Acute flaccid myelitis & enterovirus infections

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Objectives

- Acute flaccid paralysis vs. acute flaccid myelitis
- Enterovirus classification
- Polioviruses
- Non-polio enteroviruses & acute flaccid myelitis
  - Etiology and differential diagnosis
  - Epidemiology of recent outbreaks
  - Clinical manifestations
  - Diagnosis
  - Management
  - Outcome

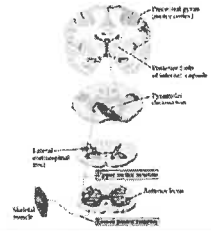
Acute flaccid paralysis versus acute flaccid myelitis

Acute flaccid paralysis
- Limb weakness due to any cause in neuromuscular axis
- Used as clinical case definition for polio eradication purposes
  - Designed to maximize sensitivity, particularly for low resource setting where polio may still be circulating

Acute flaccid myelitis
- Limb weakness caused by injury to the anterior horn cells of the spinal cord
- This subset of acute flaccid paralysis is typical for polioviruses and non-polio enteroviruses

Etiology of acute flaccid paralysis

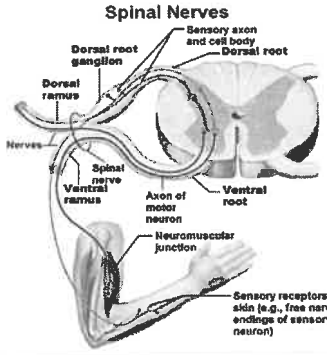
Lateral Corticospinal Tract



Acute myelopathy
Transverse myelitis
Focal [illegible]
Anterior horn cell
Poliovirus
Vaccine-associated paralytic poliomyelitis
[illegible]
Other viruses (Japanese encephalitis virus, West Nile virus, European tick-borne encephalitis virus, etc.)
Polyradiculoneuropathy
Guillain-Barré syndrome
Peripheral neuropathy
Infection related: diphtheria, tick bite paralysis, Lyme disease, relapsing fever
Chemical ingestion related: poisonous plants (type fruit of *Karwinskia humboldtiana* [coral cherry], [illegible] mercury [elemental Hg], chemicals [lead, arsenic, thallium], methylene [colchicine, ivermectin])
Neuromuscular junction
Myasthenia gravis
Botulism toxin
Tetanus toxin
Animal toxin (snake venom, shellfish poison, puffer fish tetrodotoxin)
Organophosphate poisoning
Muscle disorders
Polymyositis
Myositis (viral)
Hypokalemic periodic paralysis
Weakness associated with critical illness

Curr Infect Dis Rep 2018;20:34

Spinal Nerves



CDC case definition for acute flaccid myelitis

Confirmed case

- An illness with onset of acute flaccid limb weakness AND
- MRI showing spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments

Probable case

- An illness with onset of acute flaccid limb weakness AND
- CSF pleocytosis (WBC count >5 cells/mm^3)

https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definitions.html

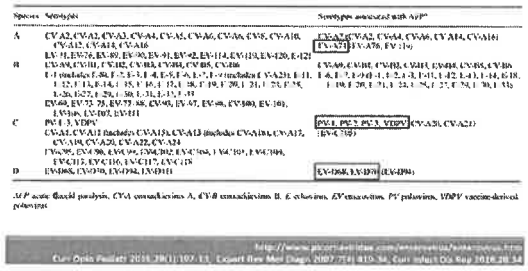
Etiology of acute flaccid myelitis

Enteroviruses
- Polioviruses 1, 2 and 3
  - Wild type poliomyelitis
  - Vaccine-derived poliomyelitis
- Non-polio enteroviruses (EV D68, EV A71 and others)

Arboviruses
- West Nile virus, Japanese encephalitis virus and other flaviviruses

Other viruses
- Herpes simplex virus
- Adenovirus

Enterovirus taxonomy and association with AFM



Species	Serotypes	Serotypes associated with AFM*
A	CV-A2, CV-A3, CV-A4, CV-A5, CV-A6, CV-A8, CV-A10, CV-A12, CV-A14, CV-A16	CV-A2, CV-A4, CV-A6, CV-A8, CV-A10, CV-A12, CV-A14, CV-A16
	EV-A71, EV-76, EV-89, EV-90, EV-91, EV-92, EV-114, EV-119, EV-120, E-121	EV-A71, EV-A76, EV-114
B	CV-A9, CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, CV-B6	CV-A9, CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, CV-B6
	E-1 (includes E-30, E-7, E-8, E-9, E-A, E-7, E-9 (includes E-CV-A21, E-11, E-12, E-13, E-14, E-15, E-16, E-17, E-19, E-20, E-21, E-25, E-33, E-50, E-52, E-53, E-54, E-55, E-69, EV-73, EV-74, EV-75, EV-77, EV-88, EV-93, EV-97, EV-98, EV-100, EV-101, EV-106, EV-B107, EV-B111	E-6, E-7, E-9 (E-1, E-2, E-3, E-11, E-12, E-13, E-14, E-18, E-19, E-20, E-21, E-24, E-25, E-27, E-29, E-30, E-33, E-53, E-54, E-55, E-69, E-73, E-74, E-75, E-77, E-88, E-93, E-97, E-98, E-100, E-101, E-106, E-107, E-111)
C	PV-1, 3, VDPV	PV-1, PV-2, PV-3, VDPV (CV-A20, CV-A21 (EV-C105))
	CV-A1, CV-A11 (includes CV-A13), CV-A13 (includes CV-A18), CV-A17, CV-A19, CV-A20, CV-A22, CV-A24	
	EV-C95, EV-C96, EV-C99, EV-C104, EV-C102, EV-C105, EV-C109*, EV-C110, EV-C113, EV-C116, EV-C117, EV-C118	
D	EV-D68, CV-D70, EV-D94, EV-D111	EV-D68, EV-D70 (EV-D94)

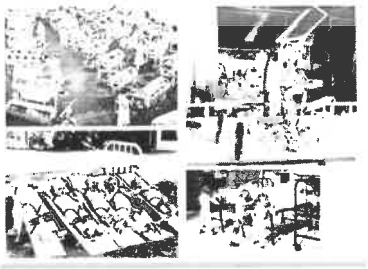
AFM acute flaccid paralysis, *CV-A* coxsackievirus A, *CV-B* coxsackievirus B, *E* echovirus, *EV* enterovirus, *PV* poliovirus, *VDPV* vaccine-derived poliovirus

http://www.picornavirus.com/enterovirus/classification.htm
Curr Opin Pediatr 2018;30(1):107-13. Expert Rev Mol Diagn 2007;7(4):419-34. Curr Infect Dis Rep 2018;20:34

Polioviruses

Clinical spectrum of poliovirus infection

Clinical syndrome	Frequency	Clinical manifestations
Inapparent infection	~95%	Asymptomatic
Abortive poliomyelitis	4 – 8%	Non-specific illness; fever, sore throat, headache, anorexia, vomiting
Non-paralytic poliomyelitis	1 – 2%	Typical features of aseptic meningitis; benign clinical course
Paralytic poliomyelitis	~0.1%	Biphasic clinical course; 2nd phase with meningeal irritation, myalgia, paresthesia, muscle weakness
Polio encephalitis	Rare	Predominantly in infants

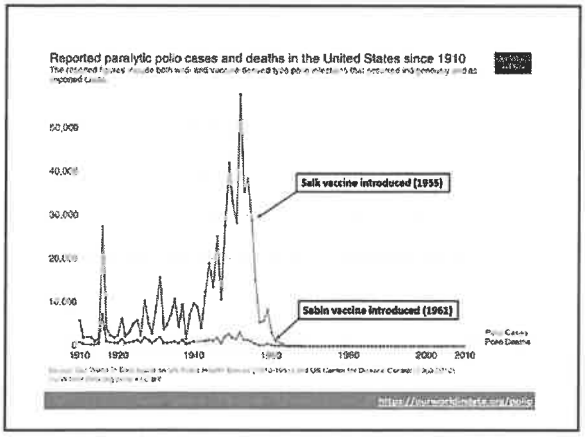


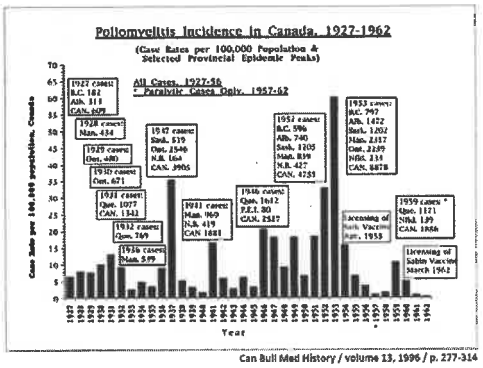
Who is this?

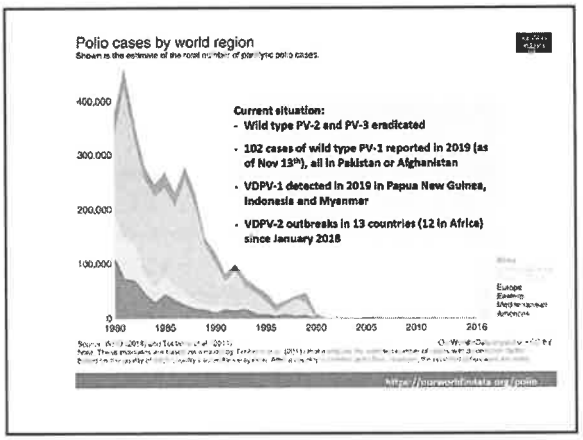
Albert Sabin, the oral polio vaccine

Polio vaccine lineups

Some pictures not printed in this slide







Vaccine-derived poliomyelitis

Classification
- Circulating VDPV (cVDPV)
- Immunodeficiency-associated VDPV (iVDPV)

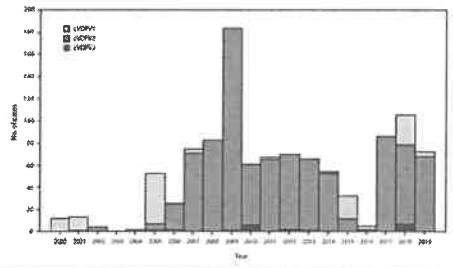
Pathogenesis
- Oral poliovirus can be excreted for up to 30-60 days in immunocompetent individuals
- Enhanced virulence acquired by mutation

VAPP incidence approximately 4.7 per 10^6 live births

Most often seen after first dose in the recipient or their close contacts

Epidemiol Infect 2017;145:413-9

Circulating vaccine-derived poliovirus outbreaks globally, 2000 – 2019



MMWR November 15, 2019 / Vol 68 / No. 45 / pp 1024-8

Polio eradication endgame

Goal one: eradication
- Interrupt wild poliovirus transmission
- Stop circulating vaccine-derived poliovirus outbreaks

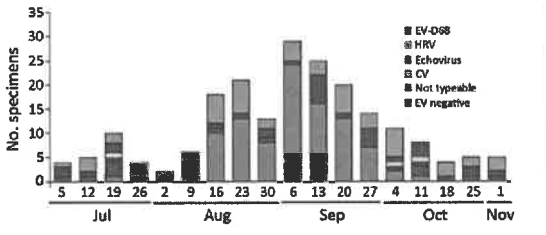
Goal two: integration
- Strengthen immunization and health systems to achieve and sustain eradication
- Ensure ongoing sensitive poliovirus surveillance
- Prepare and respond to future outbreaks and emergencies

Goal three: certification and containment
- Certify the eradication of wild poliovirus
- Contain all polioviruses

http://polioeradication.org/wp-content/uploads/2019/06/english-polio-endgame-strategy.pdf

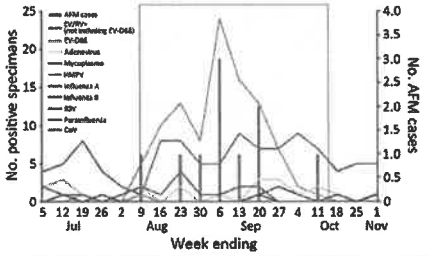
Non-polio enteroviruses

Respiratory isolate, ICU patients, 2014, Colorado



Emerg Infect Dis 2016;22(8):1387-94

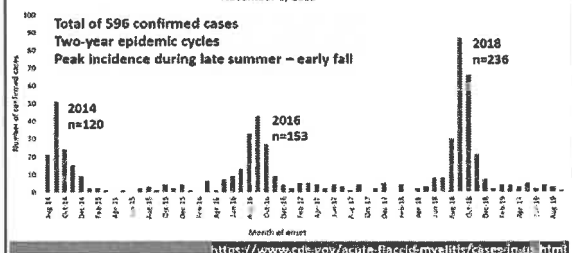
Pathogens isolated from AFM cases, 2014, Colorado



Emerg Infect Dis 2016;22(8):1387-94

AFM Epidemiology, United States (2014 – 2019)

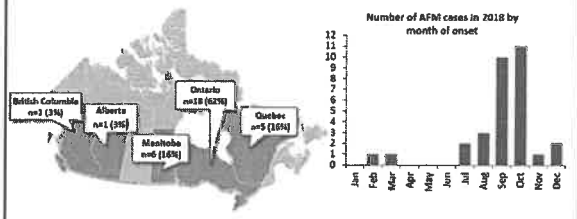
Number of confirmed U.S. AFM cases reported to CDC by month of onset, August 2014 - November 1, 2019 ***



https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

Pediatric AFM in Canada, 2018

31 cases in 5 provinces, July – Dec 2018



Yea et al. 2019 American Academy of Neurology Annual Meeting (ANN), May 4-10, 2019, Philadelphia, PA

Pediatric AFM in Canada, 2018
Microbiologic results

	Site	Positive/total samples
EV	CSF	1/29 (3%)
EV/RV	Respiratory tract	12/27 (44%)
EV-D68	Respiratory tract	6/27 (22%)
EV	Stool	1/15 (7%)

EV = enterovirus; RV = rhinovirus

Yea et al. 2019 American Academy of Neurology Annual Meeting (ANN), May 4-10, 2019, Philadelphia, PA

Does EV-D68 cause AFM and why now?

Association of EV-D68 with AFM in children is strong, consistent, and exhibits temporality

Mouse model evidence of EV-D68 neurovirulence

- Causes paralytic myelitis
- Loss of motor neurons from anterior horn region demonstrated
- EV-D68 isolated from spinal cord of paralysed mice transmits paralytic disease to naïve mice

In vitro evidence of neurovirulence

- Contemporary strains (compared to historic strains) have acquired ability for viral entry and replication in human neuronal cells
- EV-D68 has shared sequence homology, nucleotide substitutions with neurovirulent strains of poliovirus, EV-A71 and EV-D70

Lancet Infect Dis 2018;8(8):e239-e247. Viruses 2019 Sep 4;11(9). pii: E821. doi: 10.3390/v11090821. mBio 2018;9(5):e01954-18. mBio 2019;10(1):e02262-18. mBio 2019;10(4):e01903-19

Clinical manifestations of non-polio enterovirus infections

- Asymptomatic
- Non-specific febrile illness
- Exanthems/enanthems
  - Hand foot and mouth disease
  - Herpangina
  - Hemorrhagic conjunctivitis
- Respiratory tract infections
- Gastroenteritis
- Myopericarditis
- Hepatitis
- Neonatal sepsis
- Meningitis
- Encephalitis
  - Meningoencephalitis
  - Brainstem encephalitis
  - Chronic encephalitis with humoral immune deficiency
- Acute flaccid myelitis

Prodromal clues to non-polio enterovirus serotype

Prodromal illness	Common enterovirus causes
Respiratory illness with or without fever	EV-D68
Hand, foot and mouth disease ǂ	CV-A16, EV-A71
Herpangina §	CV-A, (CV-B)
Hemorrhagic conjunctivitis	EV-D70

ǂ HFMD can also be cause by other coxsackievirus A, some coxsackievirus B and echovirus strains
§ Herpangina can be caused by many different coxsackievirus A and B strains

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Clinical features of acute flaccid myelitis

Non-specific prodromal illness that is improving as neurologic manifestation develop
- Prodrome manifestations can be a clue to the enterovirus serotype

Neurologic symptom onset
- Typically 5-7 days after onset of prodromal illness
- Associated with recrudescence of fever
- Muscle pain (often precedes weakness onset)
- Meningeal manifestations (headache, stiff neck, back pain)
- Paresthesias

Curr Infect Dis Rep 2018;20:34; Clin Infect Dis 2016;63(6):737-45; Ann Neurol 2014;80(3):326-38; J Child Neurol 2017;32(3):301-7

Clinical features of acute flaccid myelitis

Acute onset of flaccid paralysis
- Hypotonia, hyporeflexia/areflexia
- Asymetric
- Proximal muscles affected more than distal muscles
- Variable severity
  - Number of limbs affected
  - Severity of weakness from minimal weakness to complete paralysis

Associated abnormalities
- Cranial nerve dysfunction (oculomotor, facial, bulbar weakness) in ~30%
- Sensory changes in ~20% (typically mild and transient)
- Encephalopathy in ~10%

Curr Infect Dis Rep 2018;20:34; Clin Infect Dis 2016;63(6):737-45; Ann Neurol 2014;80(3):326-38; J Child Neurol 2017;32(3):301-7

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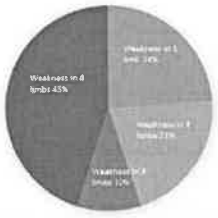
Pediatric AFM in Canada, 2018
Clinical features



rea et al. 2019 American Academy of Neurology Annual Meeting (ANN). May 4-10, 2019; Philadelphia, PA

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Laboratory findings

Cerebrospinal fluid
- Mild lymphocytic pleocytosis (~90%)
- Normal or slightly elevated protein (~40%)

Microbiological detection
- Rarely detected in CSF
- Best detected in non-sterile sites
  - EV-D68 best detected in nasopharyngeal swabs within 7 days of respiratory symptom onset
  - Polioviruses, EV-A71 best detected in stool, or rectal/oropharynx swabs

Curr Infect Dis Rep 2018;20:38. Clin Infect Dis 2016;63(6):737-45; Arch Pediatr 2010;17(3):326-30. J Child Neurol 2017;32(3):301-7

Treatment

Mainstay is supportive care
- Intensive care support when needed
- Aggressive physiotherapy and occupational therapy

Specific treatment modalities
- No convincing evidence for efficacy
- Intravenous immune globulin
- Antiviral medications
  - EV-specific medications (pocapavir, pleconaril, rupintrivir)
  - Fluoxetine
- Immune modulating treatments
  - Corticosteroids
  - Plasmapheresis

Neurology 2018;92(18):e2118-26; Antiviral Res 2016;131:83-5; PLoS 2016;5(1):53-62; J Infect Dis 2017;215(3):335-43

Motor outcome, SickKids 2018 cases (n=12)

Median follow-up 4 months (IQR 1.5 months) after disease onset

Graph not printed

Yea et al. 2019 American Academy of Neurology Annual Meeting (ANN), May 4-10, 2019, Philadelphia, PA

Picture not included

A. Atrophy of left proximal upper extremity and shoulder girdle 8 months after onset
B. Atrophy of proximal left arm and chest 11 months after onset
C. Inability to raise left arm 6 months after onset
D. Two-year old with asymetric atrophy of left leg and inability to bear weight 1.5 years after onset

Neurology 2017;89:129-37

Nerve transfer therapy

A potential option for patients with no recovery after 6-9 months

https://www.youtube.com/watch?v=KEEheUsxVRs

Picture not included

Conclusions

Non-polio enteroviruses, especially EV-D68 and EV-A71, currently the predominant causes of acute flaccid myelitis

Many unanswered questions

- Pathogenesis – direct infection vs. immune mediated
- Treatment – immune modulation versus antivirals
- Long term outcome
- The role of preventive vaccines