Acute Flaccid Myelitis (AFM)

Thursday, October 13th at 12:00pm
Today’s Speakers

- Sue Hong, MD (Lurie)
- Marielle Fricchione, MD, FAAP (Rush)
- Stephanie Gretsch, MPH (CDPH)
- Heather Reid, CHES (IDPH)
Patient Presentation

▪ Typical patient
  ▪ Median age 5.2 years old
  ▪ Usually previously healthy
    ▪ May have a history of asthma

▪ Prodromal illness is common (90%)
  ▪ Occurs at a median of 5 days prior to onset of limb weakness
  ▪ Respiratory symptoms are the most common prodrome (78%)
  ▪ Fever is also common (72%)
  ▪ Gastrointestinal symptoms less common (32%)
Patient Presentation

- Acute onset of neurologic symptoms
  - Preceding neck/back pain, headache, limb pain in limb that will be affected
  - Weakness occurs over hours to days
  - Extremity weakness
    - Hyporeflexic (although early on may be hyperreflexic)
    - Low tone (flaccid)
    - Upper extremities more commonly involved than lower extremities
    - Can involve all 4 extremities (28%)
    - Asymmetric
    - Proximal > distal weakness
  - Cranial nerve dysfunction (26%) including bulbar weakness

McLaren N et al. Emerging Infectious Disease 2020; 26(2).

https://www.cdc.gov/acute-flaccid-myelitis/hcp/references-resources.html
Patient Presentation

- Uncommon Symptoms
  - Encephalopathy
  - Sensory changes other than neuropathic pain

60% of children had at least 1 interaction with medical providers (outpatient, urgent care, emergency department) prior to eventual hospitalization for AFM

- No cases of multiple people within the same household developing AFM


Unpublished data, National AFM Working Group

Differential Diagnoses and Misdiagnoses

- Transverse Myelitis
- Auto-antibody Myelitis
  - anti-NMO and anti-MOG
- ADEM
- Guillain-Barre Syndrome
- Stroke
- Acute cord compression
- Musculoskeletal injury

Reported Misdiagnoses

- Bickerstaff encephalitis/myelitis
- Dehydration
- Toxic hip
- Nursemaid’s elbow
- Nothing wrong
- Conversion/Psychogenic Disorder
- Behavioral

Hardy D et al. Arch Dis Child 2020; 105(9):842-47
Diagnostic Evaluation – Biologic Samples

- Lumbar Puncture
  - May need sedation depending on child’s age and cooperation
  - Commonly will see CSF pleocytosis with lymphocytic predominance, normal glucose, normal to elevated protein
  - Investigation for infectious etiologies: arboviral panel, meningitis/encephalitis PCR panel

- Blood Draws
  - Investigation for infectious etiologies according to geography/season: West Nile Virus, Lyme
  - Investigation for inflammatory/autoimmune etiologies: anti-AQP4, anti-MOG

- Stool Sample
  - Enterovirus testing

- Nasopharyngeal Swab
  - Respiratory viral panel PCR
AFM is a subset of Acute Flaccid Paralysis (AFP)

- Historically CDC AFP surveillance focused on Polioviruses, until 2014...
  - A retrospective search for AFM cases among MRI results and EMRs at 5 large pediatric medical centers found low # of cases from 2005-2013, but an increase in cases in 2014 → suggesting a new or changing etiology
  - AFM has distinct gray matter findings on MRI compared to other causes of AFP → viral evolution → altered tissue tropism
- AFP has multiple infectious and noninfectious etiologies
  - Poliovirus, nonpolio enteroviruses, flaviviruses like West Nile Virus, adenoviruses
  - Neuroinflammatory conditions or spinal vascular disease

Clinical manifestations and epidemiology of confirmed AFM cases strongly suggests infectious etiology, probably viral.

1) Most AFM cases have prodromal symptoms consistent with a viral illness before onset of limb weakness

2) AFM patients in peak years are significantly more likely to have prodromal respiratory illness or fever than those in nonpeak years

3) The 2014 increase in AFM coincided with an unusual increase in severe respiratory illness caused by enterovirus D68 in the US
   - 11 (20%) of 56 AFM patients whose respiratory specimens were tested at CDC in 2014 were positive for EV-D68
Mechanisms of Neuronal Damage

- Post-2014 EV-D68 strains can enter neurons, replicate, and cause neurotoxic infection in cell culture and animal models.

- Spinal cord neuronal damage not likely autoimmune-mediated
  - Median 5 days between prodrome onset and limb weakness suggests direct viral injury 2/2 immediate inflammatory response

- Antibody-dependent enhancement?
  - Like Dengue, coxsackie B, EV-A71


Brown et al. 2018. Figure 1

Why Can’t We Find Proof of CNS Enterovirus Infection in AFM Specimens?

- Timing of specimen collection can impact virus detection – **should obtain as close to onset of symptoms as possible.**
  - Yield of EV/RV and EV-D68 testing among AFM patients higher among respiratory specimens collected within 5–7 days of illness onset
  - In 2016 and 2018, 38% of all AFM patients with >1 clinical specimen tested at CDC were positive for EV/RV, EV-D68 was detected in 21%, enterovirus A71 (EV-A71) in 5%, and various other EV/RV were detected in 12%.
  - We now also need to consider polio as a cause of AFP – more commonly identified in the stool, rarely in CSF

- AFM patients were more likely than non-AFM controls to have enterovirus-specific IgG identified in their CSF

Electron micrograph of EV-D68
Image source: Cynthia S. Goldsmith and Yiting Zhang, CDC

MRI findings in AFM

Gray-matter predominance

Longitudinally extensive
Cervical cord predilection
<table>
<thead>
<tr>
<th>Diagnostic items</th>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H1</strong>: 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><strong>H2</strong>: Prodromal fever or illness†</td>
<td>P/A</td>
<td>P/A</td>
<td>P/A</td>
<td>P</td>
</tr>
<tr>
<td><strong>E1</strong>: 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><strong>E2</strong>: 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><strong>E3</strong>: 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><strong>MRI</strong>: 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>
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<tr>
<td><strong>CSF</strong>: Pleocytosis (white cell count &gt;5 cells/L)¶</td>
<td></td>
<td>A or ND</td>
<td>P/A or ND</td>
<td>P/A or ND</td>
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P – present
A – absent
ND – Not done

Acute Treatment for Suspected AFM

- Admit for observation in a hospital with ability to support respiratory failure
  - >98% hospitalized
    - ~60% admitted to ICU
  - Risk for respiratory failure
    - 10-40% require mechanical ventilation
  - Risk for autonomic dysfunction
    - Life threatening hemodynamic instability can occur
    - Also monitor for constipation and urinary retention
  - Supplemental feeding and hydration
    - Weakness may require artificial methods of nutrition

Lopez A et al. MMWR 2019; 68(2):608-14
Disease Targeted Therapies

- There is no evidence-based treatment

- Immunomodulatory therapy is commonly used
  - Intravenous immunoglobulin (IVIg)
    - In a mouse model of AFM – IVIg reduced motor impairment in a time dependent fashion
  - Corticosteroids
    - In a mouse model of AFM – steroids increased viral titer, motor impairment, and mortality
  - Plasma exchange

- Future potential therapies
  - Monoclonal antibody
  - EV-D68 vaccine

https://www.cdc.gov/acute-flaccid-myelitis/hcp/clinical-management.html
Vogt MR et al. Science Immunology 2020; 5(49):eaba4902
https://www.intravacc.nl/products/
Subacute/Chronic Treatment

Martin JA et al. Neurology 2017; 89(2):129-37
Nerve Transfer

Diaphragm Pacing


Edmiston et al. Spinal Cord Ser Cases 2019; 5:67
Outcomes & Prognosis

- Most have some recovery which occurs most significantly in the first few months but can continue for after a year
- Few with complete recovery (<10% with complete recovery)
- Persistent weakness
  - The most affected extremity is least likely to recover
  - Complications: Muscle atrophy, Joint dislocation/subluxation
  - Scoliosis
- Continued technology dependence
  - Some require long-term tracheostomy and ventilator
    - 10% still on vent after 1 year
  - Some require long-term artificial nutrition

Martin JA et al. Neurology 2017; 89(2):129-37
Surveillance for AFM

- Illness that meets any of the following criteria should be considered a possible AFM case and reported to the local health department (LHD):
  - A person with an illness with acute onset of flaccid limb weakness (clinical criteria) AND an MRI showing a spinal cord lesion in at least some gray matter and spanning one or more vertebral segments* (laboratory/imaging criteria), OR
  - A person whose death certificate lists AFM as the cause of death or a contributing cause of death, OR
  - A person with autopsy findings that include histopathologic evidence of inflammation largely involving the anterior horn of the spinal cord
- Review of case information and assignment of final case classification (confirmed, probable, suspect) for all patients under investigation for AFM is done by experts in national AFM surveillance. Classification process is for surveillance purposes only.
  - Not meant to supersede the patient diagnosis or delay treatment and management decisions.

* Excluding persons with gray matter lesions in the spinal cord resulting from physician diagnosed malignancy, vascular disease, or anatomic abnormalities.
Reporting Algorithm for AFM & Polio

**Patient with:**
- Acute flaccid limb weakness, AND
- MRI with at least some gray matter lesions in the spinal cord

**Assess risk for polio:**
- Un- or under-vaccinated?
- Recent travel to areas of risk?
- Contact with person with recent travel to areas of risk?

**If YES:**
- Consider URGENT stool collection and testing
- Flag as suspect polio

**Poliovirus negative**
- Continue reporting processes for AFM

**Poliovirus positive**
- Confirm through laboratory testing of stool
- Continue reporting processes for POLIO

*2 specimens taken at least 24 hours apart during the first 14 days after onset of limb weakness*
Confirmed AFM Cases Reported to CDC

701 confirmed cases nationally since CDC began tracking AFM in August of 2014. 18 confirmed cases in Illinois.
Increase in acute respiratory illnesses (ARI) among children and adolescents observed during summer 2022

This rise is likely attributable, in part, to increased RV/EV circulation and specifically circulation of EV-D68

- Weekly percentage of positive RV/EV test results in 2022 appears to be increasing at a rate comparable to that in past EV-D68 outbreak years (Source: National Respiratory and Enteric Virus Surveillance System)
- Among children and adolescents with ARI seeking emergency care or requiring hospitalization enrolled at New Vaccine Surveillance Network sites, the percentage of positive EV-D68 test results during July and August 2022 was higher than that during the same months of 2017 and 2019–2021 and similar to peak levels observed in 2018

KEY TAKEAWAY: Clinicians should have high index of clinical suspicion for AFM in patients with acute flaccid limb weakness, especially after respiratory illness or fever, and ensure prompt hospitalization and referral to specialty care for such cases
Local Activity and Reported AFM Cases

- Similar trends in RV/EV observed locally;
  - RV/EV test positivity rose sharply in September
- Nationally, 22 confirmed AFM cases out of 51 PUIs have been identified in 2022
  - Two PUIs in Illinois

*Weekly aggregate testing data is submitted to the Chicago Department of Public Health by 5 hospital and 2 commercial laboratories. Data are published weekly [here](#).
REPORTING AFM
Initial Reporting Criteria

- Acute flaccid limb weakness with spinal cord lesions in at least some gray matter spanning one or more spinal segments.
  - Exclude persons with lesions results from physician diagnosed malignancy, vascular disease, or anatomic abnormalities.
Reporting Steps

1. Providers should report suspect AFM cases to the **LHD**.
2. The case should also be entered into INEDSS by the facility or LHD as an ACUTE FLACCID MYELITIS case.
3. The LHD (in consultation with IDPH) will review the report to make sure the case criteria for reporting is met. (Acute flaccid limb weakness with spinal cord lesions in at least some gray matter spanning one or more spinal segments and exclude persons with lesions resulting from physician diagnosed malignancy, vascular disease, or anatomic abnormalities.)
4. The LHD should work with the provider to complete the **Patient Summary Form**, obtain the MRI report, and neurology consult notes with images.
5. The patient summary form should be submitted to the LHD and then to CDC by IDPH.
6. A secure CDC web link for uploading images and records will be provided to the LHD and provider when a suspect case is reported.
Please ensure your facility is ready to provide images and records. This is part of the surveillance reporting process.

CDC will not be able to review the case until images are received and often this holds up the process.

Making official medical records requests is not ideal so if you can facilitate this process through infection control or other means that is best.
Reporting Forms

- A copy of the patient summary form should ALSO be sent with laboratory specimens.
- Forms can be found on the IDPH public website or on CDC’s website [here](#).
Follow up form (last page).

Follow up is conducted by LHD.

LHD will reach out to case’s family/guardian to answer these questions.
Collect specimens as early as possible in cases where AFM is suspect.

Specimens that should be collected:
- cerebrospinal fluid (CSF)
- serum
- stool
- NP swab

Laboratories should work with their local health dept and IDPH lab to ensure proper collection and submission. Laboratories or HCP should contact their local health dept before shipment of specimens to IDPH lab.

The LHD will assign an authorization number once submission is approved.
Specimen Shipment

- After authorization from your LHD, specimens should be shipped to IDPH lab.
- A completed IDPH test requisition form must also be included: available [here](#).
- The authorization number obtained from your LHD should be included on the submission form.
- Ensure you ship and store at appropriate temps and length of time.
- Additional instructions can be found on CDC’s website [here](#).
60 Day LHD Follow-Up

- LHDs will obtain additional medical records and submit them to IDPH/CDC
  a. Admission notes/History and Physical
  b. Infectious disease consultation notes
  c. Additional MRI reports and images
  d. Diagnostic lab reports
  e. Vaccination records
  f. Discharge summary
  g. EMG report (if done)

- The LHD will complete the 60 day follow up interview with the parent/guardian (found on the back of the patient summary form) and submit this to IDPH (Fax or secure email; IDPH will enter this into CDC Redcap project).
## Surveillance Case Classifications

<table>
<thead>
<tr>
<th>Case Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>Confirmed</td>
<td>Meets clinical criteria with confirmatory laboratory/imaging evidence, OR Meets other classification criteria.</td>
</tr>
<tr>
<td>Probable</td>
<td>Meets clinical criteria with presumptive laboratory/imaging evidence.</td>
</tr>
<tr>
<td>Suspect</td>
<td>Meets clinical criteria with supportive laboratory/imaging evidence, AND Available information is insufficient to classify case as probable or confirmed.</td>
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</tbody>
</table>
EXTRA RESOURCES

- CDC 2020 webinar
- CDC FAQ
- IDPH AFM Page
THANK YOU

Communicable Disease Control Section

Vaccine Preventable Disease

217-782-2016

www.dph.illinois.gov
Case-Based Review
Case Presentation

- A 5-year-old, previously healthy female presents with a history of 5 days of cough, congestion, and sore throat, which had been improving.

Yesterday, she developed pain in the back of her neck and left arm.

Today, she stopped moving her arm and had difficulty holding up her head, so her family brought her to the emergency department.
Poll Question: Which of the following features of her history are commonly present in children with acute flaccid myelitis?

A. Preceding viral illness  
B. Asymmetric limb weakness  
C. Pain in the affected limb  
D. All the above  
E. None of the above
Which of the following features of her history are commonly present in children with acute flaccid myelitis?

**Explanation:**

- Characteristic features of patients with AFM include:
  - Preceding viral illness
  - Asymmetric flaccid weakness of extremities
  - Cranial nerve involvement is common
  - Onset of weakness within hours to days
  - Pain in the affected extremity(ies)

- If significant encephalopathy or seizures are present, consider an alternative diagnosis
Poll Question: Which of the following diagnostic tests can be used to confirm the diagnosis of acute flaccid myelitis?

A. MRI of the brain and spinal cord
B. Shoulder X-Ray
C. CT scan of the brain and spinal cord
D. Basic metabolic panel
E. Inflammatory markers
Case, continued

- An MRI of the brain and spinal cord was obtained to evaluate for characteristic AFM abnormalities or AFM mimics.

- The MRI revealed longitudinally extensive gray-matter predominant hyperintensities in the cervical cord.
Poll Question: This patient fulfills which of the following initial public health reporting criteria?

A. Acute flaccid limb weakness
B. Spinal cord lesions in at least some gray matter spanning one or more vertebral segments
C. Evidence of vascular disease
D. Evidence of malignancy
E. A + B
This patient fulfills which of the following initial public health reporting criteria? 

**Explanation:**

- This suspect AFM case should be reported to the appropriate local public health department (LHD).
- The LHD will work with the provider to complete the Patient Summary Form, obtain the MRI report, and neurology consult notes with images.
- The provider can assist the LHD by working with infection control to provide all of the above without an official medical record request. Since AFM is a reportable condition by law, the submission of this patient information is a reporting requirement covered under IL communicable disease code.
Poll Question: If suspicious for AFM, which specimens should be collected as early as possible in the course of illness, preferably on the day of onset of limb weakness?

A. NP swab and serum
B. Stool
C. CSF
D. All of the above
If suspicious for AFM, which specimens should be collected as early as possible in the course of illness, preferably on the day of onset of limb weakness?

Explanation:

- Laboratory evaluation includes:
  - NP swab for respiratory pathogens
  - Cerebrospinal fluid studies to evaluate for infectious and inflammatory/autoimmune causes
  - Serum tests for infectious and inflammatory/autoimmune causes
  - Stool tests for infectious pathogens

- These tests should be run internally but also set aside for shipping to the nearest IDPH lab as part of AFM reporting.

- Laboratories should work with their local health dept (LHD) and IDPH lab to ensure proper collection and submission. Labs/HCP should contact their LHD before shipment of specimens to IDPH lab. The LHD will assign an authorization number once submission is approved.
Poll Question: What are potential life-threatening complications of acute flaccid myelitis?

A. Respiratory failure
B. Hemodynamic instability
C. Kidney failure
D. Choices 1 & 2
E. All of the above
What are potential life-threatening complications of acute flaccid myelitis?

Explanation

- Acute flaccid myelitis can cause bulbar and respiratory muscle weakness which can lead to respiratory failure.
- Autonomic dysfunction can be severe and can cause hemodynamic instability.
- Bowel and bladder function should be monitored.
- All children with acute flaccid myelitis should be admitted to the hospital for close monitoring.
Any questions? Please put them in the chat.

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