Update on acute flaccid myelitis: recognition, reporting, aetiology and outcomes

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ABSTRACT

Acute flaccid myelitis, defined by acute flaccid limb weakness in the setting of grey matter lesions of the spinal cord, became increasingly recognised in 2014 following outbreaks in Colorado and California, temporally associated with an outbreak of enterovirus D68 respiratory disease. Since then, there have been biennial increases in late summer/early fall. A viral infectious aetiology, most likely enteroviral, is strongly suspected, but a definitive connection has yet to be established. Patients typically present with asymmetric weakness, maximal proximally, in the setting of a febrile illness. MRI demonstrates T2/FLAIR abnormalities in the central grey matter of the spinal cord, and cerebrospinal fluid typically shows a lymphocytic pleocytosis with variable elevation in protein. The weakness may be progressive over several days and involve respiratory muscles, making early recognition and close monitoring essential. Other complications in the acute period may include autonomic instability and bowel/bladder involvement. There is no clear recommended treatment at this time, although intravenous immunoglobulin, steroids and plasma exchange have been used. Intensive therapies and rehab services have shown benefit in maximising function, and surgical interventions may be considered in cases without optimal response to therapies. Close attention should also be paid to psychosocial factors. Prognosis is generally guarded, and additional factors that predict final outcome, including host factors and treatment effects, have yet to be elucidated. Multicentre collaborative efforts will be required to provide answers about this rare but serious disorder.

What is already known?

- Acute flaccid myelitis (AFM) presents with sudden paralysis and grey matter abnormality of the spinal cord, related to enteroviruses. Patients have residual disability, and optimal management is unclear.

What this study adds?

- Concise review of current knowledge, including defining clinical characteristics, need for close monitoring in the acute period, outcomes and questions for further study.

INTRODUCTION

Acute flaccid myelitis (AFM) came to national attention in 2014 after reports from Colorado and California of an increase in children presenting with acute onset of flaccid paralysis with MRI findings of grey matter lesions of the spinal cord.[1 2 3] The outbreak of AFM in Colorado occurred during an outbreak of enterovirus D68 (EV-D68) respiratory disease; however, it has taken some time to conclude a more definitive causal relationship with this virus.[4–6] The classic presentation of AFM is acute onset of flaccid paralysis in the setting of a febrile illness. There may be marked asymmetry, even monoparesis. The diagnosis of AFM must be considered in children with any flaccid paralysis given that worsening paralysis can develop quickly in patients with AFM resulting in life-threatening respiratory compromise.

The initial AFM outbreaks in California and Colorado prompted the Centers for Disease Control and Prevention (CDC) to establish a case definition (boxes 1 and 2) in effort to enhance nationwide surveillance of AFM.[7 8] There have been biennial increases in AFM since that time. Despite the increasing recognition of children affected by this illness, much remains to be discovered in regards to predisposing factors, most appropriate diagnostic testing and optimal management of AFM. This review discusses our current knowledge of AFM and its association with EV-D68 and enterovirus A71 (EV-A71), including epidemiology and updates on surveillance, aetiology, common diagnostic approaches and management strategies.

EPIDEMIOLOGY AND REPORTING OF AFM

The first recognition of polio-like acute flaccid paralysis in the USA was in 2012 in California after three cases of unexplained flaccid paralysis were reported to the California Department of Public Health.[1 2] This was followed by identification of a cluster of similar cases in Colorado in 2014.[1 3] The CDC subsequently made a national request for information about patients with acute onset of focal limb paralysis with longitudinal grey matter lesions of the spine on MRI, which led to increased awareness and surveillance of cases concerning for AFM. The evolution of the surveillance case definition is documented in boxes 1 and 2, which includes recent changes by the US Council of State and Territorial Epidemiologists to be implemented in 2020.[7] Key changes are the elimination of age criteria in 2015, the inclusion of flaccid in the 2017 case definition and now the requirement of MRI abnormalities for both confirmed and probable cases, and exclusion

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Box 1 Past case definitions for acute flaccid myelitis as defined by the Council of State and Territorial Epidemiologists

2014–2015 AFM case definition

Onset of acute limb weakness on or after 1 August 2014, and an MRI showing a spinal cord lesion largely restricted to grey matter in a patient age ≤21 years.

2015–2017 AFM case definition

Acute onset of focal limb weakness and an MRI showing spinal cord lesion largely restricted to grey matter and spanning one or more spinal segments, regardless of age.

2017:

Confirmed

- Acute onset of flaccid paralysis.
- Confirmatory laboratory evidence: MRI showing spinal cord lesion largely restricted to grey matter and spanning one or more spinal segments.

Probable

- Acute onset of flaccid paralysis.
- Supportive laboratory evidence: cerebrospinal fluid showing pleocytosis (white cell count >5 cells/mm^3).

Source: CDC AFM case definition (https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definition.html).

Box 2 Current (2020 update) case definitions for confirmed, probable and suspect acute flaccid myelitis as defined by the Council of State and Territorial Epidemiologists

Clinical criteria

A person with onset of acute flaccid limb weakness.

Laboratory Criteria

An MRI showing a spinal cord lesion in at least some grey matter and spanning one or more vertebral segments.

Excluding persons with grey matter lesions in the spinal cord resulting from physician diagnosed malignancy, vascular disease or anatomic abnormalities.

2019 Case classification

Confirmed

- Clinically compatible case with confirmatory laboratory/imaging evidence (MRI showing spinal cord lesion with predominant grey matter involvement and spanning one or more vertebral segments) and absence of a clear alternative diagnosis attributable to a nationally notifiable condition.

Probable

- Clinically compatible case with presumptive laboratory/imaging evidence (MRI showing spinal cord lesion where grey matter involvement is present but predominance cannot be determined) and absence of a clear alternative diagnosis attributable to a nationally notifiable condition.

Suspect

- Clinically compatible case and available information is insufficient to classify case as probable or confirmed.

Source: https://cdn.ymaws.com/www.cste.org/resource/resmgr/2019ps/final/19-ID-05_AFM_final_7.31.19.pdf, and https://wwwn.cdc.gov/nndss/conditions/acute-flaccid-myelitis/case-definition/2020/

of cases with a clear diagnosis of malignancy, vascular disease or anatomic abnormalities.

Cases have thus far followed a biennial pattern of late summer/early fall spikes with increases in 2016 and 2018.[8 9] A total of 120 cases of AFM were confirmed in 2014, 153 cases in 2016, with the incidence reaching 237 cases confirmed across 41 states in 2018[8] (figure 1). Geographic involvement in the USA has varied each year. Cases have also been seen in other parts of the world, including Europe, Canada, Asia and South America.[4 5 10 11] There is a slight male predominance in AFM cases[1 8] with a recent, although small case series of 28 patients with AFM suggesting a predisposition in patients with a history of asthma, atopic dermatitis or head trauma.[12] A possible increased risk in children of Asian descent in this small sample has not been confirmed in other datasets.[12 13] The median age of patients affected is about 6 years.[9 13]

AETIOLOGY OF AFM

While the precise aetiology of AFM has yet to be determined, clinical evidence strongly supports a viral cause asmany cases are associated with a viral prodrome, including fever, upper respiratory or gastrointestinal (GI) symptoms.[1–3 13–15] Surveillance data for 2015–2017 recently published by the CDC found that 161/193 patients (83%) had fever, upper respiratory or GI symptoms, a median of 5 days before the onset of limb weakness.[13] In regards to a specific virus causing AFM, EV-D68 has been highly suspected given its temporal and geographic associations with AFM cases in the USA.[1 3 16]

EV-D68 is a picornavirus, a member of the enterovirus family, which includes poliovirus and EV-A71, which has been associated with AFM in multiple cohort studies and case series.[17–19] In a mouse model, four out of five EV-D68 strains from the 2014 epidemic in Colorado caused acute flaccid paralysis analogous to human AFM.[20] Enterovirus D68 has been shown to exhibit neurotropism.[21] In addition, two recent papers applied Bradford Hill criteria to investigate evidence for a causal relationship between EV-D68 and AFM. Both found that the Bradford Hill criteria supports a causal relationship between EV-D68 and AFM by fulfilling the strength, consistency, temporality, plausibility, coherence, experiment and analogy criteria.[4 5]

A major challenge with determining a definitive aetiology in cases of AFM has been that no infectious agents of clear significance have been identified in the CSF of cases reported to the CDC. In cases reported from 2015 to 2018, there were scattered positive results from infectious testing of CSF,[9 13] including 4/170 CSF samples tested from 2015 to 2017 that were positive for enteroviruses via local testing, but only one of these was positive for enterovirus at the CDC (typed as Coxsackievirus

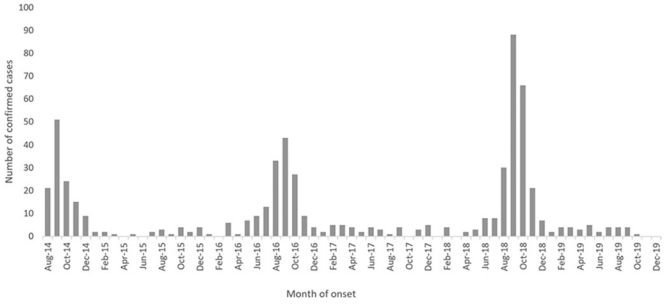

Figure 1 Confirmed cases of AFM reported to CDC, August 2014–January 2, 2020. Source: CDC https://www.cdc.gov/acute-flaccid-myelitis/afm-cases.html, current as of 7 January 2020. AFM, acute flaccid myelitis; CDC, Centers for Disease Control and Prevention.

–A16). Of the 2018 cases, 74 had CSF specimens sent, and only two had positive viral testing (one for EV-D68 and one for EV-A71).[9] This is not necessarily surprising, however, given that poliovirus and EV-A71 have also been difficult to identify in the CSF of affected patients.[1 4 5 22] In fact, poliovirus was only rarely found in the CSF of affected patients but found more readily in the stool of patients,[5 22] thus increasing the plausibility that EV-D68 could be causing outbreaks of AFM, despite not being isolated in CSF samples. Moreover, in a study looking at the duration of poliovirus excretion in children, it was found that poliovirus detection declines significantly by 14 days after disease onset.[22] This suggests the timing of specimen collection is crucial to identifying a potential viral pathogen. In addition to timing of specimen collection, the methods used to collect the specimens may also contribute to the lack of our identification of a viral aetiology. Recent data using phage immunoprecipitation sequencing techniques demonstrated the presence of antibodies to enterovirus peptides in the CSF of 69% (29/42) of patients with AFM compared with 7% (4/5) of other neurological disease controls with a failure to identify enteroviral RNA in these same samples.[23] This implies that the use of RNA detection methods may not provide optimal detection of the viruses and that new methods as well as timely acquisition of samples may be required to fully verify a link between outbreaks of AFM and enteroviruses.

Going beyond CSF testing, several non-polio enteroviruses were identified in respiratory or stool specimens of patients with AFM in the 2012–2015 series, with EV-D68 being the most common. Of the 193 cases with AFM confirmed by the CDC from 2015 to 2017, 151 patients had respiratory specimens tested, 61 (46%) were positive for enteroviruses or rhinoviruses and 22 of 90 tested (24%) were positive for EV-D68.[13] The most recent US outbreak, in 2018, had 233 confirmed cases of AFM. Of the 123 respiratory specimens collected, 44% (54) were positive for either EV-D68 (30 patients), EV-A71 (10 patients) or other untyped enteroviruses or rhinoviruses (14 patients).[9]

While enteroviruses are strongly suspected in these biennial increases in AFM, it should be noted that other viruses, including flaviviruses, have been associated with sporadic cases. Specifically, several case series have described West Nile Virus as an important cause of acute flaccid paralysis in children[14 24 25] including one study performed in Colorado in 2003. This study identified 32 patients with West Nile Virus-associated paralysis, 27 of which were found to have a poliomyelitis-like syndrome.[24] Thus, West Nile Virus testing should be considered in the evaluation of a child presenting with acute flaccid limb weakness.

CLINICAL PRESENTATION AND DIAGNOSIS

While there have been no prospective studies of AFM to date, numerous papers have analysed retrospective cohorts to identify common clinical characteristics and neurodiagnostic findings. The typical presentation is a prodromal or concurrent febrile illness followed by acute onset flaccid weakness with decreased deep tendon reflexes in one or more extremities that occurs over hours to days. Upper extremities are more commonly affected than lower extremities, and proximal muscles are more commonly affected than distal groups[26 27] Multiple studies have reported limb pain followed by progressive weakness as the predominant initial presentation of AFM.[26 27] Onset of paralysis may be associated with cranial nerve abnormalities, headache, neck pain, back pain and bowel/bladder abnormalities.[1 27] Sensory examination is typically normal, although there may be transient sensory abnormalities in the setting of edema.[1 6 27]

Box 3 Key clinical pearls

- Acute flaccid myelitis (AFM) is a rare disease characterised by acute flaccid limb weakness corresponding to a predominantly grey matter longitudinally extensive spinal cord lesion.
- The exact aetiology of AFM is unknown; however, infectious aetiologies, specifically the enteroviruses, have been associated with outbreaks of AFM.
- Physicians should be consider AFM in their differential for any child presenting with:
  - Acute onset of asymmetric limb paralysis often following a prodromal viral illness.
  - Neurological exam demonstrating flaccid limb paralysis often affecting proximal more than distal muscles, absent or decreased reflexes in the affected limb, intact sensory exam and ±cranial nerve deficits.
- If AFM is suspected, prompt neuroimaging with MRI of the spine with and without contrast should be performed.
- Neuroimaging in AFM classically demonstrates spinal cord lesion predominately affecting the grey matter and spanning one or more vertebral segments.
- Cerebrospinal fluid (CSF) commonly demonstrates a pleiocytosis but can be normal.
- CSF and serum testing for viral aetiologies including Herpes Simplex Virus (HSV), Enterovirus, Epstein Barr Virus (EBV) and West Nile Virus (WNV)should be obtained for suspected cases.
- Current treatment strategies in the acute setting include close respiratory and neurological observation, intravenous immunoglobulin and plasmapheresis.
- Long-term management focuses largely on aggressive physical and occupational therapy.
- Further investigation into the utility of nerve transfer procedures will be crucial to the advancement of therapeutic strategies for AFM.
- All cases of AFM should be quickly reported to health authorities.

Clinical pearls for diagnosis and management may be found in box 3.

If a diagnosis of AFM is suspected based on clinical presentation, the first step is to ensure the patient's airway is protected. Children with AFM require close respiratory monitoring, as paralysis can quickly progress leading to severe respiratory compromise, with 33% of patients from 2015 to 2017 requiring respiratory support.[13] Once the respiratory status has been appropriately evaluated, neurodiagnostic testing can be pursued. The common neurodiagnostic studies in AFM include neuroimaging, CSF analysis and electrodiagnostic studies. MRI of the spine generally demonstrates T2 hyperintensities in the grey matter of the spinal cord or more focally in the anterior horn cells (figure 2). There may be associated enhancement of the nerve roots.[1 6 27 28] The most common site of involvement in AFM is the cervical cord followed by the thoracic cord and conus medullaris.[14] MRI of the brain can be normal but can also demonstrate T2 hyperintensities in the brainstem including the dorsal pons, medulla and occasional involvement of the dentate nucleus of the cerebellum.[29] Supratentorial lesions are less common.[1 9] CSF studies often demonstrate a lymphocytic pleocytosis, occasionally an elevated protein level and absence of specific pathogens.[1 6 8] Electrodiagnostic studies, namely electromyography (EMG) and

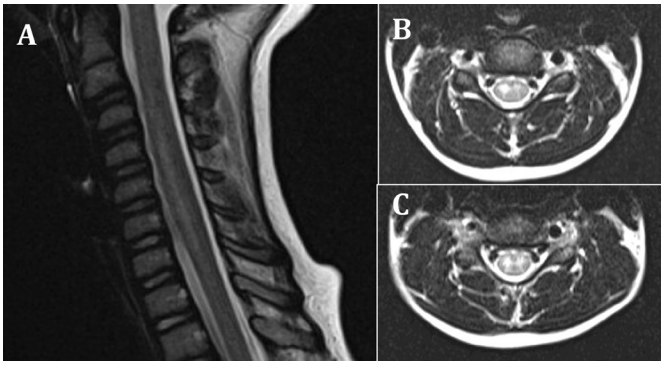

Figure 2 MRI of the cervical spine demonstrating longitudinally extensive lesion spanning from C2 to C7 on sagittal T2 image (A) and T2 axial imaging revealing predominantly grey matter involvement right greater than left (B and C).

nerve conduction studies (NCS) demonstrate a motor neuropathy or neuronopathy in the affected limbs. Motor NCSs have classically shown reduced response amplitudes, fibrillation potentials and reduced recruitment of motor neurons with no sensory nerve conduction abnormalities.[1 15]

Differential diagnosis includes Guillain-Barre syndrome (GBS), neuromyelitis optica (NMO), antimyelin oligodendrocyte glycoprotein-associated demyelination (anti-MOG), acute disseminated encephalomyelitis (ADEM), meningitis, transverse myelitis (TM) and spinal cord infarction. AFM can be clinically differentiated from GBS by the asymmetric presentation with upper limbs more commonly affected in AFM compared with the symmetric and often lower extremity involvement in GBS. Spinal imaging helps to further differentiate AFM from GBS as central grey matter lesions would be expected in AFM, but not in GBS. NMO is associated with AQP4 antibodies in the CSF and spinal cord lesions with more white matter involvement than seen in AFM. Anti-MOG associated demyelination can also mimic AFM radiographically when the spinal cord is involved.[30] Clinically and diagnostically, however, patients with anti-MOG disease have preserved and often brisk reflexes, more prominent sensory findings and marked clinical improvement with immunomodulatory therapies. Patients with ADEM present with encephalopathy typically in the setting of large, poorly demarcated, asymmetric brain and brainstem lesions, unlikely in AFM. Meningitis and encephalitis are associated with more prominent systemic signs and symptoms such as high fevers, malaise, nuchal rigidity and elevated inflammatory markers and can be distinguished from AFM by the presence of seizures, encephalopathy and the presence of focal neurological symptoms referable to the cerebral cortex.

TM can look similar to AFM at onset. TM may present with diminished reflexes and flaccid weakness; however, in TM, upper motor neuron signs (increased deep tendon reflexes, upgoing toes) and sensory deficits quickly become more prominent. AFM is often more asymmetric with the affected limb being persistently areflexic, and sensory symptoms are much less prominent or absent. Acute spinal cord infarction can be differentiated from AFM by the hyperacute onset in stroke as well as the absence of CSF pleocytosis, absence of viral prodrome and the presence of stroke risk factors or trauma.[27 31] Spinal cord infarcts are extremely rare in children and, when they do occur, they typically affect the thoracic region of the cord due to tenuous blood supply in this region as opposed to the cervical cord, which is most commonly affected in AFM.[31]

Notably, some patients with the above diagnoses will meet surveillance case definition criteria for AFM.[15] It is essential for clinicians to keep this in mind and be aware that the CDC criteria are not intended for clinical diagnosis.

Management

There is no cure or standardised treatment protocol for AFM at this time. Management currently focuses on prompt diagnosis and close neurological and respiratory monitoring. Some patients may require observation in the intensive care unit given the risk of respiratory deterioration and autonomic instability. Once stabilised, transition to intensive rehabilitation is essential. Immunomodulatory therapies including intravenous immunoglobulin (IVIG), plasmapheresis and steroids have been used in AFM patients, but none have demonstrated consistent neurological improvement.

Fluoxetine was initially thought to be a possible therapy for treatment of AFM. Initial in vitro studies using cell-based assays to assess antiviral activity of 15 compounds demonstrated that fluoxetine could inhibit the EV-D68 strain at concentrations of 0.34–1.05 μM[32]. Unfortunately, a retrospective study involving 56 patients with AFM from 12 centres showed that treatment with fluoxetine, although without clear serious adverse effects, demonstrated no clinical improvement in limb strength.[33]

Steroids have shown no definitive evidence for improvement in AFM and recommendations for their use are mixed. Some have suggested that steroids may be harmful in cases that are clearly associated with enteroviruses.[19 33] If extensive cord swelling is noted on neuroimaging, or if there are secondary long tract signs, steroids may be of benefit.

IVIG is used by most centres, in hopes that if administered quickly it may boost the humoral response. When used in a mouse model of EV-D68-induced paralysis, there was a reduction in paralysis and decreased spinal cord viral loads in the treated mice suggesting that IVIG might be a promising therapy for AFM. Interestingly, dexamethasone administrated in these mice led to worsening motor function, increased mortality and increased viral loads,[22] and fluoxetine had no effect on motor impairment or viral loads. Retrospective cohort studies, however, have failed to demonstrate benefit from IVIG.[1 34 35] Further studies are needed to assess the true benefit of therapies and whether timing of administration may have an impact.

Bowel and bladder dysfunction may be prominent, particularly in the acute period. Constipation is prominent, related to the low muscle tone and decreased movement in these children. A good bowel regimen and regular bladder ultrasounds for residual urine are important, particularly as bowel and bladder dysfunction may worsen autonomic dysfunction. Psychosocial concerns may also arise. In our experience, adjustment disorder, anxiety and depression are common with a recent diagnosis of AFM, and there should be a low threshold for psychology involvement.

Intensive physical therapy, occupational therapy and ultimately rehabilitation services are a major component in the overall management of patients with AFM, with improvement of function in some patients with therapies even a year or more out from diagnosis.[36–38] Clinicians should also be aware of potential secondary complications, including joint subluxation or dislocation, scoliosis[37] and decreased bone density in patients unable to bear weight. Nerve and/or tendon transfer surgery is receiving increased consideration as another treatment option. Nerve transfer surgery involves removal of a nerve with redundant function to reconnect muscles that have lost innervation.

Pino *et al*[39] reported results of nerve transfer in 11 AFM patients with follow-up data, with recovery of elbow flexion and extension in 87% and 67% of patients, respectively. There was less improvement in shoulder strength, although there was resolution of shoulder pseudosubluxation in 9/10 patients.

OUTCOMES

The overall reported outcomes for cases of AFM vary but with most patients suffering from persistent motor deficits. There have been rare reports of recovery.[1 2 31 36 40] The time course of recovery is also variable with some patients demonstrating continued improvement even after 12 months of symptom onset.[1 2 26 27 40] Proximal muscle strength appears to be the weakest and slowest to recover, with distal muscle strength generally showing better recovery in most patients.[1 36] Methods to predict outcomes including spinal MRI and EMG/NCS are still being investigated.[36 40 41] Further studies will be needed to determine the best methods to evaluate disease burden, treatment and outcome.

SUMMARY

AFM is a rare and currently poorly understood illness that predominately affects children leading to a syndrome characterised by acute flaccid limb weakness with associated spinal cord lesions predominantly involving the grey matter. Although this illness is increasingly recognised in the USA, predisposing factors and ideal treatment remain unknown. The year-to-year variation in geographic distribution requires all clinicians, even those in areas that have seen few cases of AFM in previous years, to be aware. Prompt diagnosis and close neurological and respiratory monitoring are crucial for the best possible outcome. Rehabilitation services are a key part of the overall management. Further investigation into the role of immunomodulatory therapies as well as the safety and efficacy of nerve transfer procedures in the management of AFM will be fundamental. Research into the precise aetiology of the disease (viral and host factors) will also be a requirement moving forward. Multicentre collaborative research will ultimately be needed to unfold the mysteries of this disease.

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