טרשת נפוצה בילדים

הסתמנות קלינית וטיפולים עדכניים

ד"ר שי מנשקו-היחידה לנוירולוגית ילדים
פרופ.ענת אחירון- המרפאה לטרשת נפוצה

[In] most of the patients affected by multi-locular sclerosis whom I have had occasion to observe … there is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality. The dominant feeling in the patients appears to be a sort of almost stupid indifference in reference to all things.

Charcot (1877)

Charcot's Triad- involvement in MS:
(1) intention tremor, **(2) nystagmus** (rhythmic movement of eyes), **(3)scanning speech** (abnormal speech characterized by a stacctolike (breaking the rhythm of the phrase or sentence)

What is **Multiple Sclerosis?**

- **Complex** genetic disease
- Mediated by **autoimmune** processes – Clonal expansion of B cells and T cells
- **Inflammation** of the central nervous system (CNS) (brain and spinal cord) white matter

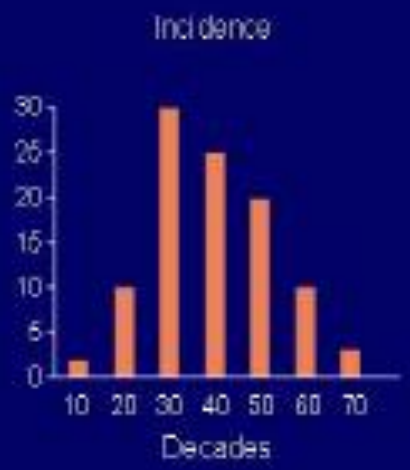
Sex, age and ethnicity susceptibility to MS

Sex

Sex ratio : 2F/1M

Age of onset

30 - 40 years



Ethnicity

High risk

Northern Europeans,
US Caucasians,
Canadians

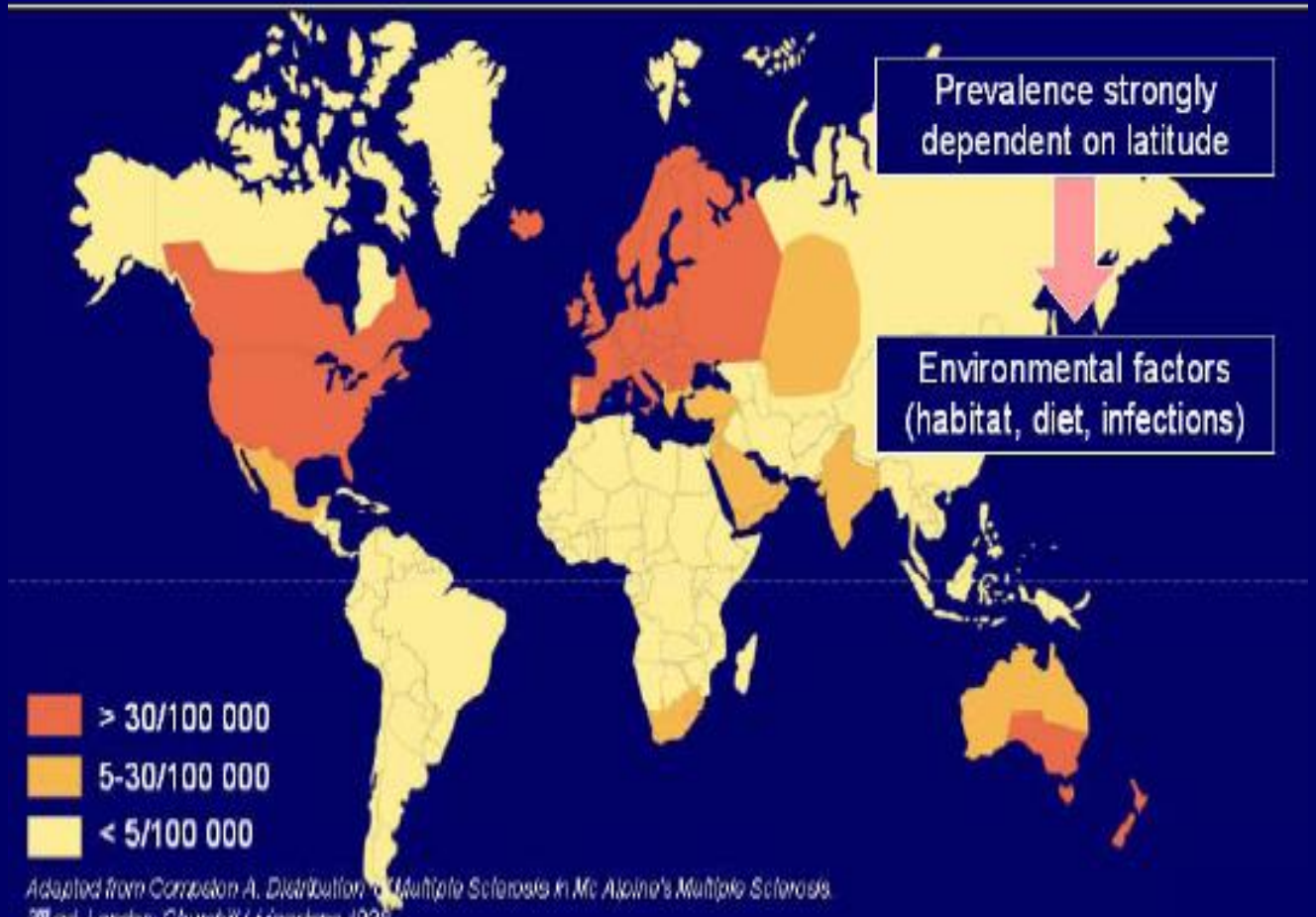
Australians
South African whites
Southern Europeans

African blacks
Orientals

Low risk

Compston A. Genetic susceptibility to Multiple Sclerosis in Mc Alpine's Multiple Sclerosis 3rd ed. London: Churchill Livingstone 1998.

Epidemiology and latitude



Adapted from Compston A. Distribution of Multiple Sclerosis in Mc Alpine's Multiple Sclerosis. 3rd ed. London: Churchill Livingstone 1998.

What causes multiple sclerosis?

- Genes
- Environmental agents
- Combination of genes and environment

Environment in MS

- **Viruses** have been implicated in MS pathogenesis (varicella, measles, rubella, mumps, and the herpes viruses)

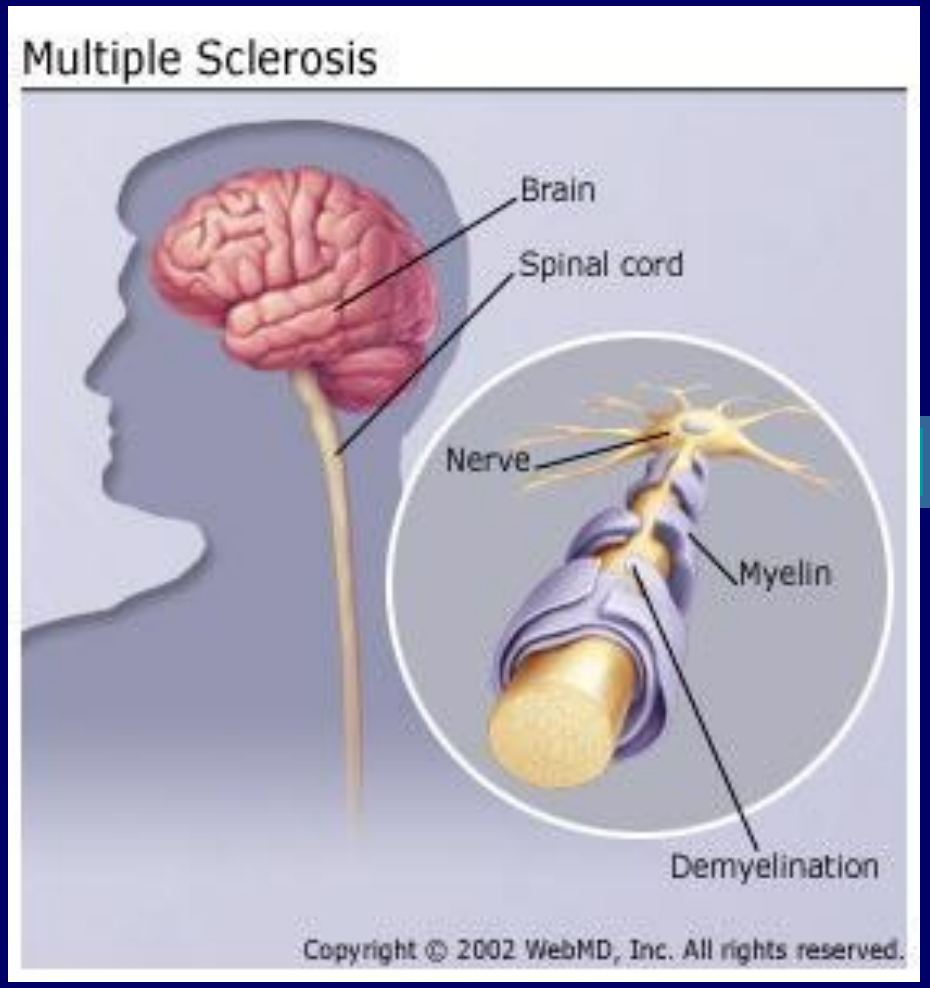
- **Bacterial infections**, nutritional and dietary factors, exposure to animals, minerals, chemical agents, metals, organic solvents, and various occupational hazards.

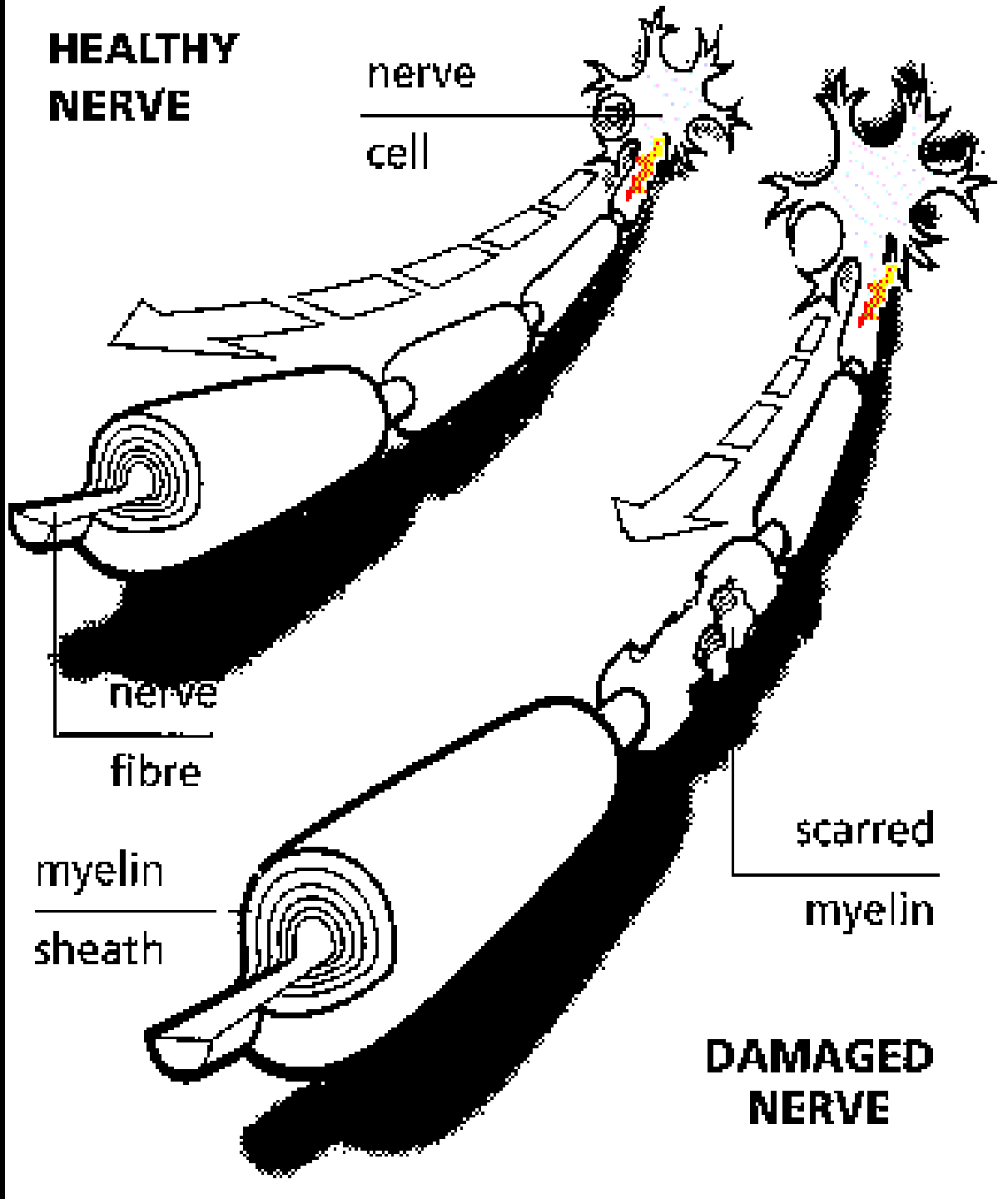
Role of the Genes in MS

- Monozygotic twin concordance rate of ~30% compared to dizygotic twin concordance rate of ~5%
- Multiple sclerosis seems to be genuinely **polygenic**
- Chromosomes **1, 6, 10, 17, and 19.**

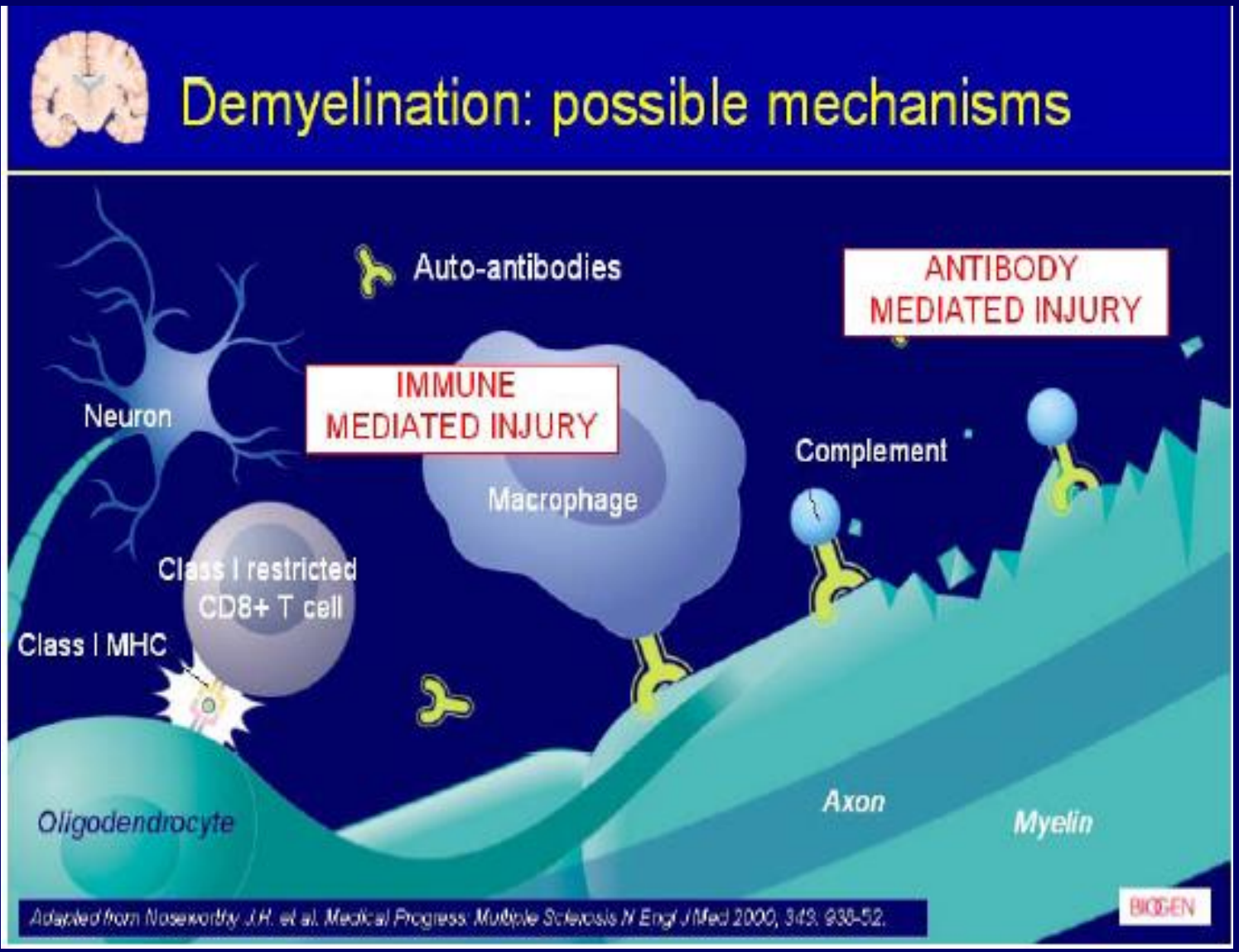
Myelin

- Myelin is made up of lipids and proteins.
- It acts as a type of insulation around the axon of nerves.
- Demyelinazation occurs when the myelin sheath becomes damaged.
  - In MS, this is the result of an abnormal autoimmune reaction.

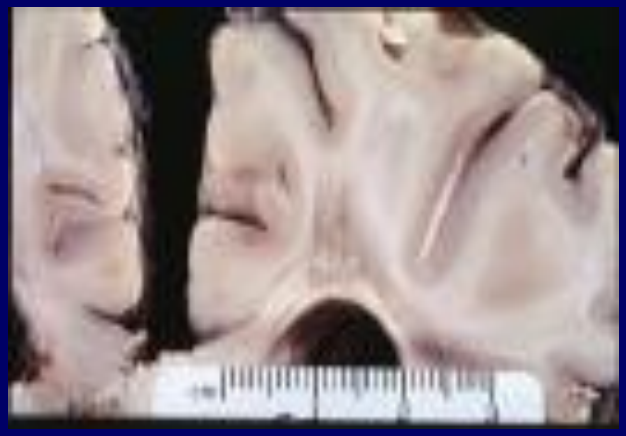



HEALTHY NERVE
nerve cell
nerve fibre
myelin sheath
scarred myelin
DAMAGED NERVE

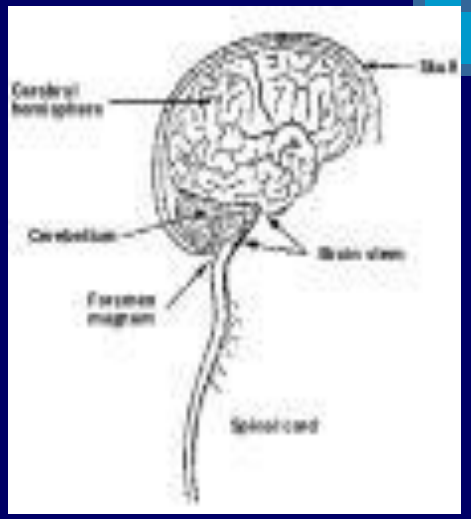
Demyelination: possible mechanisms



MS: Pathology



- Demyelination occurs throughout the CNS
- Lesions occur throughout the CNS primarily in white matter



Fast Facts

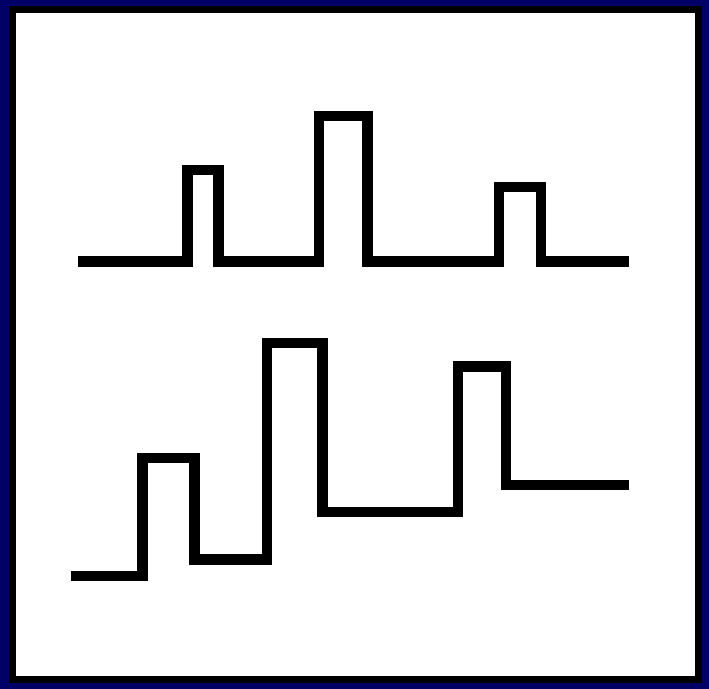
- Approximately 400.000 people in the US have MS. (1.5-2 million worldwide)
- Invisible disease.
- Not considered fatal.
- Not contagious.
- More common in northern European ancestry.
- Twice as common in women as men.

Types of MS

- There are four main types of MS:
  - Relapsing/Remitting (RRMS)
  - Secondary Progressive (SPMS)
  - Progressive Relapsing/Remitting (PRMS)
  - Primary Progressive (PPMS)

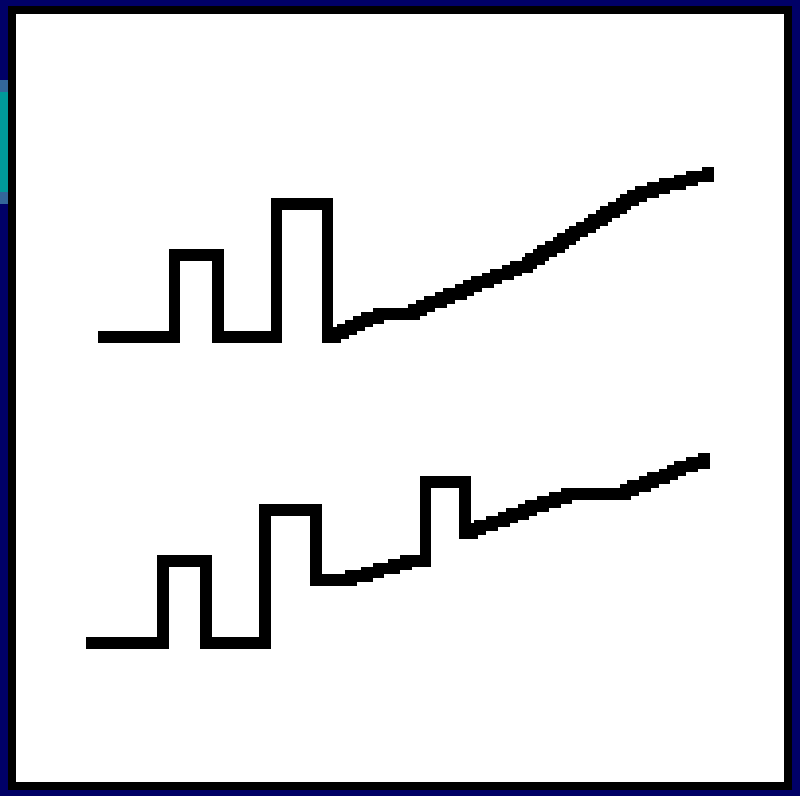
http://www.nationalmssociety.org/What%20is%20MS.asp

Relapsing/Remitting (RRMS)



- This is generally the first diagnosis of MS in the 20's to 30's.
- Approximately 85% of cases.
- Women are twice as likely to have this diagnosis.
- Characterized by relapses or exacerbations followed by periods of remission.

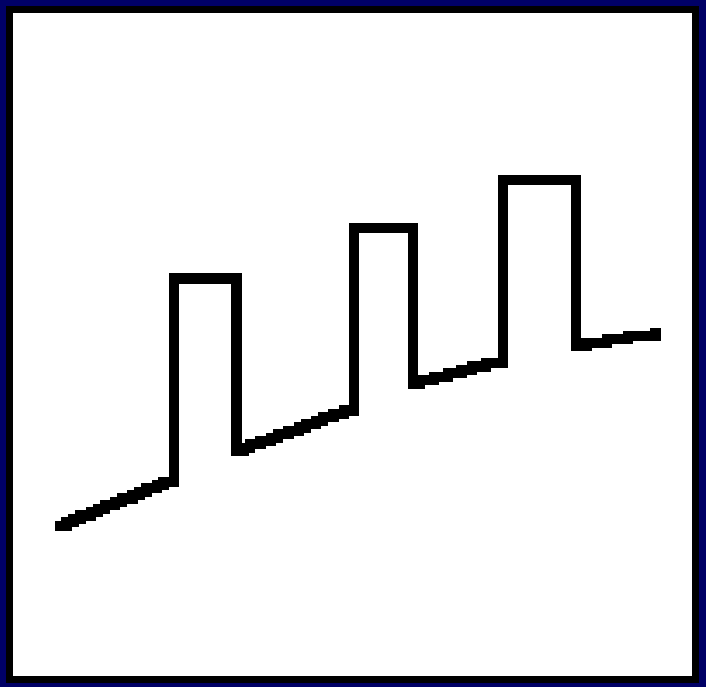
Secondary Progressive (SPMS)



- About half of individuals with RRMS will develop this type of MS after a number of years.
- This starts out as RRMS, however over time there will not be real recovery after relapses, just a worsening progression of symptoms.

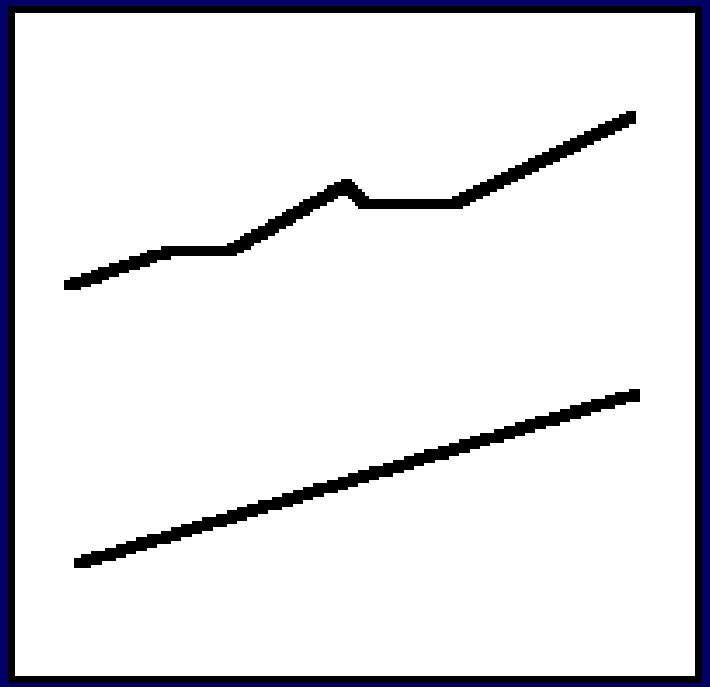
Progressive Relapsing/Remitting (PRMS)

- Characterized by relapses followed by periods of remission, however, during those periods of remission there is a general worsening of symptoms.
- Approximately 5% of cases.



Primary Progressive (PPMS)

- There are no real remissions with this type of MS. Instead there is a gradual worsening of symptoms over time.
- Onset is generally around late 30's to early 40's.
- Men are just as likely as women to be diagnosed.
- Primary onset is in the spinal cord, but may travel to the brain.
- Individuals with this type of MS are less likely to suffer from brain damage.
- Approximately 10% of cases.



Exacerbations

- Characterized by a sudden worsening of symptoms.
  - Last at least 24 hours
  - Separated from last exacerbation by at least one month
- Can last from a couple days to a few weeks.
- Followed by demyelinazation.

Pseudoexacerbations

- Symptoms are present in the same form as regular exacerbations except:
  - Something triggers the symptoms to come out.
    - Fever, infection, hot weather, etc.
  - When the trigger disappears the symptoms disappear as well.

Symptoms

- Very unpredictable!
- Symptoms vary from one individual to the next, and also from one exacerbation to the next.
- Symptoms can fully disappear after exacerbations.

Symptoms include…

- Fatigue
- Muscle weakness to paralysis
- Slurred speech
- Tremor
- Diplopia
- Bladder problems
- Pain
- Depression
- Sexual dysfunction
- Numbness/Tingling
- Vertigo
- Visual problems
- Cognitive decline
- Spasticity

Pediatric Multiple Sclerosis

- 400,000 US patients with MS

- Up to 15% of these will have presentations before age 18.

- Incidence 1-2 per 100,000 kids

- Earliest documented autopsy case is 10 months of age.

Diagnosis

- Can be difficult to diagnose because of the nature of the symptoms.
- No specific laboratory tests available to test for MS.
- MRI's are most often used in diagnosing and monitoring MS.
  - Other tests that can be used are spinal taps and evoked potential tests

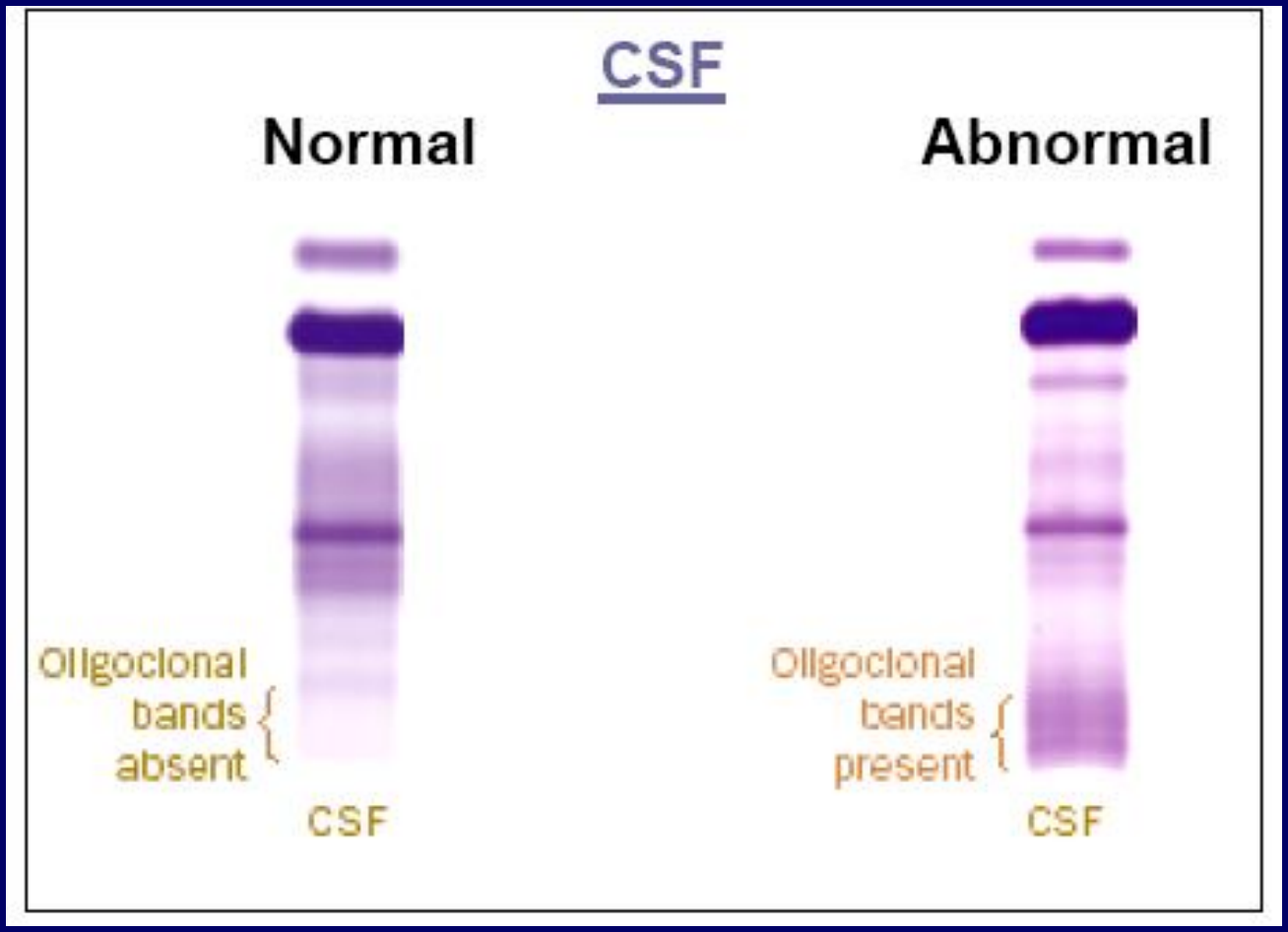
Diagnosis is the same as adult patients: Two or more discrete neurologic events separated in time.

- Optic neuritis (50%), sensory disturbance (16%), or transverse myelitis (10-15%). Motor symptoms are low in primary presentations (8%).

- 71% of children have a rapid initial presentations (hrs to a few days).

Lab features

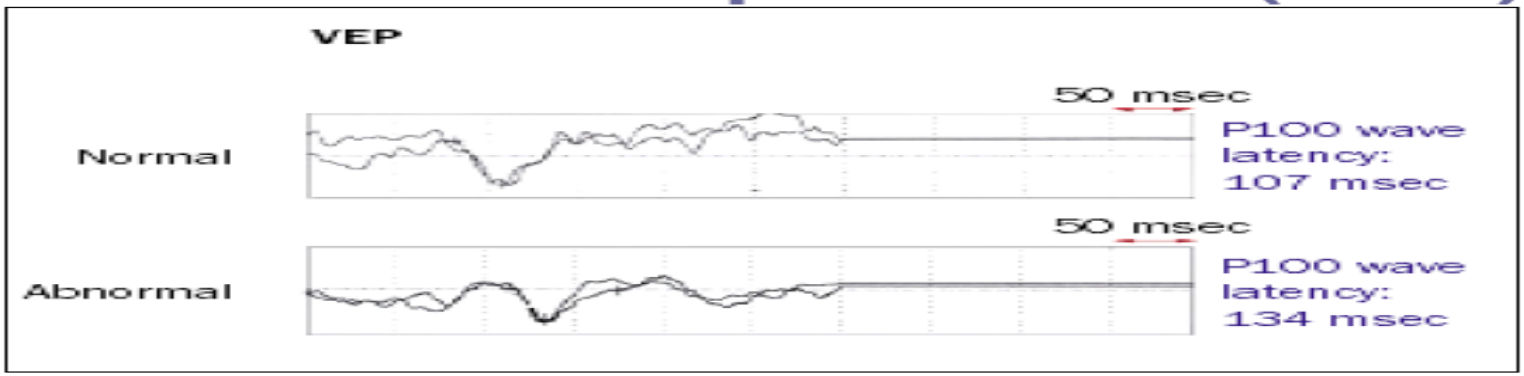
- **60%** of routine CSF analyses is normal in children with MS.
- Lymphocytosis (<50 cells/mm3)
- Increased CSF protein (<75 mg/dL)
- 80% of children with MS have increased CSF IgG synthesis
- Oligoclonal bands are present in 40-87% of Children with MS.
- Sometimes the OCB appear during the convalescence or relapse phase.


CSF
Normal
Abnormal
Oligoclonal bands absent
CSF
Oligoclonal bands present
CSF

Evoked Potentials (82% of children had one abnormal EP):

- VEP – 95% abnormal EP after first attack
- SSEP-57% abnormal EP after first attack
- BAEP-46% abnormal EP after first attack

Visual evoked potentials (VEP)



Visual evoked potentials (VEPs) and **somatosensory evoked potentials** (SEPs)

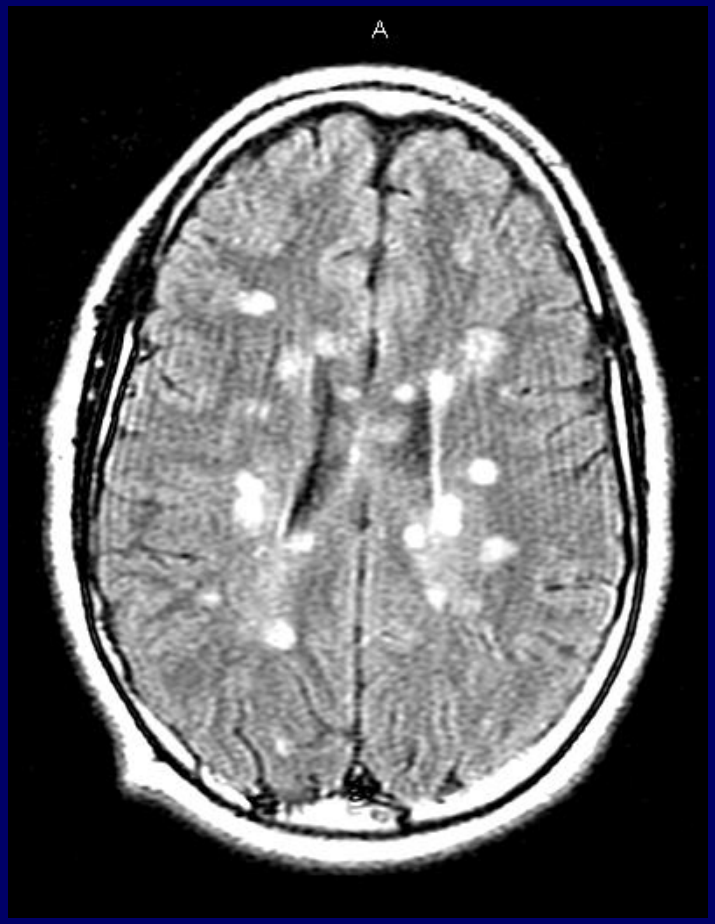
- An electrical potential recorded following presentation of a stimulus
- The brain of a person with MS often responds less actively to stimulation of the **visual** (optic nerve), **auditory**, and **somatosensory** nerves.
- Decreased activity on either test can reveal demyelination which may be otherwise asymptomatic.

McDonald criteria (2001)

2 or more attacks (relapses) * 2 or more objective clinical	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
* 2 or more attacks * 1 objective clinical lesion	Dissemination in space, demonstrated by: * MRI * or a positive CSF and 2 or more MRI lesions consistent with MS * or further clinical attack involving different site
* 1 attack * 2 or more objective clinical lesions	Dissemination in time, demonstrated by: * MRI * or second clinical attack
* 1 attack * 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: * MRI * or positive CSF and 2 or more MRI lesions consistent with MS **and** Dissemination in time demonstrated by: * MRI * or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined) and Two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF

Use of MRI in Diagnosis of MS

- 50-67% of clinical definite pediatric MS patients fit the McDonald imaging criteria
- Smaller number of total lesions at presentation.
- High incidence of deep WM ring enhancing lesions (tumefactive lestion) in pediatric MS patients.
- Long axis callosal lesions plus other well defined focal lesions may define pediatric MS from ADEM.
- ADEM tends to have GM lesions and subcortical WM lesions as opposed to periventricular WM lesions typical more in pediatric MS patients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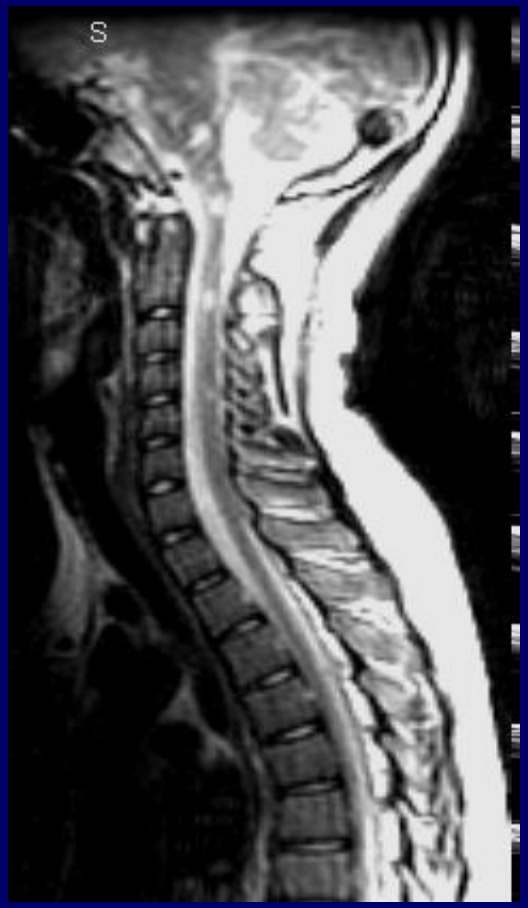
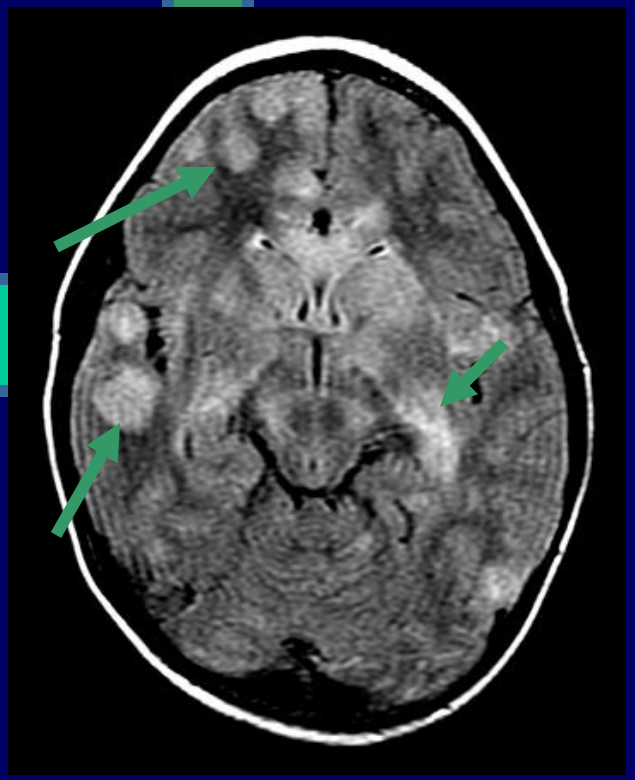
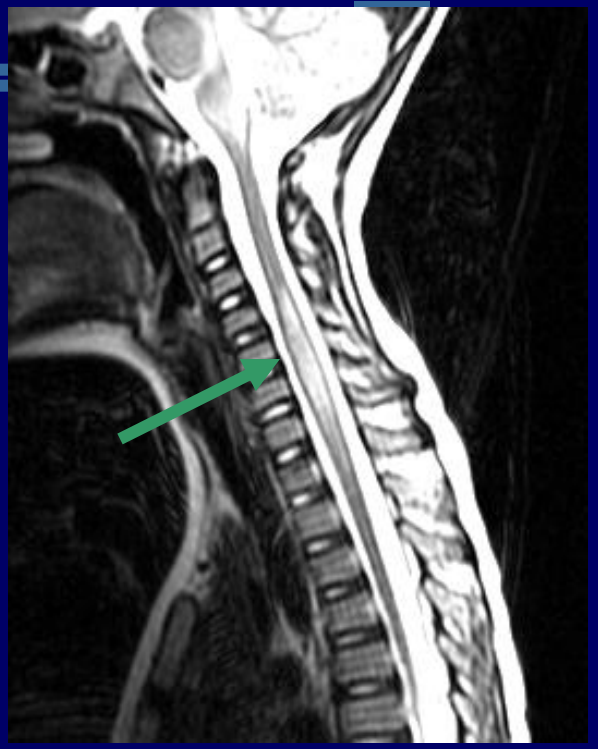

S

MRI

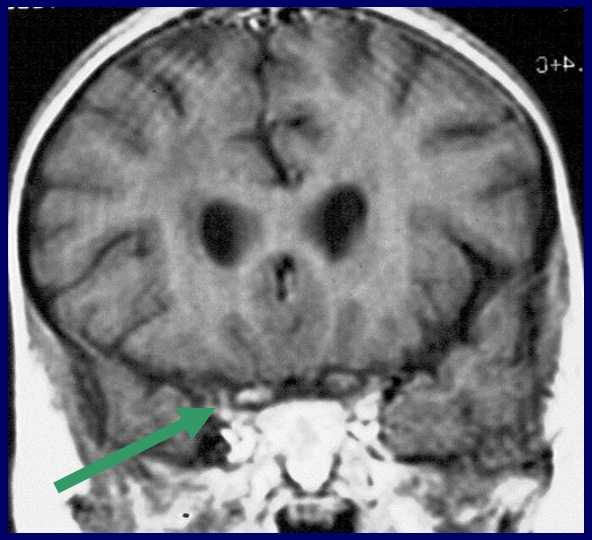


ADEM



Transverse Myelitis

Optic Neuritis



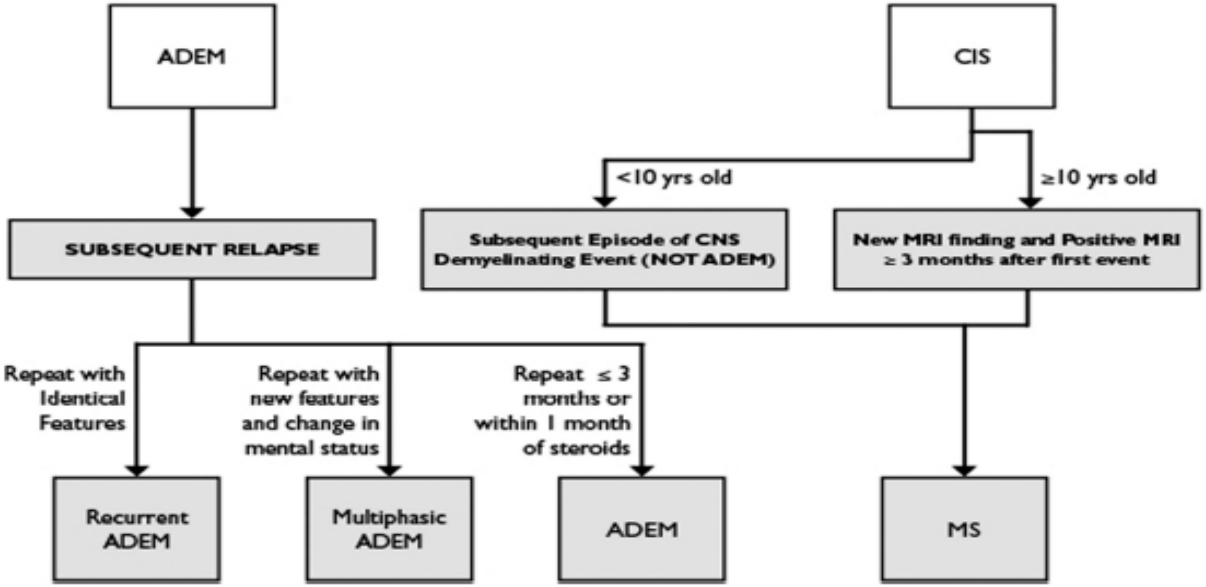


Figure. Flow chart/decision tree for the diagnosis of acute disseminated encephalomyelitis (ADEM), recurrent ADEM, multiphasic ADEM, and pediatric multiple sclerosis.

***Table** Comparison of typical features of ADEM and MS*

Typical features	ADEM	MS
Demographic	More frequently younger age groups (<10 years); no gender predilection	More frequently adolescents; girls predisposed more than boys
Prior flu-like illness	Very frequent	Variable
Encephalopathy	Required in definition	Rare early in the disease
Seizures	Variable	Rare
Discrete event	A single event can fluctuate over the course of 12 weeks	Discrete events separated by at least 4 weeks
MRI shows large lesions involving gray and white matter	Frequent	Rare
MRI shows enhancement	Frequent	Frequent
Longitudinal MRI findings	Lesions typically either resolve or show only residual findings*	Typically associated with development of new lesions
CSF pleocytosis	Variable	Extremely rare, white blood cell count almost always <50
Oligoclonal bands	Variable	Frequent
Response to steroids	Appears favorable	Favorable

Consensus definitions proposed fo pediatric multiple sclerosis and related disorders

Lauren B. Krupp, MD; Brenda Banwell, MD; and Silvia Tenembaum, MD;
for the International Pediatric MS Study Group*

D.D

Category	Examples
Demyelinating	ADEM, ON, complete TM, NMO
Inflammatory	SLE, neurosarcoidosis, aPL antibody syndrome, Sjögren disease
Leukodystrophy	MLD, ALD, Krabbe, PMD
Genetic/metabolic	Inborn errors of metabolism, amino acidurias, cerebral folate deficiency, mitochondrial disorders, LHON
Infectious disorders	Neuroborreliosis (Lyme), HIV, HTLV-1, neurosyphilis, PML, SSPE, Whipple's disease, TB, fungal infection (histoplasmosis)
Vascular disorders	CADASIL, migraine, CNS vasculitis
Nutritional	B_{12} or folate deficiency, Celiac disease
Neoplastic	Lymphoma, astrocytoma
Endocrine	Thyroid disorder
Other	Langerhan's cell histiocytosis, hemophagocytic lymphohistiocytosis

ADEM—acute disseminated encephalomyelitis; ALD—adrenoleukodystrophy; aPL—antiphospholipd; CADASIL—cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS—central nervous system; HTLV-1—human T-lymphotropic virus-1; LHON—Leber's Hereditary Optic Neuropathy; MLD—metachromatic leukodystrophy; NMO—neuromyelitis optica; ON—optic neuritis; PMD—progressive muscular dystrophy; PML—progressive multifocal leukodystrophy; SLE—systemic lupus erythematosus; SSPE—subacute sclerosing panencephalitis; TB—tuberculosis; TM—transverse myelitis.

Table 2 Clinical evaluation of disorders mimicking multiple sclerosis

Clinical presentation	Differential diagnosis (selected)	Work-up
Progressive neurologic decline with tumefactive lesion on MRI	Lymphoma, medulloblastoma, other malignancy or infection	Consider MR spectroscopy, CSF analysis, or biopsy
Progressive decline, developmental delay, family history of white matter disorders, involvement of the peripheral nervous system, extraneural organ involvement, widespread confluent white matter lesion on MRI	Metachromatic leukodystrophy, Fabry disorder, childhood ataxia with cerebral hypomyelination (mutation of eukaryocytic initiation factor)	Complete blood count, serum long chain fatty acids, lysosomal enzymes, carnitine, acylcarnitine profiles
Developmental delay, episodic neurologic dysfunction, including seizures, ataxia	Aminoaciduria (e.g., maple syrup urine disease)	Plasma and urinary amino acids and urinary organic acids
Intermittent or progressive neurologic decline, hearing loss, myopathy, cardiomyopathy, vision loss	Mitochondrial disorders, Leber hereditary optic neuropathy, MELAS, MERRF	CSF lactate, pyruvate, genetic testing, muscle biopsy, ophthalmologic evaluation
Spinal cord dysfunction	Transverse myelitis, spinal cord tumor, neuromyelitis optica (Devic disease)	MRI cervical-thoracic spine with gadolinium, VER, CSF, serum autoantibody marker
Nonspecific white matter changes on MRI	Nutritional disorders	B12, folate, complete blood count
Headache, migraine, TIA, stroke	CADASIL, antiphospholipid antibody, migraine, AVM, moyamoya syndrome	MR angiography/MRI, conventional angiography, antiphospholipid antibodies
History of rheumatological disease, joint pain and swelling, skin lesions, kidney disease	Systemic lupus erythematosus, antiphospholipid antibody syndrome, system vasculitis, Behçet disease	Antiphospholipid antibodies, ESR, C-reactive protein, antinuclear antibodies, anti-dsDNA, angiotensin converting enzyme, anticardiolipin antibody, urine analysis, chest x-ray
Encephalopathy in which infection is suspected	Herpes simplex, varicella zoster, Epstein-Barr virus, HIV, cytomegalovirus, enterovirus, neuroborreliosis, streptococcal infection, mycoplasma, HTLV-I	Serology for suspected organisms, CSF viral, fungal, and bacterial cultures, CSF viral polymerase chain reaction assay

MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; MERRF = myoclonic epilepsy with ragged red fibers; VER = visual evoked response; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; AVM = arteriovenous malformation; ESR = erythrocyte sedimentation rate; HTLV = human T-cell lymphotrophic virus.

How Frequent is CNS Demyelination in Children?

- Yann Mikaeloff MD et al in Journal of Pediatrics 2004
- Included Children under 16 yrs between 1985-1991 admitted to 12 Pediatric Neurology Centers in France
- Exclusion criteria include preceding neurologic abnormality, metabolic cause, infectious cause, systemic immunologic disorder

FIRST EPISODE OF ACUTE CNS INFLAMMATORY DEMYELINATION IN CHILDHOOD: PROGNOSTIC FACTORS FOR MULTIPLE SCLEROSIS AND DISABILITY

Data at first attack	All patients n = 296	Final diagnosis: MS† n = 168	Final diagnosis: Monophasic ADEM n = 85	Final diagnosis: Single focal episode* n = 43
Age at onset (y)				
Mean ± SD	9.9 ± 4.5	12 ± 3.4	7.1 ± 4.3	8.8 ± 4.7
Median (range)	11 (0.7–16)	13.1 (2–16)	6.4 (0.7–16)	9.8 (0.7–16)
Sex, male	127 (43)	55 (33)	48 (56)	24 (56)
Familial history MS	15 (5)	12 (7)	2 (2)	1 (2)
White	235 (79)	133 (79)	63 (74)	39 (91)
Infection during month preceding onset	94 (32)	27 (16)	43 (51)	24 (56)
Vaccination during 6 mo preceding onset	16 (5)	11 (7)	3 (4)	2 (4)
Symptoms at first attack				
Polysymptomatic	230 (78)	113 (67)	85 (100)	32 (74)
Transverse myelitis	42 (14)	13 (8)	2 (2)	27 (63)
Long-tract dysfunction	226 (76)	116 (69)	73 (86)	37 (86)
Brainstem dysfunction	121 (41)	61 (36)	47 (55)	13 (30)
Optic neuritis	67 (22)	58 (35)	6 (7)	3 (7)
Severe mental status change	85 (28)	21 (13)	64 (75)	0
Other symptoms	136 (46)	46 (27)	76 (89)	14 (32)
MRI at first attack				
Suggestive of ADEM	119 (40)	34 (11)	85 (100)	0
Suggestive of MS	96 (32)	96 (57)	0	0
Subtentorial lesion	196 (66)	121 (72)	73 (86)	2 (4)
Thalamus and/or basal ganglia lesion	47 (16)	13 (8)	34 (40)	0
Optic nerve lesion§	12 (4)	10 (6)	0	2 (4)
Subtentorial lesion	110 (37)	64 (38)	39 (46)	7 (16)
Spinal cord lesion	54 (18)	32 (19)	9 (11)	13 (30)
Tumor-like lesion	36 (12)	20 (12)	15 (18)	1 (2)
Gadolinium enhancement	64 (21)	47 (28)	9 (11)	8 (18)
Positive cerebral TDM at onset	39 (13)	22 (13)	16 (19)	1 (2)
CSF findings at first attack				
Cells ≥10/μL	118 (40)	62 (37)	43 (51)	13 (30)
Proteins ≥0.5 g/dL	71 (24)	31 (18)	31 (36)	9 (21)
Oligoclonal bands‡	72 (24)	68 (40)	4 (5)	0

Mikaeloff Y, et al., J Pediatr 2004,144(2):246-52.

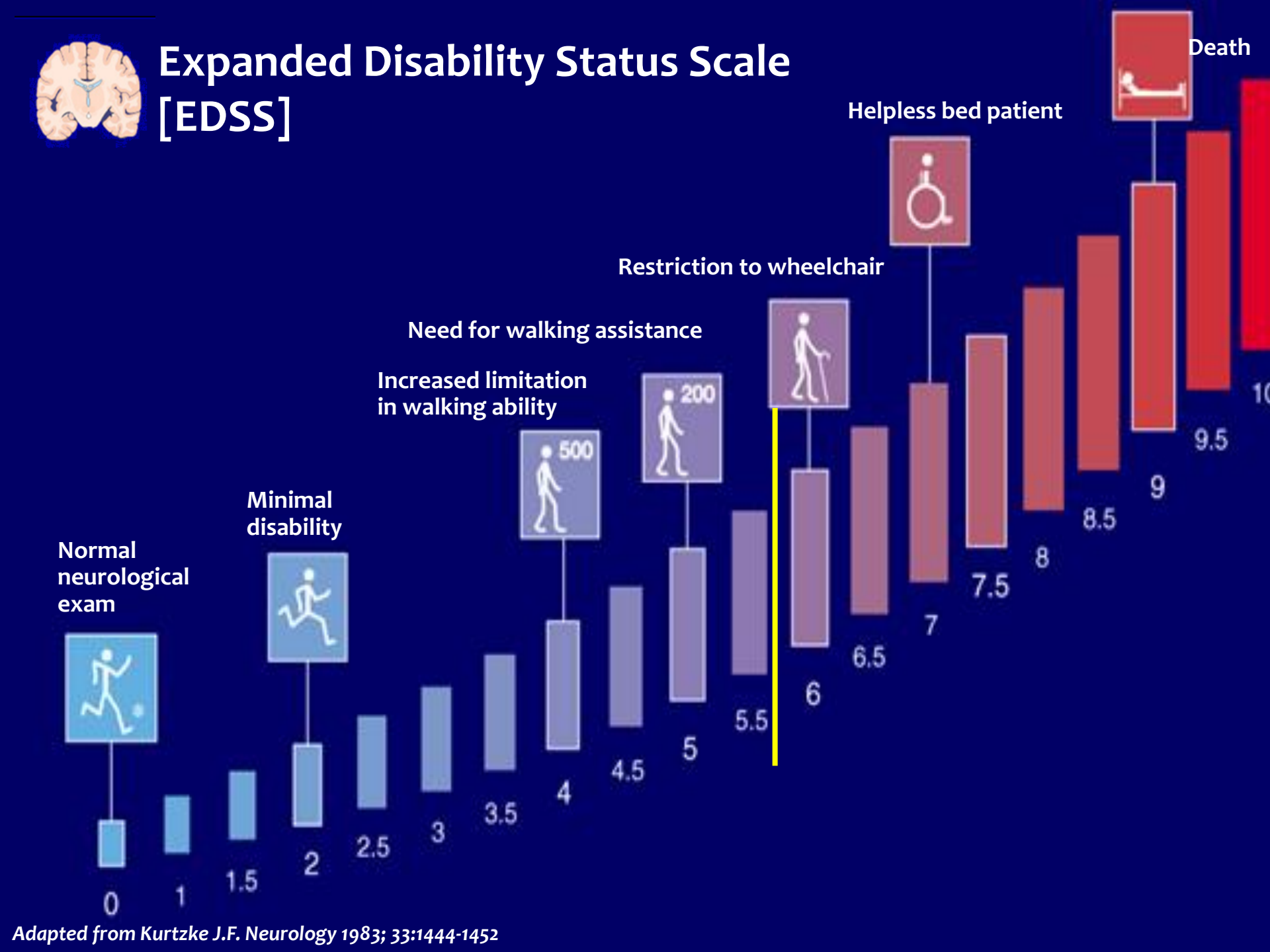
Other distinguishing characteristics

- Infection during preceding month (ADEM/Focal episode 51-55% vs MS 16%)
- TM was high (63%) with a single focal episode (low in MS 8% or ADEM 2%)
- Optic Neuritis was more common in MS (35%) vs ADEM (7%)
- Brainstem dysfunction was common in ADEM (55%) vs MS (36%)
- Severe mental status changes are more common in ADEM (75%) vs MS (13%)

CSF Findings

- >10 WBC cells- MS (37%) vs ADEM (51%)
- >0.5 gm/dl protein- MS (18%) vs ADEM (36%)
- Oligoclonal bands- MS (40%) vs ADEM (5%)

Expanded Disability Status Scale [EDSS]



Adapted from Kurtzke J.F. Neurology 1983; 33:1444-1452

Treatment

- There is currently no cure for MS.
- Treatments focus on:
  - Slowing down the disease (disease modifying)
  - Specific symptom treatment
  - Exacerbation treatment