Multiple Sclerosis: Management in Primary Care

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22nd May 2025

What we will cover today

1. Meet the GWH team
2. What is multiple sclerosis (MS)?
3. When to suspect MS?
4. When to refer and how?
5. How to manage MS?
6. Time for questions

Part 1: Meet the GWH MS team

Patient cohort:
>700 patients with MS
336 patients on DMT

The team:
2 part-time MS consultants
2 part-time MS specialist nurses
1 neurology pharmacist
1 neuroradiologist
1 neurology secretary
Other admin support

Local access to Botox clinic, other specialties and therapy teams.

Full access to Regional MS MDT.

What we don't have:

1. Community MS nurse in Swindon area.

   Sustainable patient caseload per full-time MS nurse:
   Recommended = 315 patients / full-time MS nurse
   UK average = 472 / full-time MS nurse
   GWH = >700 / full-time MS nurse

2. Disease modifying treatment coordinator.
3. ICB funding for Sativex (cannabinoid).

Our long-term aspirations (see MS Optimum Pathway)

1. Diagnose MS within 12 weeks of GP referral.
2. All patients with MS should be under the care of a specialist MS neurologist for categorisation of the patients' disease and access to therapies.
3. MS nurse appointment within 4 weeks of diagnosis.
4. All patients should be assessed for DMT eligibility and started on DMT within 12 weeks of a decision.
5. Provide **local** access to all UK-licensed DMTs, providing treatment at home where possible.
6. Annual follow-up with a member of the MS team.
7. Respond to unscheduled patient or GP concerns within 3 working days.
8. Urgent relapse appointments - ?timescale but ideally within 1-2 weeks.
9. Increase **local** access to clinical trials for MS patients under our care.
10. Participate in MSBase international patient registry.

Role of primary care

- Recognition of possible MS and early referral.
- Managing comorbidities.
- Managing vaccinations pre-initiation of treatment.
- Managing relapses (with support from us).
- Helping with access to therapy services – we can all refer.

Part 2: What is MS?

Definitions / terminology

How do we define MS?

Relapses and progression

Poser (1983) criteria – clinical dissemination in space and time

McDonald criteria incorporated MRI findings (2001, 2005, 2010, 2017, …2025)

Subtypes / nomenclature:

RIS *CIS* *RRMS* *PPMS* *SPMS*

Active vs inactive

With or without progression

Epidemiology

MS is the most common cause of non-traumatic disability in people < 40y

F:M ratio 3:1, peak incidence 20-50 years old

UK prevalence: > 130,000 pwMS (1 in 500) [similar to Parkinson's disease]

UK incidence: 7,000 / year (130 / week)

'Average' UK GP practice: 20 patients with MS and one new diagnosis per year.
(Assuming even distribution between > 6500 GP practices in the UK)

Aetiology

- Genes and the environment (approximately 50:50)
- EBV (especially late exposure) – RR of 2 following glandular fever
- Low vitamin D in early life and low maternal vitamin D
- Distance from the equator
- Obesity – possibly diet
- Smoking

Heritability

30% of pwMS report a family member with MS

54% of risk is calculated to be due to genetics

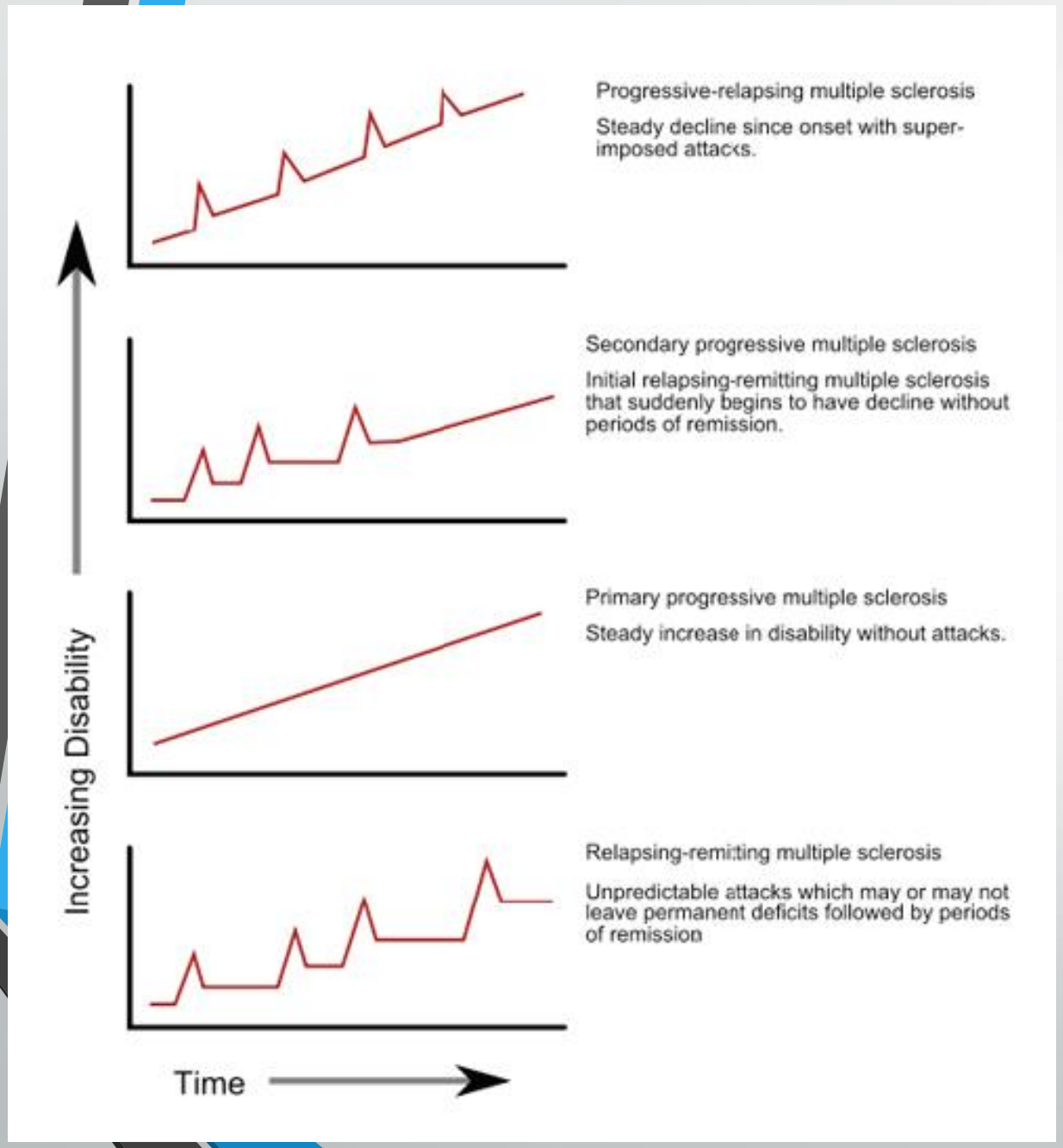
Polygenic inheritance – more than 200 alleles linked to MS

2 copies of HLA-DRB1 1501 → 8-fold increase in risk of MS

One genetic variant has been linked with rate of progression (2023)

Lifetime risk

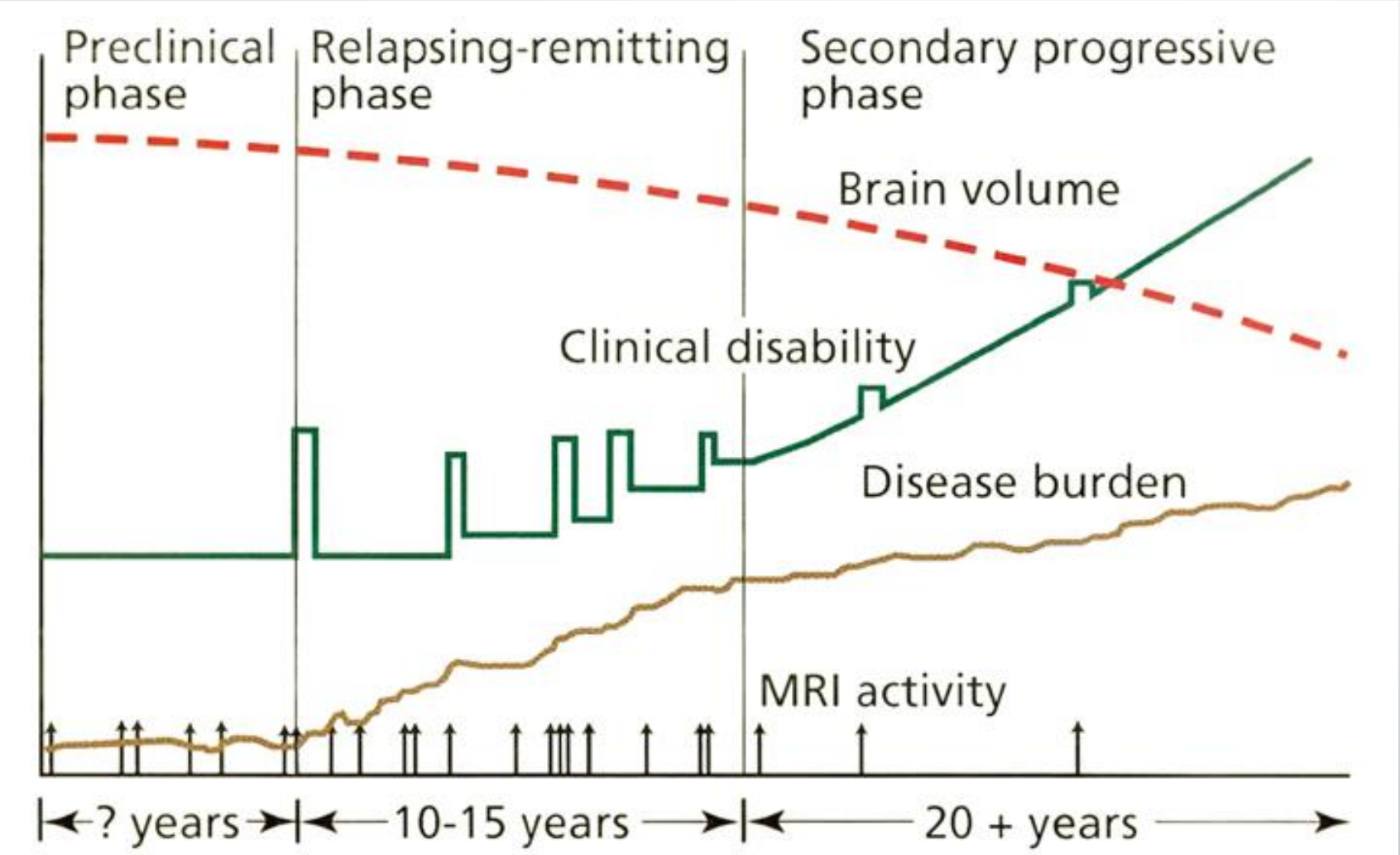
• General population:	1 in 330	
• One parent with MS:	1 in 67	(relative risk 5x higher)
• One child with MS	1 in 48	(relative risk 7x higher)
• Sibling with MS:	1 in 37	(relative risk 9x higher)
• Identical twin with MS:	1 in 5	(relative risk 66x higher)



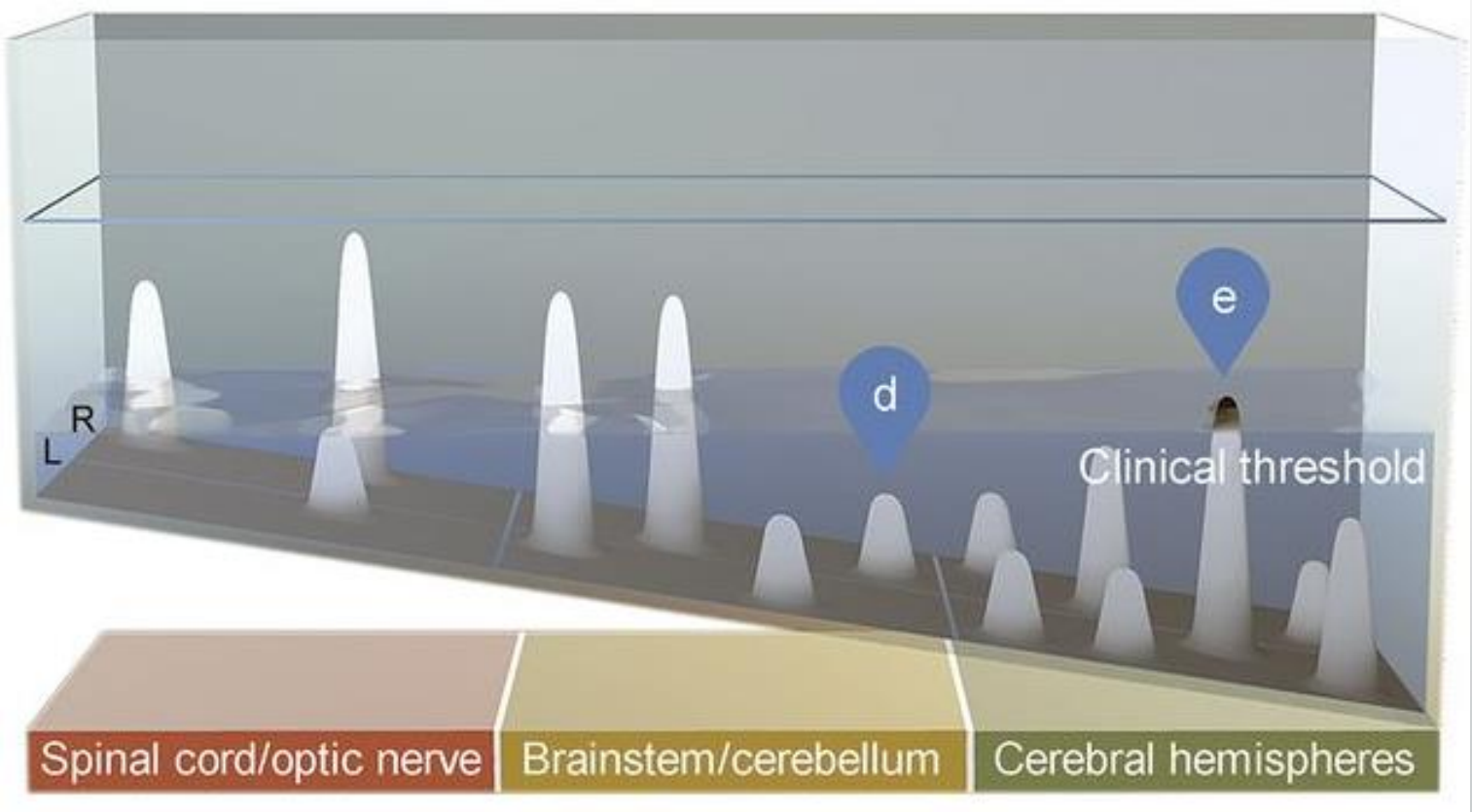
1. Relapsing-remitting – 85%
2. Primary progressive MS – 15%
3. RRMS →Secondary progressive MS

Secondary progression:

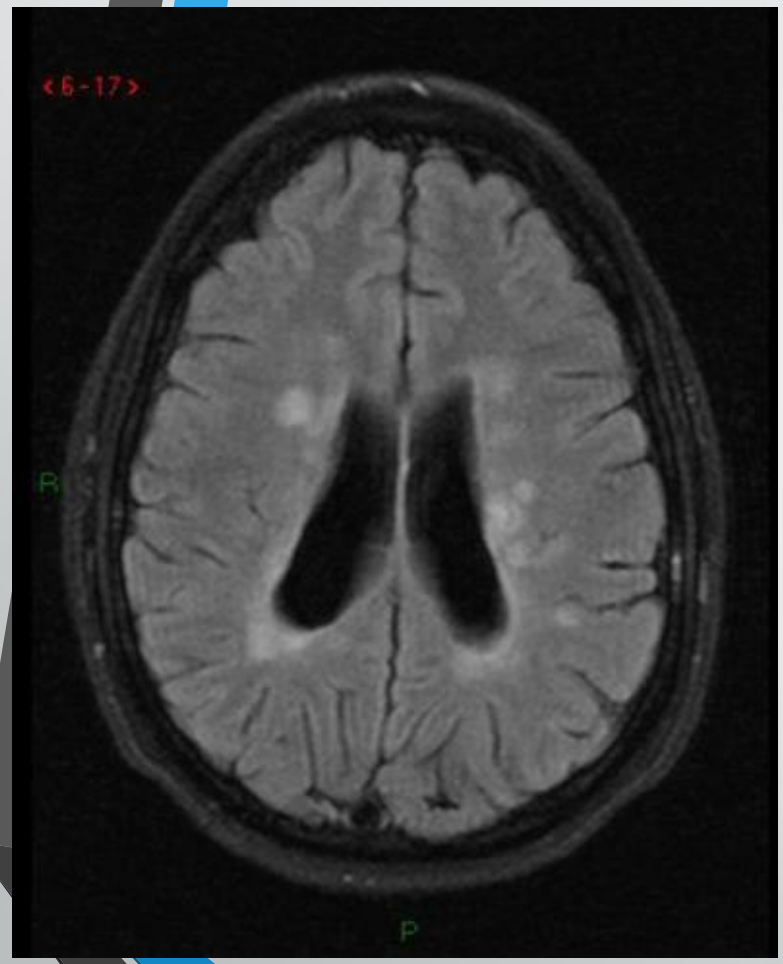
- Typically around age 40-60.
- 70% with RRMS by 20 years.
- SPMS more likely with more relapses in first 5 years, smoking, less time in education.
- Genetic component, one known genetic variant so far.

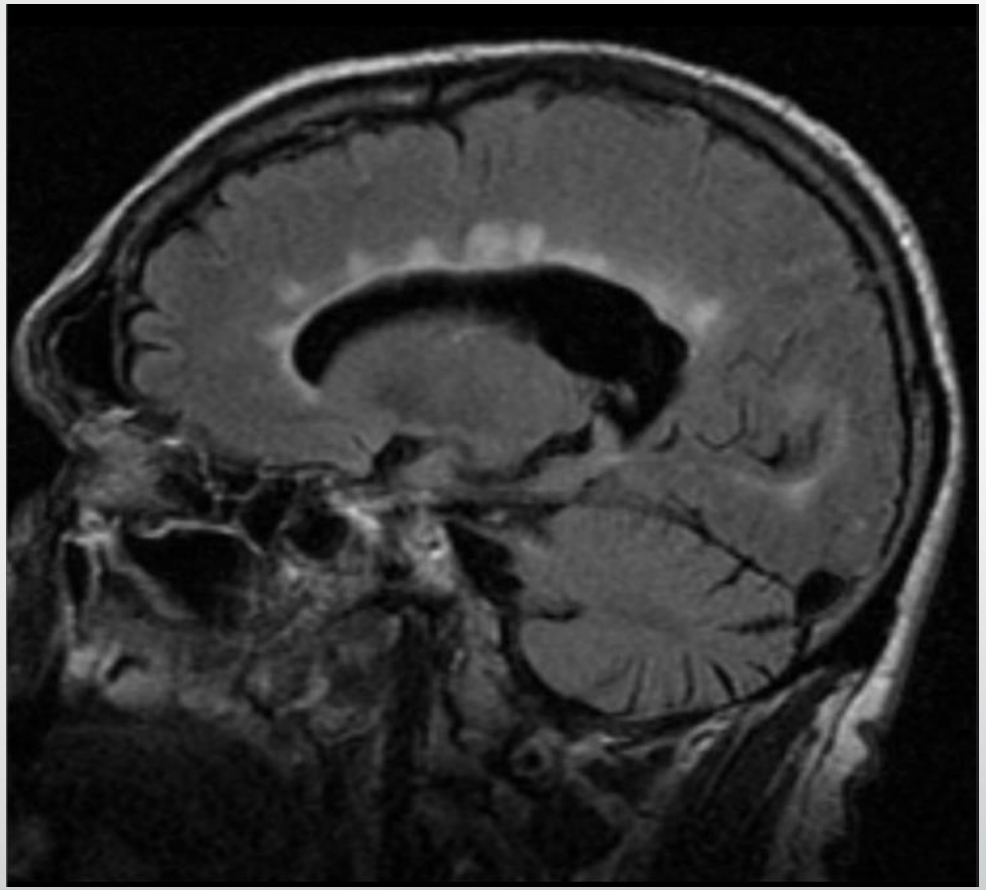

Preclinical phase
Relapsing-remitting phase
Secondary progressive phase
Brain volume
Clinical disability
Disease burden
MRI activity
? years
10-15 years
20 + years

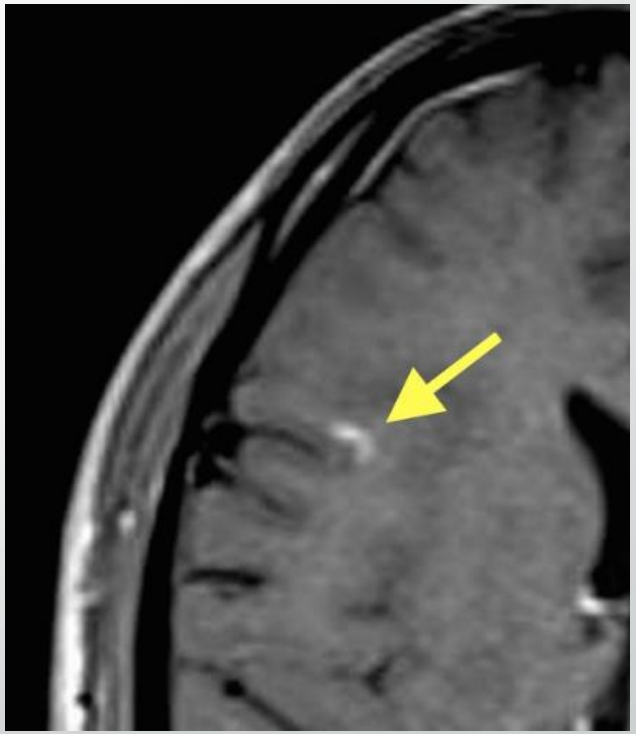
The topographical model of multiple sclerosis



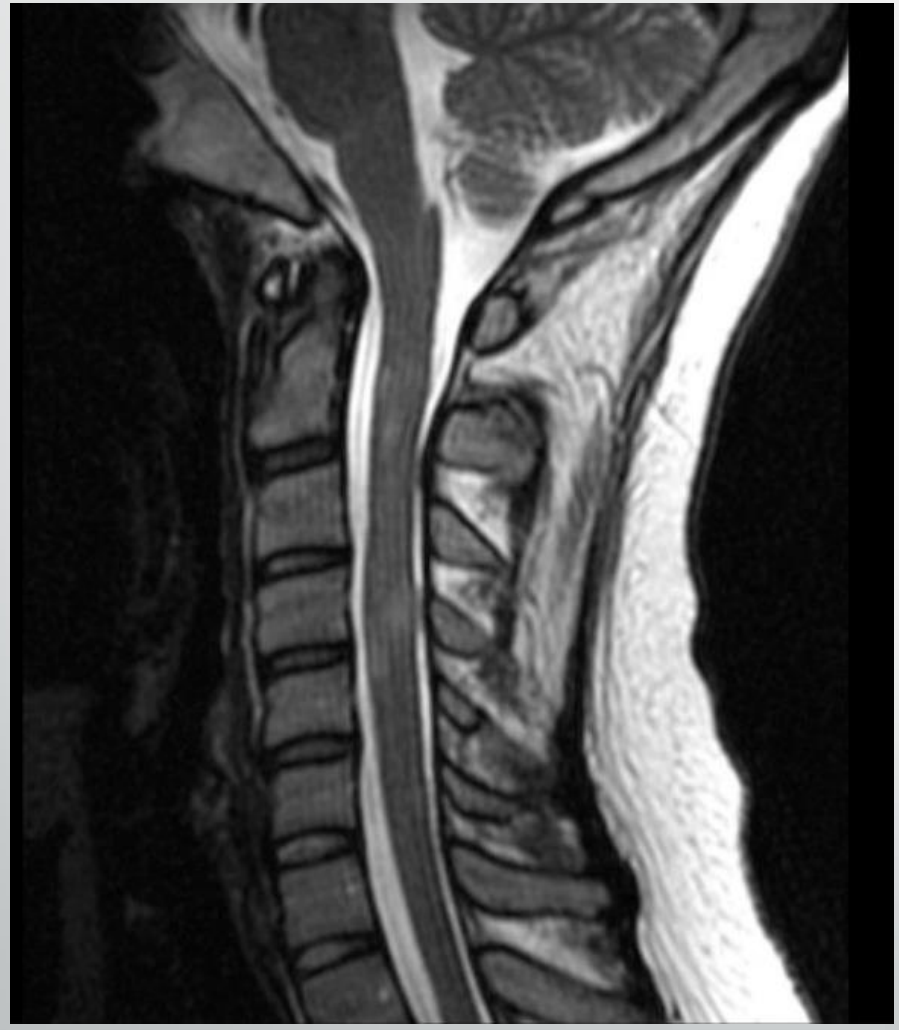
Krieger SC, Cook K, De Nino S, Fletcher M. The topographical model of multiple sclerosis: A dynamic visualization of disease course. Neurol Neuroimmunol Neuroinflamm. 2016 Sep 7;3(5):e279.

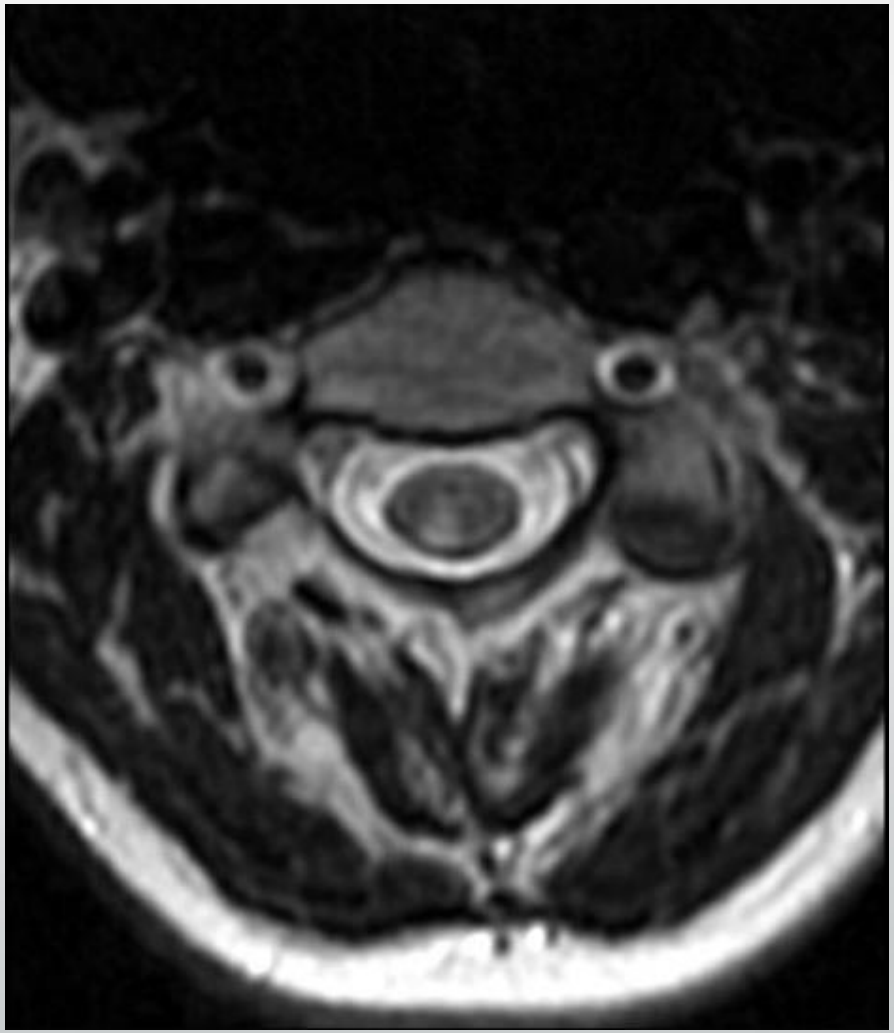






Images from radiopaedia.org





Images from radiopaedia.org

Part 3: When to suspect MS?

When to suspect an MS relapse

- Neurological symptoms lasting > 24h.
- But **typically** evolving over days to weeks, with resolution over weeks.
- In the absence of fever or infection.

Caveats:

- Multifocal relapses can occur, but more often there is one localisable lesion.
- Occasionally: new onset of paroxysmal symptoms, e.g trigeminal neuralgia or other fluctuating/recurrent sensory disturbance (beware migraine).

  Symptoms may return in future with fever/infection – “pseudorelapse”.

Typical MS relapses

- Retrobulbar optic neuritis, i.e. no optic disc swelling
- Brainstem syndrome, e.g. diplopia, vertigo, trigeminal neuralgia, facial sensory disturbance or weakness, dysarthria/dysphagia
- Partial transverse myelitis
  - Mostly mild sensory relapses, but severe relapses can be associated with deafferentation, weakness and sphincter dysfunction
  - +/- Lhermittes phenomenon during cervical cord relapse
  - +/- “MS hug”

Cerebellar syndrome

Other symptoms (not necessarily relapse-related)

- Lhermitte's phenomenon
- Uhthoff's phenomenon
- Exertional foot drop
- Asymmetrical spastic paraparesis or hemiparesis
- Cerebellar symptoms and signs (limbs, gait, speech)
- Neuropathic pain and 'MS hug'
- Sexual and sphincter dysfunction
- Cognitive dysfunction and 'brain fog'

Rubral tremor is seen in advanced MS

Examination findings

- Optic atrophy +/- relative afferent pupillary defect (RAPD)
- Internuclear ophthalmoplegia (INO)
- Brisk reflexes or other UMN signs, especially if asymmetrical – ankle clonus most objective
- Weakness following incomplete recovery from relapse, or more commonly due to progression
- Pseudo-weakness due to loss of proprioception – may mimic functional weakness
- Objective sensory changes, especially reduced vibration sense is common and easy to detect – sometimes a sensory level, though less common
- Impaired abdominal reflexes – cord pathology
- Post-void residual bladder volume > 100ml (late feature)

Neurological signs

- Relative Afferent Pupillary Defect - YouTube
- Bilateral Internuclear ophthalmoplegia (INO) – YouTube

When is MS unlikely?

- Evolution over minutes and resolution within hours, with or without headache – **migraine**
- Sudden onset neurological symptoms – **stroke/TIA ***
- Dysphasia, homonymous hemianopia*, inattention – **stroke/TIA**
- Fatigue and/or widespread pain without relapse history or neurological signs – **non-organic** (associated with fibromyalgia, CFS, POTS, Ehlers-Danlos, PTSD…)
- Innumerable changeable symptoms, without neurological signs – **non-organic**
- Acute encephalopathy is very rare in MS, dementia is only a late feature in MS
- Seizures – unusual in early MS, except in tumefactive MS

Part 4: When to refer and how?

Who to refer?

Presentation	Recommendation
Optic neuritis	Refer to Eye Casualty.
Disabling neurology	Send to ED / refer to medical take.
Suspected MS	Refer – we will see in general neurology or triage directly to MS clinic.
Incidental white matter changes on MRI	Advice and Guidance – may not need review in clinic.
All patients with known RRMS and progressive MS *who can come to clinic*	Refer – we will see directly in MS clinic. All patients benefit from monitoring, holistic review of symptoms, and access to clinical trials.
Patients with progressive MS who cannot come physically to clinic	Advice and Guidance. Community nursing and therapy team input where available. +/- Palliative care.

Common mimics referred as ?MS

- Migraine aura interpreted as optic neuritis or transverse myelitis (especially when there is functional overlay).
- Functional neurological disorder – strong possibility if also fibromyalgia, chronic fatigue syndrome, POTS, Ehlers-Danlos, or long COVID.
- Incidental white matter changes on MRI – often explained by small vessel disease or migraine.

Referring to Neurology

Useful information to include in referral	Consider at time of referral
• Nature of history: episodic vs progressive • Timing of possible relapses if known • Examination findings • Highly discriminating symptoms/signs: **optic neuritis**, **Lhermittes**, **INO**, etc.	• Check vitamin D: replace with vitamin D (no calcium) 2000 IU OD if <50 nmol/L • Motor/sensory symptoms: check vitamin B12/folate, HbA1c, TSH • Restless legs: check ferritin – aim for > 75 • Screen for causes of fatigue if appropriate (ferritin, TSH) • Physio/OT/SALT referrals can be considered prior to diagnosis if issues are identified

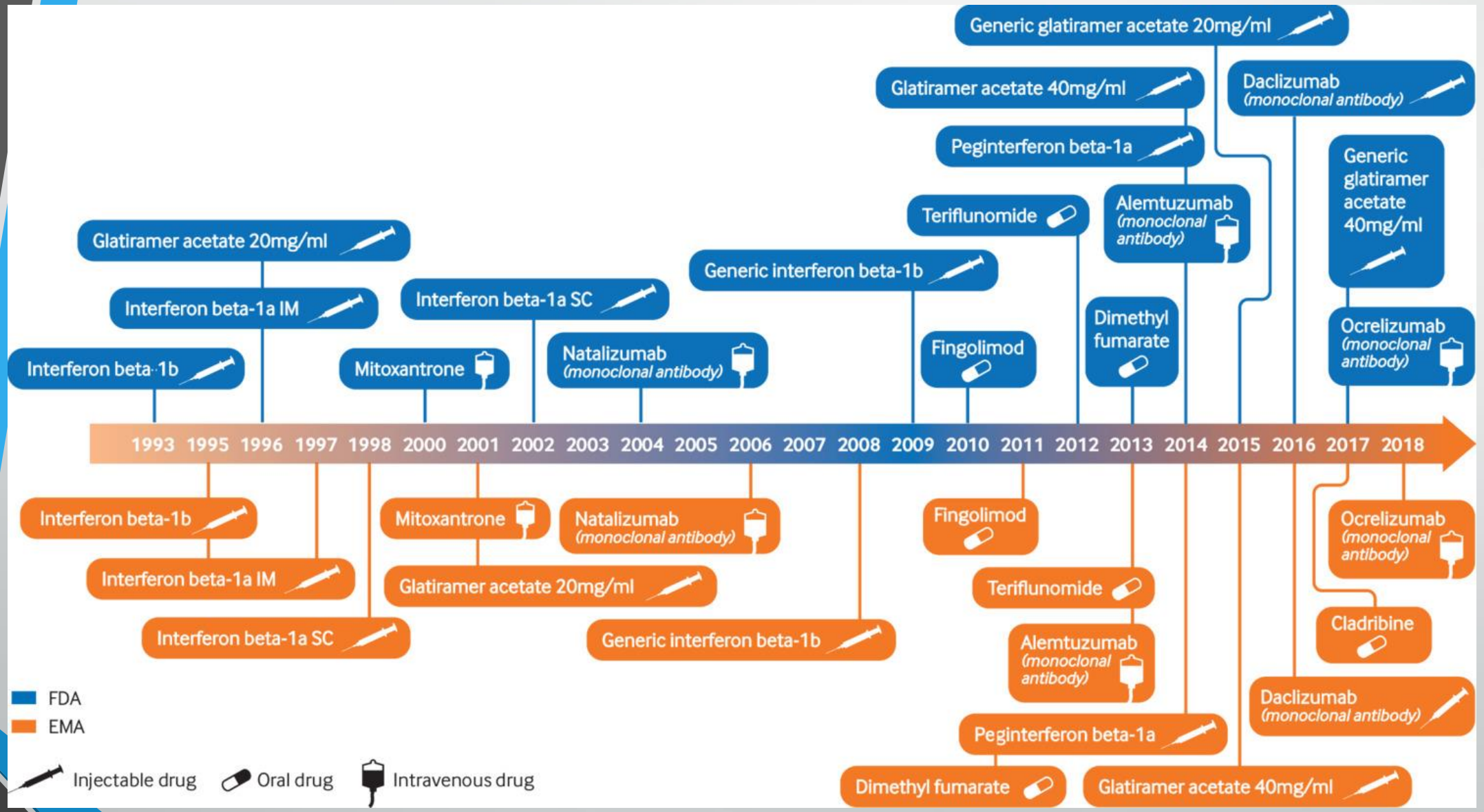
Part 5: How to manage MS?

How we treat MS

1. Patient education
2. Disease modifying therapy: 19 licensed options
3. Relapse management
4. Symptom management

Lifestyle advice

- **STOP SMOKING**
- Exercise – no evidence of harm, but many benefits including weight loss
- Several books pushing special diets / lifestyles – no convincing support
- No evidence to support the use of hyperbaric oxygen
- Pregnancy needs to be planned



F De Angelis and WJ Brownlee, **"Disease-modifying therapies for multiple sclerosis,"** *BMJ* 2018;363:k4674.

DMT for relapsing-remitting MS

Moderate – 30% relapse reduction	**Beta-interferon (self-injection)** **Glatiramer acetate (self-injection)** **Teriflunomide (tablets)** **(Steroid-sparing agents)**
More effective – 50% relapse reduction	Dimethyl fumarate (tablet), diroximel fumarate Fingolimod (tablet), ponesimod (tablet)
Most effective – 70% relapse reduction (all monoclonal antibody therapies)	Alemtuzumab (induction therapy) *Cladribine (induction therapy) – less effective Ocrelizumab (6-monthly infusion) Ofatumumab (monthly self-injection) *Natalizumab (monthly infusions on day unit – most effective) AHSCT – probably the most effective

DMT for Progressive MS

- Relapsing-progressive MS: Extavia
- Primary progressive MS: Ocrelizumab (active PPMS, within 15 years)
- Secondary progressive MS: Siponimod (active SPMS)

DMT for Progressive MS

- Relapsing-progressive MS: Extavia no longer available
- Primary progressive MS: Ocrelizumab (active PPMS, within 15 years)
- Secondary progressive MS: Siponimod (active SPMS)

Relapses

Patients are advised to ring the MS nurses about new symptoms / relapses.

With GP: Bloods and urine dipstick / MC&S to exclude infection.

For a disabling relapse, we will suggest:

- Oral methylprednisolone 500mg OD PO for 5 days.
- Consider admission if unable to self-care in community.

Counsel patients regarding the risks of steroids:

Hyperglycaemia, insomnia, psychomotor disturbance, (rarely) avascular necrosis of the hip.

Symptomatic treatment: neuropathic pain

- Gabapentin / Pregabalin
- Amitriptyline / Nortriptyline (TCAs)
- Duloxetine (SNRI)
- Pain clinic – mainly for access to psychology (pain management programme)

Symptomatic treatment: spasticity

- Baclofen 5mg – 30mg TDS
- Gabapentin 100mg – 1200mg TDS
- Pregabalin usually up to 150mg BD (max. 300mg BD)
- Tizanidine usually up to 24mg/day (max. 36mg/day) in divided doses
- Dantrolene usually 75mg TDS (but up to 100mg QDS)
- (Sativex – THC/CBD – NICE approved but postcode lottery)
- Intrathecal baclofen

Symptomatic treatment: bladder

- Continence nurse referral
- Reduce caffeine and fluid intake
- Mirabegron or solifenacin, or in combination
  - Exclude post-void residual volume > 100ml
- Intermittent self catheterisation if high residual volume
- Bladder Botox injections for intractable urinary urge incontinence
- Suprapubic catheter

Symptomatic treatment: bowels

- Linseed/flaxseed
- Ispaghula husk (Fybogel) – bulk-forming laxative
- Macrogol and senna may cause cramps
- Bowel irrigation system, e.g. Peristeen

Symptomatic treatment: fatigue

- Amantadine - ?effective
- Unlicensed use of ADHD drugs, e.g. modafinil

Management of other symptoms

- Oscillopsia: gabapentin
- Trigeminal neuralgia: **carbamazepine**, gabapentin, baclofen, lamotrigine
- Paroxysmal symptoms due to ephaptic transmission: carbamazepine
- Dysphagia: SALT
- Tremor: weighted cutlery, etc.
- Mobility: community physiotherapy or neurophysioterapy review; walking aids
- Foot drop: OT referral for ankle-foot orthoses, FES (functional electrical stimulation)

Summary

- MS is a common and disabling condition that presents in all age groups.
- Frequently missed or diagnosed late, but also misdiagnosed.
- Early diagnosis and treatment leads to better outcomes.
- There is a range of DMTs of varying efficacy – role of AHSCT to be determined, and new treatments on the horizon.
- Symptomatic treatment remains very important.

Any Questions?

Thank you for listening!

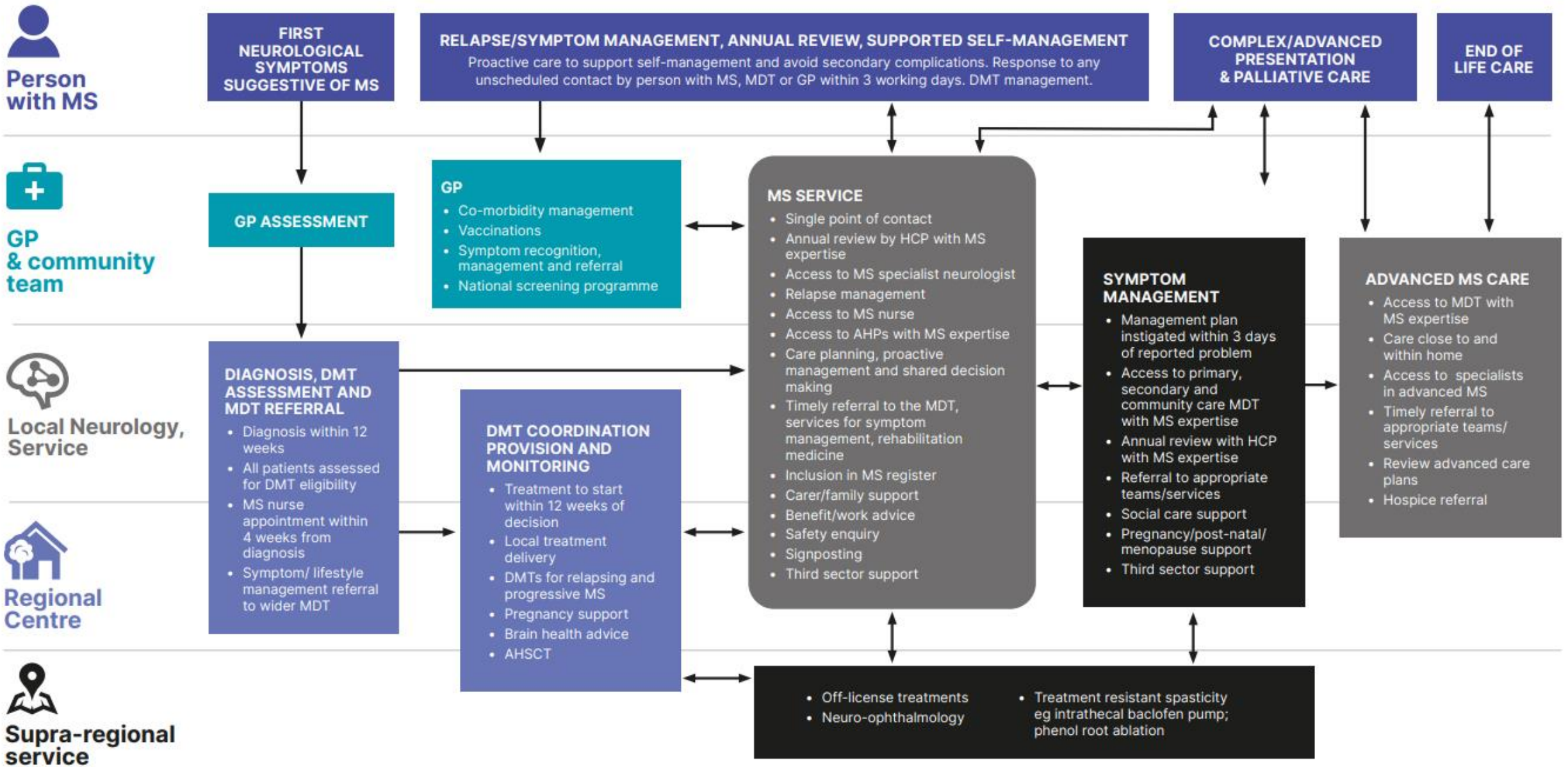
References

- Optimal clinical care pathway for adults: Multiple Sclerosis, National Neurosciences Advisory Group, November 2014.
- MS Society and MS Trust websites
- MS Decisions website: https://mstrust.org.uk/information-support/ms-drugs-treatments/ms-decisions
- F De Angelis and WJ Brownlee, **"Disease-modifying therapies for multiple sclerosis,"** *BMJ* 2018;363:k4674.
- Krieger SC, Cook K, De Nino S, Fletcher M. **"The topographical model of multiple sclerosis: A dynamic visualization of disease course."** Neurol Neuroimmunol Neuroinflamm. 2016 Sep 7;3(5):e279.
- https://radiopaedia.org – good source of neurological imaging examples.

Appendix

Multiple Sclerosis Optimum Pathway

GOAL: Appropriate, timely, proactive, quality care at every stage
ON-GOING: Patient and carer information, education, shared decision-making, supported self-management, lifestyle advice, opportunity to participate in research



Summary of 2017 McDonald Criteria for the Diagnosis of MS

✓ *Requires elimination of more likely diagnoses*

✓ *Requires demonstration of dissemination of lesions in the central nervous system in space and time*

DIT = dissemination in time **DIS** = dissemination in space	**CNS** = central nervous system **CSF** = cerebrospinal fluid	**T2 lesion** = hyperintense lesion on T2-weighted MRI

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None, DIS and DIT have been met
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by <u>one</u> of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial, or spinal cord **AND** DIT shown by <u>one</u> of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least <u>two</u> of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical, or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

No <u>one</u> diagnostic test

Diagnosis based on:

History + examination
MRI brain
MRI cervicothoracic spine

+/- to help demonstrate DIT:

Interval MRI
MRI with gadolinium
Lumbar puncture for OCBs

+/- to help demonstrate DIS:

Visual evoked potentials
Motor evoked potentials
Sensory evoked potentials

+/- to rule out mimics:

Anti-MOG antibody
Aquaporin-4 antibody
Vitamin B12, serum ACE/calcium, HIV, syphilis, [Borrelia/Lyme], HTLV-1/2 (progressive MS only)

Red flags (more for your interest)

Atypical optic neuritis:

- Severe optic neuritis with papilloedema (MOG antibody disease)
- Recurrent optic neuritis upon steroid withdrawal (CRION)
- Bilateral optic neuritis (NMOSD: neuromyelitis optica spectrum disorder)

Other features:

- Intractable hiccups (area postrema syndrome – NMOSD)
- Rapidly progressive symptoms from onset (NMOSD)
- Uveitis or respiratory/skin disease – consider sarcoid
- Oral and genital ulceration (especially with Middle Eastern / Mediterranean / East Asian background) – consider Behcet's disease

  Night sweats, fevers, weight loss – lymphoma

Pregnancy and DMTs

- Teriflunomide: accelerated elimination procedure before trying to conceive.
- Fingolimod: stop at least 2 months before conception.
- Dimethyl fumarate: stop during pregnancy or preferably prior to conception.

- Cladribine: avoid pregnancy until 6 months after the year 2 course.
- Ocrelizumab and ofatumumab: stop once pregnant, restart after pregnancy.

- Compatible with pregnancy and breastfeeding: brand-name Copaxone, beta-interferons, natalizumab (last dose at 34 weeks).