Webinar Series



CAN DO Multiple Sclerosis

MS National Multiple Sclerosis Society

MS Multiple Sclerosis Society of Canada

Pediatric-Onset Multiple Sclerosis:
Unique Features and Considerations

August 13, 2019

Presented by:

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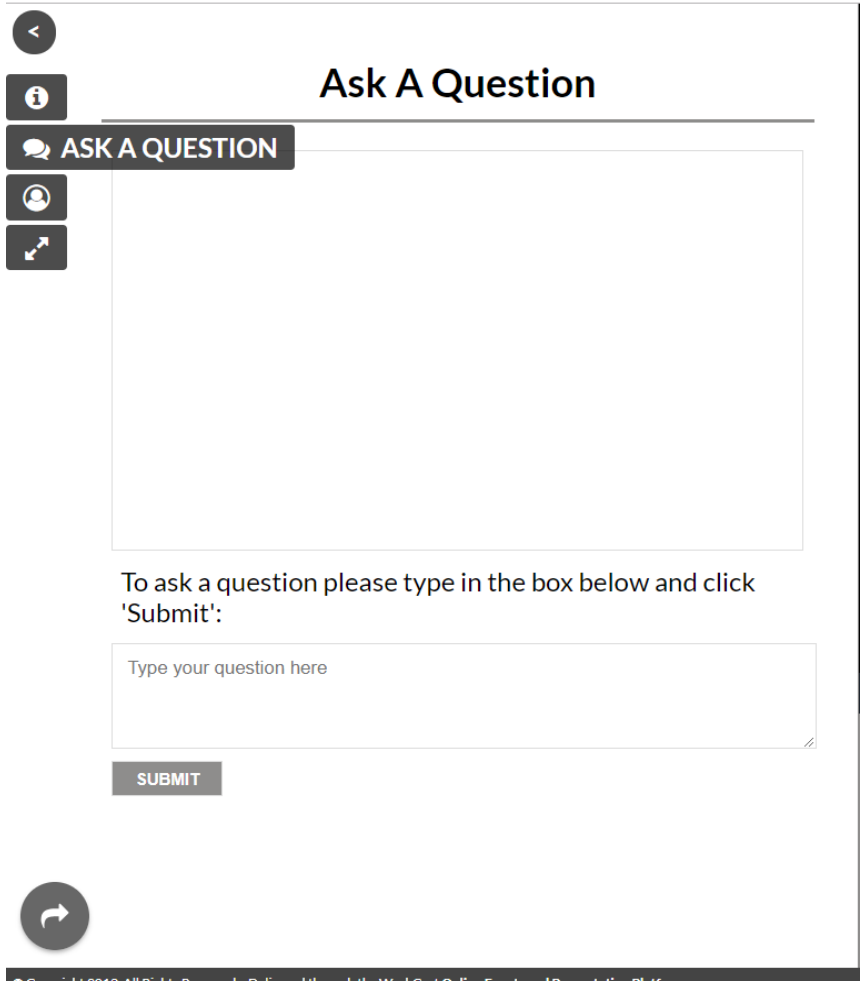
How to Ask Questions During the Webinar:

- Type in your question in the “Ask A Question” Box,
- This can be found by expanding the second box in your control panel on the left side of your screen.



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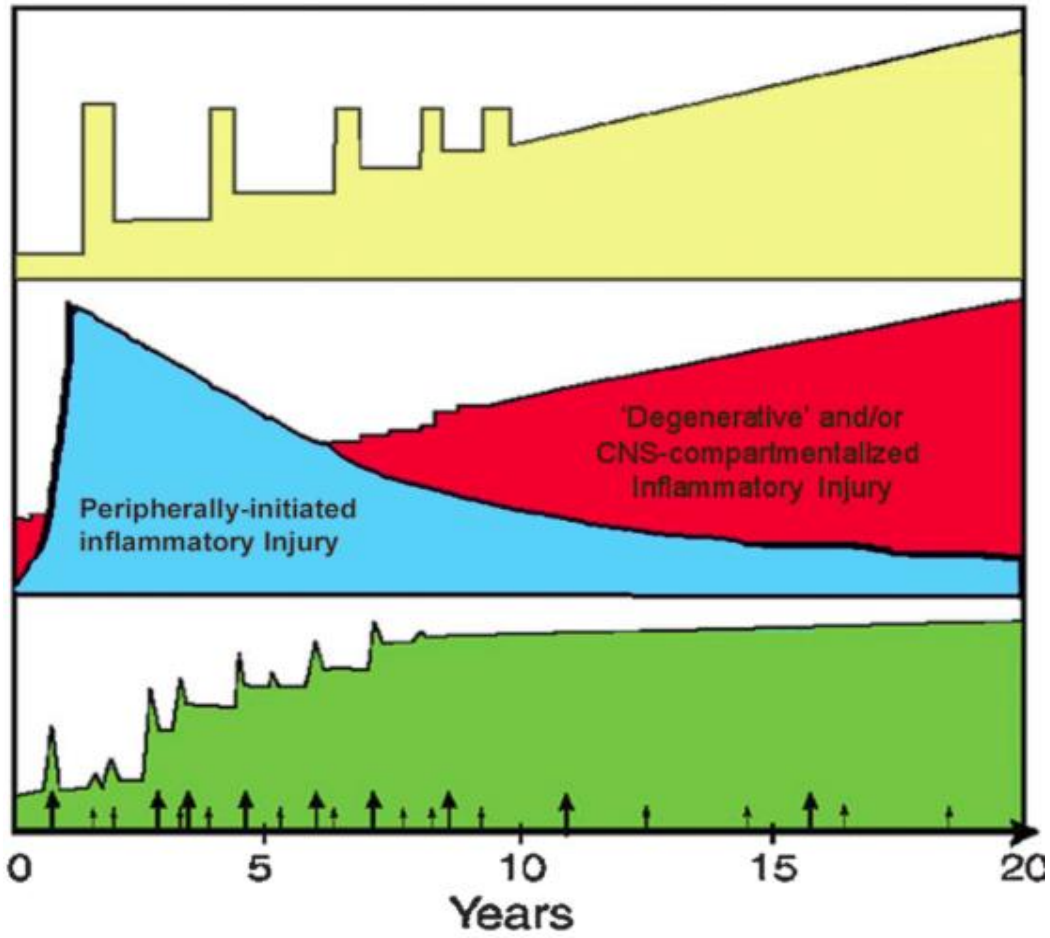
Webinar Learning Objectives

- Who gets it, how common is it, and what do symptoms and disease course look like?
- Approaches to selecting a disease-modifying therapy and symptomatic treatment
- Special considerations such as academic and social challenges, as well as strategies for wellness and support
- Resources: MSIF brochure, Society materials

Pediatric-Onset MS

- Defined as onset of symptoms prior to age of 18 years
- Most common cause of non-traumatic neurological disability in young adults
- Estimated 2.5 million people with MS worldwide
  - Estimated 2000-4000 cases of pediatric-onset MS worldwide
- Up to 10% of adults with MS recall that their first symptoms started prior to the age of 18 years

MS Course in Children



Clinical

MRI

Bar-Or A, *2008*.

How is Pediatric-Onset MS Different From Adult-Onset?

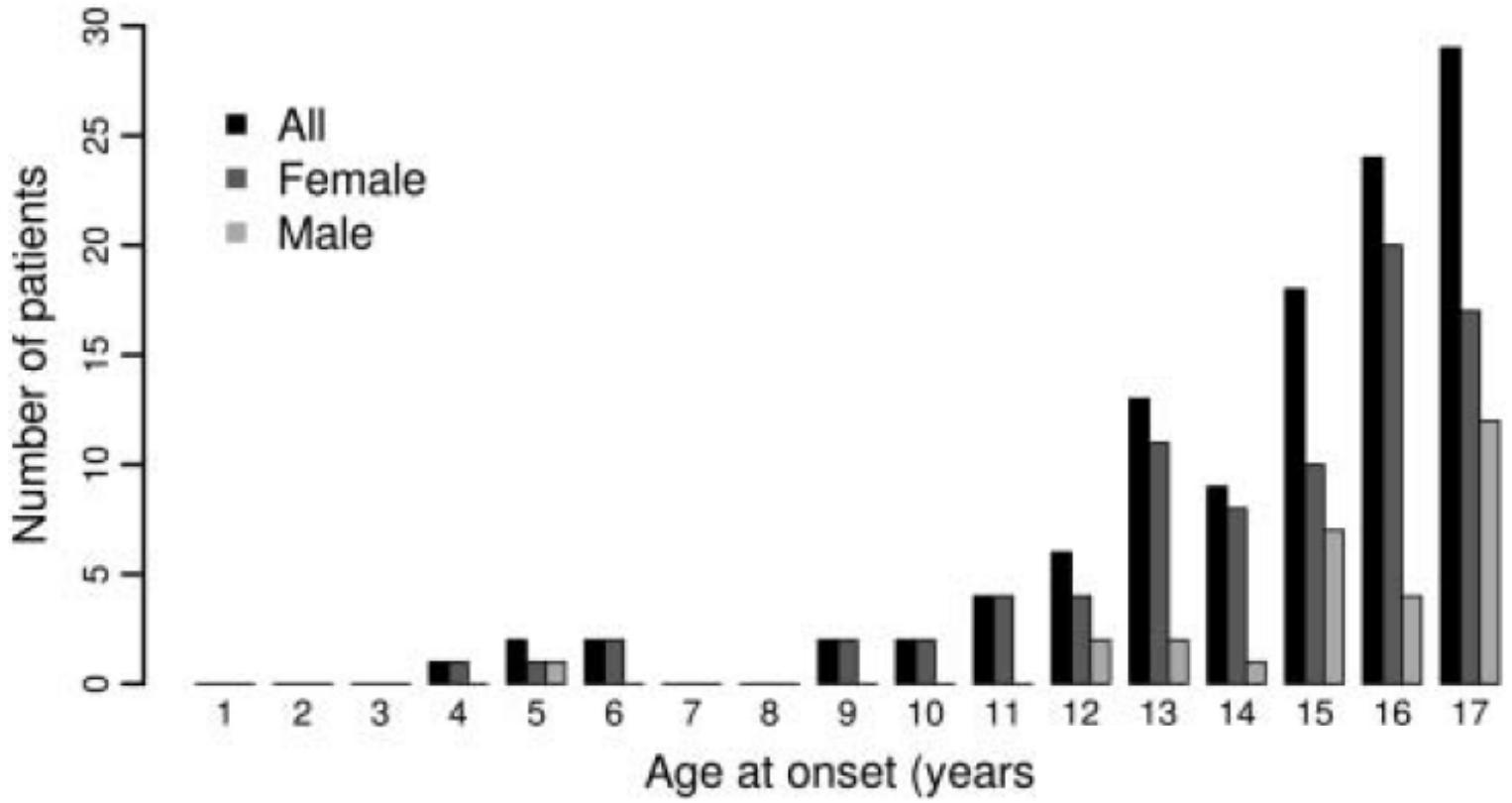
Distinguishing Features

- High MRI lesion burden
- More frequent relapses, particularly in the first year
- Less time in between relapses
- Unique treatment considerations
- Cognition can be affected even without physical disability

Gorman MP et al., 2009.

Age, Sex, and Clinical Presentations

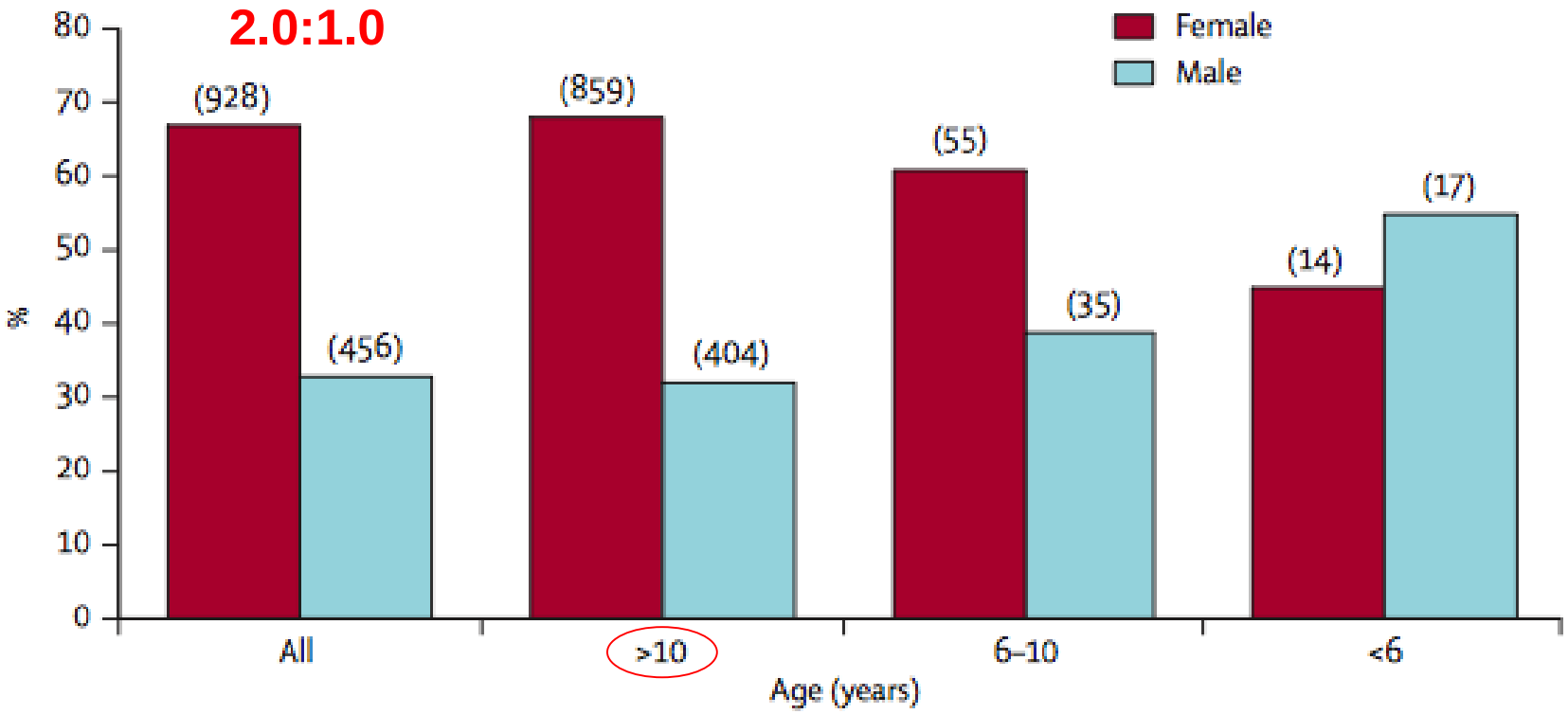
Age of Onset



Harding et al **JNNP** 2013

Harding KE et al., 2013.

Relationship Between Age and Sex



Banwell B et al., 2007.

Common Clinical Presentations

- Optic Neuritis (ON)
- Transverse Myelitis (TM)
- Brainstem Syndrome
- Acute Disseminated Encephalomyelitis (ADEM)

Krupp L et al., 2013.

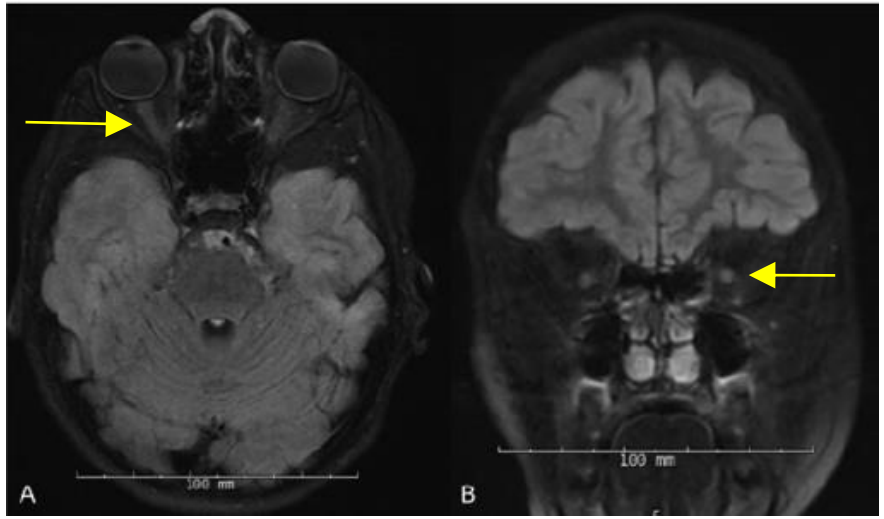
Optic Neuritis

Symptoms:

- *Rapid onset of visual loss*
- *Pain with eye movement*

Examination:

- *Reduced visual acuity*
- *Abnormal blind spots*
- *Loss of red color vision*
- *Optic disc swelling*



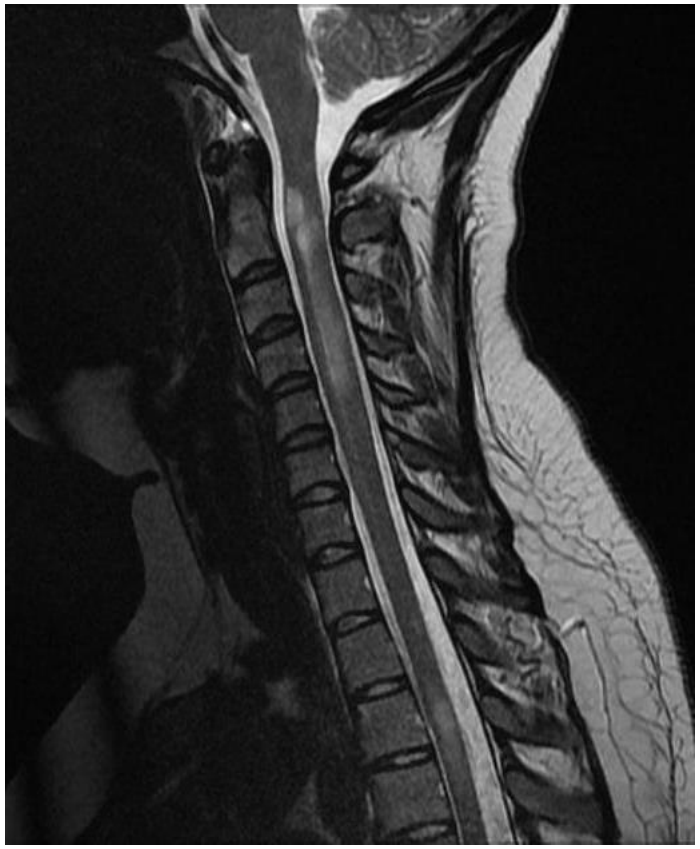
Transverse Myelitis

Symptoms:

- *Limb numbness/tingling*
- *Limb weakness*
- *Lhermitte's sign (electrical zap)*
- *Urination/bowel dysfunction*

Examination:

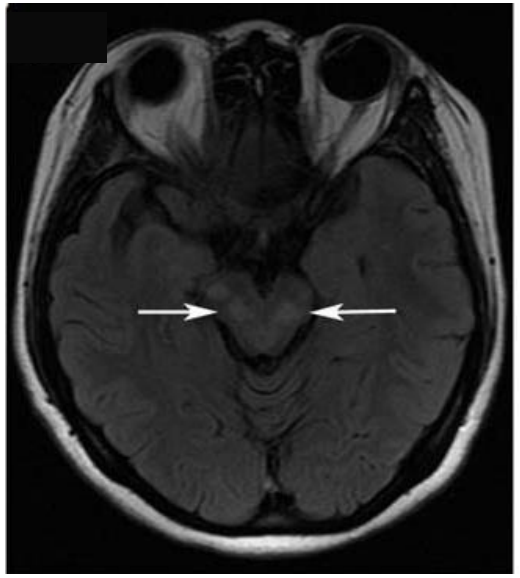
- *Limb motor deficits*
- *Limb sensory loss*
- *Sensory level*
- *Asymmetric reflexes*

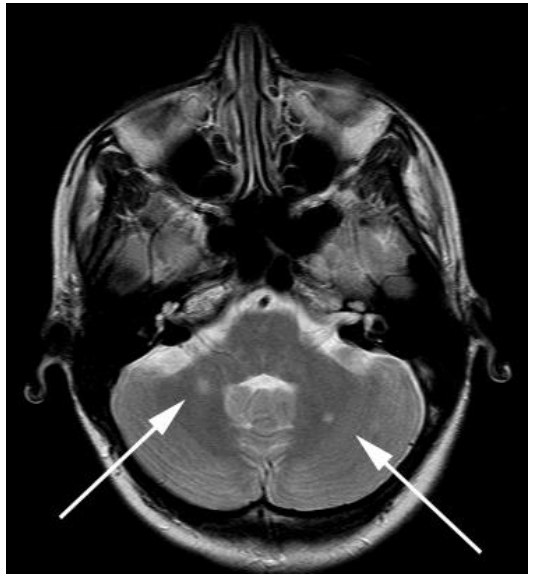


Brainstem Syndrome

Symptoms and Examination:

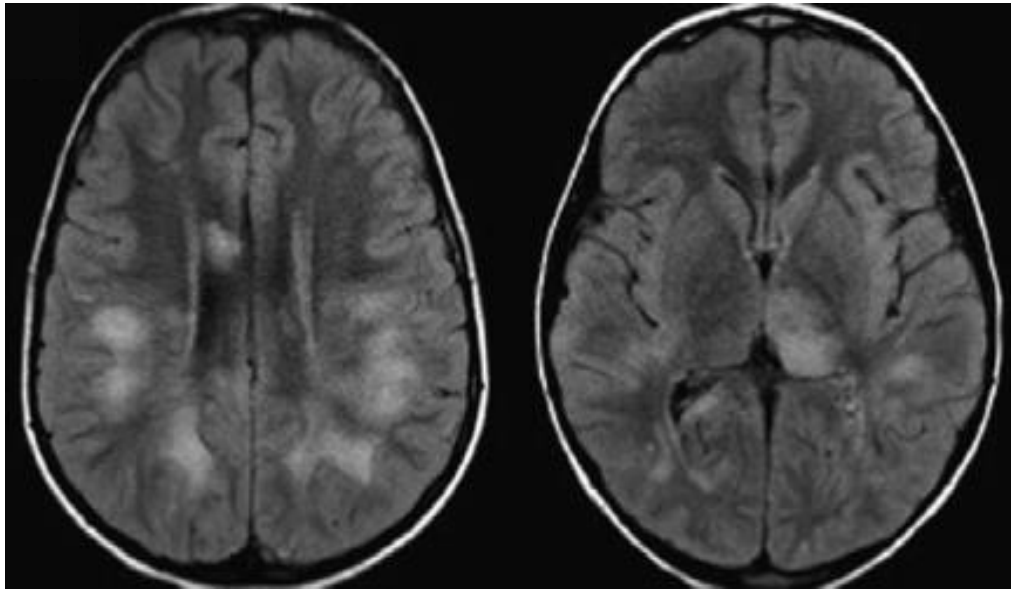
- *Cranial nerve dysfunction (e.g., eye movement abnormalities, facial sensory loss, dizziness)*
- *Coordination/balance dysfunction*





Acute Disseminated Encephalomyelitis

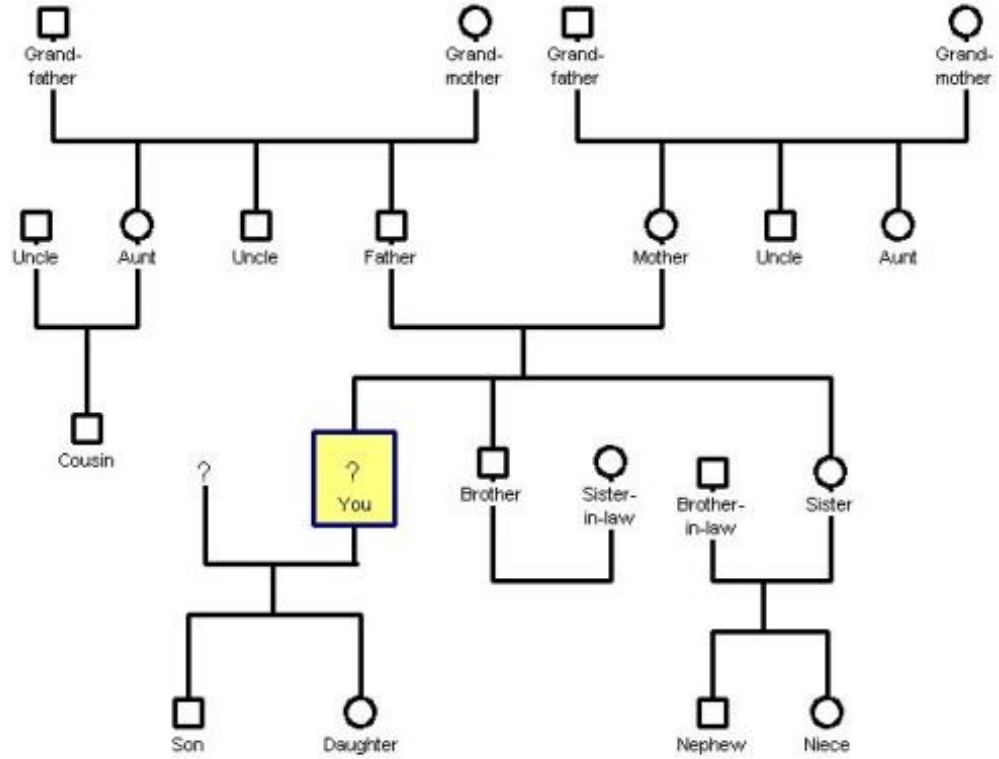
- Symptoms and Examination:
- Encephalopathy (altered mental status, lethargy), seizures, polyfocal neurologic deficits with corresponding exam findings



Genetic and Environmental Risk Factors

Genetics of MS

- Incidence of MS:
  - Higher in 1st degree relative and monozygotic twins
  - Most consistent allele: HLA-DR1501



Environmental Risk Factors

- Vitamin D
- Infection – EBV?
- Obesity
- Cigarette Smoking

Vitamin D Deficiency

Baseline Characteristics	
Number of children	36
Mean age	15.3 y (8.8-19.6)
Mean time from presentation	3.46 y (0-8.9)
Female to male	2.3:1
Place of birth Canada Middle East Asia Not known	N(%) 29 (80.6) 1 (2.8) 4 (11.1) 2 (5.6)
Mean 25(OH)D (nmol/L)	53.4 (12-113)

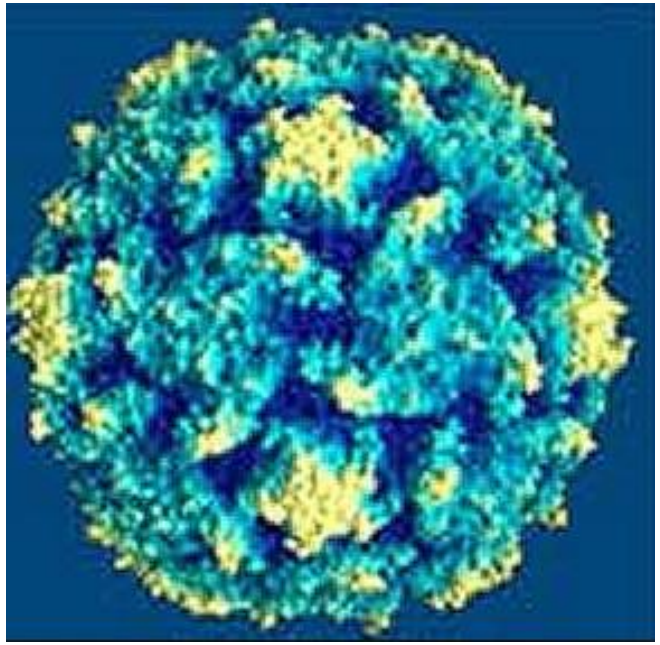
Makhani N et al., 2008.

Vitamin D Levels and Risk

Specific Features	All (n=208)	ADS (n=167)	MS (n=41)	P-value
Age at onset, mean (SD)	9.8 (4.4)	9.3 (4.4)	12.1 (3.4)	*< 0.001*
Female sex (n, %) Female : Male Ratio	104 (50) 1.0	79 (47) 0.91	25 (61) 1.6	0.117
Ancestry (n, %) - European - Non-European	 136 (65) 72 (35)	 110 (66) 57 (34)	 26 (63) 15 (37)	 0.767
Days to MS diagnosis	--	n/a	242 (290)	--
25(OH)D (nmol/L), mean (SD)	63.5 (28.5)	66.2 (29.0)	52 (23.0)	*0.004*
HLA-DRB1*15 Positive (n, %)	73 (35)	51 (31)	22 (54)	*0.005*

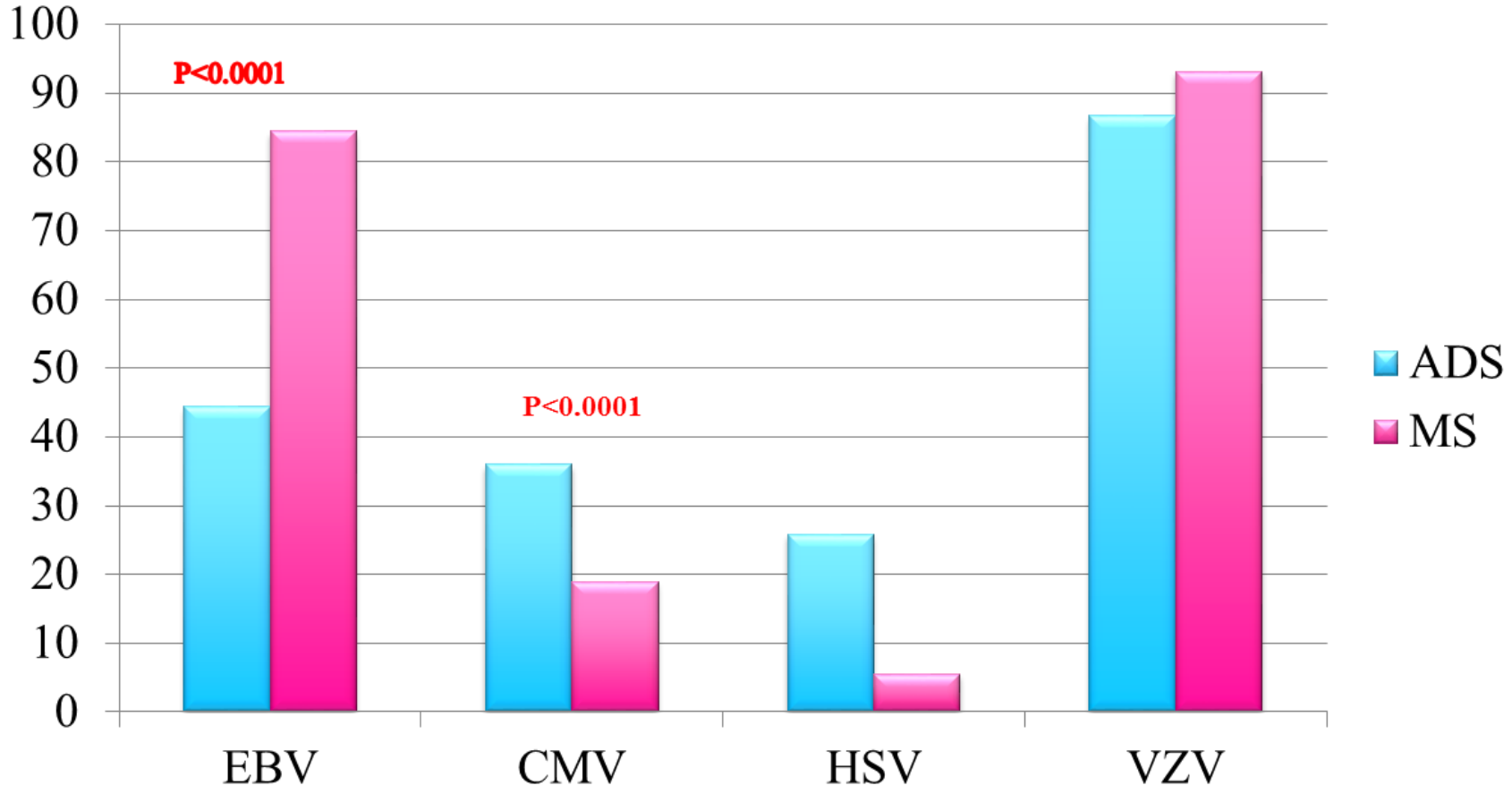
Hanwell HE et al., unpublished.

Epstein-Barr Virus



- Herpes group DNA virus
- 90% people infected by adulthood
- Often asymptomatic in young children
- Infectious mononucleosis in 40-50% if acquired later in childhood or adolescence

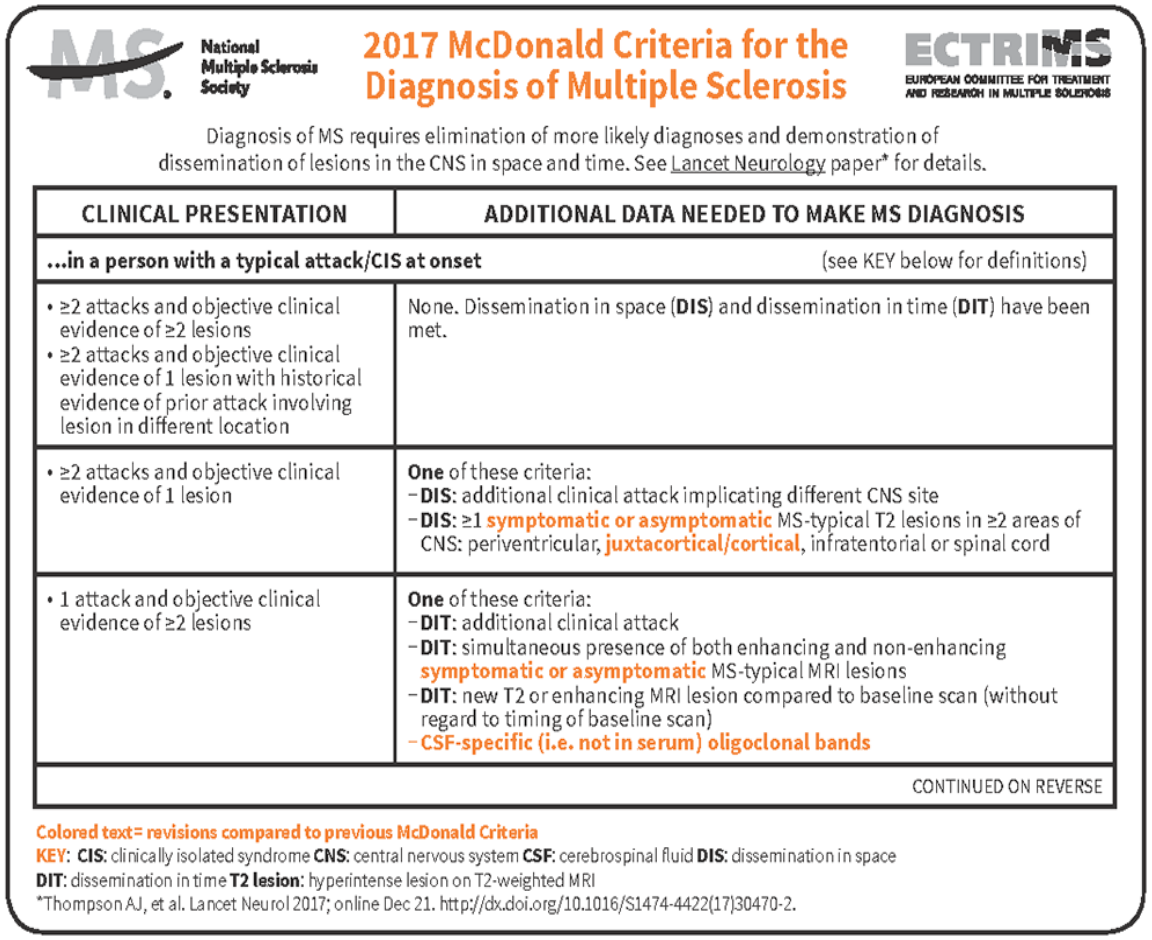
Viral Exposures and Risk



Makhani N et al., 2016.

Diagnosis and Relapse Course

2017 McDonald Criteria for MS



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2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time. See Lancet Neurology paper* for details.

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset	(see KEY below for definitions)
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space (**DIS**) and dissemination in time (**DIT**) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS:** additional clinical attack implicating different CNS site – **DIS:** ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	**One** of these criteria: – **DIT:** additional clinical attack – **DIT:** simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT:** new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**

CONTINUED ON REVERSE

Colored text= revisions compared to previous McDonald Criteria
KEY: CIS: clinically isolated syndrome **CNS:** central nervous system **CSF:** cerebrospinal fluid **DIS:** dissemination in space **DIT:** dissemination in time **T2 lesion:** hyperintense lesion on T2-weighted MRI
*Thompson AJ, et al. Lancet Neurol 2017; online Dec 21. http://dx.doi.org/10.1016/S1474-4422(17)30470-2.

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis (continued)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (continued)	(see KEY on reverse for definitions)
• 1 attack and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS:** additional attack implicating different CNS site – **DIS:** ≥1 MS-typical **symptomatic or asymptomatic** T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria: – **DIT:** additional clinical attack – **DIT:** simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT:** by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**
...in a person with progression of disability from onset	
• progression from onset	– 1 year of disability progression (retrospective or prospective) **AND** **Two** of these criteria: – ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxtacortical/cortical** or infratentorial) – ≥2 T2 spinal cord lesions – CSF-specific (i.e. not in serum) oligoclonal bands

The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the National MS Society and the European Committee for Treatment and Research in Multiple Sclerosis.
More resources for clinicians: https://www.nationalmssociety.org/For-Professionals/Physicians

Thompson AJ et al., 2018.

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2017 Criteria As They Apply to Children

- Improved diagnostic accuracy across the age span, particularly because of inclusion of oligoclonal bands from cerebrospinal fluid
- More sensitive than 2010 criteria for predicting clinically definite MS in children, but less specific
- As compared to the 2010 criteria, can use these in children < 12 years age (if no encephalopathy during ADS)

Fadda G et al., 2018.
Wong YYM et al., 2018.

High MRI Lesion Burden

Table 2. MRI Characteristics on the First Brain Scans[a]

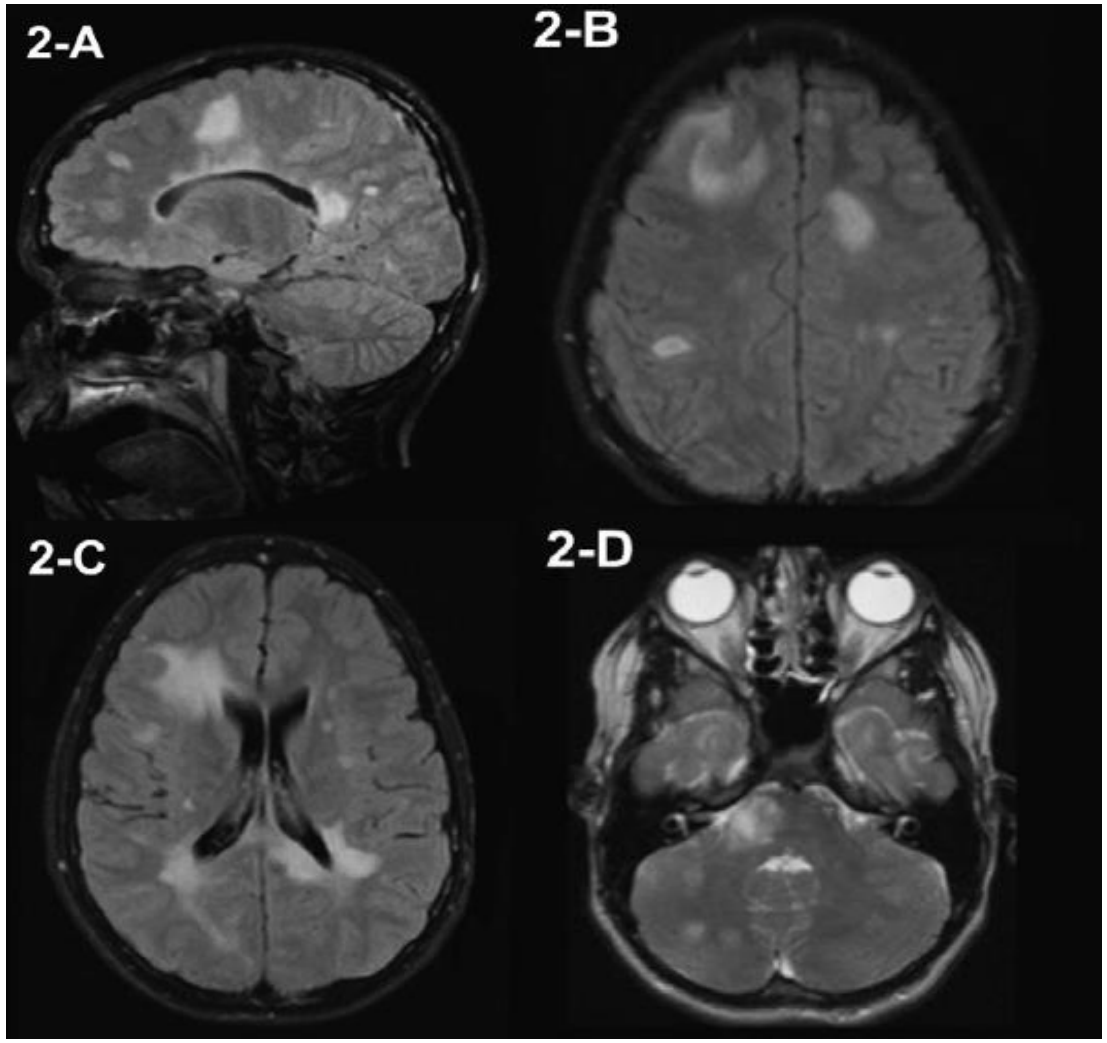
Characteristic	No. of Lesions, Median (Range): Pediatric MS (n=41)	Adult MS (n=35)	*P* Value
Total number of T2-bright foci	21 (0-74)	6 (0-76)	<.001
Nonovoid, poorly defined T2-bright foci	3 (0-55)	0 (0-4)	<.001
Ovoid, well-defined T2-bright foci	12 (0-69)	5 (0-75)	.006
Large (≥1 cm) T2-bright foci	4 (0-26)	0 (0-5)	<.001
Gadolinium-enhancing lesions	2 (0-60)	0 (0-5)	<.001
Juxtacortical lesions	9 (0-48)	1 (0-8)	<.001
Periventricular lesions	6 (0-21)	2 (0-12)	<.001
Cerebellar lesions	0 (0-8)	0 (0-2)	.01
Brainstem lesions	1 (0-6)	0 (0-3)	.002
Corpus callosum lesions	1 (0-8)	0 (0-3)	.07

Table 3. Proportion of Patients With Specific Lesion Types and Locations[a]

Characteristic	%: Pediatric MS (n=41)	Adult MS (n=35)	*P* Value
Large (≥1 cm) T2-bright foci	87.8	48.6	<.001
Gadolinium-enhancing lesions	68.4	21.2	<.001
Confluent T2-bright foci	19.5	22.8	.72
Infratentorial T2-bright foci	68.3	31.4	.001
Cerebellum T2-bright foci	41.5	17.1	.02
Brainstem T2-bright foci	58.5	25.7	.004
Corpus callosum T2-bright foci	63.4	40	.04
Juxtacortical T2-bright foci	90.2	57.1	.001
Deep gray matter T2-bright foci	34.1	28.6	.60

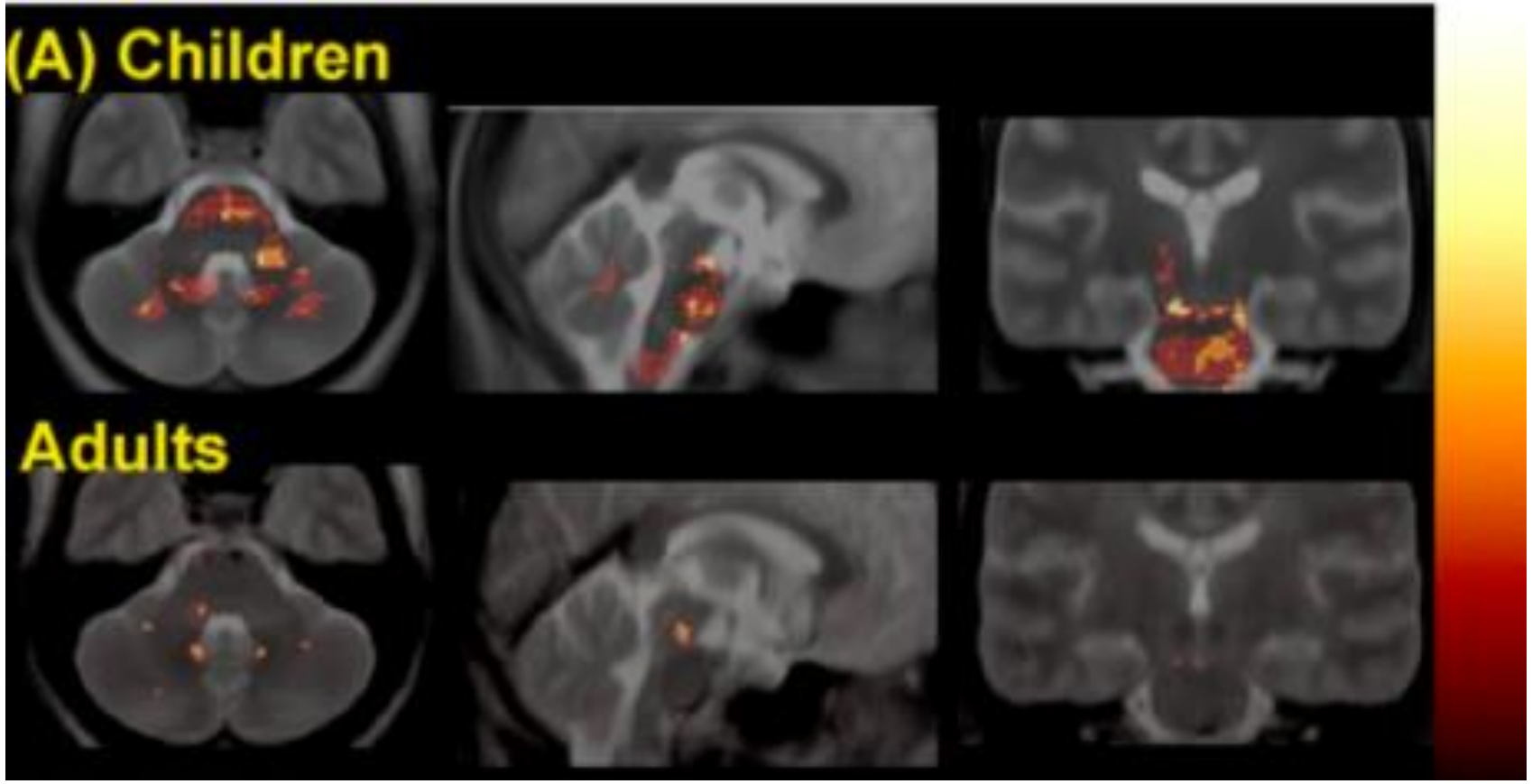
Waubant E et al., 2009.

High MRI Lesion Burden, Cont.



Verhey LH et al., 2013.

More Posterior Fossa Lesions



Ghassemi R et al., 2014.

High Relapse Rates in Pediatric MS

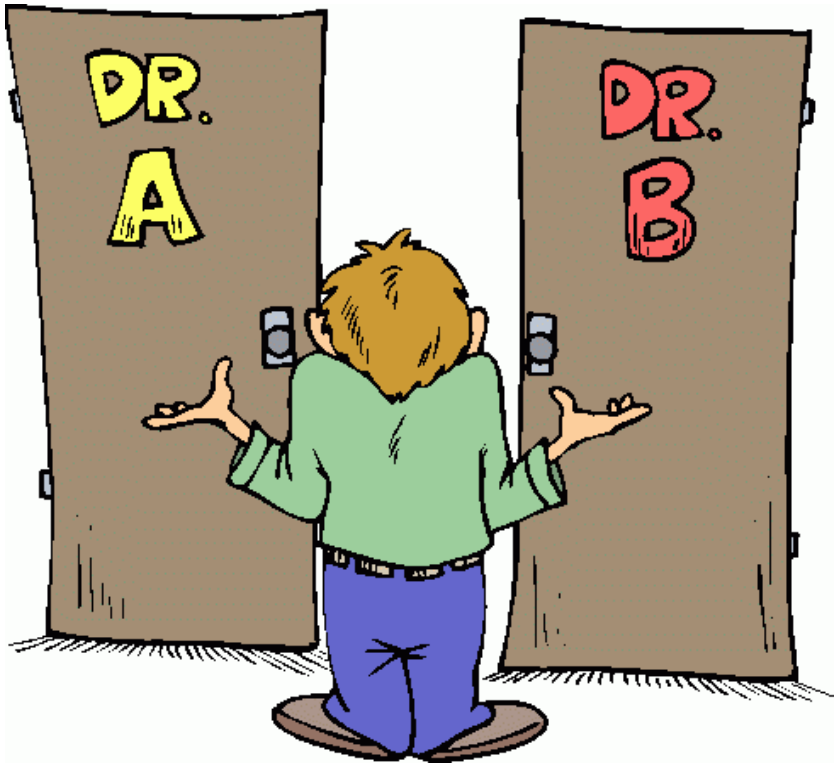
Characteristic	Annualized Relapse Rate: Pediatric-Onset MS	Annualized Relapse Rate: Adult-Onset MS	*P* Value
Overall			
Including first attack	1.40	0.65	<.001[a]
Excluding first attack	1.13	0.40	<.001[a]
Pretreatment			
Including first attack	2.76	1.78	.01[a]
Excluding first attack	1.20	0.57	.01[a]
Posttreatment	1.12	0.35	<.001[a]
Attacks treated with steroids, %	78.7	59.1	<.001[b]
Attacks confirmed by physician examination, %	72.2	63.0	.1[b]
First interattack interval, median, mo	5.6	13.8	<.001[c]

Gorman M et al., 2009.

Treatment Considerations

Treatment Selection Factors for Children with MS

- Frequency of injections
- Size of the needle
- Frequency of blood work
- Side effects



Factors Affecting Compliance

- Sense of immortality
- Need of autonomy
- Need for peer acceptance
- Role in decision-making

Medications Used in MS

	Manufacturer/Distributor & Year of FDA Approval
Aubagio®	Genzyme, a Sanofi company — 2012
Avonex®	Biogen Idec — 1996
Betaseron®	Bayer HealthCare Pharmaceuticals, Inc. — 1993
Copaxone®	Teva Neuroscience — 1996
Extavia®	Novartis Pharmaceuticals Corp. — 2009
Gilenya®	Novartis Pharmaceuticals Corp. — 2010
Lemtrada™	Genzyme, a Sanofi company — 2014
Novantrone®	EMD Serono, Inc./Immunex Corporation — 2000
Plegridy™	Biogen Idec — 2014
Rebif®	EMD Serono, Inc./Pfizer, Inc. — 2002
Tecfidera®	Biogen Idec — 2013
Tysabri®	Biogen Idec — 2006

Treatment Options

- **Traditional First-line Agents**
  - Interferon beta 1a and 1b
  - Glatiramer acetate (Copaxone)
- **Traditional Second-line Agents/ Severe Disease at Onset**
  - Natalizumab
  - ~~Cyclophosphamide~~
- **Oral agents**
  - Dimethyl fumarate (Tecfidera)
  - Fingolimod (Gilenya)*
  - ~~Teriflunamide (Aubagio)~~
- **Other**
  - Rituximab
  - Ocrelizumab
- **Vitamin D**

*Only medication with FDA approval in children

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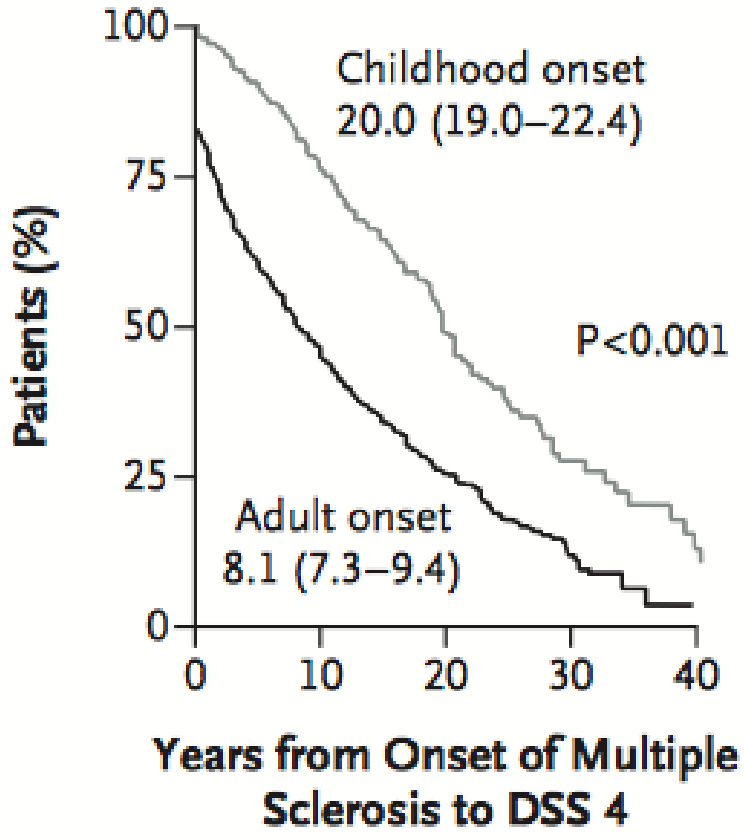
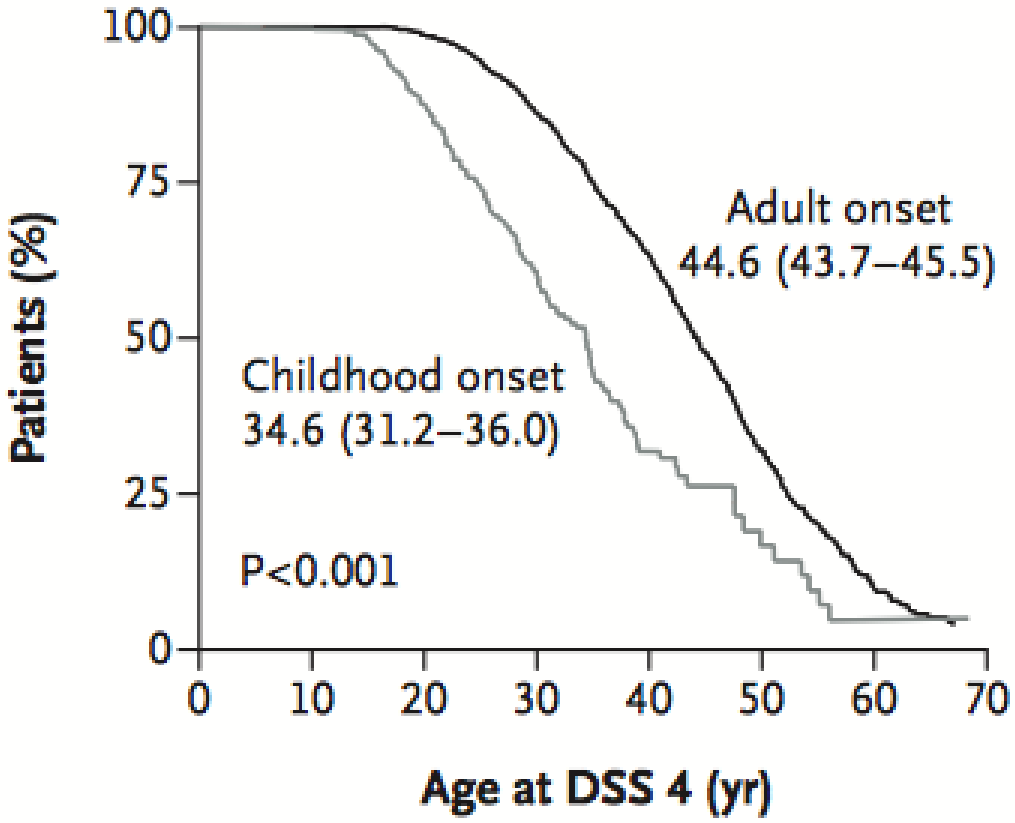
Motor and Cognitive Outcomes

Physical Disability Earlier in Life

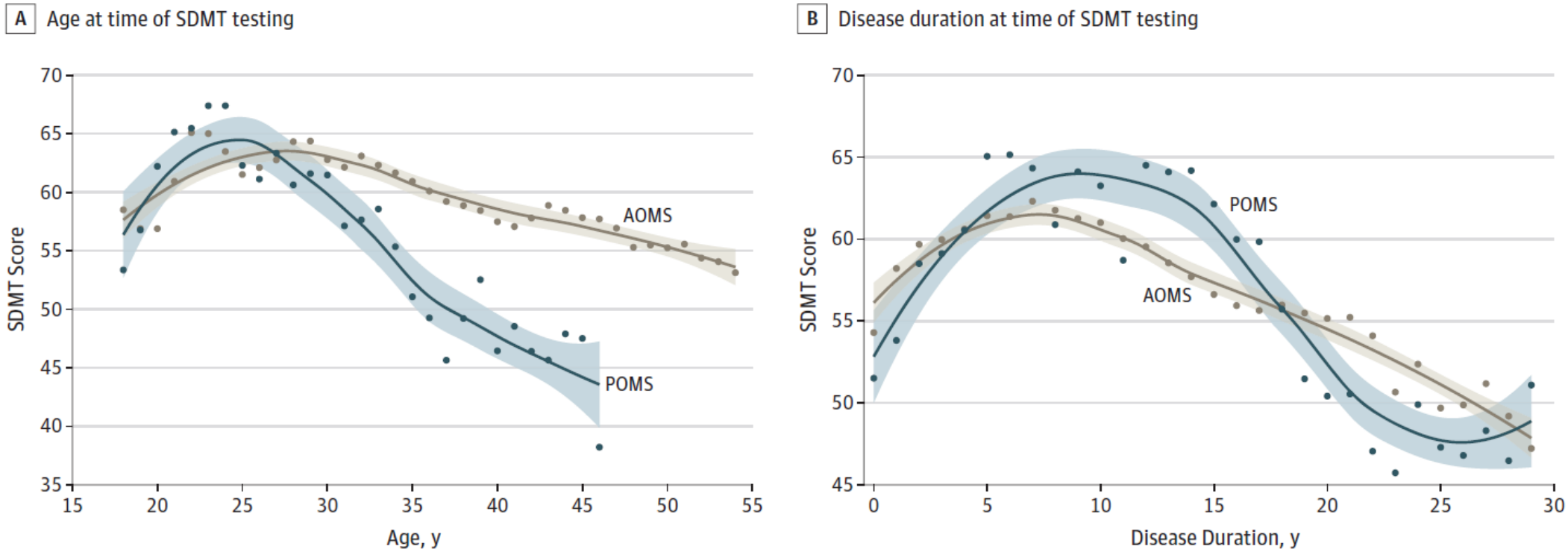




Renoux C et al., 2007.

Cognitive Decline Earlier in Life

Figure. Mean Symbol Digit Modalities Test (SDMT) Scores for Patients With Pediatric-Onset (POMS) and Adult-Onset (AOMS) Multiple Sclerosis



Lines indicate mean; shaded area, SD; and data points, mean per age. The SDMT scores range from 0 to 120, with higher scores indicating greater information-processing efficiency.

McKay et al., JAMA Neurology 2019

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Cognitive Difficulties in School

- Attention and learning difficulties are common
- Cognitive issues can make it difficult to perform in school, which can negatively affect self esteem
- Early cognitive difficulties can set a negative trajectory for higher education, employment, and quality of life

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Welcome to High School

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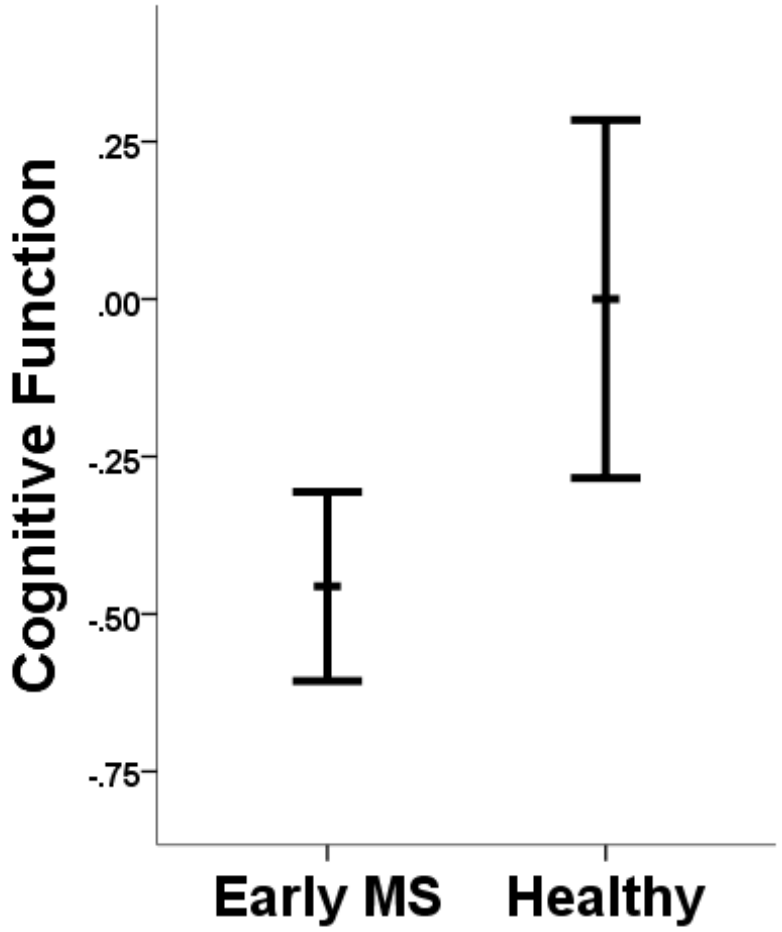
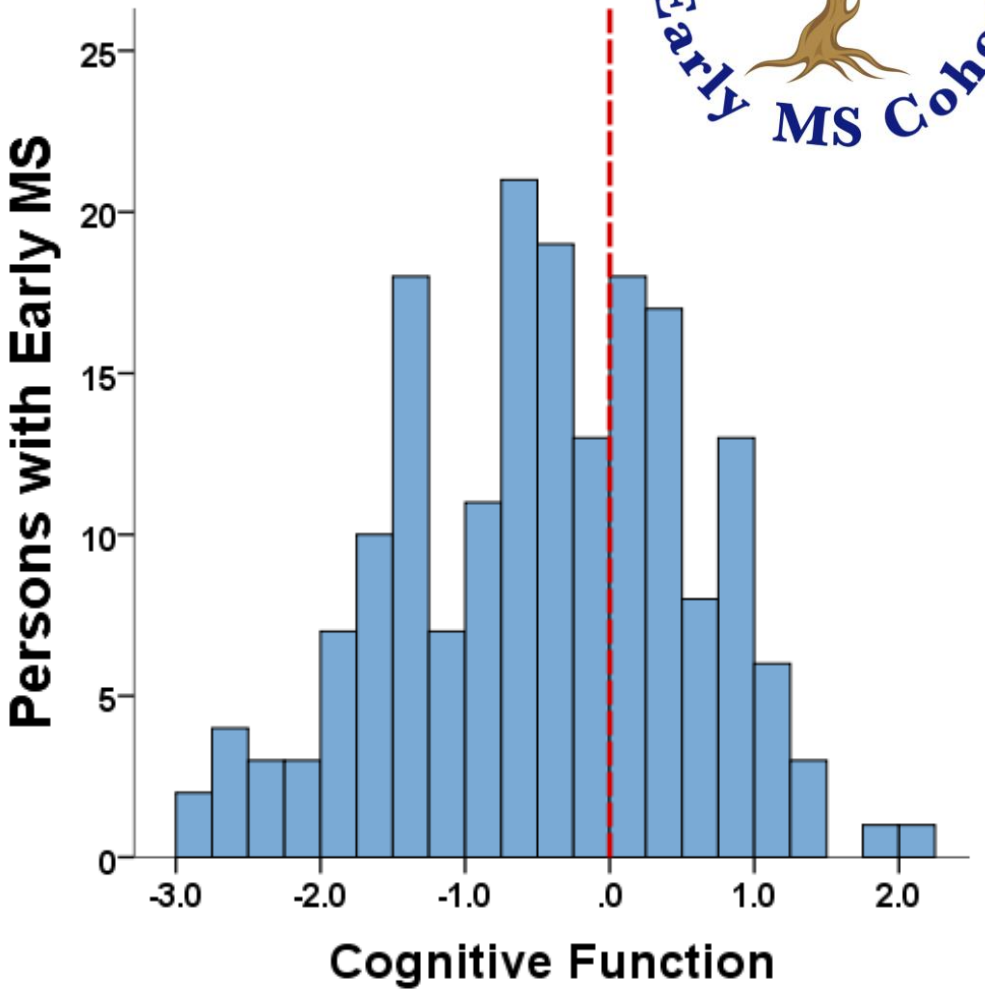
Providing the Supports to Succeed

Cognition in Early in MS





RESERVE
Early MS Cohort

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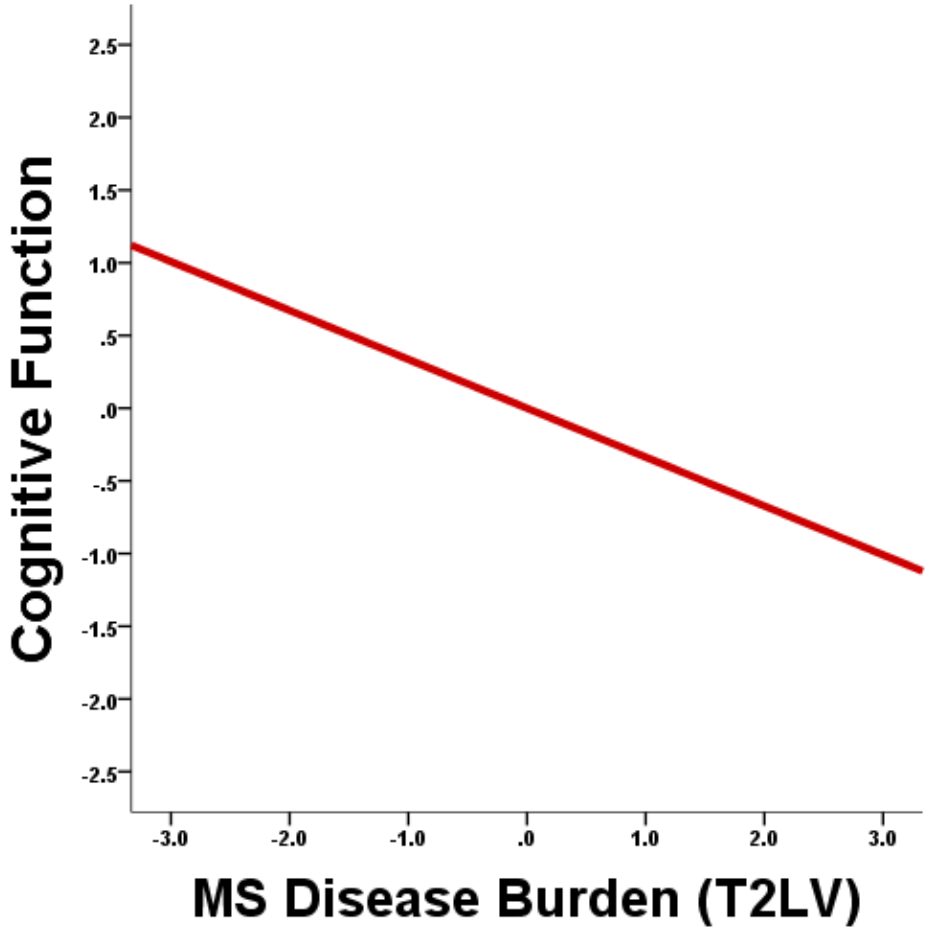
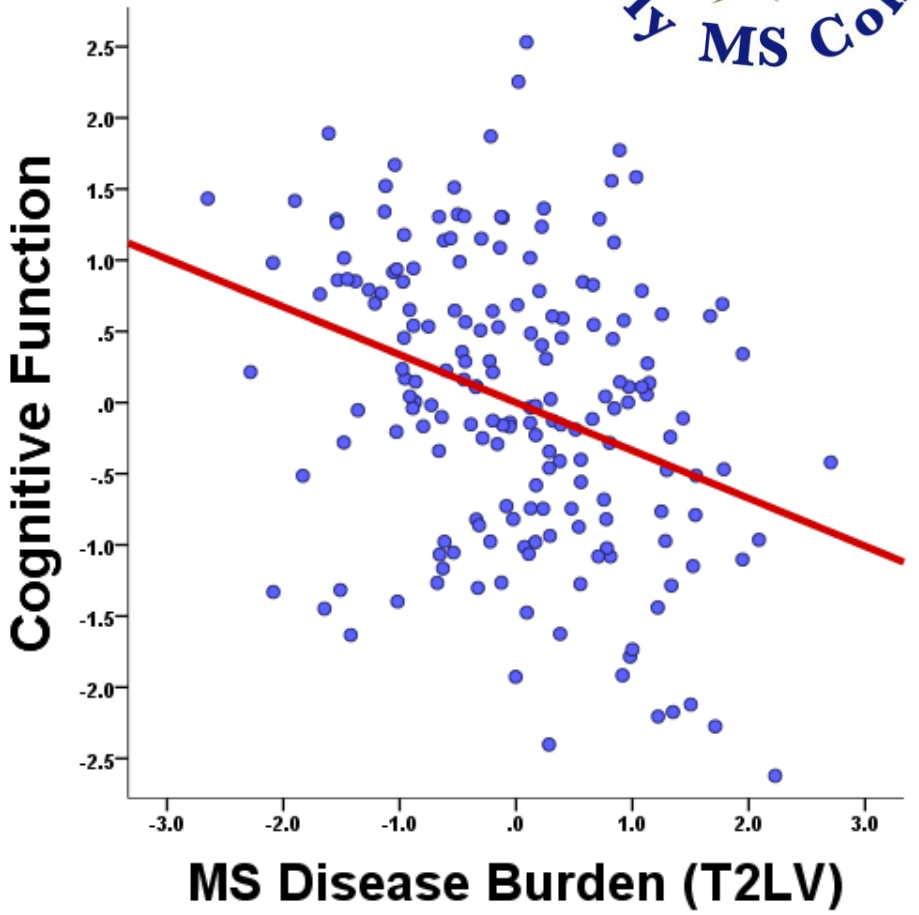
MS Lesions and Cognition





Taking Charge: Obesity

ARTICLE

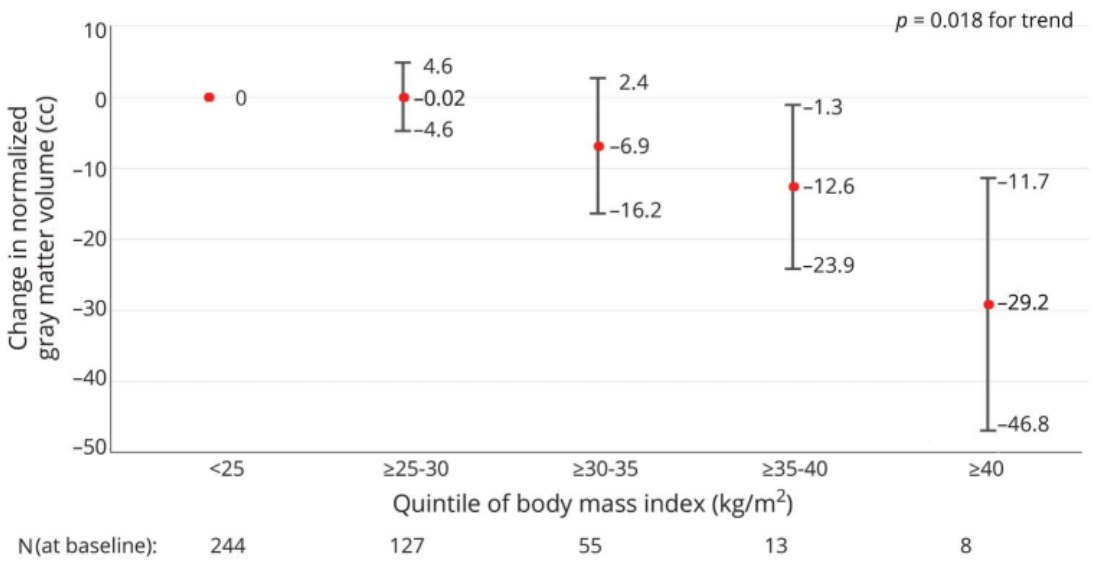
Body mass index, but not vitamin D status, is associated with brain volume change in MS

Ellen M. Mowry, MD, MCR, Christina J. Azevedo, MD, MPH, Charles E. McCulloch, PhD, Darin T. Okuda, MD, Robin R. Lincoln, BS, Emmanuelle Waubant, MD, PhD, Stephen L. Hauser, MD, and Daniel Pelletier, MD

Correspondence
Dr. Mowry
emowry1@jhmi.edu

Neurology® 2018;91:e2256-e2264. doi:10.1212/WNL.0000000000006644

Figure Change in nGMV by BMI quintile

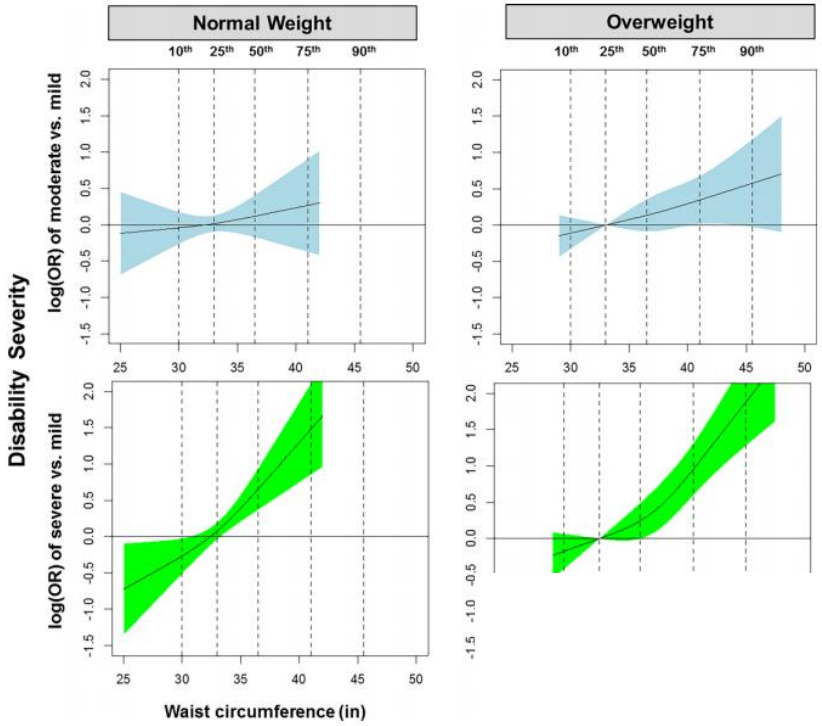


MULTIPLE SCLEROSIS JOURNAL | MSJ

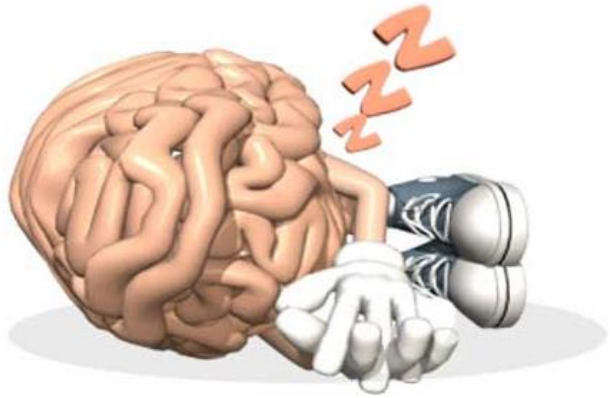
Original Research Paper

Measures of general and abdominal obesity and disability severity in a large population of people with multiple sclerosis

Kathryn C Fitzgerald, Amber Salter, Tuula Tyry, Robert J Fox, Gary Cutter and Ruth Ann Marrie



Taking Charge: Sleep



Systems/Circuits

Sleep Restriction Impairs Blood–Brain Barrier Function

Junyun He, Hung Hsuchou, Yi He, Abba J. Kasti
Blood–Brain Barrier Group, Pennington Biomedical Research C

The blood–brain barrier (BBB) is a large regulatory an
that changes of the BBB contribute to many pathophysio
achieve CSR that mimics a common pattern of human sl
consecutive sleep recording. We then tested the hypotl
endothelial and inducible nitric oxide synthase, endothe
it also decreased 2-deoxy-glucose uptake by the brain. T
level of cyclooxygenase-2 increased. This coincided with
fluorescein and biotin. CSR for 6 d was sufficient to impa
returned to baseline after 24 h of recovery sleep. This m
and clinical practice.

Key words: BBB; glucose metabolism; sleep duration; sl

SLEEP

The memory function of sleep

Susanne Diekelmann and Jan Born

Abstract | Sleep has been identified as a
acquired information in memory, deper
timing of sleep. Consolidation during sl
changes of memory representations. Th
and electric field potential oscillations,
(REM) sleep support system consolidati
SWS, slow oscillations, spindles and ripp
the re-activation and redistribution of h
sites, whereas during REM sleep, local i
activity — at high cholinergic and theta
consolidation of memories in the cortex

Sleep Medicine Reviews (2006) 10, 323–337

ELSEVIER

SLEEP MEDICINE reviews

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CLINICAL REVIEW

Sleep loss, learning capacity and academic performance

Giuseppe Curcio[a,*], Michele Ferrara[a,b], Luigi De Gennaro[a]

[a]*Department of Psychology, University of Rome 'La Sapienza', Rome, Italy*
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Taking Charge: Mood & Resilience

ARTICLE

Comorbid anxiety, depression, and cognition in MS and other immune-mediated disorders

Christiane E. Whitehouse, BSc, John D. Fisk, PhD, Charles N. Bernstein, MD, Lindsay I. Berrigan, PhD, James M. Bolton, MD, Lesley A. Graff, PhD, Carol A. Hitchon, MD, MSc, James J. Marriott, MD, MSc, Christine A. Peschken, MD, MSc, Jitender Sareen, MD, John R. Walker, PhD, Sherry H. Stewart, PhD, and Ruth Ann Marrie, MD, PhD, for the CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease

Correspondence
Dr. Marrie
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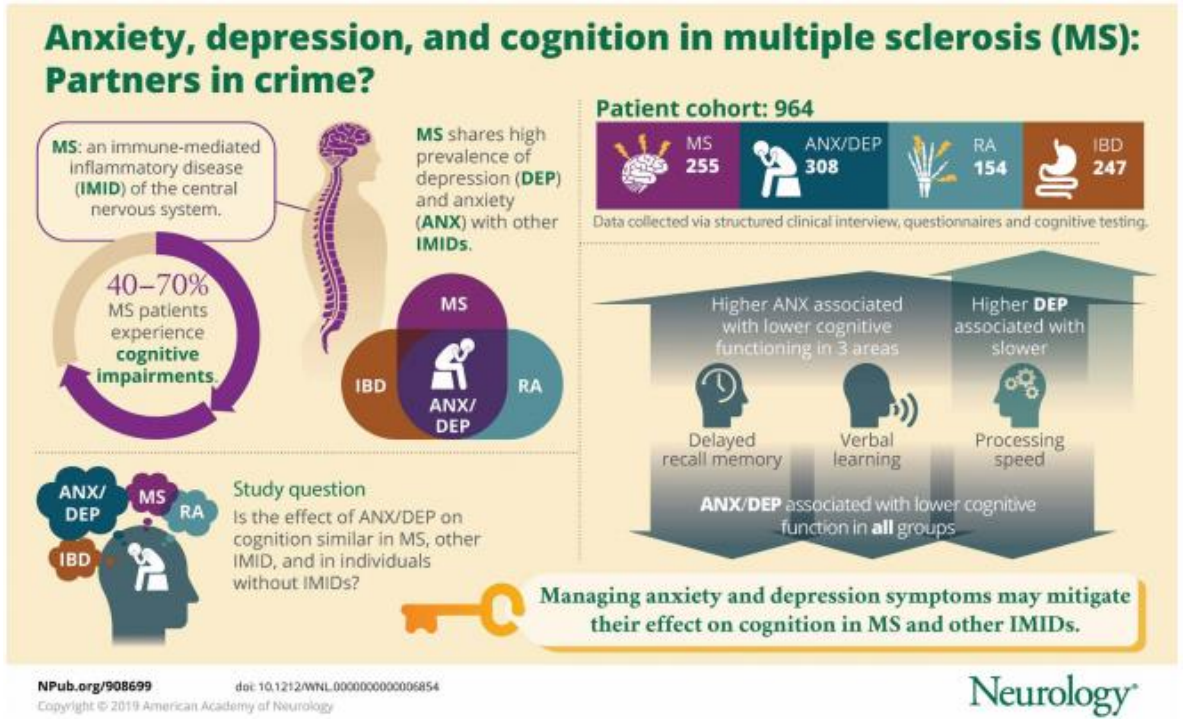
Neurology® 2019;92:e406-e417. doi:10.1212/WNL.0000000000006854

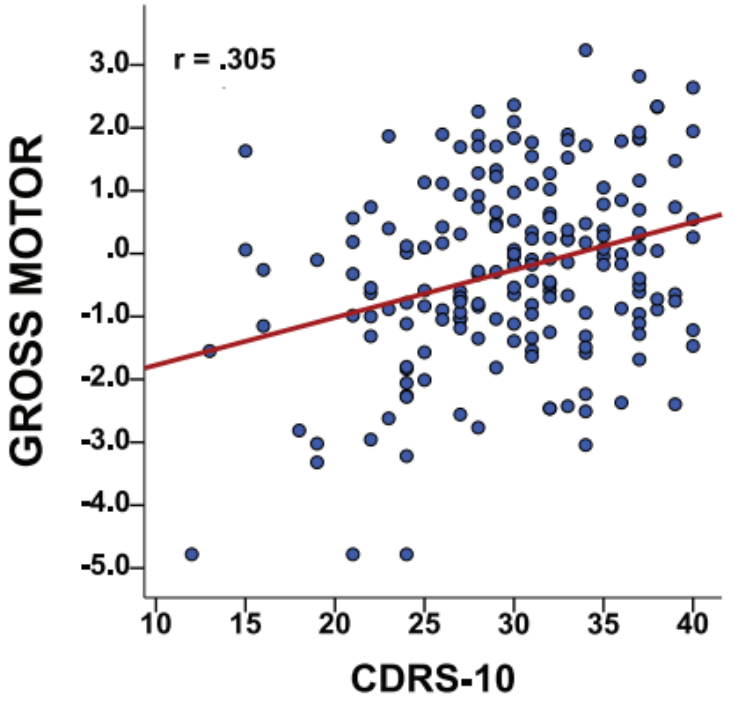


MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Psychological resilience is linked to motor strength and gait endurance in early multiple sclerosis

Sylvia Klineova, Rachel Brandstadter, Michelle T Fabian, Ilana Katz Sand, Stephen Krieger, Victoria M Leavitt, Christina Lewis, Claire S Riley, Fred Lublin, Aaron E Miller and James F Sumowski



Conclusions

- MS is being increasingly diagnosed in children
- Clinical and MRI features vary from adults
- Treatment options for children with MS are increasing
- Cognitive difficulties may be seen, even early on
- Further research is needed
  - Identify new risk factors
  - Evaluate new treatments
  - Monitor outcomes and modifiable associated factors

Q & A

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