UNDERSTANDING PEDIATRIC ADEM, AFM, MOGAD, NMOSD, ON AND TM

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DISCLOSURES

- I receive salary support from the US Centers for Disease Control and Prevention for activities related to AFM Surveillance

- I am the site PI for the NIH AFM Natural History Study and the International Pediatric Opsoclonus Myoclonus Registry.

- I will be discussing the off-label use of medications.

OBJECTIVES

- Review some basic background about neurology and neuroimaging, and basic work-up
- Discuss typical symptoms and some background about ADEM, AFM, MOGAD, NMOSD, ON and TM
- Discuss similarities and differences in management

HOW DO WE FIND THE PROBLEM?

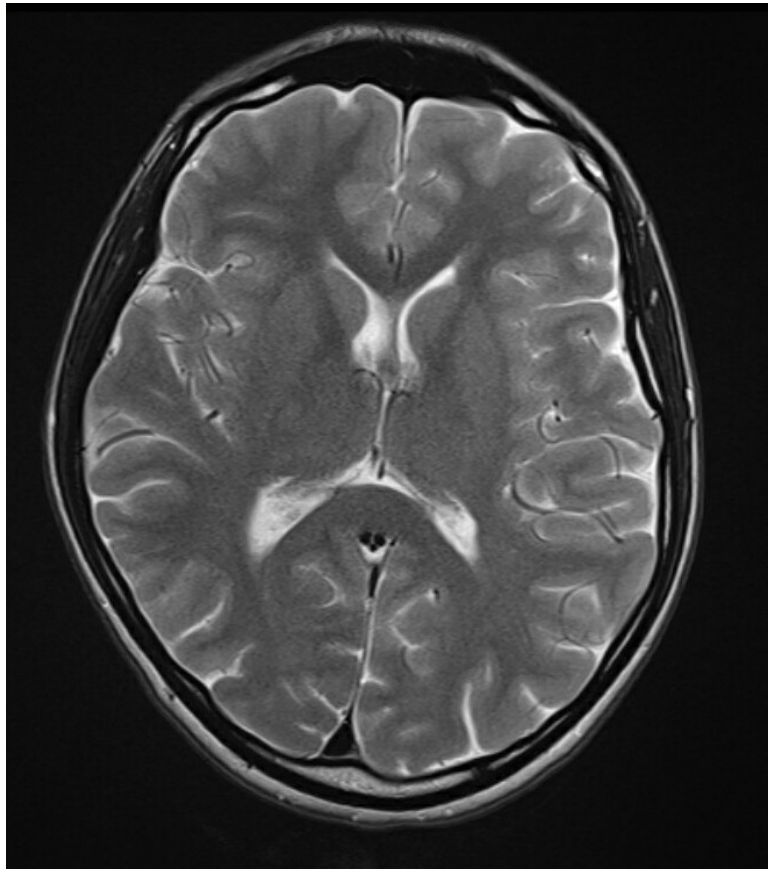
Upper Motor Neuron weakness: muscles are weak, they are tight, reflexes are increased.
Lower Motor Neuron weakness: muscles are weak, but they are floppy, reflexes are decreased
Deep Tendon Reflexes can also tell you about level of the problem if the spinal cord is involved

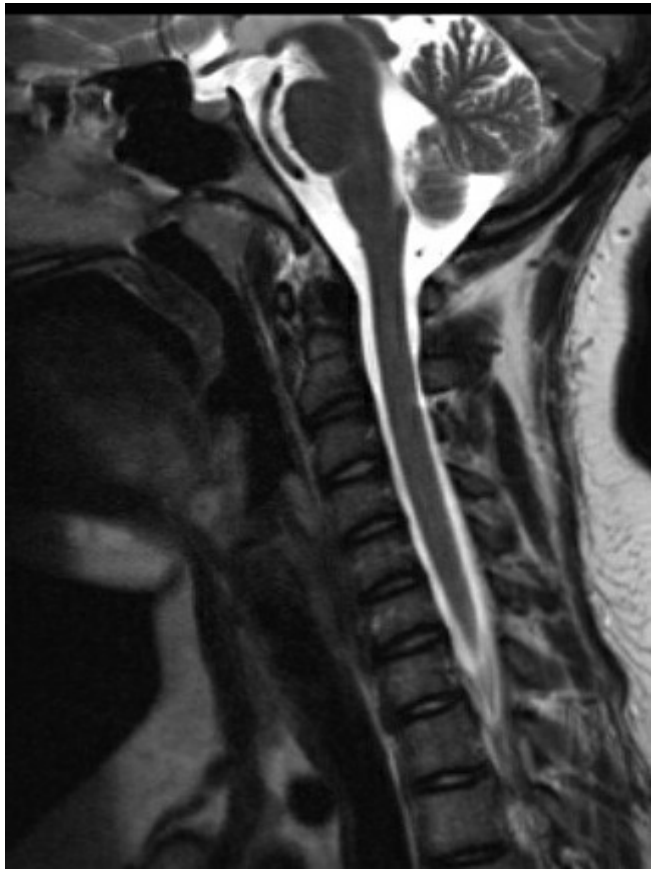
Arms – cervical/upper thoracic
Legs – cervical/thoracic/lumbar

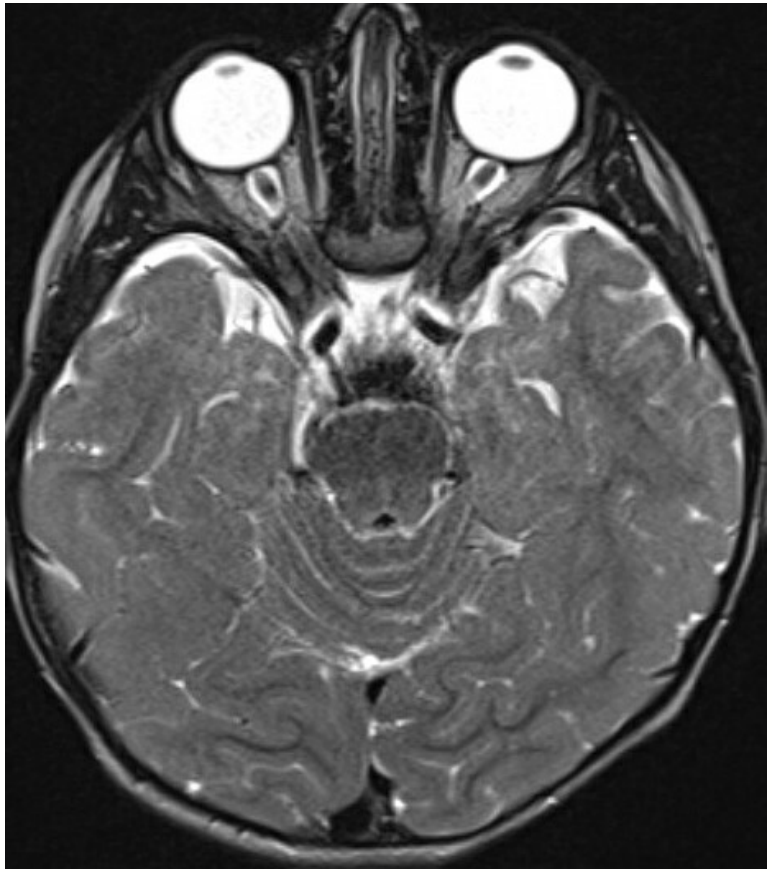
Sensory changes can also help to localize the problem
Bowel/bladder involvement

GETTING ORIENTED TO MAGNETIC RESONANCE IMAGING (MRI)

T2 IMAGES – SPINAL FLUID (CSF) IS BRIGHT, CORTEX (NERVES CELLS) ARE RELATIVELY BRIGHT, AND WHITE MATTER IS DARK







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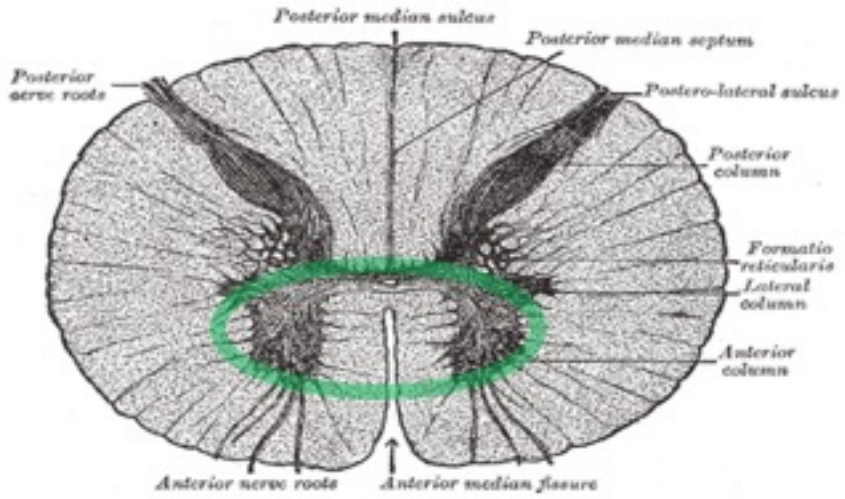
SPINAL CORD CROSS SECTION



Modified from: Gray's Anatomy (public domain)

HOW DO WE FIND THE CAUSE OF THE PROBLEM?

Good history
Imaging: Some disorders have specific imaging patterns
Bloodwork: look for evidence of inflammation and neuroimmune conditions (ESR, CRP, ANA, MOG, NMO) and infection (Lyme, Bartonella), and vitamin deficiencies (especially for myelitis) and sometimes metabolic disorders
Lumbar puncture: Look for evidence of infection, inflammation, and neuroimmune conditions
Ideally, we collect these and save specimens so that tests can be added on later if needed

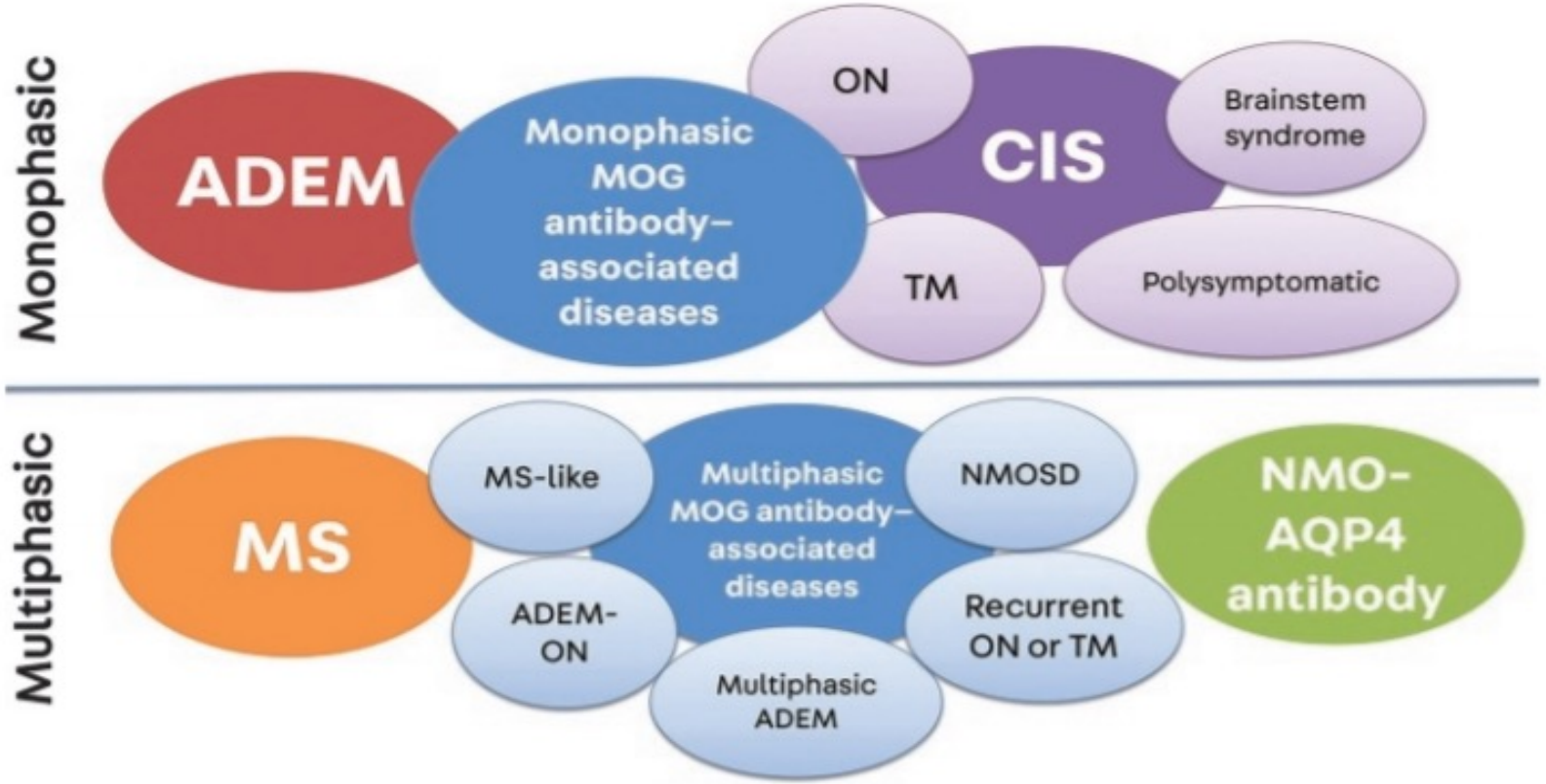


FIGURE 11-2

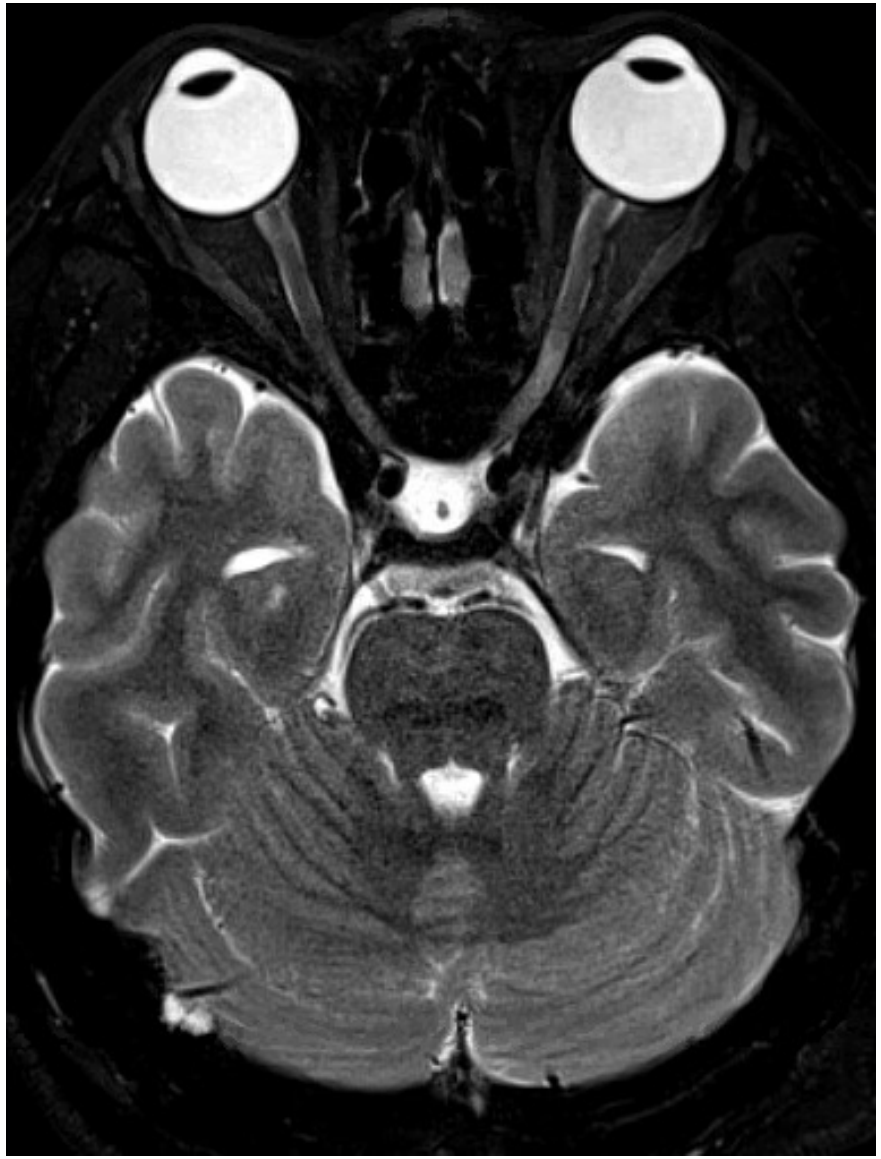
Spectrum of monophasic and multiphasic demyelinating disorders in children.

ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin-4; CIS = clinically isolated syndrome; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; ON = optic neuritis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; TM = transverse myelitis.

Chitnis T. Pediatric Central Nervous System Demyelinating Diseases. Continuum 2019; 25(3):793-814.

OPTIC NEURITIS

- Pain with eye movements
- Blurry/decreased vision
- Decreased ability to see colors
- May be 1 eye or both
- May be idiopathic or associated with MS/ADEM/NMO/MOG/ infections (Lyme, Bartonella, viruses)
- Treated with high dose steroids



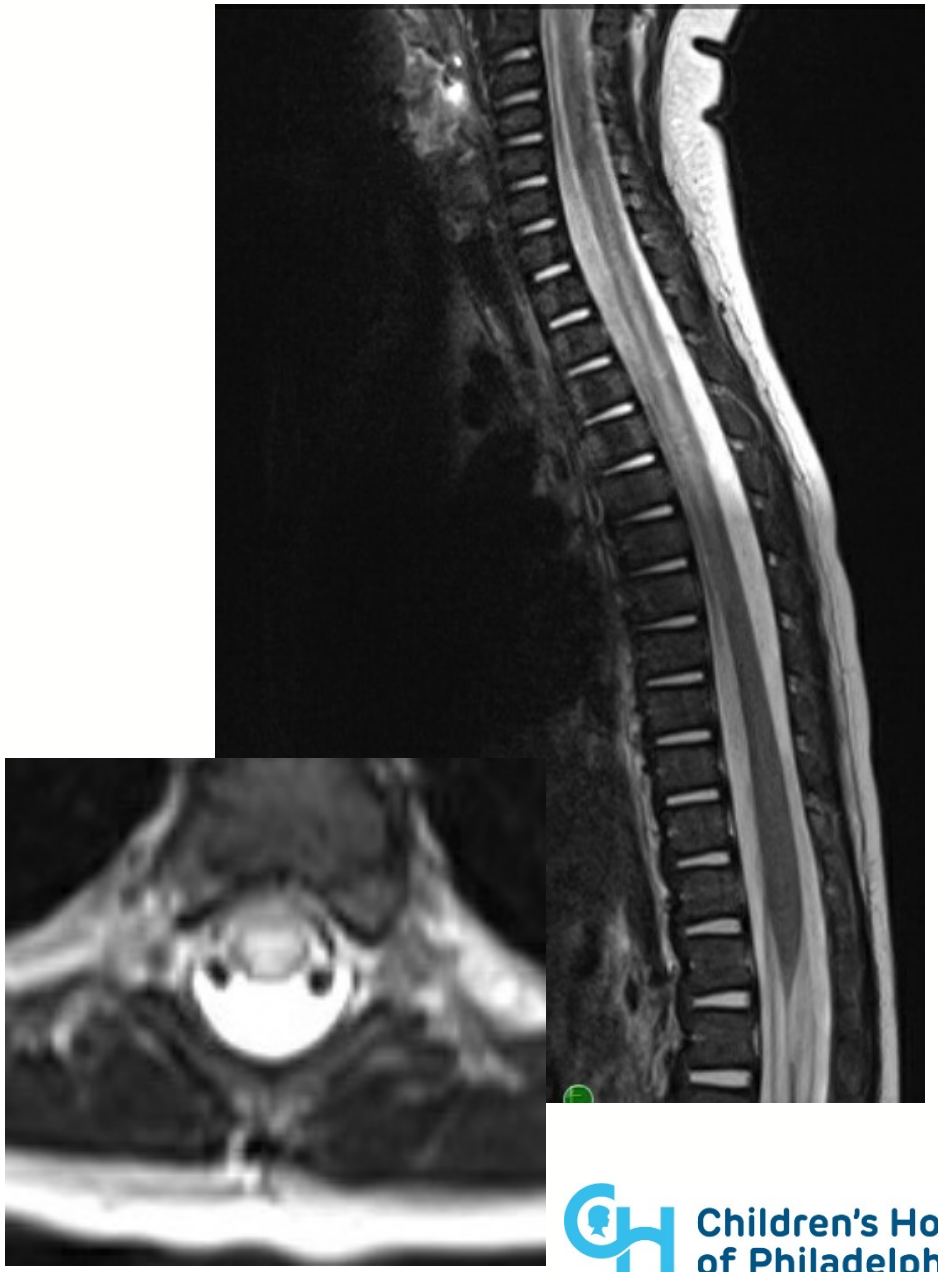
OPTIC NEURITIS

- 58-97% of children experience full recovery of high contrast visual acuity
- 13-36% of children with ON eventually diagnosed with MS.
  Higher with white matter lesions, but as low as 2% if no white matter lesions.
- There may be subjective residual vision difficulty
- There will be less vision recovery in a patient with a diagnosis of NMO, and additional treatment may be needed.

Yeh, et al. Pediatric Optic Neuritis. Neurology.2016;87:supplement.

TRANSVERSE MYELITIS

- Spinal cord dysfunction (weakness, sensory alterations, and bowel or bladder dysfunction) that develops over hours or days
- Upper motor neuron signs
- Associated with inflammation
- No evidence of a compressive lesion
- May be idiopathic or associated with MS/ADEM/NMO/MOG/infections
- Treated with steroids/IVIG/plasma exchange, cyclophosphamide in severe cases.



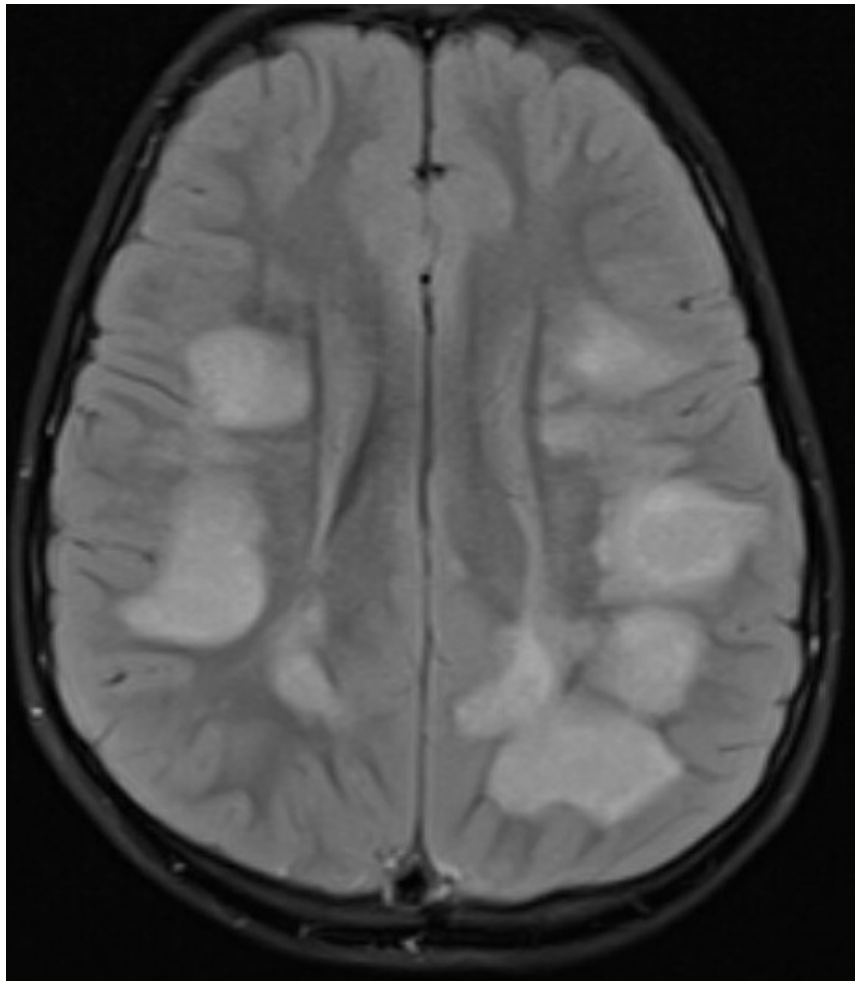
TRANSVERSE MYELITIS – PEDIATRIC OUTCOMES

- Rehabilitation is an essential part of recovery
- Historically the rule of thirds (in adults), however, some newer studies suggest that outcomes may be somewhat better in children.
- Often children continue to make progress over ensuing years
- 79 children with monophasic TM
  - 55 (70% with good outcome) (Deiva)
- 102 children with TM (62 with monofocal TM)
  - 82 recovered completely, 19 with incomplete recovery (O'Mahony).

Deiva K, Absoud M, Hemingway C, et al. Acute idiopathic transverse myelitis in children: early predictors of relapse and diability. Neurology. 2015; 84(4): 341-9.
O'Mahony J, Marrie RA, Laporte A, et al. Recovery from Central Nervous System Acute Demyelination in Children. Pediatrics. 2015;136(1):e115-23.

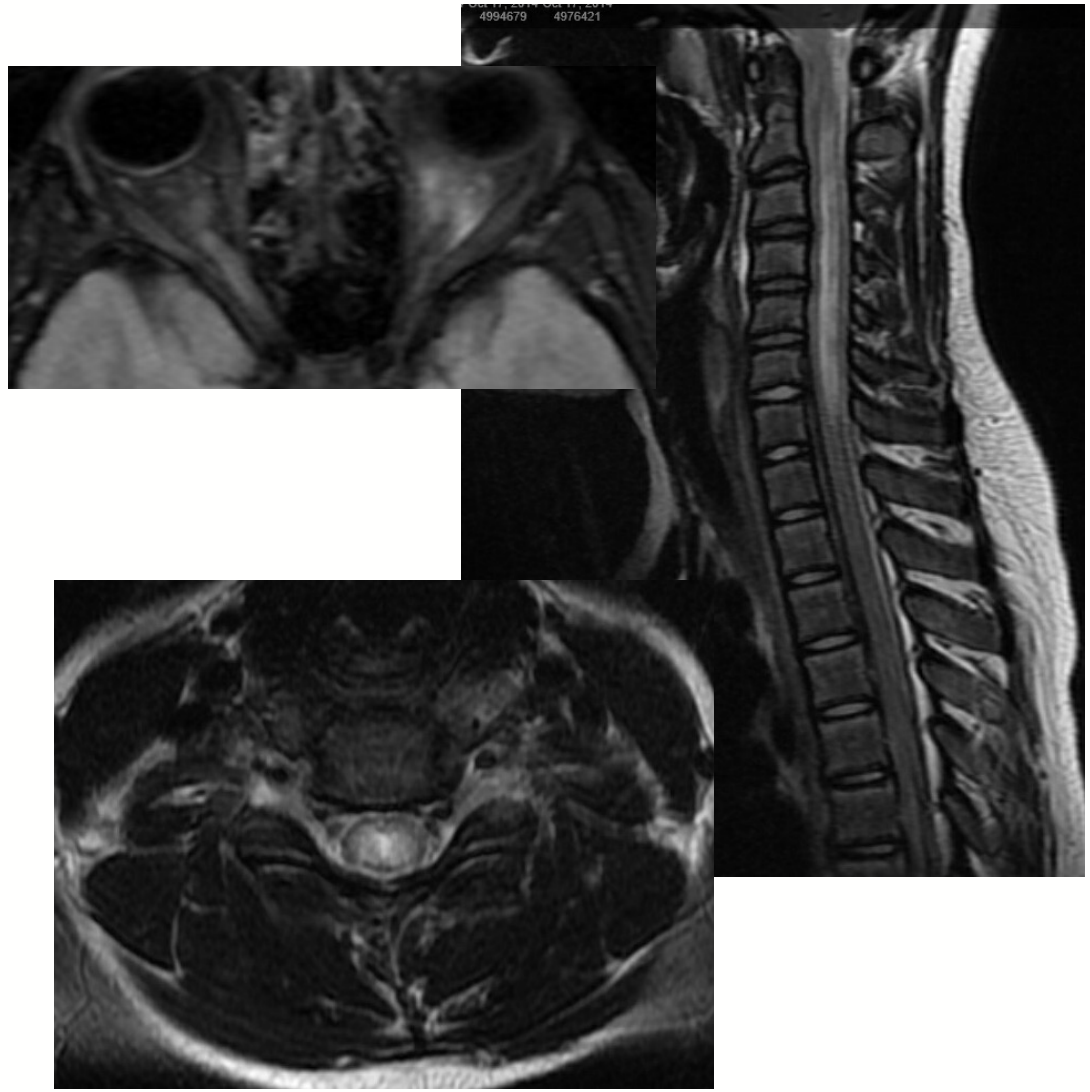
ACUTE DISSEMINATED ENCEPHALOPMYELITIS (ADEM)

- Typically, a pediatric disorder (ages 5-8)
- Patient must have altered mental status (encephalopathy) with multifocal symptoms.
- May be idiopathic/post-infectious or associated with MOG
- Treated with steroids
- Patients typically do very well, but may have attention/focus or cognitive difficulties, or mild motor issues.
- Some severe subtypes



NEUROMYELITIS OPTICA

- Rare
- Devic's Disease (1864)
- Known autoantibody
- Wide range of ages, average 40 years, but may occur in even very young children
- Recurrent episodes of optic neuritis and transverse myelitis
- May have findings referable to the brainstem (hiccups or vomiting) or thalamus (symptomatic narcolepsy)
- These episodes often have severe sequelae
- Steroids are often relatively ineffective
- Long term immunosuppression is needed



2015 NMOSD DIAGNOSTIC CRITERIA

AQP-4 Positive antibody and 1 core clinical characteristic OR

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OR

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AQP4-antibody negative/unknown and 2 core clinical characteristics with one being either (1) ON, (2) TM, or (3) APS

Core Clinical Characteristics

- Optic Neuritis
- Myelitis
- Area Postrema syndrome (APS)
- Symptomatic narcolepsy or diencephalic syndrome with typical diencephalic lesions
- Acute Brainstem Syndrome
- Symptomatic cerebral Syndrome with typical MRI brain lesions

NEUROMYELITIS OPTICA

- Worldwide prevalence ranges from 0.5-4.4 cases per 100,000
- Most commonly present between the ages of 35-45
- **Pediatric NMOSD occurs between 3-5% of all NMOSD**
- Women comprise 70-90% of all cases
- Worldwide, more common in East Asian and non-white populations
- Generally a sporadic disease
  - ~3% of patients with NMO have relatives with the disease

Prasad, Sashank et al. Seminars in Neurology. 2019 Dec; 39 (6):718-731
Papadopoulos, Marios et al. Lancet Neurol. 2012 June; 11(6):535-544
Lana-Peixoto, M et al. Biomedicines. 2019 Jun; 7(2): 42.

NMOSD: OUTCOMES

- Poorer outcomes compared to MS and MOG associated disorders (higher EDSS score w/i 2 years of disease)
- Within 5 years of disease onset, >50% of patients are blind in one or both eyes or require assistance with ambulation
- Predictors of worse prognosis: (1) severity of first attack, (2) Number of relapses in first 2 years, (3) having SLE or relate autoimmune d/o or autoantibodies
- Pediatric NMOSD more favorable outcome than in adult
  - Lower relapse rate compared to adults
  - Longer time to reach EDSS score of 4 and 6 compared to adults
  - Lower mortality rate compared to adults

Gombolay, G and Tanuja Chitnis. Curr Treat Options Neurol (2018) 20: 19
Kim SH, et al. Neurology. 2018 Nov 27; 91(22):e2089-e2099
Hudda, Saif et al. Clin Med (Lond). 2019 Mar; 19(2): 169–176.

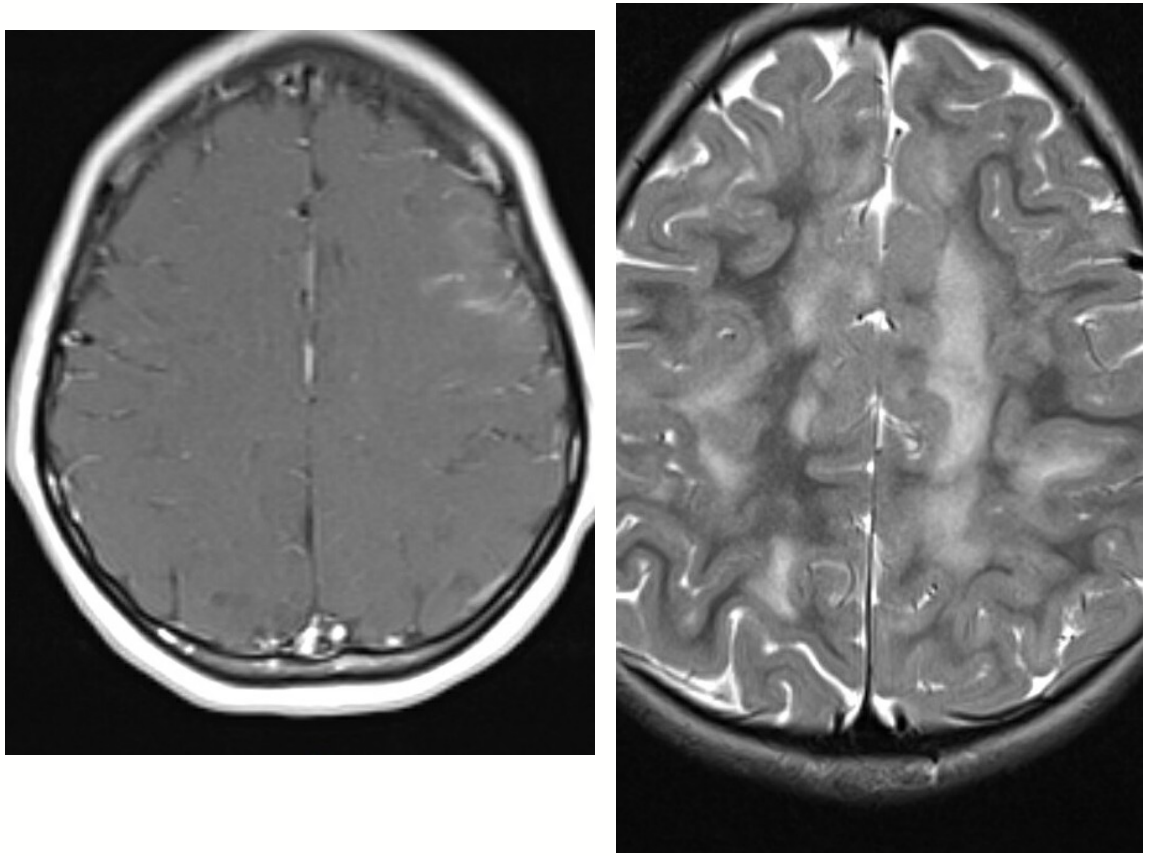
NMOSD: DISEASE COURSE

- Relapsing course in ~90% of patients
- Median time to first relapse ranges from 5-12 months
- Attacks are generally more severe and full recovery is less common compared to other demyelinating disorders
- Secondary progressive phase is rare in NMOSD

Wingerchuk, Dean et al. Neurology, 60 (2003): 848-853
Prasad, Sashank et al. Seminars in Neurology. 2019 Dec; 39 (6):718-731

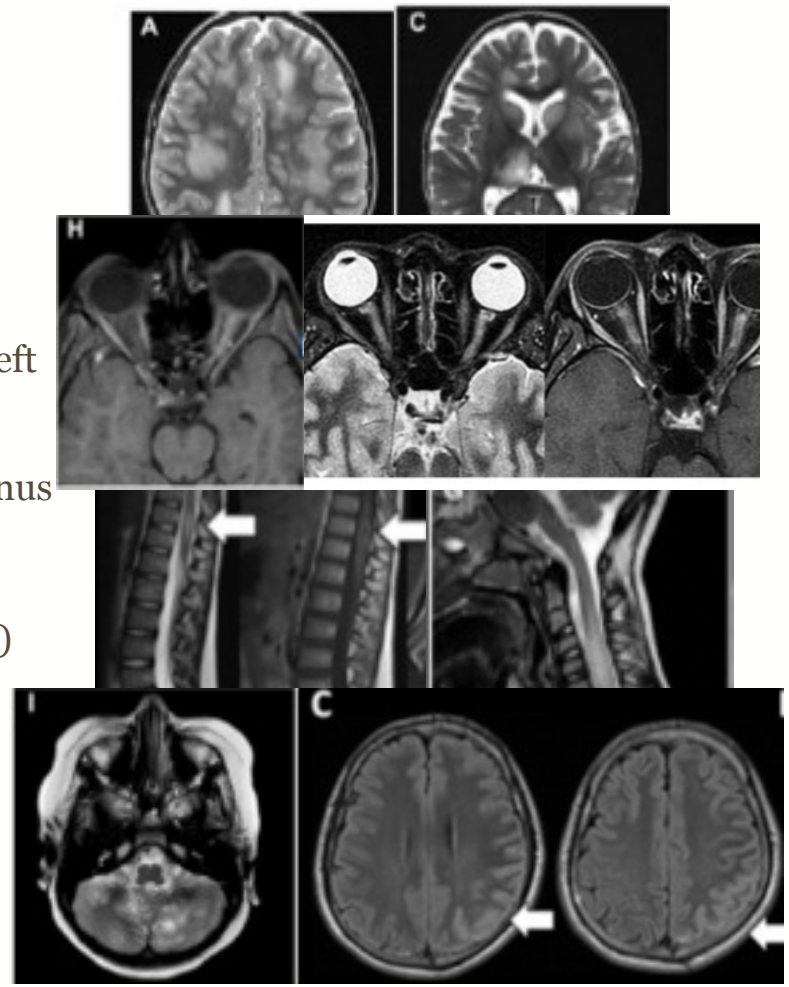
MYELIN OLIGODENDROCYTE ASSOCIATED DEMYELINATION (MOG-AD)

- Can essentially present as anything in the demyelinating disease spectrum
- Unclear whether it is always pathological (MOG ab are sometimes increased in other disorders)
- Sometimes standard treatments work but may need IVIG/rituximab.



MOG-Associated Disorders: Classic Phenotypes and MRI findings

- Most Common Phenotypes:
  - **ADEM-like presentation**
    - Widespread, diffuse lesions
    - Often involvement of the myelon including the conus
    - Lesions can resemble leukodystrophies
  - **Optic Neuritis**
    - Often bilateral and recurrent (bilateral more common than in NMO or MS)
    - Optic disc swelling
    - Most cases resolve well with only 10-20% of patients left with permanent visual deficits
  - **Transverse Myelitis**
    - LETM often affects the lower thoracic cord and the conus medullaris*
    - Residual bowel, bladder, and sexual dysfunction is common
    - Can also present with STM (more commonly in adults)
- Other Presentations
  - Seizures
  - Cortical encephalitis
  - Brainstem encephalitis
  - Encephalopathy (with or without ADEM phenotype)
  - Isolated Cerebrellitis
  - Often febrile



Juryncyk et al. Practical Neurology 2018
Hennes EM, Baumann M, Lechner C, Rostásy K. *Neuropediatrics*. 2018.

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MOG-ASSOCIATED DISORDERS: DISEASE COURSE

- Disease can be **monophasic or relapsing**
  - The majority of pediatric patients demonstrate a monophasic disease course (~70-80%)
  - Up to 50% of adult patients relapse within the first 2-3 years
- **Non-MS disease course**
- Persistent MOG seropositivity does not necessarily predict relapsing disease course
- Most common relapsing phenotype is optic neuritis

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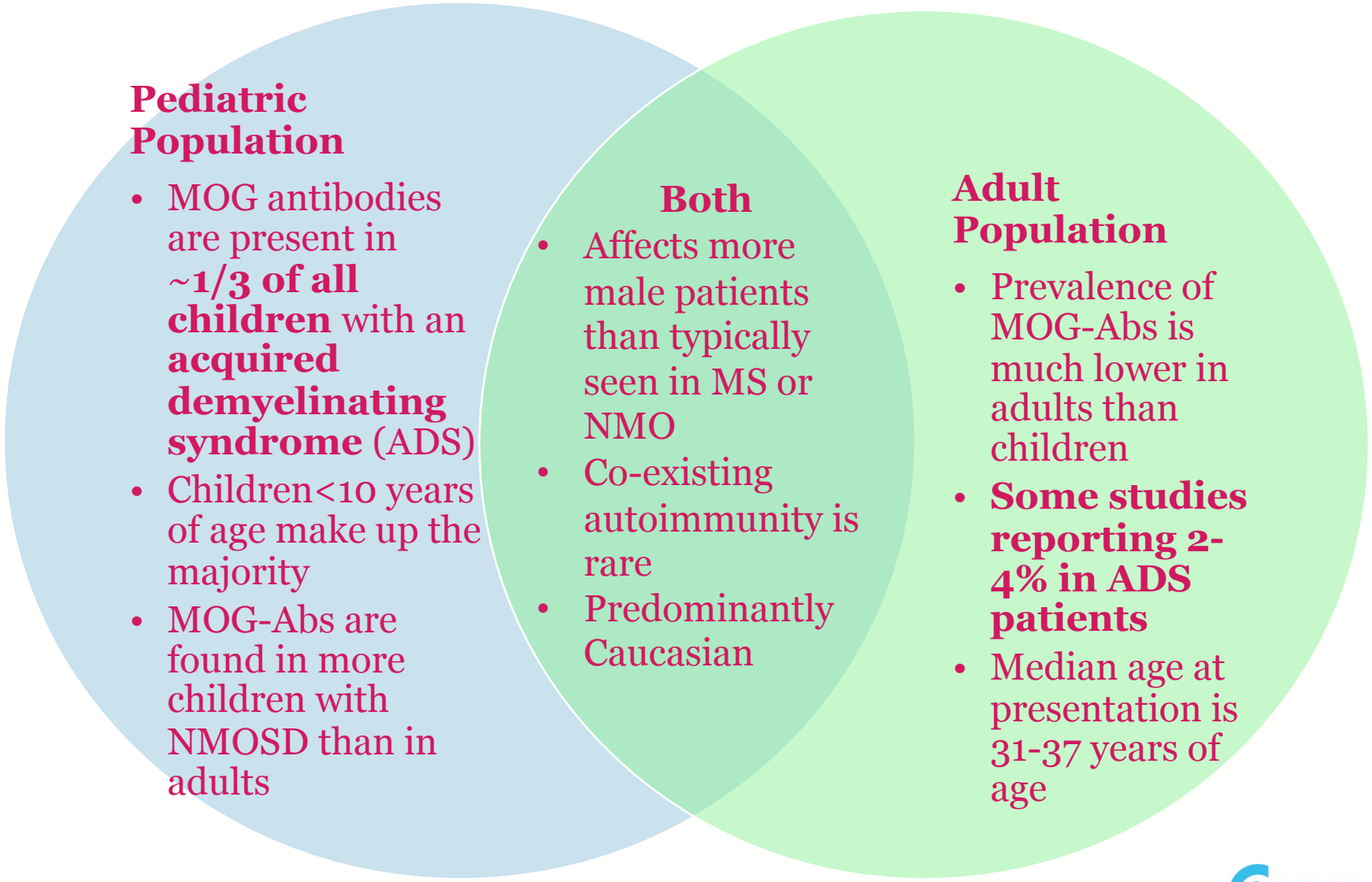
Waters P, Fadda G, Woodhall M, et al. *JAMA Neurol*. September

MOG-ASSOCIATED DISORDERS: EPIDEMIOLOGY



Jurynczyk, Maciej et al. Brain 2017;14-;3128-3138
Cobo-Calvo, et al. Neurology 2018
Hennes, et al. *Neurology*. 2017
Waters P, Fadda G, Woodhall M, et al. *JAMA Neurol*. September 2019

SERIAL ANTI-MOG ANTIBODY ANALYSES AND OUTCOMES IN CHILDREN WITH DEMYELINATING SYNDROMES

Study Population

- 274 **ped**
  - 84 pa
  - MRI s
    post-e
  - 67/84

Results

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- 16/67 (~
- 9 of 24 p
- 5 of 38 c
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Main take-home points:

- The majority of MOG patients have a monophasic disease course
- Persistent MOG seropositivity does not necessarily predict a relapsing disease course
  - Persistently positive MOG patients are more likely to relapse than MOG patients that have seroconverted to MOG negative status
- Long term immune modulatory treatment should NOT be initiated at first presentation of MOG antibody associated disorder

Waters P, Fadda G, Woodhall M, et al. *JAMA Neurol*. September 2019

MOG-ASSOCIATED DISORDERS: OUTCOMES

- Typically favorable outcome
  - Pediatric>Adults
- Complete recovery from the onset attack is very common both clinically and radiographically
- Patients with initial presentation of optic neuritis are more likely to have relapses
- Relapses can lead to permanent disability (up to ~47%; disability from onset attack in the majority)
  - Visual impairment
  - Erectile dysfunction and bladder sphincter function

Cobo-Calvo et al. *Neurology*. 2018
Jurynczyk M, Messina S, Woodhall MR, et al. *Brain*. 2017

TYPICAL TREATMENTS CONSIDERED

- **Acute Treatment**
  - **IV methylprednisolone** for 3-5 days
  - **IVIG** and/or **plasma exchange** if methylprednisolone does not work

- **Chronic Treatment**
  - Monthly IVIG (MOG)
  - Rituximab (NMO)
  - Cyclopphosphamide (difficult to treat cases)
  - Other immunosuppressants (mycophenolate, tocilizumab, eculizumab on a case by case basis)

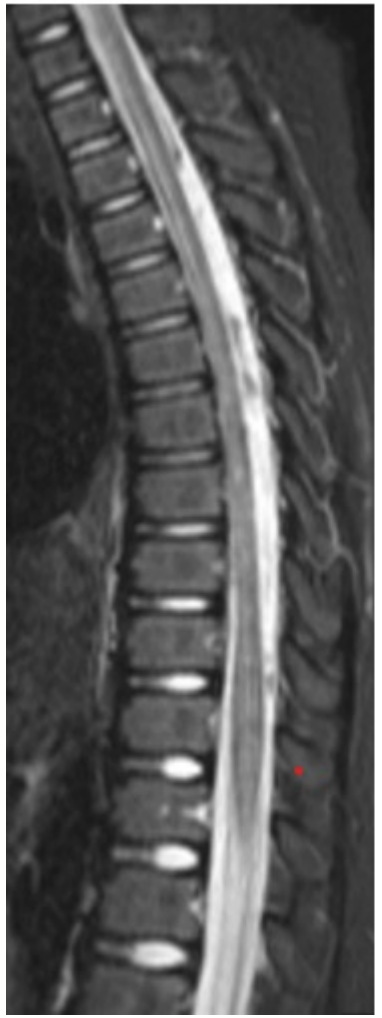
JUST AS IMPORTANT AS MEDICAL TREATMENT

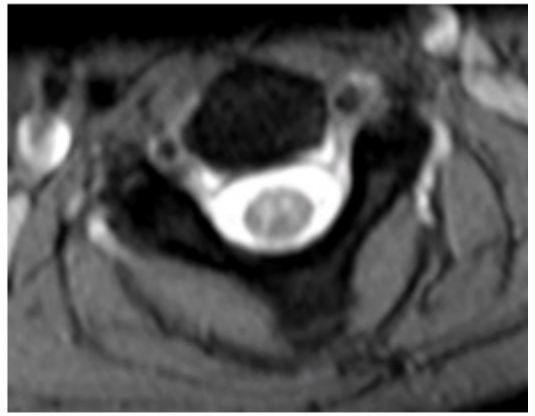
- **Psychosocial Support**
  - Child life
  - Behavioral Medicine
  - Maintaining contact with school, working through this as possible

- **Rehabilitation Services**
  - Early PT/OT/Speech consults
  - Rehabilitation Medicine Consults
  - A significant amount of the improvement that we see comes from rehabilitation.

ACUTE FLACCID MYELITIS

- Recognized in 2012, biennial
- Acute onset of flaccid paralysis (lower motor neuron) of 1 or more extremities, usually in the setting of febrile illness
- Nearly always asymmetric and proximal>distal
- May be accompanied by stiff neck, headache, pain in the affected limb, cranial nerve abnormalities
- Longitudinal lesions involving mostly the gray matter of the spinal cord
- Related viral infection (enterovirus D68)





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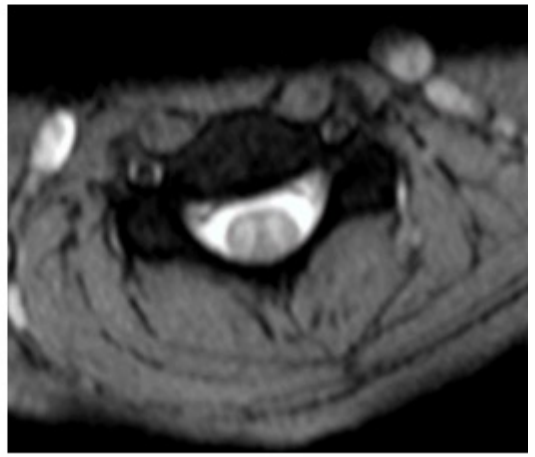

AFM

- Onset may be hyperacute, and progressive.
- Takes up to 5-6 days to reach nadir
- Patients with cervical lesions may have rapid progression to respiratory weakness.
- There is a range of outcomes, from normal to quadriplegic and ventilator dependent.
- No proven treatment, but IVIG is often given, steroids and plasma exchange therapies may be used for certain clinical situations
- The diagnosis can be challenging, and patients are often missed at onset.

THANK YOU!

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