Acute Flaccid Myelitis

Andrew M. White, MD, PhD
Chief, Pediatric Neurology
Denver Health Medical Center

Case Report – J.N.

- 6 year old previously healthy female
- Presents with
  - Sore throat
  - Neck, left shoulder 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

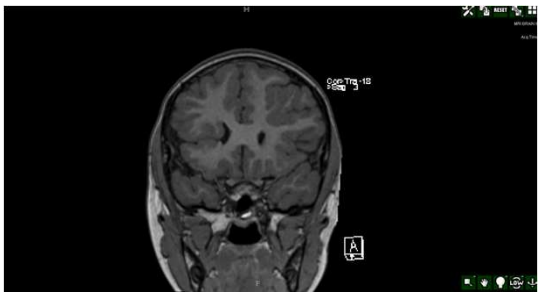
Case Report – J.N.

- 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 pallucidum
    - Spine was normal (non-contrast)

MRI Showing R Schizencephaly



Case Report – J.N.

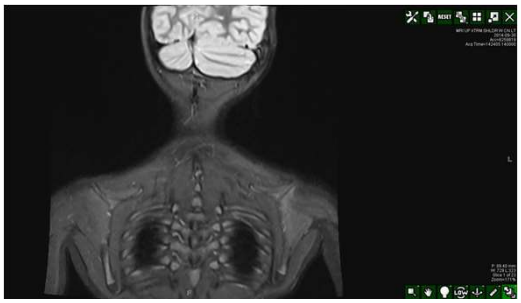
- EEG was performed to r/o prolonged Todd's
  - Normal

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

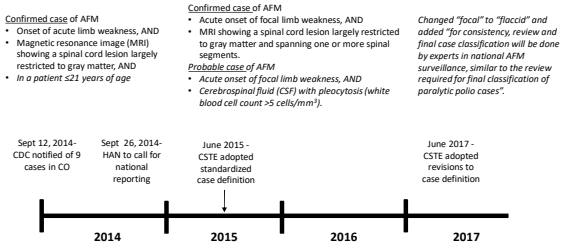
- Acute Flaccid Paralysis (AFP)
  - Sudden (acute) weakness in the arm(s) or leg(s), along with loss of muscle tone and decreased or absent reflexes. In some cases, there is pain or there can be an impact on the nerves controlling the head and neck, causing facial weakness, drooping of the eyelids, and 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.
  - Coined in 2014 to describe patients with sudden onset limb weakness of unknown cause
  - Identical in clinical presentation to polio

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

Council of State and territorial Epidemiologists. Standardized case definition for acute flaccid myelitis: centers for disease control and prevention; 2015.

Evolution of Case Definition



Polio Epidemiology

- Average cases of paralytic polio (1951-54)
  - 16,316/year
- Average deaths from polio (1951-54)
  - 1879/year

Epidemiology of AFM

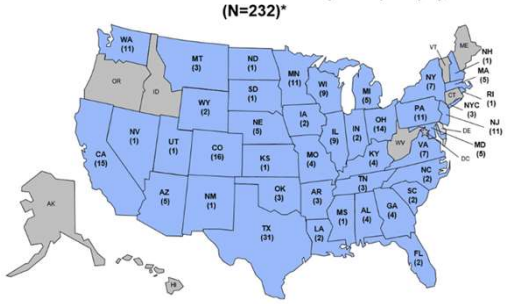
- Reemerged in 2012; 3 pts. In CA
  - Originally associated with polio virus
- From 6/2012 – 6/2014, 23 cases reported
- 12 in Colorado 8/2014 – 10/2014
- 120 patients from 34 states presented between August and December, 2014
  - CA, CO, MA, PA, and UT with >5 cases
- CDC Surveillance established 2015

Epidemiology

- Current incidence is less than 1 in 2 million children
- Increases every two years
- Often preceded by respiratory or febrile illness
- Onset usually August through October
- Over 90% are children
- 46 states and DC
- 60% male; avg. age – 6.3 yo

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

2018 confirmed cases of acute flaccid myelitis (AFM) by state (N=232)*

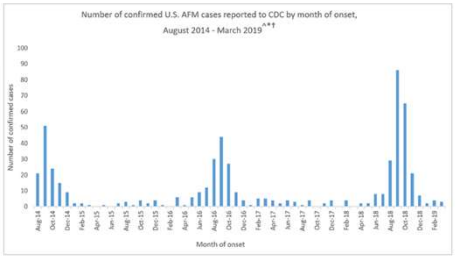


*Confirmed AFM cases as of May 31, 2019. Patients under investigation are still being classified, and the case counts are subject to change. One of the confirmed cases is a foreign resident (based on the country of usual residence) and therefore not included in the state map.

https://www.cdc.gov/acute-flaccid-myelitis/afm-surveillance.html accessed 6/30/19

AFM Confirmed U.S. Cases

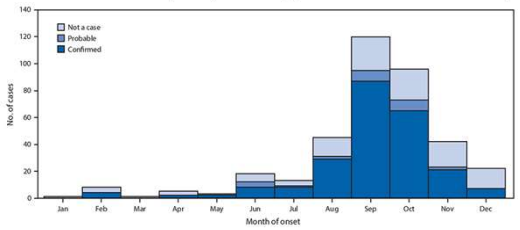
Español (Spanish)



^ Confirmed AFM cases that CDC has been made aware of as of February 1, 2019 with onset of the condition through January 31, 2019. The case counts are subject to change.
* The data shown from August 2014 to July 2015 are based on the AFM investigation case definition: onset of acute limb weakness on or after August 1, 2014, and a magnetic resonance image (MRI) showing a spinal cord lesion largely restricted to gray matter in a patient age ≤21 years.
† The data shown from August 2015 to present are based on the AFM case definition adopted by the Council of State and Territorial Epidemiologists (CSTE): acute onset of focal limb weakness and an MRI showing spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments, regardless of age.

https://www.cdc.gov/acute-flaccid-myelitis/afm-cases.html accessed 6/30/19

FIGURE 2. Cases of acute flaccid myelitis reported to CDC, by case classification status — United States, 2018



https://www.cdc.gov/mmwr/volumes/68/wr/mm6827e1.htm?s_cid=mm6827e1_w#F1_down accessed 7/10/19

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 – 232 cases in 40 states
- Total of 430 cases from 8/14 – 11/18
- 2019 – 9 cases so far as of 6/30/19

Epidemiology

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

Epidemiology

	Number of cases with enterovirus D68 from any source (year of presentation)	Number of cases with enterovirus D68 in CSF
Argentina[4,23]	4 (2016)	1
Australia[24]	2 (2010)	0
Canada[4,25]	7 (2014)	0
Democratic Republic of the Congo[26]	1 (year not reported)	0
France[4,27,28,66]	2 (2014), 4 (2016)	0
Germany[4,29]	2 (2016)	0
Italy[4,30]	2 (2016)	1
Japan[66]	3 (2013, 2015)	0
Netherlands[4,66]	2 (2016)	0
Norway[31,66,67]	2 (2014)	0
Spain[66]	1 (2015), 2 (2016)	0
Sweden[31]	3 (2016)	0
UK[4,9,32]	1 (2014), 2 (2015), 6 (2016)	0
USA[1,4,9,17,33–41,66,72]	1 (2005), 1 (2008), 3 (2012), 12 (2014), 15 (2016)	3
Total	78 cases in 14 countries on six continents	5

CSF=cerebrospinal fluid. *Includes cases of acute flaccid paralysis or acute flaccid myelitis with enterovirus D68 detected from respiratory, stool or rectal, blood, or CSF specimens.

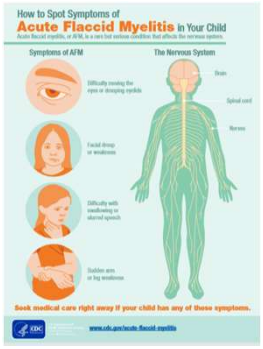
Table: Acute flaccid paralysis or acute flaccid myelitis cases with enterovirus D68 identified from biological specimens*

www.thelancet.com/infection Vol 18 August 2018

AFM Symptomatology

- Sudden (hours-few days) 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
  - Hoarse or weak cry
- Can include dysuria and dyspnea
- Rarely with sensory deficits
- Preceding illness 1-2 weeks prior to symptoms

CDC Handout



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
    - Diptheria, 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

	AFM	Transverse Myelitis	AIDP	ADEM
Preceding illness	URI, GI, 7 days prior	URI, GI are common	URI, GI are common	URI, vaccine
Associated symptoms	Fever, meningeal signs, back pain	Dysesthesia, Paresthesia, Back pain	Leg pain, unsteady gait	Fever, meningeal signs, encephalitis
Progression	Hours to days	Hours to days	Ascending weakness	Multifocal deficits 4-7 day
Distribution	Asym, U.E>L.E.	Sym or asym	Symmetric	Asymmetric
Tone	Flaccid	Flaccid – Spastic	Flaccid	Spastic
DTR's	Decreased	Dec – Increased	Decreased	Increased
Sensory	Variable	Common, level	Distal paresthesias	Common
Autonomic	Bowel/bladder	Bowel, bladder	CV instability	Possible
CN deficit	Common	Uncommon	Uncommon (MF)	Possibly (ON)
Muscles	Proximal	Variable	Distal	Variable

Characteristic Findings

- US 2012-2015
- US 2014-2018
- Japan 8-12/2015
- US 2018

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%

TABLE 2. Laboratory results from cerebrospinal fluid (CSF), respiratory, and stool specimens collected from patients with confirmed acute flaccid myelitis (N = 233) — United States, 2018

Specimen source	No. with specimens available (% of 233)	No. (%) positive	Positive test results (No.)
CSF	74 (32)	2/74 (3)	EV-A71 (1)
			EV-D68 (1)
Respiratory	123 (53)	54/123 (44)	EV-D68 (30)
			EV-A71 (10)
			Other/Untyped EV/RV (14)
Stool	100 (43)	13/100 (13)	EV-D68 (1)
			EV-A71 (2)
			Echovirus 11 (1)
			Coxsackievirus (3)
			Parechovirus (4)
			Other/Untyped EV/RV (2)

Abbreviations: EV = enterovirus; RV = rhinovirus.

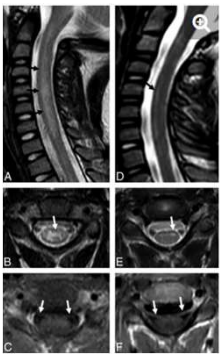
https://www.cdc.gov/mmwr/volumes/68/wr/mm6827e1.htm?s_cid=mm6827e1_w#F1_down accessed 7/10/19

MRI imaging

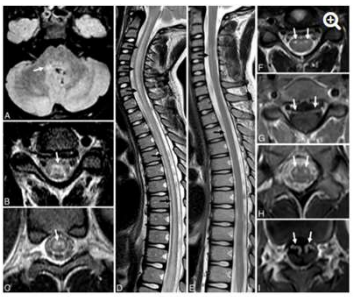
- Use 3 Tesla if possible
- Imaging may be normal in first 72 hours
  - Repeat if indicated
- Axial/Sagittal images are best
- Image entire spine
- With cranial nerve lesions, image brainstem

MRI Findings (2012 – 2015)

- 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%



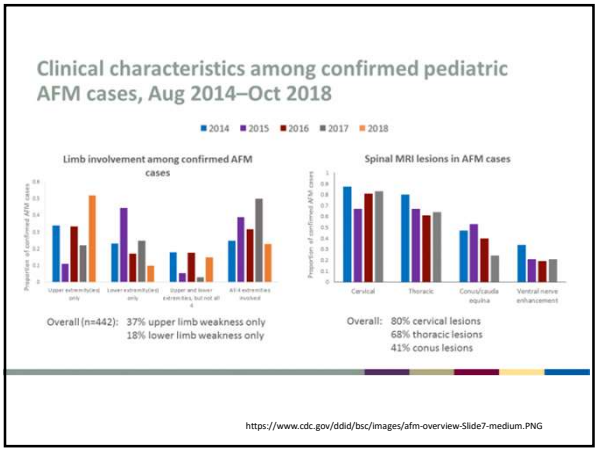
A–C, In Patient 2 scanned at 2 days, the central cord hyperintensity is more ill-defined and involves the entire central gray matter (*black arrows, A; white arrow, B*). Nerve roots do not enhance (*white arrows, C*). *D–F*, Patient 8, scanned at 25 days, demonstrates T2 hyperintensity confined to the anterior horn cells asymmetric to the left (*black arrow, D; white arrow, E*) and nerve root enhancement (*white arrows, F*).



A–D, Acute imaging performed at 2–3 days in patient 1 demonstrates T2 hyperintensity in the right dorsal pons (*white arrow, A*) and more ill-defined central gray matter hyperintensity seen more commonly in the acute phase (*white arrows, B* and *C; black arrows, D*). *E–I*, Subacute imaging of the spine performed in the same patient at 38 days demonstrates contraction of the cord T2 hyperintensity to focally involve the anterior horn cells (*black arrows, E; white arrows, F* and *H*) and nerve root enhancement of ventral cervical roots (*white arrows, G*) and the cauda equina (*white arrows, I*).

EMG Findings (2012-2015)

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



https://www.cdc.gov/ddid/bsc/images/afm-overview-Slide7-medium.PNG

Preceding illness of pediatric confirmed AFM cases, Aug 2014–Oct 2018

Preceding Illness	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	Total n (%)
Number of cases	120	18	143	32	129	442
Any respiratory illness	95 (81)	5 (28)	106 (74)	16 (50)	104 (81)	326 (74)
Any gastrointestinal illness*	n/a	2 (11)	33 (23)	10 (31)	48 (37)	90(28)
Any febrile illness	74 (64)	6 (33)	93 (65)	21 (66)	105 (81)	299 (68)
Respiratory or febrile illness	105 (90)	8 (44)	122 (85)	23 (72)	125 (97)	383 (87)

*Gastrointestinal illness data collection began mid-2015

https://www.cdc.gov/ddid/bsc/images/afm-overview-Slide7-medium.PNG

AFM Diagnostic Testing 8/14 – 11/18

- CSF had EV-D68, EV-A71 and Cox A16 (4 cases)
- Upper respiratory specimen (49% in 2018)
  - 20-30% EV-D68; 10% EV-A71
  - 1/3rd with other viruses
  - 1/3rd with no pathogen
- Stool (14% in 2018)
  - EV-A71 (1), EV-D68(1), Echo (1), Coxsackie (3), Parecho (1), Rhino (1)
- All stool negative for poliovirus

https://www.cdc.gov/ddid/bsc/images/afm-overview-Slide7-medium.PNG

Additional Characteristics for AFM (2018)

- 96% hospitalized
  - 58% in ICU
- 81% CSF pleocytosis
  - Median cell count – 104
  - Lymphocytic predominance
- No deaths in 2018 (but 1 in 2017)
- Days from illness to limb weakness
  - Febrile – 2
  - GI – 2.5
  - Respiratory - 5

TABLE 1. Demographic and clinical characteristics of patients with confirmed and probable cases of acute flaccid myelitis (AFM) and non-AFM cases, and timing to medical care and reporting to public health — United States, 2018

Characteristic	No. (%) Confirmed (N = 233)	Probable (N = 26)	P-value*	No. (%) Noncase (N = 115)	P-value†
Demographics					
Median age, yrs (range, IQR)	5.3 (0.5–81.8, 3.3–8.2)	2.9 (0.3–55.3, 1.0–10.1)	0.04	8.8 (0.1–78.1, 3.9–19.7)	<0.001
Male sex	136/233 (58)	14/25 (56)	0.83	67/111 (60)	0.81
Race					
Asian	9/233 (4)	1/26 (4)	0.87	8/115 (7)	0.40
Black or African American	22/233 (9)	4/26 (15)		17/115 (15)	
Native Hawaiian/Pacific Islander	1/233 (0)	0/26 (0)		0/115 (0)	
White	147/233 (63)	14/26 (54)		69/115 (60)	
Multiracial	4/233 (2)	1/26 (4)		1/115 (1)	
Unknown	50/233 (21)	6/26 (23)		20/115 (17)	

Abbreviations: CSF = cerebrospinal fluid; ICU = intensive care unit; IQR = interquartile range; MRI = magnetic resonance imaging.
* P-value represents comparison of confirmed and probable cases of AFM.
† P-value represents comparison of confirmed and non-AFM cases.
§ Median includes only those cases with pleocytosis (>5 white blood cells per cubic mm).

https://www.cdc.gov/mmwr/volumes/68/wr/mm6827e1.htm?s_cid=mm6827e1_w#F1_down accessed 7/10/19

TABLE 1. Demographic and clinical characteristics of patients with confirmed and probable cases of acute flaccid myelitis (AFM) and non-AFM cases, and timing to medical care and reporting to public health — United States, 2018

Laboratory finding					
Lumbar puncture	219/229 (96)	26/26 (100)	0.60	102/111 (92)	0.21
Pleocytosis	180/207 (87)	26/26 (100)	0.05	46/88 (52)	<0.001
Median, cells/mm³ (range, IQR)	92 (6–814, 42–158)	42 (7–730, 16–128)	0.01	53 (7–920, 27–146)	0.19
Spine MRI performed	231/232 (99)	25/26 (96)	0.19	109/114 (96)	0.02
Clinical illness					
Upper limbs only	98/233 (42)	6/26 (23)	0.09	12/115 (10)	<0.001
Lower limbs only	31/233 (13)	8/26 (31)	0.04	30/115 (26)	0.004
In the 4 weeks before onset of limb weakness					
Any illness	219/229 (96)	25/26 (96)	1.00	85/108 (79)	<0.001
Any respiratory illness	184/222 (83)	18/26 (69)	0.11	54/109 (50)	<0.001
Any fever	170/217 (78)	19/24 (79)	1.00	46/101 (46)	<0.001
Any respiratory illness or fever	214/233 (92)	24/26 (92)	1.00	71/115 (62)	<0.001
Any gastrointestinal illness	80/225 (36)	9/26 (35)	1.00	42/108 (39)	0.63
Hospitalized	227/231 (98)	26/26 (100)	1.00	113/115 (98)	1.00
ICU	127/210 (60)	12/21 (57)	0.82	54/107 (50)	0.09

https://www.cdc.gov/mmwr/volumes/68/wr/mm6827e1.htm?s_cid=mm6827e1_w#F1_down accessed 7/10/19

TABLE 1. Demographic and clinical characteristics of patients with confirmed and probable cases of acute flaccid myelitis (AFM) and non-AFM cases, and timing to medical care and reporting to public health — United States, 2018

Timing of preceding illness to onset of limb weakness, median days (range, IQR)					
Any illness	5 (0–27, 2–8)	4 (0–19, 2–10)	0.84	5 (0–28, 2–10)	0.78
Any respiratory illness	5 (0–27, 3–8)	4 (0–19, 3–11)	0.67	6.5 (0–28, 3–11.5)	0.63
Any fever	3 (0–21, 1–5)	3 (0–19, 1.5–8.5)	0.25	4 (0–28, 1–7)	0.12
Any respiratory illness or fever	5 (0–27, 2–7)	3 (0–19, 2–11)	0.77	5 (0–28, 2–10)	0.40
Any gastrointestinal illness	2.5 (0–23, 1–7)	4 (0–17, 2–5)	0.61	4 (0–19, 1–6.5)	0.22
Timing from onset of limb weakness to medical care, specimen collection, and reporting to public health, median days (range, IQR)					
Hospitalization	1 (0–54, 0–2)	3 (0–8, 1–4)	0.03	1 (0–62, 0–3)	0.48
Lumbar puncture	2 (0–31, 1–3)	4 (0–30, 1–7)	0.03	2 (0–140, 1–5)	0.05
MRI	2 (0–164, 1–3)	4 (0–12, 2–7)	0.02	3 (0–113, 1–8)	0.002
Specimen collection					
CSF	2 (0–31, 1–4)	7 (2–19, 6–11)	0.01	5 (0–63, 2–9)	0.09
Respiratory	3 (0–35, 2–6)	13 (2–65, 6–21)	0.004	6 (1–66, 3–11)	0.03
Serum	4 (0–31, 2–7)	9 (3–65, 6–19)	0.007	8.5 (1–64, 5–14)	<0.001
Stool	7 (0–44, 4–11)	13 (2–65, 6–17)	0.13	8 (0–65, 6–14)	0.33
Completion of patient summary form	8.5 (1–175, 4–25)	14 (4–105, 8–23)	0.10	20 (0–277, 9–56)	<0.001
CDC notified	18 (0–208, 7–35)	18.5 (4–111, 12–26)	0.75	36 (1–282, 14–70)	0.003

https://www.cdc.gov/mmwr/volumes/68/wr/mm6827e1.htm?s_cid=mm6827e1_w#F1_down accessed 7/10/19

Organisms Recovered

	CSF	Resp	Stool	Total
EV- or RV-positive no. (%)	2 (10)	31 (53)	17 (38)	50
Subtype, no. (%) positive†				
EV-A71	1 (50)	10 (32)	10 (59)	21 (42)
EV-D68	1 (50)	13 (42)	1 (6)	15 (30)
EV-D68/PeV-A6	0 —	1 (3)	0 —	1 (2)
RV-A38	0 —	1 (3)	0 —	1 (2)
RV-A101	0 —	1 (3)	0 —	1 (2)
RV-A24/PeV-A6	0 —	1 (3)	0 —	1 (2)
RV-A81	0 —	1 (3)	0 —	1 (2)
RV-A54	0 —	1 (3)	0 —	1 (2)
CVA2	0 —	0 —	1 (6)	1 (2)
CVA4	0 —	0 —	1 (6)	1 (2)
CVA9	0 —	0 —	1 (6)	1 (2)
CVA16	0 —	0 —	1 (6)	1 (2)
PeV-A1	0 —	0 —	1 (6)	1 (2)
Nontyped EV/RV	0 —	2 (6)	1 (6)	3 (6)

Abbreviations: CSF = cerebrospinal fluid; CVA = Coxsackie A virus; PeV-A6 = parechovirus A6.

McKay SL, Lee AD, Lopez AS, et al. Increase in Acute Flaccid Myelitis — United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:1273–1275. DOI: http://dx.doi.org/10.15585/mmwr.mm6745e1

Presentation in Japanese Patients

- 59 patients (1 with probable AFM); 8-12/2015
  - 7/20 positive with EV-D68 (3 resp, 3 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%

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***
- WNV
- ***EV-A71***
- EV-D70
- Coxsackievirus A16 (CSF – 1 case)
- Japanese Encephalitis
- Hopkin's Syndrome (AFP following asthma)
- ***EV-D68***

Polio Virus

- Two types of Polio Virus
  - WT = wild type
    - 3 strains; only WT1 since 2012
  - cVDPV = circulating vaccine-derived poliovirus
- In 1988, polio was endemic in 125 countries, sickening and paralyzing 350,000 children
- Total of 32 reported cases of WTPV in Afganistan and Pakistan during 2018
- Impacts primarily children <5 yo

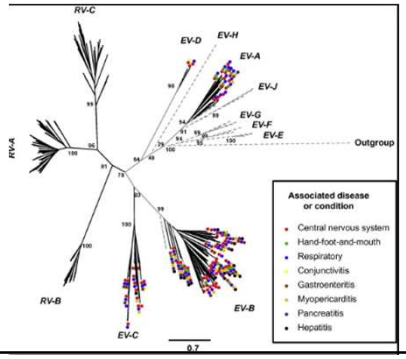
Polio Virus

- No cases of polio in the USA since 1979
- Transmission is fecal-oral, contaminated food
- Clinical
  - Most people do not know they have it
  - Can present with fever, fatigue, headache, vomiting, stiffness, pain in limbs
  - 1-2% result in aseptic meningitis
  - 0.5% result in poliomyelitis
    - 5-10% of these die when respiratory muscles paralyzed
- None of the current AFM patients had stool positive for polio

Main Viral Findings in Recent AFM

- EV-D68
- EV-A71
  - Previously associated with brainstem encephalitis

Enterovirus/Rhinovirus Types



Tappare, C, et.al. Picornavirus and enterovirus diversity with associated human diseases Author links open overlay panel. Infections, Genetics and Evolution Volume 14, March 2013, Pages 282-293

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
- Dramatic increase in 2014 (1153 cases)
- 6 Clades
  - B1 is the clade associated with AFM, evolved in 2010

EV-D68 Virus

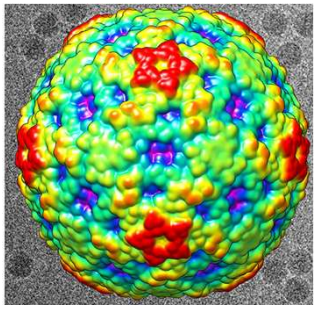
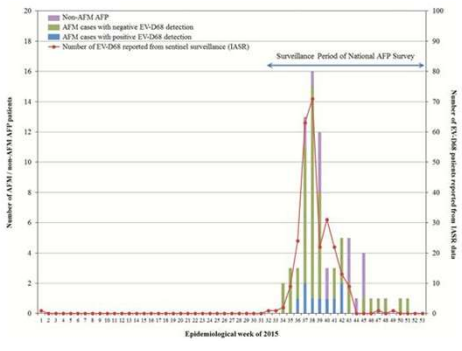


Image source: Yue Liu and Michael G. Rossmann, Purdue University
The publication of this study was by Yue Liu, Ju Sheng, Andrei Fokine, Geng Meng, Woong-Hee Shin, Feng Long, Richard J. Kuhn, Daisuke Kihara, Michael G. Rossmann (all at Purdue University)

Association of AFM, EV-D68

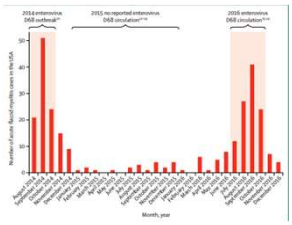
- Bradford Criteria
  - Strength
  - Specificity
  - Consistency
  - Specificity
  - Temporality
  - Biological Gradient
  - Plausibility
  - Coherence
  - Experiment
- 6 are fully met, 2 (specificity and strength) are partially met, and 1 (biological gradient) is minimally met

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



Cause

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



Enterovirus D68 and **acute flaccid myelitis**-evaluating the evidence for causality.
Messacar K, Asturias EJ, Hixon AM, Van Leer-Buter C, Niesters HGM, Tyler KL, Abzug MJ, Dominguez SR.
Lancet Infect Dis. 2018 Aug;18(8):e239-e247. www.thelancet.com/infection Vol 18 August 2018

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
- Respiratory monitoring
  - Negative inspiratory force
  - Forced vital capacity

Types of Treatment Used

- US (2012-2015)
  - IVIG – 74%
  - Plasmapheresis – 17%
  - IV Steroids – 58%
  - Antivirals – 5%
- Japan (2015)
  - IVIG – 19%
  - IV steroids – 15%
  - Steroids + IVIG – 59%
  - Plasmapheresis – 5%

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

Treatment

- Treatment decisions should be made in conjunction with neurology and infectious diseases experts
- Potential benefits of using corticosteroids for spinal cord edema or white matter involvement must be balanced by potential harm due to immunosuppression in the setting of a possible viral infection
- There is no indication for the use of other immunosuppressive agents in the management of AFM
- Fluoxetine is a selective serotonin reuptake inhibitor that demonstrates activity against enteroviruses
  - Both in a mouse model and retrospective case comparison of AFM patients, neither showed improvement of neurologic outcomes
  - There is no indication that fluoxetine should be used for the treatment of AFM
- For other anti-viral medications or interferon, there are currently no data to indicate benefit

Treatment

- Nerve transfers
  - **Nerve Transfers for Enterovirus D68- Induced Acute Flaccid Myelitis: A Case Series for the Treatment of a PolioLike Endemic.** Eliana Saltzman, et.al.
  - **A stepwise surgical algorithm using nerve transfers for the treatment of upper extremity acute flaccid myelitis** Erin L Weber, et.al.

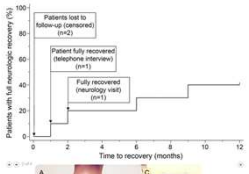
Outcome Study #1

- 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

Martin JA, et.al. Outcomes of Colorado children with acute flaccid myelitis at 1 year. Neurology July 11, 2017; 89(2)

Outcomes of Colorado Cases at 1 year

- 12 Cases
- KM plot
- Muscle atrophy



Martin JA, et.al. Outcomes of Colorado children with acute flaccid myelitis at 1 year. Neurology July 11, 2017; 89(2)

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 kids

Outcome Study #2

- 16 patients from Johns Hopkins
  - MRI showed improvement in spine
    - Worse in cervical, lumbar regions
  - No patient had complete functional recovery
    - 4 month f/u
    - 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

Gordono-Lipkin E, et.al. Comparative Quantitative clinical, neuroimaging, and functional profiles in children with acute flaccid myelitis at acute and convalescent stages of disease. Dev Med and Child Neur 2018

Outcome Study #3

- 14 children from CHOP
  - 5 from 2014, 9 from 2016
  - Evaluated in 2017
  - Of the 2014 group, 4/5 had significant improvement
  - Of the 2016 group, all have significant weakness

Hopkins S, et.al. Acute Flaccid Myelitis: Characteristics and Outcomes in 2014 and 2016 Clusters. Neurology Apr 2017 (S40.008)

Outcome Study #4

- 59 Cases from Japan (2015)
  - 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 Study #5

- 28 patients at Kaiser Permanente

Improvement	At discharge	Within 6 months	Within 12 months
None	4	0	0
Partial	24	19	16
Full Recovery	0	8	11

- Recovery not predicted by initial presentation
- At 12 months, 2 patients required a trach, 4 patients had a G-tube
- On death at less than 18 months from complications

Kane MS, Sonne C, Zhu S, Malhotra A, Van Haren K, Messacar K, Glaser CA. Incidence, Risk Factors and Outcomes Among Children With Acute Flaccid Myelitis: A Population-based Cohort Study in a California Health Network Between 2011 and 2016. The Pediatric Infectious Disease Journal. Volume 38 Number 7 July 2019

Additional Outcomes

- 2/5 ventilator dependent at 18 months
- Of 120 cases identified by CDC in 2014
  - 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

Kirolos A, et.al. Dev Med Child Neurol. 2018 Nov 12

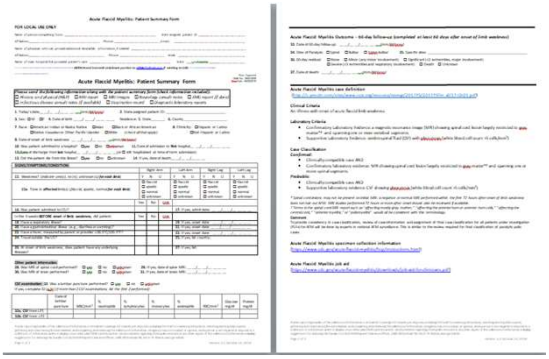
Prevention

- Vaccination against polio virus
- Avoid WNV with mosquito repellant
- Avoid enteroviruses by avoiding contact with sick people, good handwashing.
- New vaccines?
  - China has developed vaccine for EV-A71
- Anti-virals?
  - Enviroxime, Pirodivir, Pleconaril, Ribavirin, Rupintravir and guanidine

Future Directions

- Understand underlying mechanism of AFM
  - Viral vs. postviral
- Determining host risk factors
- Evaluate treatments (Antivirals, Immunosuppressants)
- Develop vaccines
- Determine long-term outcome

CDC Form for AFM



Acute Flaccid Myelitis: Patient Summary Form

Acute Flaccid Myelitis: Patient Summary Form

Acute Flaccid Myelitis Outcome – 60-day follow-up (completed at least 60 days after onset of limb weakness)

Acute Flaccid Myelitis case definition

Clinical Criteria

Laboratory Criteria

Case Classification

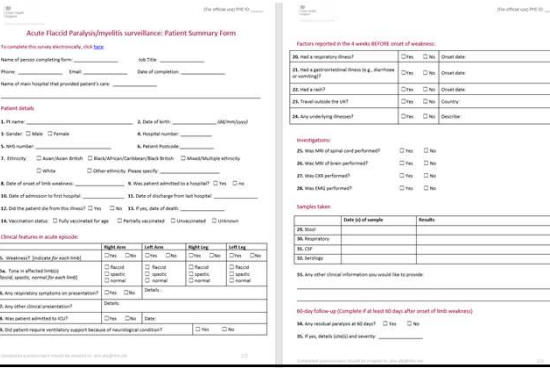
Confirmed

Probable

Acute Flaccid Myelitis specimen collection information

Acute Flaccid Myelitis job aid

Public Health England Form



Acute Flaccid Paralysis/myelitis surveillance: Patient Summary Form

To complete this survey electronically, click here

Name of person completing form: _____ Job Title: _____

Phone: _____ Email: _____ Date of completion: _____

Name of main hospital that provided patient's care: _____

Patient details

1. PI name: _____ 2. Date of birth: _____ (dd/mm/yyyy)

3. Gender: ☐ Male ☐ Female 4. Hospital number: _____

5. NHS number: _____ 6. Patient Postcode: _____

7. Ethnicity: ☐ Asian/Asian British ☐ Black/African/Caribbean/Black British ☐ Mixed/Multiple ethnicity

☐ White ☐ Other ethnicity. Please specify: _____

8. Date of onset of limb weakness: _____ 9. Was patient admitted to a hospital? ☐ Yes ☐ no

10. Date of admission to first hospital: _____ 11. Date of discharge from last hospital: _____

12. Did the patient die from this illness? ☐ Yes ☐ No 13. If yes, date of death: _____

14. Vaccination status: ☐ Fully vaccinated for age ☐ Partially vaccinated ☐ Unvaccinated ☐ Unknown

Clinical features in acute episode:

	Right Arm	Left Arm	Right Leg	Left Leg
15. Weakness? [Indicate for each limb]	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
15a. Tone in affected limb(s) [Flaccid, spastic, normal/for each limb]	☐ Flaccid ☐ spastic ☐ normal	☐ Flaccid ☐ spastic ☐ normal	☐ Flaccid ☐ spastic ☐ normal	☐ Flaccid ☐ spastic ☐ normal

16. Any respiratory symptoms on presentation? ☐Yes ☐No Details:

17. Any other clinical presentation? Details:

18. Was patient admitted to ICU? ☐Yes ☐No Date:

19. Did patient require ventilatory support because of neurological condition? ☐ Yes ☐ No

Factors reported in the 4 weeks BEFORE onset of weakness:

20. Had a respiratory illness?	☐Yes ☐ No	Onset date:
21. Had a gastrointestinal illness (e.g., diarrhoea or vomiting)?	☐Yes ☐ No	Onset date:
22. Had a rash?	☐Yes ☐ No	Onset date:
23. Travel outside the UK?	☐Yes ☐ No	Country:
24. Any underlying illnesses?	☐Yes ☐ No	Describe:

Investigations:

25. Was MRI of spinal cord performed? ☐ Yes ☐ No

26. Was MRI of brain performed? ☐ Yes ☐ No

27. Was CXR performed? ☐ Yes ☐ No

28. Was EMG performed? ☐ Yes ☐ No

Samples taken

	Date (s) of sample	Results
29. Stool		
30. Respiratory		
31. CSF		
32. Serology		

33. Any other clinical information you would like to provide:

_____

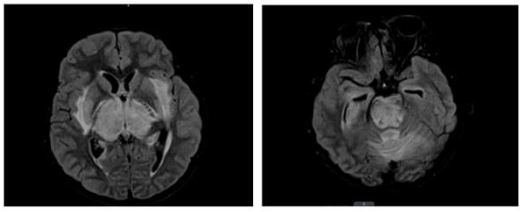
_____

60-day follow-up (Complete if at least 60 days after onset of limb weakness)

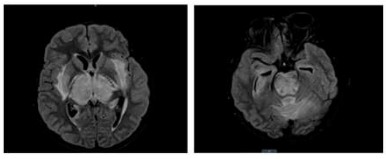
34. Any residual paralysis at 60 days? ☐ Yes ☐ No

35. If yes, details (site(s) and severity: _____

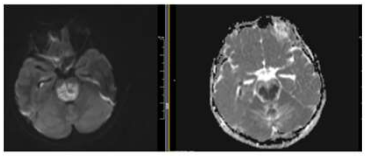
Impact of Flu



Flair images of Thalamus, Brain stem



Flair images of Thalamus, Brain stem



Diffusion weighted imaging and ADC image of brain stem

Vaccinate

References

- Council of State and Territorial Epidemiologists – 17-ID-01
- Greninger AL, et.al. A novel outbreak enterovirus D68 strain associated with acute flaccid myelitis cases in the USA (2012 – 2014): A retrospective cohort study. Lancet Infect Dis 2015; 15:671-82.
- Messacar, K, et.al. Acute Flaccid Myelitis: A clinical Review of US cases 2012-2015. Ann Neurol 2016; 80:326-338.
- Centers for Disease Control and Prevention. About acute flaccid myelitis. Available at: https://www.cdc.gov/acute-flaccid-myelitis/. Accessed 24 Dec 2018.
- McKay SL, Lee AD, Lopez AS, et al. Increase in Acute Flaccid Myelitis — United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:1273–1275. DOI: http://dx.doi.org/10.15585/mmwr.mm6745e1
- Jan A. Martin, Kevin Messacar, Michele L. Yang, John A. Maloney, Jennifer Lindwall, Terri Carry, Patricia Kenyon, Stefan H. Sillau, Joyce Oleszek, Kenneth L. Tyler, Samuel R. Dominguez, Teri L. Schreiner. Outcomes of Colorado Children with Acute Flaccid Myelitis at One Year. Neurology Jul 2017, 89 (2) 129-137;
- Messacar K, Schreiner TL, Maloney JA, et al. A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA. *Lancet* 2015;385:1662–1671.

References

- Shiyang Sun,Lianlian Bian,Fan Gao,Ruixiao Du,Yalin Hu,Ying Fu,Yao Su,Xing Wu,Qunying Mao,Zhenglun Liang. A neonatal mouse model of Enterovirus D68 infection induces both interstitial pneumonia and acute flaccid myelitis. **Antiviral Research.** Volume 161, January 2019, Pages 108-115
- Chong P., Kira R., Mori H., Okumura A., Torisu H., Yasumoto S., et al. (2018). Clinical features of acute flaccid myelitis temporally associated with an enterovirus D68 outbreak: results of a nationwide survey of acute flaccid paralysis in Japan, August-December 2015. *Clin. Infect. Dis.* 66 653–664. 10.1093/cid/cix860.
- Dyda A., Stelzer-Braid S., Adam D., Chughtai A., Raina MacIntyre C., Amalie D., et al. (2018). The association between acute flaccid myelitis (AFM) and *Enterovirus* D68 (EV-D68) – what is the evidence for causation? *Euro Surveill.* 23:17-00310. 10.2807/1560-7917.ES.2018.23.3.17-00310.
- Maloney J., Mirsky D., Messacar K., Dominguez S., Schreiner T., Stence N. (2015). MRI findings in children with acute flaccid paralysis and cranial nerve dysfunction occurring during the 2014 enterovirus D68 outbreak. *Am. J. Neuroradiol.* 36 245–250. 10.3174/ajnr.A4188

References

- Messacar K., Asturias E., Hixon A., Van Leer-Buter C. M., Niesters H., Tyler K., et al. (2018). Personal view enterovirus D68 and acute flaccid myelitis—evaluating the evidence for causality. *Lancet Infect. Dis.* 18 e239–e247. 10.1016/S1473-3099(18)30094-X
- Saltzman E., Vu A., Schwenker A., Raney S., Sneag D., Yakuboff K., et al. (2016). Nerve transfers for enterovirus D68-induced acute flaccid myelitis. *HAND* 11:97S. 10.1016/j.pediatrneurol.2018.07.018
- The Global Poliovirus Eradication Initiative [GPEI] (2018). *Global Polio Eradication Initiative.* Available at http://polioeradication.org/where-we-work/polio-endemic-countries/ [accessed December 24, 2018] 10.1136/practneurol-2017-001609
- World Health Organization [WHO] (2018). *Poliomyelitis.* Available at: http://www.who.int/mediacentre/factsheets/fs114/en/ [accessed December 24, 2018]
- Amir Kirolos, et.al**. Outcome of paediatric acute flaccid myelitis associated with enterovirus D68: a case series.** Dev Med and Child Neurol, First published: 12 November 2018. https://doi-org.proxy.hsl.ucdenver.edu/10.1111/dmcn.14096
- Messacar K, Abzug MJ, Dominguez SR. The changing epidemiology of acute flaccid paralysis warrants a paradigm shift in surveillance. *J Med Virol* 2018; 90: 1–2.

References

- Hixon AM, Yu G, Leser JS, et al. A mouse model of paralytic myelitis caused by enterovirus D68. *PLoS Pathog* 2017; 13: e1006199.
- Jamie Lopez Bernal, Ming Lim, Kevin Brown, Maria Zambon, Daniel Bradshaw, Nalini Iyanger, Jake Dunning, Shamez Ladhani, Richard Pebody, Mary Ramsay. Public Health England. **Clinical management of acute flaccid paralysis / acute flaccid myelitis (AFP/AFM).** Information for health professionals. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/766703/Treatment_of_AFP_information_for_healthcare_professionals.pdf [Accessed 12/24/18].
- Messacar K, Burakoff A, Nix WA, et al. *Notes from the Field:* Enterovirus A71 Neurologic Disease in Children — Colorado, 2018. MMWR Morb Mortal Wkly Rep 2018;67:1017–1018. DOI: http://dx.doi.org/10.15585/mmwr.mm6736a5.