MULTIPLE SCLEROSIS

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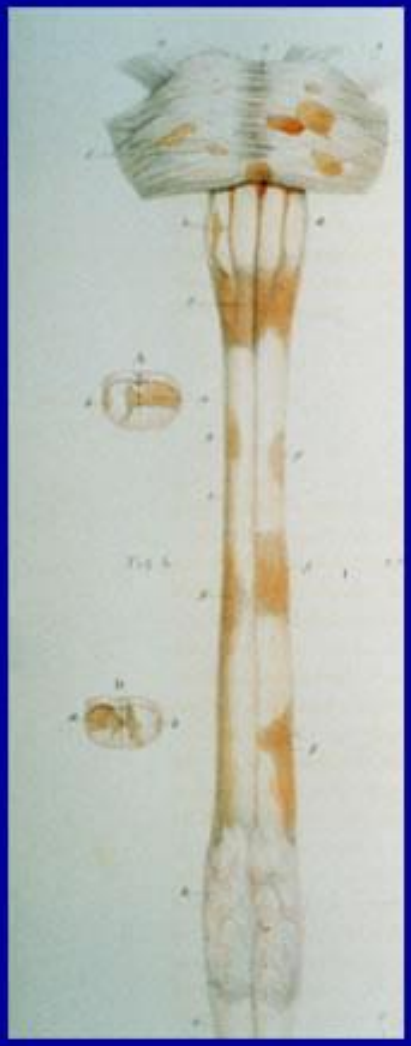
Earliest Known Description of a Case of MS

(St. Lidwina of Schiedam 1380-1433)



Robert Carswell (1793-1857)

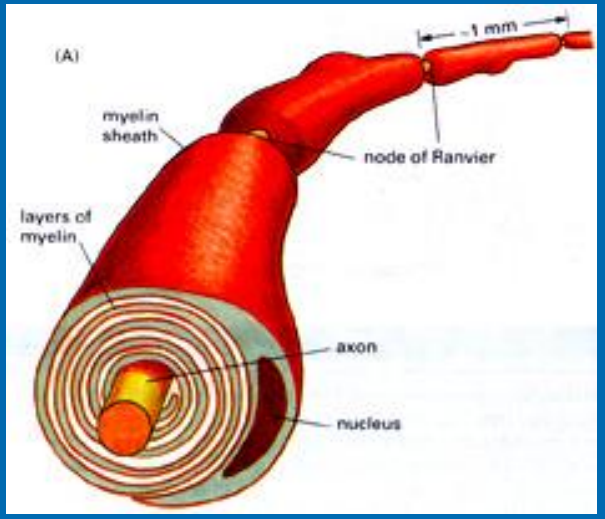
- First steps towards a recognition of the pathology of MS
- Recorded strange lesions in the spinal cord

Jean-Martin Charcot (1825-1893)

- First to describe the clinical condition
- MS recognised as a distinct disease entity
- Diagnostic criteria
- First complete histological account

Definitions (What is MS?)

- Chronic Inflammatory Disease of the CNS (brain & spinal cord),



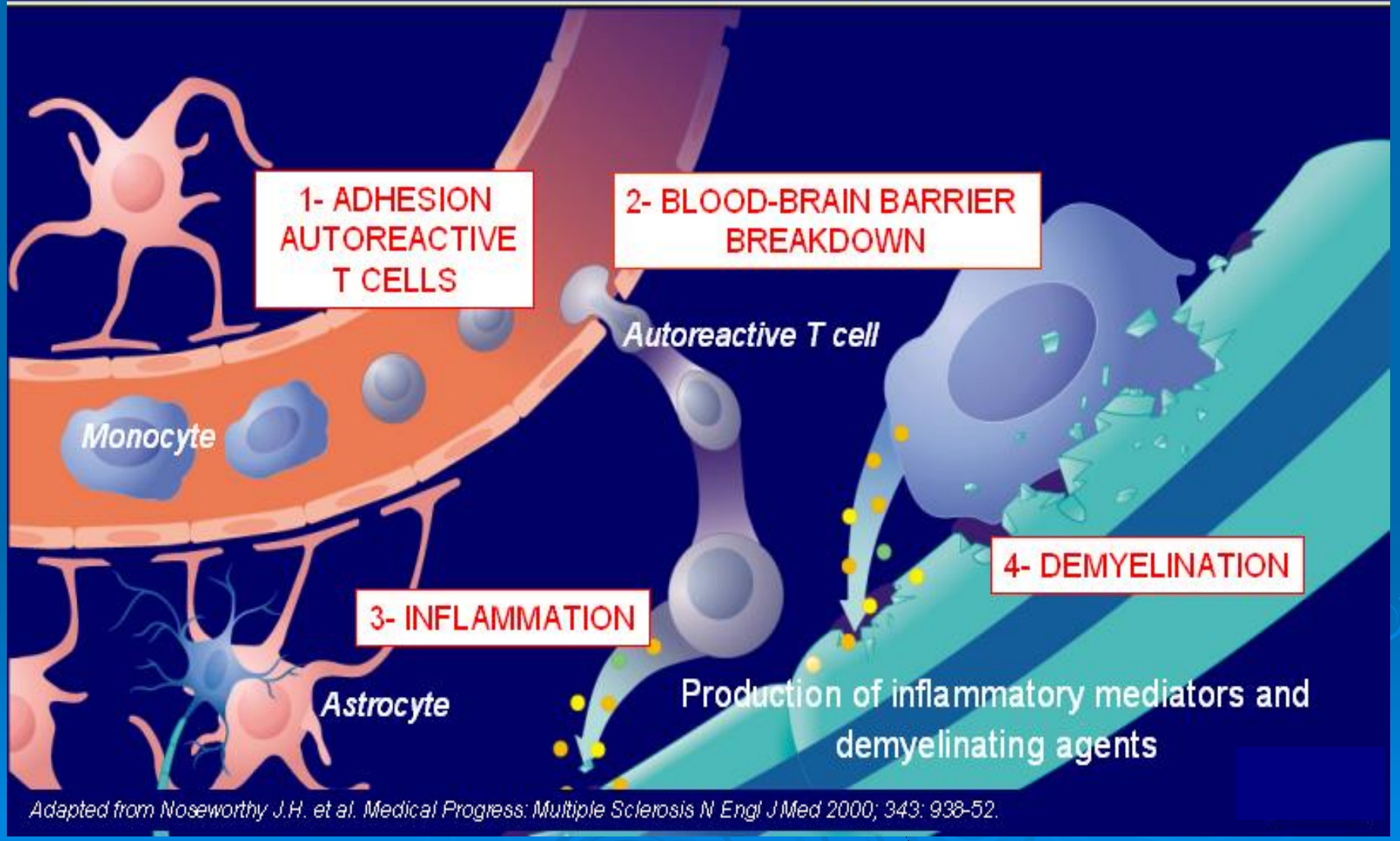
- Autoimmune

  (self-destruction of myelin)

- Characterised by relapses and remissions

- One of the most common cause of disability amongst adults at working age

Possible pathogenic mechanisms: the role of the immune system



Adapted from Noseworthy J.H. et al. Medical Progress: Multiple Sclerosis N Engl J Med 2000; 343: 938-52.

Cellular Model For Multiple Sclerosis

(i) Normal Axon

(ii) Acute
Demyelination

(iii) Chronic
Demyelination

(iv) Degenerated Axon

White blood cells recruited in the brain

⇓

Blood Brain Barrier disruption

⇓

inflammation

⇓

Recovery Repair

Demyelination, axonal damage

⇓

axonal transection

⇓

disability

Axonal Transection in active Multiple Sclerosis lesions

SMI-32 (non-phosphorylated neurofilament) -demyelinated axons and swellings
MBP intact axons

Bruce Trapp et al., NEJM 338, 278 (1998)

Multiple Sclerosis Demography

- 1 /100,000- 100/100,000 adults

Why? Environmental and genetic factors

750’000 patients WW

- Predominantly Caucasian

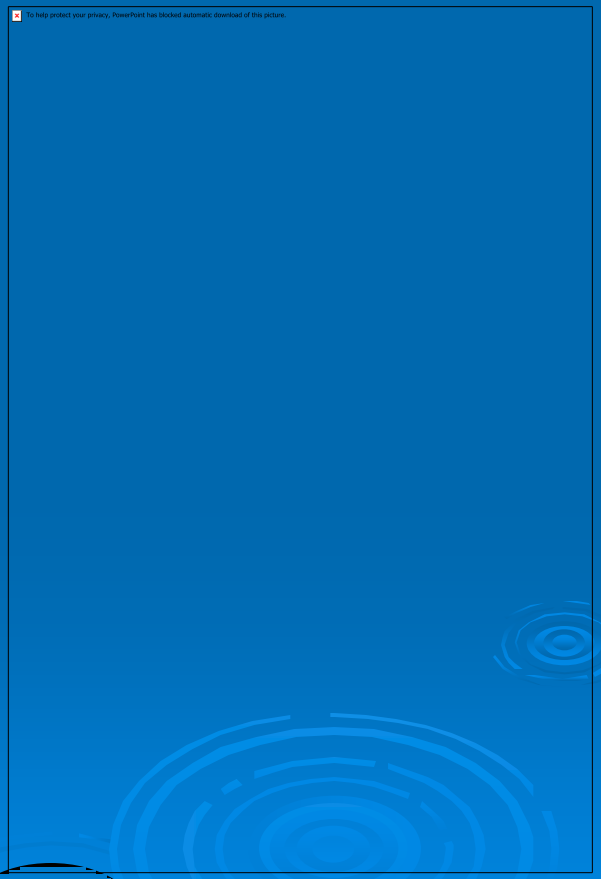
- Starts in early adult life

Symptoms emerge between 20-40 yrs in 70%

Mean 30 years. Peak 23-24

- Women > Men

2:1



Genetic Factors

- Compelling evidence

Approx 20% of patients with MS had a first, second or third degree relative with the disease.

Lifetime risk of MS in first degree relatives of patients with MS is 3-5% (pop as a whole 0.2%)

Monozygotic twins (30%) Dizygotic pairs (3-5%)

Canadian Collaborative project on genetic susceptibility.

Usual clinical presentation

- Optic neuritis
- Brainstem syndrome
- Spinal cord syndrome
- Sensory symptoms : Most common initial feature

Symptoms

Symptom	Total (percent)
Visual loss	16
Motor (subacute)	9
Diplopia	7
Gait disturbance	5
Motor (acute)	4
Balance problems	3
Sensory in face	3
Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)	2
Vertigo	2
Bladder problems	1
Limb ataxia	1
Acute transverse myelopathy	1
Pain	<1
Other	3
Polysymptomatic onset	14

Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess 2002; 6:1.

Symptoms of Established MS

Non- specific,

- initially mild, transitory and isolated (difficult to diagnose)
  - Fatigue (20%)
  - Optic neuritis (16%)
  - Vertigo (2-14%)
  - Sensory loss (30-50%)
  - Cognitive changes
  - Bladder disturbance

  Spasticity (10%)
  Nystagmus (20%)
  Gait disturbances (18%)
  Increased reflexes (20%)
  Depression
  Sexual dysfunction

- Changes visible on MRI

2 types of MRI: T1 and T2

T1-Weighted Scans	T2-Weighted Scans
Markers for Disease Activity	Markers For Burden of Disease
New Active Lesions	Established Lesions

Gadolinium: shows blood brain barrier leaks

T1 weighted images

MRI in DIAGNOSIS

Chances of developing MS within 5 years.

Single episode of optic neuritis PLUS:

0 lesions - 20%

1-3 lesions - 50%

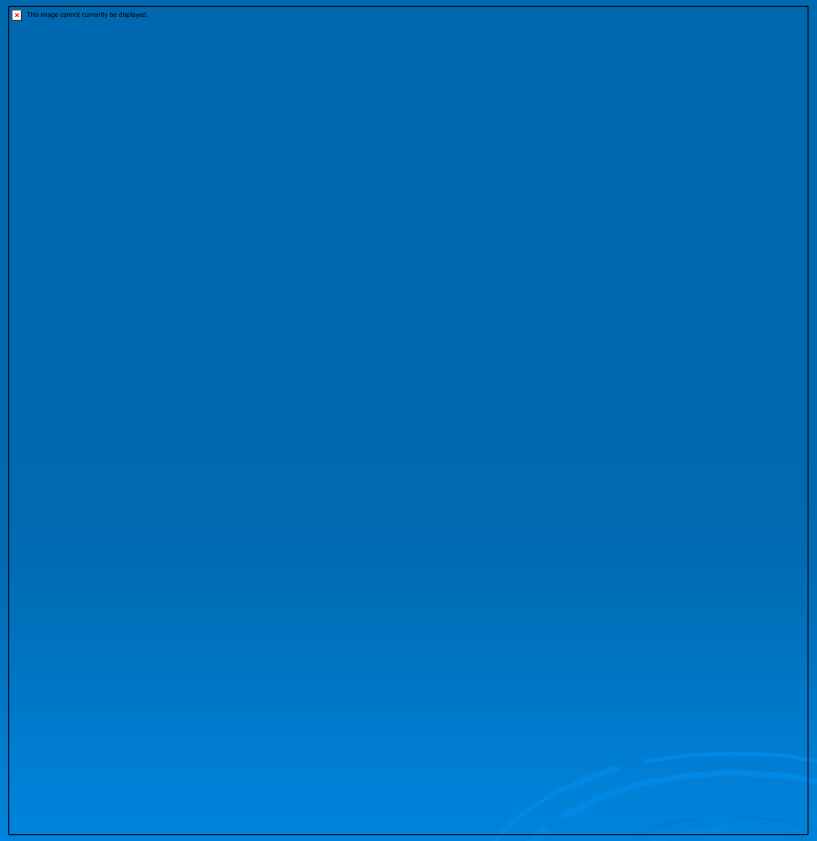
> 4 lesions - 90%

Other investigations

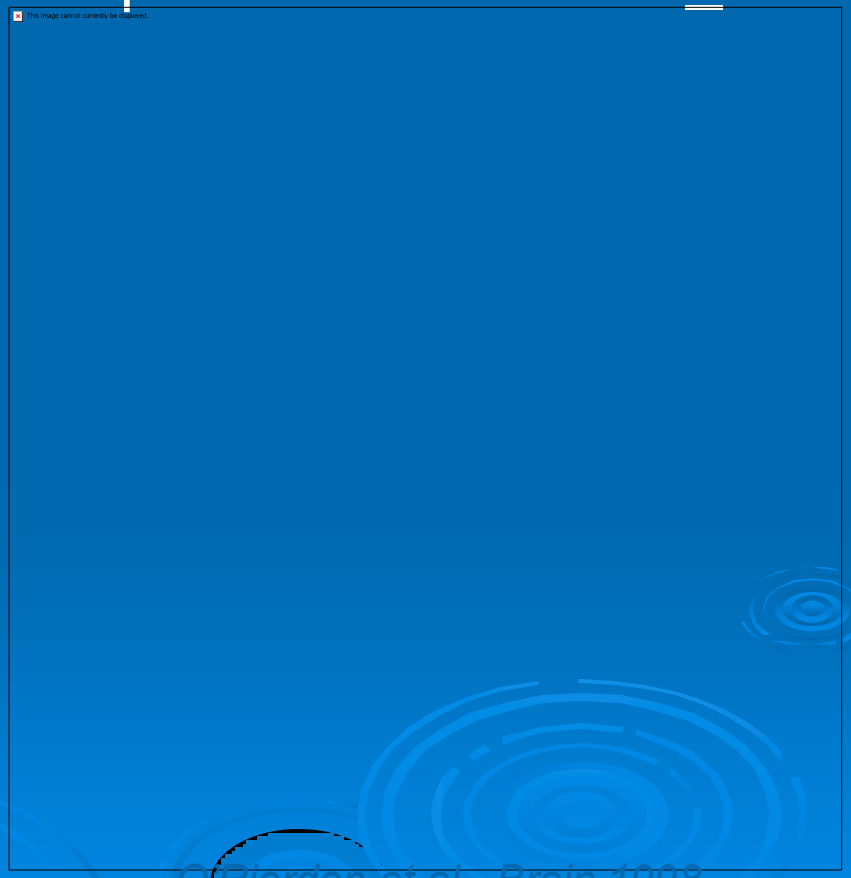
- CSF
  - Oligoclonal bands +ve in 85-95%
- Visual evoked potentials (50 – 90%)

MRI lesions ‘predict’ disease development after 10yrs

% patients with EDSS >3



% patients with EDSS ≥6



O’Riordan et al, Brain 1998

Revised McDonald criteria 2010

Dissemination in space (MRI)

- One or more T2 lesions in at least two of four MS-typical regions
  - Periventricular
  - Juxtacortical
  - Infratentorial
  - Spinal cord
- Or the development of a further clinical attack implicating a different CNS site.
- For patients with brainstem or spinal cord syndromes, symptomatic MRI lesions are excluded from the criteria.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology*. 2011;69(2):292-302.

Revised McDonald criteria 2010

Dissemination in time (MRI)

- simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time
- Or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing

- Or the development of a 2nd clinical attack

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology*. 2011;69(2):292-302.

Clinically isolated syndrome

- First attack compatible with MS (eg, optic neuritis, brainstem syndromes, or transverse myelitis)
- Does not fulfil diagnostic criteria.

MS progression

- Most Patients start with RR-MS
- 50% progress to Secondary Progressive MS within 10-15 years

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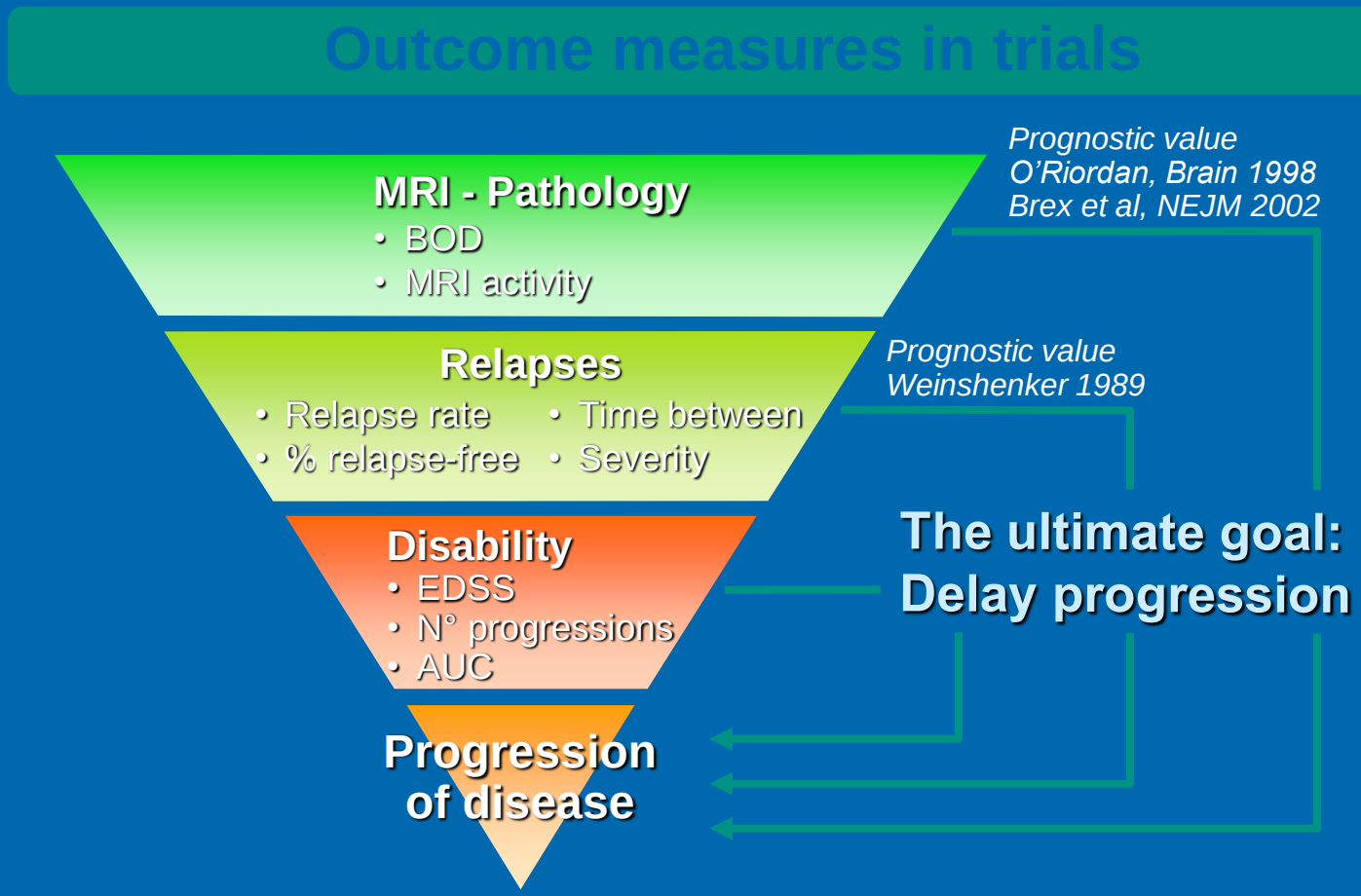
Efficacy is Most Important



Evidence-Based Medicine Approach:

1. Does treatment reduce the attack rate of MS?

Attack rate
measured clinically

Attack rate
measured by MRI

2. Does treatment reduce the severity of MS?

Clinically: Confirmed
disability progression

MRI: Disease Severity
by MRI T2 Burden

Neurology 2002, 58: 169-178

Selection criteria for DMT

- ABN Criteria

  Remitting relapsing Multiple sclerosis

  2 relapses in the last two year

- Aggressive disease

Drugs

- Injectables
  - Inteferons
  - Glatiramer acetate
  - Natalizumab
  - Alemtuzumab
- Oral
  - Fingolimod
  - Teriflnomide
  - Dimethyl fumarate

Efficacy of DMT

- Reduces relapses by 30% -80%
- Reduces severe relapses
- Delays disease progression
- Delays cognitive impairment
- Reduces level of fatigue

Can I get cannabinoids?

- Sativex/Nabiximol
- Can be used for refractory spasticity
- Side effects dizziness, drowsiness, nausea, headache, fatigue

Effect of MS on pregnancy

- Does not affect:
  - fertility
  - pregnancy
  - labour
  - delivery

Effect of pregnancy on MS

- Relapse rate decreases during pregnancy, particularly in the 3rd trimester
- Relapse rate increases in the first 3 months post partum
- Pregnancy has no effect on the progression in the long-term
- Teratogenic side effects of drugs

Will my child get MS?

- Not directly inherited
- Risk 2 – 4%
- 96% chance that they won't

THANK YOU