests were not performed and their results might have led to a different final classification.

2.3. Differentiating features

To further identify features that differentiate between AFM and other causes of AFP beyond the criteria suggestive for an alternative diagnosis, these cases, finally classified as definite, probable, or possible AFM and those classified as 'uncertain', were compared to cases with an alternative diagnosis.

For this comparison, we used demographic and clinical features and results of ancillary investigations including MRI of the spinal cord and brain, CSF, nerve conduction studies (NCS), auto-antibodies and virological tests.

2.4. Statistics

Relative numbers are given for dichotomous or ordinal variables. Median, interquartile range and full range are used for continuous variables.

3. Results

3.1. Classification and dilemmas

A total of 141 patients younger than 18 years with rapidly progressive weakness, diagnosed in 2014–2019 in ten hospitals in The Netherlands, and with sufficient data available for classification were included [21]. The 'positive' criteria were applied, resulting in the subgroups as shown in Fig. 2. Features suggestive of an alternative diagnosis were present in 7/10 cases fulfilling the positive diagnostic criteria for definite AFM, 11/11 for probable AFM (9/11 when excluding absence of CSF pleocytosis), 12/14 for possible AFM and 43/43 for 'uncertain' (21/43 when excluding absence of CSF pleocytosis). After discussing cases in which it was difficult to make a final classification, cases were subdivided into diagnostic groups (Fig. 2). Nineteen cases eventually retained the label from the initial classification, even if features suggestive of an alternative diagnosis were present (including 13 patients with absence of CSF pleocytosis). In twelve cases additional features were required for classification, including the presence of demyelinating features on NCS in nine of the cases, initially classified as uncertain. In fifteen cases further discussion with experts was necessary, as further described below.

3.2. 'Definite' AFM'

According to recently published criteria, a definite diagnosis of AFM requires a combination of acute flaccid limb weakness with hyporeflexia and hypotonia in the affected limb, a spinal cord lesion with predominant grey matter involvement on MRI, and pleocytosis in CSF (Table 1) [4]. In our cohort, ten children fulfilled these criteria. Seven of them were finally classified as definite AFM (Supplementary Table 1).

These seven patients all had a prodromal illness, followed by limb weakness, which was asymmetric in five. A respiratory sample was taken in four of seven (day 1–3 after onset), three of which were positive for EV-D68. In one of these seven patients, MOG-antibodies were found in serum (Box 1). In two cases, sensory deficits were found at onset of disease. The presence of predominant proximal and asymmetric

Box 1
Illustrative case

An 11-year-old patient presented in 2016 with asymmetric flaccid weakness of the limbs, three days after a prodromal illness with head- and neck pain. The arms were more severely affected than the legs and weakness was predominantly proximal. There were no sensory deficits. Because of respiratory failure, mechanical ventilation was required for 15 days. CSF showed a mononuclear pleocytosis and the MRI showed mostly centrally located myelopathy of the entire spinal cord. MOG-antibodies tested in serum at day 3 after onset, before initiation of treatment, were positive with a low titer. Only CSF was tested for viruses, showing negative results. The presence of MOG-antibodies led to an initial diagnosis of MOG-associated disease (MOGAD). The persistence of asymmetric, flaccid weakness predominantly of the arms four years after onset, as well as the absence of sensory deficits and bladder- or bowel dysfunction made us decide to finally classify this case as definite AFM.

weakness at onset, the persistence of flaccid weakness and the absence of a sensory level, led to a final classification of definite AFM. One patient with definite AFM had encephalopathy at onset. The presence of predominant proximal asymmetric weakness in the arms, the absence of supratentorial white matter abnormalities on MRI, and NCS abnormalities compatible with motor axonal damage led to the final diagnosis of AFM.

Three of the ten patients fulfilling the 'positive criteria' for AFM were finally classified as 'no AFM'. In one of them, a nasopharyngeal and fecal sample were tested and found negative at the first day after onset of weakness. In two patients, a diagnosis of ADEM was made, with encephalopathy in one patient and supratentorial white matter abnormalities in both patients. In the other patient a diagnosis of TM was made, based on the combination of bilateral sensory and autonomic abnormalities, symmetric weakness of only the legs and hyperreflexia at follow-up, combined with the presence of MOG-antibodies.

3.3. 'Probable' AFM

For a probable diagnosis of AFM, a combination of acute flaccid limb paralysis and a spinal cord lesion on MRI, predominantly affecting the grey matter, is required (Table 1) [4]. Eleven patients fulfilled these criteria, three of whom were finally classified as probable AFM (Supplementary Table 2).

In these three patients CSF investigations were performed early (one day before until two days after onset of weakness). In two patients with a prodromal illness, a respiratory sample was investigated (day 2–3 after onset), one of which was positive for EV-D68. In one patient sensory deficits were present on examination, without a sensory level. The MRI of this patient showed predominant central conus involvement, but serum MOG-antibodies were negative.

Eight of eleven patients fulfilling the criteria for probable AFM were finally classified as 'no AFM'. In only one of these eight a respiratory sample was tested (day 3 after onset) and was found negative. In six, a diagnosis of TM was made, five of them with a sensory level on examination. CSF investigations were performed early in the disease course in these patients (two days before until one day after onset of weakness). In the patient diagnosed with TM, but without a sensory level, the presence of sensory deficits and the development of spasticity at follow-up was deemed more compatible with TM than with AFM. In another patient, diagnosed with TM, MOG antibodies were found. This patient also had two separate spinal cord lesions on MRI. In two of the eight patients finally classified as 'no AFM', the clinical diagnosis was uncertain, but spinal cord ischemia was considered. One of these patients had a sensory level; the other patient did have sensory deficits and developed spasticity at follow-up, again making spinal cord ischemia more probable than AFM.

3.4. 'Possible' AFM

For a possible diagnosis of AFM, a combination of acute onset limb weakness and MRI spinal cord lesions predominantly affecting the grey matter is required. Hyporeflexia does not necessarily have to be present (Table 1) [4]. Fourteen patients fulfilled these criteria, of whom three were finally classified as possible AFM (Supplementary Table 3).

In these three cases, a central longitudinally extensive myelopathy was seen on MRI. In one of the two patients in which CSF investigations were performed, pleocytosis was found. Virological testing of feces and a nasopharyngeal aspirate (day 3 after onset) was performed in one of the three, showing parechovirus, adenovirus and rhinovirus. One of these patients had asymmetric proximal weakness, more dominant in the arms with persistent proximal arm weakness over time. Two of these three patients had symmetric diffuse weakness of the legs and sensory deficits, without a sensory level. In one of these two patients there was also bladder involvement.

Of the fourteen patients fulfilling the positive criteria for possible AFM, eleven were finally classified as 'no AFM'. Ten of these eleven were diagnosed with TM and one with ADEM. In five of these patients virological testing was performed on a respiratory sample, all of which were negative.

Of the ten patients with a final diagnosis of TM, five had a sensory level on examination. Supratentorial abnormalities on MRI were present in five patients, including both patients with MOG-antibodies. In five of eight patients in whom CSF investigations were done, pleocytosis was found. Two patients who were diagnosed as TM did not have a sensory level nor supratentorial MRI abnormalities. One had asymmetric weakness, predominantly distal in the arms and proximal in the legs, while the other had symmetric leg weakness. At follow-up both patients had persistent hyperreflexia; one patient also had extensor plantar responses and spasticity. Two children had isolated involvement of the central conus on MRI. In these patients the presence of sensory deficits as well as the prominent bladder and/or bowel dysfunction were considered more consistent with a diagnosis of TM than with AFM.

The patient with a final diagnosis of ADEM had encephalopathy at onset. Furthermore, the MRI of the brain showed abnormalities in the supratentorial white matter.

3.5. Uncertain diagnosis

Cases with acute flaccid limb weakness and a prodromal illness or fever would be classified as uncertain if no MRI is performed or reliable assessment of the MRI is not possible, and if CSF analysis is normal or has not been performed (Table 1) [4]. In our cohort, 43 patients fulfilled these criteria. Of those, eleven were finally classified as uncertain (Supplementary Table 4).

Of these eleven patients classified as uncertain, one patient had an MRI of the spinal cord twice, both of which could not reliably be

Box 2
Illustrative case

A 16-year-old patient with a final diagnosis of TM, had predominantly proximal flaccid weakness of the right arm. On examination a cervical sensory level was found. MRI showed a longitudinally extensive central myelopathy at the cervical level and subtle aspecific supratentorial abnormalities in the cerebral white matter. CSF showed no pleocytosis. Nerve conduction studies were not performed. At follow-up after 18 months there was persistent proximal weakness of the right arm with slight atrophy of the shoulder muscles and sensory abnormalities of the right leg. While the pattern of weakness is suggestive for AFM, the presence of a sensory level and the supratentorial abnormalities were deemed more compatible with TM.

Box 3
Illustrative case

An eight-month-old child had global symmetric weakness of the legs and bladder dysfunction. On examination there were hyperreflexia and sensory deficits, but a sensory level could not be found. MRI showed a longitudinally extensive central lesion of the cervical and thoracic cord, CSF showed a mononuclear pleocytosis. PCR of feces and respiratory material was positive for parechovirus, adenovirus and rhinovirus. After three years there was persistent leg weakness. This case was classified as possible AFM, since a sensory level was not identified. However, the symmetric leg weakness, the sensory deficits and bladder dysfunction suggest a diagnosis of TM.

assessed because of movement artifacts. This patient, who was diagnosed in a period of increased EV-D68 circulation (July 2016), had asymmetric predominantly proximal weakness. CSF showed a mononuclear pleocytosis and abnormalities compatible with motor axonal damage were seen on NCS. No respiratory or fecal samples were taken; serology did reveal positivity for enterovirus IgM, providing a possible clue for an enterovirus infection.

The other ten patients had symmetric weakness which was diffuse or predominantly distal in nine. None of these ten patients had sensory deficits and a significantly raised protein in CSF was found in eight. Virological testing on a respiratory sample was done in four (day 3–9), showing *Haemophilus Influenzae* in one patient. Five patients were completely recovered at final follow-up. Two of these ten patients had NCS compatible with acute motor axonal injury (Box 4). They were initially diagnosed with acute motor axonal neuropathy, both in a period of increased EV-D68 circulation. Although in these ten patients a diagnosis of an axonal variant of GBS may be considered, especially in the patients with complete recovery, these patients were classified as uncertain, as no MRI was performed.

Of the 43 patients fulfilling the criteria for an uncertain AFM diagnosis, 32 were finally classified as 'no AFM'. Virological tests on a respiratory sample were performed in eight, one of which was positive for an adenovirus. Of these, 31 were diagnosed with GBS. One patient who recovered spontaneously several days after onset of weakness was diagnosed with probable functional limb weakness.

Of the 31 patients diagnosed with GBS, 20 had sensory abnormalities. CSF was performed in 29 patients and showed a raised protein without pleocytosis in 25. NCS was performed in 29 patients, showing features of a demyelinating neuropathy in twelve and of an axonal neuropathy in two.

3.6. No AFM

A total of 63 patients did not fulfill the criteria for AFM. These included 42 patients with GBS, five patients with TM, six patients with ADEM, nine patients with another diagnosis and one patient with AFM, further described in box 5. A substantial number of patients had acute onset flaccid limb weakness, but none had MRI abnormalities in the spinal cord grey matter.

4. Discussion

In this qualitative study, the current criteria for AFM were evaluated by applying them to a cohort of children with acute onset weakness. It may be difficult to make a correct diagnosis in children presenting with AFP and to differentiate AFM from other conditions, in particular at onset of disease. While the diagnostic criteria for AFM mostly performed well, in some cases additional features were required for proper classification. Furthermore, in many cases investigations required to make the diagnosis more or less likely were not adequately or timely performed.

Despite limited evidence for treatment in the acute phase of AFM, arguments for an early diagnosis of AFM include the need for clinical monitoring, and improved counselling to patients and parents [18]. Furthermore, early consideration of AFM would lead to early and

Box 4
Illustrative case

A 15-year-old patient had symmetric distally predominant flaccid weakness of the limbs, five days after a gastrointestinal infection. The legs were more severely affected than the arms. There were no sensory deficits. CSF showed a slightly raised protein and no pleocytosis. NCS at 11 days after onset of weakness showed a motor axonal neuropathy, without sensory abnormalities. No MRI was performed. At follow-up after two months there was persistent distal weakness of the legs.

This patient was classified as uncertain as no MRI was performed, but clinically a motor axonal variant of GBS seems to be the most likely diagnosis.

Box 5
Illustrative case

A two-year-old patient had asymmetric mostly proximal flaccid weakness of all limbs with the legs being more severely affected. One day before onset there was a respiratory infection. CSF showed a mononuclear pleocytosis. NCS showed absent motor responses in the legs. In a respiratory sample EV-D68 was isolated. Repeated MRI scans of the brain and spinal cord at the first and eighth day after onset of weakness showed no abnormalities, even after careful reassessment.

While the clinical presentation and the identification of EV-D68 are compatible with a diagnosis of AFM, this patient was initially included in the 'no-AFM group' because of the absence of abnormalities on MRI of the spinal cord.

Table 2
Summary of features, additional to those included in the diagnostic criteria, supportive for the diagnosis of AFM or for an alternative diagnosis. AFM: acute flaccid myelitis; CSF: cerebrospinal fluid; EV-D68: enterovirus D68; GBS: Guillain-Barré syndrome; MOGAD: Myelin oligodendrocyte glycoprotein antibody associated disease; MRI: magnetic resonance imaging; NCS: Nerve conduction studies; PCR: polymerase chain reaction; SCI: spinal cord ischemia; TM: transverse myelitis.

Supportive features for the diagnosis AFM	Features supportive for an alternative diagnosis	Supportive for alternative diagnosis
Predominantly proximal weakness	Predominantly distal weakness	GBS
Asymmetric weakness	Strictly symmetric weakness	GBS
Arms more severely affected than legs	Only involvement of the legs	TM, SCI
Time course from prodrome till onset of <5 days	Sensory level	TM, SCI
Features suggestive of axonal damage on NCS	Hyperreflexia in affected limbs	TM, SCI
PCR positive for EV-D68 or another associated virus in any material	Development of spasticity over time	TM, SCI
	Demyelinating features on NCS	GBS
	Significantly raised CSF protein level, especially in absence of pleocytosis	GBS
	Isolated conus involvement on MRI	TM/MOGAD

adequate investigations, which is necessary to confirm the diagnosis, as CSF and MRI abnormalities may disappear and associated viruses may be undetectable later in the disease course [1,22].

We will discuss clinical and diagnostic features suggestive for AFM or for an alternative diagnosis, both from this study and previous studies, and evaluate the items included in the diagnostic criteria [4]. The additional features that were used for a final classification are summarized in Table 2.

4.1. Clinical features

For definite or probable AFM, as well as for an uncertain diagnosis, the presence of acute flaccid limb weakness with hyporeflexia in at least one affected limb is required [4]. The presence of flaccid weakness at onset often does not differentiate between AFM and other causes of AFP, such as TM and GBS. However, the pattern of weakness may provide distinguishing features [12,15]. Both this study and previous studies indicate that asymmetry of weakness, predominance of proximal weakness, and involvement of arms more than legs, are supportive for AFM [1,15]. In addition, strictly symmetric and predominantly distal weakness are more compatible with GBS [12,23]. In TM, symmetric involvement of only the legs is a commonly observed pattern, but other patterns such as asymmetric predominant proximal weakness may be seen. While differentiation between AFM and TM may be difficult at onset, in most TM cases, spasticity with hyperreflexia, often accompanied by extensor plantar responses, will develop over time.

Cases of acute weakness with normo- or hyperreflexia may fulfill the criteria for possible AFM. In many of these cases a diagnosis of TM or another cause of spinal cord injury with central pyramidal involvement is more probable, which can be further supported by additional features such as the pattern of weakness and the presence of sensory deficits. These sensory deficits are included in the diagnostic criteria as a feature suggestive for an alternative diagnosis [4]. The finding of a sensory level on examination would in our opinion exclude AFM, but it may be quite difficult to identify this especially in young children [13,24]. Sensory deficits have been identified in cases of AFM, possibly associated with spinal cord edema, which may be seen in the acute phase [1].

Encephalopathy is uncommon in AFM and may point to a diagnosis of ADEM. In AFM, encephalopathy may occur due to respiratory failure or metabolic abnormalities. At onset of disease, it may be difficult to determine whether this explains the encephalopathy. Other features such as the pattern of weakness and MRI abnormalities may then help in differentiation between AFM and ADEM.

Bladder and bowel dysfunction has been reported in AFM as well as GBS, with bladder dysfunction being more common in the latter. However, in cases with predominant and persistent dysfunction a diagnosis of TM or MOGAD may be more likely, as this is associated with diffuse spinal cord involvement or significant involvement of the conus and caudal roots [1,25,26].

4.2. MRI

Abnormalities of the spinal cord grey matter on MRI are obligatory for a definite, probable or possible diagnosis of AFM, while their absence on adequately timed scans of sufficient quality would exclude AFM [4]. The spinal cord grey matter of the whole spinal cord may be involved in AFM and extensive lesions are common with the cervical cord being most often affected [4,27,28]. Isolated involvement of the conus is uncommon in AFM and should lead to consideration of another diagnosis such as MOGAD [29].

In our study, one child with a final clinical diagnosis of AFM associated with EV-D68 did not show MRI abnormalities even on repeated MRI-scans and after reassessment by experienced pediatric neuroradiologists. In another child with AFM the MRI was of insufficient quality to assess the presence of grey matter abnormalities leading to a classification as uncertain. While these scenarios may be rare and would lead to considering alternative diagnoses, our experience is that MRI abnormalities may be subtle especially early after onset of weakness. This urges the need for adequate and high-quality scans of the spinal cord in suspected AFM cases. Furthermore, MRI scans should be carefully assessed by radiologists with experience in spinal cord imaging.

4.3. CSF

CSF pleocytosis is identified in most patients with AFM, but is required for a classification as definite AFM, while the absence of pleocytosis would suggest an alternative diagnosis [4]. Similar to TM, pleocytosis may also be not yet found if CSF is examined in the first hours after onset of weakness. The presence of a significantly raised CSF protein (>100 mg/dL), especially in absence of pleocytosis, should lead to reconsidering the diagnosis, as this is more compatible with GBS [30].

4.4. Nerve conduction studies

Results from neurophysiology studies have not been included in the working group criteria, while others have suggested that the findings of a pure motor axonal neuropathy is supportive of the diagnosis [30,31]. While this finding is not exclusive for AFM in our cohort, but may also be seen in acute motor axonal neuropathy (AMAN) patients, we do believe that it supports the diagnosis, in particular in differentiating AFM from TM. On the other hand, NCS showing demyelinating features would exclude the diagnosis and point to a demyelinating variant of GBS [12,32]. Therefore the performance of NCS may be helpful in cases where differentiation remains difficult. It is not yet known what the optimal timing in AFM is.

4.5. Virology

Different viruses have been associated with AFM, including EV-D68 and EV-A71. EV-D68 is mostly identified in respiratory material, while EV-A71 is mostly found in fecal material, similarly to poliovirus. Associated viruses are only rarely identified in CSF [9,33,34]. The identification of an associated virus, in particular EV-D68, is not included in the

current criteria, but it has been suggested as a confirmative item by other authors [31]. While different viruses have been associated with AFM, the evidence for EV-D68 as a cause for AFM has been increasing and therefore the identification of this virus in any material in a patient with AFP would in our opinion strongly support the diagnosis [2,3,8].

4.6. Autoantibodies

AQP4-antibodies, causing neuromyelitis optica spectrum disorder, and MOG-antibodies, present in MOGAD, need to be determined in any child with suspected myelitis [4].

In our cohort, AQP4-antibodies were not identified in any case, in line with the rare identification of these antibodies in children [35]. Its presence would however lead to the exclusion of AFM. MOG antibodies were identified in some patients in this study, most with a diagnosis of TM. While there is a spectrum of acquired demyelinating syndromes in which MOG antibodies may be seen, their significance is still being explored as they may also be seen in other conditions [29,36]. In our study, one patient with a clinical picture compatible with AFM showed weak positivity for MOG-antibodies. Therefore, while the presence of MOG-antibodies would suggest MOGAD, it does not exclude AFM, particularly with low titers.

4.7. Limitations

Our study is limited especially by the retrospective design in which a final classification was made based on expert opinion. While this final classification was carefully considered by experts in the field, this is still subjective, as there is no confirmative test for the diagnosis of AFM and as the features required for a definite diagnosis may not persist over time. This does however match clinical practice in which clinicians have to make a diagnosis based on clinical features and findings of further investigations.

The retrospective nature of this study leads to incompleteness of clinical data and investigations. In some cases, proper classification was therefore difficult or only possible by using clinical features at follow-up. This limits the recommendations made for early diagnosing AFM in clinical practice, but underlines the need for adequate testing.

In the selection process initially used for the epidemiological study, some cases of acute weakness may not have been included, because they did not have a diagnostic code matching the inclusion criteria. Furthermore, some cases, for example those with structural abnormalities, were excluded. At onset of disease, before imaging studies are performed, differentiation from other causes of AFP may be difficult. For these reasons, to confirm certain distinctive features of AFM found in this study and to explore further early diagnostic characteristics in children with AFP, a prospective study, ideally in a large, unselected cohort of children, is necessary.

5. Conclusion

The diagnostic criteria for AFM were created by the AFM Working Group, hoping to create uniformity in the diagnosis and management, as no confirmative test for the diagnosis exists [4]. The possibility of atypical features was commented on by the working group, underlining the difficulty in making a set of criteria covering all AFM cases [4]. Here we show, that the diagnostic criteria usually perform well, but that additional features may be required to distinguish AFM from other conditions that may present as AFP. These features were summarized and may help clinicians in establishing the challenging diagnosis of AFM. As early and adequate diagnostic tests are required to make a definite diagnosis, we provide a suggested clinical work-up for clinicians, which can be used when confronted with a case of AFP (Table 3).

Table 3
Suggested investigation in a child with acute flaccid paralysis, adapted from Helfferich et al. [16]. *MOG: Myelin-oligodendrocyte glycoprotein, AQP4: Aquaporin 4, GM1: Ganglioside M1, GD1a: Ganglioside D1a, GQ1b: Ganglioside Q1b, CSF: Cerebrospinal Fluid. WNV: West Nile Virus, NCS: nerve conduction studies.*

Suggested investigations in children with acute flaccid paralysis	
Blood	- Auto-antibodies (Anti-MOG IgG, anti-AQP4, anti-GM1, Anti-GD1a, Anti-GQ1b) - Oligoclonal bands and IgG (both serum and CSF) - Microbiology: Serology for enterovirus, Borrelia, WNV[a]
CSF	- Routine investigations (Cell count, protein, glucose) - Oligoclonal bands and IgG (both CSF and serum) - Virology: PCR for enterovirus - Serology for Borrelia, WNV [1]
Further microbiologic testing	- PCR for enterovirus of a respiratory sample, preferably a nasopharyngeal aspirate - PCR for enterovirus of a fecal sample, preferably a stool sample
Imaging	- Contrast enhanced MRI of the brain and spine
Neurophysiologic testing	- NCS with motor and sensory investigation of an affected limb

[a] For patients that have travelled to or live in areas where WNV is prevalent.

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Ethical statement

The 'Dutch Medical Research Involving Human Subjects Act' was considered not applicable for the study from which data was used.

Local approval of the initial study protocol was obtained by the ethical committees of the participating hospitals according to their individual institutional research policy requirements. Data sharing agreements were concluded for each participating hospital, in line with the General Data Protection Regulation.

Informed consent from the patients and/or parents described in the boxes with illustrative cases was obtained.

Declaration of competing interest

The authors declare no conflict of interest, relevant to this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2023.03.002.

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