



University of California
San Francisco

Viruses and Acute Flaccid Myelitis



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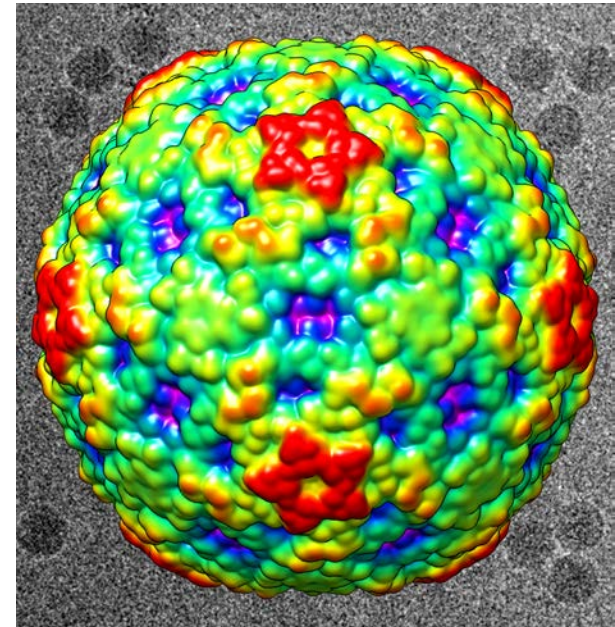
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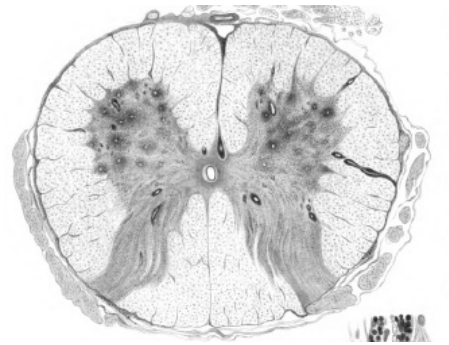
University of California, San Francisco

AFM Virtual Symposium, June 4th, 2020



Terminology

- **Acute Flaccid Paralysis**: clinical syndrome of acute onset focal weakness in any part of the body
 - Epidemiologic case definition used for poliovirus surveillance
 - Includes wide variety of infectious and non-infectious etiologies
- **Poliomyelitis** [*polios*=gray, *myelos*=marrow (spinal cord), *itis*=inflammation]: pathologic syndrome of spinal cord gray matter inflammation
 - Poliovirus subsequently named after syndrome
- As additional infectious causes identified, various terms used
 - poliomyelitis, “polio-like” paralysis, AFP with anterior myelitis, acute flaccid myelitis, etc.



Case Definition of Acute Flaccid Myelitis

- Epidemiologic Case Definition:

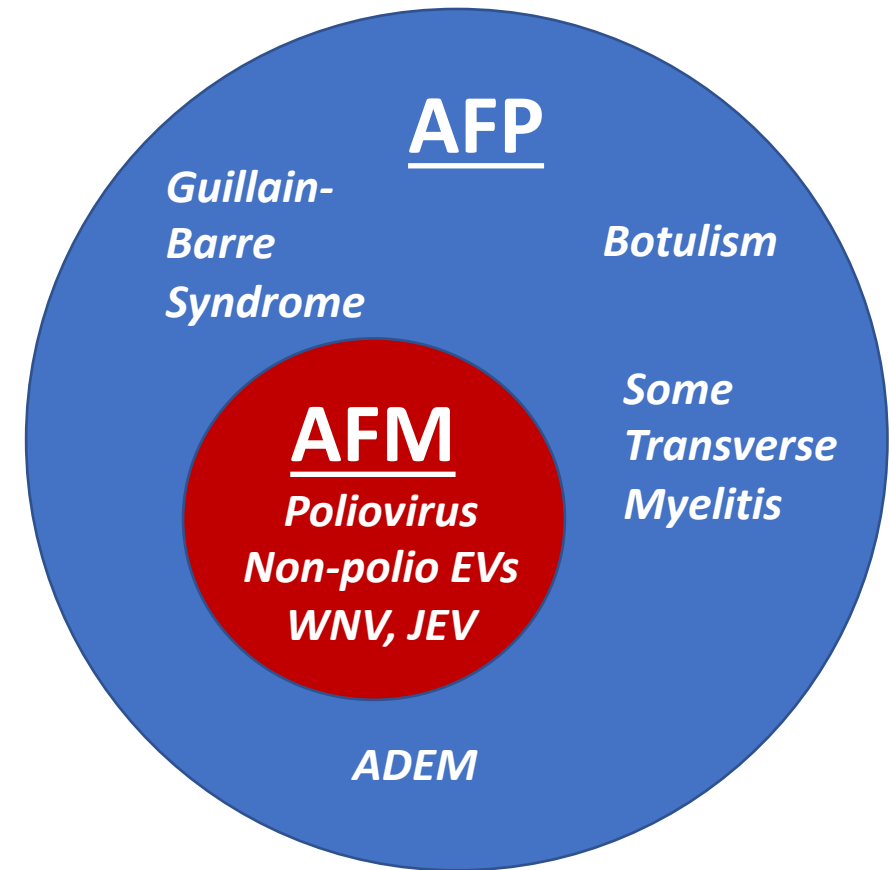
Clinical criteria: Acute onset flaccid limb weakness (AFP)

+ Imaging criteria: MRI with spinal cord lesion largely restricted to gray matter and spanning one or more spinal segments (confirmed)

or

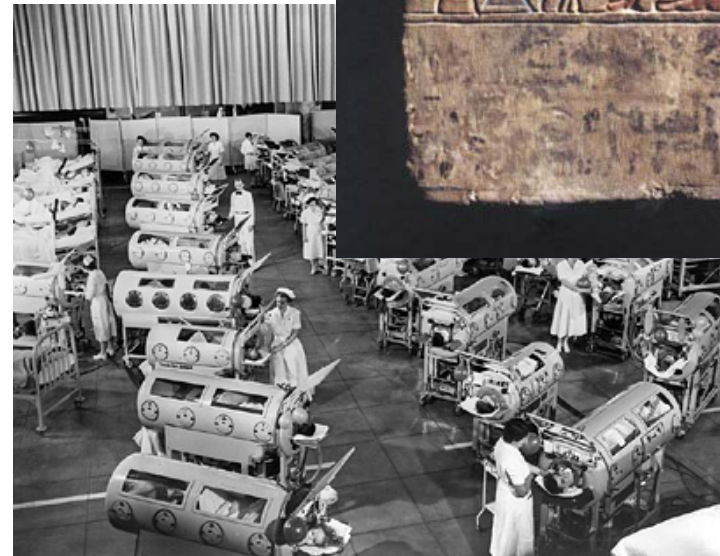
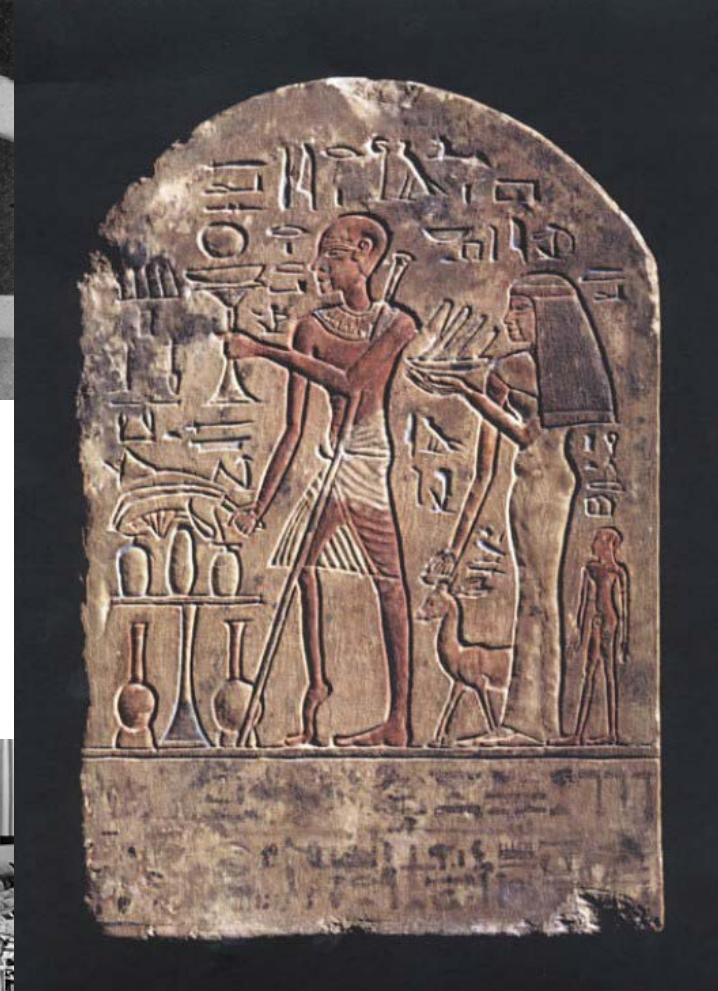
[+CSF pleocytosis: > 5 WBCs (probable)]

- AFM is a subset of Acute Flaccid Paralysis



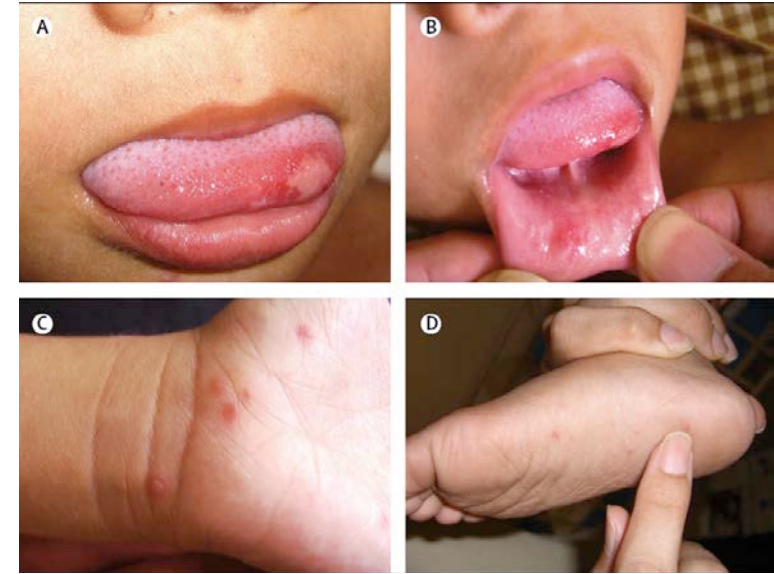
Poliomyelitis

- Primarily fecal-oral transmission
- Fewer than 1% infected get paralytic disease
- Prodromal fever and sore throat
- Progressive flaccid weakness, persists
 - Bulbar (2%), spinal (79%), bulbospinal (19%)
- Cerebrospinal fluid with mild lymphocytic pleocytosis, mildly elevated protein
- Detected in stool for weeks-months, **rarely in CSF (<1% of the time)**



Enterovirus A71 Myelitis

- Fecal-oral transmission
- Hand-foot-mouth disease often accompanies
- Brainstem and longitudinal anterior spinal cord lesions on MRI
- Flaccid limb weakness, most recover
- Detected in stool, skin lesions, **rarely in CSF**
- 1970s : epidemics in N. America, Europe, Africa, Australia; now endemic in Asia-Pacific
 - Taiwan 1998: 1.5 million infected, 405 with neurological disease



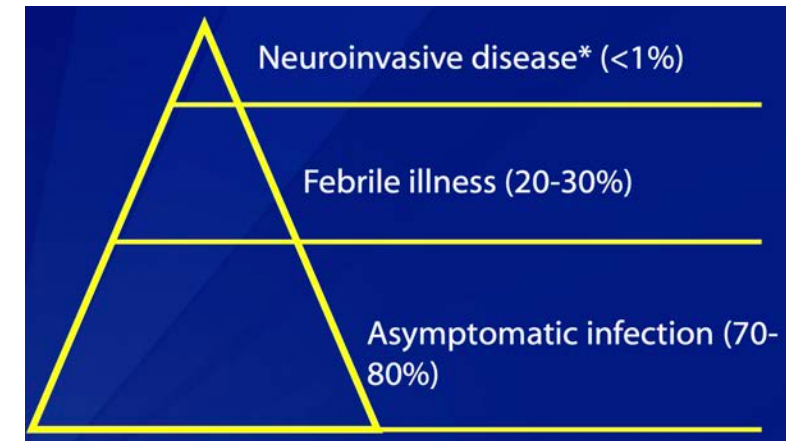
Ooi, M. H., et al. (2010). "Clinical features, diagnosis, and management of enterovirus 71." The Lancet Neurology 9(11): 1097-1105.

Solomon, T., et al. (2010). "Virology, epidemiology, pathogenesis, and control of enterovirus 71." Lancet Infect Dis 10(11): 778-790.

Hu, Y., et al. (2015). "Clinical Analysis of 134 Children with Nervous System Damage Caused by Enterovirus 71 Infection." Pediatr Infect Dis J 34(7): 718-723.

West Nile Virus Myelitis

- Flavivirus transmitted by mosquito; bird reservoir
 - Organ donation, transfusion alternate routes
- Arrived in North America 1999, endemic with seasonal epidemics (2002-3, 2012)
 - Leading cause of neuroinvasive arboviral disease in US
- 80% asymptomatic, <1% neuroinvasive disease
 - Neuroinvasive disease in adults more than children
- Longitudinal anterior myelitis with flaccid weakness
- **CSF typically negative by PCR at time of clinical presentation**
 - Neuroinvasive infection confirmed by detecting intrathecal antibody production (IgM)



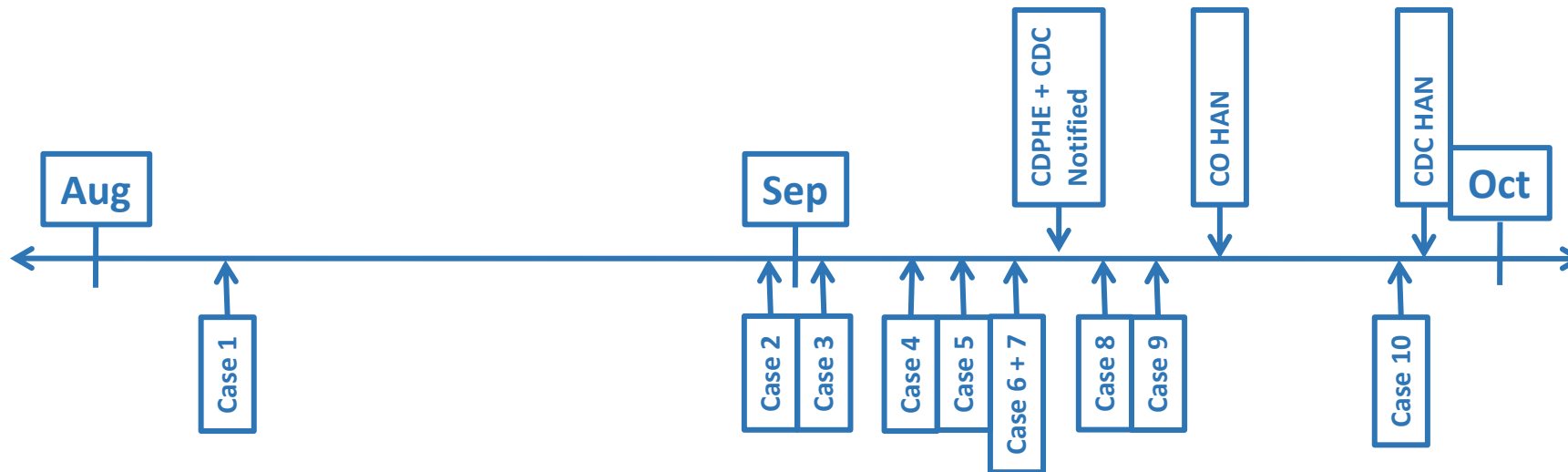
Powassan Virus Acute Flaccid Myelitis

- Neurotropic flavivirus spread by *Ixodes* ticks (same tick that carries *Borrelia burgdorferi*, the bacterium that causes Lyme disease)
- Fever, headache, “common cold” → rapidly progressive neurologic disease, including spastic and flaccid paralysis
- CSF lymphocytosis; **PCR often negative**; IgM serology to diagnose acute infection



2012-2014 “Outbreak” of Poliomyelitis-like Cases in the United States

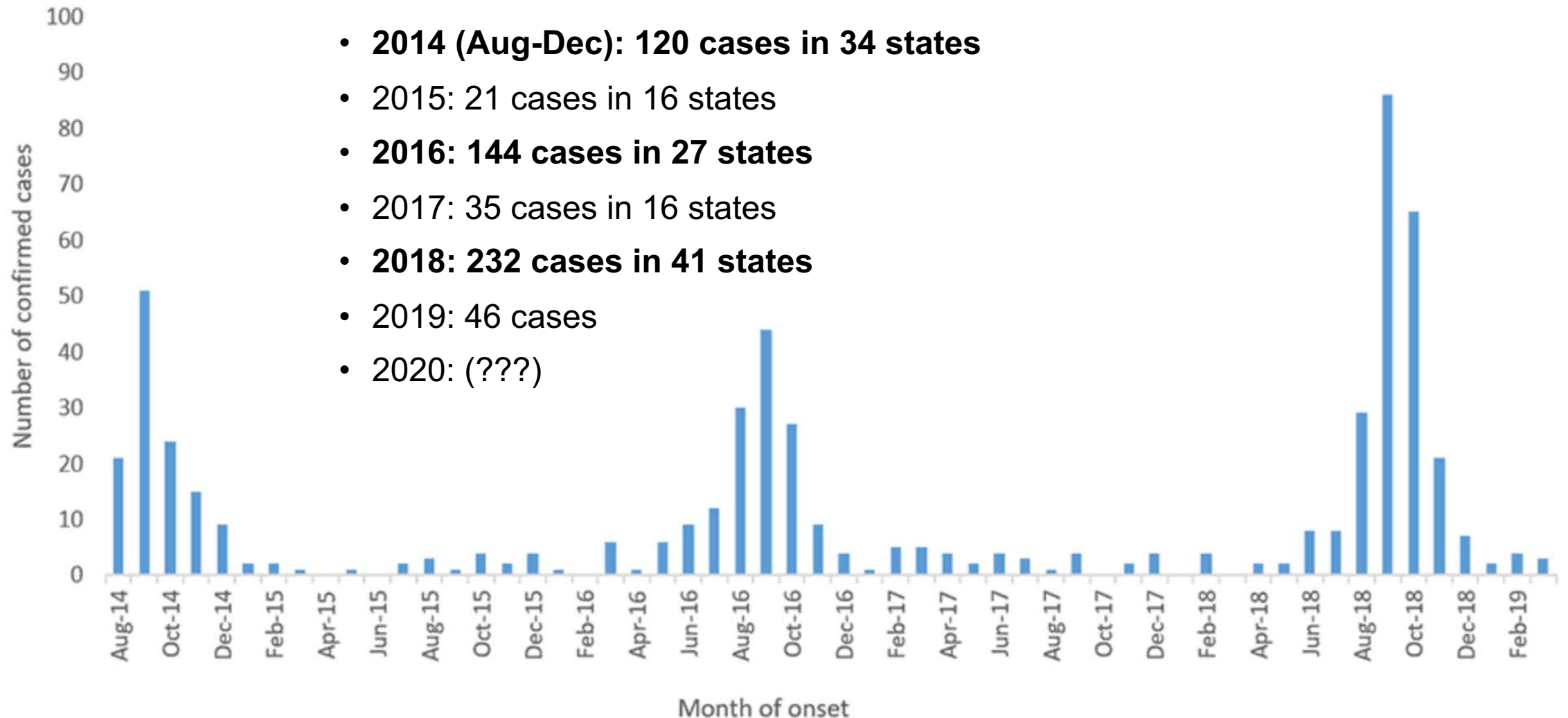
- Fall 2012: California Dept of Public Health received reports of unexplained paralysis requesting poliovirus testing (Dr. Carol Glaser, California Encephalitis Project)
 - CDPH instituted state-wide surveillance: acute onset flaccid limb weakness with MRI or EMG with anterior horn cell damage
- August 2014: Unusual cluster of similar paralysis cases in Colorado



Acute Flaccid Myelitis Surveillance in the United States: 2014-present

Number of confirmed U.S. AFM cases reported to CDC by month of onset,

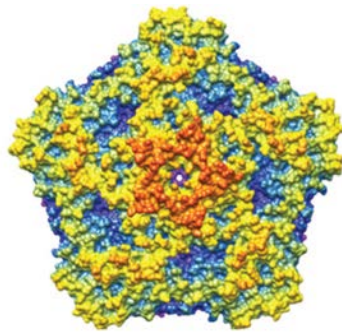
August 2014 - March 2019^{^*†}



AFM Etiology?

- No infectious agents of clinical significance identified in CSF
 - Including metagenomic next-generation sequencing
- No poliovirus in CSF, stool, rectal samples
- No WNV or other arboviruses detected
- In 2014 and 2016, EV-D68 most common pathogen detected from non-sterile sites (primarily respiratory)

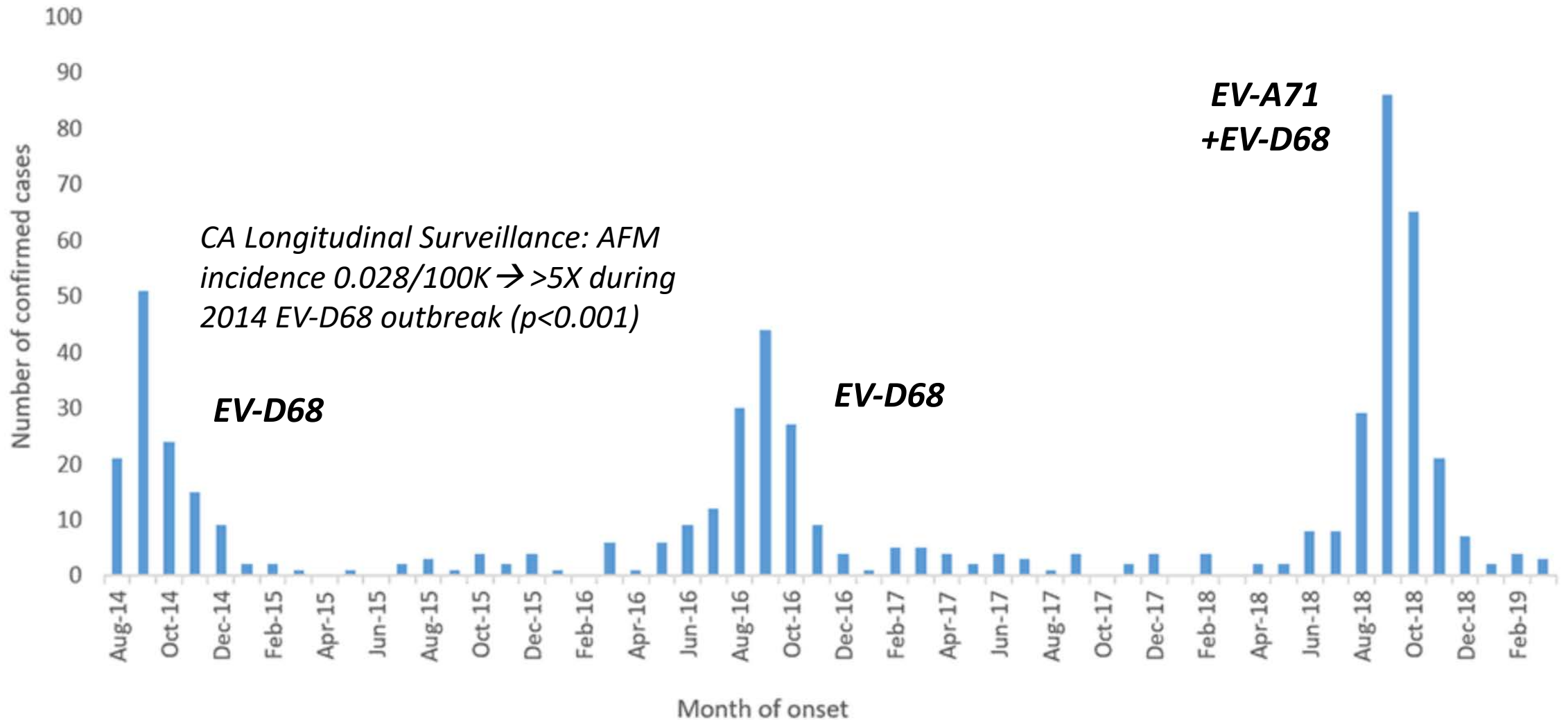
EV-D68



- Discovered 1962 in respiratory specimens from CA children with pneumonia
- Non-polio EV with biological and clinical properties similar to human rhinoviruses
- Grows at 33°C, acid labile
 - Transmitted by respiratory droplet, causes primarily respiratory disease
- 1970-2005: 26 cases of EV-D68 infection reported to National Enterovirus Surveillance System (NESS)
- 2008-2010: clusters of respiratory illness in Europe, Asia, US
- 2014: Largest, most widespread outbreak of EV-D68 respiratory disease in North America: 1153 confirmed infections in US

Is EV-D68 a Cause of AFM?

Number of confirmed U.S. AFM cases reported to CDC by month of onset,
August 2014 - March 2019^{^*†}



Is EV-D68 a Cause of AFM?

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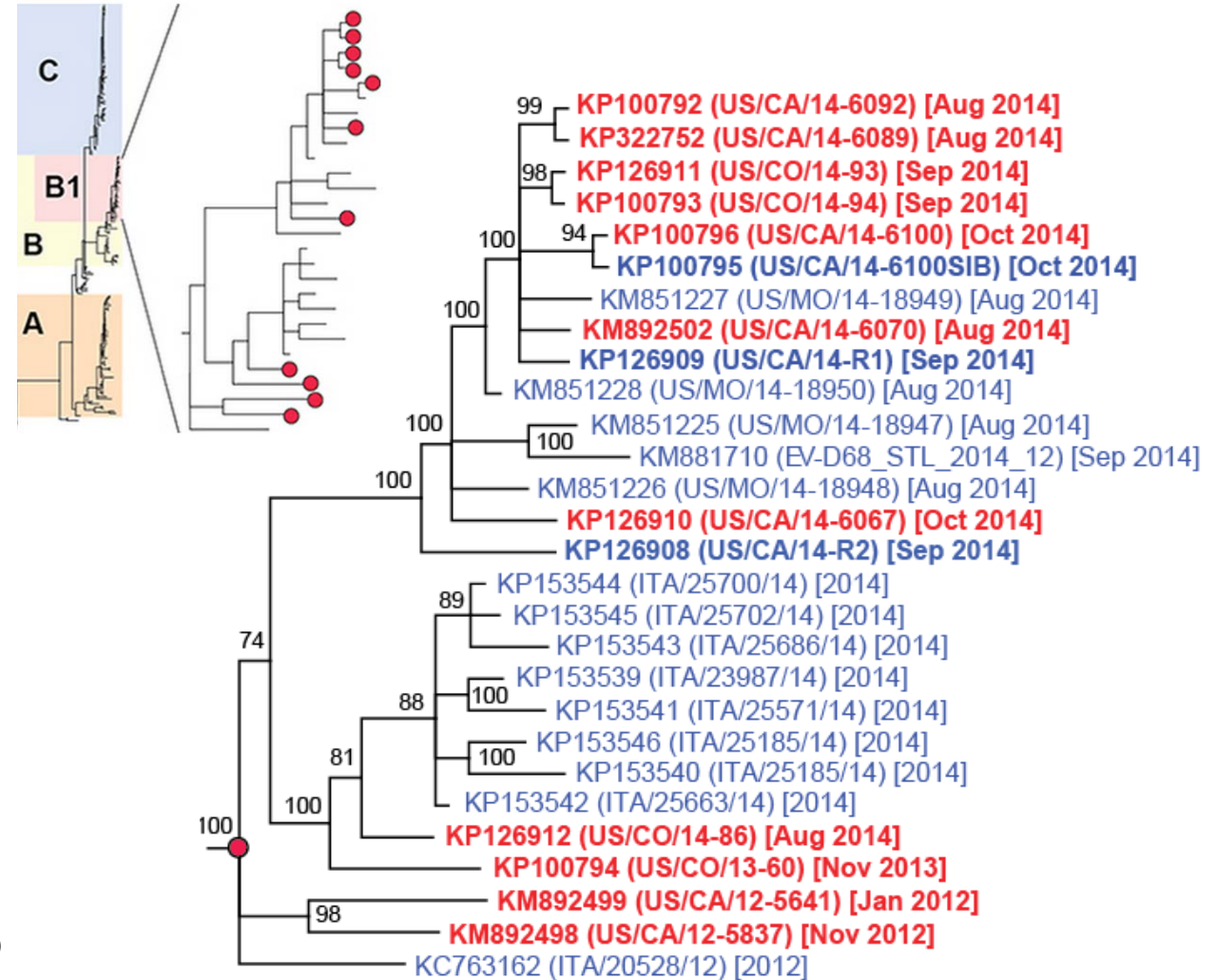
Next Article >

Articles

A novel outbreak enterovirus D68 strain associated with acute flaccid myelitis cases in the USA (2012–14): a retrospective cohort study

Alexander L Greninger, MD[†], Samia N Naccache, PhD[†], Kevin Messacar, MD, Anna Clayton, BSc, Guixia Yu, BSc, Sneha Somasekar, BSc, Scot Federman, BA, Doug Stryke, BSc, Christopher Anderson, BSc, Shigeo Yagi, PhD, Sharon Messenger, PhD, Debra Wadford, PhD, Dongxiang Xia, MD, James P Watt, MD, Keith Van Haren, MD, Samuel R Dominguez, MD, Carol Glaser, MD, Prof Grace Aldrovandi, MD, Dr Charles Y Chiu, MD

Cases with EV-D68 detected in respiratory secretions prior to paralysis onset; average 5-day prodrome



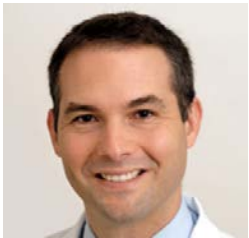
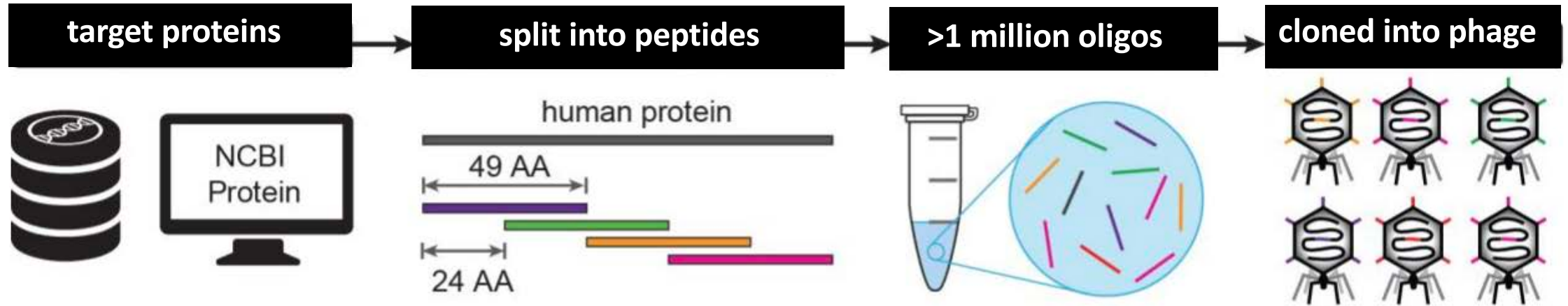
Is EV-D68 a Cause of AFM?

EV-D68 strain	Inoculation	Phenotype
Fermon (prototype strain)	IC	No clinical pathology (9/9)
Rhyne (prototype strain)	IC	No clinical pathology (10/10)
US/MO/14-18949	IC or IM	Limb paralysis (3/10)
US/IL/14-18956	IC	Limb paralysis (4/9); death (1/9)
Mock	IC	No clinical pathology (10/10)

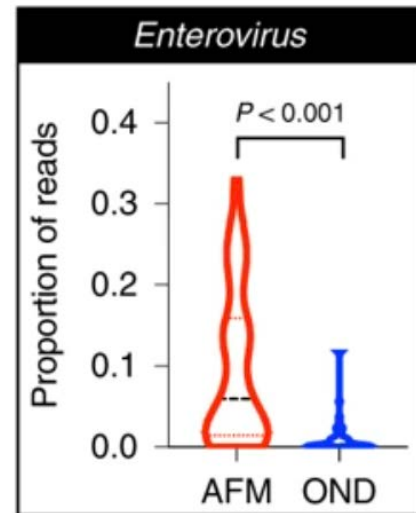


Hixon, A. M., et al. (2017). "A mouse model of paralytic myelitis caused by enterovirus D68." *PLoS Pathog* **13**(2): e1006199.

Pan-Viral Serology Implicates Enteroviruses in AFM



Michael
Wilson,
MD



OND ($\bar{x}_{AFM} - \bar{x}_{OND}$) AFM

Letter | Published: 21 October 2019

Pan-viral serology implicates enteroviruses in acute flaccid myelitis

Ryan D. Schubert, Isobel A. Hawes, [...] Michael R. Wilson

Nature Medicine 25, 1748–1752(2019) | [Cite this article](#)

6869 Accesses | 7 Citations | 587 Altmetric | [Metrics](#)

Host Response Profiling of Spinal Fluid Discriminates Enterovirus Signatures in Acute Flaccid Myelitis

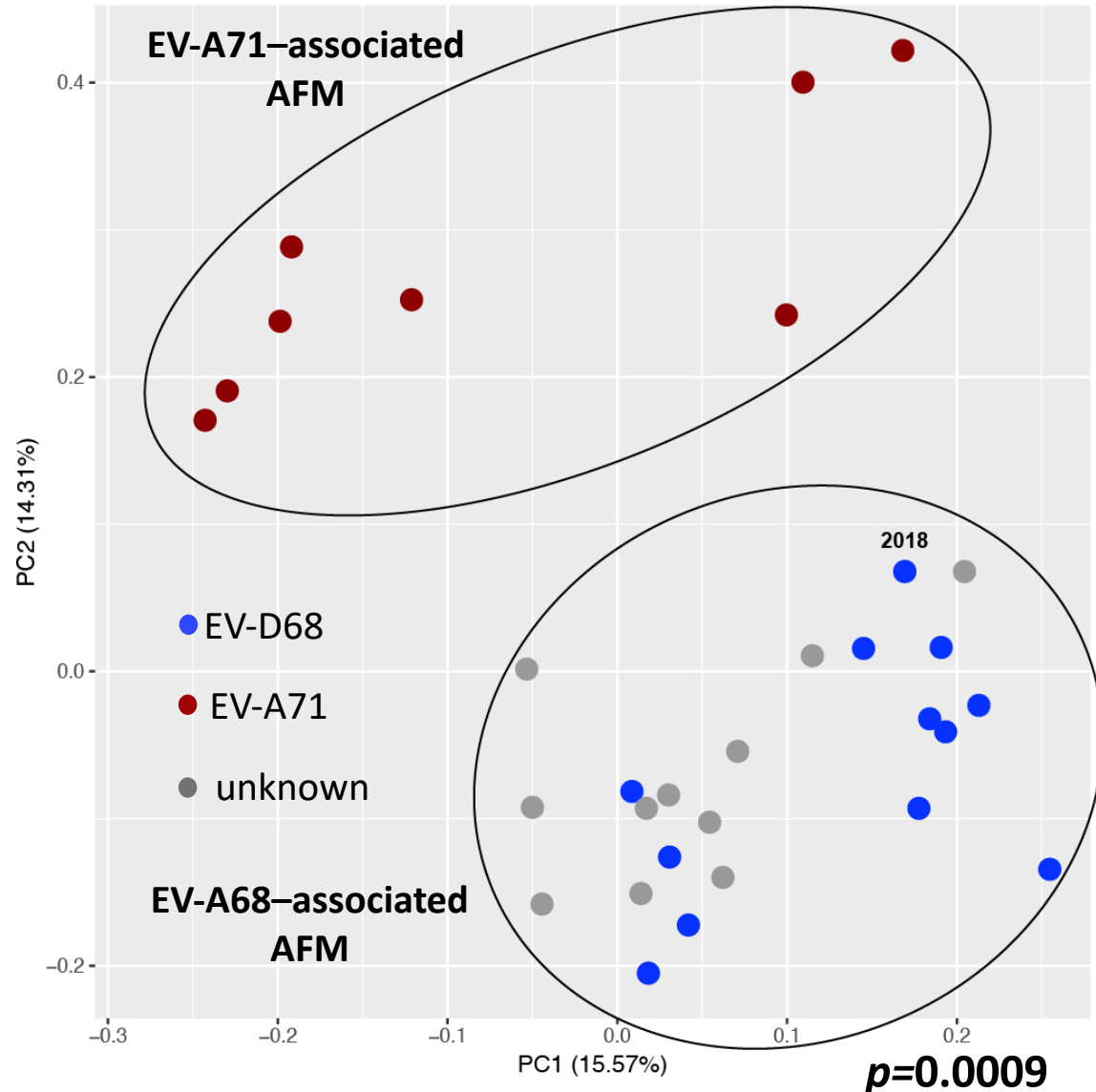
Top Differentially Expressed Pathways (n=490 DEGs)



Benjamin Briggs, MD, PhD



Yale Santos, MS



negative regulation of cell fate commitment
spinal cord association neuron differentiation
negative regulation of cell differentiation
negative regulation of cell fate specification
negative regulation of neurogenesis
negative regulation of gastrulation
negative regulation of nervous system development
dorsal spinal cord development
negative regulation of multicellular organismal process
negative regulation of developmental process
negative regulation of cell development
positive regulation of endoplasmic reticulum calcium ion concentration
regulation of transcription involved in primary germ layer cell fate commitment
negative regulation of neuron differentiation
regulation of gene expression
regulation of cell fate commitment
regulation of cell fate specification
positive regulation of neural precursor cell proliferation
olfactory pit development
dorsal/ventral pattern formation
epithelial cell differentiation
neurogenesis
negative regulation of necrotic cell death
central nervous system neuron differentiation

Briggs, Santos, et al., 2020 (manuscript in preparation)

SARS-CoV-2 and Neurological Illness?

- 14-year-old boy from San Francisco Bay Area
- Presented with new-onset generalized tonic-clonic seizures in mid-March 2020
- On admission, WBC $14.5 \times 10^9/L$, CXR with peribronchial thickening
- Brain MRI unremarkable
- Over days 2-3 of admission, clinical status worsened: orofacial dyskinesia, speech impairment, altered mental status, new focal seizures
- LP day 3 – WBC 117 with lymphocytic predominance
- Tested positive for SARS-CoV-2 on NP swab in March 2020, day 1 and day 10
- Extensive testing for other bacterial, fungal, viral etiologies negative
- CSF PCR testing negative for SARS-CoV-2
- CSF positive for NMDA-receptor antibody (1:160)
- SARS-CoV-2 IgG antibody testing – day 3 negative, day 19 positive
- Treated with immunomodulatory therapy and improved

Presumptive Dx: **COVID-19 triggered autoimmune encephalitis**

The impact of COVID-19 pandemic on enterovirus circulation and AFM



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