SAPMEA/ECHO Multiple Sclerosis discussion

April 28, 2022

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MS disease activity over the lifespan

Susceptibility to developing MS

Common Presentations

Investigation of suspected MS

Focus on early MS symptom management

Disease modifying therapies in 2022

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Corrected: Author Correction

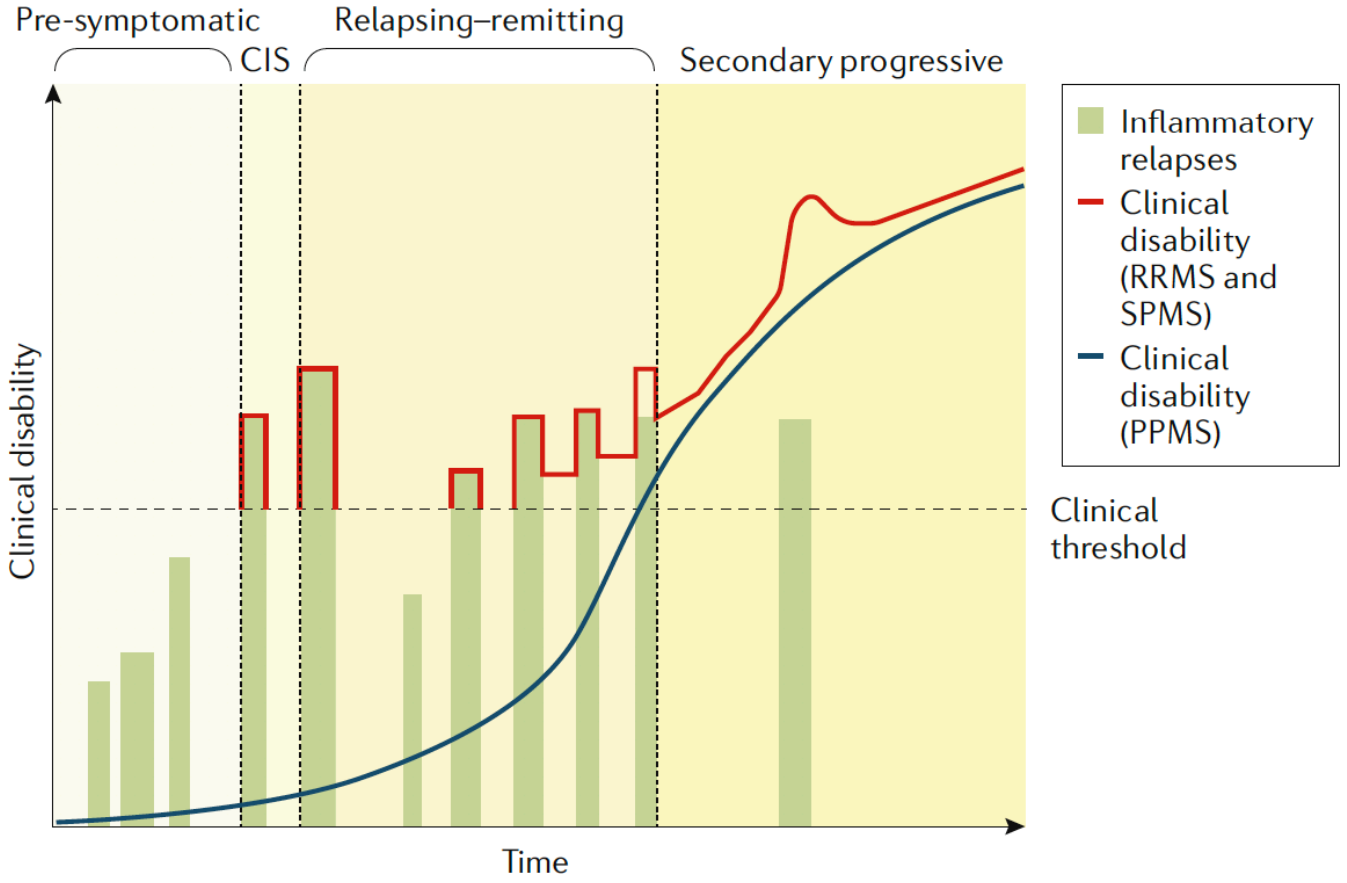
PRIMER

Multiple sclerosis

Massimo Filippi[1,2], Amit Bar-Or[3], Fredrik Piehl[4,5,6], Paolo Preziosa[1,2], Alessandra Solari[7], Sandra Vukusic[8] and Maria A. Rocca[1,2]*

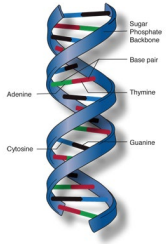
NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2018) 4:43

- 80+ % will have initial attacks and little initial residual disability
  - "relapsing remitting MS"
- Nearly all of these people lose relapses over time and accumulate disability slowly
  - "secondary progressive MS"
- 5-10% have no/few attacks but just accumulate disability from onset
  - "primary progressive MS"

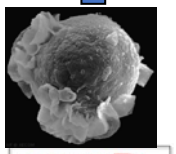


Multiple Sclerosis: In one picture

>200 SNP's
Mainly HLA

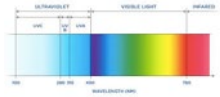


EBV

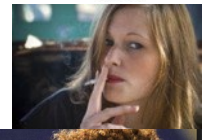


Vit D

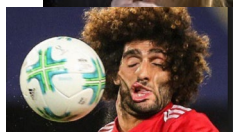
UVB

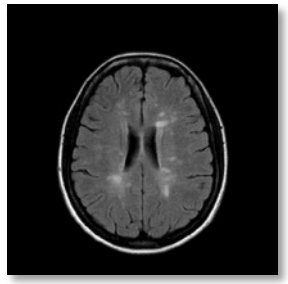


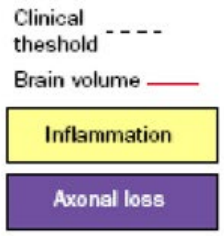
Smoking

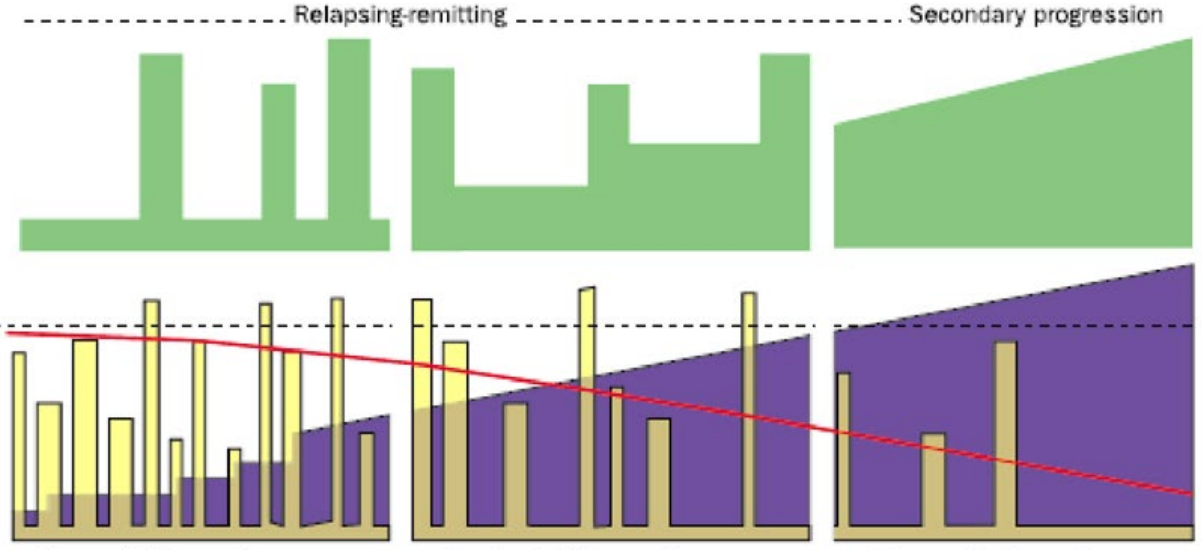


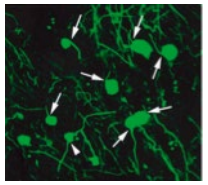
Concussion

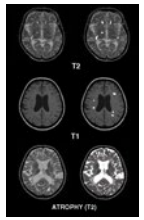


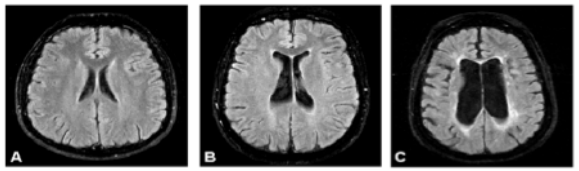










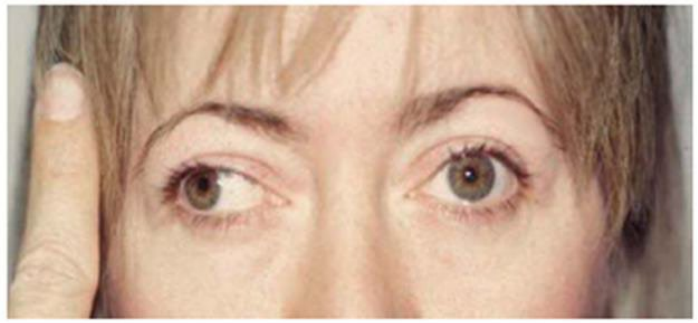


Susceptibility

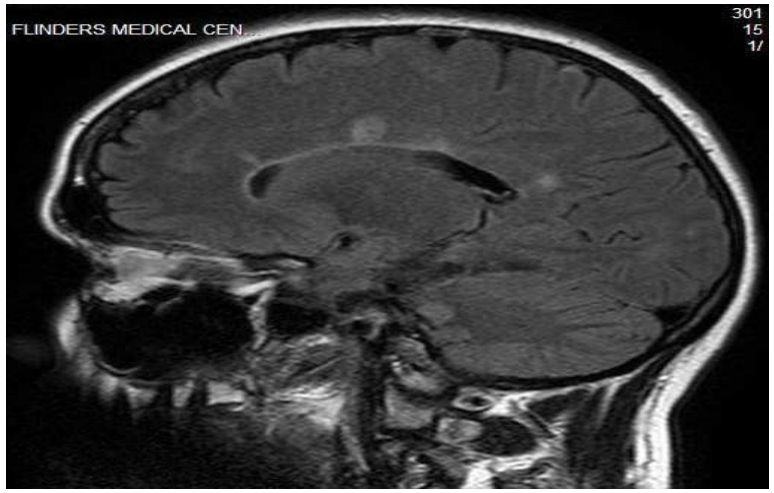
Early disease

Late disease

Clinical Presentation with relapse or history of such

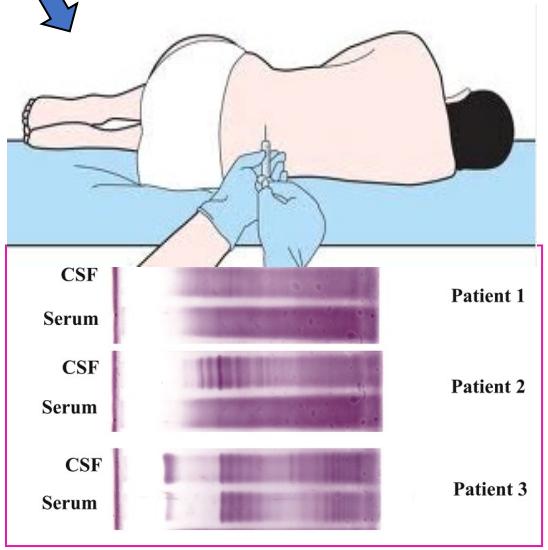


Clinical Assessment



MRI brain and Cord

Sometimes



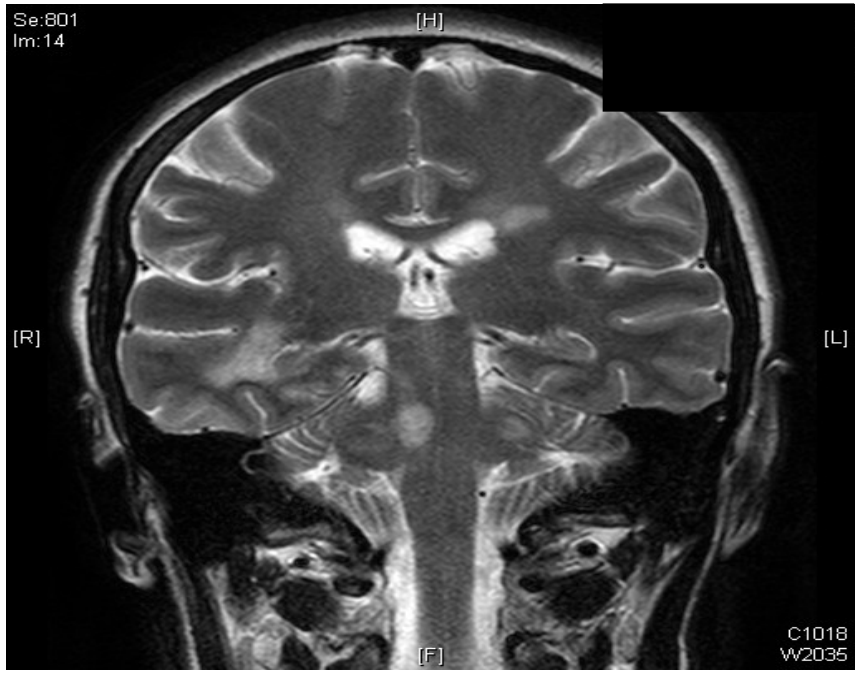
Lumbar Puncture

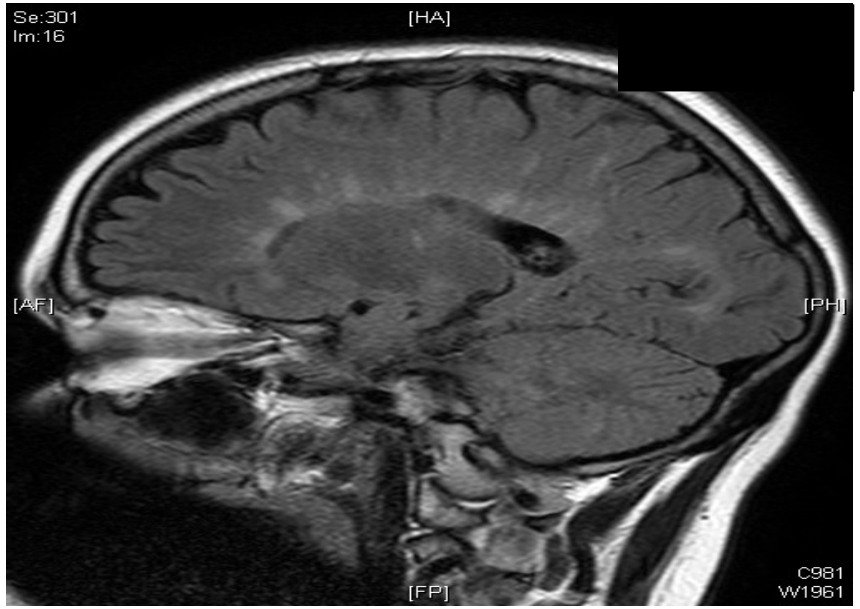
No better explanation

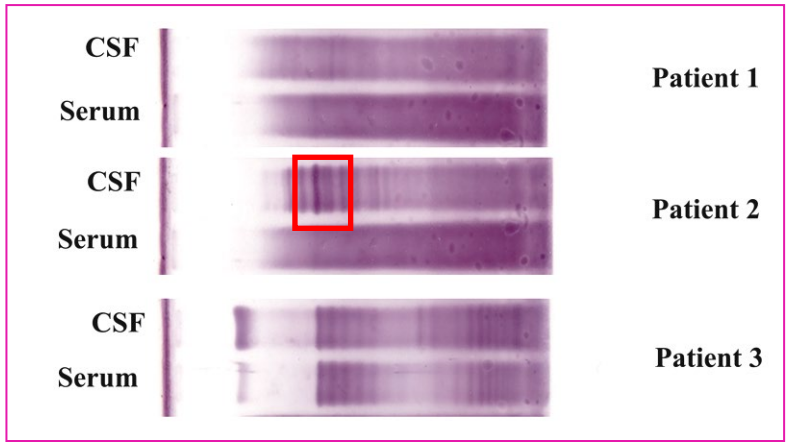
What is an MS relapse?

What is a pseudo-relapse?

Paraclinical tests in MS

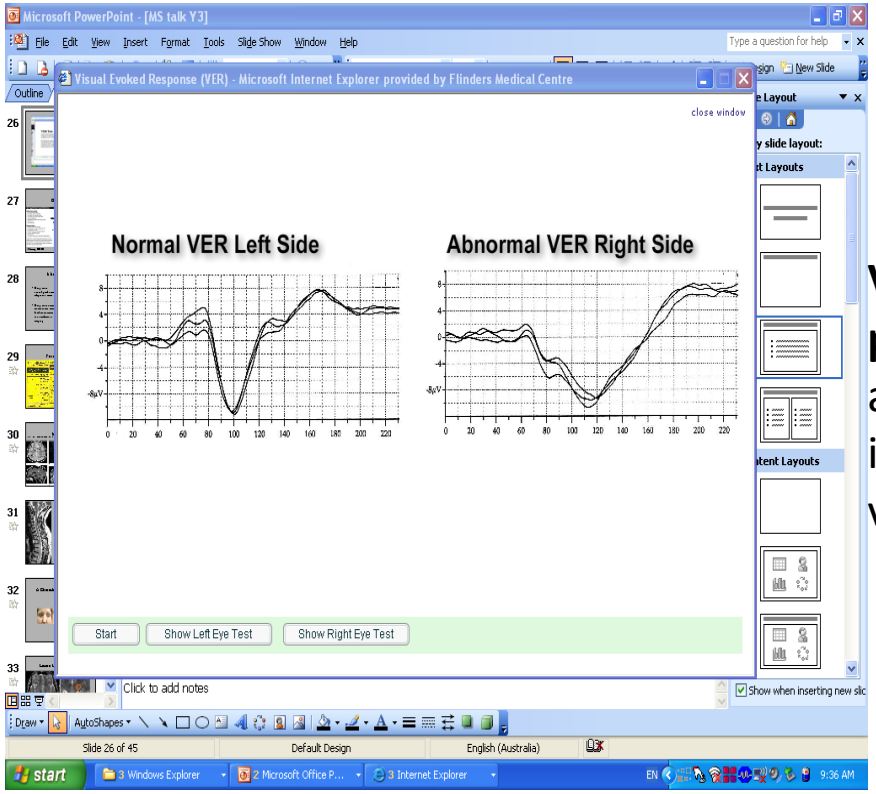






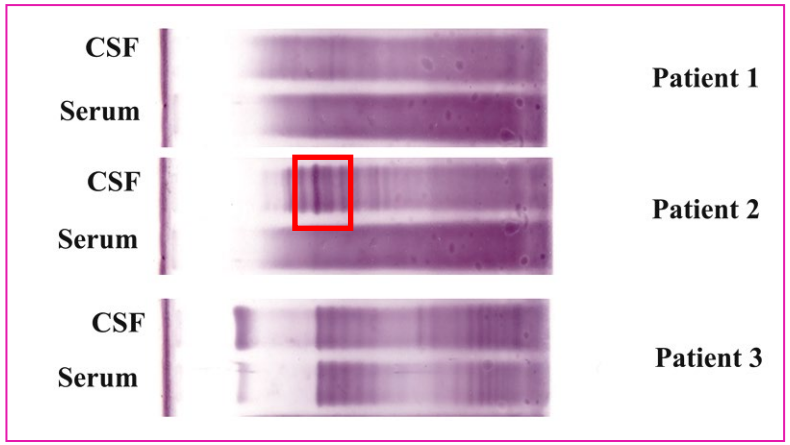
CSF Oligoclonal IgG bands via Lumbar puncture

Courtesy D. Beroukas, FMC Immunology



Visual evoked potentials – assessment of integrity of anterior visual pathways

Mythbusting about
CSF oligoclonal IgG bands and MS



CSF Oligoclonal IgG bands via Lumbar puncture

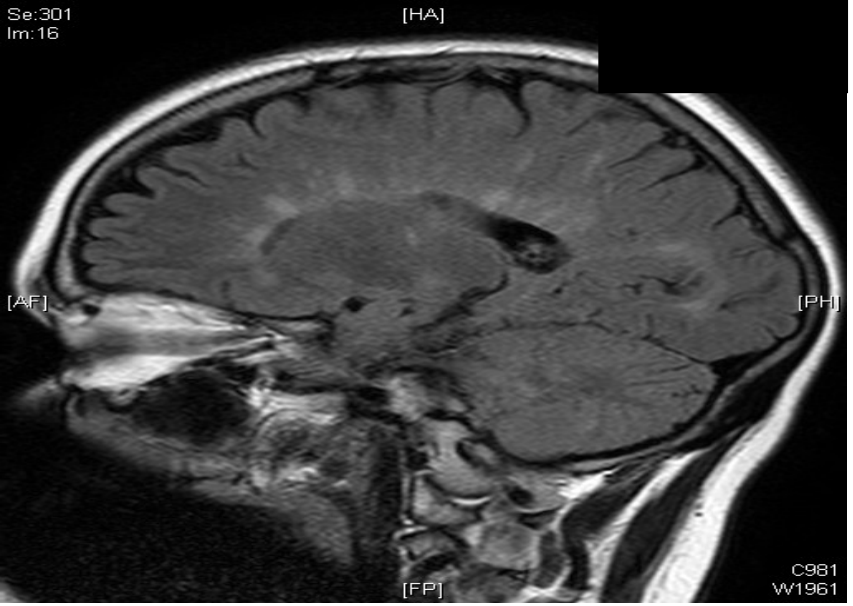
MS-typical CSF

- Mild to moderate increase in CSF mononuclear cells (0-approx. 30mm3)
- Protein usually normal
- CSF-restricted oligoclonal Immunoglobulin bands NOT seen in serum

MS-typical CSF is supportive of a diagnosis of MS but NOT DIAGNOSTIC

- Can be seen in other non-MS inflammatory CNS disease
- Can be absent and the diagnosis still be MS

LP usually undertaken when the clinical and MRI features of the disease are atypical for MS



Are multifocal cerebral white matter lesions specific for MS?

No. The criteria below relate to the 2018 McDonald MRI criteria for MS…..

Dissemination in space

Dissemination in space requires ≥1 T2-hyperintense lesions (≥3 mm in long axis), symptomatic and/or asymptomatic, that are characteristic of multiple sclerosis in two or more of the four following locations [5]:

- periventricular (≥1 lesion, unless the patient is over the age of 50 in which case it is advised to seek a higher number of lesions)
- cortical or juxtacortical (≥1 lesion)
- infratentorial (≥1 lesion)
- spinal cord (≥1 lesion)

Notably, T2-hyperintense lesions of the optic nerve, such as those in a patient presenting with optic neuritis, cannot be used in fulfilling the 2017 revised McDonald criteria [5].

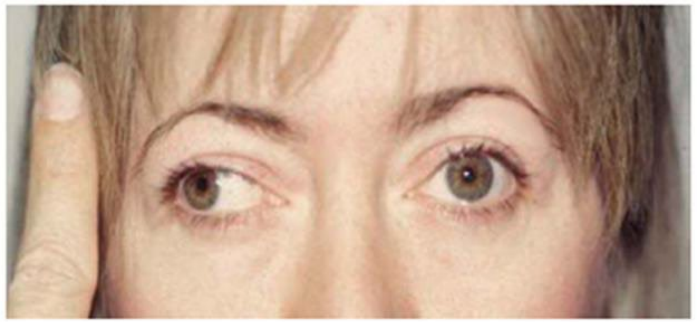
Dissemination in time

Dissemination in time can be established in one of two ways [5]:

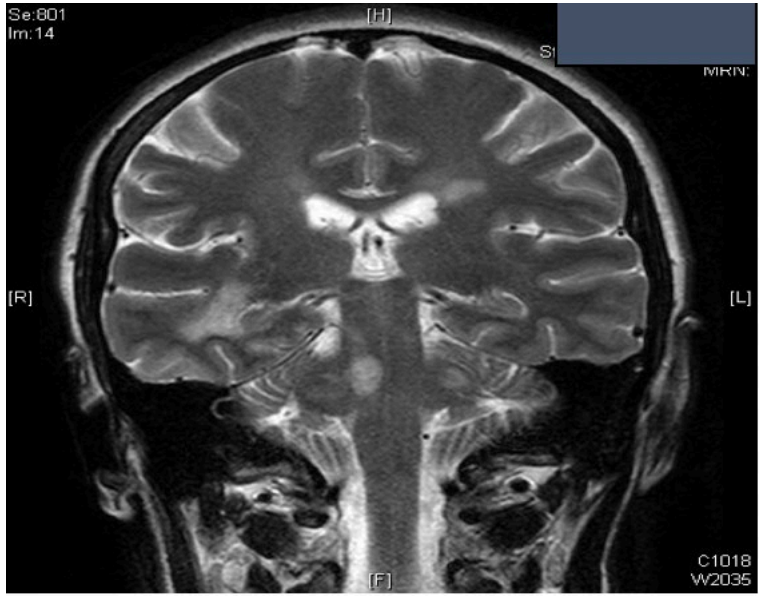
- a new T2-hyperintense or gadolinium-enhancing lesion when compared to a previous baseline MRI scan (irrespective of timing)
- simultaneous presence of a gadolinium-enhancing lesion and a non-enhancing T2-hyperintense lesion on any one MRI scan

However, when radiologically there are multifocal T2 hyperintensities on cerebral MRI many reporting radiologists will include MS in the differential, which is a VERY wide differential and requires careful clinical context.

Total disease burden = clinical events (relapses) + MRI evident events. Relapses are ”tip of the iceberg”.



“Clinical relapse”

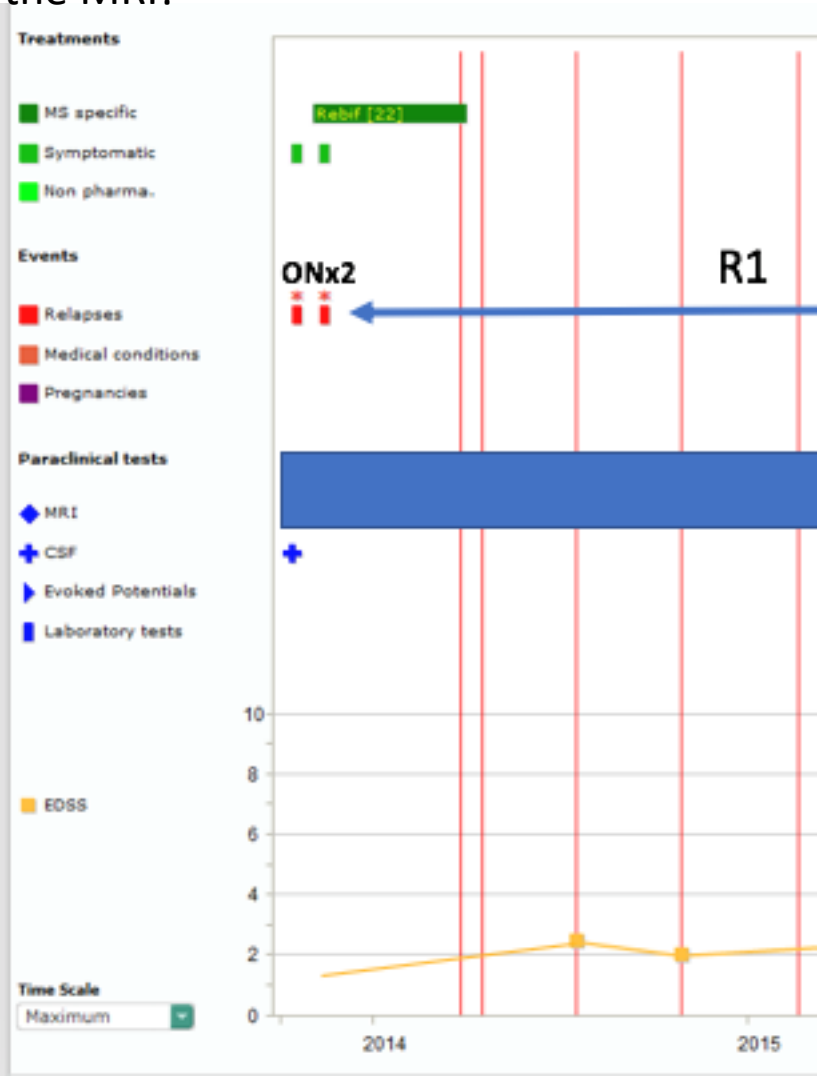


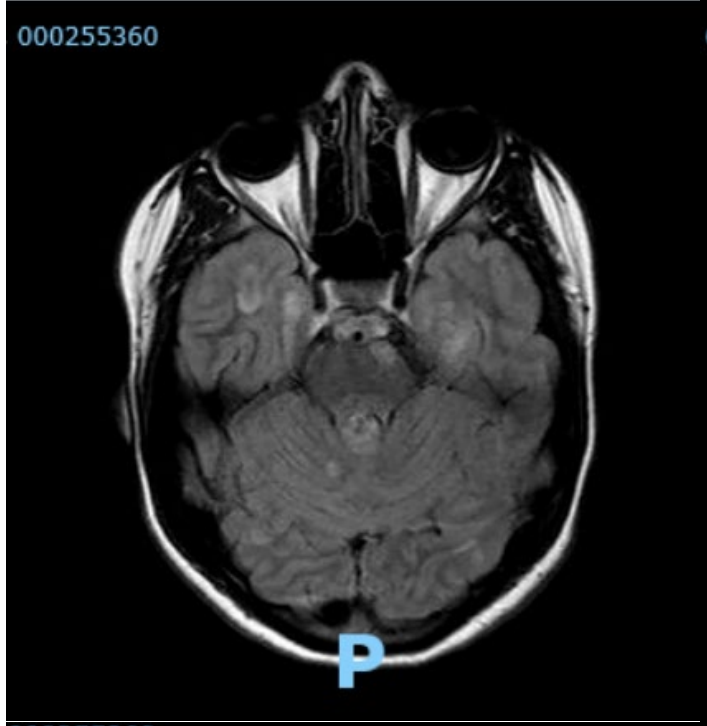
“MRI relapse”
= new spot visible on MRI but no
New symptoms

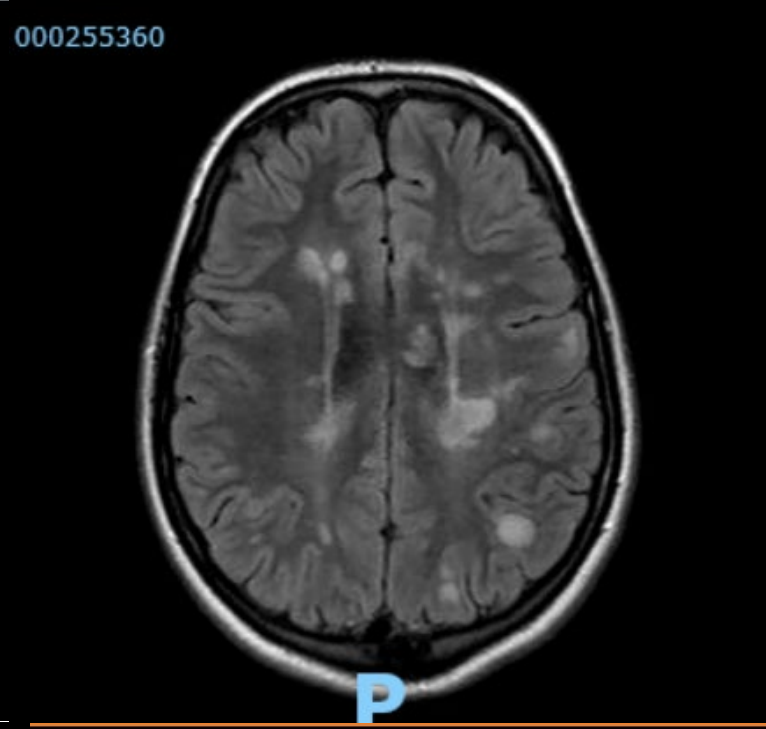
The majority of the inflammatory burden of the disease is subclinical such that the ratio of MRI lesions to clinical relapses is about 10:1

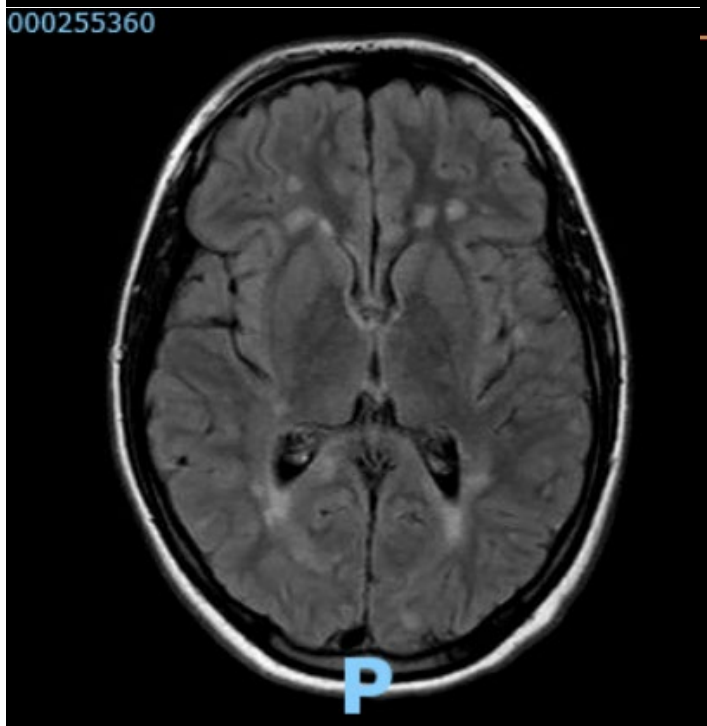
Most of the disease is SUBCLINICAL

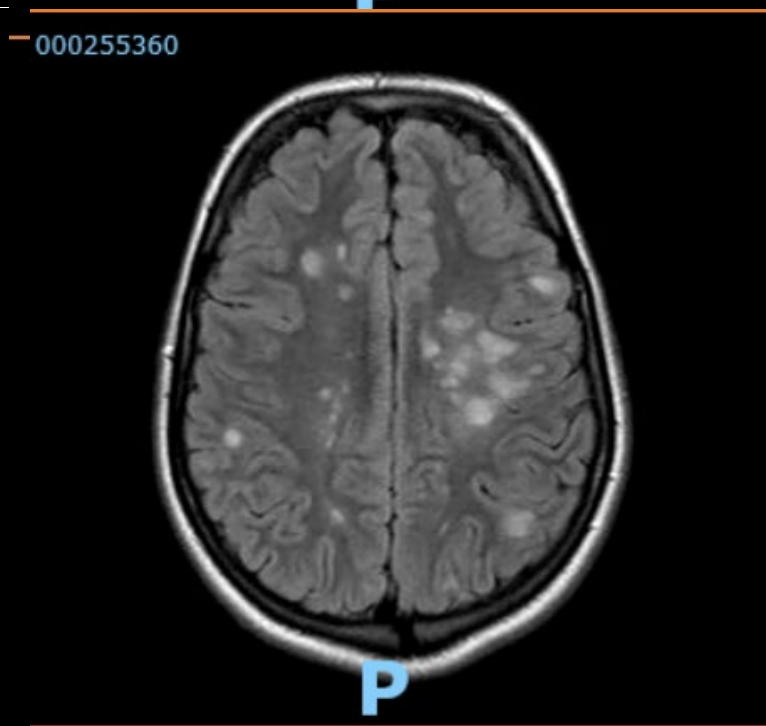
14F, 2 x optic neuritis evident clinically
Look at the MRI!



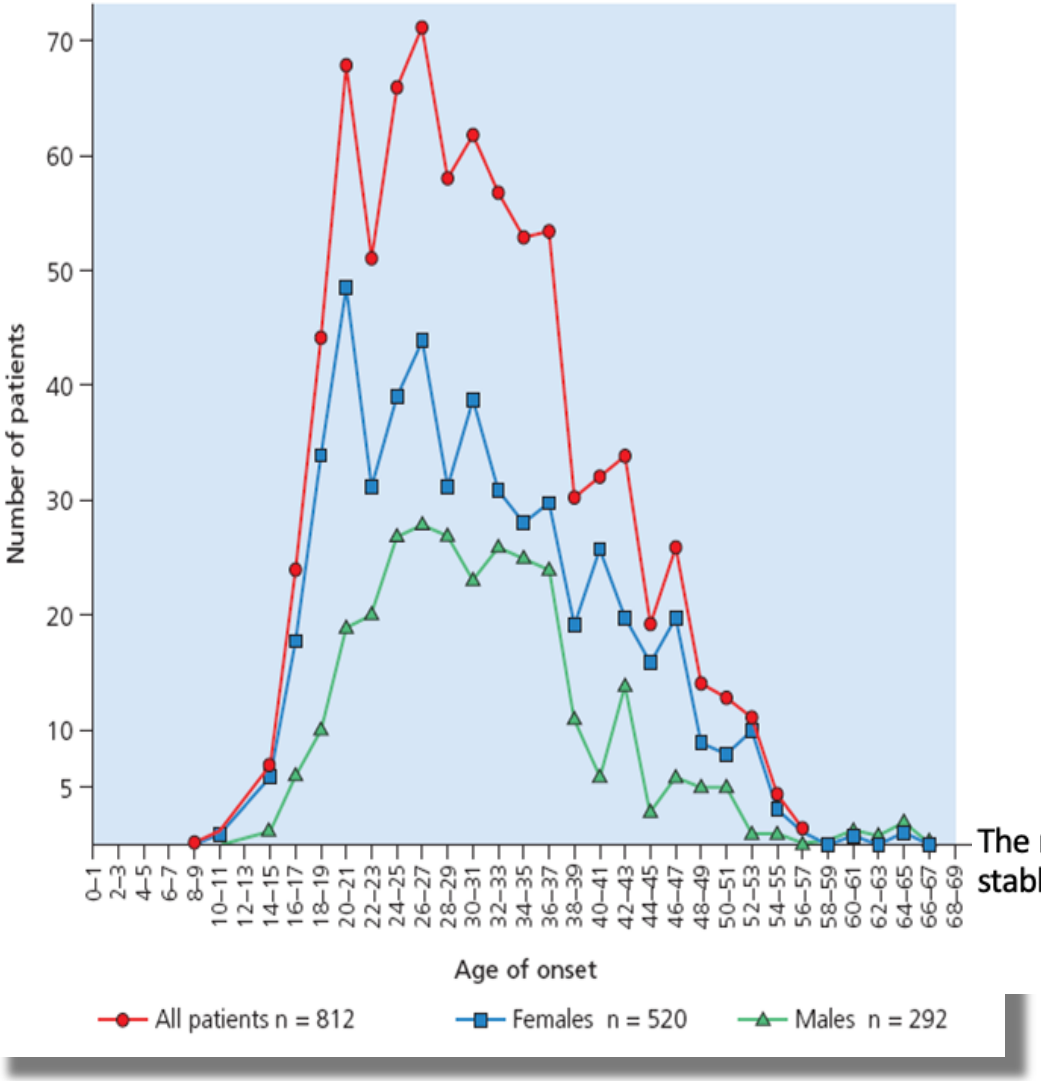




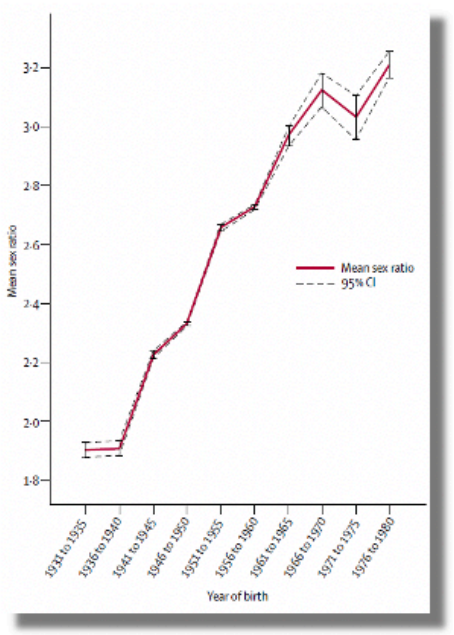


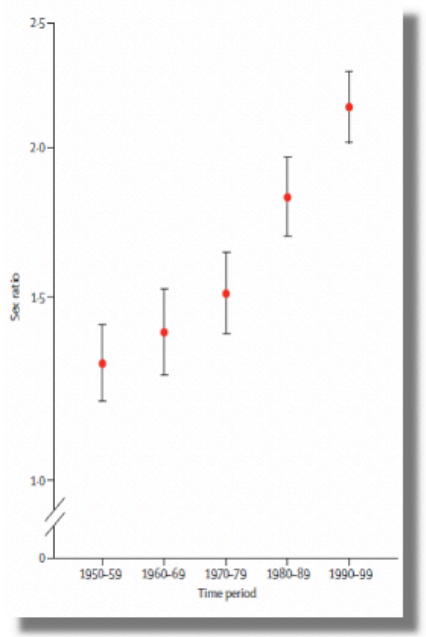


Age of onset



Gender ratios



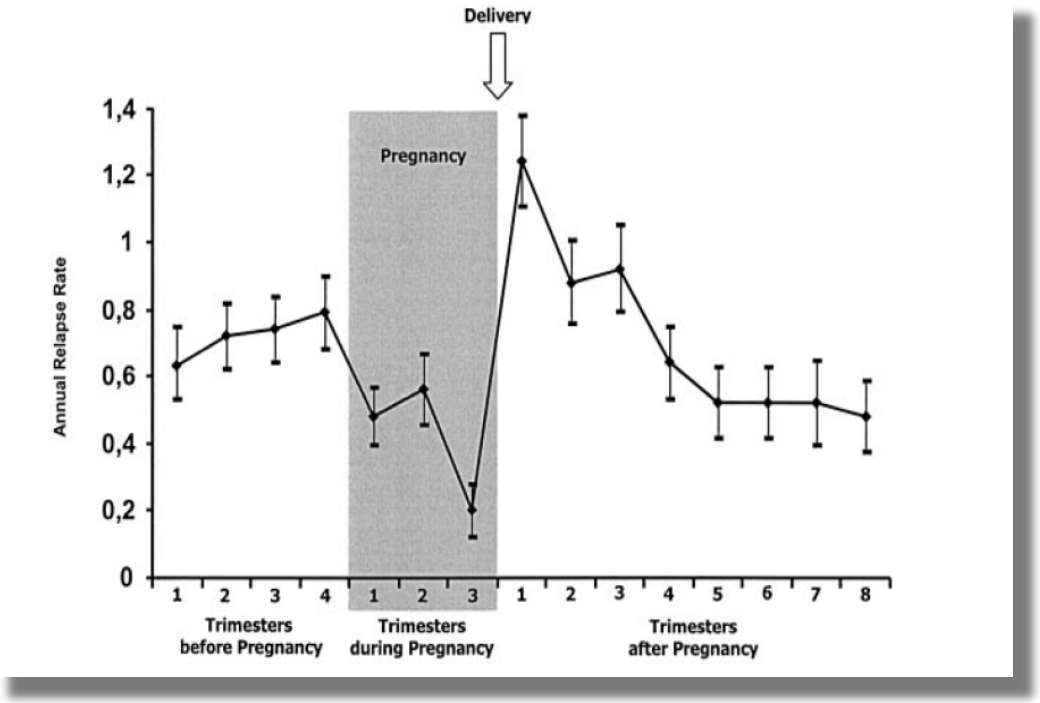


The rate of MS in females is increasing rapidly while the male rate of MS has remained stable.

Orton et al, 2006; Koch-Henriksen and Sorenson 2010

Peak age of MS onset is between 20-40 years. Paty and Ebers, 1998

Pregnancy and MS



1. The relapse rate drops during the 2nd and 3rd trimester and rebounds post-partum.
2. We think this relates to the state or relative immunosuppression that occurs in pregnancy that is good for MS.
3. There is a suggestion that multiparous woman have a better long-term prognosis than nulliparous woman.

Vukusic et al, 2004

Are MS patients at risk of other autoimmune diseases?

	Female			Male		
	MS probands (n=3733)	Spousal controls (n=771)	p	MS probands (n=1298)	Spousal controls (n=1936)	p
Type 1 diabetes	14 (0·4%)	5 (0·6%)	0·28	5 (0·4%)	9 (0·5%)	0·35
Rheumatoid arthritis	123 (3·3%)	29 (3·8%)	0·51	30 (2·3%)	37 (1·9%)	0·43
Ulcerative colitis	6 (0·2%)	2 (0·3%)	0·55	3 (0·2%)	2 (0·1%)	0·37
Crohn's disease	10 (0·3%)	2 (0·3%)	0·97	1 (0·1%)	2 (0·1%)	0·81
Pernicious anaemia	115 (3·1%)	14 (1·8%)	0·06	8 (0·6%)	11 (0·6%)	0·86
Autoimmune thyroid disease	363 (9·7%)	74 (9·6%)	0·92	32 (2·5%)	42 (2·2%)	0·58
Systemic lupus erythematosus	27 (0·7%)	5 (0·7%)	0·82	1 (0·8%)	2 (1·0%)	0·82
Vitiligo	32 (0·9%)	5 (0·7%)	0·56	3 (0·2%)	7 (0·4%)	0·51
Myasthenia gravis	5 (0·1%)	1 (0·1%)	0·98	2 (0·1%)	2 (0·1%)	0·69
Psoriasis	220 (5·9%)	43 (5·6%)	0·73	73 (5·6%)	103 (5·3%)	0·72

Table 5: Occurrence of autoimmune diseases in sex-stratified MS probands and controls

Contrary to the current dogma in many textbooks, people with MS don't appear to be at increased risk of other autoimmune diseases.

Ramagopalan et al, 2007

Key elements in diagnosis of MS

- 2 or more clinical events consistent with inflammatory central nervous system disease
  - But in some can be diagnosed after 1st event – the "clinically isolated syndrome" (enhancing and non-enhancing disease on baseline MRI) or presence of OCB
- Events separated in time and in space in the CNS
- For which no better explanation exists
- Supported usually by paraclinical (MRI/spinal fluid testing) evidence of immune CNS dysfunction

Clinical Presentation - symptoms & signs

- **Motor** - spasticity, weakness and gait abnormalities.
- **Sensory** - positive (pins & needles) and negative sensory phenomena (loss of sensation).
- **Cerebellum** - inco-ordination and unsteady gait.
- **Brain Stem** - diplopia, vertigo, nystagmus, dysarthria
- **Optic Nerves** - optic neuritis (blurred vision)
- **Bladder and Bowel** - incontinence
- **Higher Functions** - depression, poor concentration, forgetfulness, etc.
- **Fatigue**

Common initial presentations in MS

Table 4.8 Distribution of patients (%) by initial symptoms according to the initial course of multiple sclerosis, among 574 patients. Adapted from Riise *et al* (1992)

	Initial course of multiple sclerosis	
	Relapsing–remitting	Progressive
Pyramidal	32	54
Cerebellar	16	23
Brainstem	24	7
Sensory	48	32
Visual	26	17

Compston et al, 2005

Table 5. Initial Signs and Symptoms of MS *

Common
- weakness in one or more limbs (40%)
- monocular visual changes suggestive of optic neuritis (22%)
- paresthesias (21%)
- diplopia (12%)

Less Common (< 5%)
- vertigo
- micturation or bowel disturbance
- Lhermitte's sign
- trigeminal neuralgia
- paroxysmal symptoms
- dysarthria
- ataxia

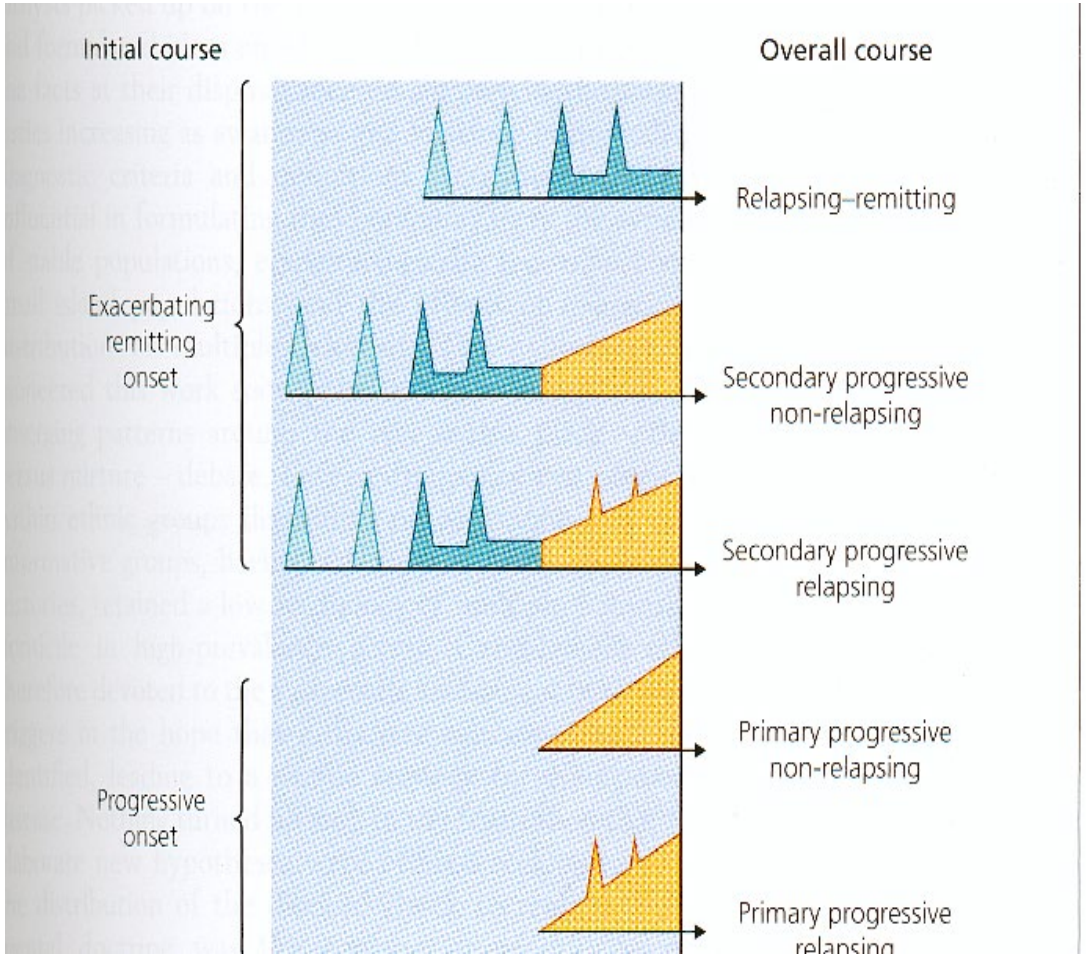
Uncommon (at onset)
- pain
- sexual dysfunction
- cognitive dysfunction
- movement disorder

* Frequencies are approximate and depend on the population under study. (11)

Fleming JO, 2000

Overall disease course

- 80+ % will have initial attacks and little initial residual disability
  - "relapsing remitting MS"
- Nearly all of these people lose relapses over time and accumulate disability slowly
  - "secondary progressive MS"
- 5-10% have no/few attacks but just accumulate disability from onset
  - "primary progressive MS"
  - Often initially presents later in life than relapsing remitting MS



A little-bit about susceptibility….

Genetics 101: Blame your parents

LIFE TIME RISK OF HAVING MS

- No family history of MS - 1%
- 1 parent with MS - 10%
- 2 parents with MS - 20%
- Sibling with MS - 3%
- Identical twin with MS - 30%
- MRI concordance in identical twins 70%

Figures courtesy of Dr Helmut Butzkeuven, RMH

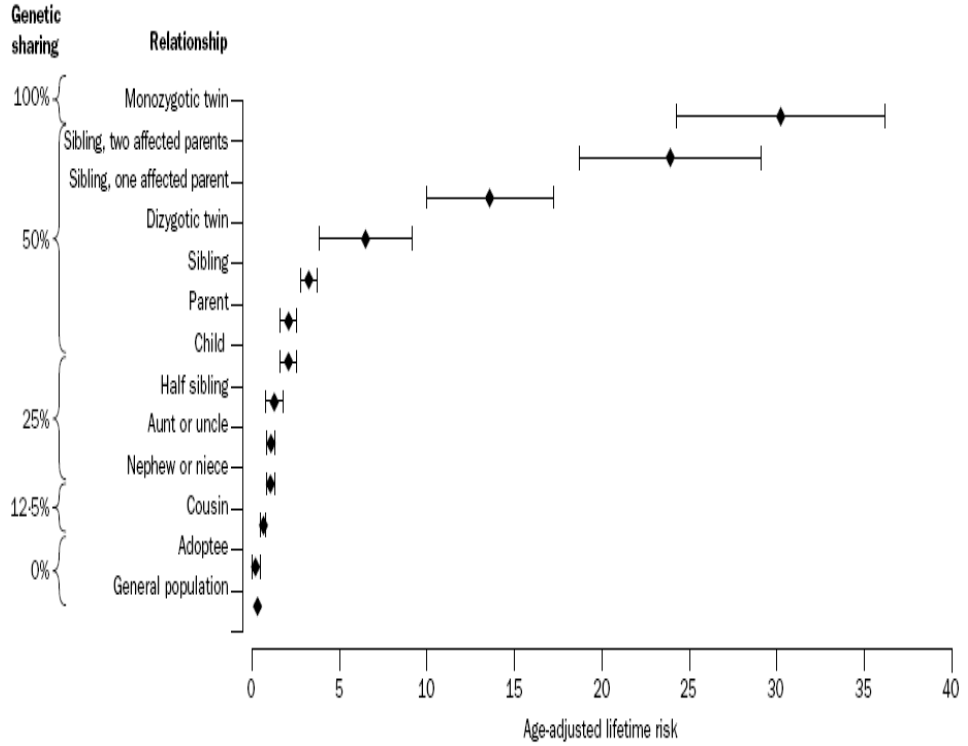
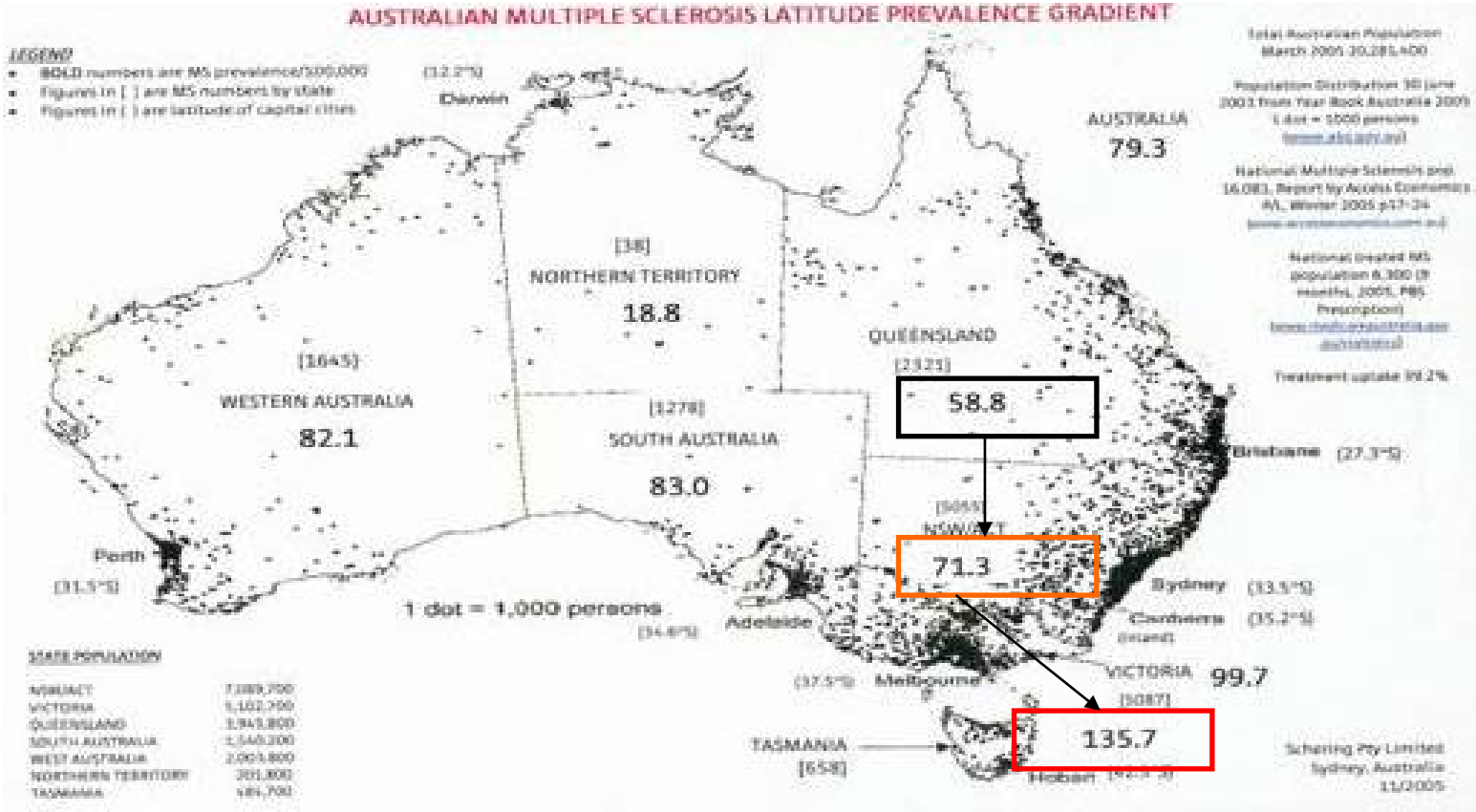


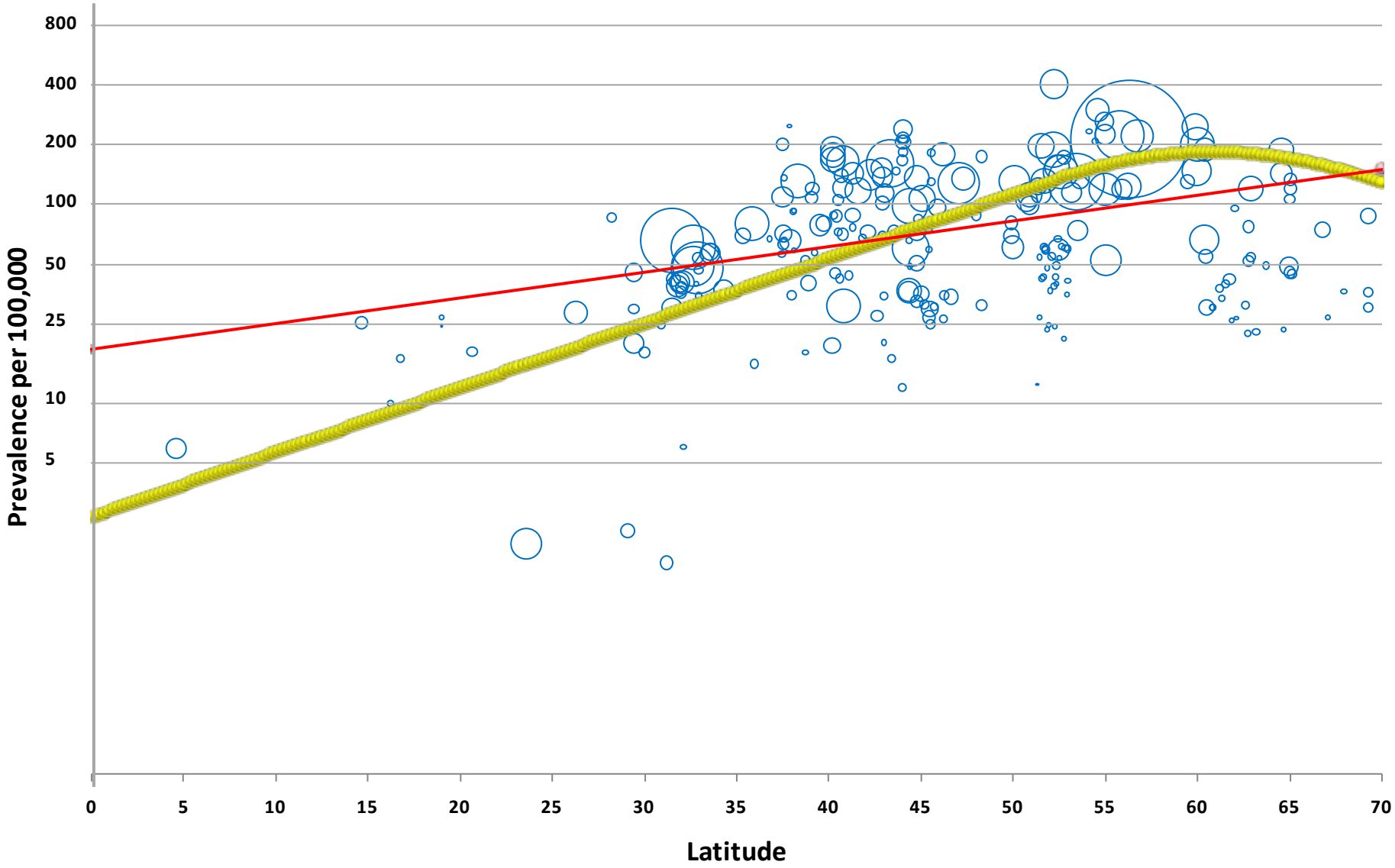
Table courtesy of A/Prof Simon Broadley

Don’t blame your parents. The problem is where you live: MS prevalence in Australia per 100,000 people



Courtesy Peter Klein, Schering

World MS Latitudinal Gradient



Season of Birth Patterns

Northern Hemisphere

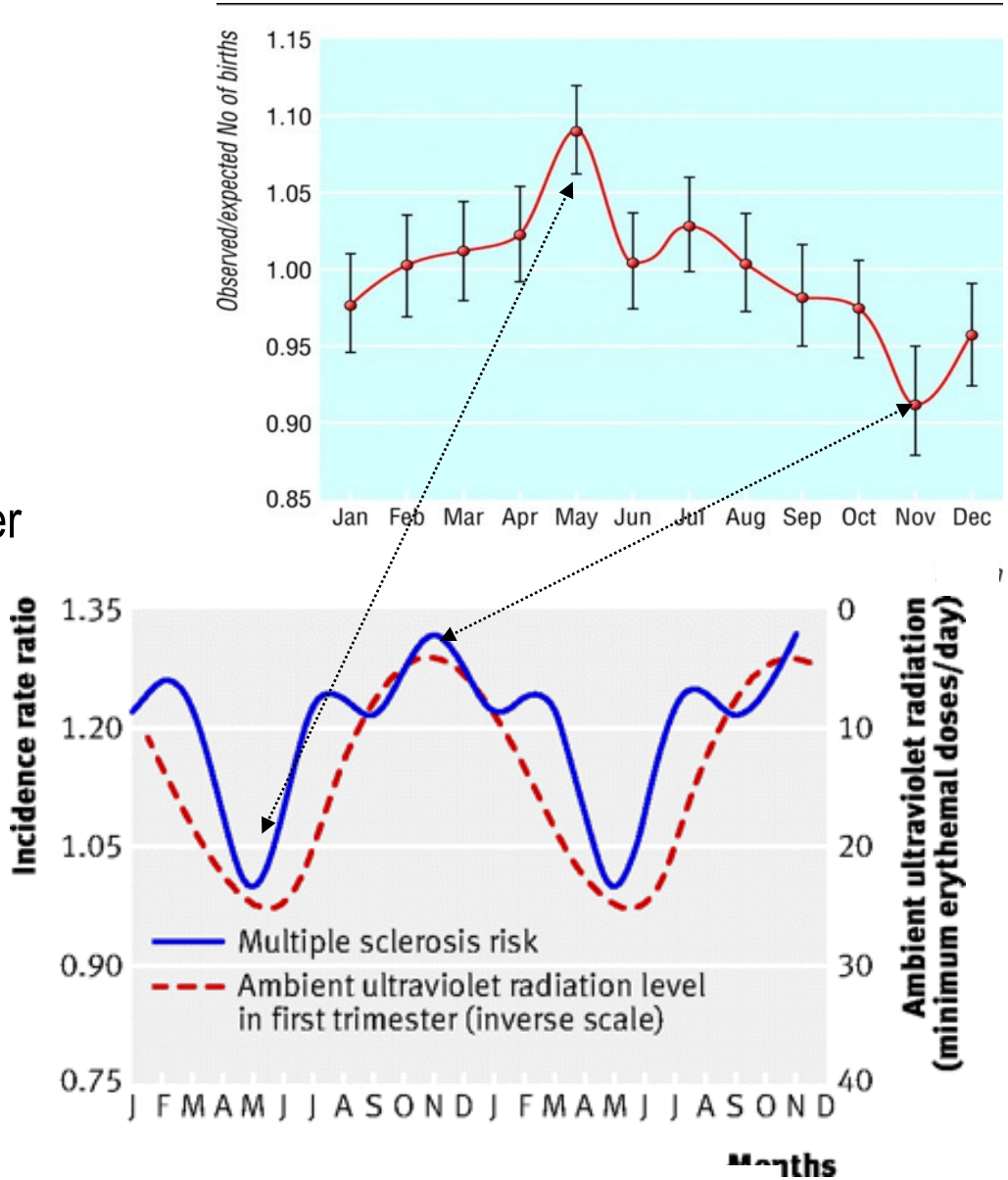
Pooled analysis for Canadian, British, Danish and Swedish studies (n=42,000)

- Excess births in May
- Deficit in November
- Possible stronger effect at higher latitude

Australia

People with MS born 1920-50

- Excess births in Nov
- Deficit in May
- Mimics a lagged UV pattern



Slide courtesy of Professor Bruce Taylor, Menzies

Willer et al BMJ 2005;330(7483):120. Staples et al BMJ 2010; 340:1640

VITAMIN D

Nurses Health Study data

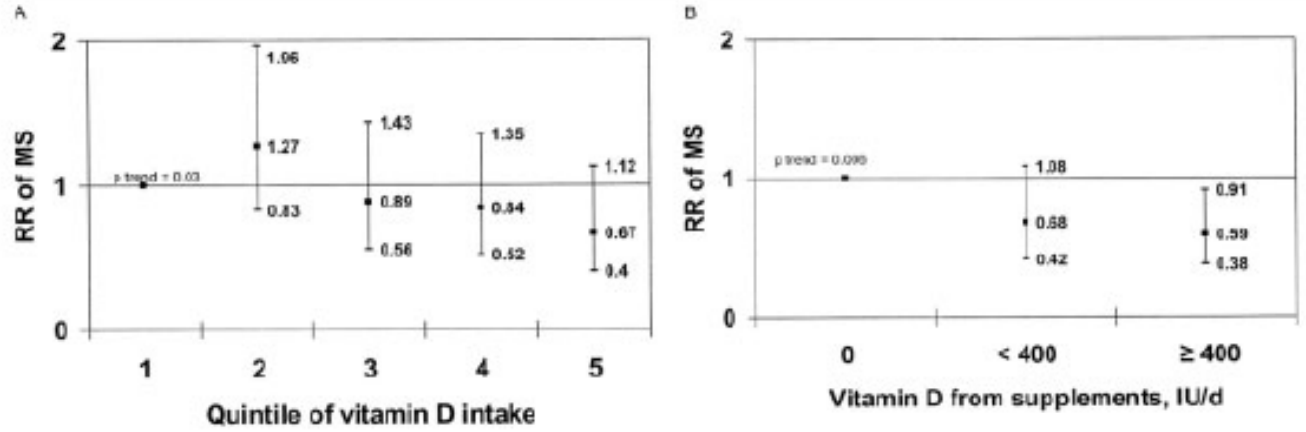
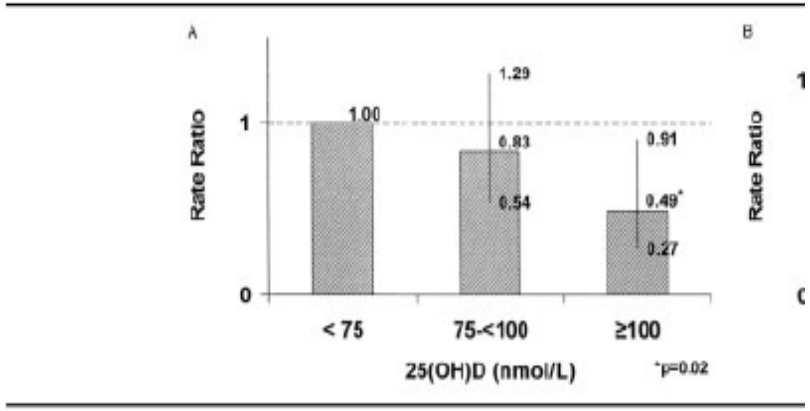


Fig 2. (A) Relative risk (RR) of multiple sclerosis (MS) according to vitamin D intake. p *for trend = 0.03. (B) Relative risk of MS according to use of vitamin D supplements.* p *for trend = 0.006. Data from Munger and colleagues.*[29]

US defence Sera repository data



Among whites, there was a 41% decrease in MS risk for every 50nmol/L increase in 25(OH)D (RR, 0.59; 95% CI, 0.36–0.97; *p* 0.04).

In categoric analyses, risk for MS was 51% less among individuals with 25(OH)D 100nmol/L as compared with those less than 75nmol/L (Fig on left).

The infectious and non-infectious candidates
Choose carefully who you kiss, *and* when you kiss them

- Strongest association found so far is for EBV
    - About 100% of persons with MS show evidence of prior EBV infection compared with 90% of the population

- Infectious mononucleosis (glandular fever) after age 18 carries a relative risk for MS of **7.9** (CI 2-38)

Martyn et al 1993

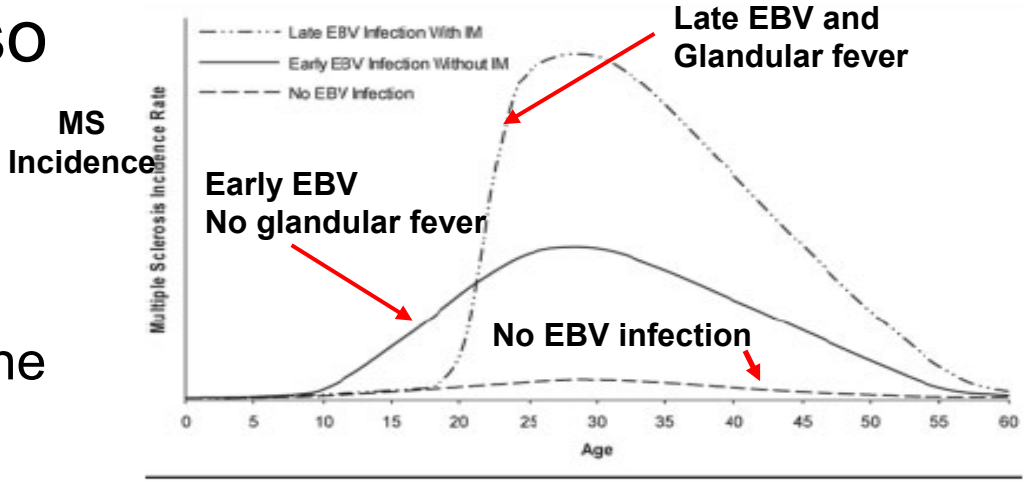


Fig 2. Schematic representation of multiple sclerosis incidence according to Epstein–Barr virus infection. Reprinted with permission from Thacker and colleagues.[54]

From Ascerio, 2007

Epstein-Barr Virus and Multiple Sclerosis

Evidence of Association From a Prospective Study With Long-term Follow-up

Gerald N. DeLorenze, PhD; Kassandra L. Munger, MSc; Evelyn T. Lennette, PhD; Norman Orentreich, MD; Joseph H. Vogelman, DEE; Alberto Ascherio, MD, DrPH

Arch Neurol. 2006;63:839-844

doi:10.1093/brain/awt139 Brain 2013: 136; 2298–2304 | 2298

BRAIN
A JOURNAL OF NEUROLOGY

Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study

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Tobacco smoking has been linked to an increased risk of multiple sclerosis. However, to date, results from the few studies on the impact of smoking on the progression of disability are conflicting. The aim of this study was to investigate the effects of smoking on disability progression and disease severity in a cohort of patients with clinically definite multiple sclerosis. We analysed data from 895 patients (270 male, 625 female), mean age 49 years with mean disease duration 17 years. Forty-nine per cent of the patients were regular smokers at the time of disease onset or at diagnosis (ever-smokers). Average disease severity as measured by multiple sclerosis severity score was greater in ever-smokers, by 0.68 (95% confidence interval: 0.36–1.01). The risk of reaching Expanded Di[illegible]ility Status Scale score milestones of 4 and 6 in ever-smokers compared to never-smokers was 1.34 (95% confidence interva[illegible]12–1.60) and 1.25 (95% confidence interval: 1.02–1.51) respectively. Current smokers showed 1.64 (95% confidence interv[illegible].33–2.02) and 1.49 (95% confidence interval: 1.18–1.86) times higher risk of reaching Expanded Disability Status Sca[illegible]cores 4 and 6 compared with non-smokers. Ex-smokers who stopped smoking either before or after the onset of the [illegible]ase had a significantly lower risk of reaching Expanded Disability Status Scale scores 4 (hazard ratio: 0.65, confidence in[illegible]l: 0.50–0.83) and 6 (hazard ratio: 0.69, confidence interval: 0.53–0.90) than current smokers, and there was no sig[illegible]t difference between ex-smokers and non-smokers in terms of time to Expanded Disability Status Scale scores 4 or 6. Our data suggest that regular smoking is associated with more severe disease and faster disability progression. In addition, smoking cessation, whether before or after onset of the disease, is associated with a slower progression of disability.

Smoking: effects on multiple sclerosis susceptibility and disease progression

Dean M. Wingerchuk

Ther Adv Neurol Disord
(2012) 5(1) 13–22
DOI: 10.1177/1756285611425694

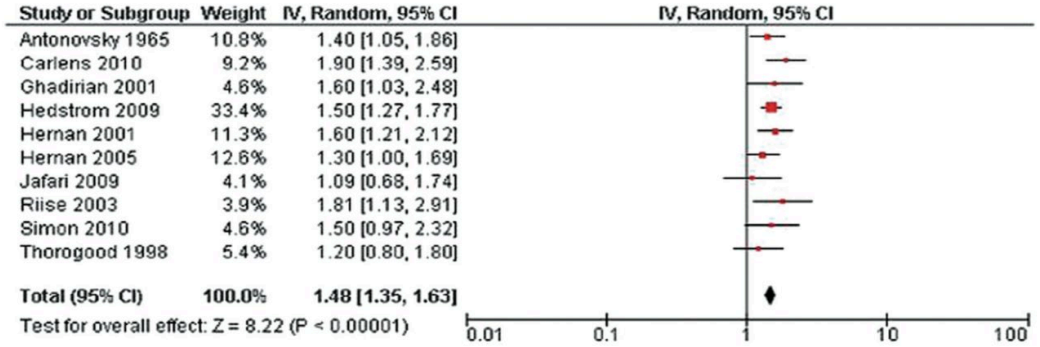
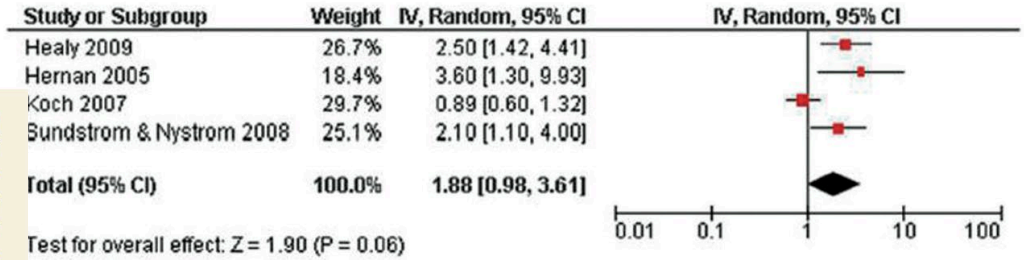


Figure 1. Forest plot of 10 studies included in conservative model meta-analysis of smoking and multiple sclerosis risk [Handel *et al.* 2011].



re 2. Forest plot of four studies included in a meta-analysis of smoking and the risk of secondary progres- multiple sclerosis [Handel *et al.* 2011].

Ann Neurol. 2017 Oct;82(4):554-561. doi: 10.1002/ana.25036. Epub 2017 Sep 25.

Concussion in adolescence and risk of multiple sclerosis.

Montgomery S[1,2,3], Hiyoshi A[1], Burkill S[2,4], Alfredsson L[5,6], Bahmanyar S[2,4], Olsson T[7].

Author information

Abstract

OBJECTIVE: To assess whether concussion in childhood or adolescence is associated with subsequent multiple sclerosis (MS) risk. Previous research suggests an association, but methodological limitations included retrospective data collection and small study populations.

METHODS: The national Swedish Patient Register (hospital diagnoses) and MS Register were used to identify all MS diagnoses up to 2012 among people born since 1964, when the Patient Register was established. The 7,292 patients with MS were matched individually with 10 people without MS by sex, year of birth, age/vital status at MS diagnosis, and region of residence (county), resulting in a study population of 80,212. Diagnoses of concussion and control diagnoses of broken limb bones were identified using the Patient Register from birth to age 10 years or from age 11 to 20 years. Conditional logistic regression was used to examine associations with MS.

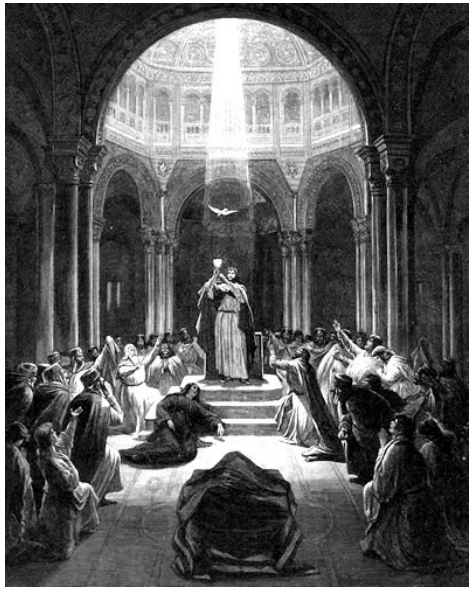
RESULTS: Concussion in adolescence was associated with a raised risk of MS, producing adjusted odds ratios (95% confidence intervals) of 1.22 (1.05-1.42, p = 0.008) and 2.33 (1.35-4.04, p = 0.002) for 1 diagnosis of concussion and >1 diagnosis of concussion, respectively, compared with none. No notable association with MS was observed for concussion in childhood, or broken limb bones in childhood and adolescence.

INTERPRETATION: Head trauma in adolescence, particularly if repeated, is associated with a raised risk of future MS, possibly due to initiation of an autoimmune process in the central nervous system. This further emphasizes the importance of protecting young people from head injuries. Ann Neurol 2017;82:554-561.

PMID: 28869671 DOI: 10.1002/ana.25036

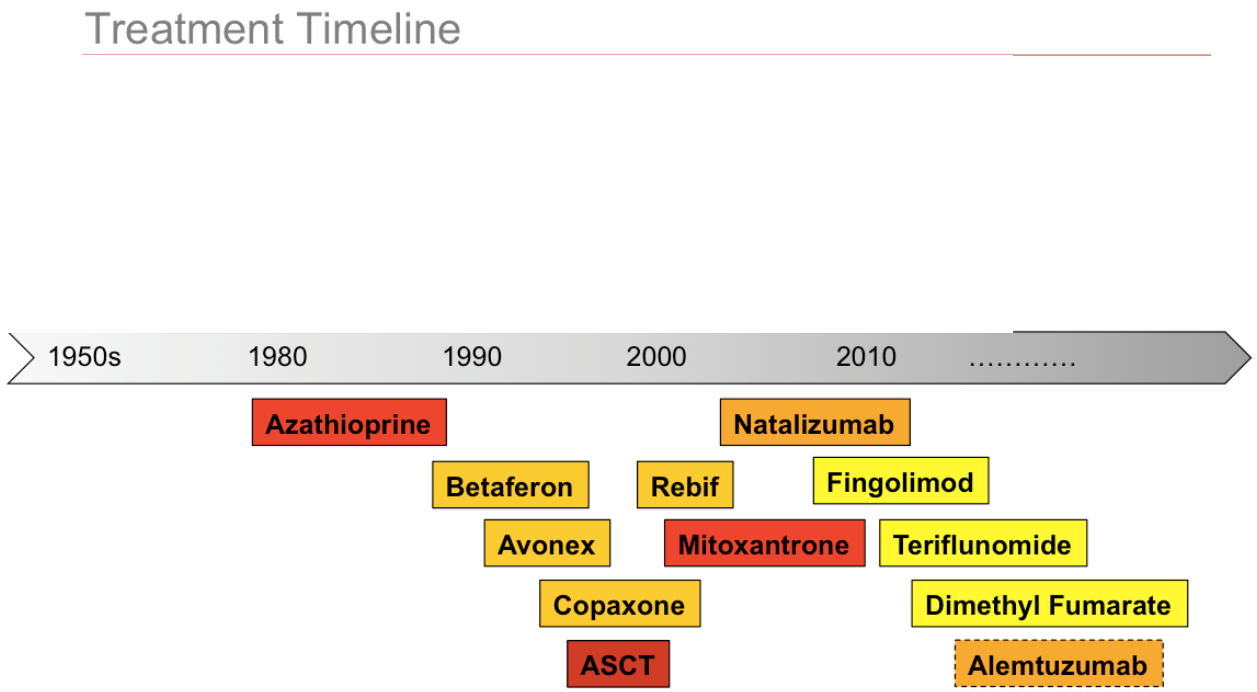
[Indexed for MEDLINE]

MS therapeutics



- Prevent the disease (watch this space)
- Reduce number of attacks/relapses and their related problems
  - yes
- Reduce (delay) disability progression
  - Yes
- Reduce symptom burden (pharmacologic/nonpharmacologic), facilitate independence
- Manage co-morbidities actively

Adult approved RRMS immunotherapy PBS to 2021 – it is a busy timeline

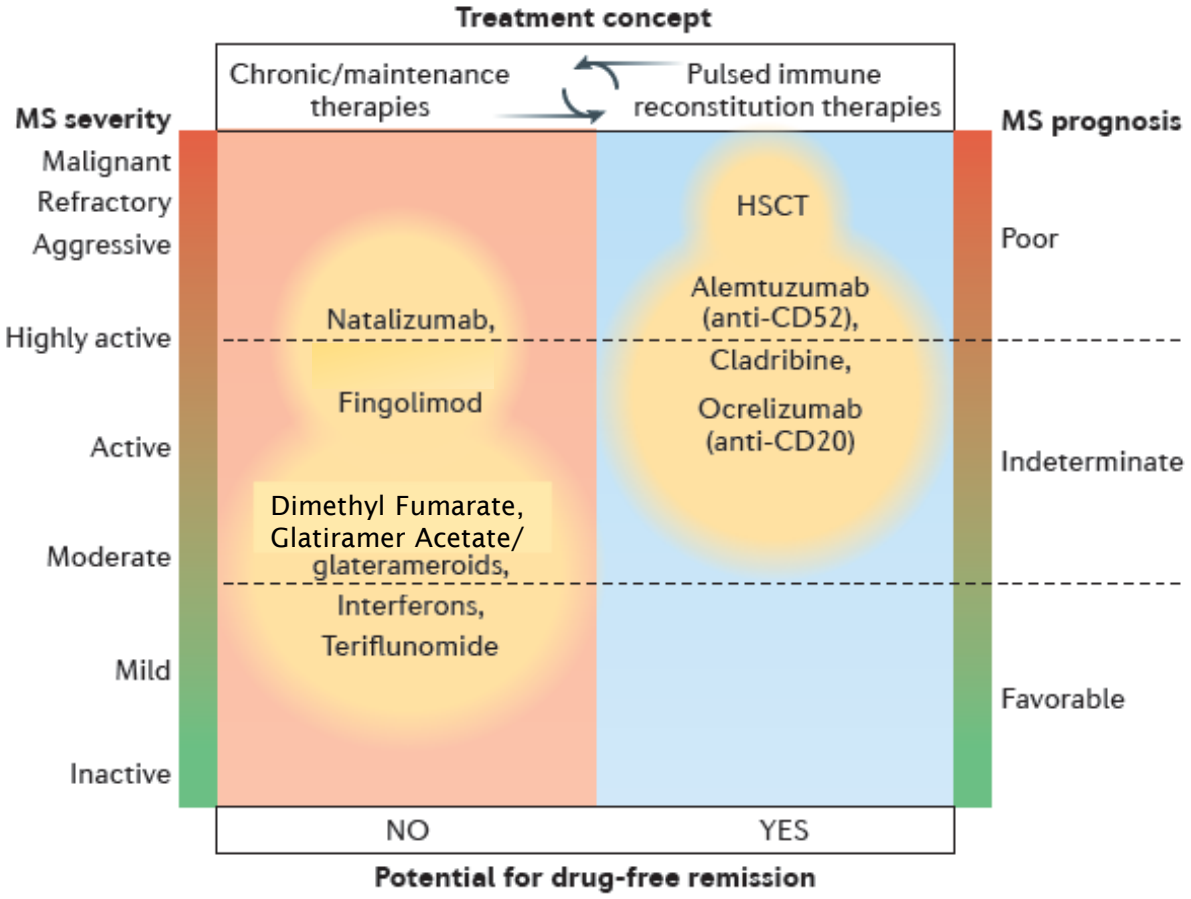


+Daclizumab 2016 (withdrawn)
+Ocrelizumab 2018
+Cladribine 2018
+Siponimod 2019
+Ofatumumab 2021

All reduce relapse rates, MRI evidence of inflammation and clinical evidence of disability progression.

MP = methylprednisolone (strong steroid)

Treatment Concepts in MS



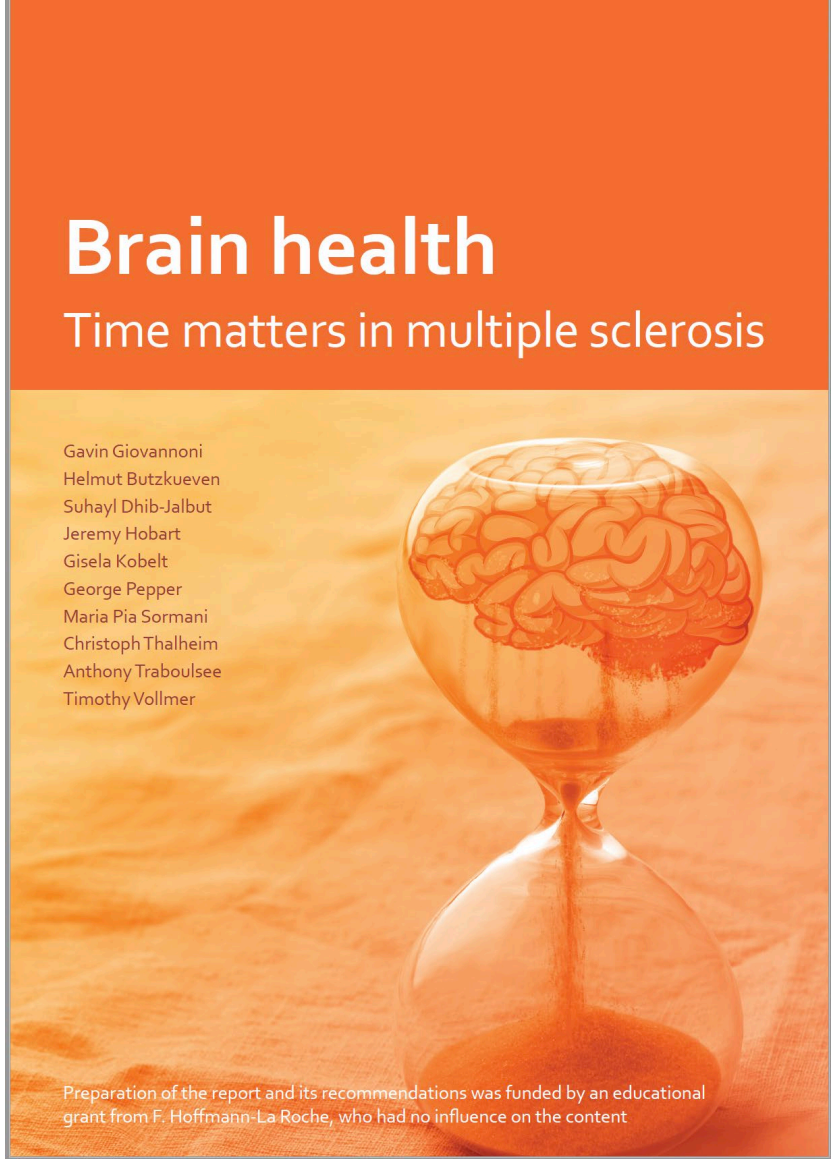
H Wiendl Nat Rev 2017

Timely accurate diagnosis

Education +++, person, family

Evidence based DMT if
disease active or poor prognostic factors

”Brain health”
Ageing with MS
Cognitive health
Mental health
Social Health
Active comorbidity mgt
Minimise CNS toxins (tobacco/alc)
Exercise, Exercise, Exercise



https://www.msbrainhealth.org/recommendations/brain-health-report/

Other slides that might be helpful:

So, in early active RRMS, what is our therapeutic goal?

No evidence of disease activity: (NEDA)

No clinically evident relapses
No clinical examination change
No MRI evidence of inflammatory disease activity

Can we achieve this in many/most newly diagnosed active RRMS pts: Yes.

Neurology® Clinical Practice

Use of B-Cell–Depleting Therapy in Women of Childbearing Potential With Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder

Alexandra Galati, Thomas McElrath and Riley Bove

Neurol Clin Pract published online January 6, 2022
DOI 10.1212/CPJ.0000000000001147

B cell depleting therapies are large IgG1 monoclonal antibodies which are minimally transferred across the placenta. Maternal transfer of immunoglobulin is negligible during the first trimester throughout organogenesis, whereas highest exposure occurs after week 32, during fetal growth.

Concentration of anti-CD20 and anti-CD19 antibodies is low in breastmilk, well under the acceptable relative infant dose. Use of these therapies can be considered in the breastfeeding mother.

Treatment of Women with Multiple Sclerosis Planning Pregnancy

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Vilija Jokubaitis, PhD[5,6]
Kerstin Hellwig, MD[7]

Curr Treat Options Neurol (2021) 23:11
DOI 10.1007/s11940-021-00666-4

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Mastura Monif[1,2]
Wei Yeh[1,2]
Julia ML Brotherton[3,4]
Stephen Reddel[5]
Anneke Van Der Walt[1,2]

Perspectives

Vaccinations in patients with multiple sclerosis: review and recommendations

In a new MS diagnosis, immunisation status may be overlooked — careful planning from early in the treatment course is key

MJA May 2021

Comprehensive review of vaccination in MS and MS therapy

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doi: 10.5694/mja2.51012

Management of Multiple Sclerosis Symptoms and Comorbidities

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

By W. Oliver Tobin, MBBCh, BAO, PhD

TABLE 9-1 Common Comorbidities and Their Impact on the Diagnosis and Disease Course of Multiple Sclerosis

Comorbidity	Increases the Risk of Developing Clinically Isolated Syndrome/ Multiple Sclerosis	Increases the Risk of Diagnostic Delay	Increases the Risk of Multiple Sclerosis Relapse	Increases the Risk of Disability
Depression		X		X
Anxiety		X		X
Hypertension		X		X
Migraine			X	
Hyperlipidemia			X	
Ischemic heart disease		X		X
Cerebrovascular disease		X		X
Obesity	X	X		X
Multimorbidity (≥3 comorbidities)		X	X	X

TABLE 9-2 Symptomatic Management of Multiple Sclerosis

Symptom	Description	Treatments
Fatigue	Multifactorial Most common symptom in patients with multiple sclerosis (MS) 80% lifetime prevalence	Limit sedating medications Screen for and treat depression, obesity, obstructive sleep apnea Energy conservation measures Prescribe a regular exercise regimen
Depression	30% point prevalence Associated with higher Expanded Disability Status Scale (EDSS) score and anxiety Screen with Beck Depression Inventory, Patient Health Questionnaire-2, or Patient Health Questionnaire-4	Evaluate all patients with a positive screen for depression Treat with cognitive-behavioral therapy, selective serotonin reuptake inhibitor (SSRI), or serotonin norepinephrine reuptake inhibitor (SNRI) Choose treatment strategy depending on depression severity and side effect profile
Pseudobulbar affect	Involuntary crying or laughing that is often disproportionate or inappropriate to the social context	Dextromethorphan/quinidine 1 tablet 2 times a day Tricyclic antidepressant, SSRI, or SNRI
Cognitive impairment	Can occur at any stage in the disease, including clinically isolated syndrome Prevalence and severity are higher in patients with progressive MS Can occur in the absence of accumulating T2 brain lesions Best screened for using serial assessments with Symbol Digit Modalities Test or similarly validated test	Evaluate for and manage tobacco use, polypharmacy, depression, fatigue, and sleep disruption Use of diaries, calendars, regular physical exercise, and regular social contact No evidence for efficacy of acetylcholinesterase inhibitors unless the patient has coexistent Alzheimer-type dementia
Paroxysmal symptoms	Trigeminal neuralgia, Lhermitte sign, tonic spasms (commonly mistaken for spasticity) Typically sensory with variable motor involvement; duration 1–90 seconds	Typically exquisitely sensitive to sodium channel blockade: carbamazepine 200 mg 2 times a day Oxcarbazepine, gabapentin, or lacosamide can be considered for second-line treatment
Temperature dysregulation	Most common in patients with a high EDSS score; symptoms include recurrent increase in prior MS symptoms, encephalopathy, pupillary dilation, and thrombocytopenia	Counsel regarding maintaining an adequate ambient temperature and wearing adequate clothing
Spasticity	Primarily driven by brainstem and spinal cord disease; patients report pain and leg spasms, particularly at night and after periods of immobility	Stretching exercises twice daily; hold stretches for 30–60 seconds Baclofen, tizanidine, or gabapentin; use limited by fatigue and worsening weakness; elevated liver enzymes with tizanidine Oral cannabis extract, synthetic tetrahydrocannabinol, or oral nabiximols spray where available Diazepam or dantrolene can be considered as a third-line treatment, but use is limited by toxicities For nonambulatory patients with severe spasticity, intrathecal baclofen pump
Gait dysfunction	Commonly associated with other comorbidities, including spasticity, weakness, fatigue, and sensory dysfunction	Ankle-foot orthosis, gait aids, dalfampridine; monitor renal function before commencing dalfampridine; monitor response with a timed 25-foot walk test
Bladder dysfunction	Common in MS, although typically does not cause a nephropathy Can present as urinary frequency, urinary urgency, or mixed urinary dysfunction May be exacerbated by constipation and obesity	Perform urinalysis and postvoid residual ultrasound of bladder in patients with urinary symptoms Fluid restriction at night; scheduled voiding; and avoidance of bladder irritants such as caffeine, tobacco, alcohol, carbonated beverages (including sparkling water), chili peppers, citrus fruits, and vitamin C supplements If postvoid residual volume is >100 mL, consider intermittent self-catheterization If postvoid residual volume is <100 mL, treat with anticholinergic medications such as oxybutynin, trospium, or darifenacin Third-line treatment includes intravesical botulinum toxin injection, tibial nerve stimulation, and consideration of surgical interventions in carefully selected patients
Sexual dysfunction	Affects up to 90% of patients Erectile dysfunction is common in men with spinal disease Anorgasmia, reduced vaginal lubrication, and reduced libido are common in women and associated with fatigue	Broaden the definition of sexual activity Adaptive modifications for positioning Consider lubricants, moisturizers, and vibrators Erectile dysfunction can be treated with phosphodiesterase inhibitors