



New Perspectives on Myelitis: The Reemergence of Acute Flaccid Myelitis

Benjamin Greenberg, M.D., M.H.S.
Director, Transverse Myelitis and NMO Program
Department of Neurology and Neurotherapeutics
Department of Pediatrics
University of Texas Southwestern Medical Center

Disclosures

- Dr. Greenberg has received consulting fees from Alexion, EMD Serono, Novartis and Celgene
- Dr. Greenberg has received grant support from NIH, NMSS, PCORI, TMA, Guthy Jackson Charitable Foundation, Meddimune, Chugai, Medday
- Dr. Greenberg is an unpaid member of the Transverse Myelitis Association Board.

Classical Descriptions of Transverse Myelitis

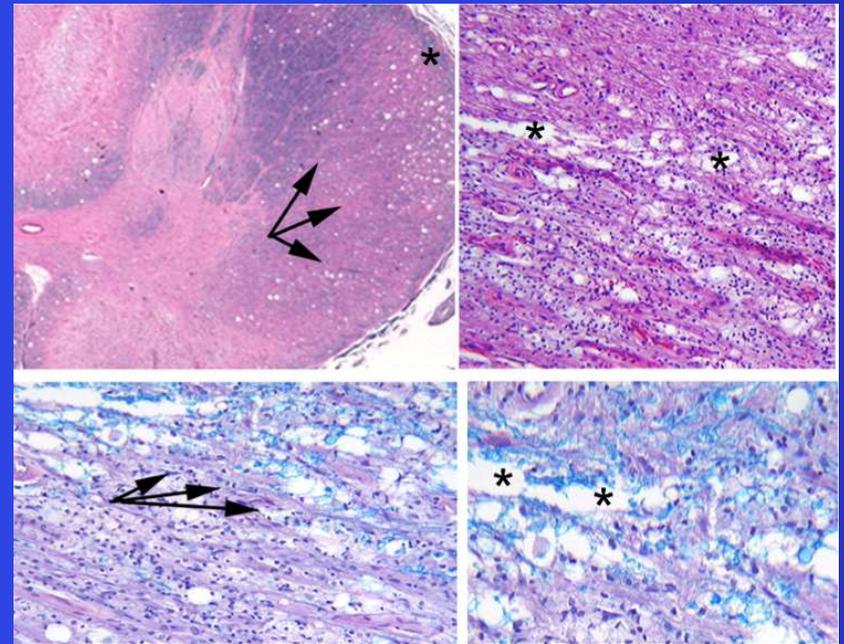
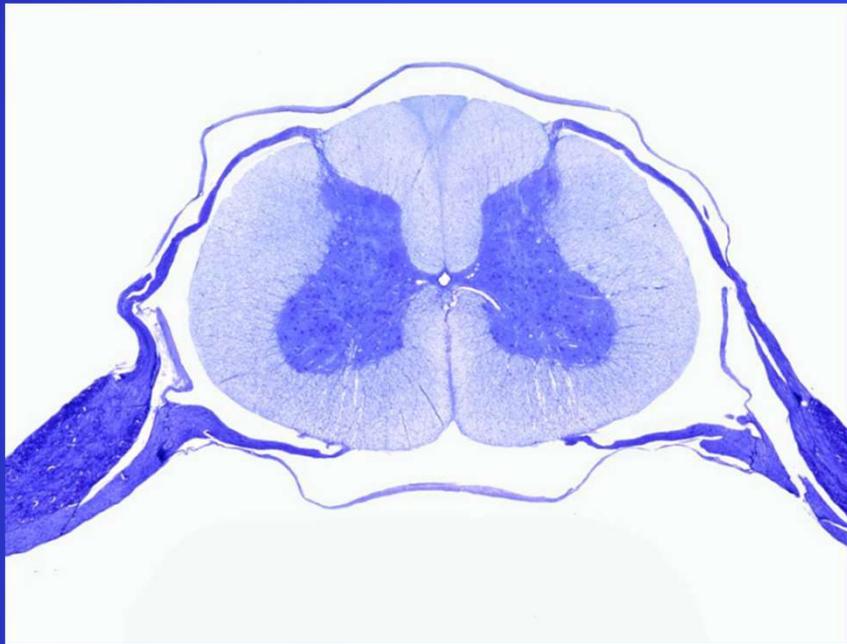
The way I was taught.....

History of Transverse Myelitis Semantics

- The term acute myelitis has been referenced for over 125 years with Dr. H.C. Bastain describing several cases with autopsy findings in 1882.
- In 1928 Dr. Frank Ford postulated that some cases of myelitis were post infectious in etiology.
- In 1931 Drs. Miller and Ross used the term “transverse” myelitis when describing a myelitis patient who had a post measles neurologic event.

ACUTE TRANSVERSE MYELITIS
COMPLICATING MEASLES
By F. G. MILLER AND A. G. ROSS,
Elk Point, Alta.
In December, 1926, a rather severe epidemic of measles occurred in the “Yankee” School District, twelve miles southeast of Elk Point, Alberta.

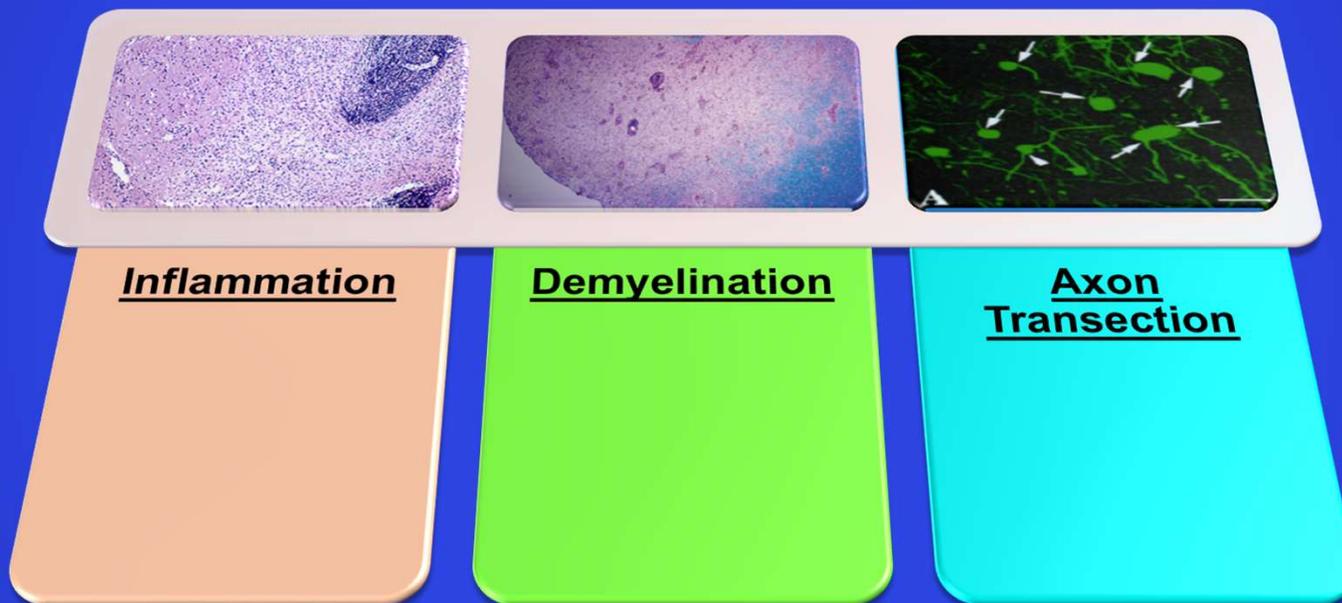
What is Transverse Myelitis?



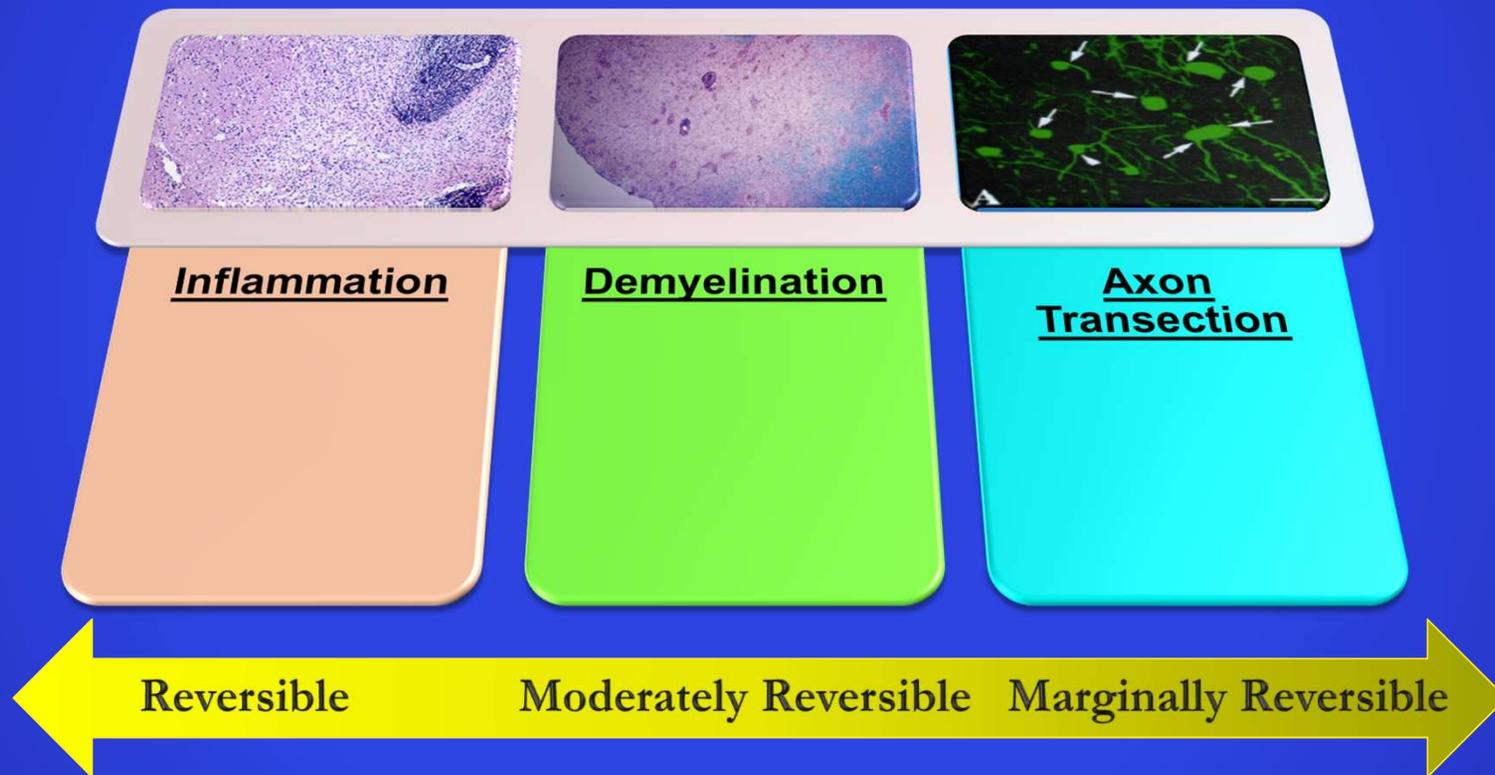
What are the Goals of Therapy in Acute Transverse Myelitis?

PUT THE FIRE OUT.

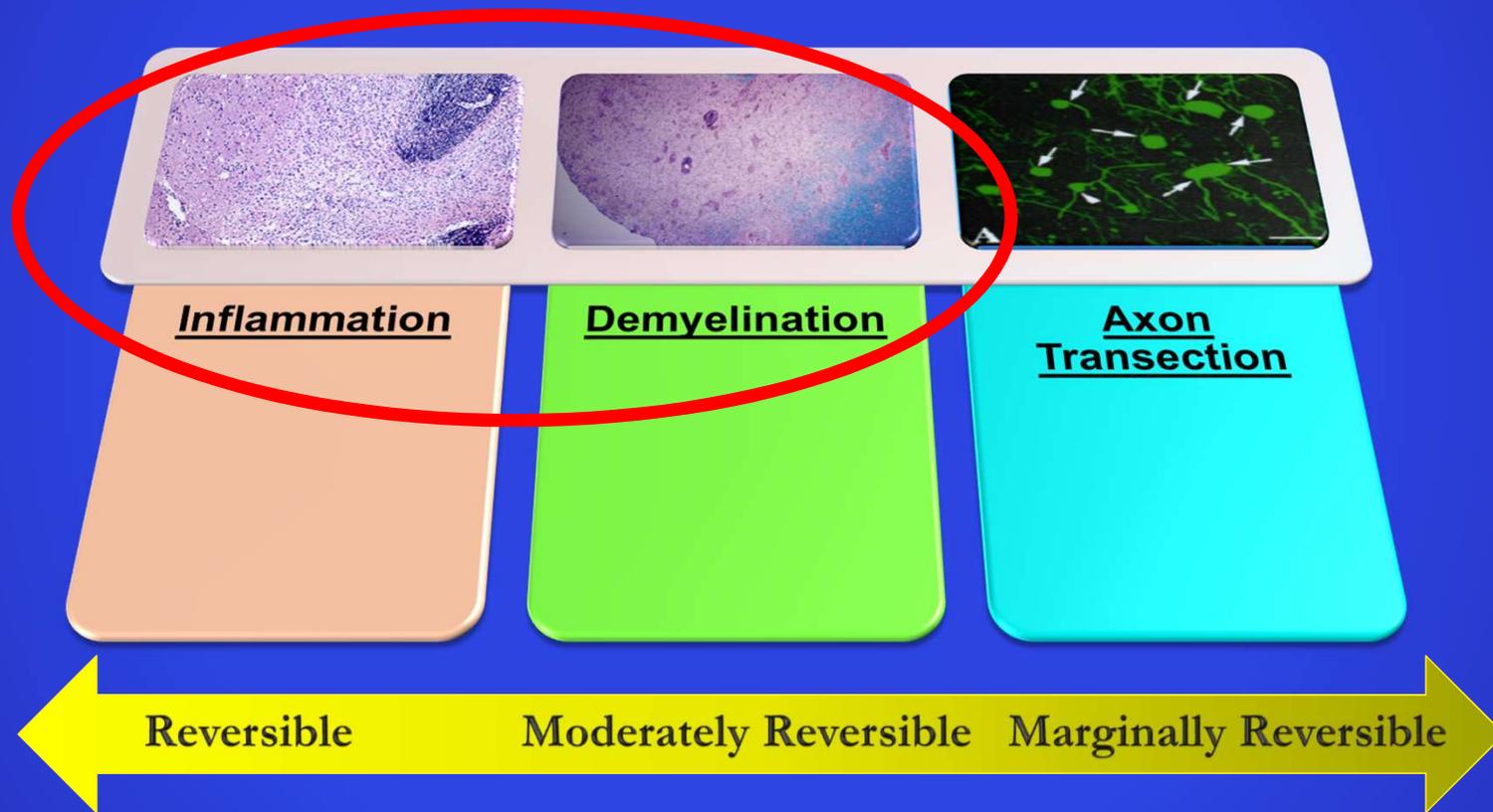
Symptoms are Mediated by Various Pathogenic Processes



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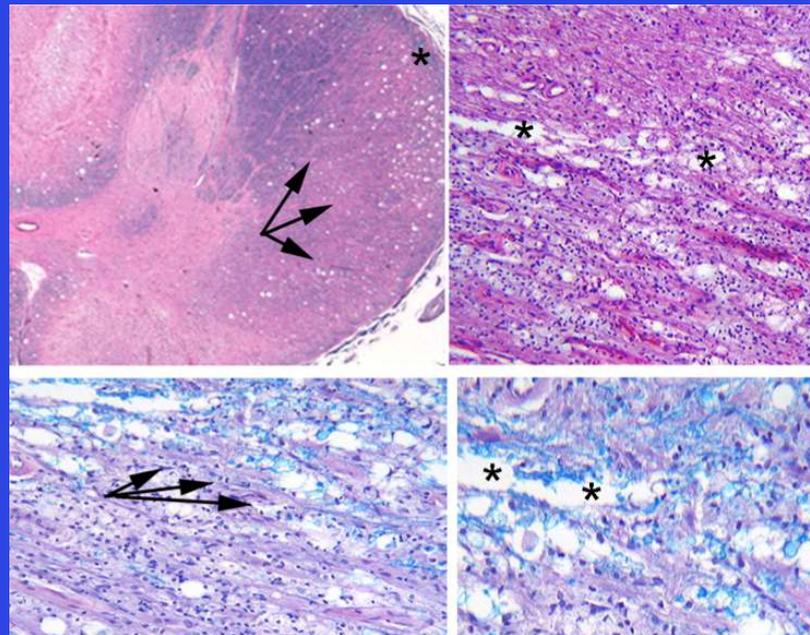


Symptoms are Mediated by Various Pathogenic Processes

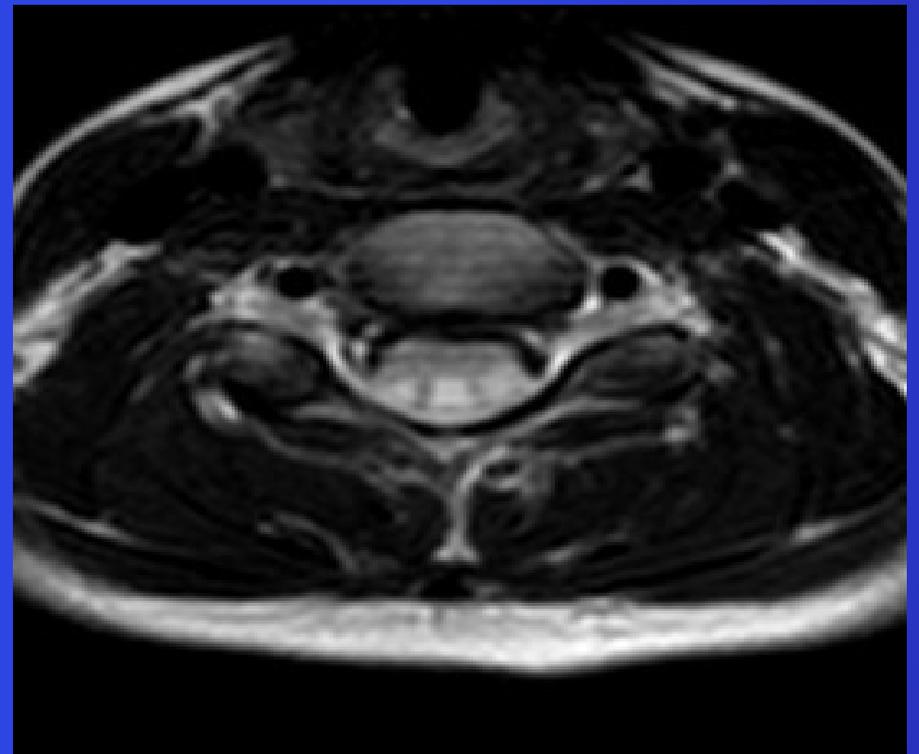
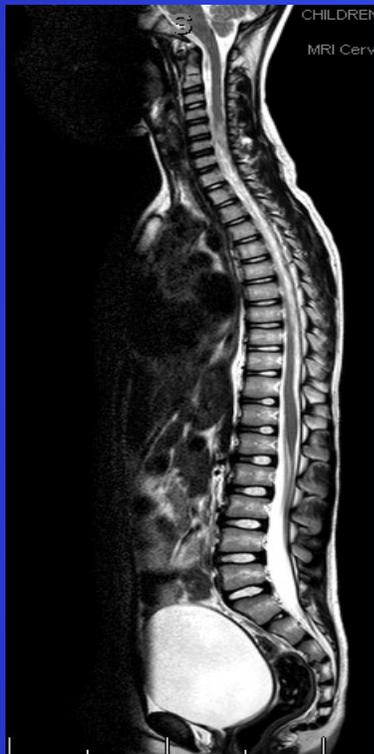


New Insights About TM Are Based on Exposing the Fallacies of Our Dogma.....

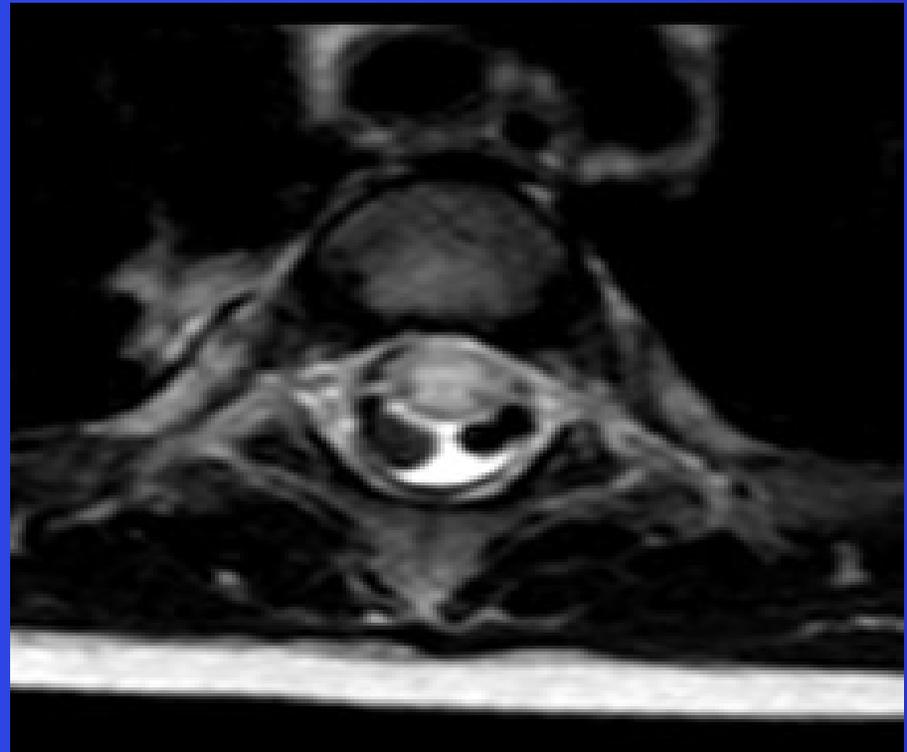
TM is Not Just a White Matter Disease



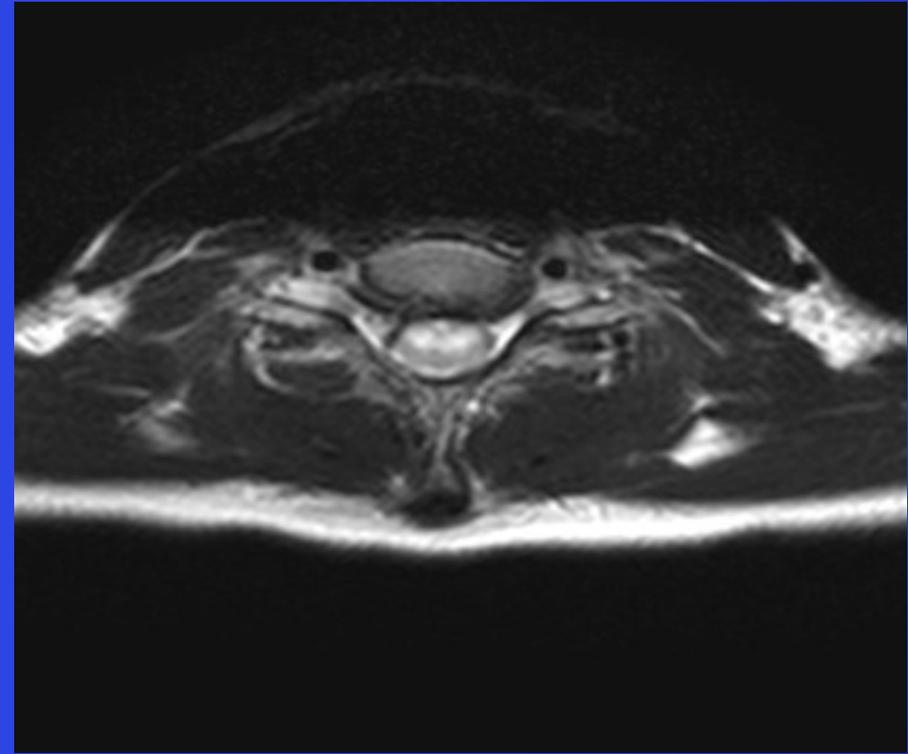
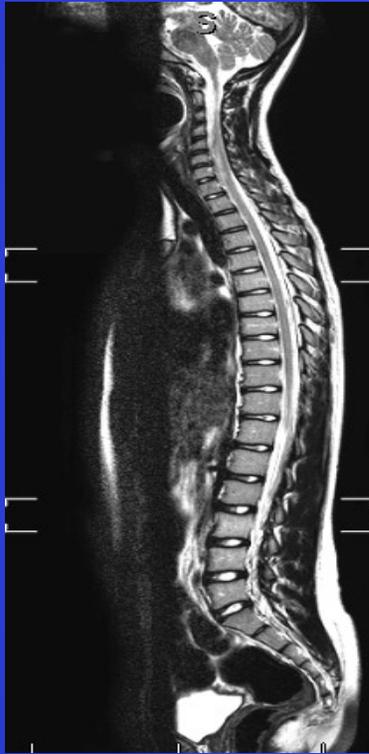
White Matter Restricted



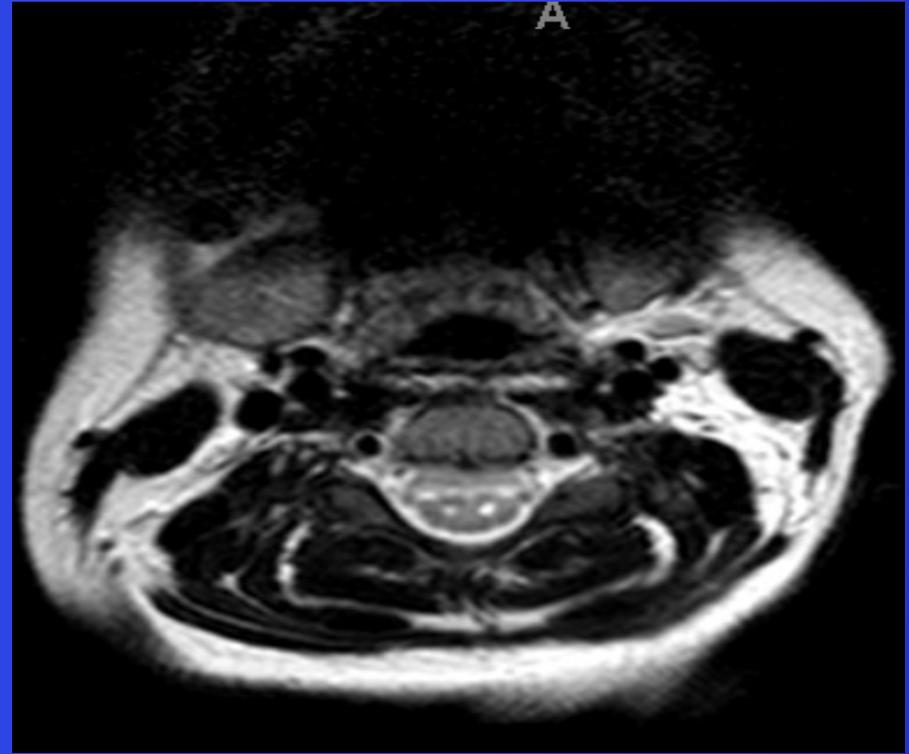
Central Cord



Mixed Gray and White Matter



Gray Matter



Review of Clinical Cases At Dallas Children's Revealed 6 Subtypes of TM

- White matter (10-20%)
 - Dorsal Column
 - Lateral Column
- Gray matter (10-20%)
- Mixed white and gray (20-40%)
- Central Cord Syndrome (10-20%)
- Anterior Cord Syndrome (10-20%)

Recognizing Subtypes of Myelitis: Acute Flaccid Myelitis

Fall 2012

- Carol Glaser, MD, CDPH, received call (while at California State Health Department*) received request for testing for polio
- Patient was young adult male, no travel, with flaccid paralysis
- MRI spine gray matter involvement, several segments longitudinally extensive
- Within 2 weeks
 - 2 additional reports of AFP with anterior horn myelitis of unknown etiology
- Continued to see cases

Cluster of Acute Paralysis in Colorado in 2014

Acute Neurologic Illness of Unknown Etiology in Children – Colorado, August-September 2014

Weekly

October 10, 2014 / 63(40);901-902

On October 3, 2014, this report was posted as an MMWR Early Release on the MMWR website (<http://www.cdc.gov/mmwr>).

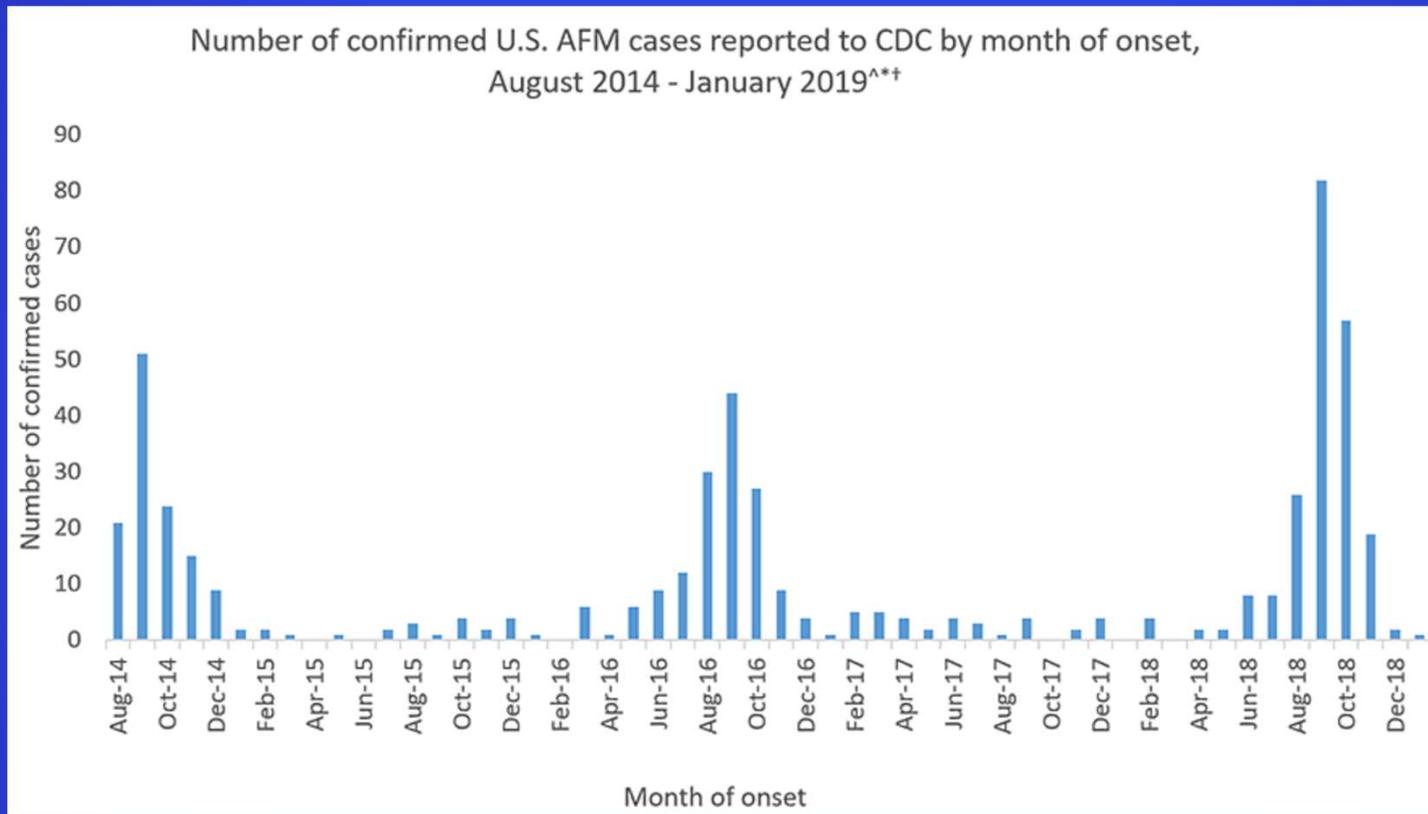
Daniel M. Pastula, MD¹, Negar Aliabadi, MD¹, Amber K. Haynes, MPH², Kevin Messacar, MD³, Teri Schreiner, MD³, John Maloney, MD³, Samuel R. Dominguez, MD³, Emily Spence Davizon, MPH⁴, Eyal Leshem, MD², Marc Fischer, MD⁵, W. Allan Nix², M. Steven Oberste, PhD², Jane Seward, MBBS², Daniel Feikin, MD², Lisa Miller, MD⁴ (Author affiliations at end of text)

UTSW Hosted Pan American Conference Call September 29, 2014

- Multiple centers seeing cases of acute paralysis.
- Recognition that multiple names were being used to describe the syndrome
- **PROPOSED NAME: Acute Flaccid Myelitis**
 - This name encompasses the important features of the condition: onset, evidence of lower motor neuron injury, spinal cord involvement, while not ascribing the condition to presumed etiologies.



AFM in Current Perspective



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Clinical Presentations

- Similar to polio
 - Flaccid weakness of one or more limbs
 - Symptoms evolve over hours to days
 - Often preceded by respiratory symptoms/fever
 - 25-40% require a ventilator
 - MRI reveal predominant gray matter involvement

UT Southwestern/Childrens Experience

Year	Inpatient
2009	
2010	
2011	
2012	
2013	
2014	3
2015	0
2016	7

UT Southwestern/Childrens Experience

Year	Inpatient
2009	8
2010	6
2011	1
2012	3
2013	2
2014	3
2015	0
2016	7

CAPTURE Study

Collaborative **A**ssessment of **P**ediatric **T**ransverse myelitis: **U**nderstand,
Reveal, **E**ducate

PCORI Funded Multicenter Study of Pediatric TM Outcomes 2013-2018

CAPTURE Study AFM Demographics

	2014	2015	2016	2017	Total
N	16	6	23	1	46
Male	9	4	16	1	30
Mean Age	7.7	10.6	4.4	16.9	6.7
Caucasian	9	5	17	1	32
African American	2	0	2	0	4
Asian	3	0	1	0	4
Hispanic	2	2	3	0	7
Non-hispanic	13	4	19	1	37

Unpublished Data

CAPTURE Study AFM Seasonality Data

Month of onset	2014	2015	2016	2017	Total
Jan	0	1	1	1	3
Feb	0	2	1	0	3
Mar	0	0	0	0	0
Apr	0	0	0	0	0
May	0	1	2	0	3
Jun	1	1	0	0	2
Jul	3	0	3	0	6
Aug	0	0	7	0	7
Sep	8	0	3	0	11
Oct	3	0	3	0	6
Nov	1	1	3	0	5
Dec	0	0	0	0	0

35 of 46 Cases (76.1%)
were July through November

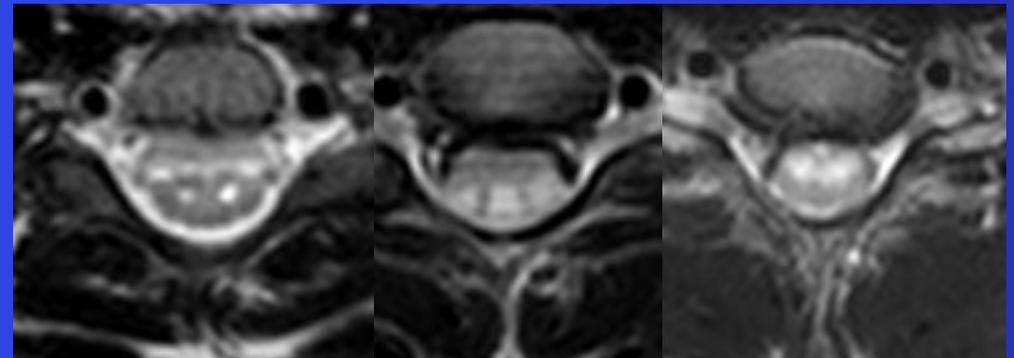
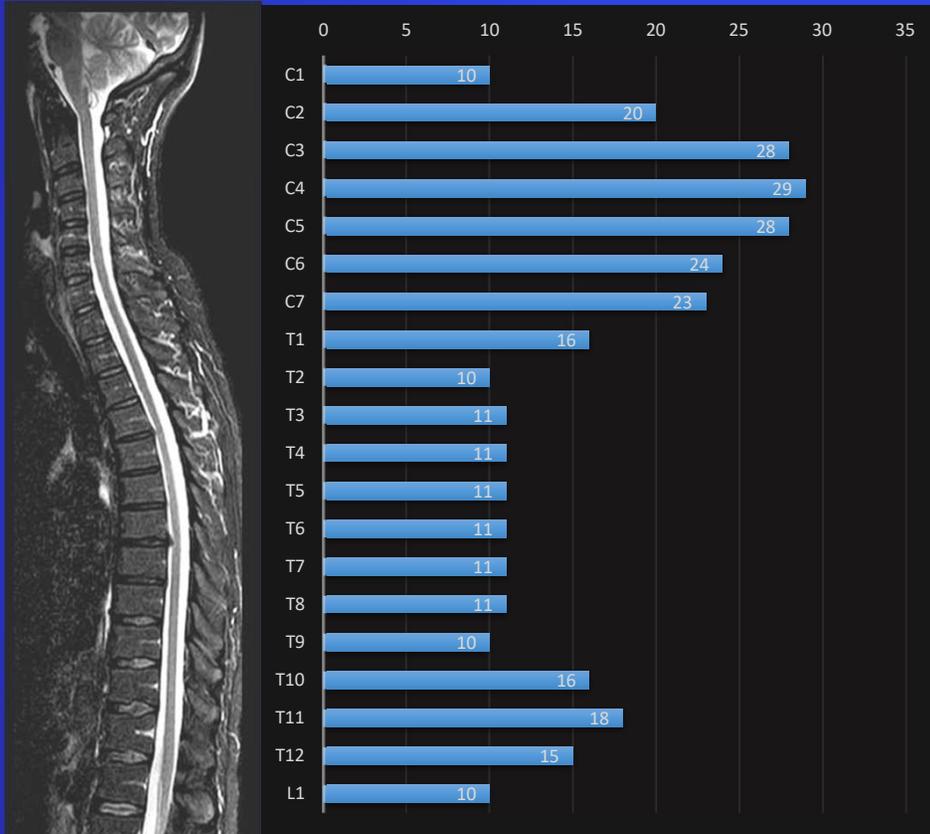
If Restricted to EVEN Years
34 of 39 cases (87.2%)
were July through November

Unpublished Data

CAPTURE Study AFM Clinical and Paraclinical Characteristics

Weakness at onset	2014	2015	2016	2017	Total
RUE	8	1	9	0	18
LUE	6	2	11	0	19
RLE	7	3	14	1	25
LLE	6	4	13	1	24
Protein Mean	61.8	33.5	95	32	
Protein Min	20	23	20	32	
Protein Max	190	41	596	32	
CSF WBC Mean	49.4	15.5	32	0	
CSF WBC Min	0	0	0	0	
CSF WBC Max	287	49	160	0	
Resp PCR pos	4	1	11	0	16
Resp PCR Neg	6	2	4	1	13
Resp PCR not done	6	0	7	0	13

CAPTURE Study AFM Cohort MRI Characteristics



Year	2014	2015	2016	2017	Total
Gray Matter Restricted	8	3	5	0	16
White Matter Restricted	0	0	1	0	1
Gray/White Mixed	8	3	6	1	18

The Challenges in Diagnosis

- Clinically difficult to differentiate
 - Spinal cord lower motor neuron damage
 - Peripheral neuropathy
 - Demyelinating
 - Axonal
 - Neuromuscular junction damage
- Testing is critical
 - MRI (timing important to interpretation)
 - Electrophysiology
 - Axonal pattern cannot differentiate between peripheral or spinal cord based damage to motor neuron!

What is Causing AFM?

Pathologies That Damage the Anterior Horns

- Neurodegenerative Disorders
 - Amyotrophic Lateral Sclerosis
 - Spinal Muscular Atrophy
- Toxic Exposures
 - Lead toxicity
- Infections
 - Flaviviruses (West Nile, Japanese encephalitis)
 - Enteroviruses (genus that include enterovirus and polioviruses)
- Immune Mediated
 - Immune mediated after exposure to porcine tissue

Acute Anterior Horn Cell Disease

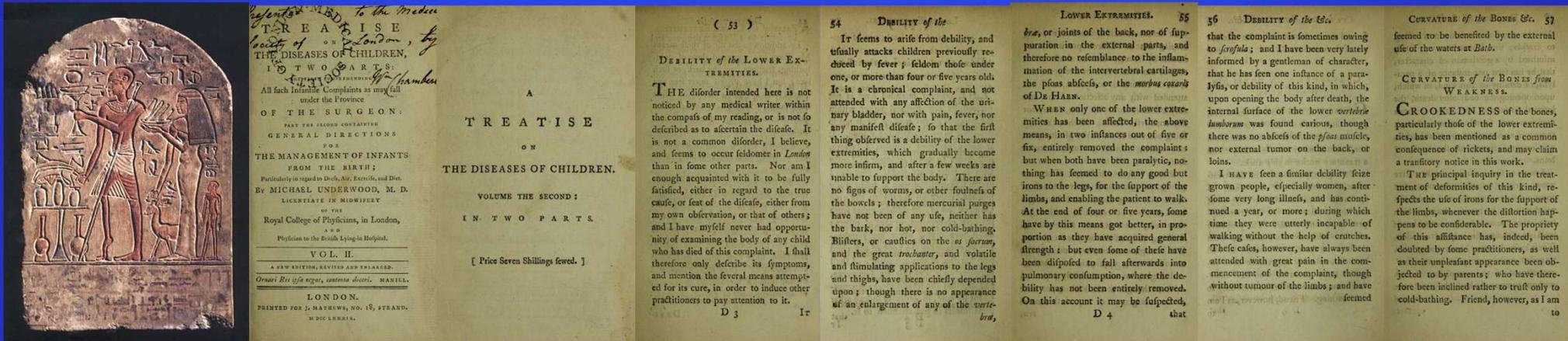
Communication between two physicians:

“.....all less than three years old, fell ill in the beginning of August with symptoms of mild fever, which disappeared within eight days; but, low and behold! the children could then no longer walk but had flaccid paralysis of their hips and lower limbs.”

Letter from Dr. Christopher Carlander to Professor Pehr Afzlius in Sweden

September 22, 1808

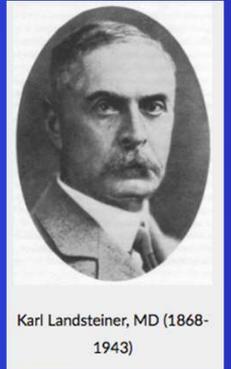
History of Poliomyelitis



Dr. Michael Underwood
 Stone Tablet from 15th Century BC
 A Treatise On the Diseases of Children
 1789

Proving Poliomyelitis Was Viral

-at a medical meeting in Vienna on December 18, 1908, the immunologist Landsteiner and his assistant Popper were able to demonstrate microscopic slides of one human and two monkey spinal cords, all showing the familiar histological picture of acute poliomyelitis. Sections from the human infection came from a boy of nine years who had died after an illness of three days. Bacterial cultures of the spinal cord had been sterile, and injection of a suspension of the ground-up cord into rabbits, guinea pigs, and mice also had given negative results.



Karl Landsteiner, MD (1868-1943)

A History of Poliomyelitis, JR Paul

Immune Response to the Polio Virus

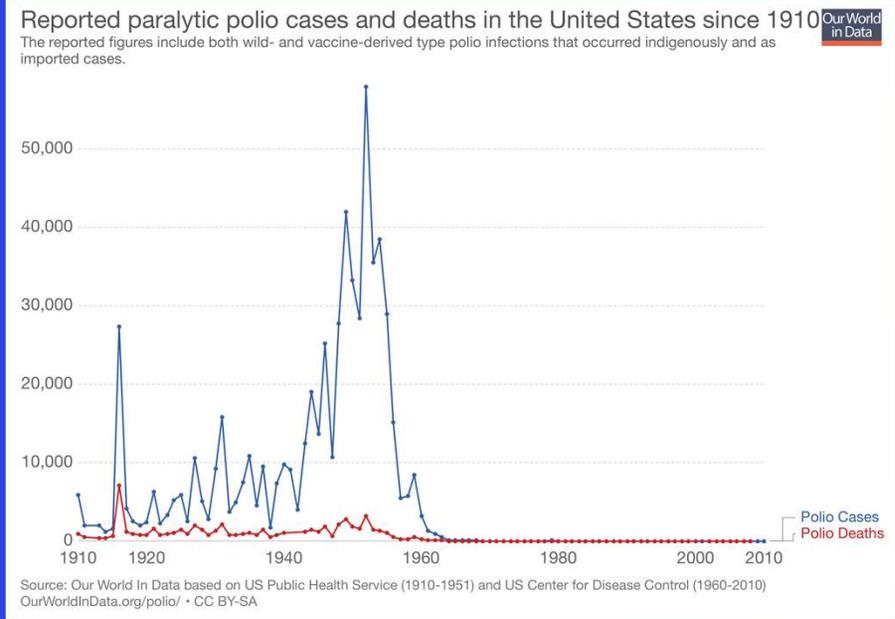


Early Polio Outbreaks

Year	Location	Cases (deaths)
1808	Göteborg, Sweden	4 (-)
1835	Worksop, UK	4 (-)
1841	Louisiana, USA	10 (-)
1868	Modums, Norway	14 (4)

Polio Before and After Vaccination

A hospital room in the US with patients in iron lungs in 1952⁷



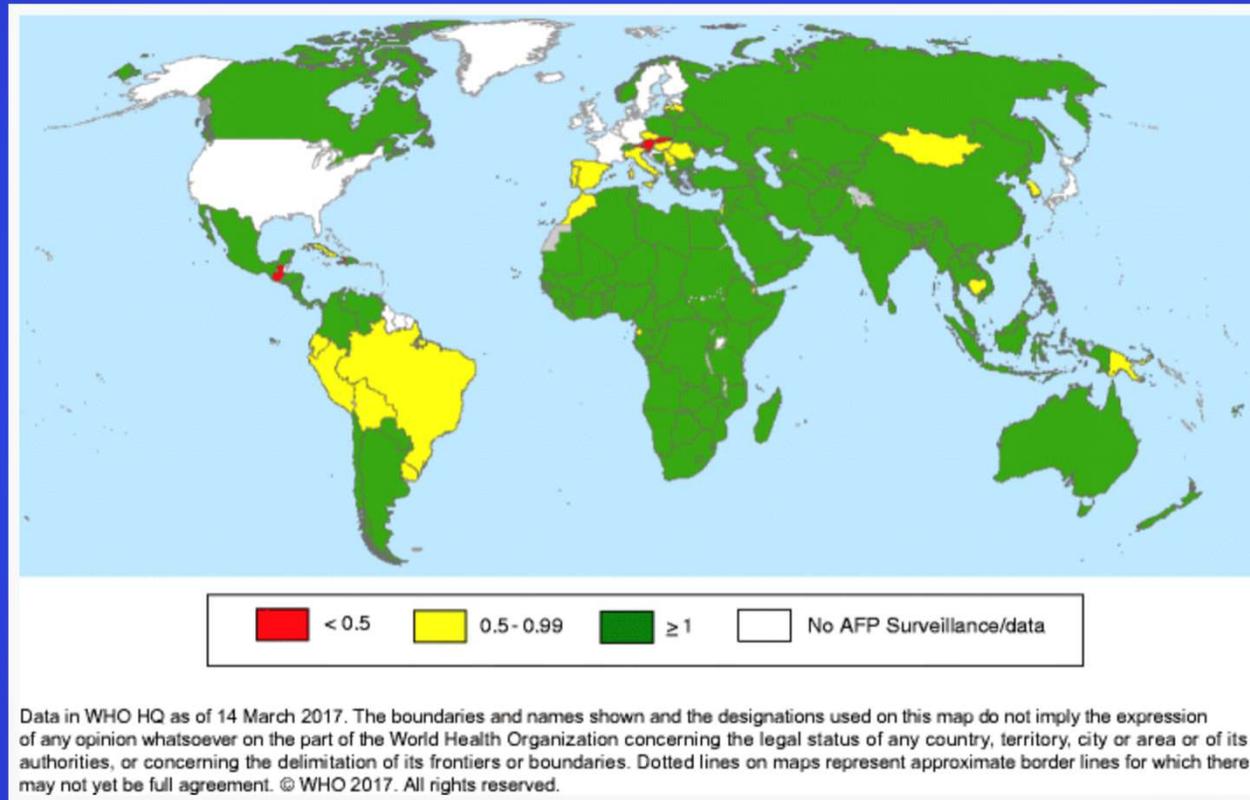
Causes of Polio Becoming Epidemic

- Relationship between increased sanitation and transition from polio being a rare event to an epidemic condition paralyzing hundreds of thousands children
 - Before epidemics, cases were seen in 0-4 year olds
 - Children had early exposures to the virus (fecal-oral transmission through contaminated water), BUT they usually had passive immunity from mother
 - This passive immunity led to limited pathology, BUT induced lifelong immunity.
 - With increased sanitation, exposure to the virus happened LATER, when passive immunity was gone

Polio Eradication and Surveillance in US

- No endogenous polio cases in US since 1979
- Vaccine associated polio continued through 1990s
- OPV use in US stopped in 2000 (risk was one in 2,000,000)
- Last wild case of Polio in Americas was 1994

Of 194 WHO member states, 179 conduct AFP surveillance and submit weekly AFP reports to WHO Regional Offices and WHO HQ, which, together with the lab results provided by the laboratories of the GPLN, allows timely outbreak detection and response.



The Role of Non-Polio Enteroviruses in Acute Flaccid Myelitis: The Value of Surveillance!

Table 1: Results of virus isolation from stool samples collected from under-15-year-olds with acute flaccid paralysis (AFP), by year, in the Americas, 1989–91

	Total with AFP	Total with stool sample	Isolate:			
			Wild poliovirus	Sabin-strain poliovirus	NPEV ^a	NPEV and Sabin-strain poliovirus
1989	1912	1595	24 (6)	122 (31)	223 (56) ^b	27 (7)
1990	2019	1707	17 (4)	92 (21)	306 (69)	26 (6)
1991	2044	1684	8 (2)	86 (21)	309 (75)	11 (3)
Total	5979	4986	49 (4)	300 (24)	838 (67)	64 (5)

^a NPEV = non-polio enterovirus.

^b Figures in parentheses are percentages of the total number of AFP cases with enterovirus isolates.

WHO Bulletin OMS. Vol 73 1995

Comparisons to Polio

Possibility and Perils

Poliomyelitis

- 1:1000 pediatric infections result in paralysis
- Fast progression from headache to paralysis possible
- Multiple phenotypes with same virus
- 1700s/1800s isolated cases
- 1900s epidemic forms

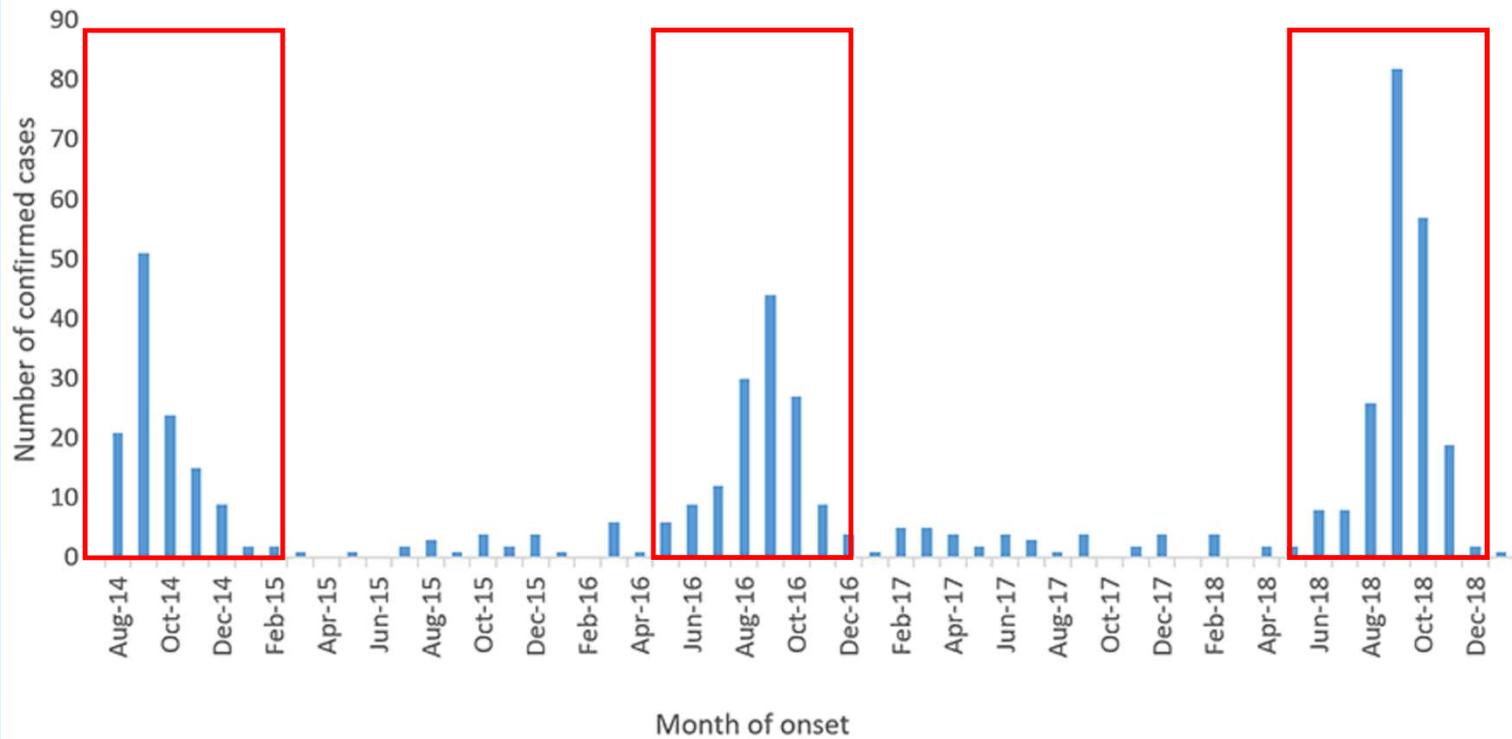
Acute Flaccid Myelitis

- EVD68 is most likely cause, but unknown rate of paralysis
- Fast progression possible
- Multiple phenotypes seen (assuming single agent)
- Isolated cases
- Questionable clusters

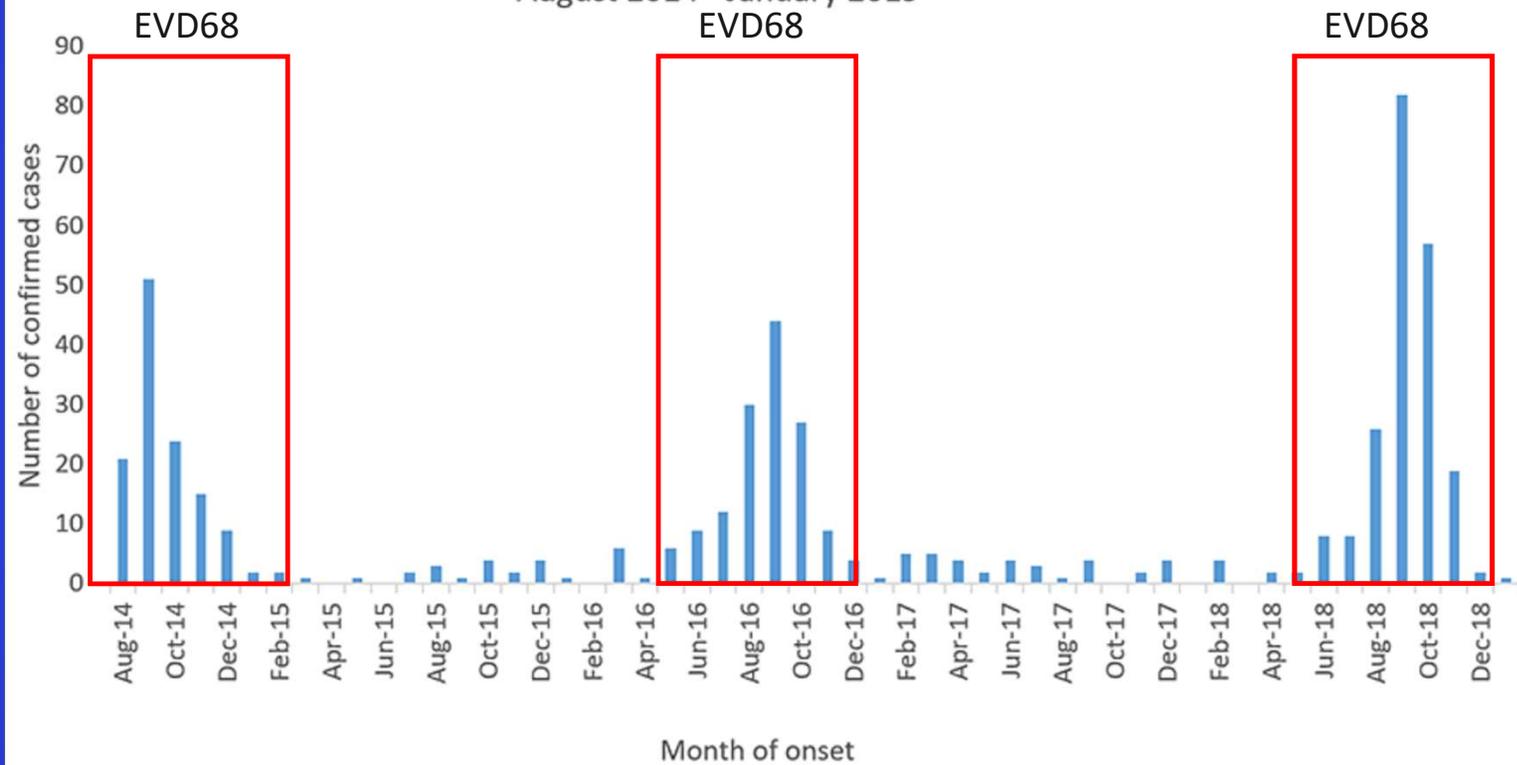
Current US Cases Test Negative for the Polio Virus

What is Causing the Current Outbreak?

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



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



What Do We Know About Enterovirus D68

- Respiratory Virus, infrequent in US until late 2000s/2009
- Since 2009, outbreaks were noted in 2012, 2014, 2016 and 2018
- Circulate Summer-Fall
- Closely related to rhinovirus
- ‘Cousin’ of Poliovirus
- Old strains are unable to cause paralysis in mice
- 2014 strain able to cause paralysis in mice

CDC.gov

What We Know

What we know about the AFM cases reported since August 2014:

- The patients' symptoms have been most similar to those caused by certain viruses, including poliovirus, non-polio enteroviruses, adenoviruses, and West Nile virus. [See a list of viruses associated with AFM.](#)
 - Enteroviruses can cause neurologic illness, including meningitis. However, more severe disease, such as encephalitis and AFM, is not common. Rather, they most commonly cause mild illness.
- CDC has tested many different specimens from the patients for a wide range of pathogens (germs) that can cause AFM. To date, we have not consistently detected a pathogen (germ) in the patients' spinal fluid; a pathogen detected in the spinal fluid would be good evidence to indicate the cause of AFM since this illness affects the spinal cord.
- The increase in AFM cases in 2014 coincided with a national outbreak of severe respiratory illness among people caused by enterovirus D68 (EV-D68). Among the people with AFM, CDC did not consistently detect EV-D68 in the specimens collected from them. In 2015 there were no cases of EV-D68 detected and so far in 2016, only limited sporadic cases of [EV-D68](#) have been detected in the United States.

Number of confirmed AFM cases by year of illness onset, 2014-2016

Year	Number confirmed cases	Number of states reporting confirmed cases
2014 (Aug-Dec)	120	34
2015	21	16
2016* (Jan-Aug)	50	24

*The case counts are subject to change.

CDC.gov

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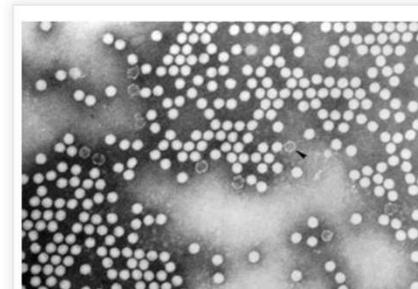
Diagnostic Methods



Poliovirus can be detected in specimens from the throat, and feces (stool), and occasionally cerebrospinal fluid (CSF), by isolating the virus in cell culture or by detecting the virus by polymerase chain reaction (PCR).

CDC laboratories conduct testing for poliovirus including:

- Culture
- Intratypic differentiation
- Genome sequencing
- Serology



Electron micrograph of the poliovirus

Virus Isolation

Virus isolation in culture is the most sensitive method to diagnose poliovirus infection. Poliovirus is most likely to be isolated from stool specimens. It may also be isolated from pharyngeal swabs. Isolation is less likely from blood or CSF.

To increase the probability of isolating poliovirus, collect at least **two stool specimens 24 hours apart from patients** with suspected poliomyelitis. These should be collected as early in the course of disease as possible (ideally within 14 days after onset).

CDC.gov

[CDC](#) > [Global Health](#) > [Polio](#) > [Polio Elimination in the United States](#) > [Laboratory Testing](#)

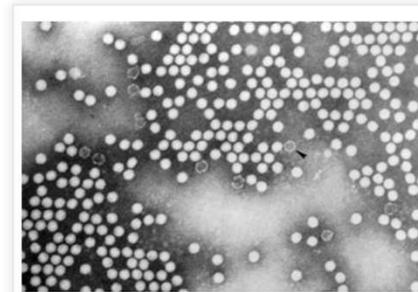
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Early Treatment Guidelines Cautioned Against Use of Corticosteroids and/or PLEX in AFM

- Concern for augmentation of a viral infection
- Not based on any data
- Has caused significant concerns for families and clinicians evaluating TM patients

CAPTURE Study AFM Cohort Treatment Exposures

First Treatment	2014	2015	2016	2017	Total
Steroids	12	5	14	0	31
PLEX	0	0	0	0	0
IVIG	4	1	9	1	15
Second Treatment					
Steroids	1	1	3	1	6
PLEX	4	3	7	0	14
IVIG	7	0	7	0	14
None	4	2	5	0	11
Third Treatment					
Steroids	0	0	1	0	1
PLEX	1	1	2	1	5
IVIG	2	1	5	0	8
None	12	4	12	0	28

**Confidential, Unpublished Data*

CAPTURE Study AFM Outcome Sample

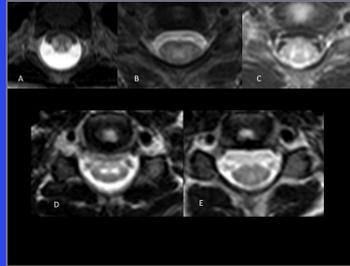
	Total	Treated With Steroids	Percent Of Total
Stand Up Good Recovery	25	21	84%
Stand Up Poor Recovery	14	7	50%
Tying Shoes Good Recovery	23	21	91%
Tying Shoes Poor Recovery	16	7	44%

CONQUER Treatment and Outcome Data

Variable	Data
Treated With Steroids	40 (90.9%)
Treated With IVIG	27 (61.4%)
Treated With PLEX	23 (52.3%)
Flaccid Limb No/Minimal Improvement (N=43)	18 (41.9%)
Flaccid Limb Moderate/Significant Improvement (N=43)	25 (58.1%)
UMN Limb No/Minimal Improvement (N=43)	0 (0%)
UMN Limb Moderate/Significant Improvement (N=43)	43 (100%)

CONQUER TM Clinic Experience with AFM/TM Prior to 2012

- Of the 31 patients included in the outcome analysis, 19 (61%) had excellent, very good or good outcomes as defined in this study (MRS < 3).



- In our cohort, the recovery of patients with predominantly gray matter damage was similar to patients with lateral and central cord injury patterns ($p=0.18$) despite a comparable use of anti-inflammatory interventions (e.g. corticosteroids and PLEX). Thus, despite concerns for viral mediated damage, there does not appear to be a harm to using anti-inflammatory therapies.

AFM and Public Health

- Need to recognize likely etiology publicly
- Need for mandatory reporting
- Need for centralized testing
- Need to not impede treatment options prematurely.....



