Acute Flaccid Myelitis: An Update

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DISCLOSURES

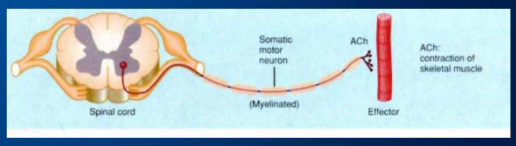
- **I have no conflict of interests to declare**

`One of the First Cases

- In 2014, on her 17th birthday, Grace Fisher, (family friend in California) started to feel extreme pain in her neck & tinging in her arms.
- In just 15 minutes she had lost the ability to walk.
- That evening she was intubated.
- She spent 5 weeks in the ICU prior to being transferred to a long term rehab center – permanently paralyzed from the neck down requiring the use of a ventilator.

Acute Flaccid Paralysis (AFP)

- This is an umbrella term to characterize the syndrome
- AFP includes a number of clinical entities:
  - Myelitis
  - Peripheral neuropathy
  - Myopathy
  - Others
- The lesion may be anywhere along the neuraxis from lower motor neuron onward



1. LOWER MOTOR NEURON (ANTERIOR HORN CELL) WITHIN THE GRAY MATTER OF THE SPINAL CORD (THE PART CONTAINING NERVE CELLS)
2. NERVE ROOTS
3. PERIPHERAL MOTOR NERVE
4. NEUROMUSCULAR JUNCTION
5. MUSCLE
- DISEASE PROCESSES THAT AFFECT ONE OR MORE OF THESE STRUCTURES CAN RESULT IN AFP

AFP Differential Diagnosis

- Neuromyelitis optica spectrum disorders
- Acute disseminated encephalomyelitis (ADEM)
- Anti-myelin oligodendroctye glycoprotein (anti-MOG) disorders
- Transverse myelitis
- Spinal cord stroke (particularly if there is trauma, vascular risk factors, or hyper-acute onset)
- Guillain-Barre syndrome

Acute Flaccid Myelitis (AFM)

- AFM is the term used to describe the cases that were occurring during summer/fall 2014 in the United States
- Specifically involves gray matter (neurons) of the spinal cord
- It is identical in clinical presentation to the illness caused by poliovirus

AFM

- Most commonly associated with poliovirus, but may be caused by numerous other viral pathogens:
  - non-polio enteroviruses
  - flaviviruses(West Nile virus, Japanese encephalitis virus),
  - herpesviruses,
  - adenoviruses

National standardized case definition adopted June 2015

Confirmed AFM

- Acute onset of focal limb weakness AND
- MRI showing a spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments

Probable AFM

- Acute onset of focal limb weakness, AND
- Cerebrospinal fluid (CSF) with pleocytosis(white blood cell count >5 cells/mm_3)

AFM HISTORY

- Fall 2012: California Department of Public Health received 3 case reports of unexplained sudden paralysis
- August 2014: Children's Hospital Colorado during an outbreak of Enterovirus D68 respiratory disease, 12 children developed focal extremity weakness with MRI findings showing multi-level gray matter lesions of the spinal cord, brainstem, or ventral nerve roots
- Between 6/2012-7/2015, 59 cases met definition for acute-onset flaccid limb weakness with spinal gray matter lesion on MRI

CDC Response

- "Interim Considerations for Clinical Management of AFM" document drafted in 2014
  - Since the recognition of AFM in 2014, CDC has received numerous requests from clinicians and public health officials for guidance on how to manage and treat patients with this condition
- In October 2014, CDC consulted subject matter experts from a range of disciplines to assist CDC in developing considerations for management of children with this neurologic illness
  - These experts were from the fields of infectious diseases, neurology, pediatrics, critical care medicine, public health epidemiology, and virology.

AFM Management

- Admission to the hospital is recommended due to the possibility of rapid deterioration and respiratory compromise.
- Monitor respiratory progression with negative inspiratory force (NIF) or similar measurements.
- Autonomic instability has been reported. Vital signs should be checked frequently early in the admission.
- Comorbid constipation is common; aggressive bowel hygiene regimen should be considered.
- Pain is frequent and therapy for neuropathic pain should be initiated (i.e. gabapentin).

Laboratory Findings

- **All specimens tested by:**
  - Enterovirus (including poliovirus)
  - EV-D68
  - Adenovirus PCR
  - Herpesviruses PCRs
  - Arbovirus serology
- **If negative for above pathogens:** Pathogen Discovery ("pan-viral" assays, Next Generation Sequence

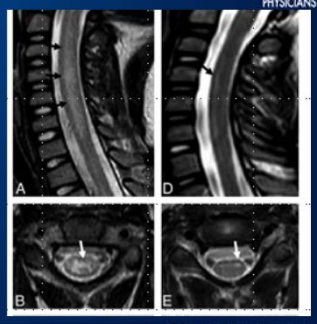
IMAGING RECOMMENDATIONS

- Imaging should be guided by clinical presentation
- Because often multiple levels of the spinal cord are involved, imaging entire spinal cord is reasonable if patient is able to tolerate procedure
- In patients with cranial nerve deficits, high cuts of brainstem should be considered
- Axial and sagittal images are most helpful in identifying lesions
- Some cases may present with some white matter involvement but for AFM cases, lesions are predominantly in gray matter

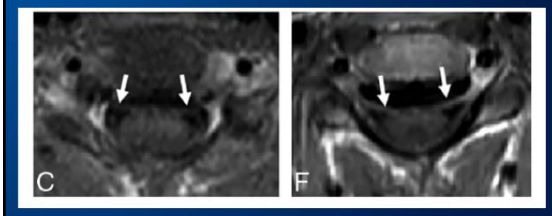
Characteristic MRI Findings

A, B. Sagittal and axial images demonstrating hyperintesity of the entire central gray matter of the thoracic spinal cord; on axial imaging, demonstrating characteristic H shape pattern

D, E: Sagittal and axial images demonstrating T2 hyperintesity confined to the left anterior horn cells



Characteristic MRI Findings



C. Axial image of thoracic spinal cord demonstrating absence of nerve root enhancement
F. Axial image of thoracic spinal cord with enhancement of nerve roots*

Notable MRI abnormalities

- Brainstem lesion involvement has been demonstrated
- Lesions involving cranial nerve nuclei in brainstem with pons frequently affected
- Spinal cord lesions largely restricted to gray matter
  - Ventral (anterior horn) cells most commonly involved
  - Some cases have entire central gray matter involved, producing characteristic "H" pattern on axial images
    - Ventral and dorsal nerve roots may demonstrate signal abnormality
    - Cord lesions often involve multiple vertebral levels, spanning multiple cervical/thoracic levels
    - Conus medullaris and cauda equina involvement frequently noted

IMPORTANT TO REMEMBER

- Spinal cord lesions may not be present on initial MRI; a negative or normal MRI performed within the first 72 hours after onset of limb weakness does not rule out AFM.
- Terms in the spinal cord MRI report such as "affecting mostly gray matter," "affecting the anterior horn or anterior horn cells," "affecting the central cord," "anterior myelitis," or "poliomyelitis" would all be consistent with this terminology

How To Report Suspected Cases

When a suspected case of AFM is identified:

1)Collect specimens for pathogen testing as early in course of illness as possible to increase chance of yielding etiology. Ideally on Day 1 of weakness and save specimens until determined if case definition met

2) Specimens to collect include:
- CSF
- Serum and/or whole blood
- NP/OP swab
- Stool for rule-out polio testing

How To Report Suspected Cases

3) Complete patient summary form –available at: www.cdc.gov/acute-flaccid-myelitis/hcp/data.html

- Send patient summary form to local/state health department who will then send form to CDC

-If case is meets case definition for AFM, send specimens to state health department for coordination of AFM testing at state and CDC

Treatment

- No indication and that any specific targeted therapy or intervention should be either preferred or avoided in the treatment of AFM.
- There are currently no targeted therapies/interventions with enough evidence to endorse or discourage their use for the treatment or management of AFM.
- Clinicians should expedite neurology and infectious disease consultations to discuss treatment and management considerations

TREATMENT OPTIONS

Corticosteroid:
- may offer benefit in managing spinal cord edema or white matter involvement but there is no evidence of efficacy
- The AFM differential diagnosis has many conditions that benefit from early steroid initiation (i.e. transverse myelitis, anti-MOG antibody related disease, acute disseminated encephalomyelitis).
- there is some evidence in a mouse model with EV-D68 that steroids may be harmful.
- use of corticosteroids has been associated with poorer outcome in observational studies of outbreaks of neuroinvasive disease due to enterovirus – 71 (EV-71) internationally and in mouse model (7,8).
- This is relevant, as an increase in EV-A71 associated neurologic disease has been reported in the United States in 2018

TREATMENT OPTIONS

- **IVIG**: has some evidence of benefit in animal models, but there is not enough evidence to determine efficacy in humans. There is no evidence that treatment with IVIG is likely to be harmful.
- **Plasmapheresis:** has no evidence in humans or animal models for efficacy
- **Fluoxetine**: mouse models & a retrospective human study that showed no benefit
- **Antiviral mediations**: should not be used unless there is suspicion for herpesvirus infection
- **Interferon**: no evidence for efficacy & carries theoretical harm if there is ongoing viral replication.

Case Reviews

- In a 2014 – 2015 case-series, treatment of AFM using IVIG was done either alone or in combination with methylprednisolone and plasma exchange
  - All patients tolerated the treatment regimens well without major complications.
  - Neurologic improvement was seen in all patients regardless of treatment, but in all except one patient, deficits persisted (3).
- Messacar, et al reported on a review of clinical cases from 2012 – 2015.
  - All cohorts that were reviewed received various combinations of IVIG, steroids, plasma exchange, and antiviral medications
  - No significant improvement or deterioration was noted with these

PROGNOSIS

- Long term data does not yet exist
- The vast majority have residual deficits one year out from diagnosis
- Lower extremity improvements exceed upper extremity improvements.

CDC Study: August 2014- June 2015

- 120 Confirmed Cases
  - 118/119 (99.2%) hospitalized
  - 34 states
- Demographics
  - Age: median 7.2 yeard (range 5 months – 20 years)
  - Sex : Male: 72 (60%); Female: 48 (40%)
- Antecedent respiratory or febrile illnesses: 92 (77%)
- Number of limbs affected
  - One Limb: 29%
  - Asymmetric Limb: 48%
  - Quadriplegia: 24%
- Neurologic Findings:
  - Cranial nerve signs: 34 (28%)
    - Facial weakness, opthalopegia, dysarthria/dysphagia
  - Evidence of brain involvement uncommon
    - AMS: 13 (12%)
    - Seizures: 5(4%)
    - CSF pleocystosis (>5 WBC) 89 (74%)

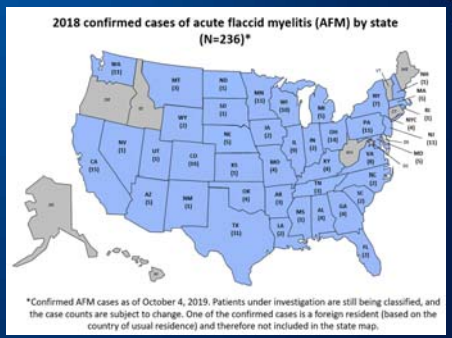
Interesting Findings

- Strong temporal association between EV-D68 respiratory outbreak and apparent increase in AFM cases
  - Despite extensive testing:18% AFM cases with evidence of EV-D68 from non-sterile site*
- Temporal association, but no 'smoking gun'

Summary of Findings

- EV-D68 identified in 10/55 (18%) respiratory specimens^
- EV-D68 not identified in any serum or stool specimens
- No arboviruses identified in any specimens
- Some serum specimens tested positive for other viruses but no single virus/virus family was consistently identified

2018: Cases by State



States with Confirmed Cases

Year	Confirmed Cases	States with Confirmed Cases
2019	22	9
2018	236	41
2017	37	16
2016	153	39 (and DC)
2015	22	17
2014 (Aug-Dec)	120	34

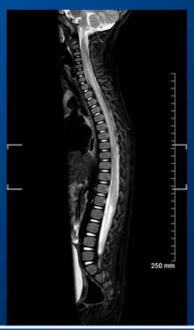
Children's Patients

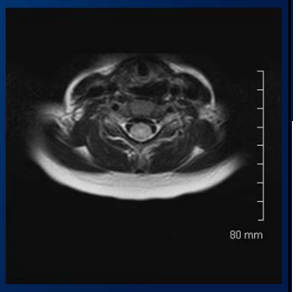
- 7 Patients – 6 Confirmed; 1 Probable
  - 6 in 2018
  - 1 in 2019
  - 6 from Nebraska, 1 from Iowa
  - 9/14/2018 – 1/2019
    - Much later In the season compared to other states
  - 4 Females, 3 Males
  - Ages: 19 months to 15 years
  - 6 had URI prior to weakness
  - 6 went to inpatient Rehab
  - 2 have been referred for nerve transfers
  - Bowel and bladder issues in

Patient 1 – 9/14/2018

- Sex: female
- Age: 3 years
- Preexisting condition: no
- Prodromal events
  - Respiratory symptoms: yes
- Neurologic illness
  - Pain
- Neurologic deficits
  - Limb weakness lower extremity
  - Sensory deficits
  - Hyporeflexia
  - Bowel/Bladder dysfunction
- Probable due to the fact all documentation used term "transverse myelitis"

Patient 1





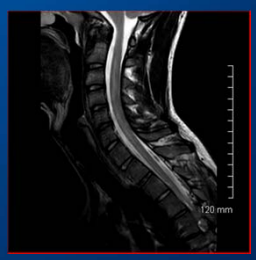
Patient 3 – 9/16/2018

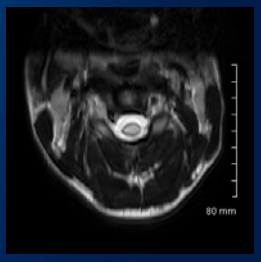
- Sex: male
- Age: 19 months
- Preexisting condition: no
- Prodromal events
  - Respiratory symptoms: yes
- Neurologic deficits
  - Limb weakness left upper extremity, neck weakness
  - Sensory deficits
  - Hyporeflexia
  - Bowel/Bladder dysfunction
- MRI: hyperintense T2 signal centrally within the spinal cord from the inferior brainstem through the lower cervical cord, expansion of the C2-C7 cord with no enhancement; hyperintense T2 signal in the posterior pons

Patient 3 – 10/24/2018

- Sex: male
- Age: 15
- Preexisting conditions: Asthma, tic disorder
- Prodromal events
  - Respiratory symptoms
  - Gastrointestinal symptoms
- Neurologic illness
  - Stiff neck
  - Pain
- Neurologic deficits
  - Limb weakness upper extremity

Patient 3

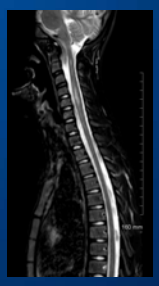


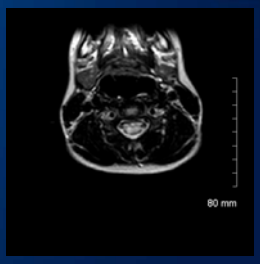


Patient 4 – 11/25/2018

- Sex: female
- Age: 11
- Preexisting condition: no
- Prodromal events
  - Respiratory symptoms (influenza vaccination three weeks prior)
- Neurologic illness
  - Stiff neck
  - Acute onset Pain
- Neurologic deficits
  - Limb weakness bilateral upper extremity, progressed to LE
  - Bowel/Bladder dysfunction
  - Autonomic symptoms

Patient 4

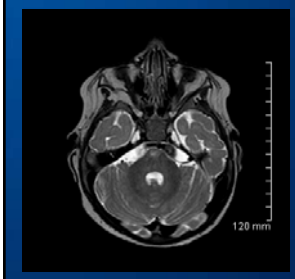


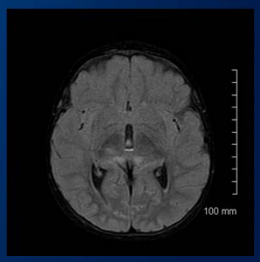


Patient 5 – 11/28/2018

- Sex: female
- Age: 2
- Preexisting condition: Leukemia, immunocompromised
- Prodromal events
  - Fever
  - Respiratory symptoms
- Neurologic illness
  - Head ache: unclear
  - Altered Mental status
- Neurologic deficits
  - Limb weakness upper extremity
  - Limb weakness lower extremity
  - Sensory deficits: unknown
  - Hyporeflexia
  - Bowel/Bladder dysfunction: yes

Patient 5





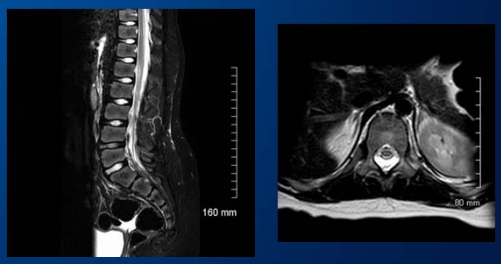
Patient 6 – 12/16/2018

- Sex: male
- Age: 8
- Preexisting condition: none
- Prodromal events
  - Respiratory symptoms
- Neurologic illness
  - Severe leg pain
  - Stiff neck
- Neurologic deficits
  - Limb weakness upper extremity
  - Limb weakness lower extremity
  - Bowel & Bladder dysfunction
  - Sensory deficits

Patient 7

- Sex: female
- Age: 8
- Preexisting condition: eczema (but not asthma)
- Prodromal events
  - Respiratory symptoms
  - Gastrointestinal symptoms
- Neurologic illness
  - Head ache
  - Stiff neck
  - Pain
  - Altered Mental status
- Neurologic deficits
  - Limb weakness upper extremity
  - Limb weakness lower extremity
  - Sensory deficits

Patient 7



AFM: Peak Season

- The CDC issued an advisory requesting increased vigilance among physicians during the late summer & autumn months, which is peak season for AFM
- In 2018 AFM resulted in 233 confirmed cases. This is the highest number since surveillance first began in 2014
- There are **22 confirmed cases so far in 2019** (CA [8 cases], GA, MD [3 cases], NC [2 cases], NE, PA, TX [4 cases], UT, WV) out of 102 reports of PUIs

CASES BY YEAR

- There have been **590 confirmed cases** since CDC began tracking AFM in August of 2014.
- CDC has been thoroughly investigating the AFM cases that have occurred since 2014, when we first noted a large number of cases being reported.
- We have seen increases in AFM cases, mostly in young children, every two years since 2014.

2014-2018: Cases by Month

- Most patients had onset of AFM between August & October, with increases in AFM cases every two years since 2014.
- At this same time of year, many viruses commonly circulate, including enteroviruses, and will be temporally associated with AFM.
- The graph shows the number of AFM cases confirmed by CDC from August 2014 through October 4, 2019, with onset of the condition through August 31, 2019.

Number of AFM cases confirmed by CDC: August 2014 through August 31, 2019.

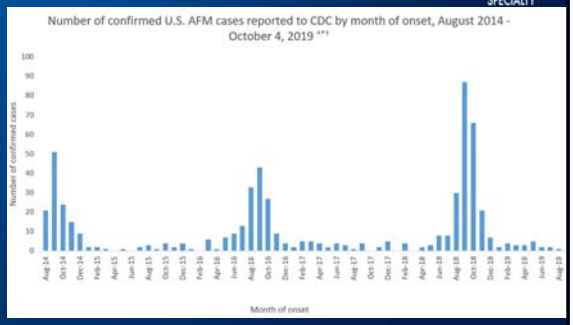


TABLE 1. Clinical Presentation of Acute Flaccid Myelitis Cases in US Cohorts 2012–2015

Source	CDPH[a]	CHCO[b]	PCH[c]	CDC[d]
No. of cases	59	12	11	120
Demographics				
Sex (% male)	56	75	91	59
Median age (range) in years	9 (0.5–73.0)	11.5 (1–18)	9 (1–14)	7.1 (0.4–20.8)
Pre-existing conditions, %	25	33	0	21
• Asthma	19	25	0	10
• Immunocompromised	5	8	0	2
Prodromal illness, %	92	100	64	90
Fever	80	100	45	64
Respiratory symptoms	71	92	NR	81
Gastrointestinal symptoms	64	0	NR	NR
Neurological Illness, %				
Headache	49	58	NR	NR
Stiff neck	34	83	NR	NR
Pain	69	67	NR	51
Altered mental status	22	0	NR	11
Neurological deficits, %				
Limb weakness	100	83	91	100
• Upper extremity weakness	73	75	64	77
• Lower extremity weakness	NR	42	36	66
• Asymmetric	NR	70	NR	47
Sensory involvement	44	0	0	21
Hyporeflexia	NR	80	NR	81
Cranial nerve dysfunction	27	83	18	28
Bowel or bladder dysfunction	51	0	18	NR

CDC Recommendations

- Many conditions may look similar to AFM on initial presentation, which makes it difficult to recognize
- ANY FOCAL WEAKNESS in a child requires immediate evaluation
  - Prompt Neurological evaluation or immediate imaging should be obtained
- Some treatments may be considered to stop progression of weakness, but there is limited data regarding the efficacy

AFM

- Respiratory symptoms or fever were reported in approximately 92% of confirmed cases within 4 weeks of onset preceding limb weakness.
- Upper limb involvement was found to affect 42% of confirmed cases
- The importance of prompt recognition, early specimen collection and rapid reporting cannot be emphasized enough

CDC Recommendations

- Using typical measures to prevent the spread of illness – hand washing, staying home if ill. And avoiding known ill contacts
- It is still unclear why some children are suscpetible to AFM
- Although AFM is seen more between August and December and tends to be severe in even calendar years (2014, 2016, 2018), AFM should still be considered in any child with a recent illness consistent with a viral illness and new onset focal flaccid weakness at any point during the calendar year

AFM Case Definition

- Adopted by the Council of State and Territorial Epidemiologists (CSTE):
  - acute onset of focal limb weakness & an MRI showing spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments, regardless of age.
- It is currently difficult to interpret trends of the AFM data. Collecting information about PUIs for AFM is relatively new. There may initially be more variability in the AFM data from year to year, making it difficult to interpret or compare case counts between years.

Update on Grace

- She was a highschool senior & had just been accepted to the Berkeley School of Music when AFM changed her life.
- She now composes music, plays the piano & paints with her mouth
- She was just accepted to UCSB to study music

For additional Information:

visit:www.cdc.gov/acute-flaccid-myelitis

Contact CDC at: limbweakness@cdc.gov

Literature Review

- https://www.cdc.gov/acute-flaccid-myelitis/index.html
- JAMA Pediatrics online November 2018 has three articles devoted to AFM
- Messacar, Kevin, et al. Acute Flaccid Myelitis: A Clinical Review of US Cases 2012-2015. Annals of Neurology, 2016; 80 (3): 326-338.
- Messacar, Kevin. Safety, tolerability, and efficacy of fluoxetine as an antiviral for acute flaccid myelitis. Neurology 2018; 92: 1-9.

Literature Review

- Funahashi, S, et al. Restoration of shoulder function and elbow flexion by nerve transfer for poliomyelitis-like paralysis caused by enterovirus 71 infection. J Bone Joint Surg Br. 2007 Feb;89(2):246-8.
- Saltzman, Eliana, et al. Nerve Transfers for Enterovirus D68-Associated Acute Flaccid Myelitis: A Case Series. Pediatric Neurology. 2018 (88) 25-30.
- Ochiai, N, et al. For how long do denervated muscles in children retain the ability to regenerate?: Restoration of elbow flexion and shoulder function by partial nerve transfer in a child with long-standing poliomyelitis-like paralysis. J Orthop Sci. 2018 Nov 10. pii: S0949-2658(18)30311-7. doi: 10.1016/j.jos.2018.10.014.