Acute Flaccid Myelitis

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Case Report – J.N.

• 6 year old previous healthy female
• Presents with
  – Sore throat
  – Neck, left shoulder and left arm weakness
  – Left arm weakness and finger paresthesias
• Dx’d with strep pharyngitis, myalgias
• Arm pain and paresthesias improved over next several days
• Arm weakness was stable, non-progressive, more proximal than distal

Case Report – J.N.

• Physical exam
  – Normal VS
  – TTP in L upper arm and neck
  – CNs intact
  – Right arm strength – normal
  – Left upper extremity motor
    • 4/5 for finger flexors, extensors
    • 1/5 for wrist flexion/extension
    • 0/5 for elbow
Case Report – J.N.

- Left upper extremity sensation
  - Decreased in left forearm and upper arm (circumferentially)
- Reflexes 1+ in LUE, 2+ otherwise
- Normal muscle tone/bulk
- No problems in b/l lower extremities.
- Normal coordination on right
- Normal gait

Case Report – J.N.

- Imaging
  - Normal radiographs of shoulder, humerus, elbow
  - MRI brain/total spine
    - Incidental finding of closed lip schizencephaly and polymicrogyria b/l, absent septum pellucidum
    - Spine was normal (non-contrast)

MRI Showing R Schizencephaly
Case Report – J.N.

- EEG was performed to r/o prolonged Todd’s
  - Normal

Case Report – J.N.

- Shoulder MRI
  - Asymmetric increase in signal on fluid sensitive sequences diffusely within the supraspinatus and infraspinatus musculature on the left side, consistent with edema
- F/U dedicated contrast enhanced MRI of C-spine
  - Showed subtle linear high T2 signal within the left side of the ventral cord from C2 to C6 as well as ventral nerve root enhancement from C4-C7

Left STIR imaging of Shoulder
Coronal STIR imaging of bilateral shoulders showing slight infraspinatus and supraspinatus signal increase

Linear signal hyperintensity seen on T2 imaging

Case Report – J.N.

• EMG
  – Neural stimulation at Erb's point along with the proximal medial upper arm was performed day #9 or less from the day of maximal neurological weakness
  – These stimulations resulted in no appreciated movement or palpable contraction of the deltoid or biceps musculature, a weak finger flexor response, and an absent CMAP recording over the biceps brachii indicating lower motor neuron involvement.
  – The results were consistent with either a localized alpha motor neuron cell injury, motor axon degeneration within the brachial plexus, or less likely, due to a complete conduction block.
Case Report – J.N.

• Film Array Respiratory Panel (BioFire Diagnostics, Inc)
  – Positive for Rhinovirus/Enterovirus
  – Sent to CDC for typing
    • Human rhinovirus B48

Definitions

• Acute Flaccid Paralysis (AFP)
  – Sudden (acute) weakness in the arm(s) or leg(s), along with loss of muscle tone and decreased or absent reflexes. In some cases, there is pain or there can be an impact on the nerves controlling the head and neck, causing facial weakness, drooping of the eyelids, and difficulty swallowing, speaking, or moving the eyes.

• Acute Flaccid Myelitis (AFM)
  – A disease involving the spinal cord (specifically anterior horn cells), with symptoms of acute flaccid paralysis.

Definitions

• CDC case definition (2014)
  – Presenting after 8/1/2014
  – Confirmed
    • Weakness and MRI evidence of predominantly gray matter lesion(s) spanning one or more spinal cord segments
  – Probable
    • Acute focal limb weakness and CSF pleocytosis (>5)

• WHO definition states that age < 15 yo

Epidemiology of AFM

• Reemerged in 2012
  – Originally associated with polio virus
• CDC Surveillance established 2015
• From 6/2012 – 6/2014, 23 cases reported
  – 59 in California 6/2012-8/2015
  – 12 in Colorado 8/2014 – 10/2014
• 120 patients from 34 states presented 8-12/2014

Epidemiology

• Current incidence is less than 1 in 2 million children
• Increases every two years
• 90% have respiratory illness/fever prior to this
• Onset usually August through October
• Over 90% are children
• 46 states and DC

https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html

2018 confirmed cases of acute flaccid myelitis (AFM) by state (N=186)*

*Confirmed AFM cases as of December 20, 2018. Patients under investigation are still being classified, and the case counts are subject to change. Case counts will be updated every Wednesday.
https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html* accessed 1/7/19
U.S. Epidemiology

- 8/2014 to 12/2014 – 120 cases
- 2015 – 22 cases in 17 states
- 2016 – 149 cases in 39 states
- 2017 – 35 cases in 16 states
- 2018 – 186 cases in 38 states (through 12/28)
- Total of 430 cases from 8/14 – 11/18

Epidemiology

- Worldwide
  - Canada
  - India
  - Wales
  - Scotland
  - France
  - Sweden
  - Norway
  - Spain
  - Japan
  - Ethiopia
  - Germany
  - Holland
  - Argentina
  - Pakistan

https://www.cdc.gov/acute-flaccid-myelitis/afm-cases.html
accessed 1/7/19
Epidemiology

AFM Symptomatology

- Sudden onset of arm/leg weakness and loss of muscle tone/reflexes
- Can also include
  - Facial droop
  - Oculomotor difficulties
  - Ptosis
  - Dysarthria/dysphagia
  - Pain in affected limb
- Can include dysuria and dyspnea
- Rarely with sensory deficits

AFM Diagnosis

- Difficult diagnosis
- Made with MRI (brain and spinal cord, with and without contrast)
- EMG can help
- CSF analysis
- Respiratory, stool cultures should also be collected
- Differential includes
  - Transverse myelitis
  - Guillain-Barre
  - Toxic neuropathy
  - Muscle disorder
Neurologic Condition Causing Acute Flaccid Paralysis

- Acute Myelopathy
  - TM
  - Cord compression
- Anterior Horn Cell
  - Poliomyelitis
    - WTPP
    - VAPP
  - Nonpoliomyelitis
    - Other viruses
- Polyradiculopathy
  - GBS
- Peripheral neuropathy
  - Infectious
    - Diphtheria, Lyme, etc...
  - Ingestion related
    - Lead, poisonous plants
- NM Junction
  - MG
  - Botulism
  - Tetanus
  - Animal toxin
  - Organophosphate
- Muscle disorders
  - Polymyositis
  - Myositis
  - Hypokalemic periodic paralysis
  - Critical illness weakness

Differential Diagnosis of AFM

<table>
<thead>
<tr>
<th>AFM</th>
<th>Transverse Myelitis</th>
<th>AIDP</th>
<th>ADEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preceding Illness</td>
<td>URI, GI, 7 days prior</td>
<td>URI, GI are common</td>
<td>URI, GI are common</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Fever, meningial signs, back pain</td>
<td>Dysesthesia, Paresthesia, Back pain</td>
<td>Leg pain, unsteady gait</td>
</tr>
<tr>
<td>Progression</td>
<td>Hours to days</td>
<td>Hours to days</td>
<td>Ascending weakness</td>
</tr>
<tr>
<td>Distribution</td>
<td>Asym, U.E.L.E.</td>
<td>Sym or asym</td>
<td>Symmetric</td>
</tr>
<tr>
<td>Tone</td>
<td>Flaccid</td>
<td>Flaccid – Spastic</td>
<td>Flaccid</td>
</tr>
<tr>
<td>DTR's</td>
<td>Decreased</td>
<td>Dec – Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Sensory</td>
<td>Variable</td>
<td>Common, level</td>
<td>Distal paresthesias</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Bowel/Bladder</td>
<td>Bowel, bladder</td>
<td>CV instability</td>
</tr>
<tr>
<td>CN deficit</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon (MF)</td>
</tr>
</tbody>
</table>

Clinical characteristics of Cases 2012-2015

- Composed of CDC, CDPH, CHCO, PCH (Utah) studies
- 61% male
- Average age – 8 yo
- Pre-existing conditions (Asthma/Immunocompromised) - 21%
- Prodromal illness (fever, URI, GI) – 89%
- Neurological Illness
  - Headache – 50%
  - Stiff neck – 42%
  - Pain – 13%
Clinical characteristics of Cases 2012-2015

- Neurological Deficits
  - Limb weakness – 98.5%
    - Upper extremities – 75%
    - Lower extremities – 62%
    - Asymmetric – 49%
  - Sensory involvement – 25%
  - Hyporeflexia – 81%
  - Cranial Nerve dysfunction – 30%
  - Bowel/bladder dysfunction – 39%

Laboratory Findings (2012-2015)

- CSF pleocytosis – 78%
  - Up to 888 WBC
- Elevated CSF protein – 48%
- Virus found in CSF – 1%
- EV-D68 in respiratory specimen – 21%
- Non-D68 rhino/enterovirus in respiratory specimen – 18%


- T2 gray matter lesions spanning multiple vertebral levels on spinal cord MRI – 94%
- Nerve root enhancement on MRI – 30%
- Brainstem lesion on MRI – 38%
- Supratentorial lesions on MRI – 16%
EMG Findings (2012-2015)

- All patients had motor findings on affected limb
- No tested patients had sensory findings on affected limb

Types of Treatment Used

  - IVIG – 74%
  - Plasmapheresis – 17%
  - IV Steroids – 58%
  - Antivirals – 5%
- Japan (2015)
  - IVIG – 19%
  - IV steroids – 15%
  - Steroids + IVIG – 59%
  - Plasmapheresis – 5%

Presentation in Japanese Patients

- 59 patients (1 with probable AFM); 8-12/2015
  - 7/20 positive with EV-D68 (3 resp, 2 stool, 1 CSF)
- Prodromal symptoms (97%)
  - Fever (88%), URI (75%), GI(19%)
- Limb paralysis (100%)
  - 1 (37%), 2 (39%), 3 (5%), 4 (19%)
  - Asymmetric (68%)
- Hyporeflexia (90%)
- Cranial nerve involvement (17%)
- Focal paresthesias (20%)
Presentation in Japanese Patients

- Imaging
  - All had longitudinal cord lesions
  - Median of 20 vertebral levels
  - Brainstem lesions in 42%
- Enhancement
  - Parenchymal – 5%
  - Ventral nerve root – 15%
  - Cauda equina – 51%

Presentation in Japanese Patients

- EMG
  - Motor conduction abnormal in 82%
  - F-waves abnormal in 73%
- CSF
  - Pleocytosis in 85%
    - Greater if done earlier
  - Elevated protein in 46%

2018 Statistics

- Median age = 4 years
- 59% male
- 86% caucasian
- Upper limb only in 47.5%; lower limb only in 8.8%; all limbs in 29%
- 59% admitted to ICUs
- No deaths
Cause of illness

• Direct infection of a virus on the motor neurons (nerves that make the muscles move)
• Indirect infection where a virus may lead to an inflammatory or immune response directed toward motor neurons
• Host genetic factors in which certain children may be more susceptible than others

https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html, accessed on 1/7/19

Cause

• When a pathogen is found in CSF it is likely the cause
• Most cases had no associated CSF pathogen
  – EV-A71, EV-D68, Cocksackie A-16 found in CSF in 4/512 cases
• Reasons for no CSF pathogen in most cases?
  – Pathogen is cleared by body
  – Pathogen is hiding in tissues
  – Pathogen triggers an immune response
• Unclear why few get AFM if many are infected with viruses

Known Viral Causes of Limb Paralysis

• Polio
  – Total of 58 cases of WTPV1 in Afghanistan, Pakistan, Nigeria
  – 1.2% result in aseptic meningitis
  – 0.1% result in poliomyelitis
  – None of the current AFM had stool positive for polio
• WNV
• EV-A71
• EV-D70
• Coxsackievirus A16 (CSF – 1 case)
• Japanese Encephalitis
• Hopkin’s Syndrome
• 7EV-D68
Main Viral Findings in Recent AFM

• EV-D68

• EV-A71
  – Previously associated with brainstem encephalitis

EV-A71

• Isolated first in late 1960’s
• Clinically
  – Hand, foot and mouth disease
  – Aseptic meningitis
  – Encephalitis (Brainstem)
  – AFM
  – Transverse myelitis
  – GBS
• Cyclical - Every 3 years
• CSF yield is low, <30% for neurologic disease
• Outcome
  – 56% with AFM has residual weakness/atrophy (12.5% in another study)
  – 80% had single limb involvement

EV-D68

• Discovered in 1962
  – Pneumonia in California
• Non-polio enterovirus
• Similar to Rhinovirus 87.
• Respiratory transmission
• Not heat or acid stable
  – Not found in stool
• 26 cases found 1970-2005
• Clusters occurred in Europe 2008-2010
• 2014 there were 1153 cases.
• 6 Clades
  – B1 is the clade associated with AFP, evolved in 2010
Association of AFM, EV-D68

- Bradford Criteria
  - Strength
  - Consistency
  - Specificity
  - Temporality
  - Biological Gradient
  - Plausibility
  - Coherence
  - Experiment
- 6 are fully met, 2 (specificity and strength) are partially met, and 1 (biological gradient) is minimally met

Dyda A. Euro Surveill. 2018 Jan;23(3)

Cause

- Strong association with EV-D68 temporally, in respiratory secretions, but not in CSF (affected tissue)
2018

- 186 confirmed cases
  - 80 studied in current article
- Median age – 4 yo
- Male – 59%
- White – 86%
- Preceding viral illness – 99%
  - Fever – 81%
  - Respiratory symptoms – 78%
  - GI symptoms – 38%
- Cause
  - 2018
    - 29% with EV-A71 (respiratory culture)
    - 37% with EV-D68
    - 34% other viruses
    - CSF – EV-A71 and EV-D68 in one patient each
- Limb involvement
  - Upper only – 47.5%
  - Lower only – 8.8%
  - 2 or 3 upper and lower limbs – 15%
  - All 4 limbs – 28.8%
- ICU admission – 59%
- CSF Pleocytosis – 83% - median of 103 WBC with lymphocytic predominance
2/4/2019

2018 AFM Statistics

![Graph showing AFM statistics over months]

Organisms Recovered

<table>
<thead>
<tr>
<th>Organisms</th>
<th>CSF</th>
<th>Resp</th>
<th>Stool</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>3000</td>
</tr>
<tr>
<td>E. coli</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>S. aureus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R. typhi</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B. cereus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other organisms</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment

- No indication that any specific targeted therapy/intervention should be preferred or avoided in treatment of AFM
- Should obtain neurology and/or infectious disease consult
Treatment

- Corticosteroids – may help with spinal cord edema, but is harmful in mouse model of EV-D68; can also result in immunosuppression.
- IVIG – no evidence for harm or benefit
  - Beneficial in mouse model (Viral load for EV-D68 is low)
- Plasmapheresis – no evidence of benefit; risk associated with procedure
- Fluoxetine – no evidence for efficacy
- Antiviral medications – no evidence for efficacy
- Interferon – no evidence for efficacy
- Immunosuppressant (other) - no evidence for efficacy

https://www.cdc.gov/acute-flaccid-myelitis/hcp/clinical-management.html

Outcome Study #1

- 12 Children from Colorado 2014 outbreak
  - 8 completed year long study
    - 2 with full recovery
    - 6 with persistent deficit
      - Proximal muscles with atrophy
  - 2 that didn’t complete study reported full recovery
  - Cranial nerve dysfunction resolved in 2/5
    - Diplopia, Facial weakness, bulbar weakness
    - Improved in all

Outcome Study #1

- Additional findings
  - Pain (2/8)
  - Depressive symptoms (3/8)
  - MRI significant improvement/normalization (6/8)
    - No enhancement
  - Repeat EMG/NCS showing ongoing denervation/chronic reinnervation (3/4)
    - Better correlated with outcome than MRI
- Despite improvement, AFM had substantial long-term functional effects on affected kidsz
Outcomes of Colorado Cases at 1 year

- 12 Cases
- KM plot
- Muscle atrophy

Outcome Study #2

- 16 patients from Johns Hopkins
  - MRI showed improvement in spine
    - Worse in cervical, lumbar regions
  - No patient had complete functional recovery
    - Distal improved more than proximal
    - 15/16 had flaccid muscle tone
    - 16/16 had decreased/absent reflexes
    - 4/16 required mechanical ventilation
    - 0/16 with sensory changes

Outcome Study #3

- 14 children from CHOP
  - 5 from 2014, 9 from 2016
  - Of the 2014 group, 4/5 had significant improvement
  - Other the 2016 group, all have significant weakness
Outcome Study #4

- 59 Cases from Japan
  - Complete motor functional recovery – 12%
    - Better for CN, paresthesias, bladder
  - 68% with muscle atrophy
  - Good outcome with normal F-wave
  - Poorer outcome with IVIG, steroid Rx

Outcome

- 2/5 ventilator dependent at 18 months
- Of 120 cases identified by CDC
  - 56 with f/u (median 4 months)
  - Only 3 with complete recovery
    - 14% fully dependent
    - 68% with some impairment
    - 18% fully functional
- Of 21 in Canadian Cohort
  - 2 fully recovered
- CDC announced it will follow outcomes now

Prevention

- Vaccination against polio virus
- Avoid WNV with mosquito repellant
- Avoid enteroviruses by avoiding contact with sick people, good handwashing.
- New vaccines?
- Anti-virals?
  - Enviroxime, Pirodivir, Pleconaril, Ribavirin, Rupintravir and guanidine
Latest Developments (12/19/18)

Investigating causes:
The majority of cases occurred in the last few weeks of September. There is no clear evidence that AFM has been spreading over time. The CDC has identified several potential causes, including:
- Viral infections
- Autoimmune disorders
- Unknown factors

Future Directions:
• Understand underlying mechanism of AFM
• Determining host risk factors
• Evaluate treatments (Antivirals, Immunosuppressants)
• Developing vaccines
• Determine long-term outcome

CDC Form for AFM
References

- Council of State and Territorial Epidemiologists – 17-ID-01

References

References


References