Acute Flaccid Myelitis: AFM Preparedness for 2022 and Beyond

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Educational objectives

• To review current clinical and epidemiology aspects of Acute Flaccid Myelitis (AFM)
• To understand current concepts on pathogenesis
• To review diagnostic approach and new concepts on management
Acute Flaccid Myelitis: 21st Century Poliomyelitis

Pictures sources: cnn.com, cbsnews.com, washingtonpost.com
Acute Flaccid Myelitis

In most of the cases of AFM there is preceding history of upper respiratory infection in almost all members of the Household
- Age 1-12 yrs in average
- No sex predilection; Male:Female

Enteroviruses are the main suspect:
- EVD68, EVA71, Coxsackie

Environmental factors associated
- Seasonality
Factors in Acute Flaccid Myelitis

Despite the presence of infection in the entire household only one younger member of the family is affected.

- Genetic predisposition?
AFM epidemiology in the USA: CDC outbreak reports and 2018 state distribution

Take-home message:
- Cases of AFM have occurred in almost all states of the USA
- Most of the cases occur at the end of the summer and fall

Source: CDC website
https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html
Data current as of June 1, 2020
2018 AFM Outbreak in the USA: Clinical Features

Based on CDC report published by Lopez A. et al, MMWR / July 9, 2019 / Vol. 68
Temporal profile in acute flaccid myelitis
Cases evaluated at Johns Hopkins 2014-2016

Comparative quantitative clinical, neuroimaging, and functional profiles in children with acute flaccid myelitis at acute and convalescent stages of disease

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CARLOS A PARDO1,5

Developmental Medicine & Child Neurology 2018
Tissue susceptibility to Enterovirus-D68 Infection

Viral infections
Immune response
Tissue damage
Areas of CNS susceptibility in AFM

Brainstem
Motor cranial nerves
Spinal cord
Nerve roots
<table>
<thead>
<tr>
<th>Differential Diagnosis in Acute Flaccid Myelitis 2021</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Acute flaccid myelitis</th>
<th>Guillain-Barré syndrome</th>
<th>Acute transverse myelitis (demyelinating or idiopathic)</th>
<th>Spontaneous spinal cord infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominal illness</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Temporal evolution</td>
<td>Hours to days</td>
<td>Days to weeks</td>
<td>Minutes to hours</td>
<td></td>
</tr>
<tr>
<td>Pattern of weakness</td>
<td>Asymmetric, arms-legs</td>
<td>Symmetric, ascending</td>
<td>Variable</td>
<td>Symmetric, severe</td>
</tr>
<tr>
<td>Facial/bulbar weakness</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Numbness/paresthesia</td>
<td>+/-/</td>
<td>+++ (except AMAN)</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Sensory level</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>-</td>
<td>-</td>
<td>+/- (e.g. ADEM)</td>
<td>-</td>
</tr>
<tr>
<td>Bowel/bladder dysfunction</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Possible associated symptoms or syndromes</td>
<td>Headache, neck pain/stiffness, neuropathic pain</td>
<td>Neuropathic pain</td>
<td>Optic neuritis, encephalitis, seizures</td>
<td>Severe back/limb pain at onset</td>
</tr>
<tr>
<td>MRI spinal cord</td>
<td>Ill-defined grey-matter predominant lesion, +/- nerve root enhancement</td>
<td>Normal cord, +/- nerve root enhancement</td>
<td>Variable, but usually a well-defined enhancing white-grey matter lesion</td>
<td>Non-enhancing anterior cord or grey-matter lesion</td>
</tr>
<tr>
<td>CSF</td>
<td>Mild-moderate pleocytosis</td>
<td>Elevated protein</td>
<td>Mild-moderate pleocytosis</td>
<td>Sometimes elevated protein or mild pleocytosis</td>
</tr>
<tr>
<td>Microbiological tests</td>
<td>See panel 1</td>
<td>Stool sample: bacterial culture, viral; RT-PCR panel: respiratory sample viral; RT-PCR panel: serum: Campylobacter jejuni and Mycoplasma pneumoniae, IgM/IgG; other organisms according to region and season</td>
<td>If indicated based on clinical presentation</td>
<td>Not usually indicated</td>
</tr>
<tr>
<td>Other useful tests</td>
<td>+/- EMG/NCS</td>
<td>EMG/NCS; serum: anti-ganglioside antibodies</td>
<td>Serum: MOG-IgG, aquaporin-4-IgG; CSF: oligoclonal bands</td>
<td>Angiography</td>
</tr>
</tbody>
</table>

AMAN = acute motor axonal neuropathy subtype. CSF = cerebrospinal fluid. ADEM = acute disseminated encephalomyelitis. EMG/NCS = electromyography and nerve conduction studies. MOG = myelin oligodendrocyte glycoprotein.

Table 2: Differentiating acute flaccid myelitis from clinical mimics.

Acute flaccid myelitis: cause, diagnosis, and management

*Lancet* 2021; 397: 334–46
Panel 1: Clinical and paraclinical evaluation of patients with suspected AFM

Initial clinical assessment
- Consider AFM in patients presenting with rapid-onset weakness, particularly when occurring during or shortly following a suspected viral illness.
- Complete neurological examination should include specific tests for proximal muscle weakness (such as standing up from a seated position on the floor), axial weakness (neck and trunk flexion and extension), and cranial nerve abnormalities.
- Clinical features atypical for AFM include encephalopathy unrelated to metabolic disturbance, seizures, extensive sensory abnormalities, or evolution to nadir over more than 10 days.
- Neurology and infectious disease specialists should be consulted (where available) to help with diagnosis, evaluation, and treatment.
- Admission to intensive care unit should be considered when indicated, and close monitoring for respiratory or autonomic deterioration, or both, is essential.
Acute flaccid myelitis and Guillain–Barré syndrome in children: A comparative study with evaluation of diagnostic criteria

<table>
<thead>
<tr>
<th>TABLE 1 Demography and clinical presentation of AFM and GBS in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
</tr>
<tr>
<td>Male:female (%) male</td>
</tr>
<tr>
<td>Age, years, median (IQR, full range)</td>
</tr>
<tr>
<td>Antecedent events</td>
</tr>
<tr>
<td>Time antecedent event-onset weakness, days, median (IQR, full range)</td>
</tr>
<tr>
<td>No antecedent event, n (%)</td>
</tr>
<tr>
<td>Respiratory tract infection, n (%)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
</tr>
<tr>
<td>Fever, n (%)</td>
</tr>
<tr>
<td>Vaccination, n (%)</td>
</tr>
<tr>
<td>Time onset</td>
</tr>
</tbody>
</table>
| Acute flaccid myelitis and Guillain–Barré syndrome in children: A comparative study with evaluation of diagnostic criteria

AFM
- Progression to nadir in days
- Asymmetric weakness
- No sensory symptoms
- CSF pleocytosis
- Spinal cord and brain stem lesions on MRI

GBS
- Progression to nadir in 1-2 weeks
- Symmetric weakness
- Sensory symptoms (except pure motor GBS)
- Demyelinating polyneuropathy on EMG

Clinical Diagnosis of Acute Flaccid Myelitis 2021

Radiological evaluation
- MRI whole spine and brain should be prioritised, including T2 and T1 pre-contrast and post-contrast sequences in both axial and sagittal planes.
- The characteristic MRI abnormality is grey-matter predominant T2 hyperintensity of the spinal cord with associated spinal cord oedema; lesion(s) are usually longitudinally extensive and non-enhancing. Nerve root enhancement might be present.
- Repeat MRI can be considered after further clinical evolution in patients with a suggestive clinical presentation but in whom early MRI of the spinal cord is apparently normal.

Low-resource settings
- When MRI is not possible, rapid completion of available laboratory testing should be prioritised (CSF analysis, microbiological sampling), and EMG/NCS can be incorporated in the initial evaluation when available.

Acute flaccid myelitis: cause, diagnosis, and management

Lancet 2021; 397: 334-46
Areas of CNS susceptibility in AFM

- Brainstem
- Motor cranial nerves
- Spinal cord
- Nerve roots
Areas of CNS susceptibility in AFM

Susceptible regions of the brainstem
- Dorsal region of pons + medulla
- Cranial nerves (VII, VIII, IX, X, XI, XII)
AFM: Ventral nerve root enhancement
CASE: Myelin Oligodendrocyte Glycoprotein (MOG) antibody disease

MOG antibody disease: POST-CONTRAST IMAGING
CASE: Spinal cord infarction
CASE: Chiari malformation
MRI spine for diagnosis of AFM

**Green flags**
- Longitudinally-extensive
- Cervical cord involved
- Hazy abnormality
- Gray matter predominant
- Minimal enhancement
  +/− nerve root enhancement

**Red flags**
- Focal discrete lesions
- Cervical cord spared
- Round/ovoid lesions
- White matter predominant
- Focal enhancement
- Cavitation/cystic
MRI brain in AFM

• **Green flags**
  - Normal
  - Posterior brainstem hazy hyperintensity
  - Deep gray matter hyperintensity (rare)

• **Red flags**
  - White matter lesions
  - Cortical lesions
  - Optic nerve lesions
  - Enhancement
Diagnostic approach for AFM: CDC surveillance 2018
Lab studies for identification of pathogens

CSF
N=74

Stool
N=100

Respiratory
N=123

Total*
N=151

<table>
<thead>
<tr>
<th>Pathogen Type</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV-D68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EV-A71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other EV/RV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EV/RV negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EV/RV positive

<table>
<thead>
<tr>
<th>Pathogen Type</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Some patients had multiple positive specimens
Laboratory evaluation

- Obtain specimens as soon as possible (i.e., within hours of clinical presentation).
- Respiratory samples (both nasopharyngeal and oropharyngeal): respiratory viral RT-PCR testing (to include enterovirus RT-PCR). When possible, a positive enterovirus RT-PCR result should be subtyped (to include enterovirus D68, enterovirus A71, and other common subtypes).
- Stool samples or rectal swab: enterovirus RT-PCR, viral culture for poliovirus when epidemiologically relevant (with RT-PCR of isolated virus to differentiate between wild-type and vaccine-derived virus).
- Blood sample: microbiological tests (enterovirus RT-PCR and other epidemiologically appropriate micro-organism tests—e.g., West Nile virus serology), and testing for specific alternative myelopathy diagnoses to include MOG IgG and aquaporin-4 IgG.
- CSF sample: cell counts, protein, glucose, oligoclonal bands, enterovirus RT-PCR (although yield is very low), and other epidemiologically appropriate micro-organism tests.
- When RT-PCR is not readily available, samples can still be acquired and frozen for future analysis or transfer to public health authorities.
- Respiratory, stool, serum, and CSF samples should also be sent to the relevant public health authorities, according to local protocols.

Acute flaccid myelitis: cause, diagnosis, and management

Lancet 2021; 397: 334-46
### A Consensus on Clinical Diagnosis of Acute Flaccid Myelitis 2021

<table>
<thead>
<tr>
<th>Diagnostic Items</th>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1: Acute onset of limb(s) weakness (period from onset to nadir: hours to 10 days)</td>
<td>P</td>
<td>P</td>
<td>P*</td>
<td>P</td>
</tr>
<tr>
<td>H2: Prodromal fever or illness†</td>
<td>P/A</td>
<td>P/A</td>
<td>P/A</td>
<td>P</td>
</tr>
<tr>
<td>E1: Weakness involving one or more limbs, neck, face, or cranial nerves</td>
<td>P</td>
<td>P</td>
<td>P*</td>
<td>P</td>
</tr>
<tr>
<td>E2: Decreased muscle tone in at least one weak limb</td>
<td>P</td>
<td>P</td>
<td>P/A</td>
<td>P</td>
</tr>
<tr>
<td>E3: Decreased or absent deep tendon reflexes in at least one weak limb‡</td>
<td>P</td>
<td>P</td>
<td>P/A</td>
<td>P</td>
</tr>
<tr>
<td>MRI: Spinal cord lesion with predominant grey matter involvement, with or without nerve root enhancement§</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>ND</td>
</tr>
<tr>
<td>CSF: Pleocytosis (white cell count &gt;5 cell/L)¶</td>
<td>P</td>
<td>A or ND</td>
<td>P/A or ND</td>
<td>P/A or ND</td>
</tr>
</tbody>
</table>

**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 supratentorial white matter or cortex, which should prompt consideration of ADEM, MOG-antibody associated disease, neuromyelitis optica spectrum disorder, encephalomyelitis, and others
4. Absence of CSF pleocytosis, which should prompt consideration of Guillain-Barré syndrome, botulism, ischaemic cord lesions, and others
5. Positive serum aquaporin-4 (AQP-4) antibody, which would exclude AFM
6. Positive serum MOG antibody, which would suggest MOG-antibody associated disease||
There is not a good treatment approach for AFM yet!!

**Treatment Approaches For Acute Flaccid Myelitis**
- Steroids??
- Plasma exchange??
- IVIG?
- Fluoxetine??
- Rehabilitation!!
- Nerve transfers ?!
Patients followed at JHM&M Center 2010-2018 n=131

Take-home messages:
- AFM patients experience long-term sequelae and reduced rate of recovery
- Patients with infectious/post-infectious and autoimmune myelopathies exhibit better rates of recovery than vascular myelopathy or AFM patients

Garcia-Dominguez, M, Gordon-Lipkin E, Murphy O, Pardo CA et al. JHM&M Center 2019, unpublished
Tissue susceptibility to Enterovirus-D68 Infection

Viral infections

Immune response

Tissue damage
Seasonality of non-polio enteroviruses in USA
Serotype-specific immunity explains the incidence of diseases caused by human enteroviruses

Margaretta Pons-Salort* and Nicholas C. Grassey

Fig. 1. Nonpolio enterovirus incidence and births in Japan (2000–2014). (A and B) Monthly number of reported enterovirus isolations from January 2000 to December 2014 for (A) nonpolio enteroviruses and (B) CV-A4. (C) Smoothed annual number of live births. (D) Average wavelet power of the square-root-transformed time series for CV-A4 showing the emergence of a biennial pattern of incidence.
Rapid Communication

Re-emergence of enterovirus D68 in Europe after easing the COVID-19 lockdown, September 2021


KSM Benschop,........, TK Fisher, H. Harvala

Figure. EV-D68 detection in Europe, 1 July–14 October 2021 (n = 139)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of cases</th>
<th>Proportion of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 months</td>
<td>7</td>
<td>5%</td>
</tr>
<tr>
<td>4–12 months</td>
<td>15</td>
<td>11%</td>
</tr>
<tr>
<td>13–24 months</td>
<td>22</td>
<td>16%</td>
</tr>
<tr>
<td>2–5 years</td>
<td>76</td>
<td>55%</td>
</tr>
<tr>
<td>6–15 years</td>
<td>9</td>
<td>6%</td>
</tr>
<tr>
<td>16–25 years</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>26–45 years</td>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>&gt; 45 years</td>
<td>6</td>
<td>4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>51</td>
</tr>
<tr>
<td>Male</td>
<td>88</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms (data reported for)</th>
<th>Number of cases</th>
<th>Proportion of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptom reported (n = 121)</td>
<td>120</td>
<td>99%</td>
</tr>
<tr>
<td>Fever (n = 111)</td>
<td>49</td>
<td>44%</td>
</tr>
<tr>
<td>Enteric symptoms (n = 120)</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Respiratory symptoms (n = 120)</td>
<td>116</td>
<td>97%</td>
</tr>
<tr>
<td>Neurological symptoms (n = 111)</td>
<td>5</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical information (data reported for)</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalised (n = 49)</td>
<td>30</td>
</tr>
<tr>
<td>Pre-existing condition (n = 45)</td>
<td>20</td>
</tr>
</tbody>
</table>

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Acute Flaccid Myelitis Working Group

A model of horizontal collaboration to achieve consensus on the clinical diagnosis, management and research focused on acute flaccid myelitis (AFM)

Objectives:
- To establish a consensus for diagnosis and management of AFM during the acute and chronic stages of disease
- Conceive, develop, and conduct collaborative clinical studies to understand the natural history of AFM
- To facilitate clinical and basic science research to accelerate the discovery of treatment approaches in AFM
Research for understanding AFM

NIAID Acute Flaccid Myelitis Natural History Study Sites
Group 1 (AFM Cases)
Inclusion and Exclusion Criteria

Inclusion Criteria:
• Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
• Onset of flaccid limb weakness involving one or more extremities suggestive of possible, probable, or confirmed AFM within previous 30 days
• MRI of spinal cord that has been or will be obtained clinically
• Age < 18 years
• Weight ≥ 7.8 kg
• Agrees to Future Use of Specimens

Exclusion Criteria:
• Known condition other than AFM causing the flaccid limb weakness
• Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

Note: Subjects enrolling in Group 1 may subsequently be determined by the Protocol Adjudication Committee to not have AFM. This assessment will not occur in real time. If a subject is deemed to have AFM, they will be classified as Group 1A cases (possible, probable, or confirmed AFM cases). If a subject is deemed to not have AFM, they will be classified as Group 1B cases (non-AFM cases) and analyzed accordingly.
Group 2 (controls)
Inclusion and Exclusion Criteria

Inclusion Criteria:
- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Residing household contact of a child enrolled in Group 1 of this study within previous 30 days
- Weight ≥ 6.0 kg
- Agrees to Future Use of Specimens

Exclusion Criteria:
- Flaccid limb weakness involving one or more extremities
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

Note: If a subject enrolled in Group 2 subsequently develops findings suggestive of AFM, they may be asked if they would like to enroll into Group 1 of the study and be followed and analyzed accordingly.
Acute Flaccid Myelitis:
What we have learned in order to be prepared

Google: AFM Virtual Symposium Youtube
Acute Flaccid Myelitis:
What we have learned in order to be prepared

Part I
https://www.youtube.com/playlist?list=PLXi60bECKjnWc16yfgMVN1u7qOuRM8d14

Part II
https://www.youtube.com/playlist?list=PLXi60bECKjnVje4VHjzW5pzkeYtSJBdq

Part III
https://www.youtube.com/playlist?list=PLXi60bECKjnV21qm1SxKm_V2QvDHfg3yR

Part IV
https://www.youtube.com/playlist?list=PLXi60bECKjnVwvAk3_fPWS700NR6JeBaS

Part V
https://www.youtube.com/playlist?list=PLXi60bECKjnVSYQ3C8lre69RmWbaguX_l