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Acute Flaccid Myelitis: Current Status and Diagnostic Challenges

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Acute flaccid myelitis (AFM) is a sudden-onset polio-like neuromuscular disability found commonly in young children. There is an increasing incidence of confirmed AFM cases in the USA and other countries in recent years, and in association with nonpolio enterovirus infection. This represents a significant challenge to clinicians and causes significant concern to the general public. Acute flaccid paralysis (AFP) is the long-known limb paralytic syndrome caused by a viral pathogen. AFM is a subset of AFP that is also characterized by a limb paralytic condition, but it has certain distinct features such as lesions in magnetic resonance imaging of the spinal cord gray matter. AFM leads to spinal cord, brainstem, or motor neuron dysfunction. The clinical phenotypes, pathology, and patient presentation of AFM closely mimic AFP. This article provides a concise overview of our current understanding of AFM and the clinical features that distinguish AFM from AFP and similar other neurological infectious and autoimmune diseases or disorders. We also discuss the diagnosis, clinical pathology, possible pathogenetic mechanisms, and currently available therapies.

Key Words acute disease, myelitis, paralysis, enterovirus.

INTRODUCTION

Acute flaccid myelitis (AFM) is a subset of acute flaccid paralysis (AFP) that encompasses long-known cases of limb paralytic syndromes.[1,2] AFM refers to the potentially fatal acute onset of flaccid weakness and muscle immobility in children at a median age of 1 to 7 years. The disability primarily results from damage to the spinal cord gray matter, brainstem, or motor neurons. AFP also afflicts children younger than 15 years with a very similar set of symptoms as those for AFM. AFP affects children of all races, ethnicities, and immunization status. In AFP, in addition to bulbar palsy, the spinal cord, peripheral nerves, neuromuscular junctions, and muscles can all be affected, resulting in sustained functional disability of the extremities.[2] Although enterovirus A71 (EV-A71) is known to cause AFP and other neurological diseases, the exact causes of AFM are still unclear.[3] A temporal association of EV outbreaks with increases in AFM cases has been reported in the USA, Australia, Norway, and France.[4,5] A small number of AFM patients with confirmed cases of the disease have tested positive for EV-D68 in the USA, while EV-A71 was identified in only a few diagnostic specimens in the USA and Japan.[6,7] The incidence of AFM was first identified in the USA in 2014, and has steadily increased in 2019 (Fig. 1) to become recognized as a serious threat to public health.[8] This review provides a concise report of our current understanding of the mechanism underlying AFM pathogenesis, its etiological factors, differential diagnosis, potential treatments, and available therapy options.

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CLINICAL PHENOTYPES AND NEUROIMAGING

In 90% of cases, AFM is characteristically preceded by clinical complications such as febrile and respiratory illness lasting for days or weeks, followed by several symptoms including severe weakness of limb muscles, ptosis, diplopia, dysphagia, or dyspnea, or even respiratory failure.[9] Most AFM patients present with the sudden and rapid onset of muscle fatigue in conjunction with the loss of coordination and balance. Paralysis frequently occurs asymmetrically, and may involve any combination of limbs, with quadriparesis in a significant minority of cases (~36%). The pattern of weakness is consistent with a lower motor neuron process and includes hyporeflexia or areflexia and hypotonia, and (eventually) rapid atrophy of affected limb muscles due to damage to the anterior horn of the spinal cord. Cranial nerve, bowel, and bladder dysfunction might be present. Sensory symptoms might also present, but they are uncommon. Most children affected by AFM experience short-term neurological deficits, with significant muscle atrophy in the affected limbs for a year or more following the disease onset. The long-term prognosis for AFM is not yet known, but affected patients can continue to improve slowly over time with ongoing rehabilitation.

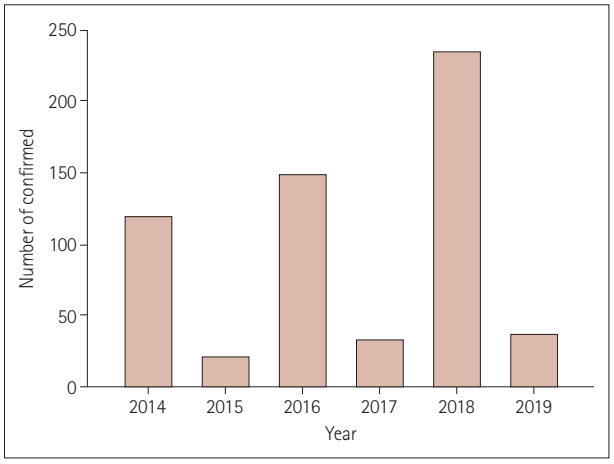

Fig. 1. Prevalence of AFM. Confirmed cases of AFM annually in the USA from 2014 to 2019. There were more reported cases than confirmed cases in some years (data not shown). AFM: acute flaccid myelitis.

AFM manifests in spinal magnetic resonance imaging

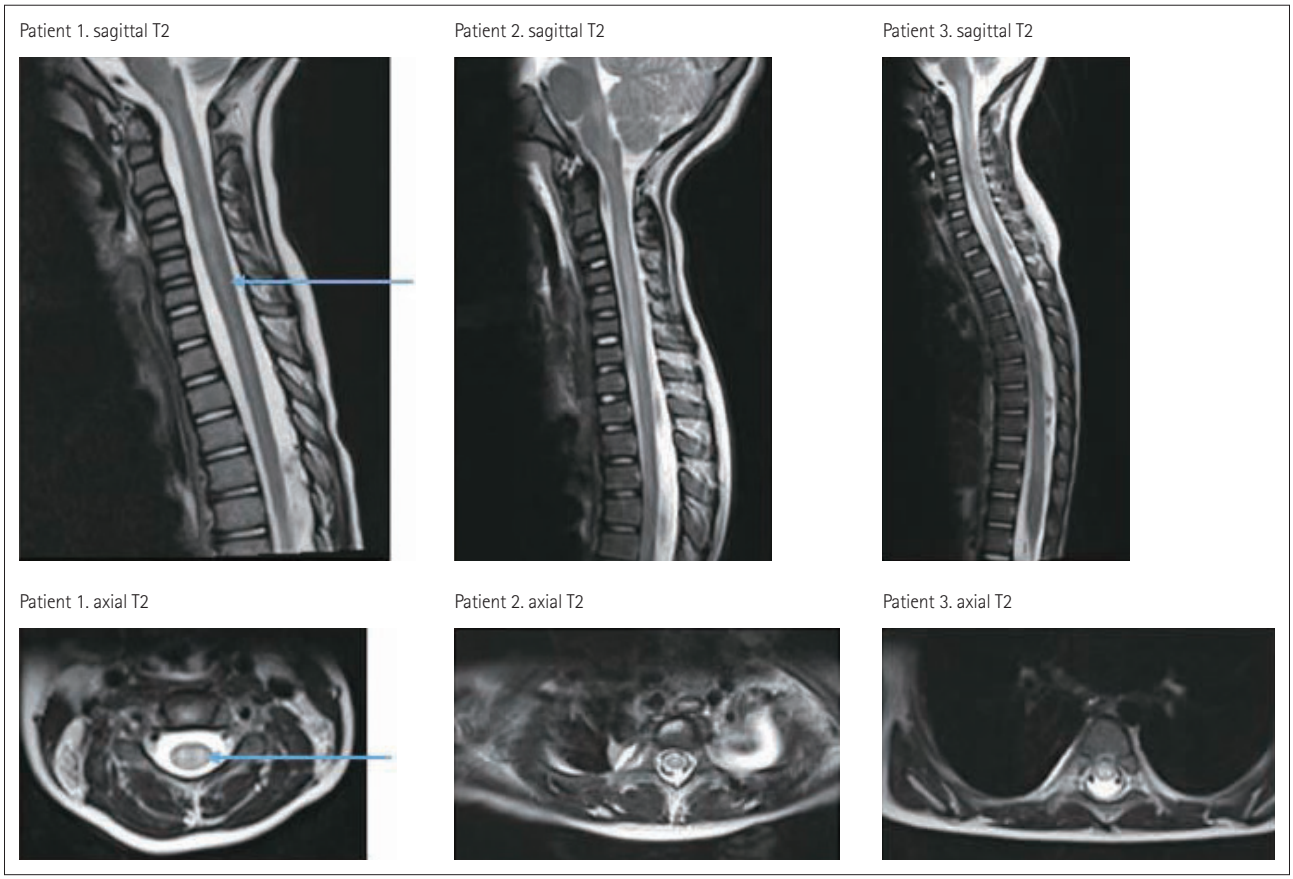

Fig. 2. Representative MRI images of the spinal cord in AFM. Spinal MRI (T2-weighted saggital and T2-weighted axial) images of three children (confirmed as enterovirus-D68-associated AFM) showing hyperintensity in central gray matter (blue arrows). The parents of these children consented to the publication of these anonymized images (figure courtesy of Jay Shetty, The University of Edinburgh, Scotland, UK). AFM: acute flaccid myelitis, MRI: magnetic resonance imaging.

(MRI) as a longitudinal area of increased T2-weighted and fluid-attenuated inversion recovery signals predominantly involving the gray matter (Fig. 2).[7] The clinical pathology of AFM does not represent other common spinal cord diseases. Peripheral demyelination does not occur in AFM, and hyperintense MRI T2-weighted lesions in the gray matter of the spinal cord can also be seen in multiple sclerosis (MS) or acute transverse myelitis (ATM).[10] These lesions are also present in the brainstem and ventral nerve roots. The criteria of the Center for Disease Control and Prevention (CDC) for the AFM diagnosis include MRI with evidence of a spinal cord gray-matter lesion that spans at least one spinal segment.

DIFFERENTIAL DIAGNOSIS

AFM is a specific entity in a group of other neuromuscular syndromes (Fig. 3). Clinical presentations of AFM mimic other neuromuscular diseases, disorders, or conditions that typically are also characterized by severe and sustained muscle fatigue and functional impairment in the extremities (Table 1). The following are some of the neurological illnesses that share some similarities with AFM but have distinct clinical pathologies:

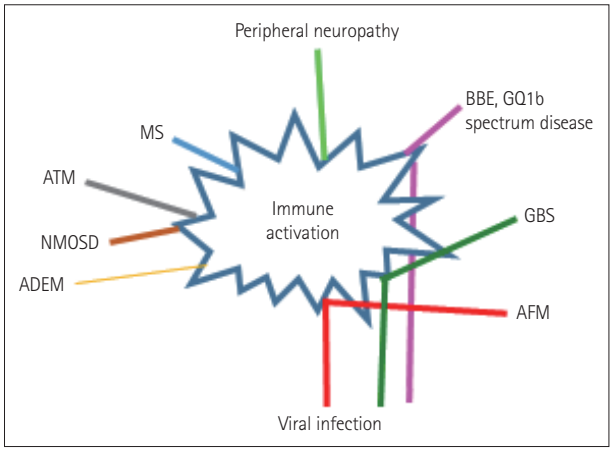

Fig. 3. Association of AFM with other neurological complications. AFM is a specific entity in a group of other neurological diseases, disorders, and syndromes. ADEM: acute disseminated encephalomyelitis, AFM: acute flaccid myelitis, ATM: acute transverse myelitis, BBE: Bickerstaff's brainstem encephalitis, GBS: Guillain-Barré syndrome, MS: multiple sclerosis, NMOSD: neuromyelitis optica spectrum disorder.

1) MS and ATM: both MS and ATM are demyelinating diseases or disorders that affect the central nervous system. ATM is a rare acquired neuroimmune spinal cord disorder that presents with the rapid onset of weakness, sensory alterations, and bowel or bladder dysfunction. ATM can also occur as an independent entity, usually as a postinfectious complication.[11] However, unlike MS and ATM, active demyelination is absent in AFM. ATM (but not AFM) is explicitly caused by inflammatory immune-mediated damage to the spinal cord.

2) Other spinal cord disorders that may mimic AFM include syringomyelia, spinal cord tumors, spinal cord infarcts, and conditions that cause compressive myelopathies (hemorrhages, tumors, and abscesses).

3) Guillain-Barré syndrome (GBS): in GBS, muscle weakness in the limbs usually occurs soon after the viral infection.[12] Unlike AFM, demyelination of peripheral nerves in association with acute inflammation occurs in this syndrome. Also, GBS is an ascending paralysis associated with sensory symptoms, and often has a good prognosis.[13]

4) Neuromyelitis optica spectrum disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM): NMOSD and ADEM are additional demyelinating diseases involving the brain and spinal cord. ATM also presents as a sign of NMOSD and ADEM.[14-16] Such demyelination does not occur in AFM.

5) Bickerstaff's brainstem encephalitis (BBE): BBE is a demyelinating disease with an infectious etiology and an autoimmune-associated pathology. Overlapping forms of BBE and GBS have been reported in patients with lower limb

Table 1. Diseases or disorders and their characteristics (for consideration in the differential diagnosis of AFM)

Disorders	Characteristics			Etiology
	NMJ damage	Spinal cord lesion	Demyelination	Viral infection
MS	No	Present	Present	Possible
ATM	No	Present	Present	Uncertain
GBS	No	No	Present	Uncertain
NMOSD	No	Present	Present	Uncertain
ADEM	No	Present or not	Present	Uncertain
BBE	No	Present or not	Present	Uncertain
Peripheral neuropathy	Varies	No	Varies (axonal vs. demyelination)	Unknown
AFM	No	Present	No	Likely

ADEM: acute disseminated encephalomyelitis, AFM: acute flaccid myelitis, ATM: acute transverse myelitis, BBE: Bickerstaff's brainstem encephalitis, EB: Epstein-Barr, GBS: Guillain-Barré syndrome, MS: multiple sclerosis, NMJ: neuromuscular junction, NMOSD: neuromyelitis optica spectrum disorder.

weakness.[17,18]

6) Peripheral neuropathy: no lesion is present in the spinal cord in peripheral neuropathy.[19]

MANAGEMENT

An accurate diagnosis for distinguishing AFM from other analogous neurological conditions is critical for the appropriate clinical intervention and management of AFM patients in the clinic. The standard protocol typically involves MRI scans of the brain and spinal cord; bronchoalveolar lavage; and diagnostic tests of serum, cerebrospinal fluid, and rectal specimens for the presence of specific viruses (e.g., EV) by real-time PCR, EV typing by nested or seminested PCR, and sequencing of the VP1 segment. MRI evidence of a lesion in the spinal cord gray matter that spans a minimum of one spinal segment with pleocytosis (infiltration of lymphocytes) in the affected region is the important reliable test available to confirm AFM, as described in the CDC guidelines (https://www.cdc.gov/acute-flaccid-myelitis/diagnosis.html).

Up to 2019, there were 607 confirmed cases of AFM recorded out of many hundreds of reports from several states, with the incidence peaking in 2018 (Fig. 1).[20] Given the current absence of an effective treatment for AFM, immunomodulatory therapies including intravenous immunoglobulin, plasmapheresis, or corticosteroid therapy are used, but these are not recommended in the CDC guidelines. The benefits of these treatments are obscure, and there remains a possibility that they will exacerbate an active infection.[21] Antivirals have also not been proven to be effective, and therefore are not recommended for treating AFM.[22] Peripheral nerve surgery that prevents muscle atrophy in some AFM patients has offered some optimism and may be an effective treatment.[23] Although the efficacy of most treatments for AFM is still unclear, they may prevent the further progression of the disease. Despite supportive care and rehabilitation, treatments that results in complete recovery from AFM have not yet been implemented.

POTENTIAL ETIOLOGY AND PATHOGENETIC MECHANISMS

Due to limitations of the research in this field, the exact pathogenetic mechanism underlying AFM is unclear, but it is thought to be associated with EV-D68 infections in children. The EV-D68 belongs to the family Picornaviridae and is characterized by a nonenveloped single-stranded positive-sense RNA genome. The 12 known EV species comprise 4 human-specific EV species (EV-A to EV-D), 5 nonhuman primates infecting EV species, and 3 human-specific rhinovirus species. The human EV-E to EV-C species cause poliomyelitis and AFP; coxsackievirus, EV-B and EV-C cause viral meningitis, conjunctivitis, myocarditis, and even type I diabetes; while EV-A71 is associated with hand-foot-and-mouth diseases and other neurological illnesses.[24] EV-D68 was first isolated from four patients with respiratory illness in California in 1962 and later identified globally as three variants (1 to 3) or clades (A to C) based on the variations in the nucleotide sequence in the VP1 structural segment of viral RNA.[25] Unlike most EVs that are acid resistant in the gastrointestinal microenvironment, EV-D68 is acid sensitive, and therefore replicates mostly in the host's respiratory tract.[26] The virus uses multiple receptors to enter the host cells for infection, of which sialic acid and decay-accelerating factor (DAF-1/CD55) are particularly important.[27,28] How EV-D68 travels to infect the anterior horn cells of the spinal cord or motor neurons is currently unknown, but this probably occurs via the peripheral circulation or neural routes. One animal-model study found that infecting mice with an intraperitoneal injection or intranasal administration of EV-D68 induced both acute myositis and forelimb paralysis. The infected mice also exhibited reduced neuromuscular junction innervation of the gastrocnemius muscles and the loss of motor neurons and infection of the spinal cord.[29]

Despite a possible association of EV with AFM due to the co-occurrence of increased AFM incidence and EV-D68 circulation in the same years, the virus has not been consistently detected in the biofluids of AFM patients. However, the samples from all patients were consistently negative for any polioviruses. The traditional method of EV detection employs conventional PCR technology, which amplifies the VP1 segment with EV-D68-specific primers. The PCR products are subsequently sequenced for determining their homology with known EV genomic sequences in GenBank. More-precise and robust alternative methods to PCR are needed for detecting viruses in the diagnostic specimens of patients. In a different approach, Mishra et al.[30] recently described a virus-capture high-throughput sequencing technique and peptide-based microarray that successfully detected the presence of EV-specific antibodies in 11 of 14 samples from AFM patients. Whereas six CSF-positive and eight seropositive samples showed immunoreactivity to EV-D68-specific peptides, the control samples in the same study were from nonspecific Kawasaki disease or normal patients that did not react with the same peptides. The results indicated a strong association of EV in triggering the manifestation of the disease. EV RNA was detected in only 1 of the 14 AFM patients when using the conventional qRT PCR assay in this study, implying the clearance of EV infections. However, the presence of EV-specific antibodies resulted from prior infections in the

host was detectable in the samples by applying the novel assay. A recent study of metagenomic next-generation sequencing of CSF RNA in AFM patients also revealed EV immunoreactivity in a pan-viral phage display assay.[31] In addition to nonpolio EV, infections with herpes, dengue, West Nile, and Zika viruses as well as the inactivated polio vaccine have been proposed as the likely triggers of AFM.[32]

It is known that the host response that forms part of the antiviral defense to a viral pathogen can often itself cause significant neurological damage.[33] Aberrant induction of immune activation in response to pathogenic infection coinciding with trauma and inflammation may cause damage to the spinal cord leading to AFM pathogenesis. Activated immune cells such as cytotoxic CD4 cells, CD8 cells, B cells, dendritic cells, monocytes, macrophages, and even polymorphonuclear neutrophils can localize to the site of infection. Through the release of inflammatory cytokines, oxidants, and lytic enzymes, activated immune cells can trigger the apoptosis or necrosis of infected cells, resulting in severe damage to the neuronal tissue. Many chronic neurological dysfunctions are known to be mediated by an inflammatory attack by immune cells. Other triggers of AFM arising from bacterial infections, toxins, heavy metals, porphyrins, steroids, neuromuscular blockers, and intramuscular vaccinations have been suggested and reported elsewhere, but these are less likely since they are generally anecdotal reports that lack any supporting evidence or a published study.[34]

CURRENT LIMITATIONS AND CHALLENGES

According to the World Health Organization, the surveillance of AFM cases is critically important to rule out the association of AFM with the polio vaccine in polio-free countries. Due to the observed instances of serious consequences from VP1 nucleotides substitution in the live-attenuated polio vaccine (Sabin vaccine strain), particularly in immunedeficient pediatric individuals, it is important to remain vigilant to the risks associated with the emergence of similar pathogenic variants[35,36] that may remain undetectable when using traditional probes or PCR primers. It might be necessary to design novel alternative or degenerate primers to amplify unknown sequences from mutant variants associated with AFM pathogenesis. Deep sequencing or next-generation sequencing might be useful for comprehensive analyses of the associated genetic and epigenetic changes.

The current methods for detecting viral genomes solely by PCR using infected cells isolated from biofluids appear to be suboptimal or inefficient. Alternative high-sensitive assays such as immunocytochemical staining of cells with fluorescent probes and confocal microscopy detection of the viral genome in infected cells present in the biofluid can be utilized. As in other EV infections, neutralizing antibodies induced in the host plasma postinfection may mediate viral clearance in an AFM patient, which is a potential reason for EV particles not being detected in the diagnostic samples of a patient. Detecting antiviral antibodies using virus-specific peptides in a peptide microarray and high-throughput sequencing are excellent alternatives to PCR detection of the virus in biofluids. However, high-throughput antibody analyses for screening the presence or subtype of a virus from a past infection might not detect the presence of latent infection or viral nucleic acids harbored within an infected neuron in AFM patients, or viruses that have a low replicative potential insufficient for inducing a humoral response. It is important to detect such a latent infection since the inactive virus may resume its activity and trigger a serious infection many years following a period of latency. The infectious viral particle may remain localized to its site of entry or spread to other sites in the body to replicate, which can also lead to cell and tissue damage. The lack of studies involving animal models (in vivo or ex vivo) and cell cultures (in vitro) greatly limits our thorough understanding of AFM pathogenesis. Laboratory-based investigative biomedical research is urgently needed to accurately determine the underlying causes and mechanistic details of AFM.

CONCLUSION

It is important to assess the genetic predisposition and contributions of other epigenetic or even nongenetic environmental factors to the onset or exacerbation of AFM. For example, the ability of host to mount appropriate adaptive and innate immune responses against pathogenic infection can facilitate virus replication, propagation, and persistent infection, and the ultimate shedding of viral particles into host biofluids.[37,38] A population-based case-control study revealed that immunodeficient children affected by the Italian 1958 poliovirus epidemic were more susceptible to paralytic poliomyelitis than were a group that was breastfed, and they subsequently exhibited adequate immunity to combat the viral infection.[39]

Novel biomarkers for AFM are critically needed to enable health-care providers to timely diagnose the illness in an unbiased way and manage the disease appropriately. Future research in this field may reveal new biomarkers and the development of effective drugs for producing successful therapeutic outcomes. Furthermore, pathogen-specific vaccines developed through preclinical research may confer individuals with lifelong protection from this disabling disease.

Author Contributions

Conceptualization: Ruksana Huda. Data curation: Ruksana Huda. Funding acquisition: all authors. Investigation: all authors. Writing—original draft: Ruksana Huda. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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