CME Conference: Updates in Neuro-ophthalmology and MS
March 2017

Teri Schreiner, MD MPH
University of Colorado

Updates: Multiple Sclerosis in Children

Disclosures

- I participate in clinical research funded by Biogen, Teva, Novartis, NIH/NINDS, MSDx, ADAMAS
- I have received speakers fees from Genentech
- I have received consulting fees from Biogen

Objectives

- Review of demyelination in children
- Update: Differential Diagnosis of MS in peds
  - Anti-MOG
- Update: Epidemiology of Peds MS
  - Dietary Salt
  - Obesity
- Treatment of Peds MS
  - Clinical trials: Fingolimod, teriflunomide
  - Tecfidera

Demyelination in Children

Acute central nervous system demyelination in children

- Monophasic Diseases
  - Acute disseminated encephalomyelitis (ADEM)
  - Clinically Isolated Syndrome (CIS)
    - Optic neuritis
    - Transverse myelitis
- Chronic Diseases
  - Multiple sclerosis (MS)
  - Neuromyelitis optica (NMO)

Acquired Demyelinating Syndrome (ADS) Incidence

- Canadian cohort
  - 0.9 per 100,000 Canadian children
- Californian cohort
  - 1.63 per 100,000 person-years
- Washington DC cohort
  - 11.79 cases per million children
- Iceland cohort
  - 1.15 per 100,000 children

- Banwell, et al. Incidence of acquired demyelination of the CNS in Canadian Children. Neurology, 2009; 72:232-239.
- Langer-Gould, et al. Incidence of acquired CNS demyelinaing syndromes in a multiethnic cohort of children. Neurology, 2011; 77:1143-1148.
- Vanderver, et al. Relative Incidence of Inherited White Matter Disorders in Childhood to Acquired Pediatric Demyelinating Disorders. Seminars in Pediatric Neurology;19:219-223.
- Gudbjornsson, et al. Nationwide Incidence of Acquired Central Nervous System Demyelination in Icelandic Children. Pediatric Neurology; 2016, 53: 503-507.

2010 McDonald Criteria (Polman 2010)

- Allows confirmation of dissemination in space (DIS) and time (DIT) in patients with a single demyelinating episode and a single MRI
- DIS:
  - ≥ 1 clinically-silent T2 lesion in at least 2 of 4 CNS regions:
    1. Periventricular
    2. Juxtacortical
    3. Infratentorial
    4. Spinal cord
- DIT:
  1. A new T2 and/or Gd lesion(s) on f/u MRI, with reference to baseline irrespective of timing of baseline scan
  2. Simultaneous presence of asymptomatic Gd and non-Gd lesions at any time

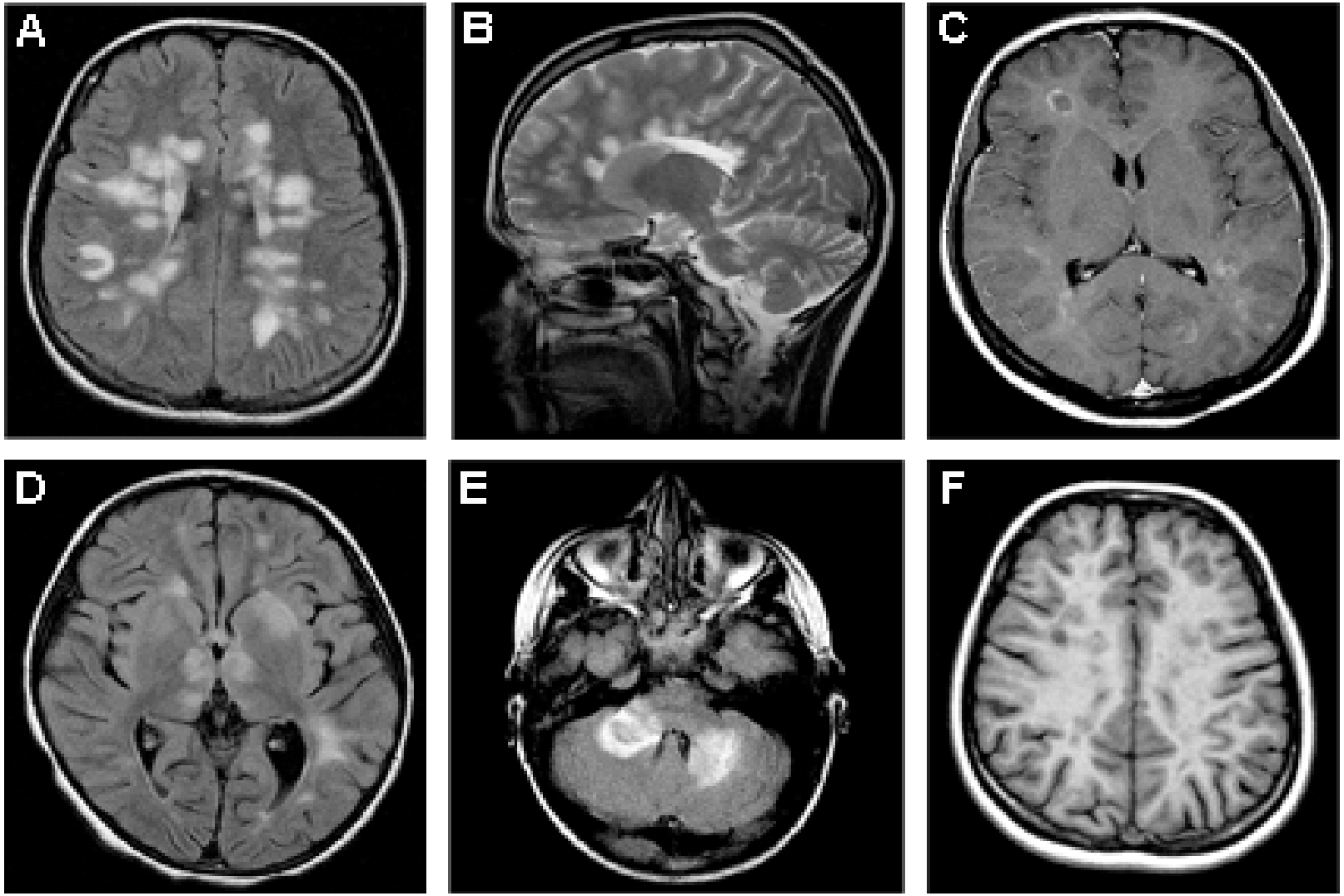
Caveat: Does not apply to children less than 12 years old or patients with encephalopathic presentation

Peds MS: Clinical features

- Polysymptomatic presentation is common
- Relapsing and remitting course
- Annual relapse rate 2-3 times that of adults
- Pediatric MS patients are more racially & ethnically diverse

Duquette 1997, Trojano 2005, Gorman 2009, Waubant 2009, Fay 2010

MRI Appearance of Pediatric MS



Banwell & Verhey, Pediatric MS, Handbook of Clinical Neurology, in Lasonde & Harnat, Dulac ed.

Differential Diagnosis

Acute central nervous system demyelination in children

- Monophasic Diseases
  - Acute disseminated encephalomyelitis (ADEM)
  - Clinically Isolated Syndrome (CIS)
    - Optic neuritis
    - Transverse myelitis
- Chronic Diseases
  - Multiple sclerosis (MS)
  - Neuromyelitis optica (NMO)

Demographic distribution of Peds MS, peds NMO and peds ADEM

Table 1 Demographics of patients with neuromyelitis optica (NMO), multiple sclerosis (MS), or acute disseminated encephalomyelitis (ADEM)[a]

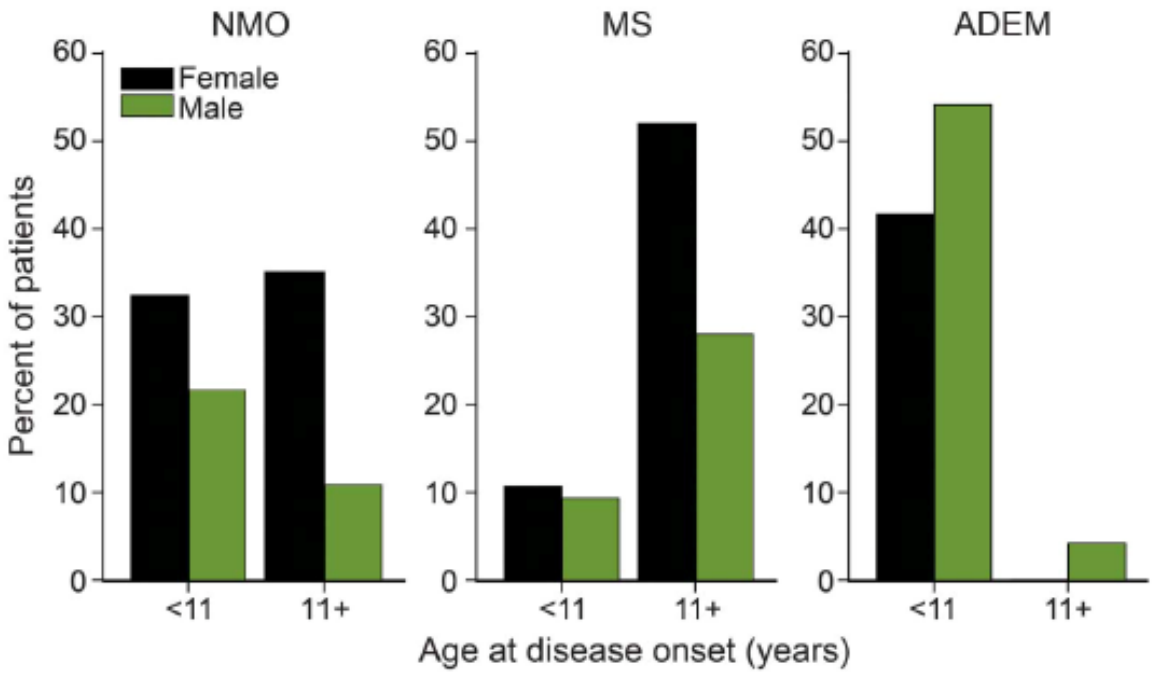
	NMO (n = 38)	MS (n = 150)	ADEM (n = 24)
Age onset, y			
Mean (SD)[b,c]	10.2 (4.7)	13.5 (3.8)	4.8 (2.9)
Age <11 y[b,c]	20 (54)	30 (20)	23 (96)
Sex			
Male	12 (32)	56 (37)	14 (58)
Female	26 (68)	94 (63)	10 (42)
Race[b,c]			
White	14 (37)	91 (61)	19 (79)
Black/African American	14 (37)	20 (13)	1 (4)
Multiracial	2 (5)	8 (5)	0 (0)
Asian/East Asian	0 (0)	4 (3)	1 (4)
Asian/South Asian	3 (8)	0 (0)	0 (0)
Asian/Southeast Asian	1 (3)	2 (1)	0 (0)
American Indian/Alaskan native	0 (0)	2 (1)	0 (0)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	0 (0)
Unknown	4 (11)	22 (15)	3 (13)
Ethnicity[b]			
Non-Hispanic/non-Latino	29 (76)	91 (61)	17 (71)
Hispanic/Latino	5 (13)	46 (31)	5 (21)
Unknown	4 (11)	13 (9)	2 (8)

[a] Frequency (%) given, unless otherwise specified. Age at onset missing for 1 patient with NMO.
[b] p Value <0.05 comparing NMO vs MS according to a Wilcoxon rank-sum test for age or Fisher exact test for all others; test for race compares white vs all others excluding unknown; test for ethnicity compares Hispanic/Latino vs non-Hispanic/non-Latino.

Chitnis, et al. Clinical features of neuromyelitis optica in Children US Network of Pediatric MS Centers report. Neurology 2016.

Comparison of sex distribution between NMO, MS and ADEM

Figure 2 **Sex distribution by age group (<11 vs ≥11 years of age) for each diagnosis classification**



ADEM = acute disseminated encephalomyelitis; MS = multiple sclerosis; NMO = neuromyelitis optica.

Chitnis, et al. Clinical features of neuromyelitis optica in Children US Network of Pediatric MS Centers report. Neurology 2016.

Racial and ethnic variability

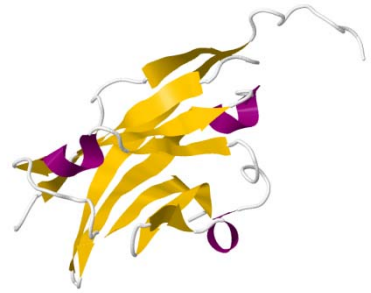
Table 1 Demographics of patients with neuromyelitis optica (NMO), multiple sclerosis (MS), or acute disseminated encephalomyelitis (ADEM)[a]

	NMO (n = 38)	MS (n = 150)	ADEM (n = 24)
Age onset, y			
Mean (SD)[b,c]	10.2 (4.7)	13.5 (3.8)	4.8 (2.9)
Age <11 y[b,c]	20 (54)	30 (20)	23 (96)
Sex			
Male	12 (32)	56 (37)	14 (58)
Female	26 (68)	94 (63)	10 (42)
Race[b,c]			
White	14 (37)	91 (61)	19 (79)
Black/African American	14 (37)	20 (13)	1 (4)
Multiracial	2 (5)	8 (5)	0 (0)
Asian/East Asian	0 (0)	4 (3)	1 (4)
Asian/South Asian	3 (8)	0 (0)	0 (0)
Asian/Southeast Asian	1 (3)	2 (1)	0 (0)
American Indian/Alaskan native	0 (0)	2 (1)	0 (0)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	0 (0)
Unknown	4 (11)	22 (15)	3 (13)
Ethnicity[b]			
Non-Hispanic/non-Latino	29 (76)	91 (61)	17 (71)
Hispanic/Latino	5 (13)	46 (31)	5 (21)
Unknown	4 (11)	13 (9)	2 (8)

[a] Frequency (%) given, unless otherwise specified. Age at onset missing for 1 patient with NMO.
[b] p Value <0.05 comparing NMO vs MS according to a Wilcoxon rank-sum test for age or Fisher exact test for all others; test for race compares white vs all others excluding unknown; test for ethnicity compares Hispanic/Latino vs non-Hispanic/non-Latino.

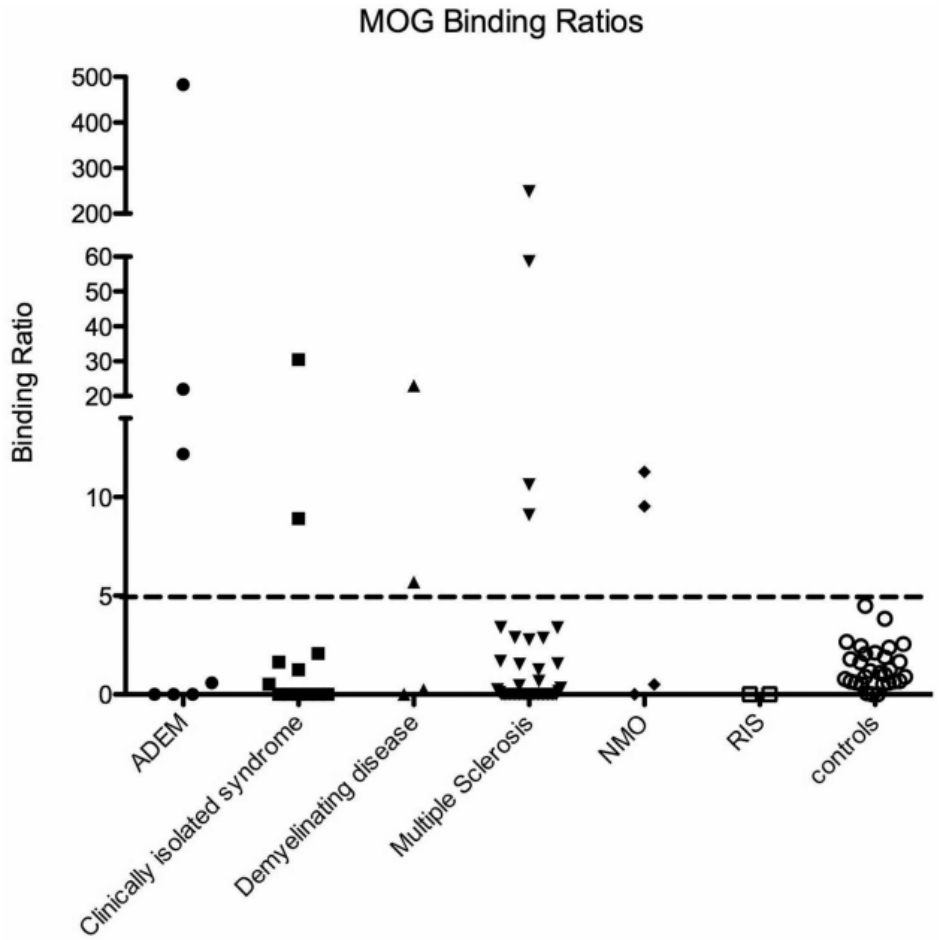
Chitnis, et al. Clinical features of neuromyelitis optica in Children US Network of Pediatric MS Centers report. Neurology 2016.

Update: anti MOG



- Previously identified in children with:
  - ADEM-like first episode
  - MS (<10 years)
  - Recurrent Optic Neuritis
  - Seronegative NMO
  - ADEM, followed by ON
- Also reported in adults with:
  - Seronegative NMO

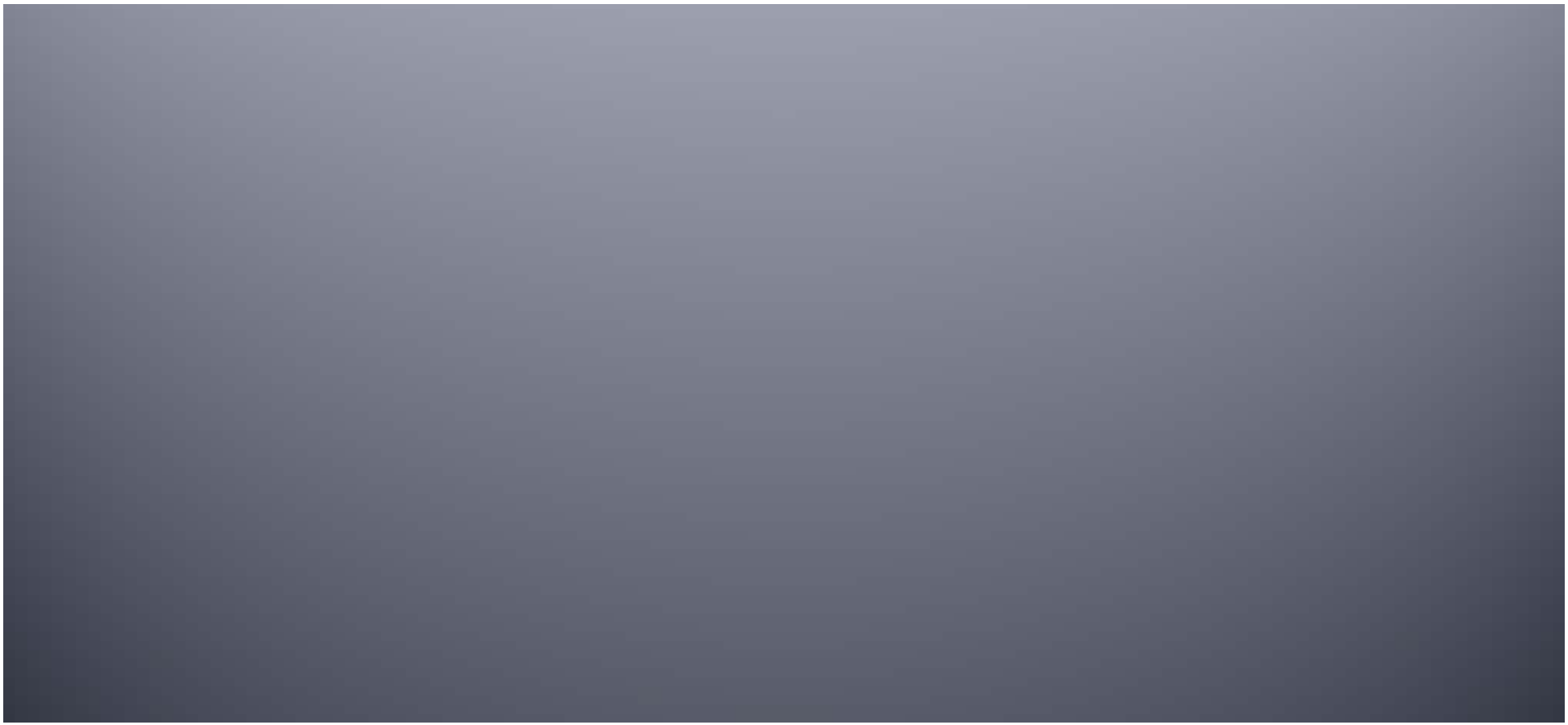
Further characterizing anti-MOG



- 74 children at MGH with suspected demyelinating disorders where tested for anti=MOG
- N=13 positive
- Seropositive:
  - More likely to have encephalopathy
  - Younger, bimodal
- No difference in multiphasic vs. monophasic
- No difference in EDSS after 2 years
- No corpus callosum lesions

Fernandez-Carbonell, Cristina et al. Clinical and MRI phenotype of children with MOG antibodies. Mult Scler 2016.

Updates: Epidemiology of Peds MS



MS Risk Factors

- Prior EBV infection
- Low vitamin D levels
- Smoking exposure
- Obesity
- Dietary salt

Childhood obesity and risk of MS in adults

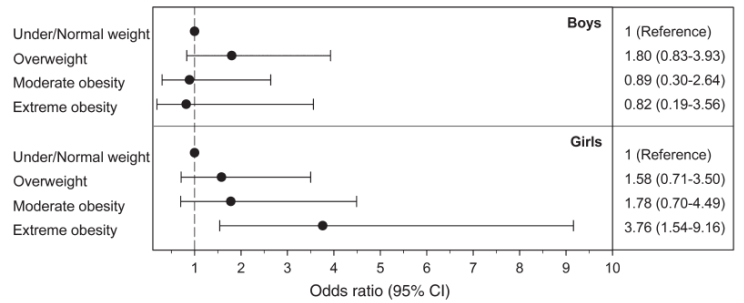
- Kaiser Permanente Medical Care Plan
  - 1235 MS cases
  - 697 controls
- Multivariate analysis adjusted for infectious mononucleosis and genetic risk factors
  - HLA DRB1*1501 & non-HLA risk alleles
- Two fold risk of MS for females with a BMI>= 30 kg/m2 at age 20

Gianfrancesco et al. Obesity during childhood and adolescence increases susceptibility to multiple sclerosis after accounting for established genetic and environmental risk factors. Obes Res Clin Pract 2014 .

Childhood obesity and risk of MS in childhood

- Kaiser Permanente South California
- N= 75
- Obesity associated with increased risk of MS/CIS in girls (p=0.005)
  - Adjusted odds ratio among overweight girls 1.58 compared to normal weight

Figure Association between weight class and pediatric multiple sclerosis/clinically isolated syndrome by sex



Depicted are the adjusted odds ratios (OR) and 95% confidence intervals (CI) of pediatric multiple sclerosis and clinically isolated syndrome (MS/CIS) with increasing weight class compared with normal/underweight children (reference category) stratified by sex. Increasing weight class was associated with increasingly higher OR for MS/CIS among girls (*p* for trend

Dietary Salt

- Studies suggest that high salt diet (>5 grams/day) may induce Th17 cells and pro-inflammatory cytokines
- Higher salt intake associated with clinical exacerbations and MRI activity

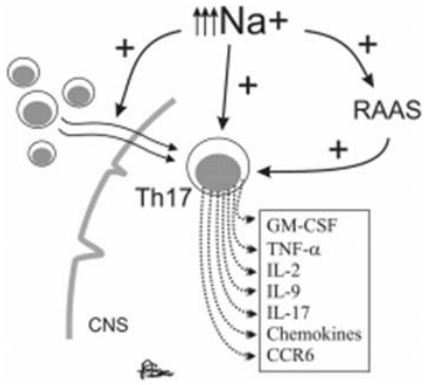


Fig. 2 Probable impact of high sodium diet on immune functions in multiple sclerosis patients (*CNS* central nervous system, *RAAS* renin–angiotensin–aldosterone system)

Farez, et al. 2015.

Dietary Salt: Cases & Controls

Published in final edited form as:
Mult Scler Relat Disord. 2016 March ; 6: 87–92. doi:10.1016/j.msard.2016.02.011.

A case-control study of dietary salt intake in pediatric-onset multiple sclerosis

Jamie McDonald[a], Jennifer Graves[a], Amy Waldman[b], Timothy Lotze[c], Teri Schreiner[d], Anita Belman[e], Benjamin Greenberg[f], Bianca Weinstock-Guttman[g], Gregory Aaen[h], Jan-Mendelt Tillema[i], Janace Hart[a], Sabeen Lulu[a], Jayne Ness[j], Yolanda Harris[j], Jennifer Rubin[k], Meghan Candee[l], Lauren B. Krupp[e], Mark Gorman[m], Leslie Benson[m], Moses Rodriguez[i], Tanuja Chitnis[n], Soe Mar[o], Lisa F. Barcellos[p], Barbara Laraia[q], John Rose[r], Shelly Roalstad[l], Timothy Simmons[l], T. Charles Casper[l], and Emmanuelle Waubant[a,*]

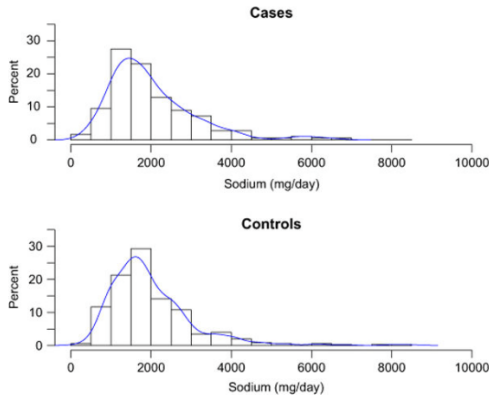


Fig. 1.
Histograms for cases and controls in order to depict the distribution of sodium intake (mg/d) between groups.

- N=174
- Mean duration of follow-up 1.8 years
- Higher salt intake was not associate with time to relapse

Zostawa, et al. The influence of sodium on pathophysiology of multiple sclerosis. Neurol Sci (2017) 38:389-398.

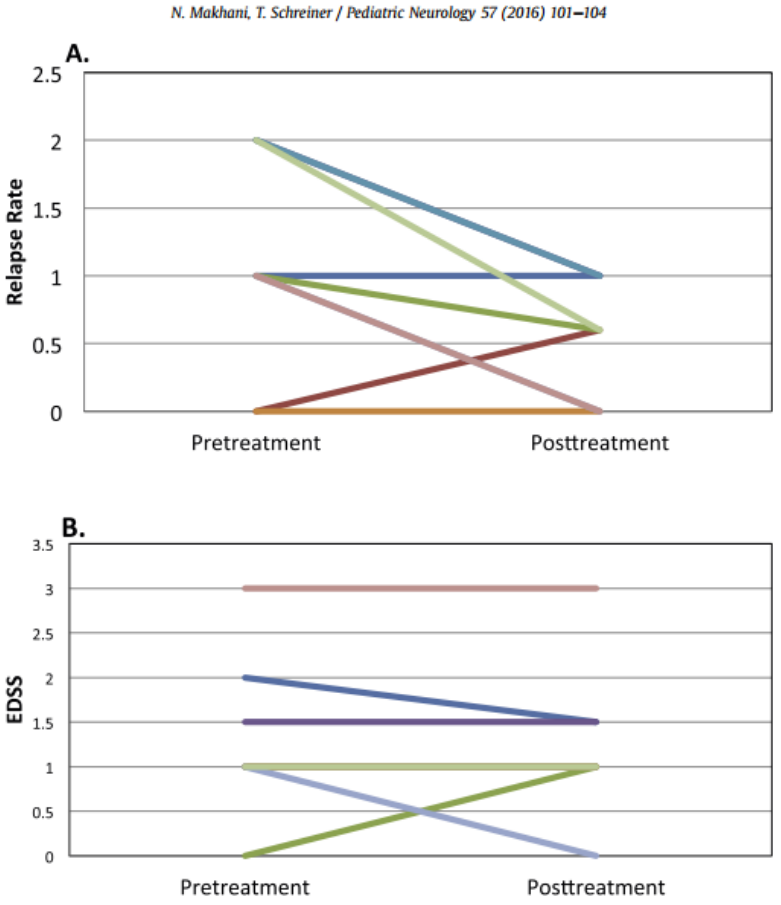
Treatment of Peds MS

Update: Treatment

- Clinical trials in US
  - Fingolimod
  - Teriflunomide
- Case series:
  - Tecfidera

Tecfidera use in children

- N=13 pediatric MS patients
- Median 15 months of treatment
- 3 children discontinued due to SE
- SE: Flushing (62%), GI distress (54%), rash (23%) and malaise (15%)
- 8/9 patients had decreased RR at 1 year



Summary

- Pediatric MS is rare
- Anti-MOG should be considered in children with demyelinating disease
- Childhood obesity is a risk factor for MS
- Dietary salt appears not to have an effect on MS susceptibility in children
- Clinical trials are ongoing
  - Retrospective data for Tecfidera shows similar tolerability and (probably) efficacy

Thank you!

Question

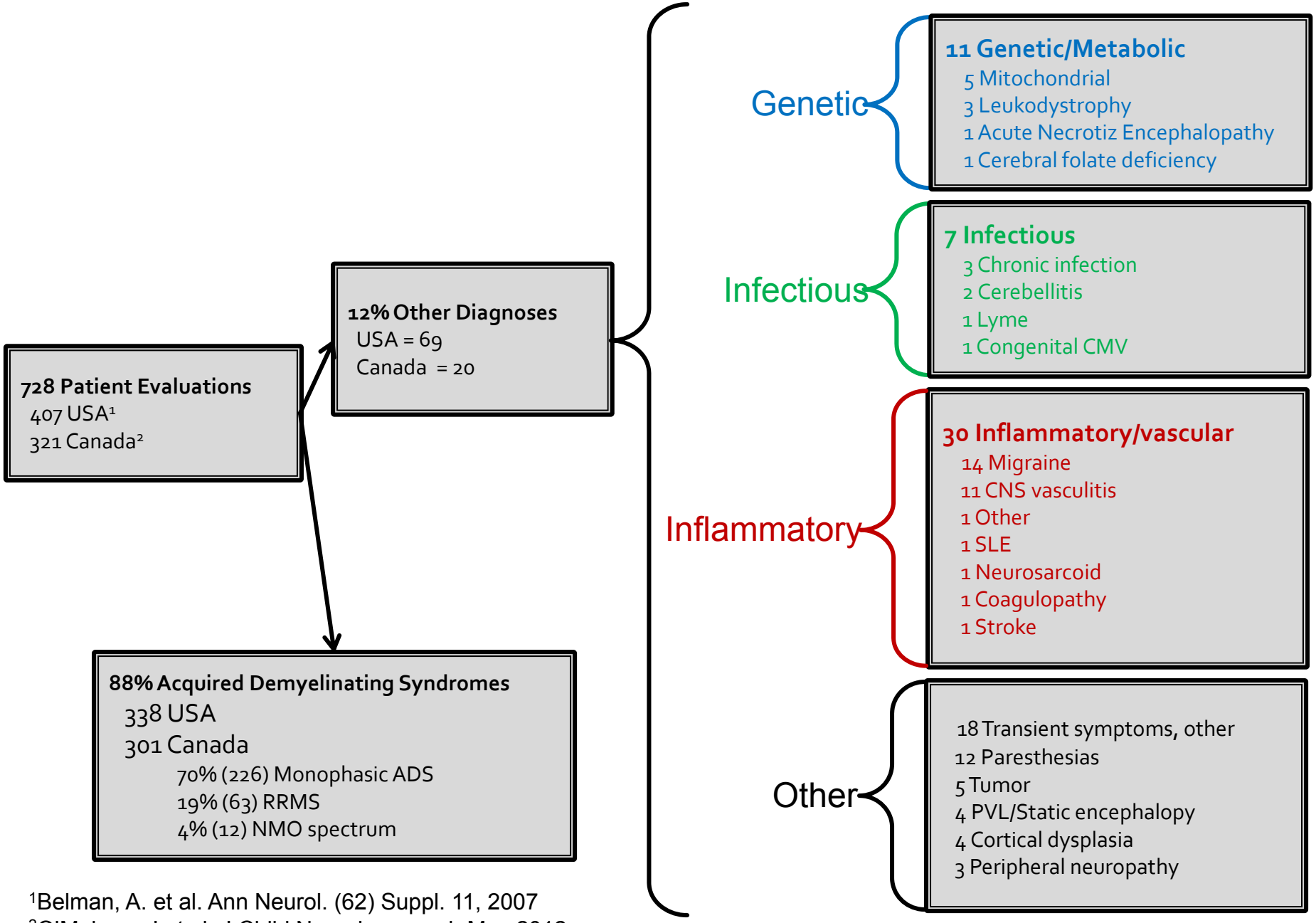
The clinical presentation of Pediatric Multiple Sclerosis varies in children younger than 11 years old in the following ways except:

A: Less likely presence of oligoclonal bands

B. More equitable sex distribution

C. More timely radiographic improvement

D. Different pathophysiology



[1]Belman, A. et al. Ann Neurol. (62) Suppl. 11, 2007
[2]O'Mahony J et al, J Child Neurology, epub May 2012

Age of onset is noticeably younger for ADEM

Table 1 Demographics of patients with neuromyelitis optica (NMO), multiple sclerosis (MS), or acute disseminated encephalomyelitis (ADEM)[a]

	NMO (n = 38)	MS (n = 150)	ADEM (n = 24)
Age onset, y			
Mean (SD)[b,c]	10.2 (4.7)	13.5 (3.8)	4.8 (2.9)
Age <11 y[b,c]	20 (54)	30 (20)	23 (96)
Sex			
Male	12 (32)	56 (37)	14 (58)
Female	26 (68)	94 (63)	10 (42)
Race[b,c]			
White	14 (37)	91 (61)	19 (79)
Black/African American	14 (37)	20 (13)	1 (4)
Multiracial	2 (5)	8 (5)	0 (0)
Asian/East Asian	0 (0)	4 (3)	1 (4)
Asian/South Asian	3 (8)	0 (0)	0 (0)
Asian/Southeast Asian	1 (3)	2 (1)	0 (0)
American Indian/Alaskan native	0 (0)	2 (1)	0 (0)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	0 (0)
Unknown	4 (11)	22 (15)	3 (13)
Ethnicity[b]			
Non-Hispanic/non-Latino	29 (76)	91 (61)	17 (71)
Hispanic/Latino	5 (13)	46 (31)	5 (21)
Unknown	4 (11)	13 (9)	2 (8)

[a] Frequency (%) given, unless otherwise specified. Age at onset missing for 1 patient with NMO.
[b] p Value <0.05 comparing NMO vs MS according to a Wilcoxon rank-sum test for age or Fisher exact test for all others; test for race compares white vs all others excluding unknown; test for ethnicity compares Hispanic/Latino vs non-Hispanic/non-Latino.

Children with ADEM are significantly younger

Chitnis, et al. Clinical features of neuromyelitis optica in Children US Network of Pediatric MS Centers report. Neurology 2016.

Sex distribution between NMO, MS and ADEM

Table 1 Demographics of patients with neuromyelitis optica (NMO), multiple sclerosis (MS), or acute disseminated encephalomyelitis (ADEM)[a]

	NMO (n = 38)	MS (n = 150)	ADEM (n = 24)
Age onset, y			
Mean (SD)[b,c]	10.2 (4.7)	13.5 (3.8)	4.8 (2.9)
Age <11 y[b,c]	20 (54)	30 (20)	23 (96)
Sex			
Male	12 (32)	56 (37)	14 (58)
Female	26 (68)	94 (63)	10 (42)
Race[b,c]			
White	14 (37)	91 (61)	19 (79)
Black/African American	14 (37)	20 (13)	1 (4)
Multiracial	2 (5)	8 (5)	0 (0)
Asian/East Asian	0 (0)	4 (3)	1 (4)
Asian/South Asian	3 (8)	0 (0)	0 (0)
Asian/Southeast Asian	1 (3)	2 (1)	0 (0)
American Indian/Alaskan native	0 (0)	2 (1)	0 (0)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	0 (0)
Unknown	4 (11)	22 (15)	3 (13)
Ethnicity[b]			
Non-Hispanic/non-Latino	29 (76)	91 (61)	17 (71)
Hispanic/Latino	5 (13)	46 (31)	5 (21)
Unknown	4 (11)	13 (9)	2 (8)

[a] Frequency (%) given, unless otherwise specified. Age at onset missing for 1 patient with NMO.
[b] p Value <0.05 comparing NMO vs MS according to a Wilcoxon rank-sum test for age or Fisher exact test for all others; test for race compares white vs all others excluding unknown; test for ethnicity compares Hispanic/Latino vs non-Hispanic/non-Latino.

Chitnis, et al. Clinical features of neuromyelitis optica in Children US Network of Pediatric MS Centers report. Neurology 2016.

Clinical History: Red Flags

- Hyperacute onset
  - Consider cerebral sinus venous thrombosis (CSVT), infarction
- Headache
  - Consider primary angiits of the CNS (PACNS), CSVT, Susac syndrome
- Recurrent or severe optic neuropathy
  - Consider NMO, Leber's Hereditary Optic Neuropathy, chronic relapsing optic neuropathy

Phelan, Jonathan A., Lowe, Lisa H. and Glasier, Charles M. Pediatric neurodegenerative white matter processes: leukodystrophies and beyond. Pediatr Radiol (2008) 38: 729-749.
Chitnis, et al. Pediatric Multiple Sclerosis. Neurol Clin 29 (2011) 481-505.
O'Mahony et al. 2012

Clinical History: Red Flags

- Seizures
  - Consider autoimmune encephalitis, PACNS, Neuro Behcet, CNS lupus
- Psychosis
  - Consider PACNS, autoimmune encephalitis, CNS lupus, Susac syndrome
- Systemic disease
  - Consider neurosarcoidosis, vasculitis, CNS lupus, Susac syndrome, Langerhans cell histiocytosis, Sjogren syndrome

Phelan, Jonathan A., Lowe, Lisa H. and Glasier, Charles M. Pediatric neurodegenerative white matter processes: leukodystrophies and beyond. Pediatr Radiol (2008) 38: 729-749.
Chitnis, et al. Pediatric Multiple Sclerosis. Neurol Clin 29 (2011) 481-505.
O'Mahony et al. 2012

Peds MS Exam: Red Flags

- Cranial nerve involvement
  - Consider neurosarcoidosis, Neuro Behcet, infection
- Joint involvement
  - Consider CNS Lupus
- Fever, constitutional symptoms
  - Consider infection, lymphoma

Peds MS Labs: Red Flags

- CSF: pleocytosis greater than 50 cells/µl
  - Consider infection, HLH, AHLE, NMO
- Elevated opening pressure
  - Consider neurosarcoidosis, PACNS, lymphoma, CSVT

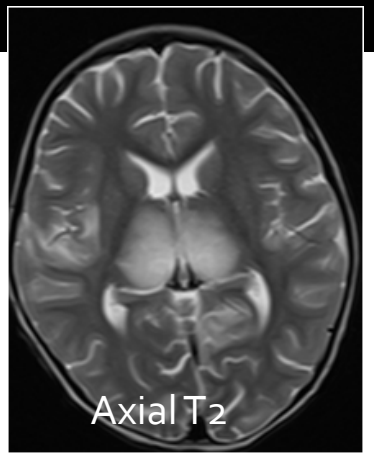
Awad, et al. Analyses of cerebrospinal fluid in the diagnosis and monitoring of multiple sclerosis. Journal of Neuroimmunology 2010; 219: 1-7.
O'Mahony, J. et al. Masquerades of Acquired Demyelination in Children: Experiences of a National Demyelinating Disease Program.Journal of Child Neurology 2012; 00:1-15.

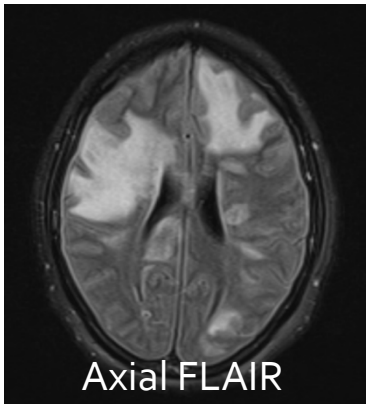
ADEM Diagnostic Criteria

Pediatric ADEM (all are required)

- A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after the onset
- Brain MRI is abnormal during the acute (three-month) phase.
- Typically on brain MRI:
  - Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
  - T1 hypointense lesions in the white matter are rare
  - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

Clarification of terminology. ADEM is a heterogeneous entity and is best viewed as a 'syndrome' rather than a specific disorder.





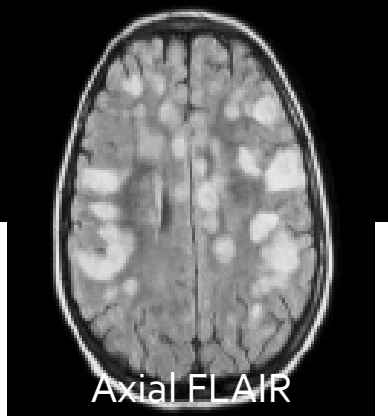
Krupp, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler 2013; 19:1261.

Comparative Incidence

- Pediatric MS: 0.51 per 100,000 person-years
- NMO (adult and child): 0.05-0.4 per 100,000 patient-years
- Primary vasculitis (adults): 0.24 per 100,000 person-years
- Neurosarcoidosis (adult and child): 0.2 per 100,000 persons
- Langerhans Cell Histiocytosis (CNS): 0.2 per 100,000 persons

Gardner-Medwin, et al. Incidence of Henoch-Schonlein purpura, kawasaki disease and rare vasculitides in children of different ethnic origins. Lancet 2002; 360:1197-202.
Hahn, et al.IPMSSG Differential Diagnosis and Evaluation in pediatric multiple sclerosis. Neurology 2007; 68 (suppl2) S18-20.
Langer-Gould, et al. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. Neurology 2011; 77: 1173-1148.
Lower, et al. Neurosarcoidosis. Clin Chest Med 29 (2008) 475-492.

ADEM



- Clinically
  - Most children present before age 10
  - Acute or subacute onset
    - Viral infection or vaccination within one month
  - Multifocal neurologic deficits with encephalopathy
  - Additional clinical features: headache, fever, meningismus, seizures
  - Monophasic, with duration up to 3 months
- Multiphasic: 2 episodes consistent with ADEM separated by 3 months

Role of MRI in the differentiation of ADEM from MS in children

Retrospective analysis of MRI scans obtained at first attack:

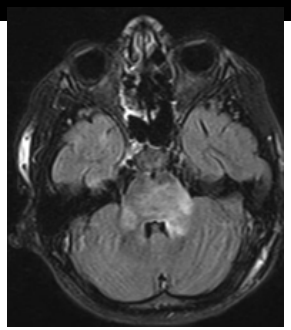
28 children subsequently diagnosed with MS

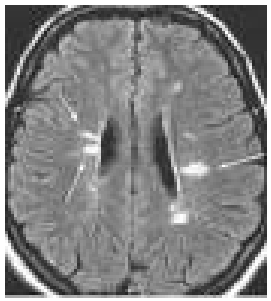
20 children diagnosed with ADEM

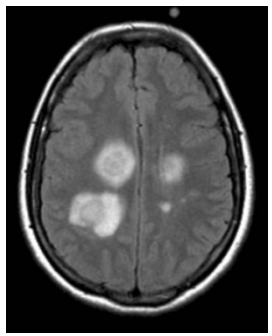
Total number of lesions did not vary between groups.

>=2 of the following (sensitivity 85%, specificity 98%):

1. Absence of a diffuse, bilateral lesion pattern
2. Presence of black holes
3. Presence of two or more periventricular lesions







- Callen, DJA, Shroff, MM et al. Role of MRI in the differentiation of ADEM from MS in children. Neurology 2009; 72:968-973.

New NMOSD Criteria

- Core clinical characteristics:
  - Optic neuritis
  - Acute myelitis
  - Area postrema syndrome (hiccoughs or N/V)
  - Acute brainstem syndrome
  - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical brain lesions
  - Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Table 1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; NMOSD = neuromyelitis optica spectrum disorders.
[a] See table 2 and text discussion on serologic considerations for recommendations regarding interpretation of clinical and serologic testing.

Wingerchuck, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015.

NeuroMyelitis Optica

- Classically: bilateral optic neuritis and transverse myelitis (>3 segments in length)
- Disease course may be progressive or relapsing and remitting
- NMO IgG autoantibody against aquaporin 4 water channel can be used for diagnosis
- NMO in seropositive children:
  - 73% caucasian, 20% African ancestry
  - Median age 12
  - 98% ON, 78% TM
  - 45% episodic cerebral sxs
    - Encephalopathy, ataxia, seizures…
  - 68% had brain abnormalities on MRI
  - 93% Recurrent

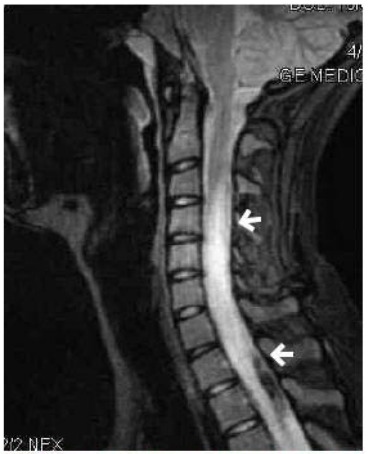
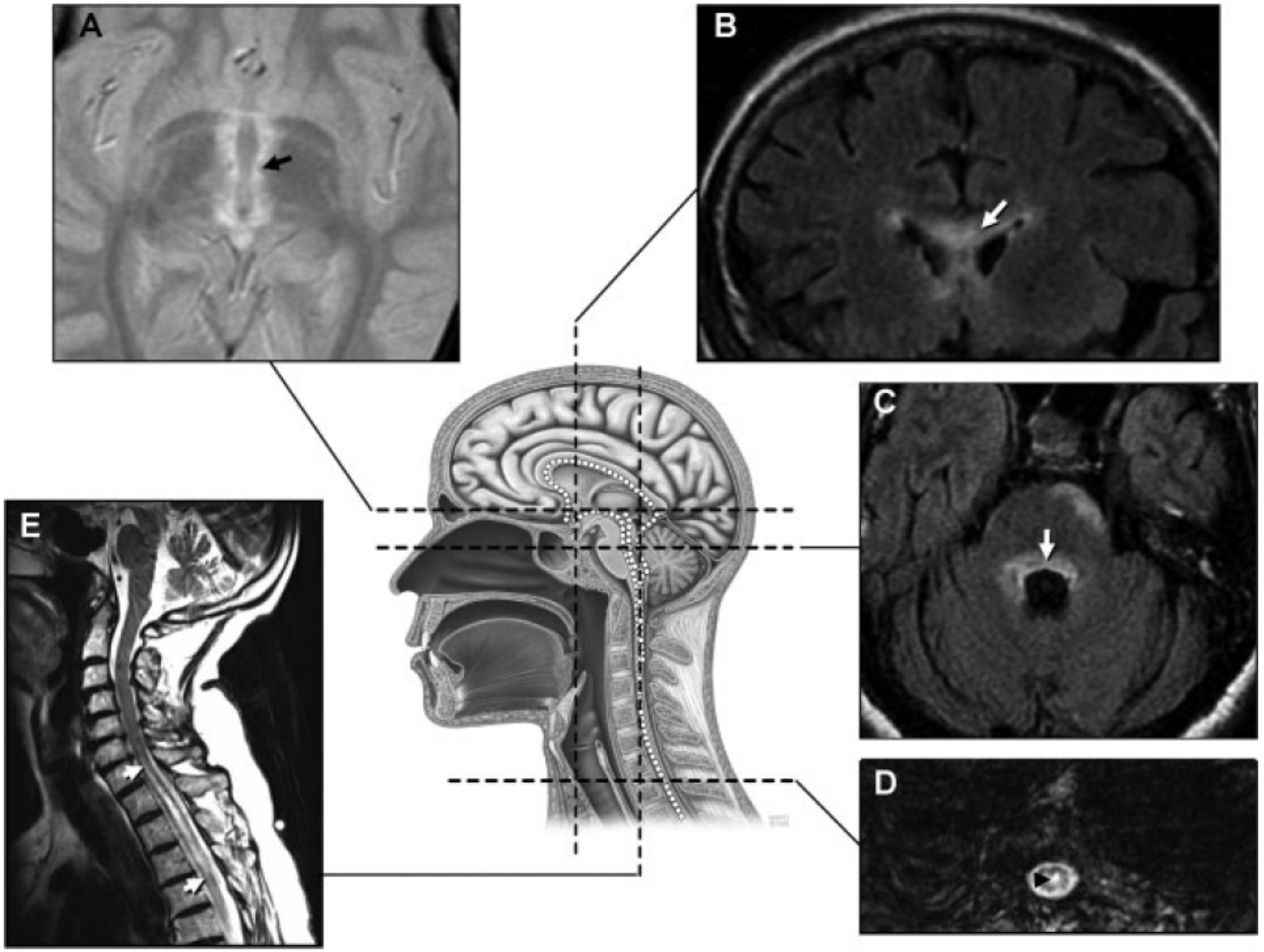


Figure 1. A longitudinally expansive (greater than three segments) lesion seen in the cervical (neck) spinal cord (between arrows).

McKeon, A . Et al. CNS Aquaporin-4 autoimmunity in children. Neurology 2008; 71; 93-100.

NMO: Location of Brain lesions



Diagnosis:Myelitis

- Acute Transverse Myelitis (ATM)
  - Onset of sensory, motor, and autonomic symptomatology over hours to days
  - Transverse ="band-like" sensory disturbance across the midline
  - Typically characterized by both gray and white matter involvement and cord swelling
- Acute Flaccid Myelitis (AFM)
  - Acute limb weakness with primarily gray matter involvement on imaging, +/- CN involvement
  - Recognized in 2014 during respiratory outbreak

Conclusion

- While rare, MS presentation before the age of 11 has a distinct clinical and paraclinical characteristics
- Recovery from exacerbations in pediatric MS is robust in the short term, but it not a benign disorder
- Differential diagnosis includes inflammatory disorders that may be monophasic or multiphasic
  - Presence of encephalopathy is not enough to distinguish between ADEM and MS
  - Watch for red flags: systemic features, seizures, psychosis, cranial nerve involvement, pleocytosis

COLORADO CASE DEFINITION

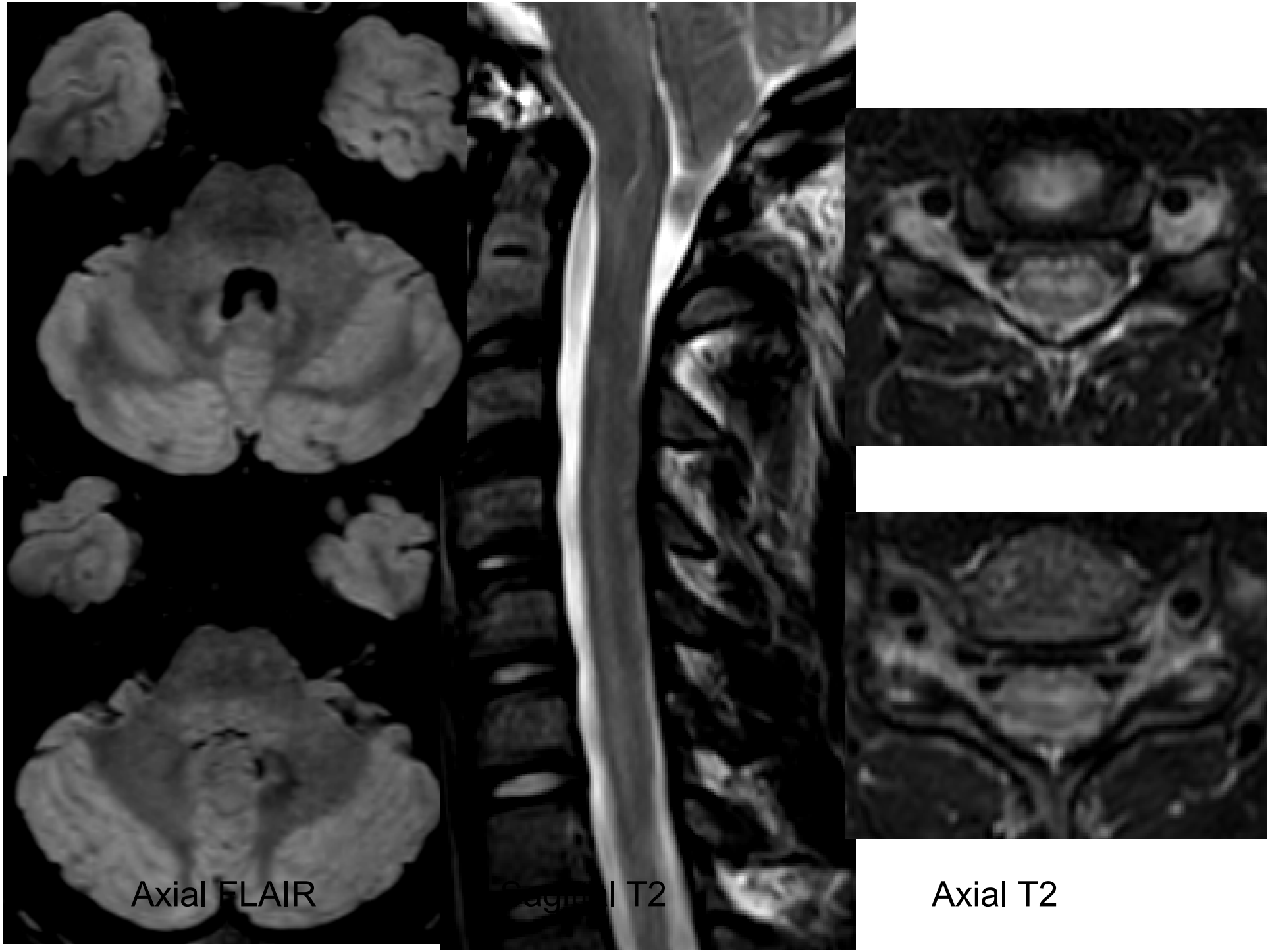
- Presenting after August 1, 2014
- Acute limb weakness and/OR cranial nerve dysfunction AND
- Spinal cord MRI showing predominantly gray matter involvement with or without brainstem lesions

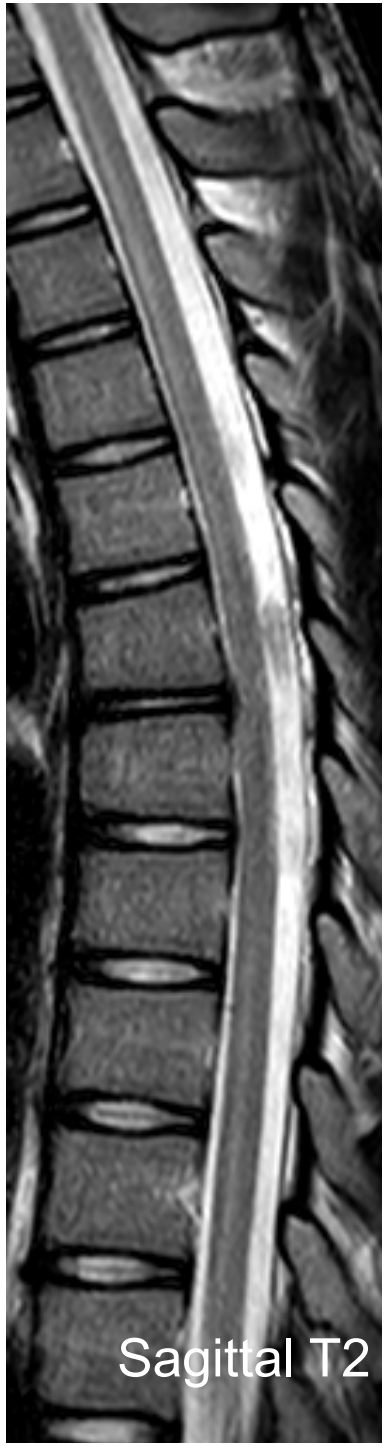
CDC CASE DEFINITION

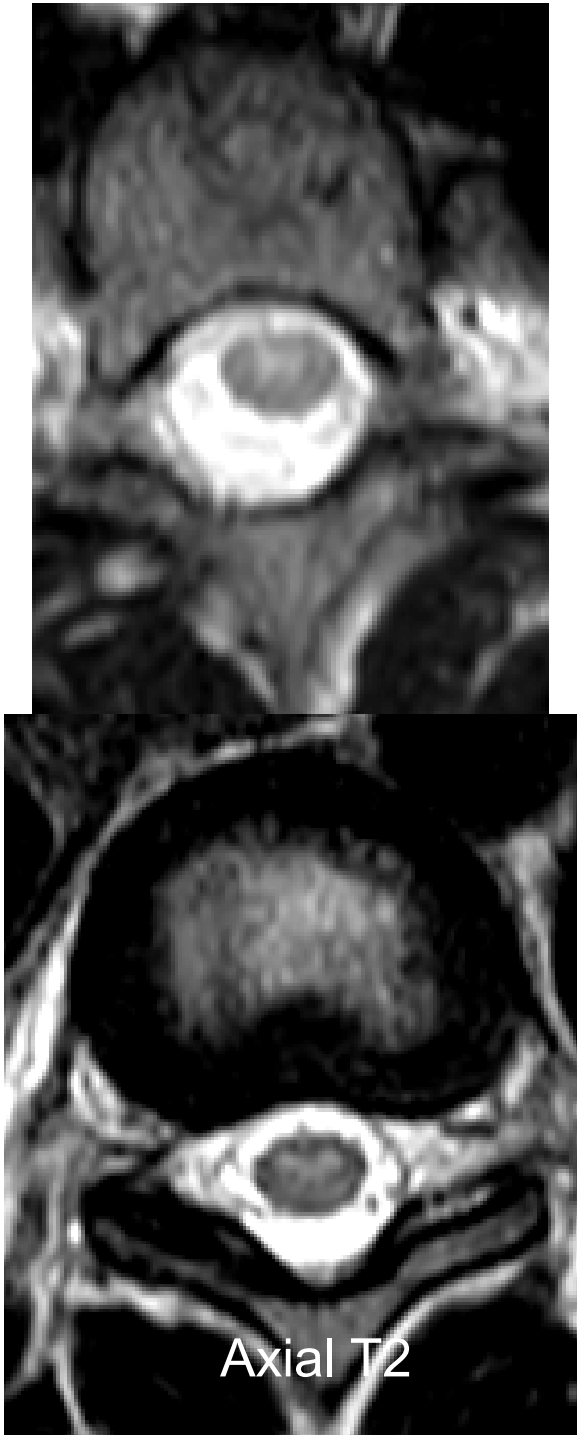
- Patients ≤21 years of age with
  - Acute onset of focal limb weakness occurring on or after August 1, 2014;
- AND
  - An MRI showing a spinal cord lesion largely restricted to gray matter

DH

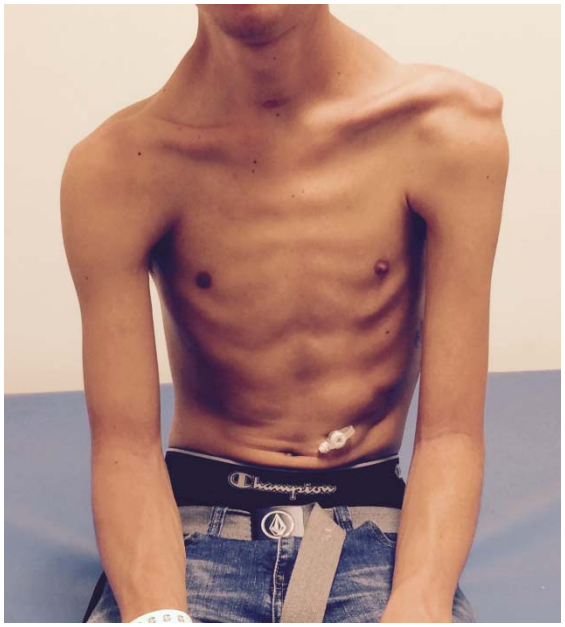
- 18 year old male – progressive bulbar dysfunction and left arm weakness following viral URI
- EV-D68+
- Imaging:
  - Brain: 4d
  - Spine: 4d

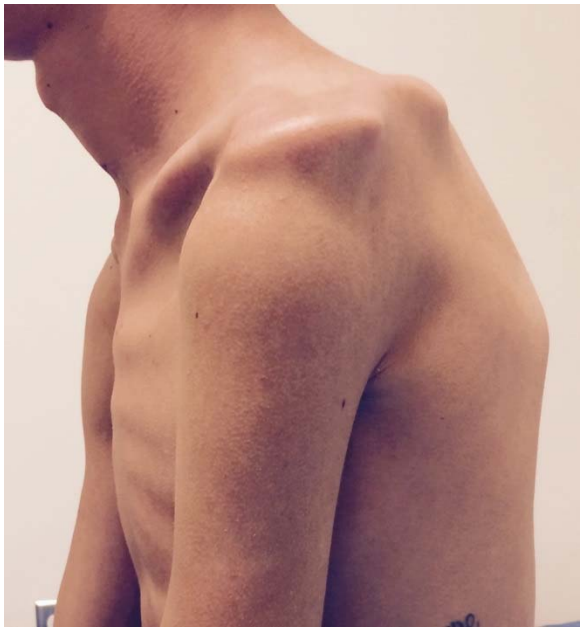

Axial FLAIR
Axial T2

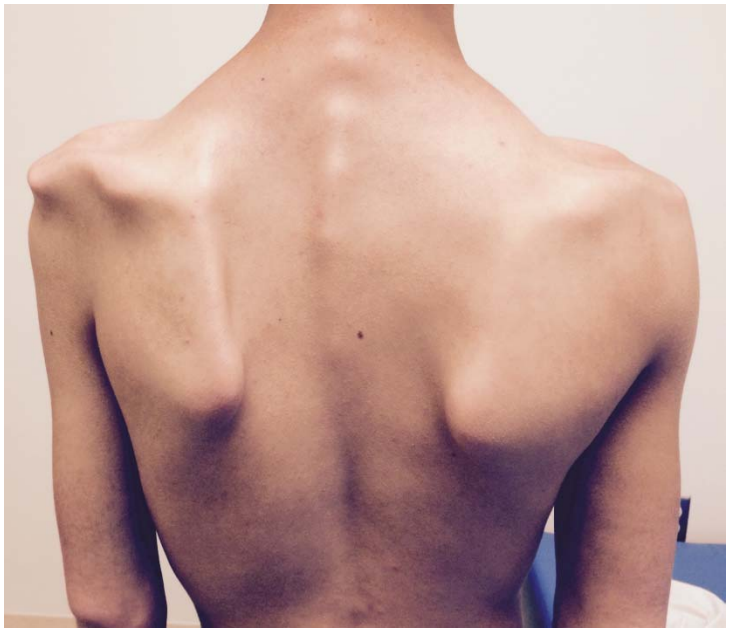

Sagittal T2


Axial T2

8 months later:
DH, 18 yo M with LUE weakness







Case: EM

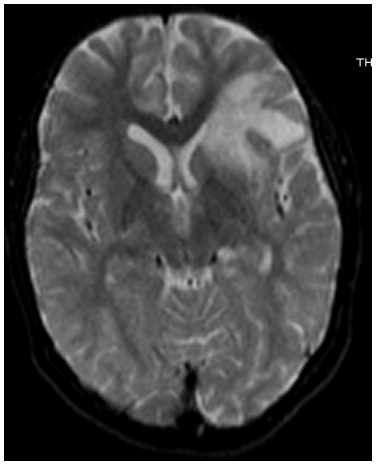
Early attacks

- **April 2006** (age 6): bilateral optic neuritis, treated with steroids, complete visual recovery
  - *No change in mental status*
  - MRI: multiple white matter lesions in the supratentorial regions bilaterally, + enhancement
- **November 2006**: Right sided weakness, *somnolence*, ataxia, urinary retention, tremor; full recovery
  - MRI: T2 hyperintense lesions in the anterior brainstem, deep gray nuclei, centrum semiovale, patchy involvement of parietal, occipital cortex; + enhancement; C3-4 signal change

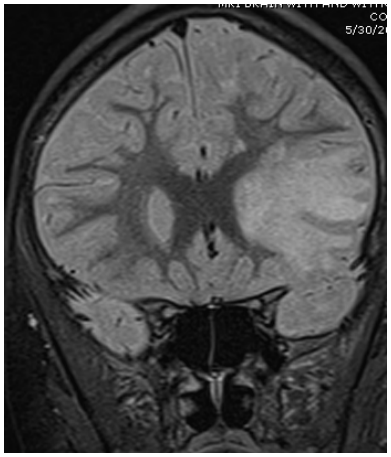
EM: Attacks continue

- **June 2007:** Left sided weakness, numbness, decreased vision on left, left facial droop, aphasia, *no change in mental status*
- **November 2007:** Left hemiparesis, ataxia, vertigo, episodes of loss of vision: "complete blackness", abdominal pain, *no change in mental status*

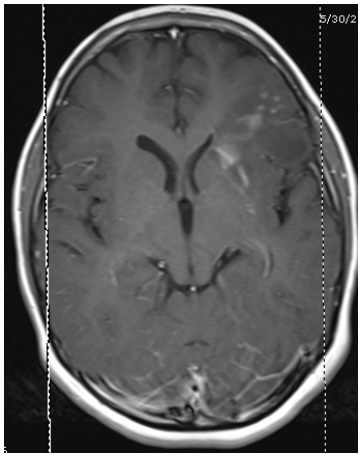
EM: 5th attack



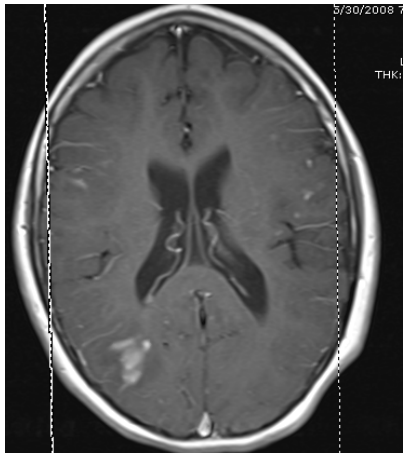
Axial T2



Coronal FLAIR



Axial T with contrast



Axial T with contrast

- Large left frontal parietal white matter signal abnormality, enhancement and mass effect
- Contrast enhancing lesion in the right occipital lobe

Question

The differential diagnosis of a patient like EM, presenting with recurrent episodes of neurologic deficit with interval recovery includes:

A. Pediatric onset multiple sclerosis
B. Multiphasic Acute Disseminated Encephalomyelitis (ADEM)
C. Neuromyelitis optica
D. Mitochondrial disorder
E. All of the above

Peds MS: MRI Features

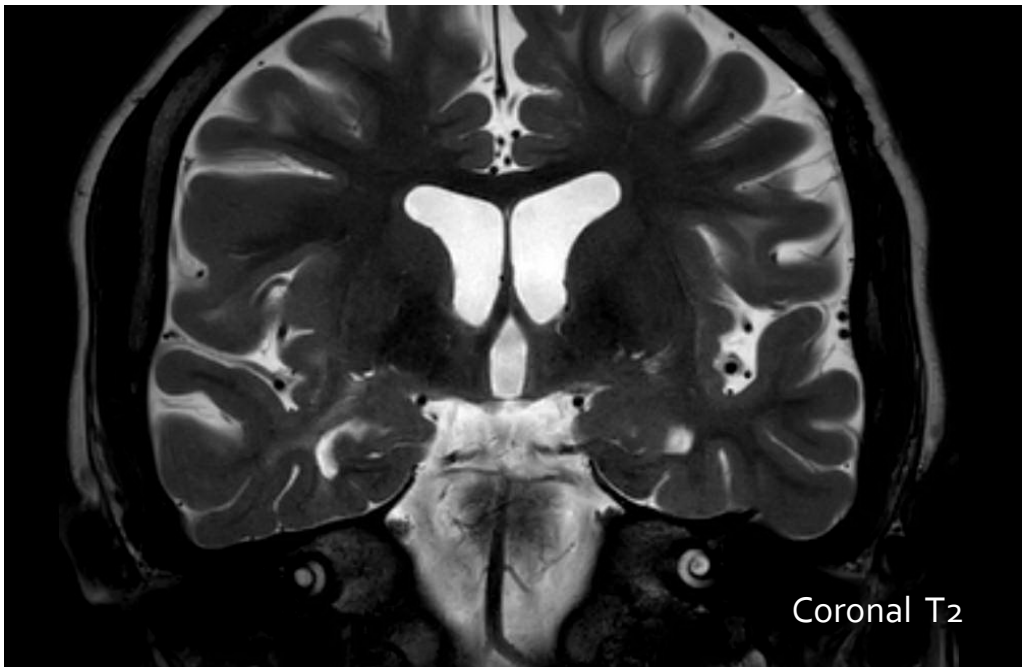
- Pre-pubertal children have better radiographic improvement 3 months after presentation
- Post-pubertal children have persistent radiographic changes 3 months after presentation

Chabas D, et al. Vanishing MS T2-bright lesions before puberty: a distinct MRI phenotype? Neurology. 2008 Sep 30;71(14).

EM: May 2008 - June 2008

- **June 2008** underwent brain biopsy
  - demyelination, extensive macrophage invasion, perivascular and parenchymal T cell infiltrates
- **July 2008:** Began interferon beta 1a
- 3 relapses in the next 18 months
- **2010:** Transitioned to natalizumab

EM: 2015



At age 15, she has mild ataxia and severe unilateral vision loss. She struggles in school and socially. She has been hospitalized for depression.

Images show brain atrophy & bilateral T2 signal change.