Acute Flaccid Myelitis –

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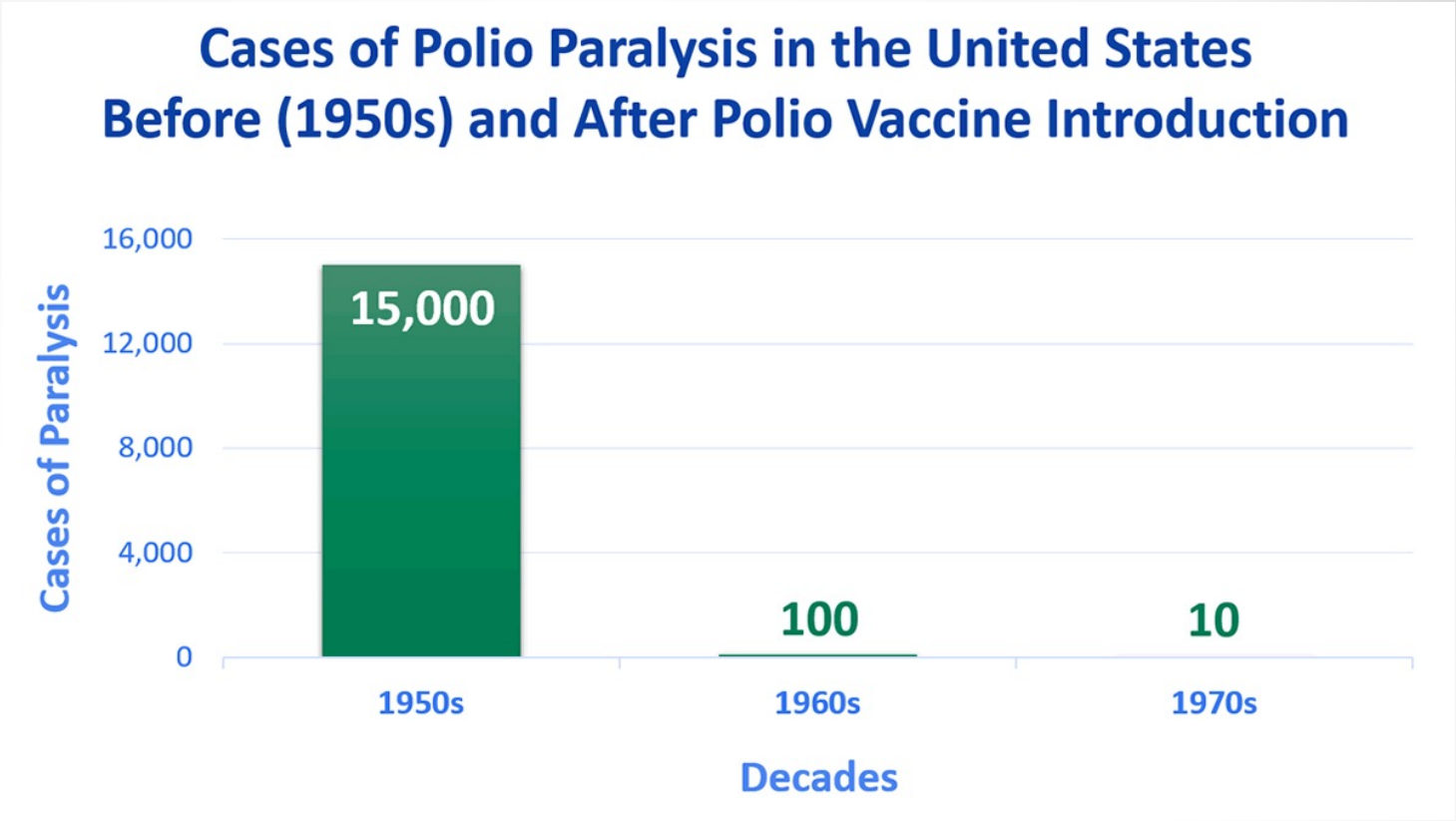
Disclosures

- MA Department of Public Health - AFM Consultant
- CDC AFM Task Force member
- AFM natural history study – site PI and case adjudication committee

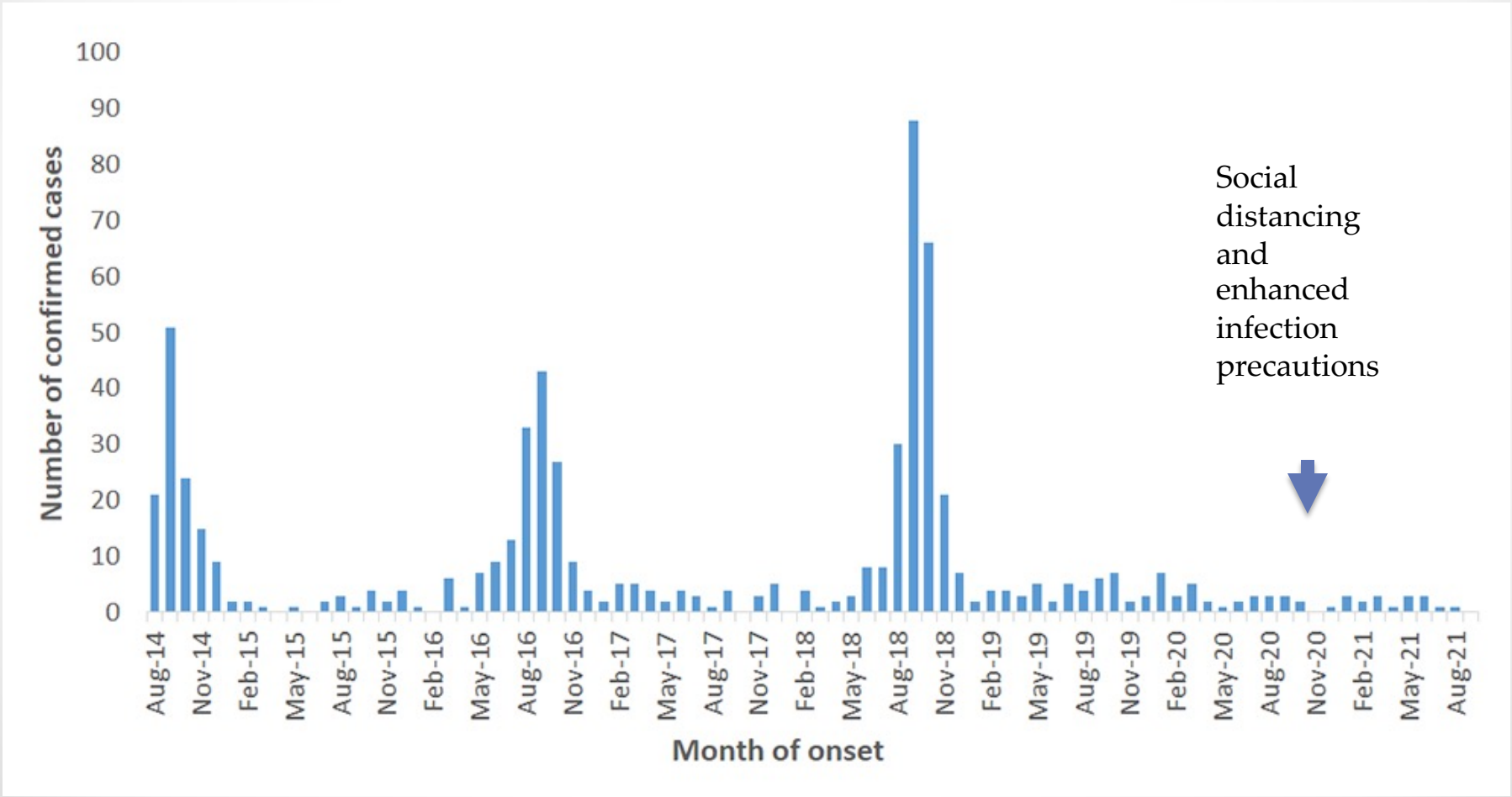
- Unrelated financial disclosures:
  - Site PI on an Alexion clinical trial
  - Roche Operetta I and II trials in multiple sclerosis
  - Vaccine injury compensation program

History



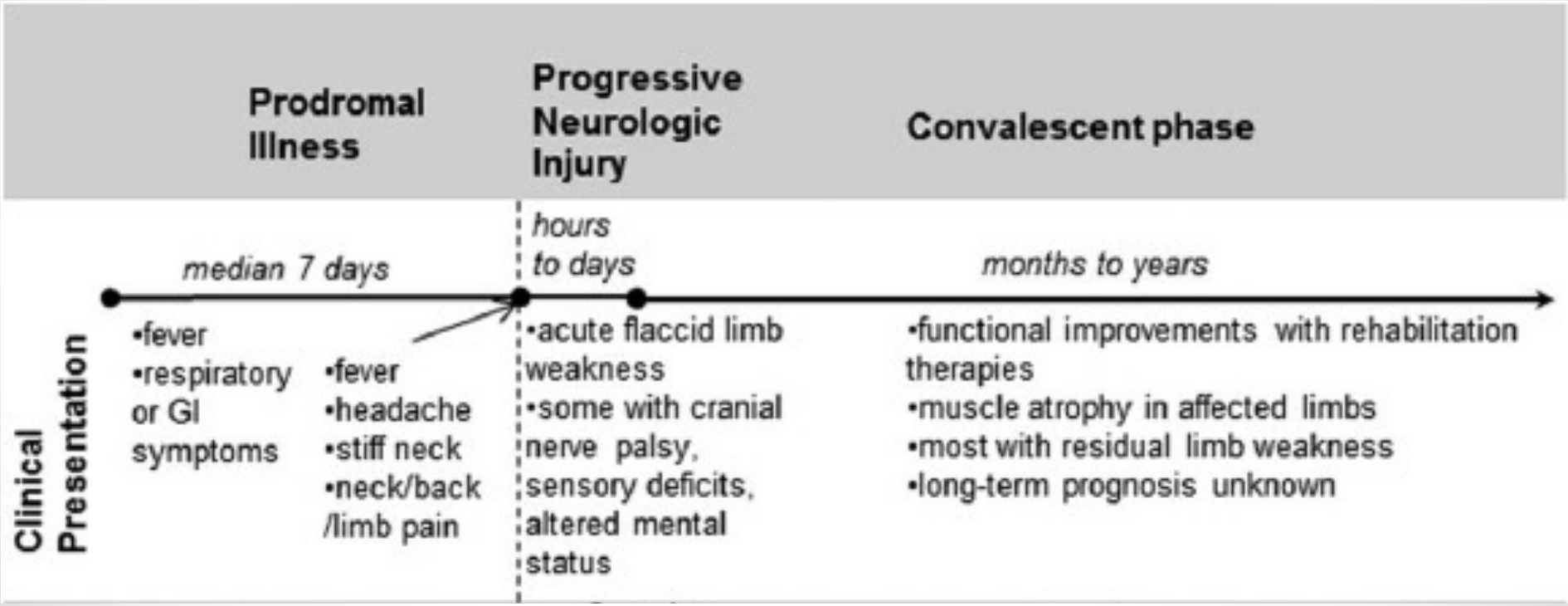
- Fall 2012 – CA surveillance and publications
- Fall 2014 – sudden increase recognized
  - Acute
  - flaccid
  - myelitis

CDC Monitoring



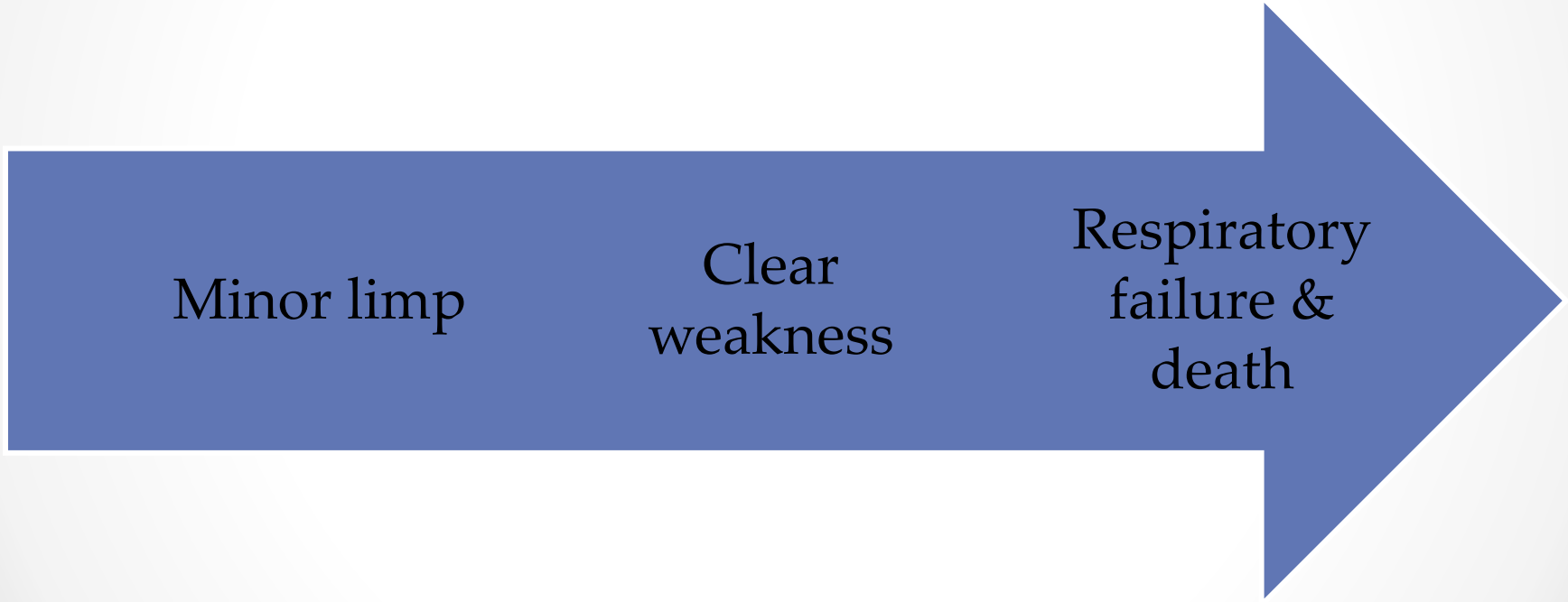
https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

Symptoms and Course



Messacar, et al. Ann Neurology. 2016

Spectrum of Disease

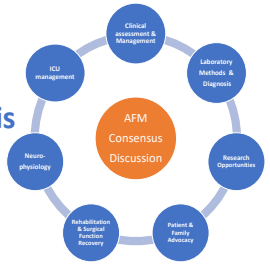


Clinical vs Epidemiologic Diagnosis

- No diagnostic biomarker
- CDC definitions are for reporting and epidemiologic study
  - https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definitions.html
- Clinical and research criteria

A Consensus on Clinical Diagnosis of Acute Flaccid Myelitis 2021

Acute Flaccid Myelitis Working Group



Diagnostic items	Definite	Probable	Possible	Uncertain
H1: Acute onset of limb(s) weakness (period from onset to nadir: hours to 10 days)	P	P	P*	P
H2: Prodromal fever or illness†	P/A	P/A	P/A	P
E1: Weakness involving one or more limbs, neck, face, or cranial nerves	P	P	P*	P
E2: Decreased muscle tone in at least one weak limb	P	P	P/A	P
E3: Decreased or absent deep tendon reflexes in at least one weak limb‡	P	P	P/A	P
MRI: Spinal cord lesion with predominant grey matter involvement, with or without nerve root enhancement§	P	P	P	ND
CSF: Pleocytosis (white cell count >5 cell/L)¶	P	A or ND	P/A or ND	P/A or ND

Factors that might suggest an alternative diagnosis

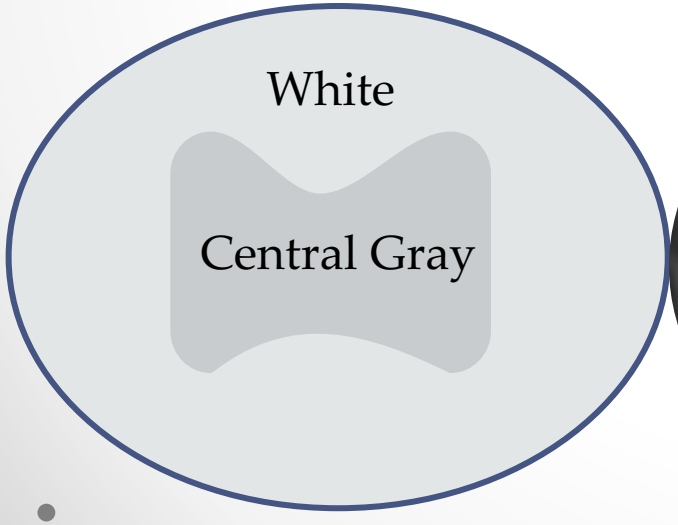
1. Encephalopathy that cannot be explained by fever, illness, respiratory distress, metabolic abnormalities, or medications
2. Presence of sensory deficits on examination||
3. Presence of lesions in supratentorial white matter or cortex, which should prompt consideration of ADEM, MOG-antibody associated disease, neuromyelitis optica spectrum disorder, encephalomyelitis, and others
4. Absence of CSF pleocytosis, which should prompt consideration of Guillain-Barré syndrome, botulism, ischaemic cord lesions, and others
5. Positive serum aquaporin-4 (AQP-4) antibody, which would exclude AFM
6. Positive serum MOG antibody, which would suggest MOG-antibody associated disease||

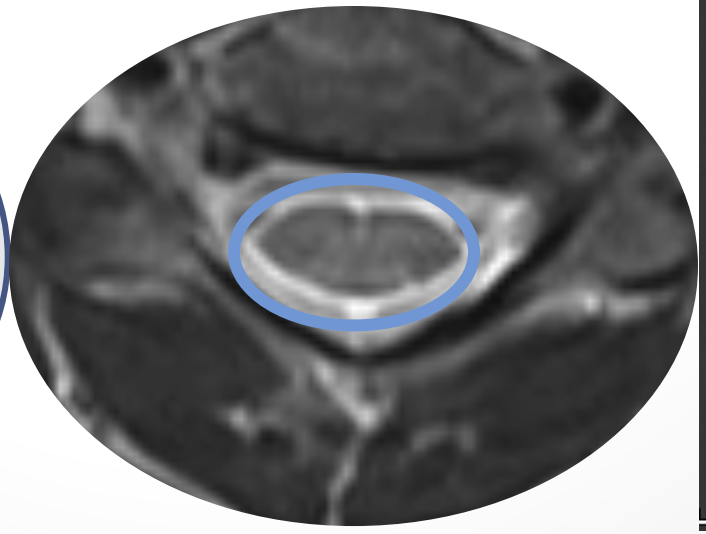
Acute flaccid myelitis: cause, diagnosis, and management

Lancet 2021; 397: 334-46

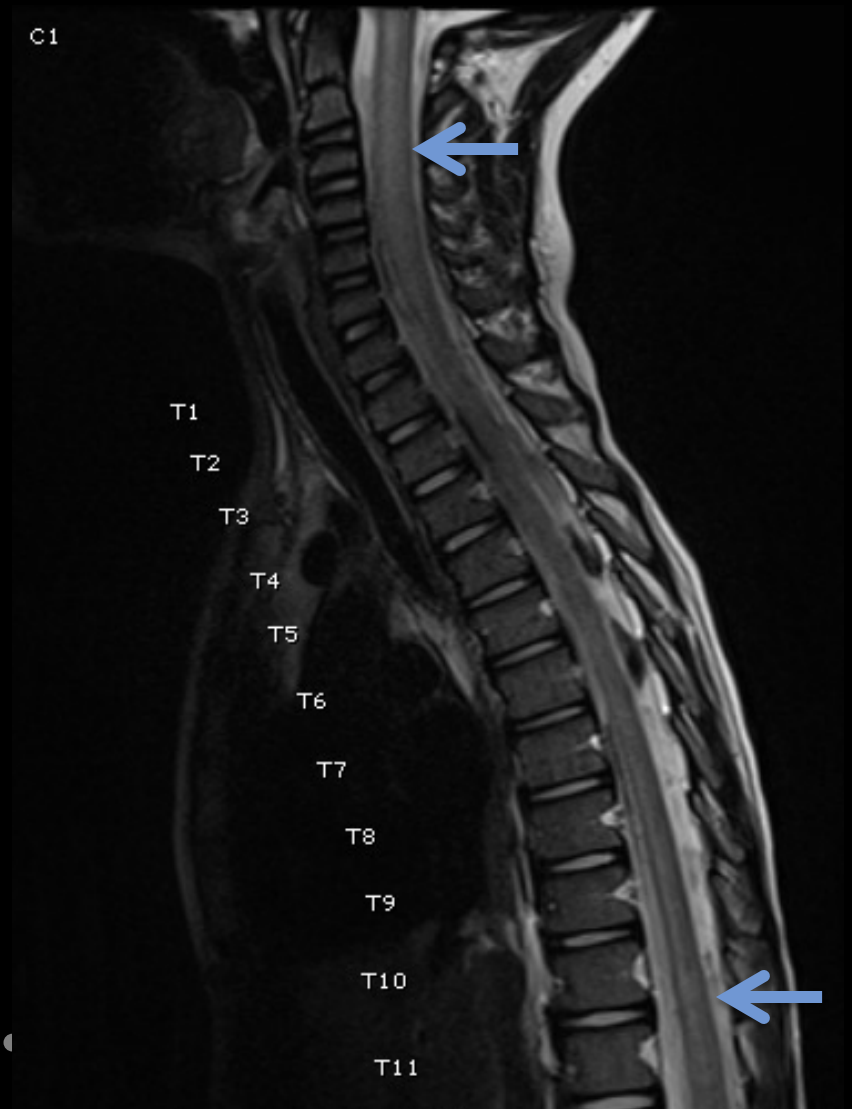
Testing

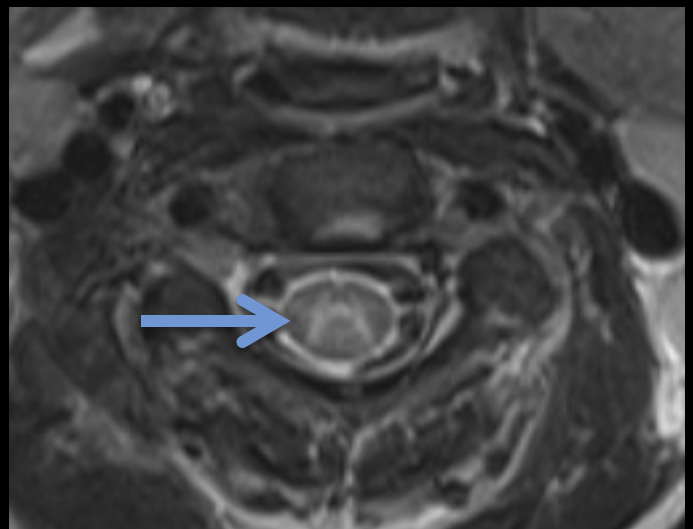
- **Imaging** – MRI
  - Entire Spine
  - With and without contrast
    - *MRI Brain*





Anterior horn/gray matter predominant lesions





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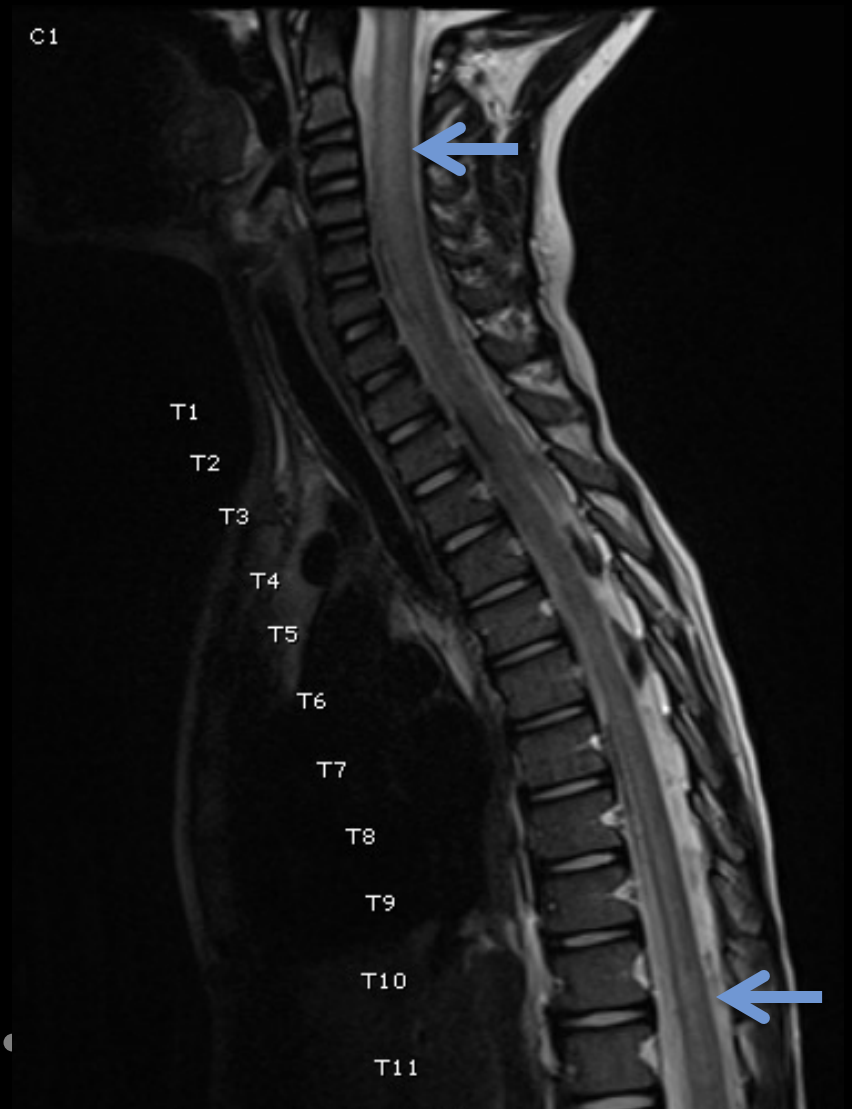

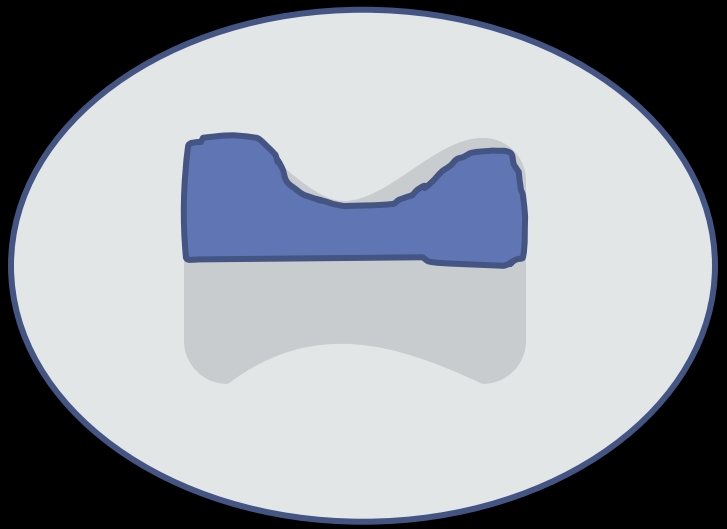

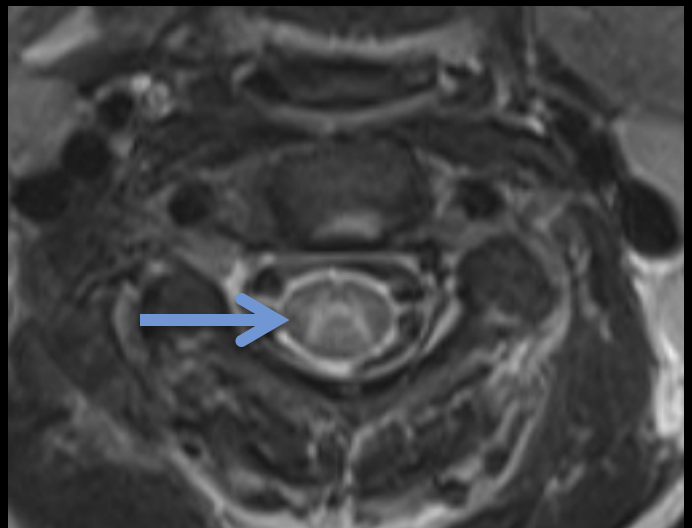

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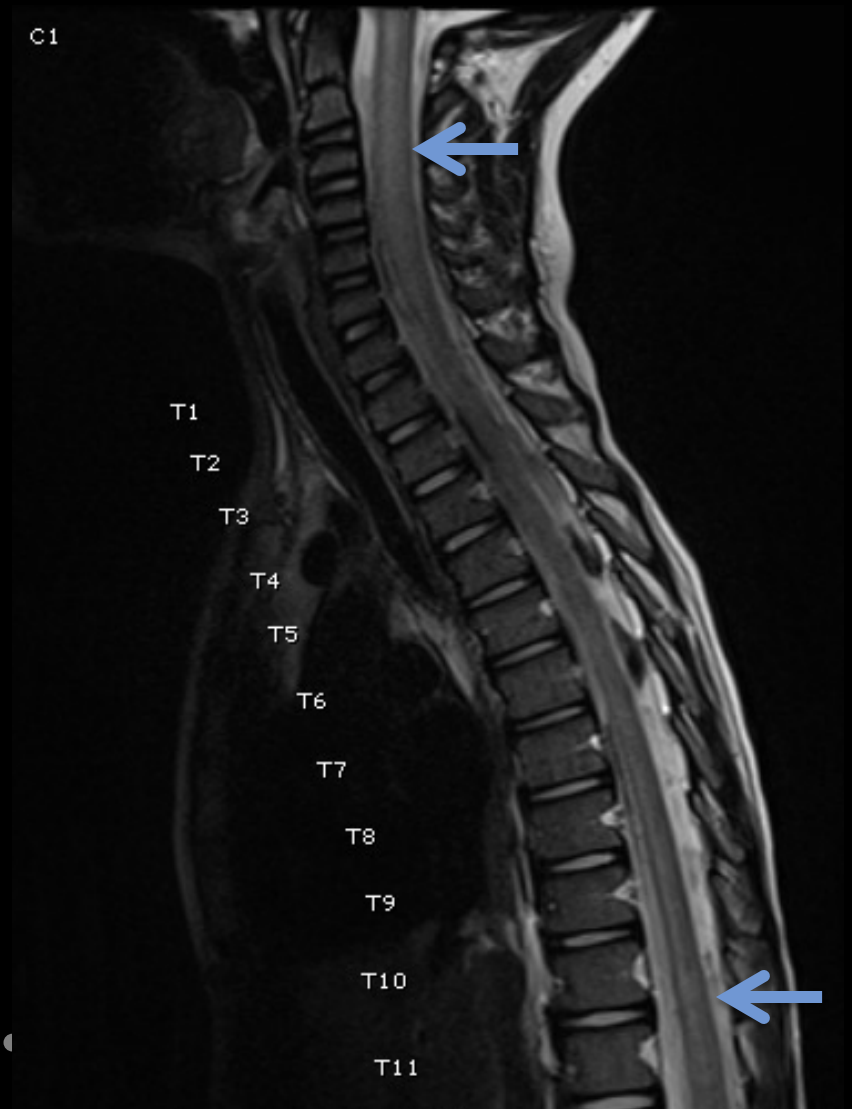
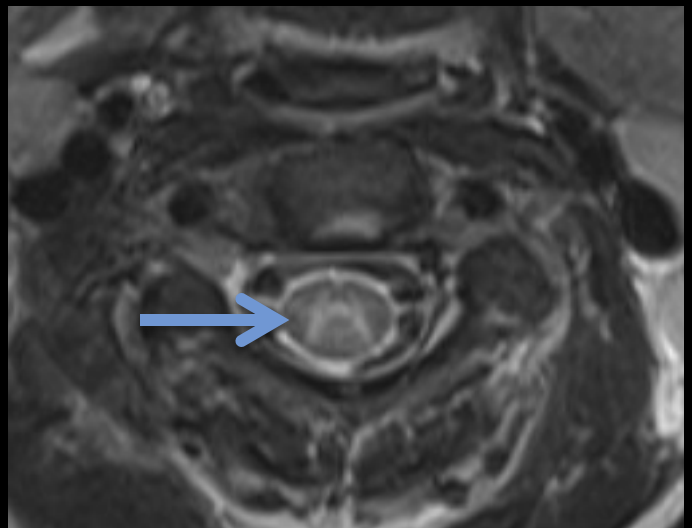
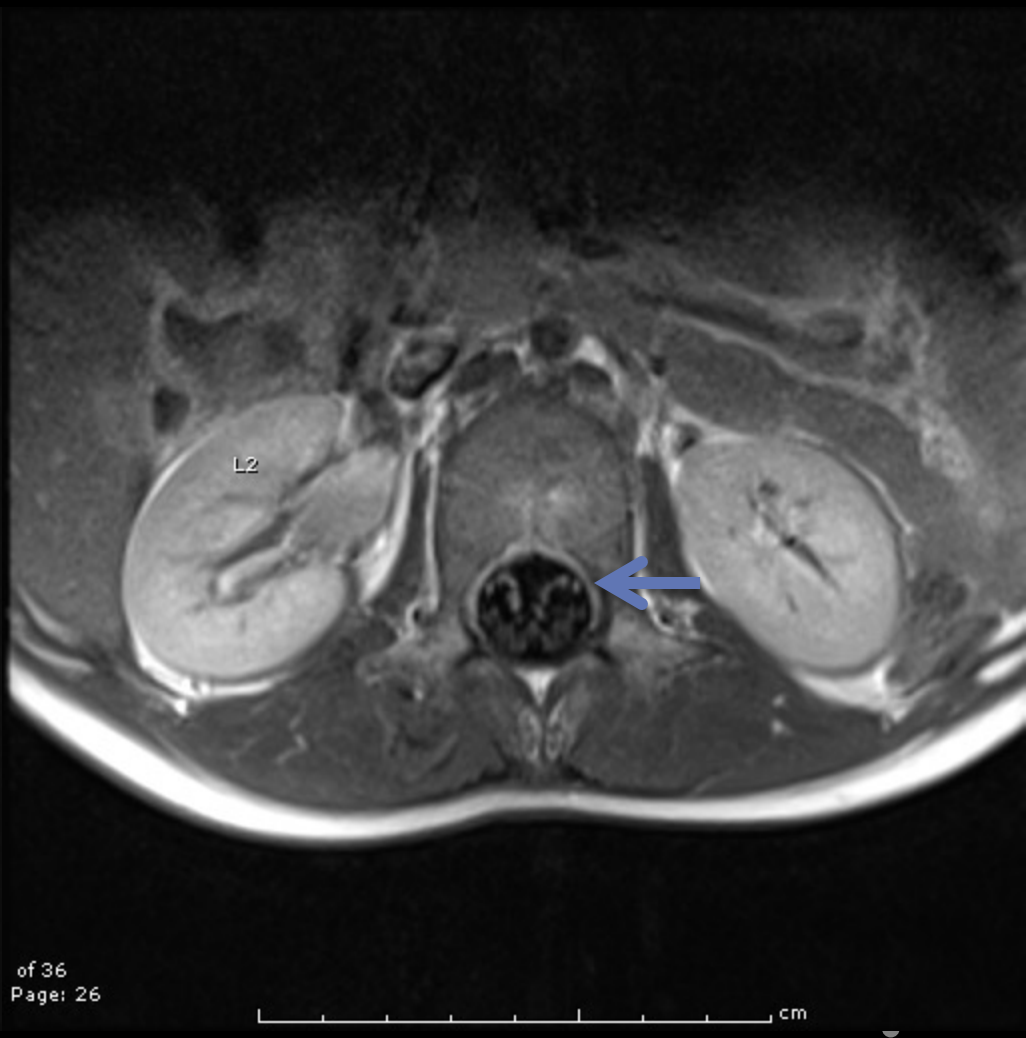




Nerve root enhancement – anterior predominant



Testing

- Labs – AS EARLY AS POSSIBLE
- **Nasal swab, oral swabs, blood, stool, CSF**
  - **State lab -> CDC**
  - **Hospital labs**
  - CSF = cerebrospinal fluid
- EVD68, other viruses
- Mimics such as MOG Antibodies

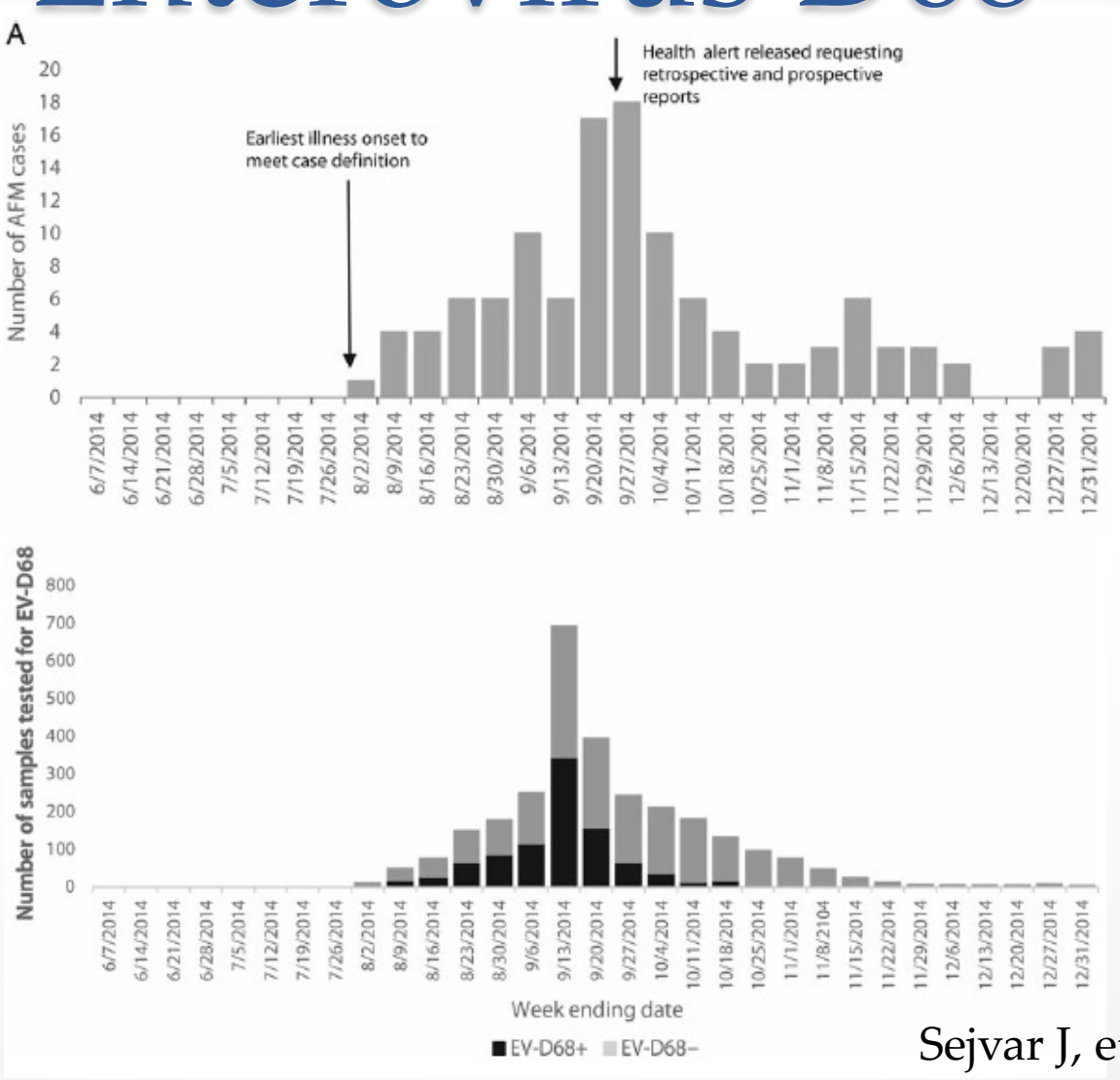
Pathophysiology~ Cause/Process

- Epidemiology
- Mice
- Viral Genes
- Neurons
- Human CSF

Hixon, et al. Viruses. 2019

AFM paralleled Enterovirus D68

- AFM
- EV D68



Sejvar J, et al. 2016

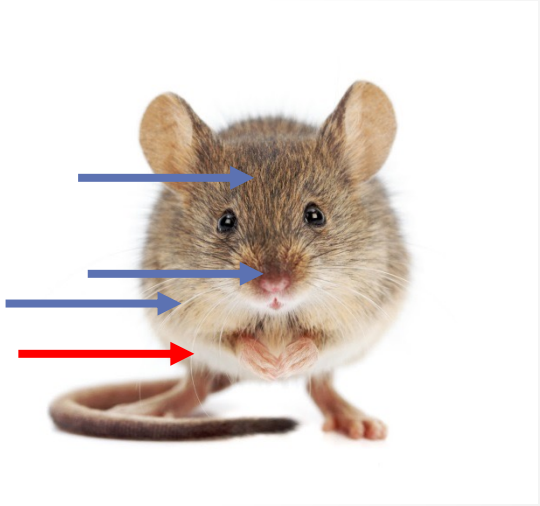
Learning From Mice

A mouse model of paralytic myelitis caused by enterovirus D68

Alison M. Hixon[1,2], Guixia Yu[3,4], J. Smith Leser[5], Shigeo Yagi[6], Penny Clarke[5], Charles Y. Chiu[3,4], Kenneth L. Tyler[5,7,8]*

AFM Pathophysiology

- 4/5 strains from 2014 → paralyzed neonatal mice
- Age dependent paralysis
- Loss of motor neurons
- Infectious virus, viron particles and viral genome in spinal cords
- Immune sera protective against paralysis



Hixon, et al. PLOS Pathogens. 2017

CSF Anti-EV Antibodies

nature medicine

LETTERS

https://doi.org/10.1038/s41591-019-0613-1

Pan-viral serology implicates enteroviruses in acute flaccid myelitis

Ryan D. Schubert[1,2], Isobel A. Hawes[1,2,18], Prashanth S. Ramachandran[1,2,18], Akshaya Ramesh[1,2,18], Emily D. Crawford[3,4], John E. Pak[3], Wesley Wu[3], Carly K. Cheung[3], Brian D. O'Donovan[5],

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RESEARCH ARTICLE
Clinical Science and Epidemiology

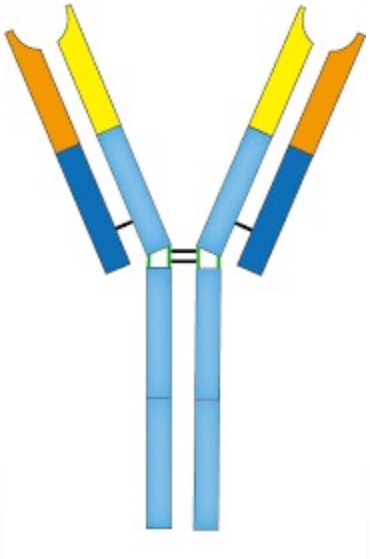
Antibodies to Enteroviruses in Cerebrospinal Fluid of Patients with Acute Flaccid Myelitis

Nischay Mishra,[a] Terry Fei Fan Ng,[b] Rachel L. Marine,[b] Komal Jain,[a] James Ng,[a] Riddhi Thakkar,[a] Adrian Caciula,[a] Adam Price,[a] Joel A. Garcia,[a] Jane C. Burns,[c] Kiran T. Thakur,[d] Kimball L. Hetzler,[e] Janell A. Routh,[b] Jennifer L. Konopka-Anstadt,[b] W. Allan Nix,[b] Rafal Tokarz,[a] Thomas Briese,[a] M. Steven Oberste,[b] W. Ian Lipkin[a]

Monoclonal antibody therapy

Human antibodies neutralize enterovirus D68 and protect against infection and paralytic disease

Matthew R. Vogt[1]*, Jianing Fu[2]*, Nurgun Kose[3], Lauren E. Williamson[4], Robin Bombardi[3], Ian Setliff[5], Ivelin S. Georgiev[3,4], Thomas Klose[2], Michael G. Rossmann[2†], Yury A. Bochkov[6], James E. Gern[6,7], Richard J. Kuhn[2], James E. Crowe Jr.[1,3,4,5‡]



Treatment Overview

- Acute
  - Inflammation directed
  - Viral directed
  - ?Neuroprotective?
  - ?Restorative?
- Symptomatic & Supportive
  - Bone health
  - Psychotherapy
  - Bracing
  - Assistive devices
  - Pain management
  - Nutrition
  - Ventilation
- Chronic/Rehabilitation
  - THERAPIES – PT, OT, speech, feeding
  - Electrical stim "e-stim"
- Surgical
  - Nerve transfers
  - Muscle transfers
  - Tendon Transfers

Restorative surgeries

Early Results of Nerve Transfers for Restoring Function in Severe Cases of Acute Flaccid Myelitis

Paula A. Pino, MD,[1] Jessica Intravia, MD,[2] Scott H. Kozin, MD,[3] and Dan A. Zlotolow, MD[3]

- Muscle transfer
- Tendon transfer
- Scoliosis interventions

Future Directions

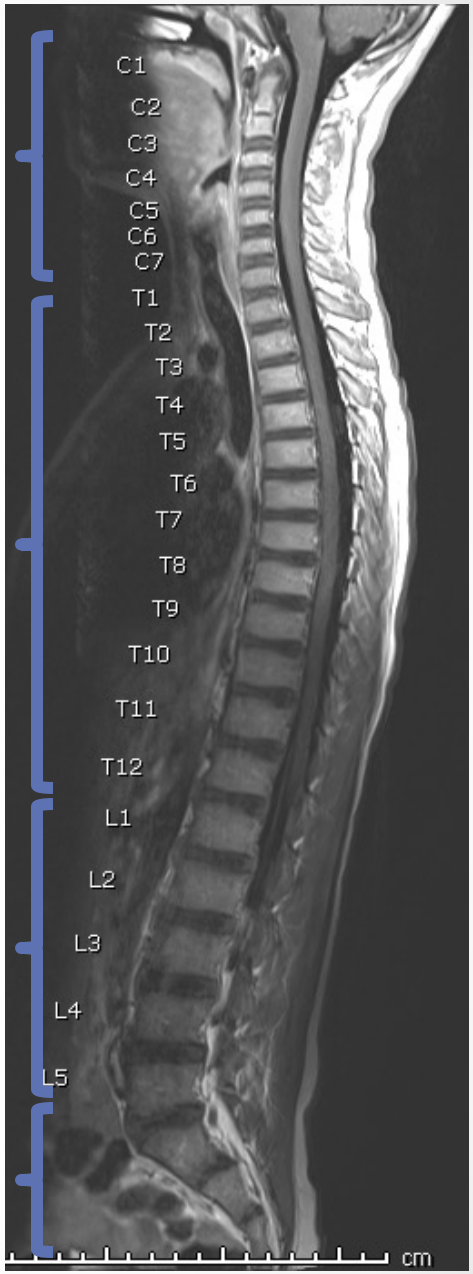
- CDC AFM Task Force
- National AFM Working Group
- NIH "Natural History Study"
- Biomarker, therapeutic and vaccine discovery research
- CSF EV-D68 Ab test
- Long term follow up studies

- Collaboration!

Geography – Level

- **Cervical**
  - Neck, arms, diaphragm/ breathing
- Thoracic
- Lumbar
- Sacral
  - Bladder and bowel function

*May affect all functions below level if connections are destroyed

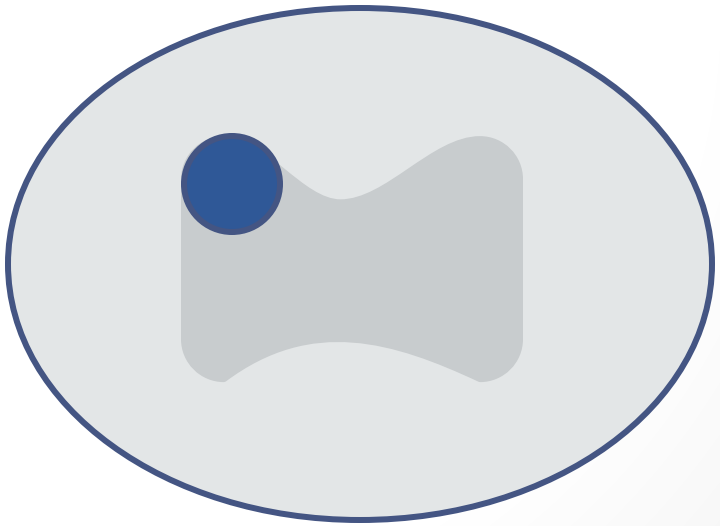


Geography

- Spinal cord side = laterality
- Regions of the spinal cord

Anterior = front

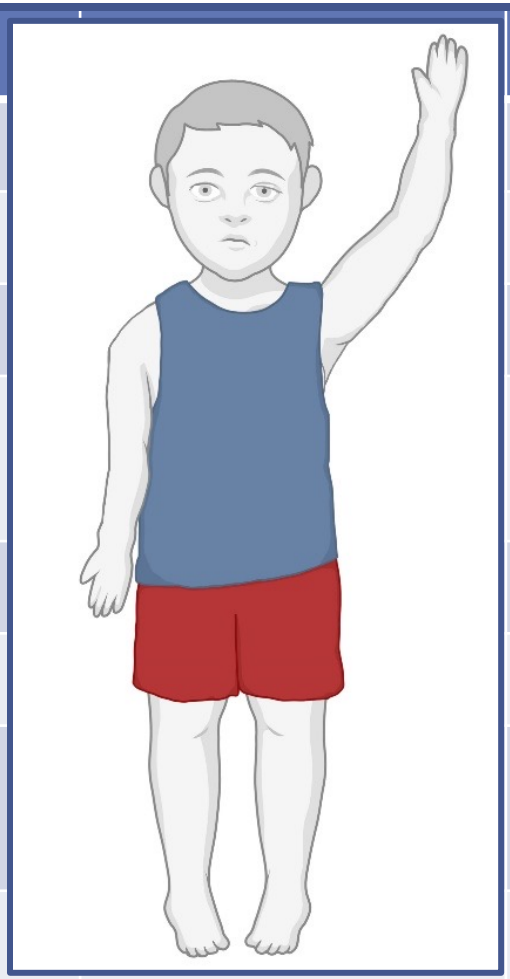
Motor neurons live in the anterior horn –> tell muscles to move

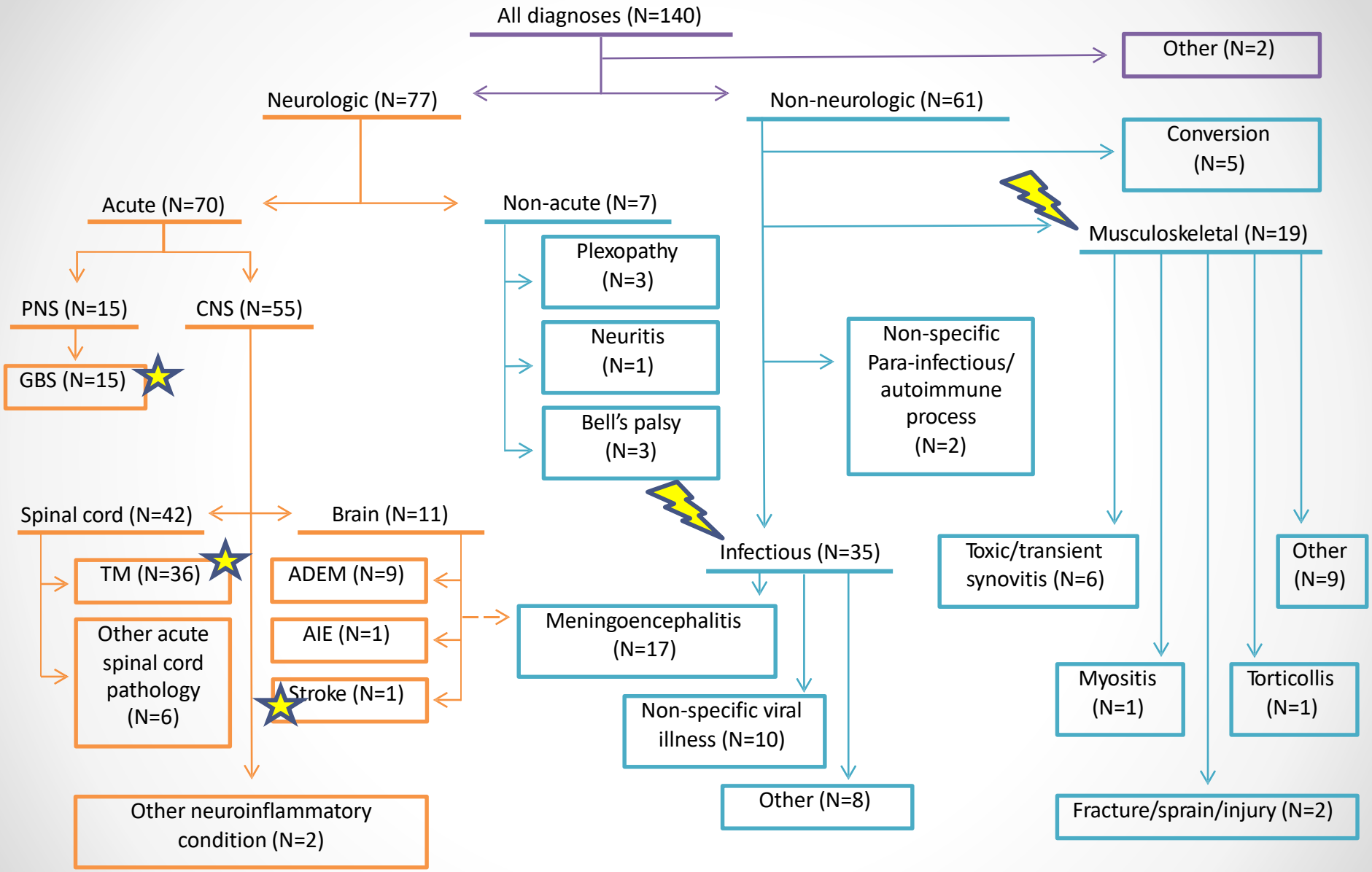


MISDIAGNOSES

- AFM Working group - 13 institutions in the US and Canada.
- Misdiagnosed =
  - alternative diagnosis(es) prior to AFM
  - evaluated by a medical provider & discharged home
- 175 AFM patients
  - → 38 Promptly diagnosed
  - → **137 Misdiagnosed**

Clinical Presentation

Ask		Examine
Fever?		Eye movements
Infectious symptoms?		Facial symmetry
Back, neck, limb pain?		Speech
Drooling?		Raise arms high to the sky
Change in voice?		Tone & symmetry
Difficulty swallowing?		Reflexes
New hand preference?		Jump, squat & recover, high knee march
Increased falling?		Gait


All diagnoses (N=140)
Other (N=2)
Neurologic (N=77)
Non-neurologic (N=61)
Conversion (N=5)
Acute (N=70)
Non-acute (N=7)
Musculoskeletal (N=19)
Plexopathy (N=3)
PNS (N=15)
CNS (N=55)
Neuritis (N=1)
Non-specific Para-infectious/ autoimmune process (N=2)
GBS (N=15)
Bell's palsy (N=3)
Spinal cord (N=42)
Brain (N=11)
Infectious (N=35)
Toxic/transient synovitis (N=6)
Other (N=9)
TM (N=36)
ADEM (N=9)
Meningoencephalitis (N=17)
Other acute spinal cord pathology (N=6)
AIE (N=1)
Myositis (N=1)
Torticollis (N=1)
Stroke (N=1)
Non-specific viral illness (N=10)
Other (N=8)
Fracture/sprain/injury (N=2)
Other neuroinflammatory condition (N=2)

Acute Treatment

- Preliminary Mouse Data
  - IVIG – GOOD, the earlier the better
  - Steroids - BAD
  - Fluoxetine – EQUIVOCAL

Tyler K. AAN 2017.