Acute Flaccid Myelitis Working Group

JOHNS HOPKINS MEDICINE

Acute Flaccid Myelitis:

AFM Preparedness for 2022 and Beyond

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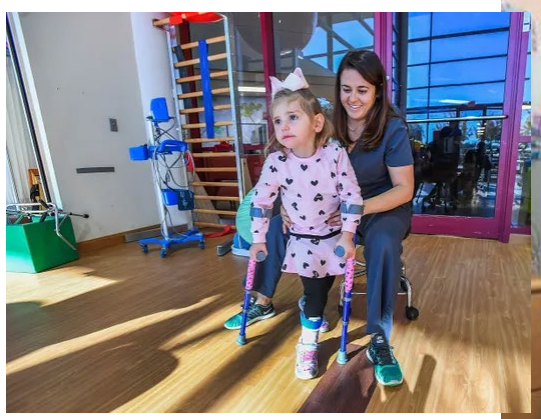
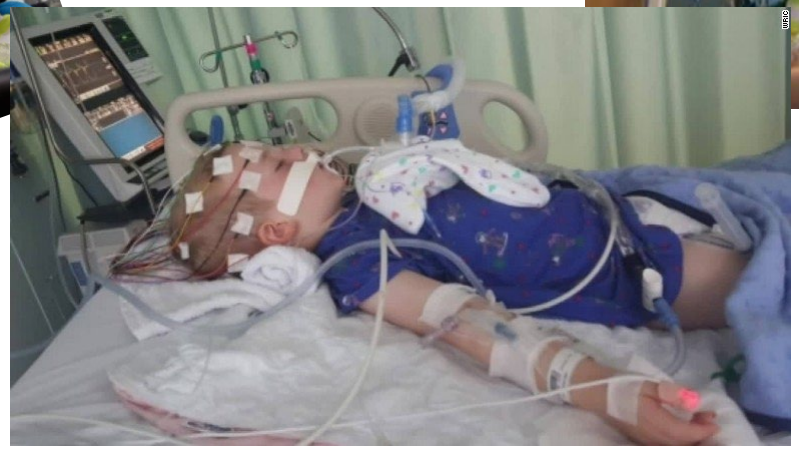
Educational objectives

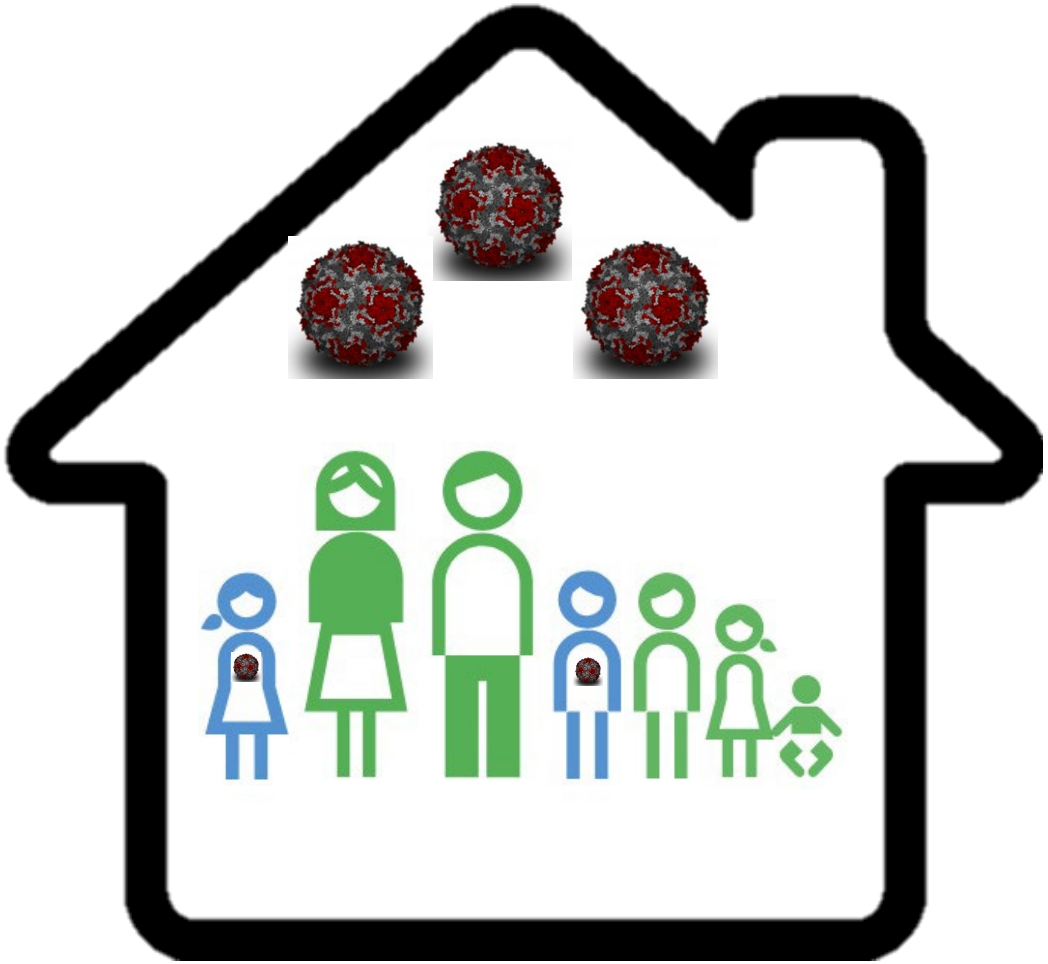
- To review current clinical and epidemiology aspects of Acute Flaccid Myelitis (AFM)
- To understand current concepts on pathogenesis
- To review diagnostic approach and new concepts on management

Acute Flaccid Myelitis:
21st Century Poliomyelitis





Pictures sources: cnn.com, cbsnews.com, washingtonpost.com



Acute Flaccid Myelitis

In most of the cases of AFM there is preceding history of upper respiratory Infection in almost all member of the Household

- Age 1-12 ys in average
- No sex predilection ; Male:Female

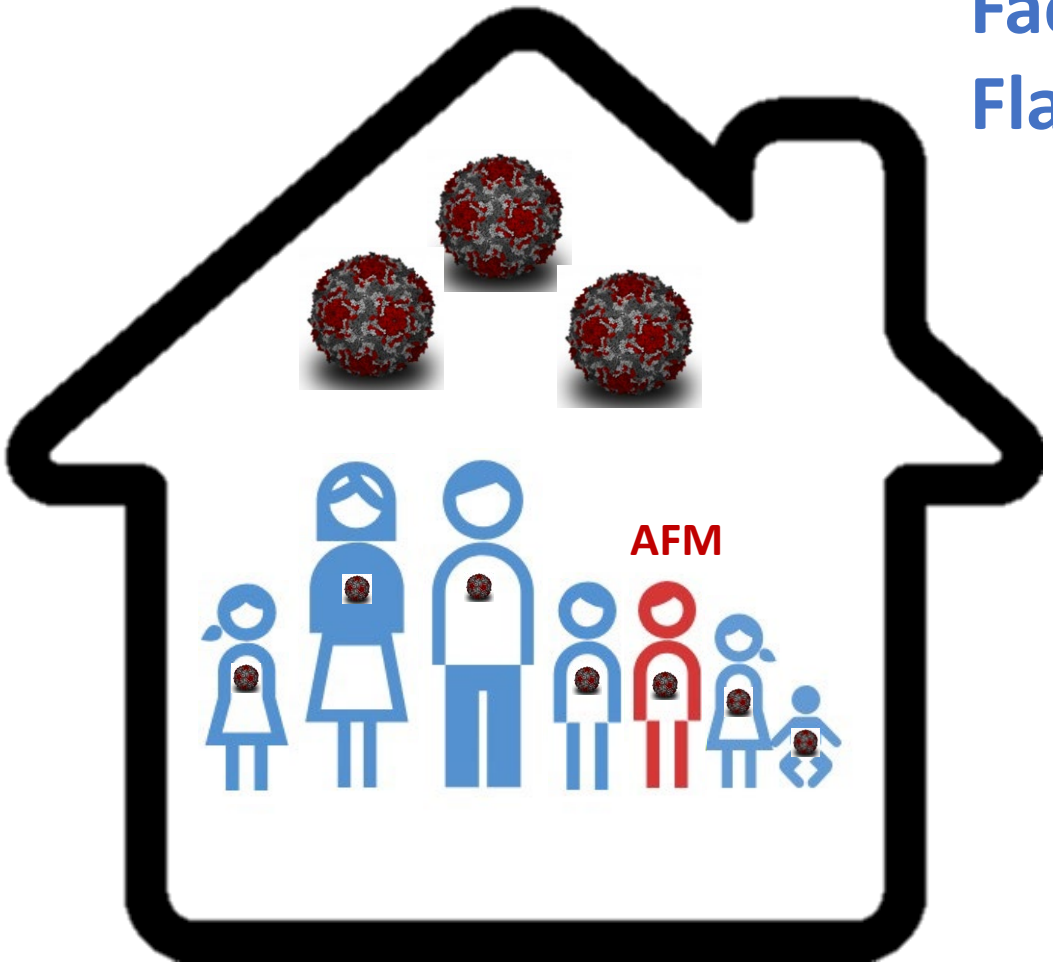
Enteroviruses are the main suspect:

- EVD68, EVA71, Coxsackie

Environmental factors associated

- Seasonality

Factors in Acute Flaccid Myelitis

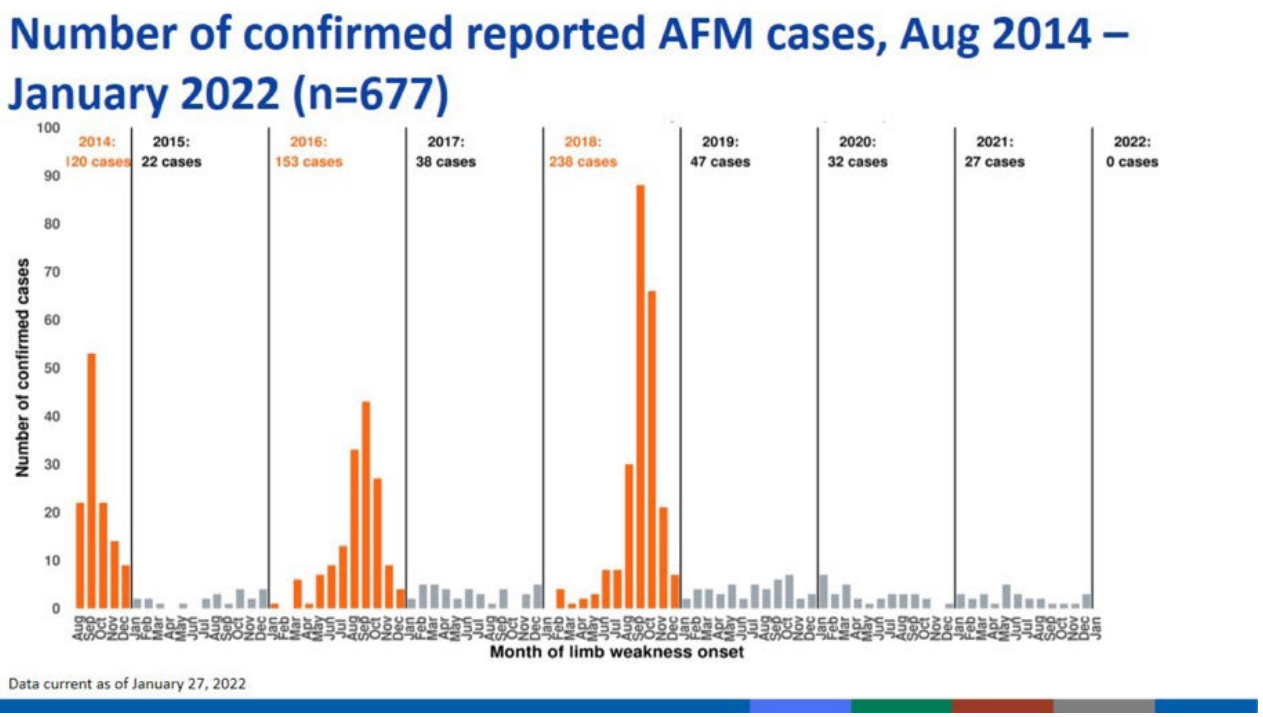


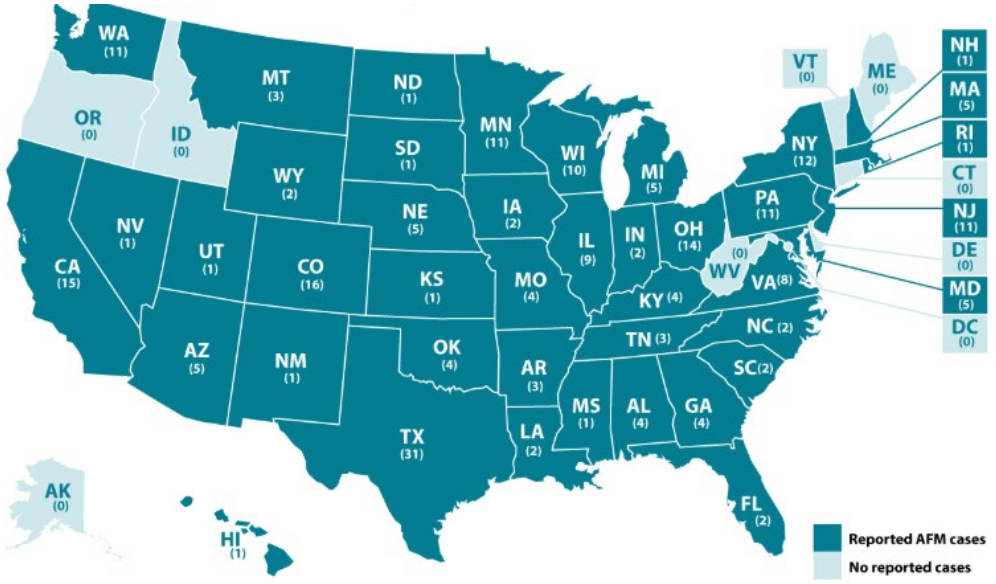
Despite the presence of infection in the entire household only one younger member
of the family is affected

- **Genetic predisposition?**

AFM epidemiology in the USA:

CDC outbreak reports and 2018 state distribution





Source: CDC website

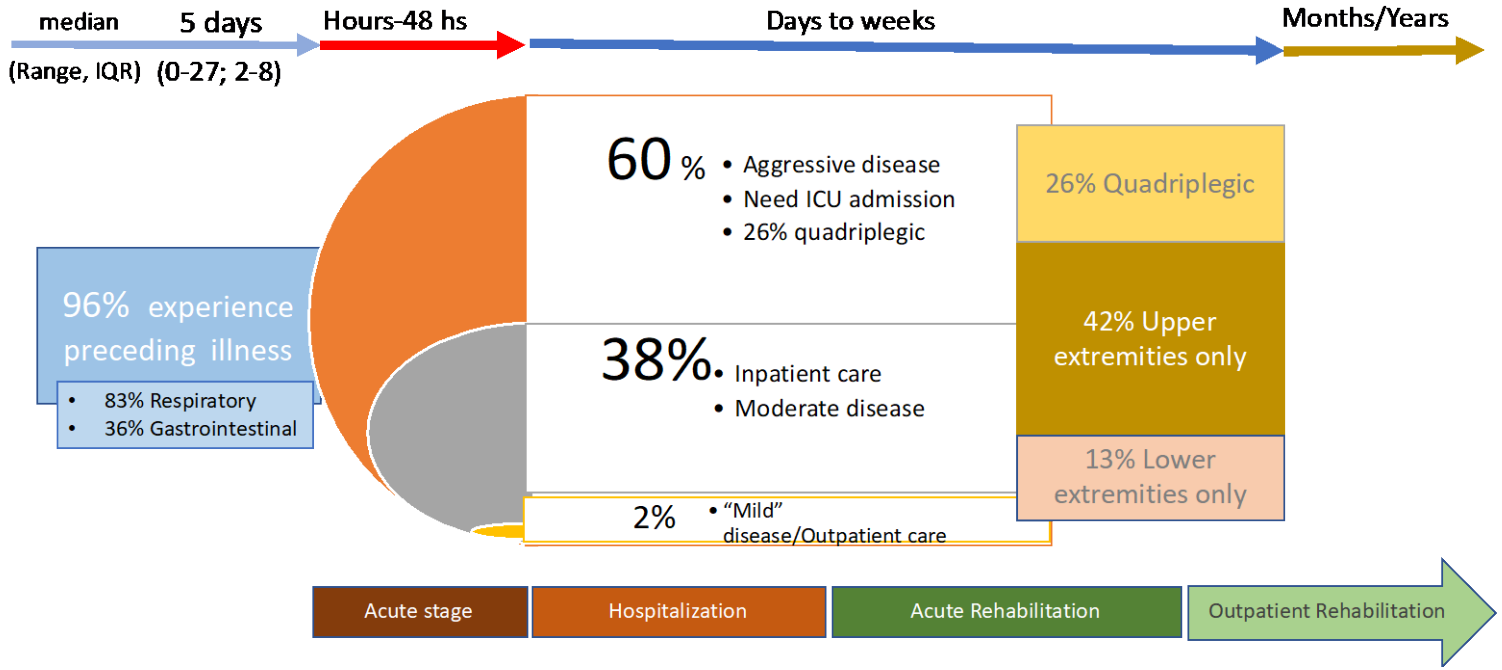
https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

Data current as of June 1, 2020

Take-home message:

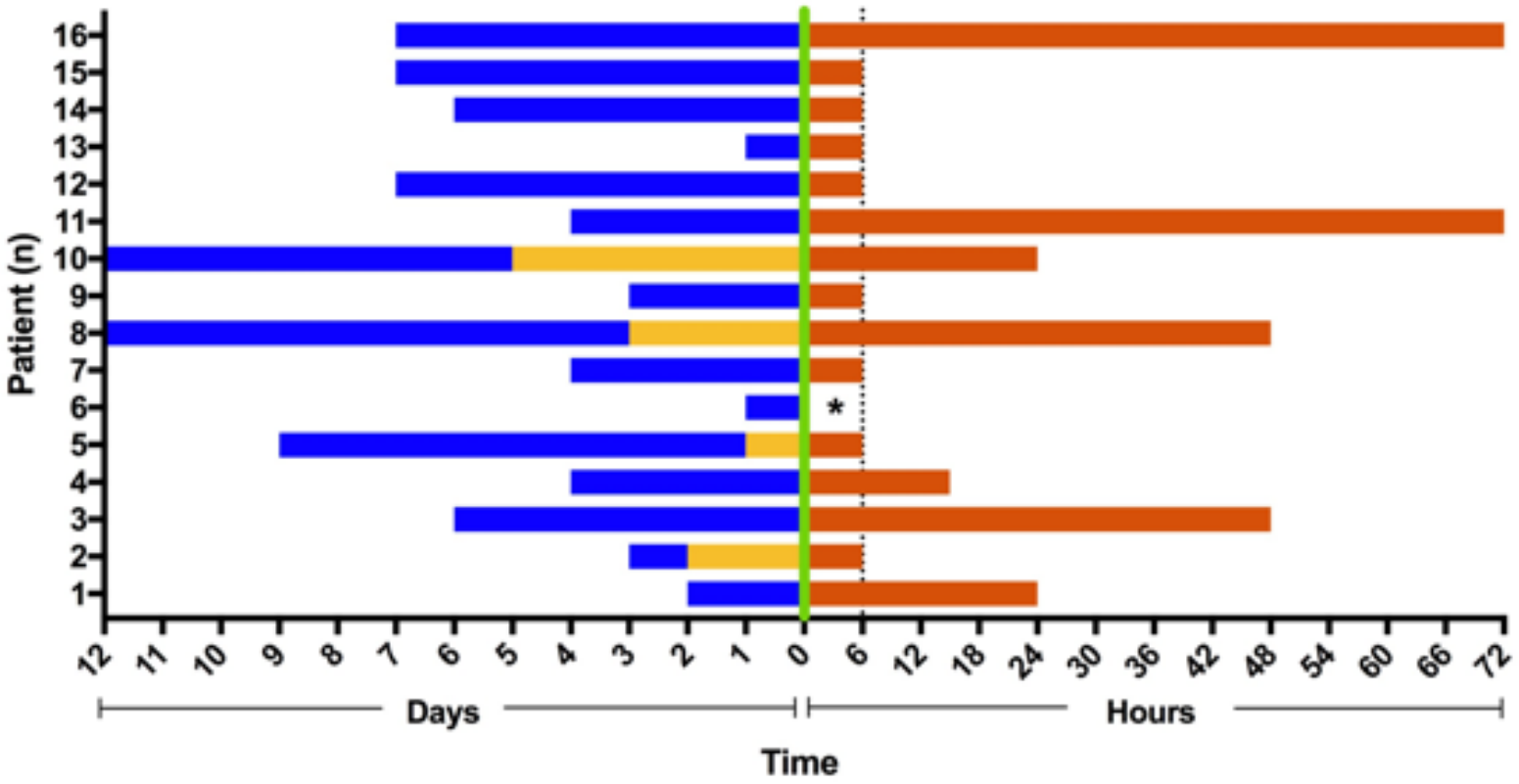
- Cases of AFM have occurred in almost all states of the USA
- Most of the cases occur at the end of the summer and fall

2018 AFM Outbreak in the USA: Clinical Features



Based on CDC report published by Lopez A. et al, MMWR / July 9, 2019 / Vol. 68

Temporal profile in acute flaccid myelitis
Cases evaluated at Johns Hopkins 2014-2016

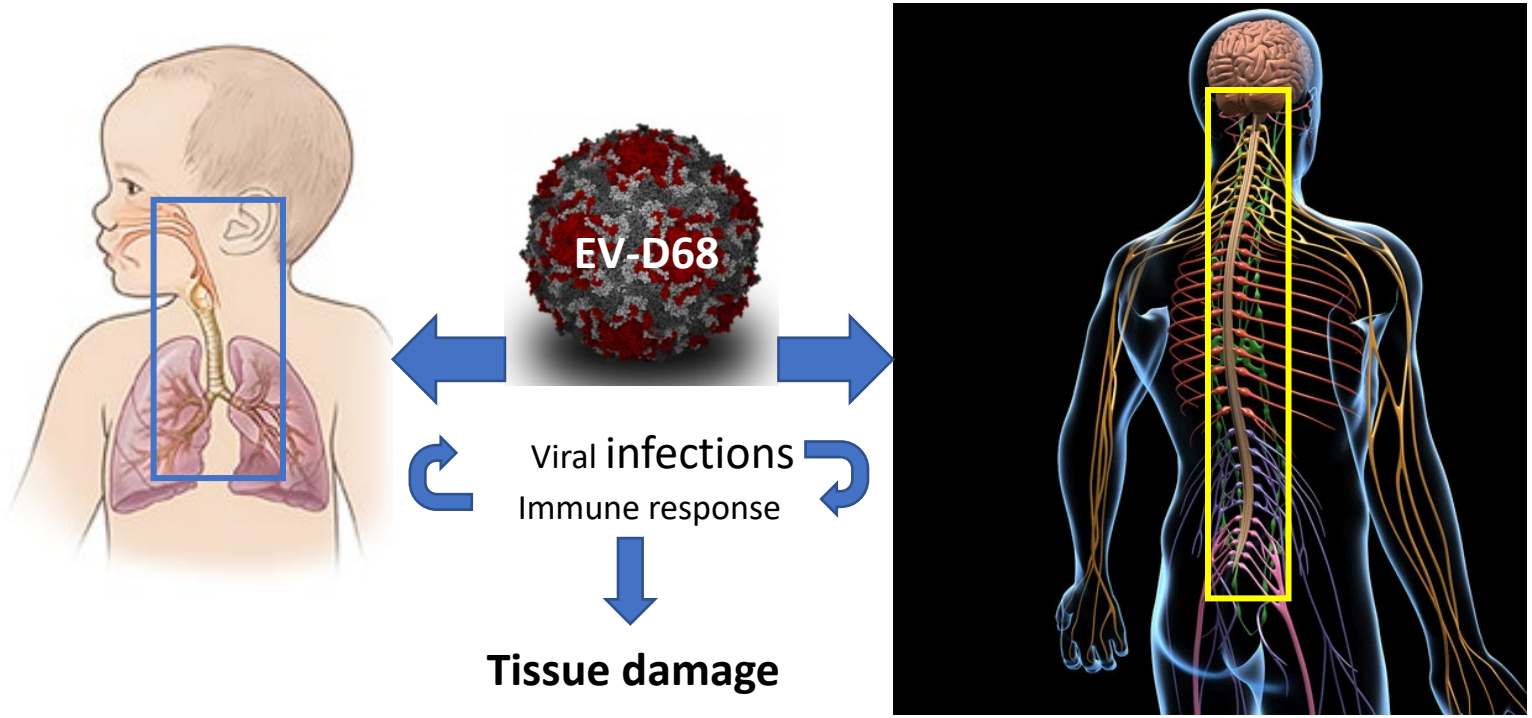


Comparative quantitative clinical, neuroimaging, and functional profiles in children with acute flaccid myelitis at acute and convalescent stages of disease

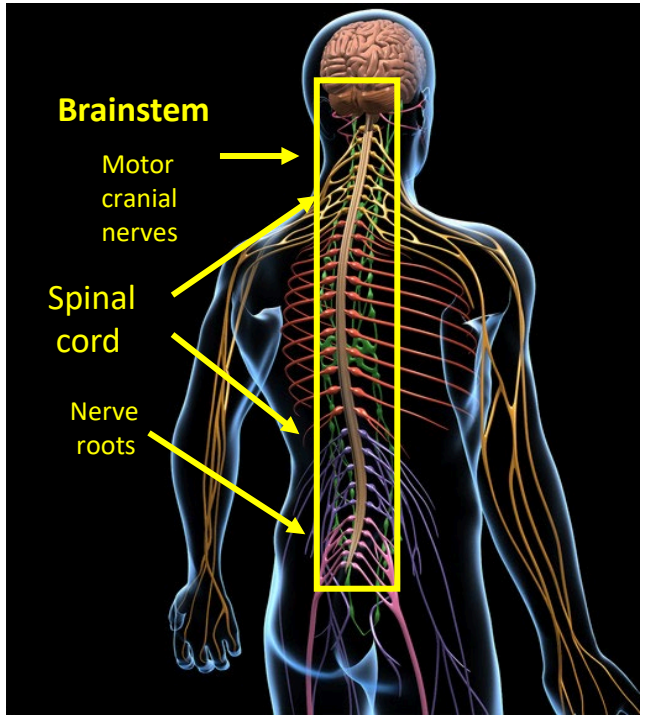
ELIZA GORDON-LIPKIN[1,2*] | LAURA S MUÑOZ[1*] | JESSICA L KLEIN[3] | JANET DEAN[2] | IZLEM IZBUDAK[4] | CARLOS A PARDO[1,5]

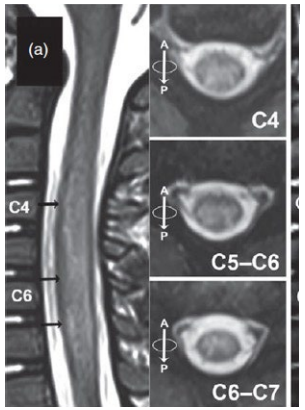
Developmental Medicine & Child Neurology 2018

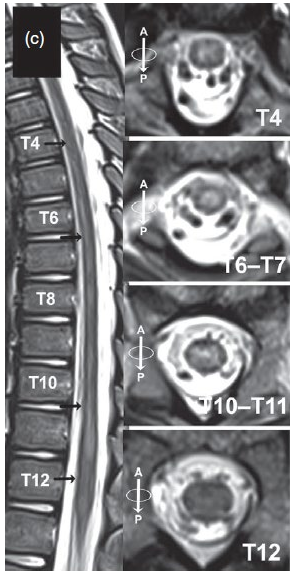
Tissue susceptibility to Enterovirus-D68 Infection

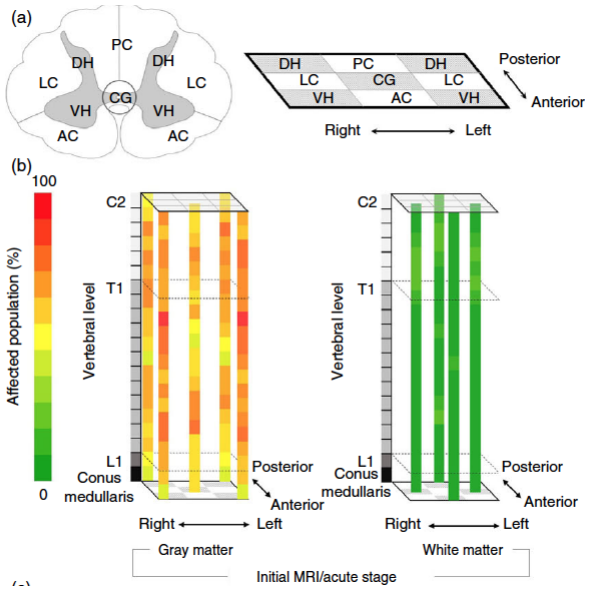


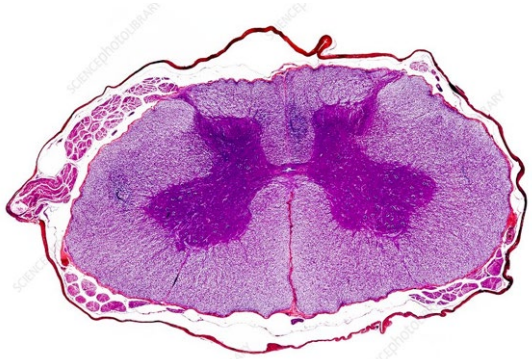
Areas of CNS susceptibility in AFM

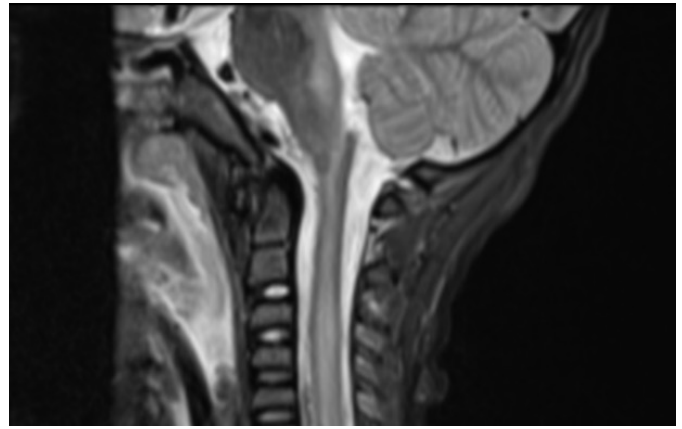


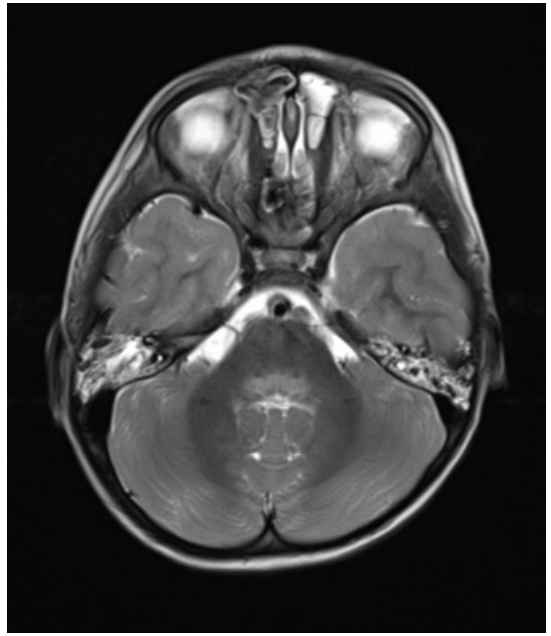












Differential Diagnosis in Acute Flaccid Myelitis 2021

	Acute flaccid myelitis	Guillain-Barré syndrome	Acute transverse myelitis (demyelinating or idiopathic)	Spontaneous spinal cord infarction
Prodromal illness	+++	+++	+/–	–
Temporal evolution	Hours to days	Days to weeks	Days to weeks	Minutes to hours
Pattern of weakness	Asymmetric, arms>legs	Symmetric, ascending	Variable	Symmetric, severe
Facial/bulbar weakness	++	++	+/–	+/–
Respiratory failure	++	++	+/–	+/–
Numbness/ paraesthesia	+/–	+++ (except AMAN)	+++	+
Sensory level	–	–	++	++
Encephalopathy	–	–	+/– (eg, ADEM)	–
Bowel/bladder dysfunction	+/–	+/–	++	+++
Possible associated symptoms or syndromes	Headache, neck pain/stiffness, neuropathic pain	Neuropathic pain	Optic neuritis, encephalitis, seizures	Severe back/limb pain at onset
MRI spinal cord	Ill-defined grey-matter predominant lesion, +/– nerve root enhancement	Normal cord, +/– nerve root enhancement	Variable, but usually a well-defined enhancing white>grey matter lesion	Non-enhancing anterior cord or grey-matter lesion
CSF	Mild–moderate pleocytosis	Elevated protein	Mild–moderate pleocytosis	Sometimes elevated protein or mild pleocytosis
Microbiological tests	See panel 1	Stool sample: bacterial culture, viral RT-PCR panel; respiratory sample: viral RT-PCR panel; serum: *Campylobacter jejuni* and *Mycoplasma pneumoniae* IgM/IgG; other organisms according to region and season	If indicated based on clinical presentation	Not usually indicated
Other useful tests	+/– EMG/NCS	EMG/NCS; serum: anti-ganglioside antibodies	Serum: MOG-IgG, aquaporin-4-IgG; CSF: oligoclonal bands	Angiography

AMAN=acute motor axonal neuropathy subtype. CSF=cerebrospinal fluid. ADEM=acute disseminated encephalomyelitis. EMG/NCS=electromyography and nerve conduction studies. MOG=myelin oligodendrocyte glycoprotein.

Table 2: **Differentiating acute flaccid myelitis from clinical mimics**

Acute Flaccid Myelitis Working Group

Acute flaccid myelitis: cause, diagnosis, and management

Lancet 2021; 397: 334–46

Clinical Diagnosis of Acute Flaccid Myelitis 2021

Acute Flaccid Myelitis Working Group

Panel 1: Clinical and paraclinical evaluation of patients with suspected AFM

Initial clinical assessment

- Consider AFM in patients presenting with rapid-onset weakness, particularly when occurring during or shortly following a suspected viral illness.
- Complete neurological examination should include specific tests for proximal muscle weakness (such as standing up from a seated position on the floor), axial weakness (neck and trunk flexion and extension), and cranial nerve abnormalities.
- Clinical features atypical for AFM include encephalopathy unrelated to metabolic disturbance, seizures, extensive sensory abnormalities, or evolution to nadir over more than 10 days.
- Neurology and infectious disease specialists should be consulted (where available) to help with diagnosis, evaluation, and treatment.
- Admission to intensive care unit should be considered when indicated, and close monitoring for respiratory or autonomic deterioration, or both, is essential.

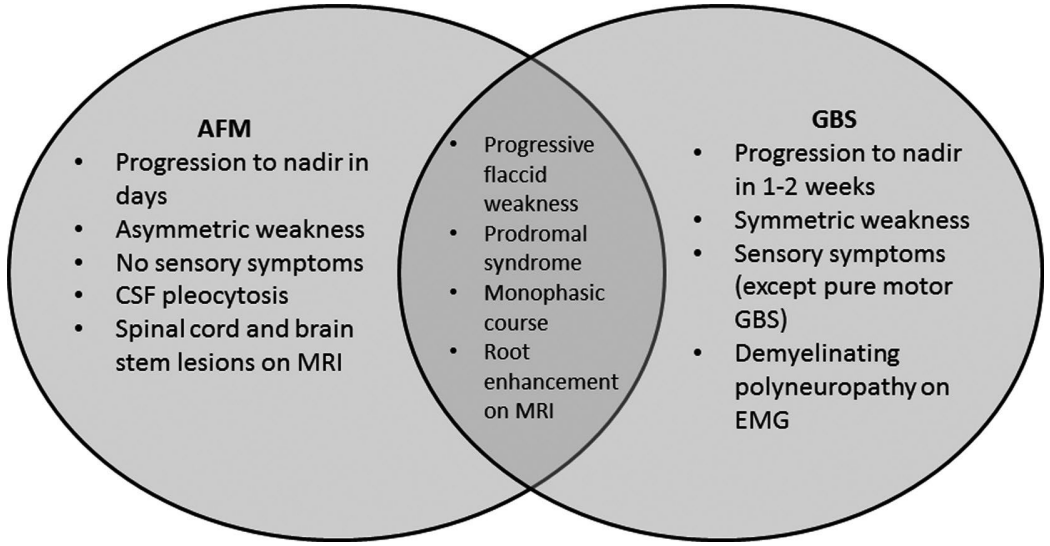
Acute flaccid myelitis: cause, diagnosis, and management

Lancet 2021; 397: 334–46

Acute flaccid myelitis and Guillain–Barré syndrome in children: A comparative study with evaluation of diagnostic criteria

TABLE 1 Demography and clinical presentation of AFM and GBS in children

	AFM, *n* = 26	GBS, *n* = 156	*p*
Demography			
Male:female (% male)	14:12 (54)	82:74 (53)	ns
Age, years, median (IQR, full range)	3 (2–5, 8)	7 (3–13, 17)	<0.001
Antecedent events			
Time antecedent event–onset weakness, days, median (IQR, full range)	7 (5–8, 10)	11 (7–15, 41)	ns
No antecedent event, *n* (%)	1/26 (4)	19/143 (13)	ns
Respiratory tract infection, *n* (%)	23/26 (89)	66/146 (45)	<0.001
Vomiting, *n* (%)	2/26 (8)	32/118 (27)	ns
Diarrhea, *n* (%)	5/26 (19)	47/145 (32)	ns
Fever, *n* (%)	22/24 (92)	51/140 (36)	<0.001
Vaccination, *n* (%)[a]	0/2 (0)	11/130 (9)	np
Time onset weakness–admission, days, median (IQR, full range)[b]	0 (0, 5)	5 (3–8, 30)	<0.001
Time onset weakness–nadir, days, median (IQR, full range)[c]	3 (2–5, 9)	8 (5–10, 38)	<0.001



Acute flaccid myelitis and Guillain–Barré syndrome in children: A comparative study with evaluation of diagnostic criteria

Jelte Helfferich[1] | Joyce Roodbol[2] | Marie-Claire de Wit[3] | Oebele F. Brouwer[1] | Bart C. Jacobs[4] | the 2016 Enterovirus D68 Acute Flaccid Myelitis Working Group and the Dutch Pediatric GBS Study Group

Euro J of Neurology, Volume: 29, Issue: 2, Pages: 593-604,
First published: 08 November 2021, DOI: (10.1111/ene.15170)

Clinical Diagnosis of Acute Flaccid Myelitis 2021

Radiological evaluation

- MRI whole spine and brain should be prioritised, including T2 and T1 pre-contrast and post-contrast sequences in both axial and sagittal planes.
- The characteristic MRI abnormality is grey-matter predominant T2 hyperintensity of the spinal cord with associated spinal cord oedema; lesion(s) are usually longitudinally extensive and non-enhancing. Nerve root enhancement might be present.
- Repeat MRI can be considered after further clinical evolution in patients with a suggestive clinical presentation but in whom early MRI of the spinal cord is apparently normal.

Low-resource settings

- When MRI is not possible, rapid completion of available laboratory testing should be prioritised (CSF analysis, microbiological sampling), and EMG/NCS can be incorporated in the initial evaluation when available.

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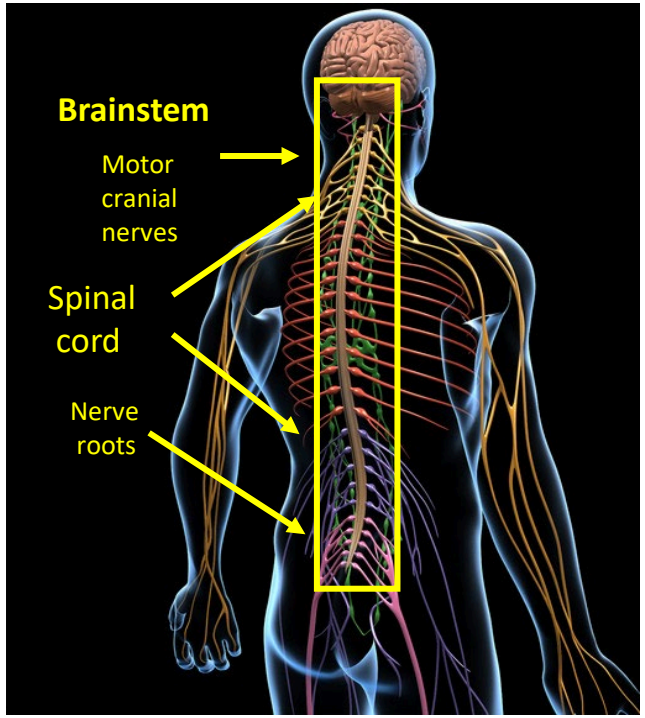

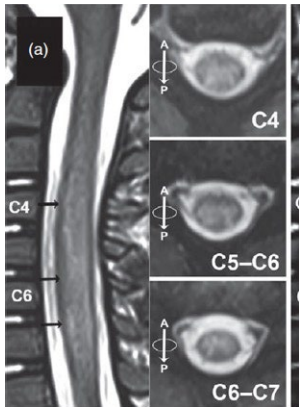

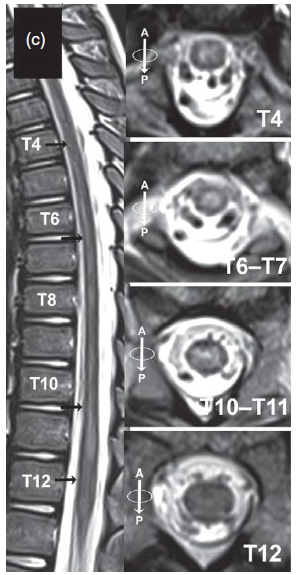

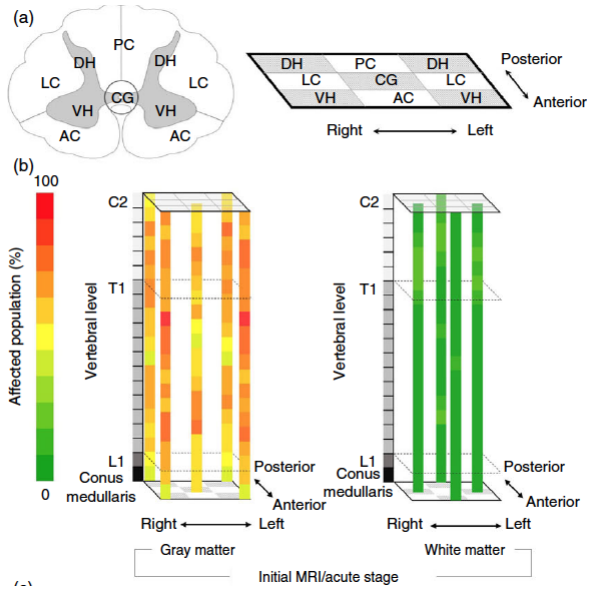

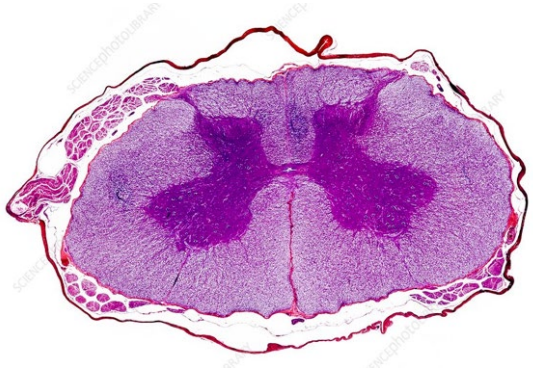

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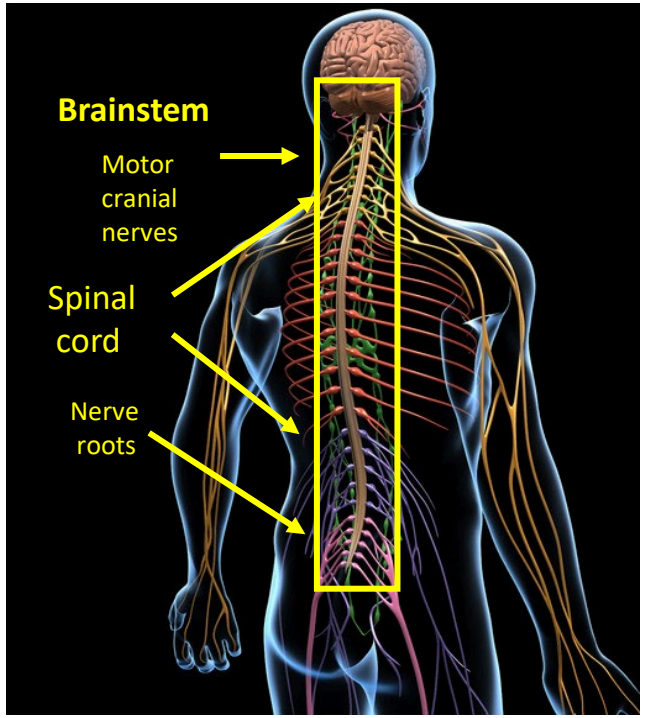
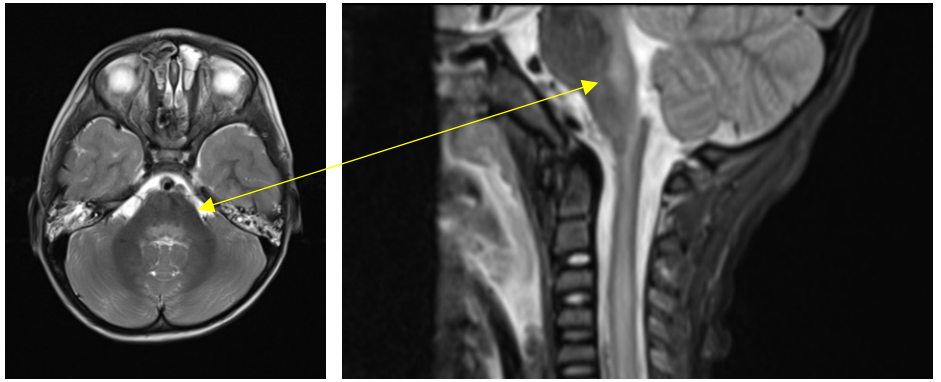
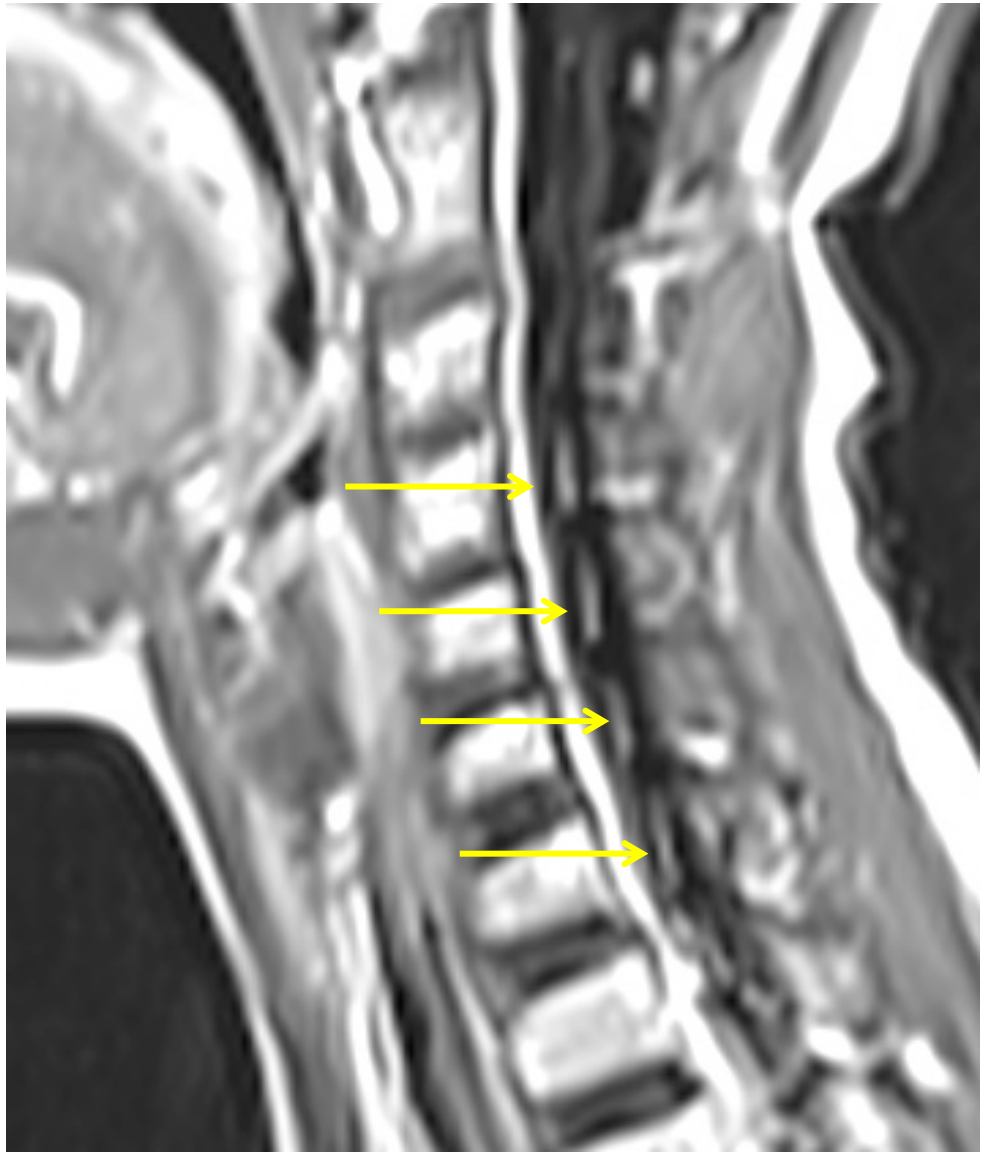


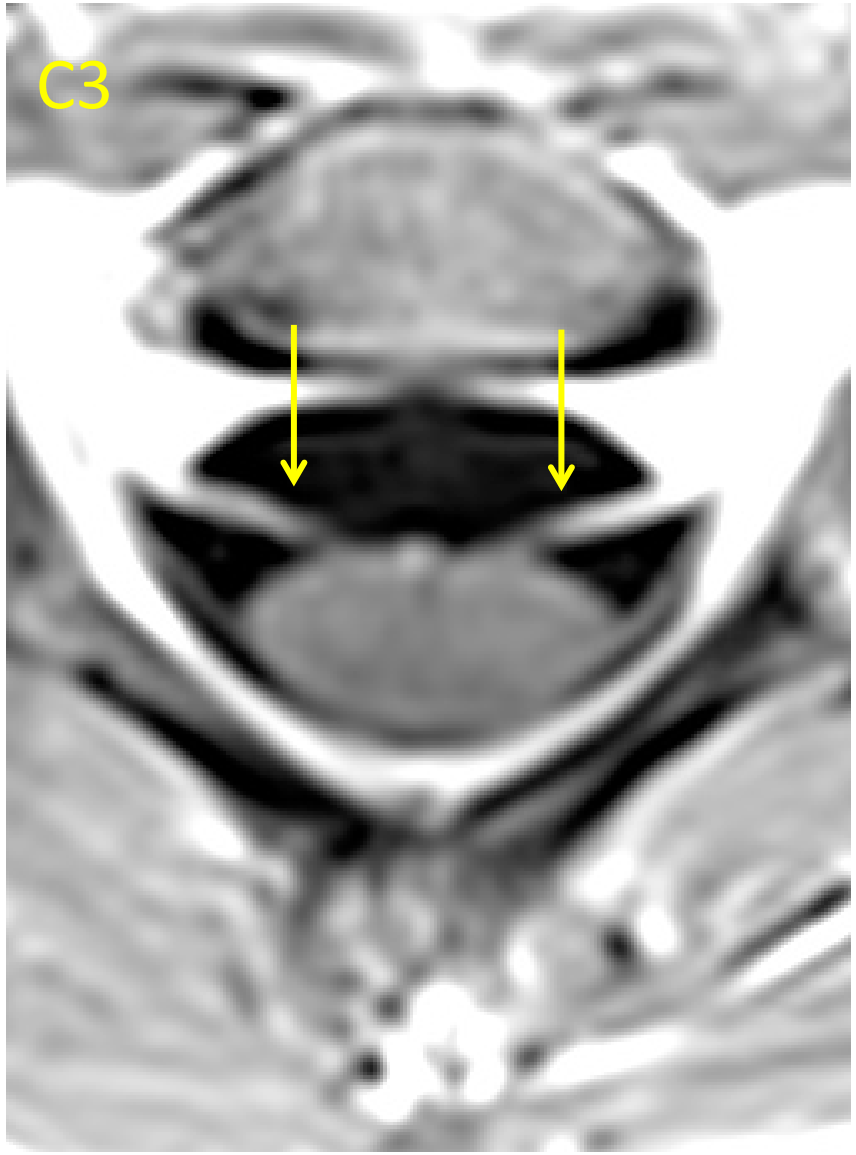


Susceptible regions of the brainstem

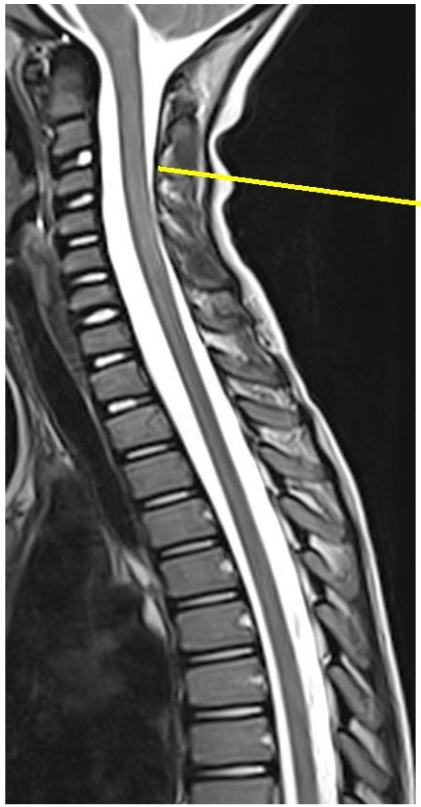
- Dorsal region of pons +medulla
- Cranial nerves (VII, VIII, IX, X, XI. XII

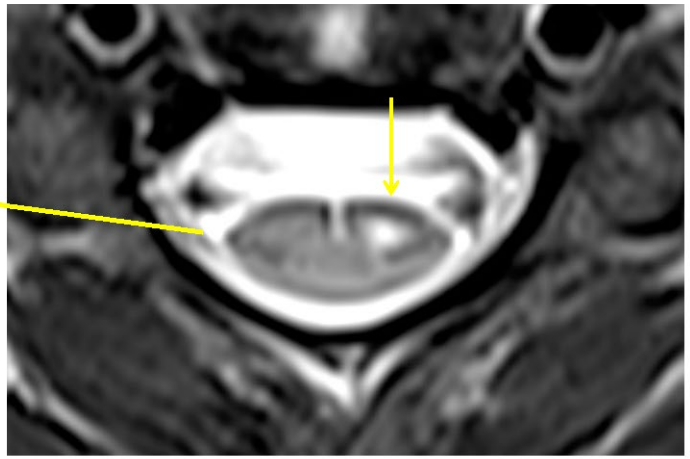
AFM: Ventral nerve root enhancement

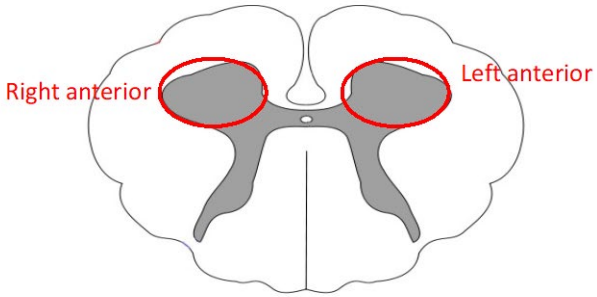




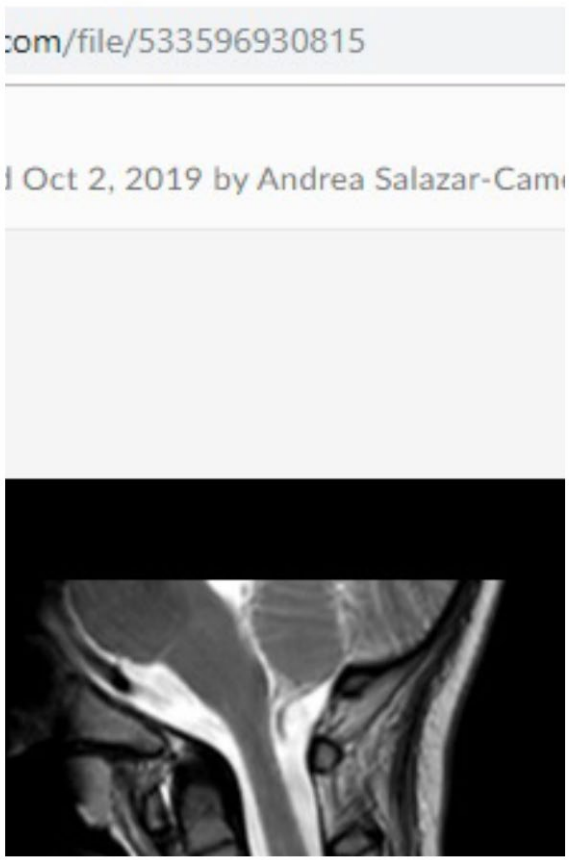
AFM: Subacute/chronic appearance

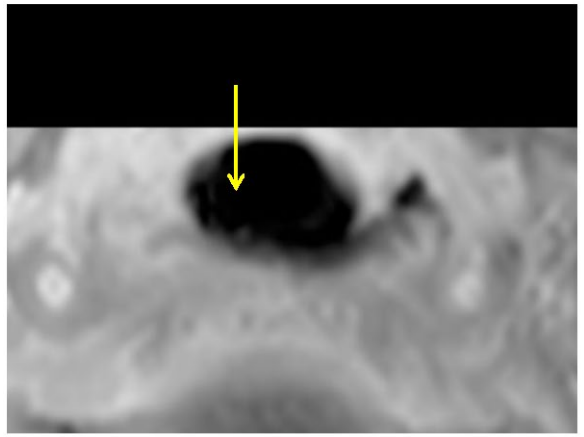






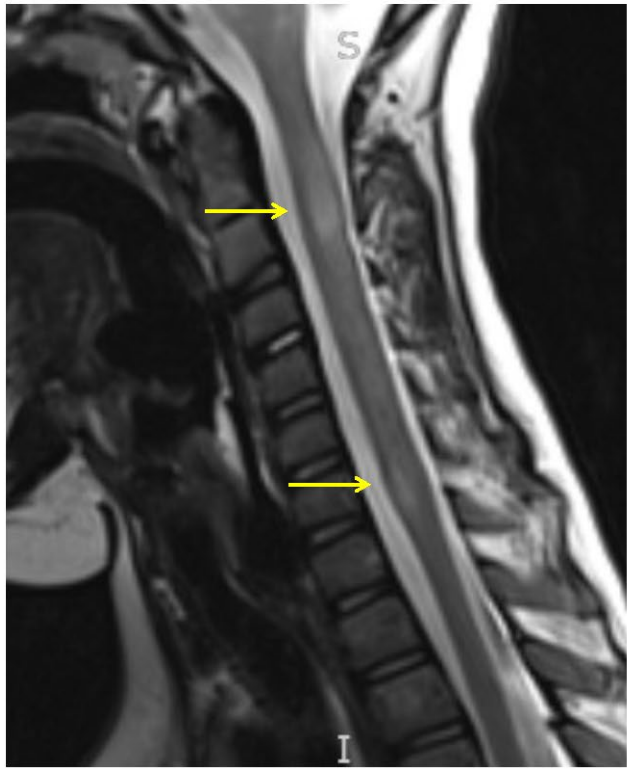
AFM: Subacute/chronic appearance

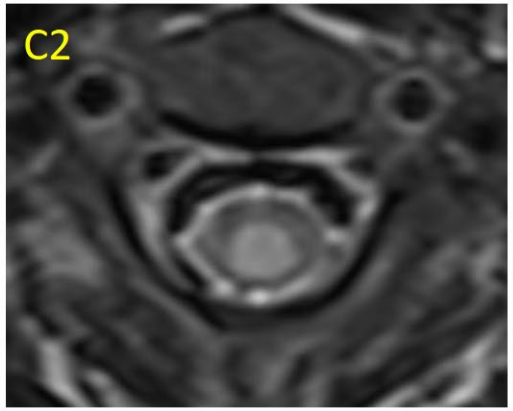


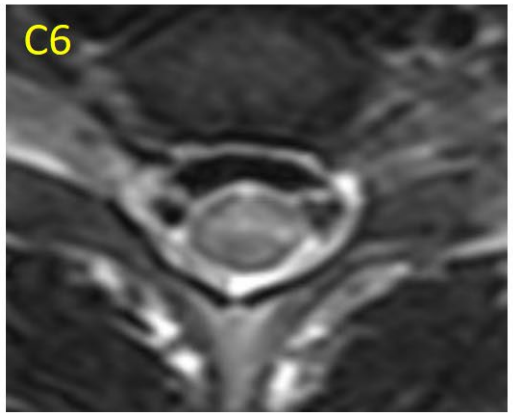


Myelin Oligodendrocyte Glycoprotein Antibody Disease

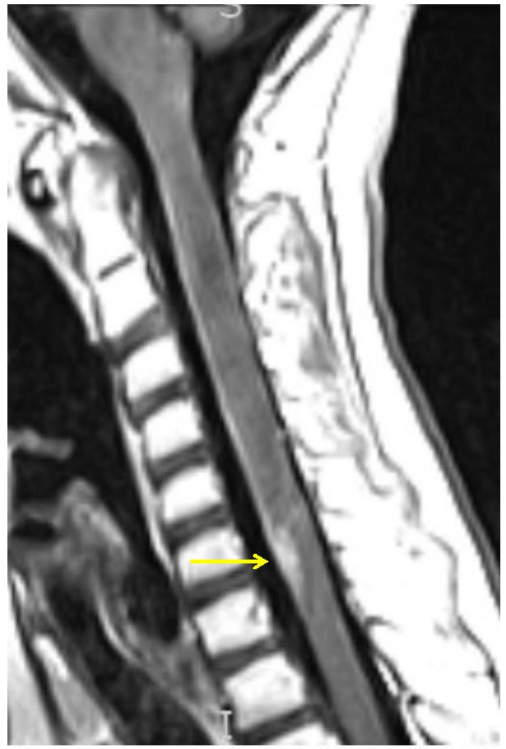
CASE: **M**yelin **O**ligodendrocyte **G**lycoprotein (MOG) antibody disease

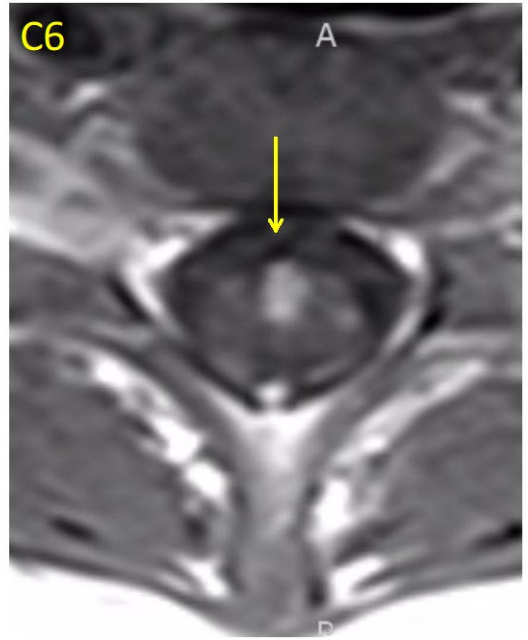




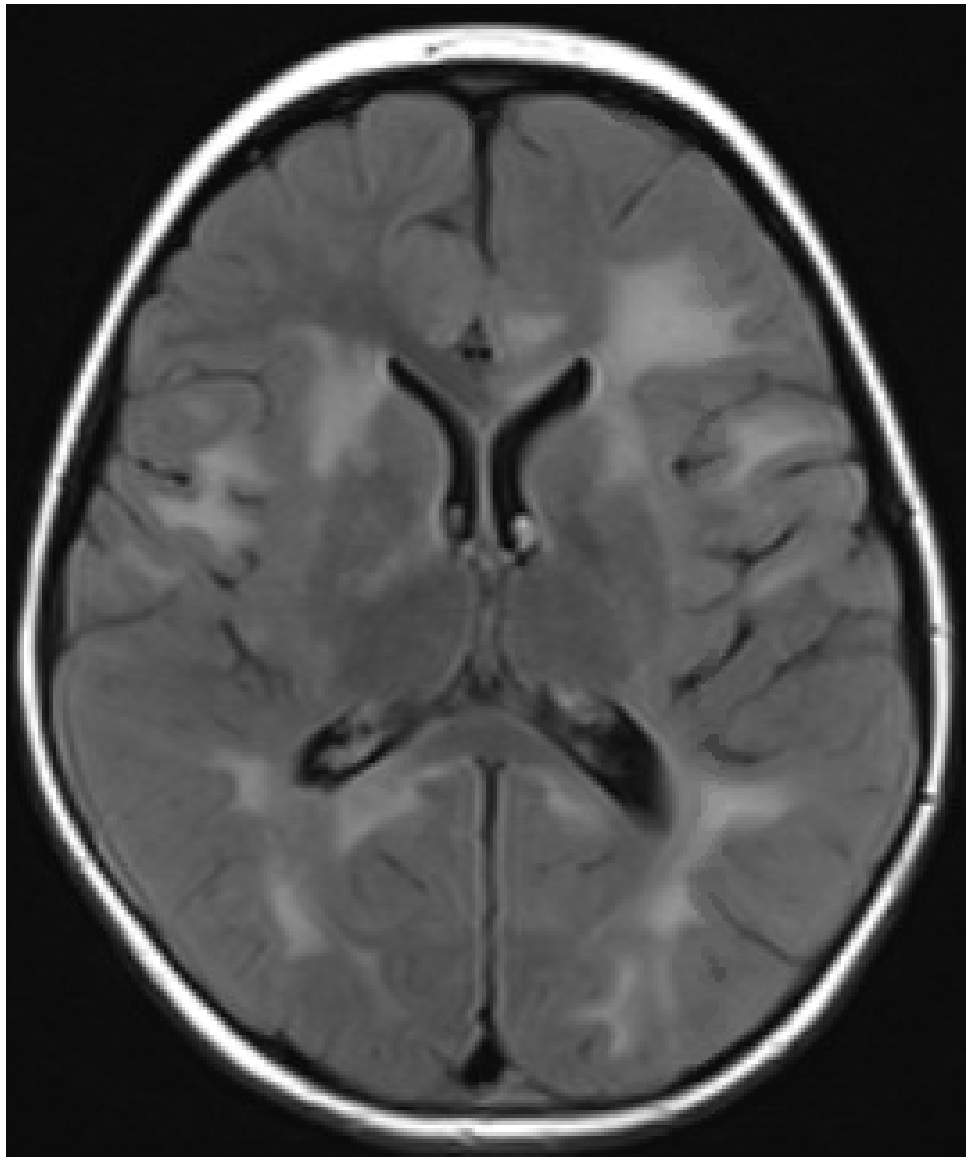


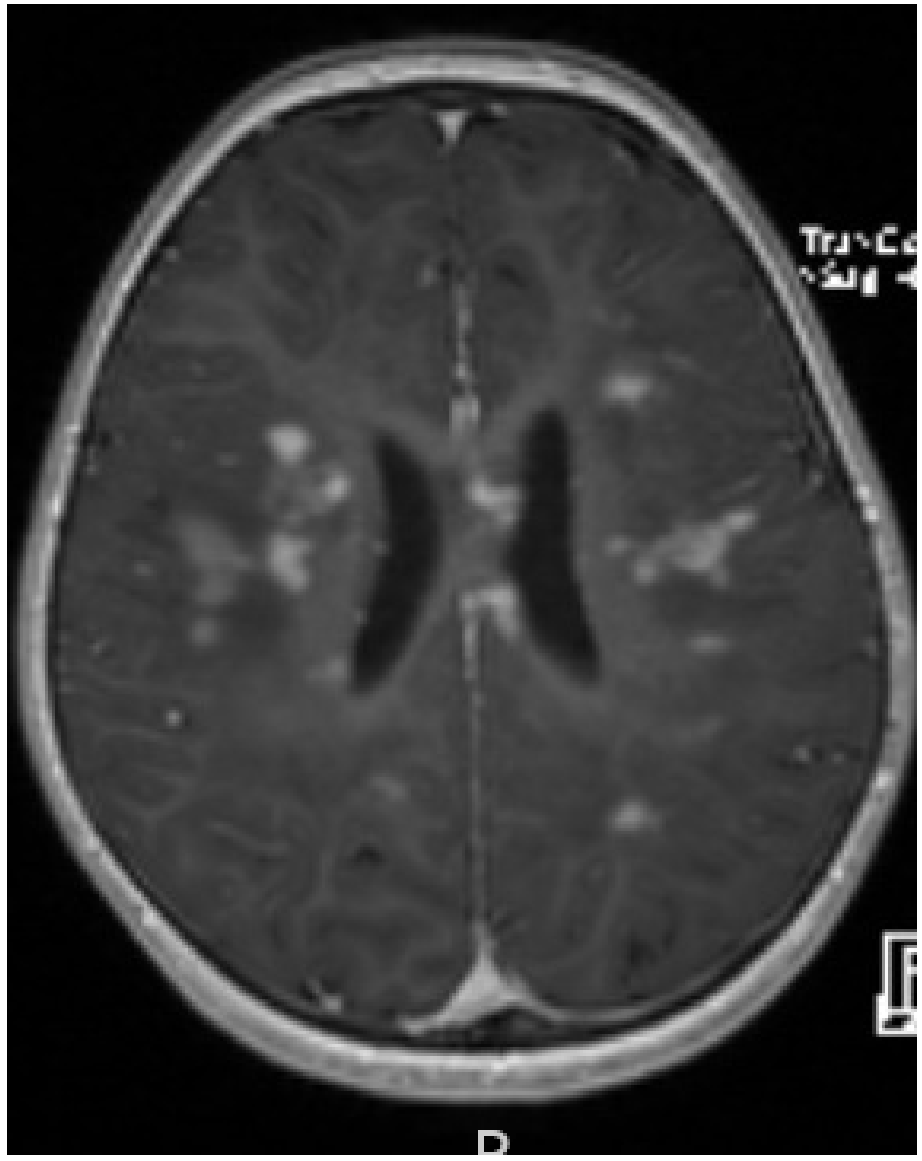
MOG antibody disease: POST-CONTRAST IMAGING



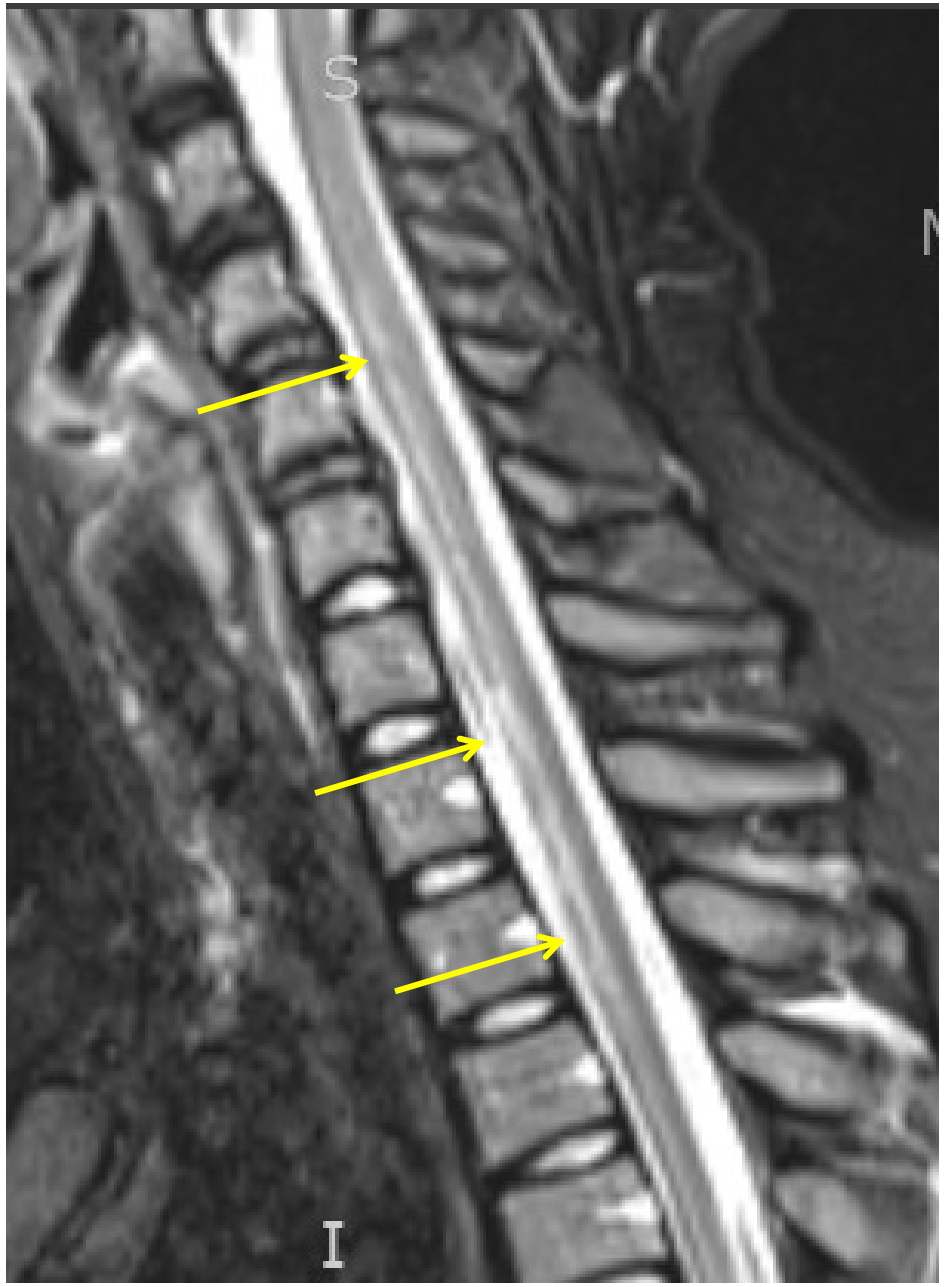


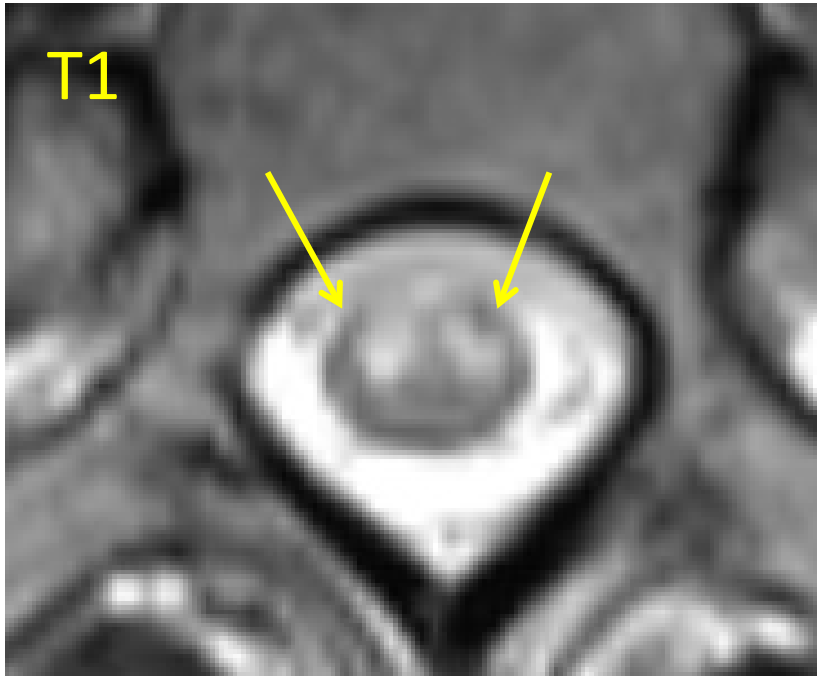
MOG antibody disease: BRAIN IMAGING



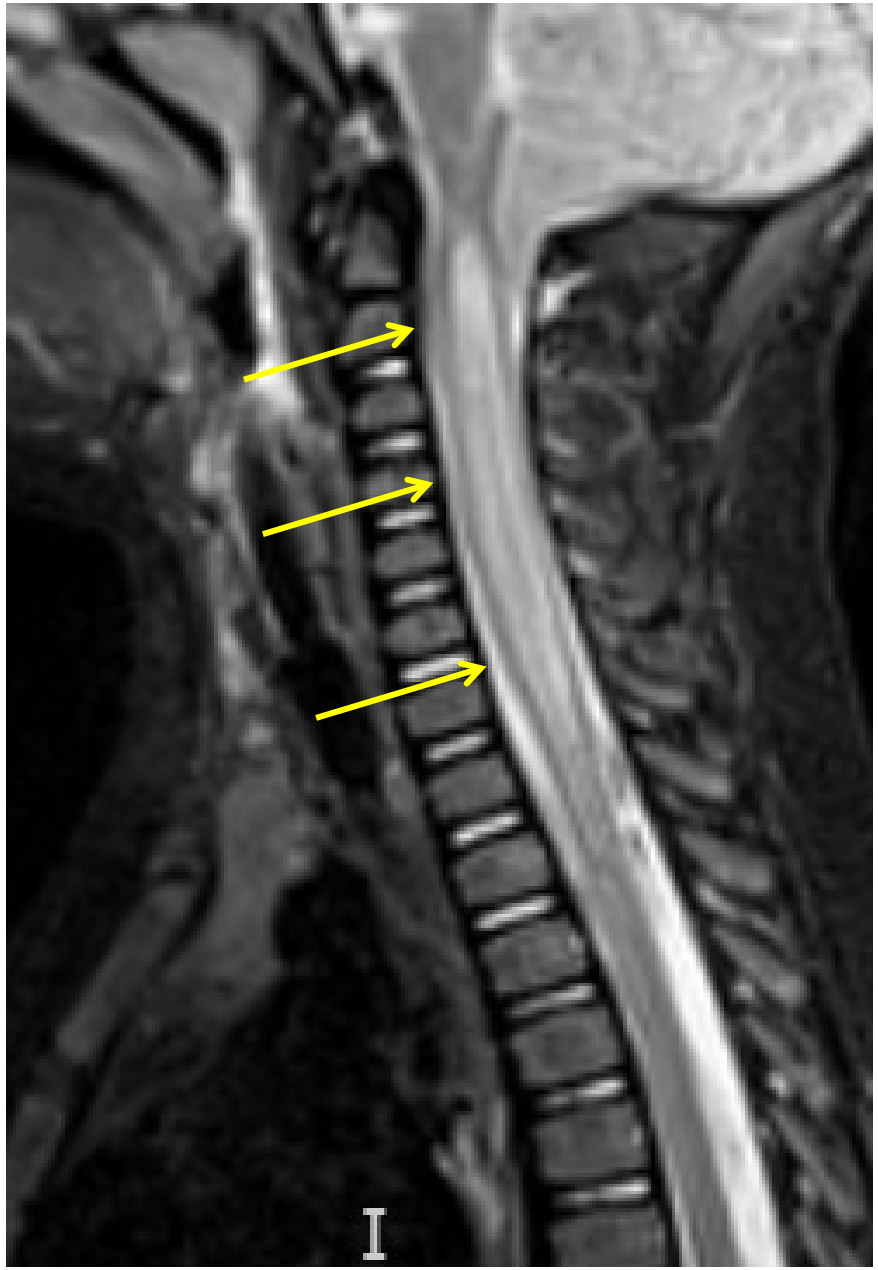


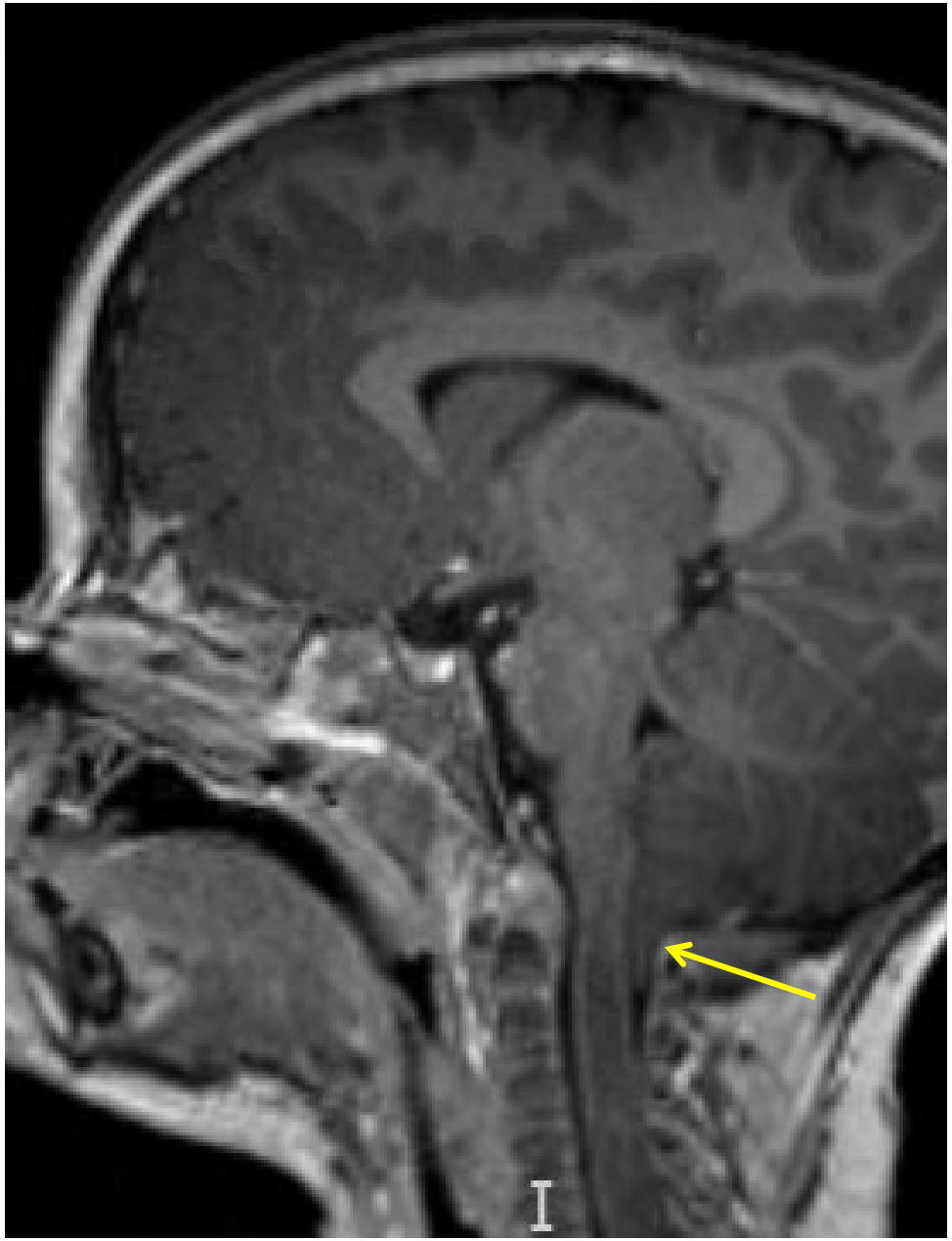
CASE: Spinal cord infarction





CASE: Chiari malformation





MRI spine for diagnosis of AFM

- Green flags
  - Longitudinally-extensive
  - Cervical cord involved
  - Hazy abnormality
  - Gray matter predominant
  - Minimal enhancement
  - +/- nerve root enhancement

- Red flags
  - Focal discrete lesions
  - Cervical cord spared
  - Round/ovoid lesions
  - White matter predominant
  - Focal enhancement
  - Cavitation/cystic

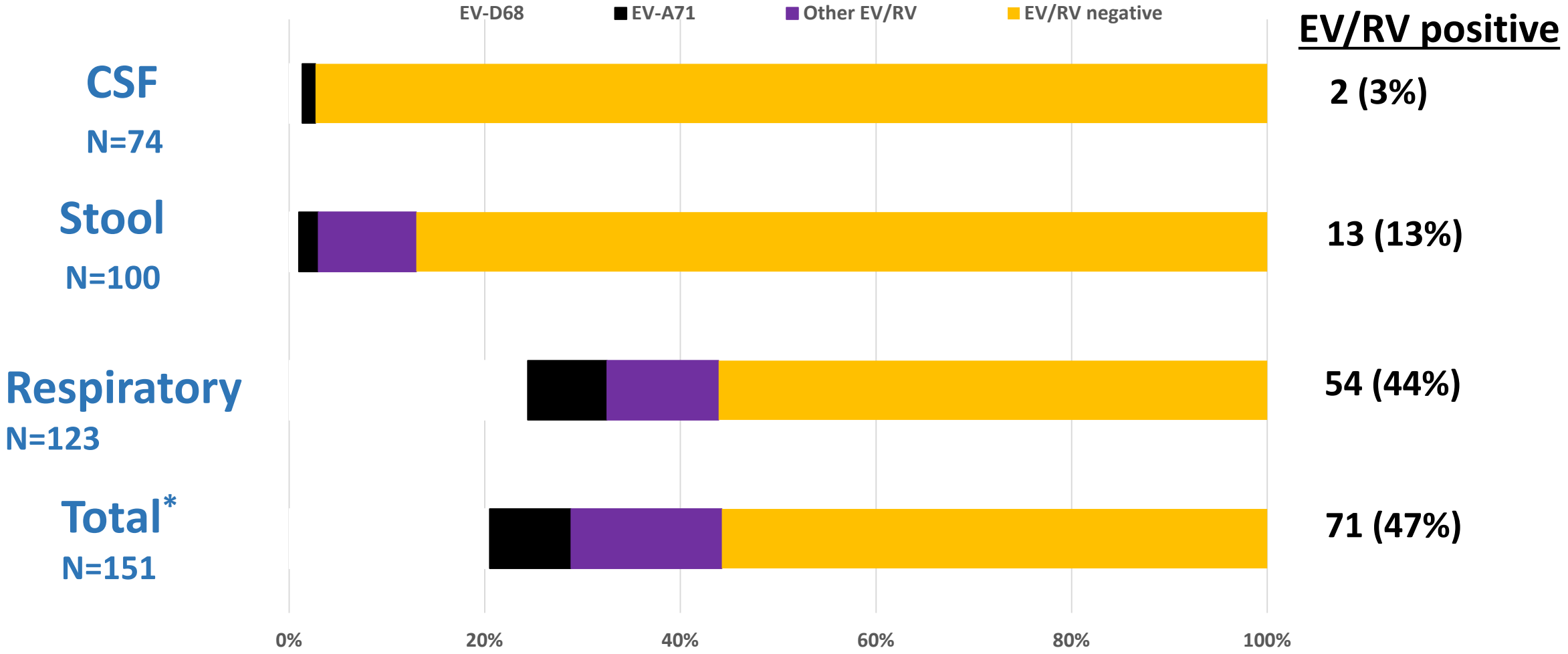
MRI brain in AFM

- Green flags
  - Normal
  - Posterior brainstem hazy hyperintensity
  - Deep gray matter hyperintensity (rare)

- Red flags
  - White matter lesions
  - Cortical lesions
  - Optic nerve lesions
  - Enhancement

Diagnostic approach for AFM: CDC surveillance 2018

Lab studies for identification of pathogens



*Some patients had multiple positive specimens

Lopez, et al. Vital Signs: Surveillance for Acute Flaccid Myelitis – US, 2018, MMWR 2019

Laboratory Testing in the Diagnosis of Acute Flaccid Myelitis 2021

Acute Flaccid Myelitis Working Group

Laboratory evaluation

- Obtain specimens as soon as possible (ie, within hours of clinical presentation).
- Respiratory samples (both nasopharyngeal and oropharyngeal): respiratory viral RT-PCR testing (to include enterovirus RT-PCR). When possible, a positive enterovirus RT-PCR result should be subtyped (to include enterovirus D68, enterovirus A71, and other common subtypes).
- Stool samples or rectal swab: enterovirus RT-PCR, viral culture for poliovirus when epidemiologically relevant (with RT-PCR of isolated virus to differentiate between wild-type and vaccine-derived virus).
- Blood sample: microbiological tests (enterovirus RT-PCR and other epidemiologically appropriate micro-organism tests—eg, West Nile virus serology), and testing for specific alternative myelopathy diagnoses to include MOG IgG and aquaporin-4 IgG.
- CSF sample: cell counts, protein, glucose, oligoclonal bands, enterovirus RT-PCR (although yield is very low), and other epidemiologically appropriate micro-organism tests.
- When RT-PCR is not readily available, samples can still be acquired and frozen for future analysis or transfer to public health authorities.
- Respiratory, stool, serum, and CSF samples should also be sent to the relevant public health authorities, according to local protocols.

Acute flaccid myelitis: cause, diagnosis, and management

Lancet 2021; 397: 334–46

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

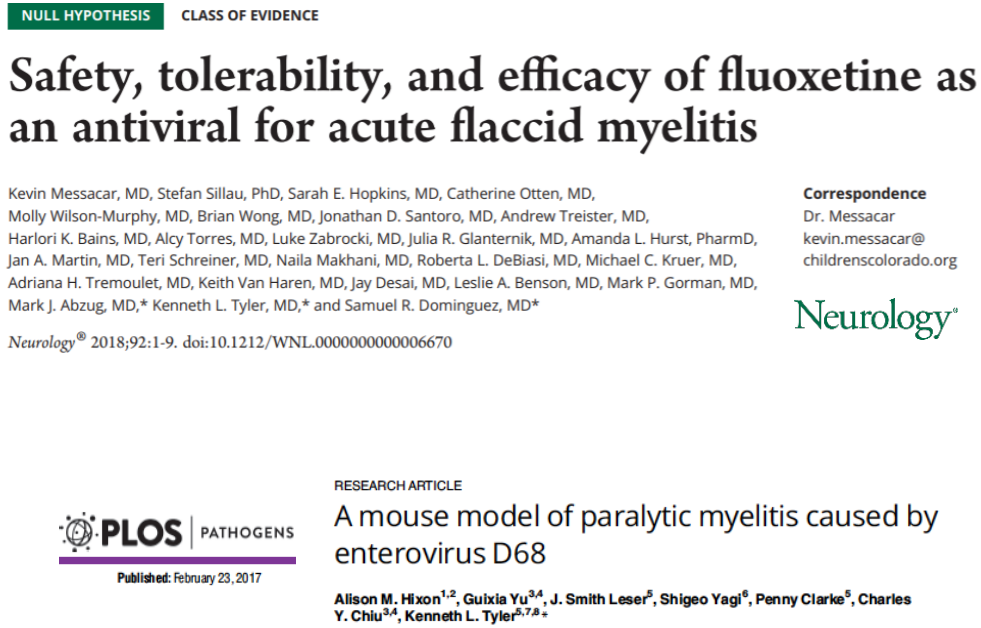
Lancet 2021; 397: 334–46

There is not a good treatment approach for AFM yet!!

Treatment Approaches For Acute Flaccid Myelitis

- Steroids??
- Plasma exchange??
- IVIG?
- Fluoxetine??

- **Rehabilitation!!**
- **Nerve transfers ?!**



NULL HYPOTHESIS CLASS OF EVIDENCE

Safety, tolerability, and efficacy of fluoxetine as an antiviral for acute flaccid myelitis

Kevin Messacar, MD, Stefan Sillau, PhD, Sarah E. Hopkins, MD, Catherine Otten, MD, Molly Wilson-Murphy, MD, Brian Wong, MD, Jonathan D. Santoro, MD, Andrew Treister, MD, Harlori K. Bains, MD, Alcy Torres, MD, Luke Zabrocki, MD, Julia R. Glanternik, MD, Amanda L. Hurst, PharmD, Jan A. Martin, MD, Teri Schreiner, MD, Naila Makhani, MD, Roberta L. DeBiasi, MD, Michael C. Kruer, MD, Adriana H. Tremoulet, MD, Keith Van Haren, MD, Jay Desai, MD, Leslie A. Benson, MD, Mark P. Gorman, MD, Mark J. Abzug, MD,* Kenneth L. Tyler, MD,* and Samuel R. Dominguez, MD*

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Neurology® 2018;92:1-9. doi:10.1212/WNL.0000000000006670

Neurology®

PLOS | PATHOGENS

Published: February 23, 2017

RESEARCH ARTICLE

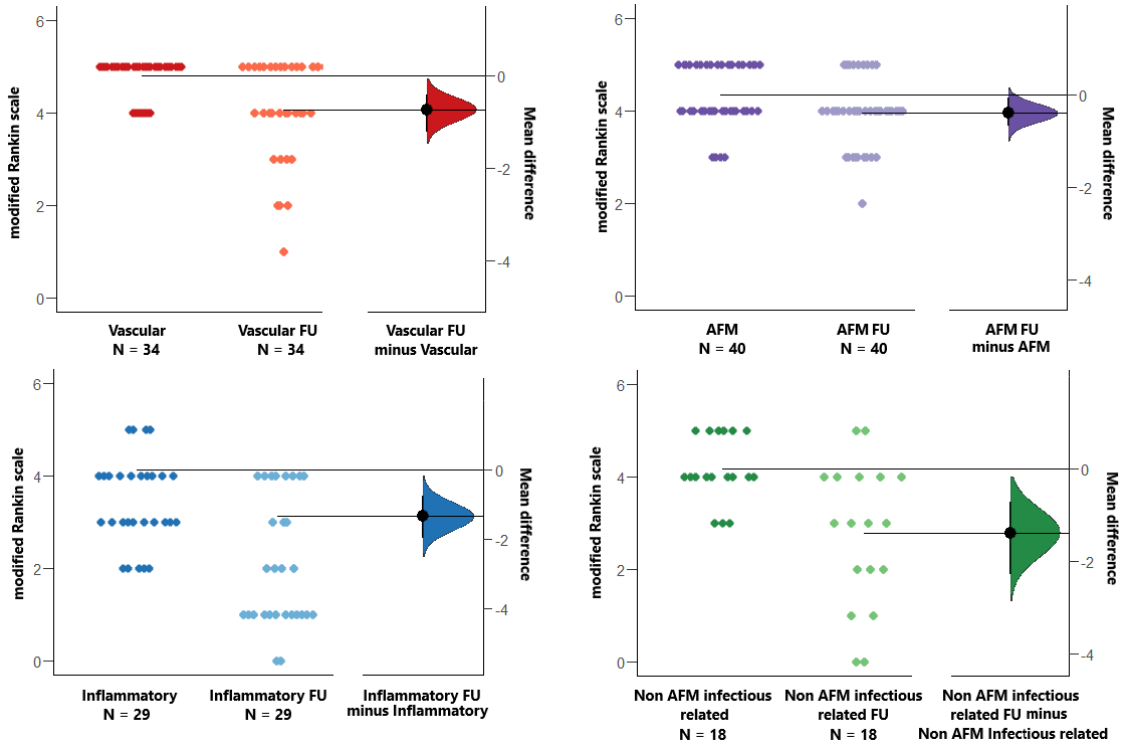
A mouse model of paralytic myelitis caused by enterovirus D68

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,+]

Hixon AM, Clarke P, Tyler KL. Evaluating Treatment Efficacy in a Mouse Model of Enterovirus D68-Associated Paralytic Myelitis.
J Infect Dis. 2017 Dec 5;216(10):1245-1253

Outcomes in Pediatric Myelopathies 2010-2018

Patients followed at JHM&M Center
2010-2018 n=131

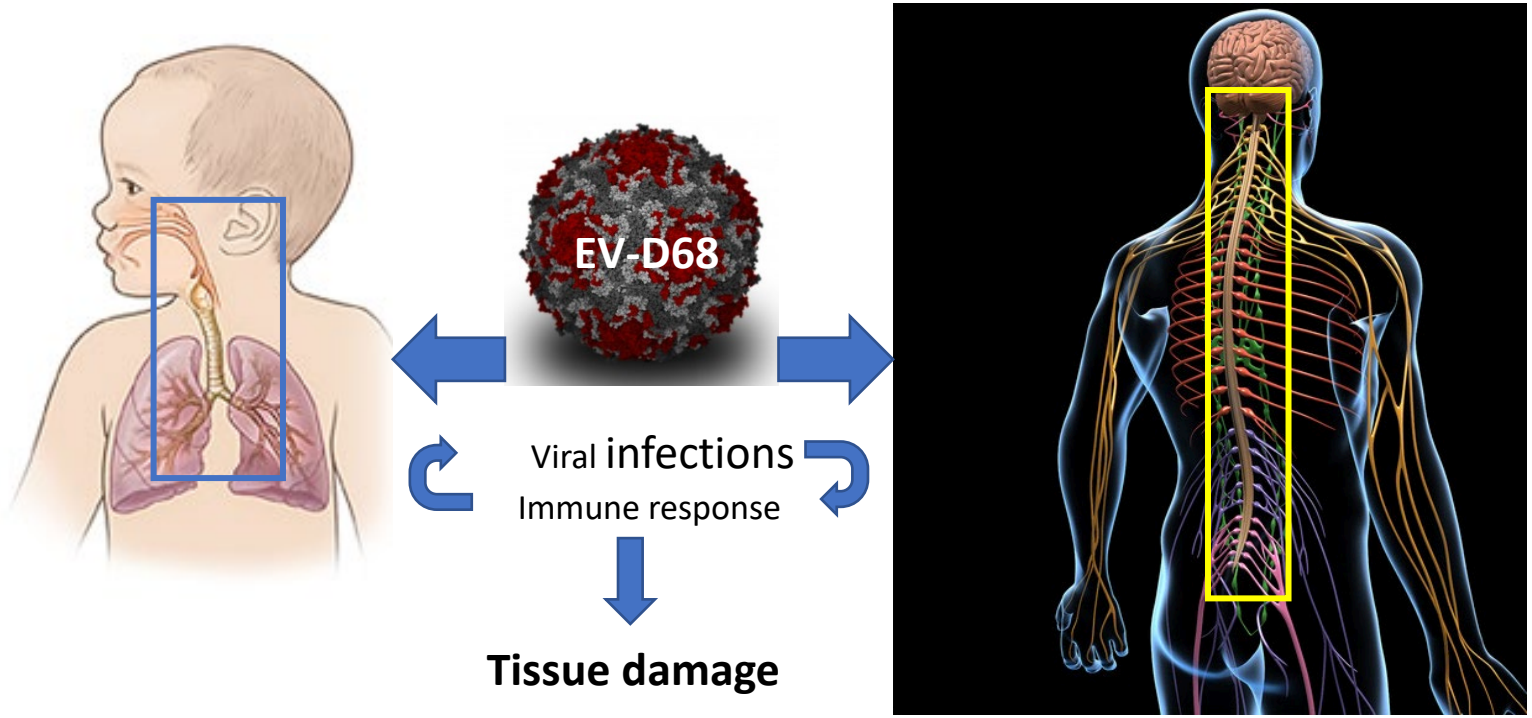


Take-home messages:

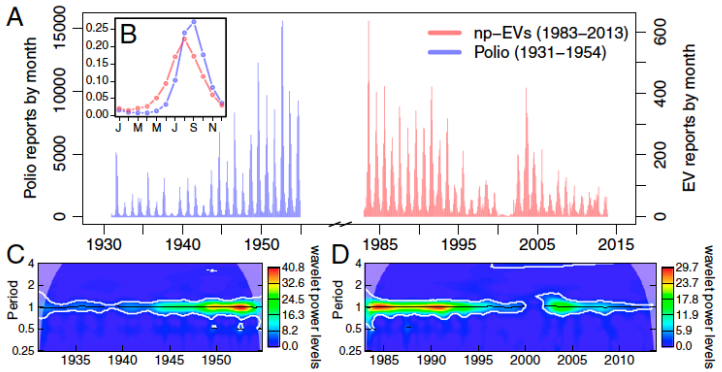
- AFM patients experience long-term sequelae and reduced rate of recover
- Patients with infectious/post-infectious and autoimmune myelopaties exhibit better rates of recovery than vascular myelopathy or AFM patients

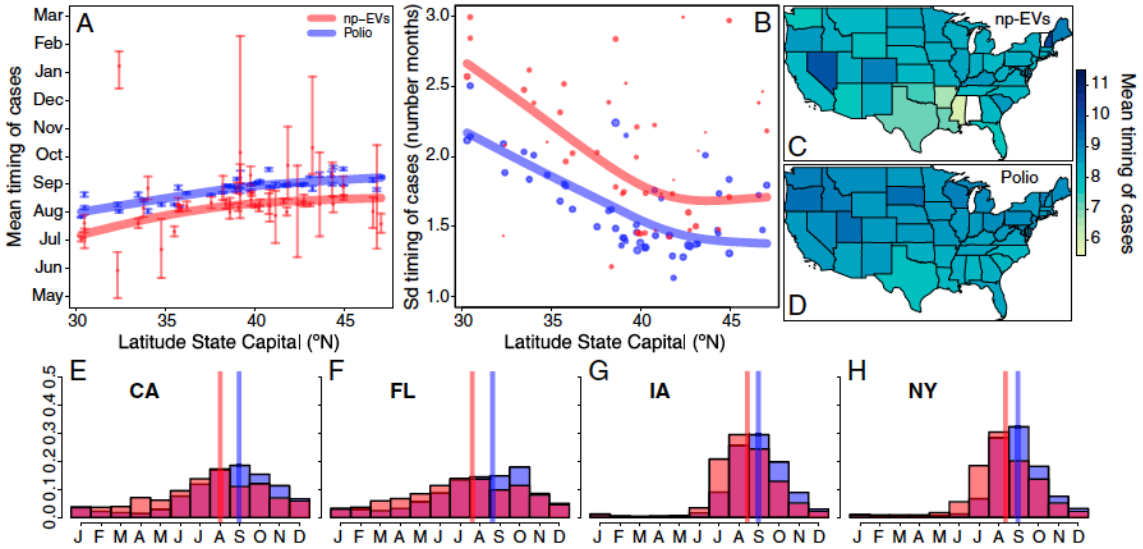
Garcia-Dominguez, M, Gordon-Lipkin E, Murphy O, Pardo CA et al.
JHM&M Center 2019, unpublished

Tissue susceptibility to Enterovirus-D68 Infection



Seasonality of non-polio enteroviruses in USA





The seasonality of nonpolio enteroviruses in the United States: Patterns and drivers

Margarita Pons-Salort[a,1], M. Steven Oberste[b], Mark A. Pallansch[b], Glen R. Abedi[b], Saki Takahashi[c], Bryan T. Grenfell[c,d], and Nicholas C. Grassly[a]

| PNAS | March 20, 2018 | vol. 115 | no. 12

Pons-Salort *et al.*, *Science* **361**, 800–803 (2018)

Serotype-specific immunity explains the incidence of diseases caused by human enteroviruses

Margarita Pons-Salort* and Nicholas C. Grassly

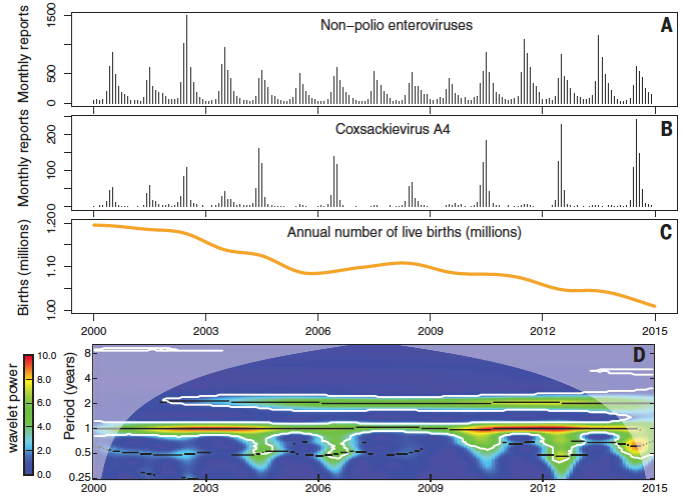
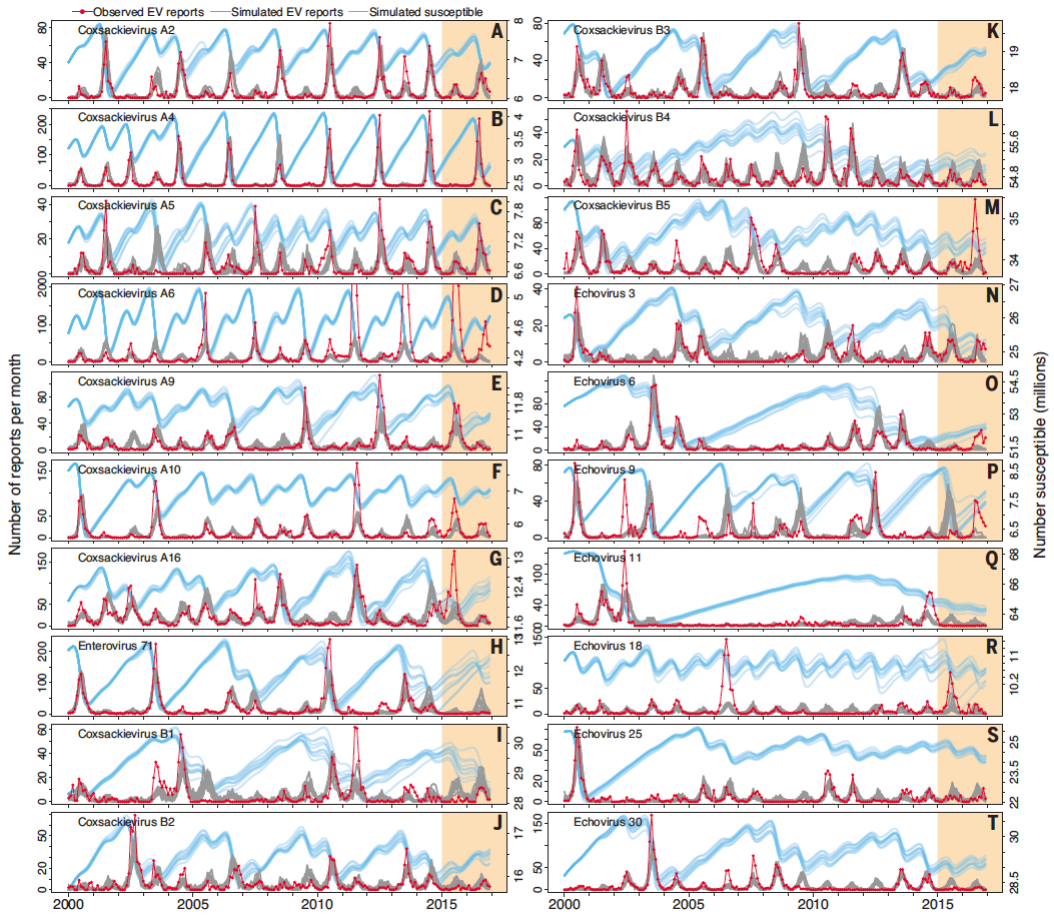


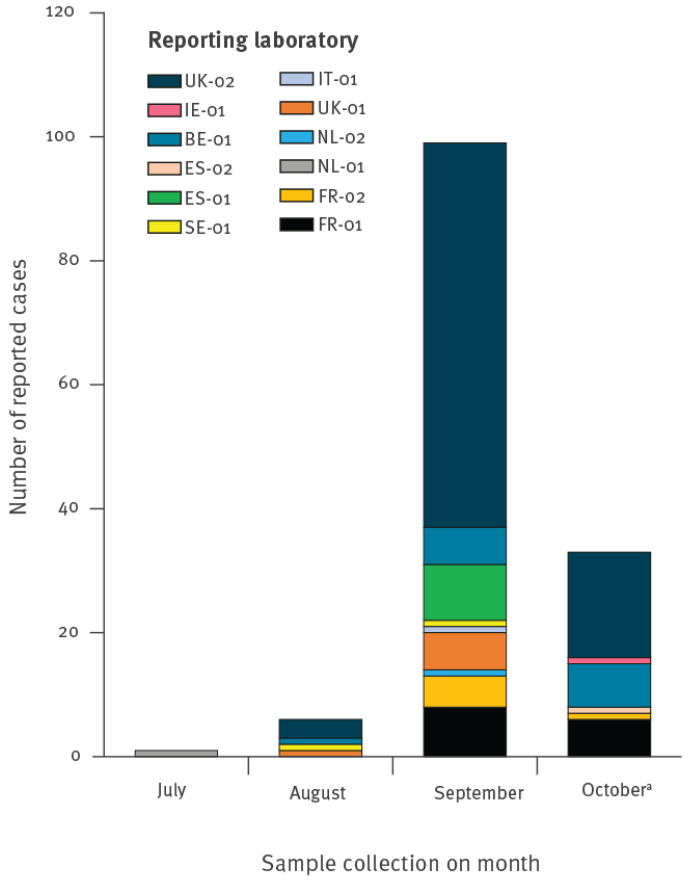
Fig. 1. Nonpolio enterovirus incidence and births in Japan (2000–2014). (**A** and **B**) Monthly number of reported enterovirus isolations from January 2000 to December 2014 for (A) nonpolio enteroviruses and (B) CV-A4. (**C**) Smoothed annual number of live births. (**D**) Average wavelet power of the square-root–transformed time series for CV-A4 showing the emergence of a biennial pattern of incidence.



Re-emergence of enterovirus D68 in Europe after easing the COVID-19 lockdown, September 2021

Euro Surveill. 2021;26(45):pii=2100998. https://doi.org/10.2807/1560-7917.ES.2021.26.45.2100998

KSM Benschop,……., TK Fisher, H. Harvala



	Number of cases	Proportion of cases
Age group		
0–3 months	7	5%
4–12 months	15	11%
13–24 months	22	16%
2–5 years	76	55%
6–15 years	9	6%
16–25 years	2	1%
26–45 years	2	1%
› 45 years	6	4%
Sex		
Female	51	37%
Male	88	63%
Symptoms (data reported for)		
Any symptom reported (n = 121)	120	99%
Fever (n = 111)	49	44%
Enteric symptoms (n = 120)	4	3%
Respiratory symptoms (n = 120)	116	97%
Neurological symptoms[a] (n = 111)	5	5%
Clinical information (data reported for)		
Hospitalised (n = 49)	30	
Pre-existing condition[b] (n = 45)	20	

Figure. EV-D68 detection in Europe, 1 July–14 October 2021 (n = 139)

Acute Flaccid Myelitis Working Group

A model of horizontal collaboration to achieve consensus on the clinical diagnosis, management and research focused on acute flaccid myelitis (AFM)

Objectives:

- To establish a consensus for diagnosis and management of AFM during the acute and chronic stages of disease
- Conceive, develop, and conduct collaborative clinical studies to understand the natural history of AFM
- To facilitate clinical and basic science research to accelerate the discovery of treatment approaches in AFM

AFM Working group Network

- Mayo Clinic (Rochester, MN)
- Children's Hospital of Wisconsin (Milwaukee)
- The Hospital for Sick Children (SickKids), U. of Toronto (Canada)

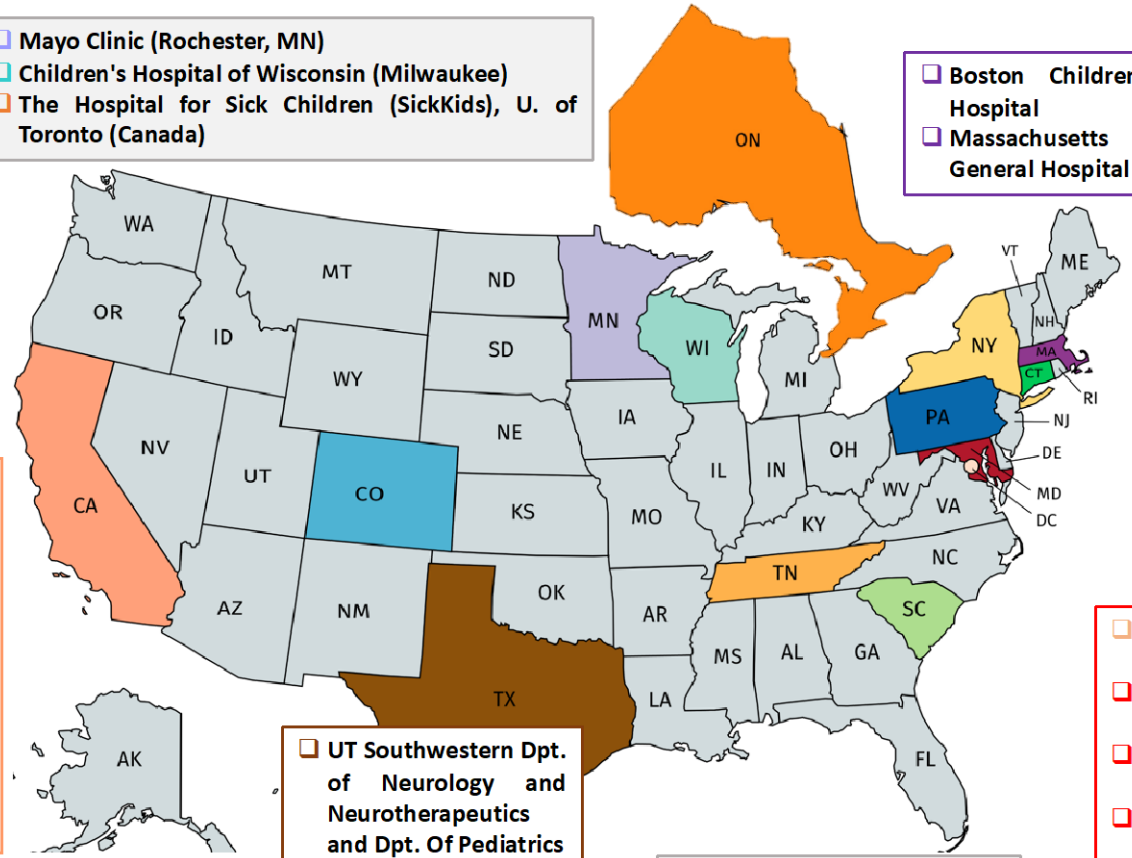
- Children's Hospital Colorado (Aurora)
- University of Colorado, Dept. of Neurology (Aurora)

- Boston Children's Hospital
- Massachusetts General Hospital

- Columbia University, Dept. of Neurology
- Columbia University Vagelos College of P &S
- Weill Cornell School of Medicine
- Mt. Sinai Hospital

- Yale School of Medicine, Dept. of Pediatrics and Neurology
- Children's Hospital of Philadelphia
- University of Pennsylvania, Dept. of Neurology

- UCSF Benioff Children Hospital
- Kaiser Permanente San Francisco Medical Center
- Stanford University, Dept. of Neurology and Pediatrics
- Children's Hospital Los Angeles
- J. Craig Venter Institute, La Jolla



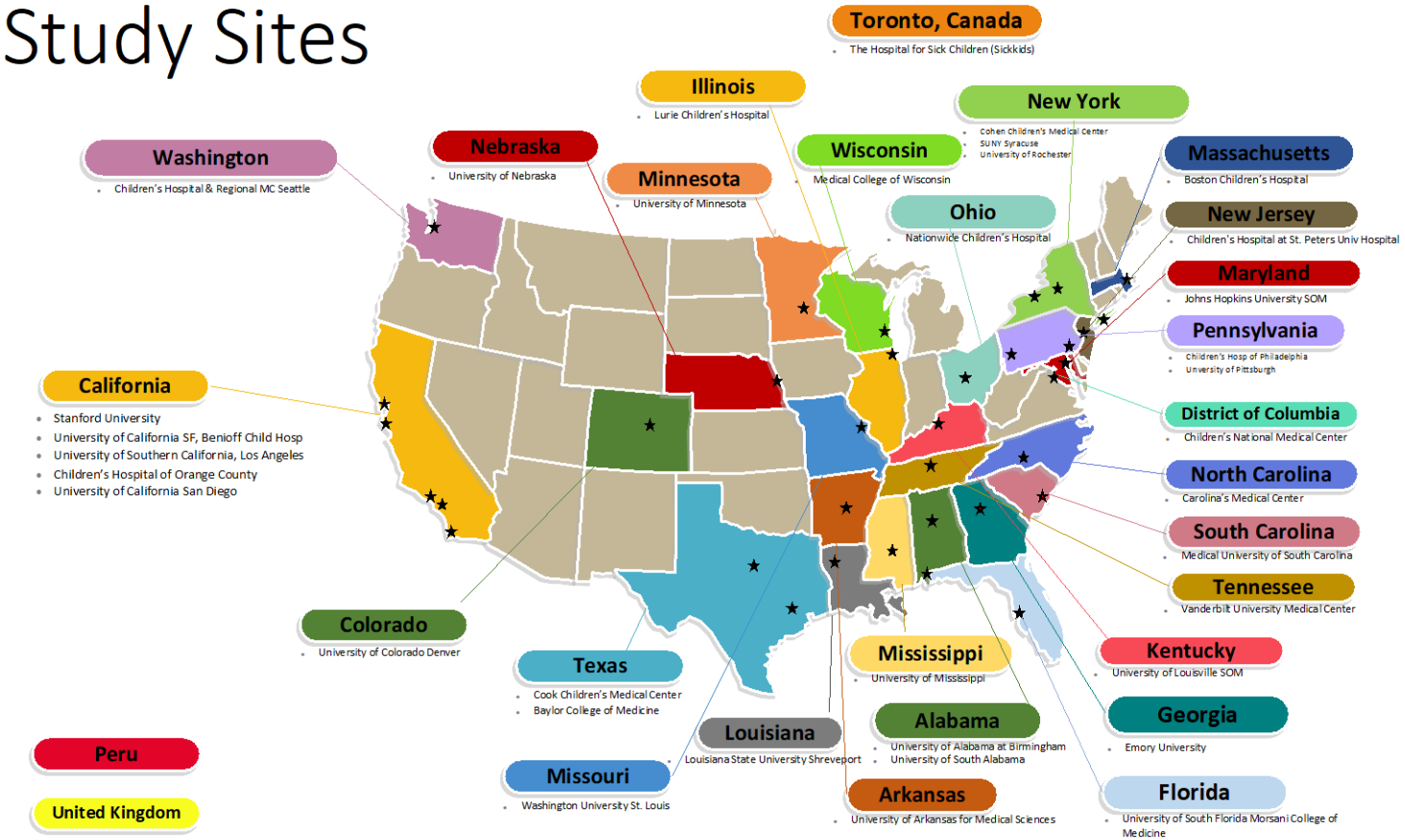
- UT Southwestern Dpt. of Neurology and Neurotherapeutics and Dpt. Of Pediatrics

- Vanderbilt University Medical Center (Nashville)
- Medical University of South Carolina (Charleston)

- Children's National Medical Center (Washington, DC)
- Johns Hopkins University School of Medicine (Baltimore)
- Johns Hopkins Bloomberg School of Public Health (Baltimore)
- Kennedy-Krieger Institute (Baltimore)
- Sinai Hospital, Dept. of Pediatric Neurology (Baltimore)
- National Institutes of Health (Bethesda)

Research for understanding AFM

NIAID Acute Flaccid Myelitis Natural History Study Sites



Group 1 (AFM Cases)
Inclusion and Exclusion Criteria

Inclusion Criteria:

- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Onset of flaccid limb weakness involving one or more extremities suggestive of possible, probable, or confirmed AFM within previous 30 days
- MRI of spinal cord that has been or will be obtained clinically
- Age < 18 years
- Weight ≥ 7.8 kg
- Agrees to Future Use of Specimens

Exclusion Criteria:

- Known condition other than AFM causing the flaccid limb weakness
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

Note: Subjects enrolling in Group 1 may subsequently be determined by the Protocol Adjudication Committee to not have AFM. This assessment will not occur in real time. If a subject is deemed to have AFM, they will be classified as Group 1A cases (possible, probable, or confirmed AFM cases). If a subject is deemed to not have AFM, they will be classified as Group 1B cases (non-AFM cases) and analyzed accordingly.

Group 2 (controls)
Inclusion and Exclusion Criteria

Inclusion Criteria:

- Signed informed consent from parent(s) or legal guardian(s), and assent from participant if indicated
- Residing household contact of a child enrolled in Group 1 of this study within previous 30 days
- Weight ≥ 6.0 kg
- Agrees to Future Use of Specimens

Exclusion Criteria:

- Flaccid limb weakness involving one or more extremities
- Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion

Note: If a subject enrolled in Group 2 subsequently develops findings suggestive of AFM, they may be asked if they would like to enroll into Group 1 of the study and be followed and analyzed accordingly.

Acute Flaccid Myelitis:

What we have learned in order to be prepared

Google: AFM Virtual Symposium Youtube

SRNA
connect. care. cure.
Siegel Rare Neuroimmune Association

2020 AFM Virtual Symposium – Part I

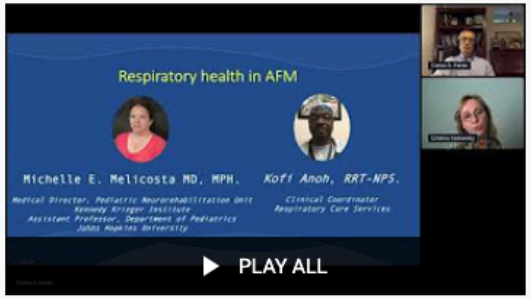
14 videos • 164 views • Last updated on Jun 14, 2020

2020 AFM Virtual Symposium – Part II

10 videos • 47 views • Last updated on Jun 15, 2020

2020 AFM Virtual Symposium – Part III

12 videos • 105 views • Last updated on Jun 20, 2020



2020 AFM Virtual Symposium – Part IV

14 videos • 46 views • Updated 7 days ago

Acute Flaccid Myelitis Working Group

Acute Flaccid Myelitis:
What we have learned in order to be prepared

SRNA connect. care. cure. | Siegel Rare Neuroimmune Association

Google: AFM Virtual Symposium Youtube

Part I https://www.youtube.com/playlist?list=PLXi60bECkjnWc16yfgMVN1u7qOuRM8d14

Part II https://www.youtube.com/playlist?list=PLXi60bECkjnVje4VHjzW5pzkeYtSJBdqt

Part III https://www.youtube.com/playlist?list=PLXi60bECkjnV2Iqm1SxKm_V2QvDHfg3yR

Part IV https://www.youtube.com/playlist?list=PLXi60bECkjnVwvAk3_fPWS700NR6JeBaS

Part V https://www.youtube.com/playlist?list=PLXi60bECkjnVSYQ3C8lte69RmWbaguX_I