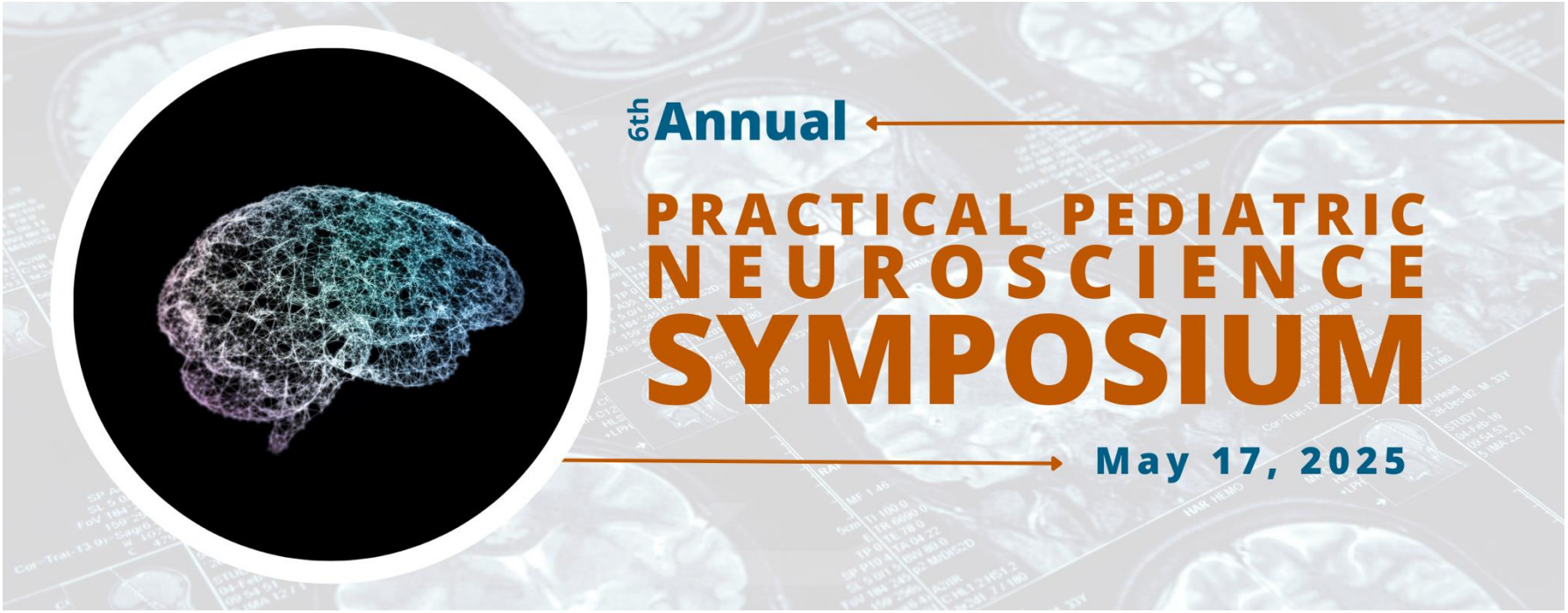

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Pediatric Multiple Sclerosis

Duriel Hardy, MD
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The video of the following presentation has been made available for free by UT Health Austin Pediatric Neurosciences at Dell Children's at:

https://www.youtube.com/watch?v=eoLY8v7Hxzo&list=PLPPnZ7QxWdeR-cpRyBnU2C2eEVh1bW1YR&index=4

To see all event presentations, please use this link for the 6th Annual Practical Pediatric Neuroscience Symposium presentation playlist:

https://youtube.com/playlist?list=PLPPnZ7QxWdeR-cpRyBnU2C2eEVh1bW1YR&feature=shared

Interprofessional Continuing Education

Disclosure

Duriel Hardy, MD

1. I have no relevant financial relationships with any ACCME-defined commercial interest* to disclose.
2. I will not discuss off label use and/or investigational use in my presentation.
3. All Ascension planners, reviewers, and course directors have no relevant financial relationships with ACCME-defined commercial interests

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A commercial interest is any entity producing marketing, re-selling, or distributed health care good and services consumed by, or used on, patients.

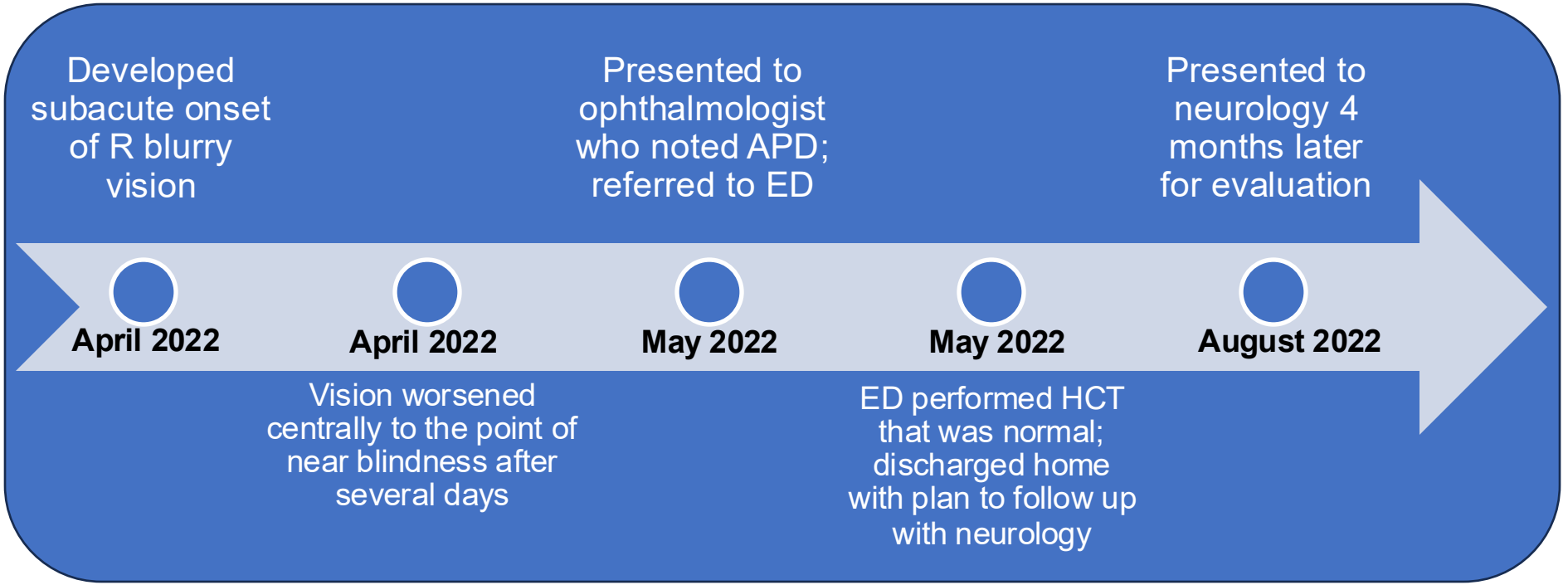
Objectives

- Describe the epidemiology and risk factors of pediatric multiple sclerosis
- Outline the clinical and paraclinical features of pediatric MS
- Discuss the diagnosis and mimics of pediatric multiple sclerosis
- Review the approach to management of POMs and summarize outcomes

Meet patient DM

- 17-year-old previously healthy male presenting with acute to subacute onset of vision loss and weakness

Patient DM: Timeline of events



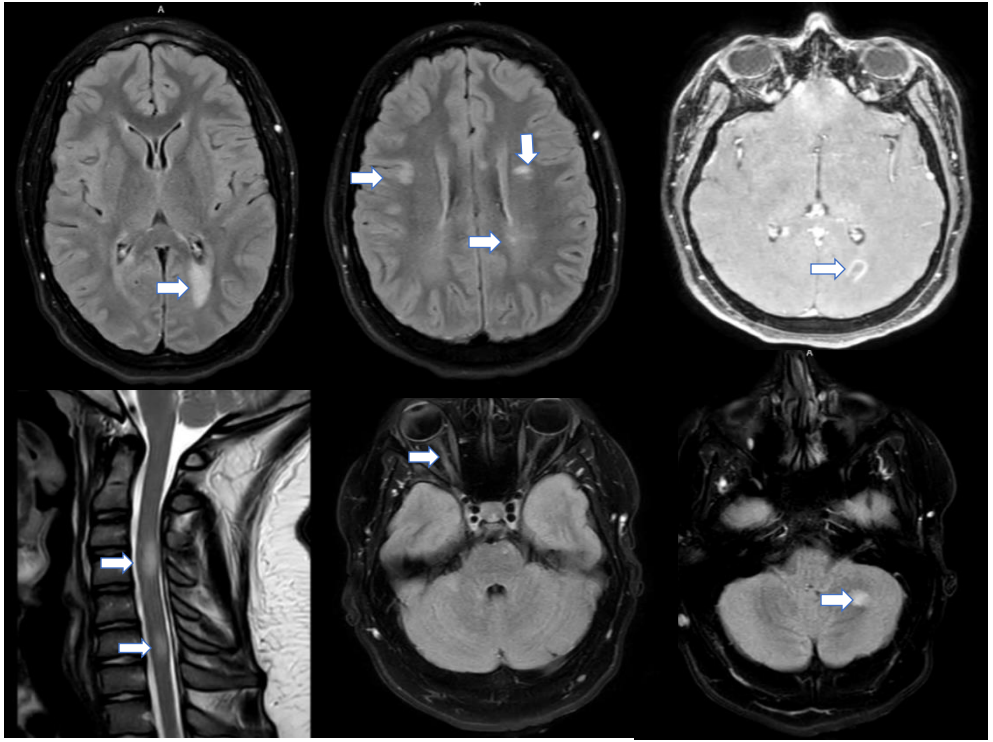
Patient DM: Neurologic exam

- Mental status: appropriate for age
- Language: normal
- Cranial nerves: **R APD**, EOMI, normal facial sensation in the V1-V3 distribution, **R facial droop**, tongue midline, normal suck and swallow
- Eyes/optho: normal fundus, no papilledema, **decreased vision in his right lower nasal VF**
- Motor: 5/5 strength throughout except **slightly decreased grip strength on R**, no pronator drift
- Sensory: normal sensation throughout to light touch, vibration, and temperature
- Reflexes: 2+ and symmetric throughout, toes down going
- Gait: **normal gait though felt unsteady, unable to tandem very well, difficulty walking on heels and toes**
- Coordination: intact to finger to nose, intact to heel to shin testing
- RAM: **slowed finger tapping with right hand compared to left**

Patient DM: Diagnostic evaluation

Laboratory evaluation

- Serum MOG: negative
- Serum AQP-4: negative
- Thyroid function was normal
- ANA negative
- Vitamin D low: 10
- HIV, RPR, VZV, and COVID all negative



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(Diagnosis: pediatric onset multiple sclerosis (POMS))

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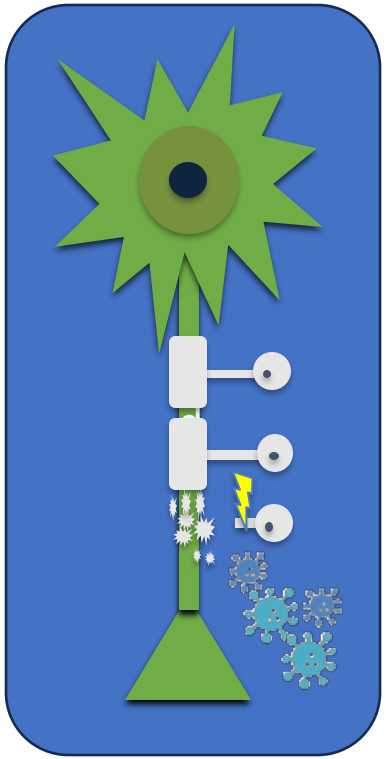
Pediatric-Onset Multiple Sclerosis (POMS)

- POMS is a chronic inflammatory autoimmune disorder of the CNS occurring in patients less than 18 years of age
- Often present more aggressively clinically and radiographically compared to adult-onset MS
  - Axonal damage occurs early in POMS
- 98% present with a relapsing-remitting course compared with 84% of adult patients
- Pathogenesis is believed to be centered on an autoimmune attack of myelin leading to oligodendrocyte cell death and axonal damage

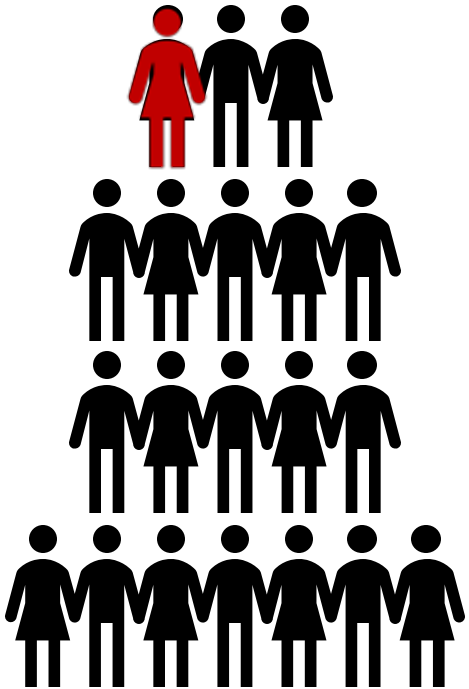


Hardy D, Banwell B. Pediatric-Onset Multiple Sclerosis. Practical Neurology. 2019.
Otallah S, Banwell B. Pediatric Multiple Sclerosis: An Update. Curr Neurol Neurosci Rep. 2018;18:76.

Epidemiology and risk factors

Epidemiology

- Multiple sclerosis (MS) is one of the leading causes of disability in young adults
- **POMS accounts for about 3-5% of all MS cases**
- Overall incidence of pediatric MS is between 0.07/100,000 and 2.9/100,000
- Median age of POMS is between 11 and 13 years
- M:F ratio varies by age:
  - Before age 6, M:F is 1:0.8
  - From 6-10 years old, M:F ratio is 1:1.6
  - >10 years old, M:F ratio is 1:2.1
  - In adolescent years, M:F ratio is 1:3



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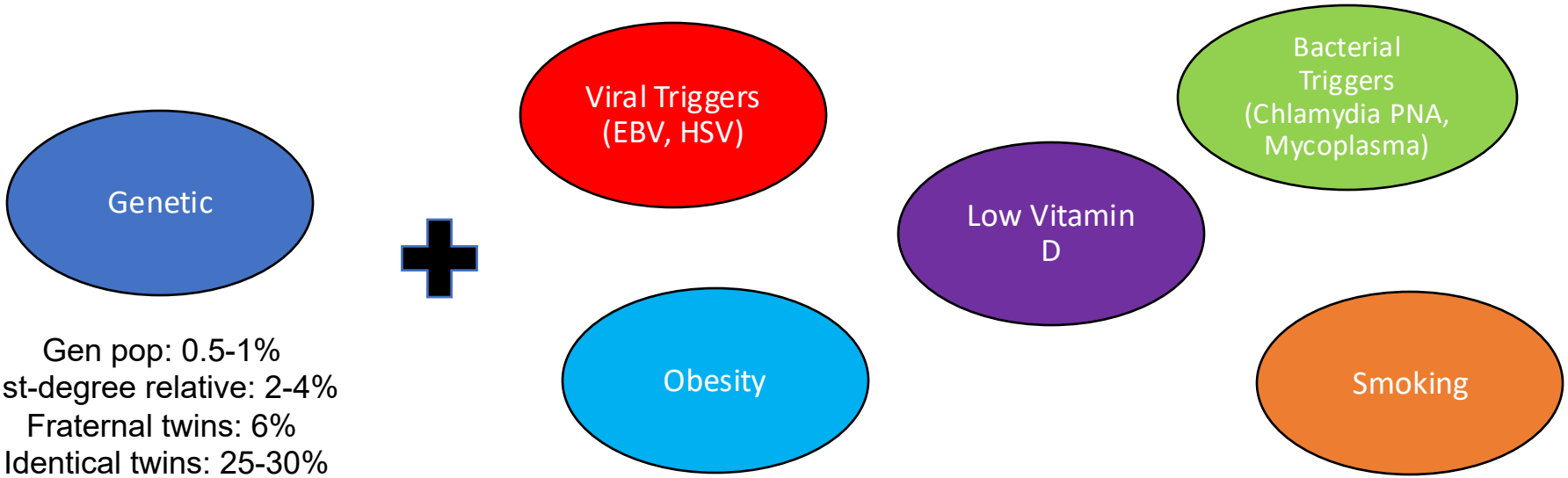
Otallah S, Banwell B. Pediatric Multiple Sclerosis: An Update. Curr Neurol Neurosci Rep. 2018;18:76.

Etiology & risk factors

- Believed to be multifactorial: genetic predisposition + environmental trigger(s):



Gen pop: 0.5-1%
1st-degree relative: 2-4%
Fraternal twins: 6%
Identical twins: 25-30%
HLA-DRB1*15:01

International MS Genetic Consortium 2015. Cree BAC, Handbook of Clinical Neurology. 2014.

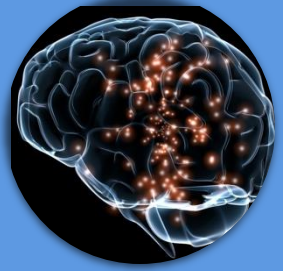
Clinical and paraclinical features

Most common initial presentations

Optic neuritis

- Most common initial presentation; first manifestation in up to 30%
- Unilateral, short segment, and posterior predominant
- Often optic disc is normal
- Classic triad of symptoms:
  - Pain with eye movement
  - Loss of vision (central)
  - Decreased color vision

Brainstem syndrome



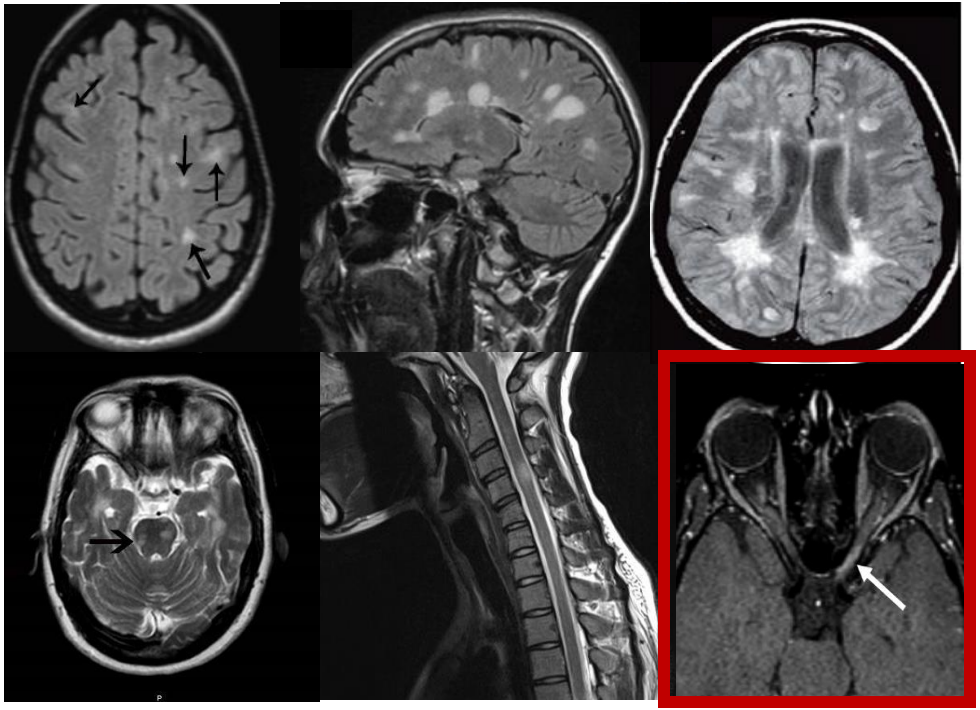
- Internuclear ophthalmoplegia is a common brainstem manifestation of MS
- Middle cerebral peduncle
- Lesions affecting the brainstem can manifest in other ways, including dizziness, ataxia, area postrema syndrome (rarely), other cranial nerve palsies, and weakness

Transverse myelitis

- Most commonly affects the dorsal portion of the cord
- More commonly affects white matter
- Short segment lesions
- Often affect C and T spine
- Common symptoms include paresthesias, numbness, weakness, bowel/bladder symptoms

Radiographic features of MS

- Often, **higher lesion burden** on MRI compared to adult-onset MS
- **Infratentorial lesions** (including brainstem) are more prevalent in POMS
  - Higher T1 lesion burden in the infratentorial region
- Global brain volume is significantly lower than in the general population
- **<u>Typical MS regions include</u>**:
  - Periventricular
  - Juxtacortical OR cortical
  - Brainstem/infratentorial
  - Spinal cord



Optic neuritis is not considered an MS-specific region!

Wildner P et al. Mult Scler Relat Disord. 2020 Jan;37:101452.
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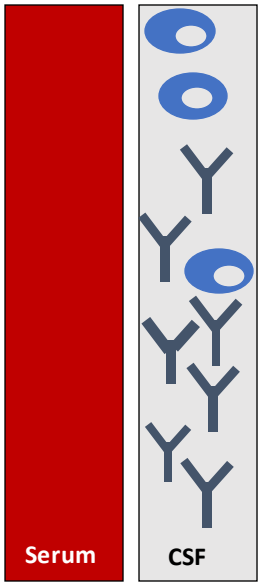
Otallah S, Banwell B. Pediatric Multiple Sclerosis: An Update. Curr Neurol Neurosci Rep. 2018;18:76.

CSF profile in MS

- Pleocytosis is common in MS
- Higher CSF WBC at diagnosis than adult-onset MS
  - Typically <20-50 WBCs
- Protein may also be elevated in CSF
- Oligoclonal bands have been reported to be positive in 64-92% of pediatric MS patients



Willis MD, Kreft KL, Dancey B. Oligoclonal bands. Pract Neurol. 2024 Sep 13;24(5):400-406.

Diagnosis

When to suspect POMS

***Example symptoms**
- Blurry vision/eye pain
- Weakness
- Paresthesias
- Ataxia
- Gait difficulty
- Bowel/bladder dysfunction
- Slurred speech
- Vertigo

Any acute to subacute neurologic deficit with associated exam findings*

Symptoms active

YES

NO

Refer to emergency department for urgent evaluation

Refer for urgent neurology evaluation and consider outpatient workup**

****Outpatient workup to consider:**
- MRI brain with and without contrast
- Serum infectious studies (HSV, VZV, Lyme, EBV, HHV-6, mycoplasma)
- Urine drug screen
- Metabolic testing
- Rheumatologic studies
- **Serum neuroinflammatory studies: MOG, AQP-4**

Differential diagnosis in POMS

Demyelinating Disorders
- NMOSD
- MOGAD
- Clinically isolated syndrome (CIS)
- Radiologically isolated syndrome (RIS)

Infection
- HIV
- HSV
- VZV
- Arboviruses
- Lyme
- Syphilis
- Bartonella
- Tuberculosis
- CMV
- Parasites

Metabolic/Genetic
- Leukodystrophy
- Mitochondrial disorders
- CADASIL
- Inborn errors of metabolism

Vascular/ Rheumatologic
- CNS vasculitis
- Stroke
- Neuro-Behcet's
- Neuro-sarcoidosis
- CNS lupus

Malignancy
- CNS lymphoma
- Metastases
- Glioblastoma multiforme

Diagnosis: 2017 McDonald criteria

Need to fulfill dissemination in space (DIS) and dissemination in time (DIT):

- Two or more clinical events with presumed inflammatory cause separated by more than 30 days and involving more than one area of the CNS **OR**
- One clinical event typical of MS associated with MRI findings showing dissemination in space and time (or +OCBs)

Major updates to 2017 criteria:

Positive (2 or more) oligoclonal bands substitute for DIT when other CSF findings are typical (WBCs <50, protein <100)

Symptomatic and asymptomatic MRI lesions can be included to determine DIS and DIT

Cortical lesions can be used to fulfill MRI criteria for DIS

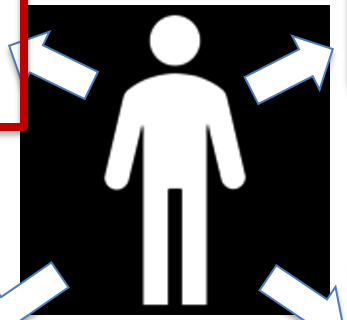
Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Lancet Neurol. 2018;17(2): 162-73.

Management and outcomes

Overall treatment: multidisciplinary approach

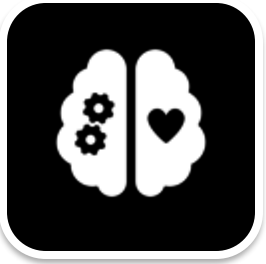
Neuroimmunologist
Primary diagnosis, immunotherapy management, surveillance

Patient



Neuropsychologist
Diagnosis, management, and surveillance of comorbid cognitive dysfunction

Social Worker
Financial, educational, emotional/psychological resources



Psychiatrist
Management of comorbid psychiatric features/disorder

Rehabilitation/PMR
Diagnosis and management of physical disability

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Acute management strategies

IVMP

20-30mg/kg/d for 3-5 days

SEs: behavioral side effects, insomnia, increased appetite

IVIG

2g/kg divided over 2-5 days

SEs: headaches, hypercoagulability

Plasmapheresis

5-7 exchanges

SEs: central line infection risk, electrolyte abnormalities/fluid shifts

Mild → **Severe**

Long-term management: disease-modifying therapies

ALL patients should be started on long-term therapy given high risk of relapse

Traditional Therapies	Higher-Efficacy Therapies
IFN-beta 1a (Avonex, Rebif)	Dimethyl fumarate (Tecfidera)
IFNB-beta 1b (Betaseron, Betaferon)	Fingolimod (Gilenya)
Pegylated IFN-beta-1a (Plegridy)	Natalizumab (Tysabri)
Glatiramer acetate (Copaxone)	Rituximab (Rituxan)

There is evidence to support use of HET as first line!

Which therapy to choose?

- Currently there are no specific guidelines
- Shared decision model
- Tailor to specific patient (i.e. comorbidities, disease severity, side effects/safety)
- Consider cost & convenience/compliance
- **Ultimately encourage high-efficacy therapy up front!**

Adults: many available options!

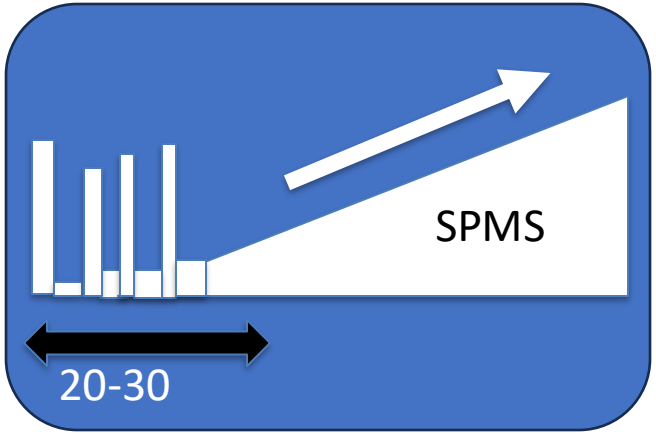
- Often start with ocrelizumab (transition my patients to ocrelizumab once 18)
- Ofatumumab, fingolimod
- Dimethyl fumarate

Pediatrics: fewer options…

- Rituximab or fingolimod as first line
- Biosimilars?
- Tysabri for severe onset with significant disease burden
- Dimethyl fumarate for more mild disease

Prognosis/Outcome

- High relapse rates with more than 75% of children having second clinical attack within 1 year
  - Tend to have complete and prompt recovery from relapses
- Time to disability is longer compared to adult MS
  - Time to acquire EDSS score of 4 is also ~10 years longer in POMS
- Secondary progression rarely occurs in childhood (~20 years after initial demyelinating event)
  - Median time to conversion to secondary progressive MS (SPMS) is ~10 years longer in POMS
- Predictors of poor outcome: brainstem attacks, poor recovery from single attack, and higher frequency of attacks
- Overall better outcome and less physical disability than adult-onset MS



Hardy D, Banwell B. Pediatric-Onset Multiple Sclerosis. Practical Neurology. 2019.
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Summary

- Multiple sclerosis, though most commonly adult-onset, can present in patients younger than 18 years of age
- Pediatric-onset MS more commonly presents with more aggressive disease early on with optic neuritis, brainstem syndrome, and transverse myelitis being the most common presentations
- Differential diagnosis is broad, but utilization of 2017 McDonald criteria allows for more rapid and accurate diagnosis
- The mainstay of treatment is disease-modifying therapy, but comorbid cognitive dysfunction, fatigue, and depression must also be addressed appropriately
- Outcomes in POMS are generally more favorable, with longer time to reach disability

Questions?

Partnering with our pediatricians: frequently asked questions

- **Can my patient receive vaccines?**
  - YES! (except avoid live attenuated vaccines)
  - May need to adjust timing of vaccines (to optimize effect of vaccines)
- **Any precautions my patient should take?**
  - Seizure precautions (if patient has seizures)
  - Encourage hand hygiene (if patient on immunosuppressive therapies)
- **What signs/symptoms should I be monitoring for that may suggest relapse?**
  - New acute onset of neurologic symptoms persisting for 24 hours
- **Are there important immunotherapy side effects I should be looking for?**
  - YES! Recurrent sinopulmonary infections (if on RTX)
  - Other side effects of RTX: liver dysfunction (elevated liver enzymes), headache, infusion-related reactions
- **Are there resources I can refer my patient to?**
  - National MS society website: www.nationalmssociety.org
- **Who do we refer to?**
  - Dell Children's Multiple Sclerosis and Related Neuroimmune Disorders Clinic: **512-628-1855**
    - Duriel Hardy, MD (pediatric and adult) and Karen Evankovich, PhD

Dr. Duriel Hardy

Dr. Karen Evankovich

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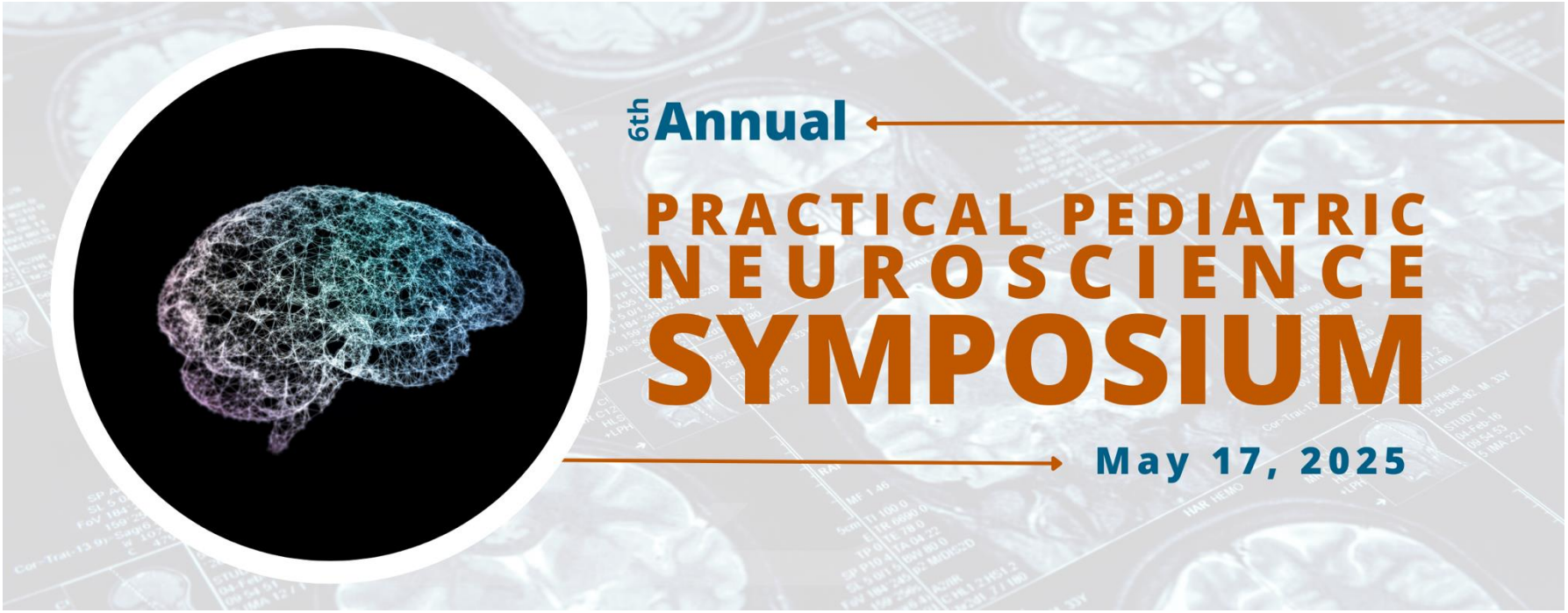

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