Acute Flaccid Myelitis

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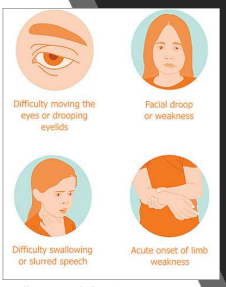
Disclosures

- I **DO NOT** have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
- I **DO** anticipate discussing the unapproved/investigative use of a commercial product/device during this activity or presentation.

Introduction

- Goals of presentation:
  - Learn the clinico-radiological characteristics of Acute Flaccid Myelitis (AFM)
  - Review the epidemiology and potential etiology of AFM
  - Review management and outcomes for patients with AFM

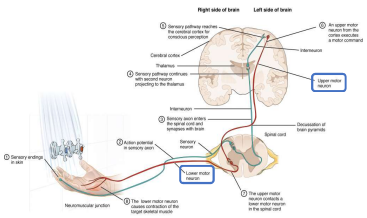
Clinical Characteristics



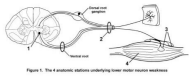
http://www.kdheks.gov/epi/AFM_info_parents.htm

- Patients present with:
  - Rapidly progressive, often asymmetric, flaccid weakness in affected muscles
    - Upper extremities > lower extremities
    - Bulbar weakness has been described
  - Muscle stretch reflexes diminished
  - Sensation and bowel/bladder function typically spared

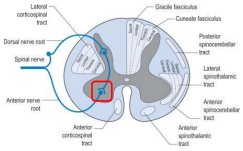
Anatomy



http://library.open.oregonstate.edu/aandp/chapter/12-3-the-function-of-nervous-tissue/



https://www.yumpu.com/en/document/read/5357880/weakness-myopathy-anterior-horn-cell-disease-neuropathies-and-



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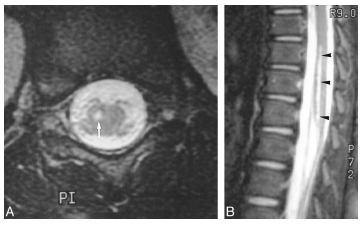
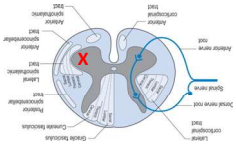
Magnetic Resonance Imaging



http://www.ajnr.org/content/22/1/200



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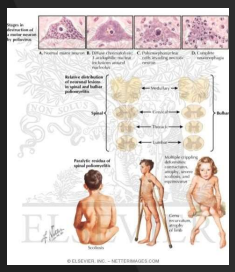
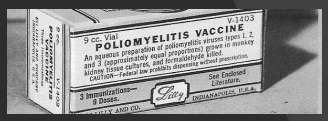
Non-Polio Acute Flaccid Myelitis





https://www.netterimages.com/images/vpv/000/000/063/63854-0550x0475.jpg

Diagnosis

- Since 2014 CDC defines:
  - **confirmed** diagnosis of AFM as:
    - Acute flaccid weakness of one or more limbs in individuals of any age
    - MRI showing a spinal cord lesion largely restricted to grey matter secondary to anterior myelitis (anterior horn cell) spanning one or more spinal segments
  - **probable** diagnosis of AFM as:
    - Clinically compatible signs and symptoms
    - Cerebrospinal fluid (CSF) pleocytosis (white blood cell count [WBC] >5/μL)

Question:

Which of the following presentations would be most consistent with AFM:

- A 5 year child with recent URI present to the ER with:
  1. Acute L hemiparesis. Has decreased sensation L side of body. Eyes forcefully deviated to the right.
  2. Acute paraparesis, urinary incontinence, and decreased sensation from umbilicus to feet, intact reflexes
  3. Acute left arm and leg weakness, no bowel/bladder dysfunction, intact sensation, diminished reflexes
  4. Acute bilateral foot drop, no bowel/bladder dysfunction, decreased sensation, diminished reflexes

Question:

To differentiate confirmed vs. probable AFM you must have:

1. Acute flaccid weakness of one or more limbs in individuals of any age
2. MRI showing a spinal cord lesion largely restricted to grey matter secondary to anterior myelitis (anterior horn cell) spanning one or more spinal segments
3. Cerebrospinal fluid (CSF) pleocytosis (white blood cell count [WBC] >5/μL)
4. Elevated CSF protein (>60 mg/100 mL)

Epidemiology and Potential Etiologies

- Overall estimated incidence of AFM is < 1 case per million individuals
- Typically affects previously healthy children
- Slight male predominance
- Most affected individuals report signs/symptoms consistent with a viral illness during preceding 4 weeks prior to presentation

Recent Clusters of AFM in the United States

- In late summer/fall of 2014
  - 120 pediatric cases of AFM reported to CDC from 34 states
  - Cases were temporally associated with enterovirus EV-68-associated respiratory virus
  - Median age was 7.1 years
  - 59% were male
  - Most experienced respiratory (81%) or febrile (64%) illness before limb weakness onset.
  - MRI abnormalities were predominantly in the cervical spinal cord (103/118).
  - All but 1 case was hospitalized; none died.
  - Cerebrospinal fluid (CSF) pleocytosis (>5 white blood cells/μL) was common (81%).

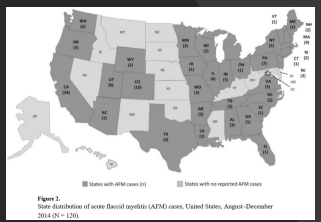


Figure 2.
State distribution of acute flaccid myelitis (AFM) cases, United States, August–December 2014 (N = 120).

Sejvar, et al: Clin Infect Dis . 2016 September 15; 63(6): 737–745. doi:10.1093/cid/ciw372

Recent Clusters of AFM in the United States

- Messacar et al reported on first geographic and temporal cluster of AFM associated with an outbreak of EV-68
  - 12 children admitted to Children's Hospital Colorado met case definition of AFM
  - Median age 11.5 years
  - All had prodromal illness preceding symptoms by median of 7 days
  - Ten (83%) children had confluent, longitudinally extensive spinal-cord lesions of the central grey matter, with predominant anterior horn-cell involvement, and nine (75%) children had brainstem lesions.
  - Ten (91%) of 11 children had cerebrospinal fluid pleocytosis.
  - Nasopharyngeal specimens from eight (73%) of 11 children were positive for rhinovirus or enterovirus (non-polio).
    - Viruses from five (45%) of 11 children were typed as enterovirus D68.
  - Improvement of cranial nerve dysfunction has been noted in three (30%) of ten children. All ten children with limb weakness have residual deficits.

Messacar, et al: Lancet 2015; 385: 1662–71

Recent Clusters of AFM in the United States

- In 2015:
  - 22 confirmed cases
- In 2016:
  - 149 confirmed cases
- In 2017:
  - 33 confirmed cases
- In 2018:
  - 230 confirmed cases*
- In 2019:
  - 7 confirmed cases*

* Confirmed cases as of May 3 2019 per CDC

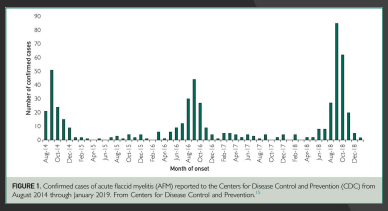


FIGURE 1. Confirmed cases of acute flaccid myelitis (AFM) reported to the Centers for Disease Control and Prevention (CDC) from August 2014 through January 2019. From Centers for Disease Control and Prevention.[7]

Fatemi and Chakraborty: https://doi.org/10.1016/j.mayocp.2019.03.011
www.mayoclinicproceedings.org

Question:

Clusters of AFM outbreaks are most common in which 2 month periods?

1. Jan, Feb
2. March, April
3. May, June
4. July, Aug
5. Sept, Oct
6. Nov, Dec

Question:

What is the etiology/pathophysiology of AFM?

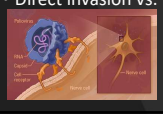
1. Viral via direct invasion
2. Viral via molecular mimicry
3. Unknown at this time

Etiology/pathophysiology of AFM

- Unknown at this time

Etiology/pathophysiology of AFM

- No clear causality
  - Coxsackievirus A16, EV-A71, and EV-D68 detected in the spinal fluid of four of 563 confirmed cases of AFM since 2014
  - For all other patients, no pathogen has been detected in spinal fluid to confirm a cause
  - EV-D68 has been temporally and geographically associated with AFM outbreaks
- Direct invasion vs. molecular mimicry?

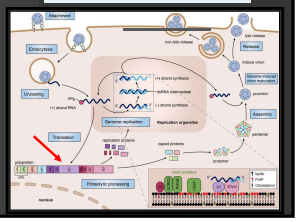


Management of AFM

- Management is primarily supportive
- Adjunctive therapies are often employed but have no demonstrated efficacy
  - High-dose corticosteroids
  - IVIG
  - Plasmapharesis
- Despite lack of proven efficacy, use of adjunctive therapy is recommended
- Antivirals?

Management of AFM

- Fluoxetine (Prozac) inhibits replication of group B and D enteroviruses by targeting viral protein 2C.
- The drug concentrates 20-fold in the CNS compared to serum, which makes it feasible to reach concentrations that exceed the 50% effective concentration (EC50) for EV-D68 at that site.



Management of AFM

NAIL HYPOTHESIS CLASS OF EVIDENCE

Safety, tolerability, and efficacy of fluoxetine as an antiviral for acute flaccid myelitis

Kevin Messacar, MD, Stefan Sillau, PhD, Sarah E. Hopkins, MD, Catherine Otten, MD, Molly Wilson-Murphy, MD, Brian Wong, MD, Jonathan D. Santoro, MD, Andrew Treister, MD, Harlen K. Bains, MD, Alcy Torres, MD, Luke Zabrocki, MD, Julia R. Glanternik, MD, Amanda L. Hurst, PharmD, Jan A. Martin, MD, Teri Schreiner, MD, Nalia Makhani, MD, Roberto L. Delgado, MD, Michael C. Kruer, MD, Adriana H. Tremoulet, MD, Keith Van Haren, MD, Jay Desai, MD, Leslie A. Benson, MD, Mark P. Gorman, MD, Mark J. Abzug, MD,* Kenneth L. Tyler, MD,* and Samuel R. Dominguez, MD*

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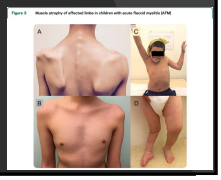
Neurology® 2019;92:e1118–e1126. doi:10.1212/WNL.0000000000006670

A multicenter cohort study of US patients with AFM in 2015–2016 compared serious adverse events, effects, and outcomes (MRC strength scale)

- 56 patients, 30 received fluoxetine
- Fluoxetine was well tolerated with no adverse events
- Not associated with improved neurological outcomes

Outcomes of AFM

- Long-term data not available
- Sporadic reports of good recovery of function
- Martin, et al Neurology® 2017;89:129–137
  - describe long-term functional, neurodiagnostic, and psychosocial outcomes of a cohort of 12 children from Colorado diagnosed with acute flaccid myelitis (AFM) in 2014 (Only 8 patients enrolled in study)
  - 6/8 had persistent motor deficits at 1 year
    - Persistent weakness in proximal > distal muscles
    - Cranial nerve dysfunction resolved in 2/5
  - At 1 year, children with AFM demonstrated functional gains but weakness persisted.
- Nerve transfers may be beneficial



Conclusions

- AFM is a syndrome that presents with acute asymmetric flaccid weakness involving face and limbs
- Cases typically cluster in late summer/early fall and may peak every 2 years
- Evidence demonstrates an association with several viral entities
  - EV-D68
- Adjunctive therapies are recommended but have no demonstrated efficacy
- Persistent motor deficits are common