Multiple sclerosis

Diagnosis, disease-modifying therapy and prognosis

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Background

Multiple sclerosis (MS) is a multifocal inflammatory central nervous system disorder. There are now many highly effective disease-modifying therapies (DMTs) available as treatment options, which have a significant impact on disease activity and long-term disability.

Objective

The aim of this article is to provide a concise overview of the diagnosis, DMTs and prognosis of MS.

Discussion

The diagnosis of MS is made on clinicoradiological grounds to prove dissemination of disease in both time and space in the nervous system. While the expanding options of DMTs have had a significant impact on disability, they make medication selection for individual patients more complicated. Patients with MS often have a model of care shared between the neurologist and the general practitioner. This review article summarises the key aspects of the diagnosis, DMTs and prognosis of MS relevant to the general practitioner.

MULTIPLE SCLEROSIS (MS) is a multifocal central nervous system (CNS) disorder characterised by inflammatory demyelinating lesions affecting white and grey matter. Steady accumulation of damage over time leads to irreversible disability characterising the advanced stages of the disease. The range and effectiveness of disease-modifying therapies (DMTs) have greatly expanded over the past decades, improving prognosis for patients with MS. This article covers the topics of diagnosis, DMT and prognosis of MS.

Investigations and diagnosis

MS is diagnosed by a combination of clinical and radiological features. The 2017 McDonald criteria are the standard used for diagnosis of all forms of MS.[1] There are five key principles underlying diagnosis:

1. A syndrome 'typical' for MS (refer to Table 1)
2. Objective evidence of CNS involvement (almost always magnetic resonance imaging [MRI] of the brain and spinal cord confirming demyelinating lesions)
3. Dissemination in space – lesions affecting multiple areas of the CNS
4. Dissemination in time – multiple clinical demyelination events, or MRI showing both contrast-enhancing lesions (indicating acute demyelination) and non–contrast enhancing (indicating chronicity)
5. No better explanation for the symptoms.

MRI of the brain and spinal cord with post-gadolinium sequences is the investigation of choice for suspected MS or clinically isolated syndrome (CIS). As a result of Medicare Benefits Schedule restrictions, the MRI will generally be requested by a neurologist. Advances in MRI scanners and post-acquisition image analysis have led to improved diagnostic accuracy.[2] Figure 1 shows examples of typical MS changes on MRI.

Cerebrospinal fluid (CSF) examination may show restricted oligoclonal bands – immunoglobulins present in the CSF but not the serum, indicating antibody production in the CNS. They can be a useful diagnostic aid in atypical or early cases. However, they are not a diagnostic requirement, nor are positive bands specific for MS. Research is underway for specific CSF and blood biomarkers, which may help predict future disease activity.[3]

Differential diagnosis

The varied presentation of MS leads to a broad range of possible differentials depending on the CNS location involved.

Misdiagnosis of MS commonly occurs when presentations atypical for MS are linked with non-specific white matter lesions on MRI.[4] White matter lesions are common, occurring in a quarter of people aged <45 years,[5] and should be interpreted with caution on the basis of the cause for initial investigation. Red flags for an alternative diagnosis include systemic and constitutional symptoms, neurological signs outside the CNS (particularly peripheral neuropathy) and atypical MRI findings.[6]

One multicentre study found that the most common entities mistaken for MS were migraine (22%), fibromyalgia (15%), nonspecific symptoms with abnormal MRI (12%), functional neurological disorder (11%), and neuromyelitis optica (NMO; 7%).[4]

Non-MS demyelinating diseases include NMO spectrum diseases, anti–myelin oligodendrocyte glycoprotein disease (a recently described condition similar to NMO) and acute disseminated encephalomyelitis. Diagnosis is based on specialist assessment of clinical, radiological and laboratory features, and treatment with conventional MS therapies is ineffective.

Natural history and disease phases

Clinically isolated syndrome

CIS refers to a solitary episode of neurological disturbance due to CNS demyelination in the absence of fever, infection or encephalopathy.[7] The disturbance is monophasic, reaching a peak within days to a few weeks and lasting at least 24 hours. Typical presentations include monocular optic neuritis, focal supratentorial syndrome, brainstem or cerebellar syndrome, or partial myelitis (Table 1). Careful history-taking for previous events is required to avoid possibly misclassifying relapsing MS.

With the advent of highly effective DMTs, there is a greater emphasis on earlier identification of MS to limit disability, making CIS a dwindling concept. Changes to the 2017 modified McDonald diagnostic criteria for MS result in some patients with a first clinical demyelinating event being diagnosed with MS if certain criteria are simultaneously met.[1]

MRI is the best imaging modality to prognosticate progression from CIS to MS. Over 20 years of follow up, the risk of a second attack is 80% if MRI demonstrates typical lesions and 20% if it does not.[7] The risk of early MS (diagnosis within four years) increases with lesion load, especially with infratentorial lesions or more than three periventricular lesions. Overall, approximately one-third of patients have no further demyelinating events even after 30 years of follow up.

Radiologically isolated syndrome

MRI of the brain or spine performed for another reason may incidentally find demyelinating lesions. Where these lesions are in a typical distribution for MS, and detailed history and examination does not find an episode of CIS, then the presentation is termed

Table 1. Common sites, signs and symptoms of clinically isolated syndrome or multiple sclerosis relapses[1]

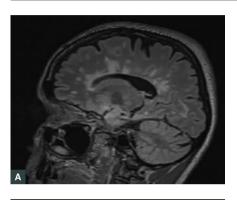| Site	Condition	Symptoms	Signs
Optic nerve	Optic neuritis	Pain on eye movement, blurred vision	Reduced monocular visual acuity, colour desaturation
			Fundoscopy may be normal or may show a swollen optic disc
Cerebrum	Focal supratentorial syndrome	Dependent on cerebral location (eg hemianopia in an appropriately located occipital lesion)	
Cerebellum	Cerebellar disease	Unsteadiness	Limb or gait ataxia; horizontal or torsional gaze-evoked nystagmus
Spinal cord (usually multifocal and asymmetric)	Partial myelitis affecting pyramidal tracts	Upper or lower limb weakness	Pyramidal distribution weakness
	Partial myelitis affecting spinothalamic, posterior columns	Unilateral or bilateral limb numbness or paraesthesias; Lhermitte's phenomenon	Sensory level
	Any spinal cord lesion	Urinary frequency or urge incontinence, constipation erectile dysfunction	
Brainstem – medial longitudinal fasciculus	Internuclear ophthalmoplegia	Blurred or double vision	Internuclear ophthalmoplegia
Brainstem – pyramidal tracts, spinothalamic and posterior columns	Similar to that described in spinal cord		

radiologically isolated syndrome (RIS).[8] Other conditions may cause similar MRI changes, particularly migraine and small vessel disease, so diagnosis requires neurologist review.
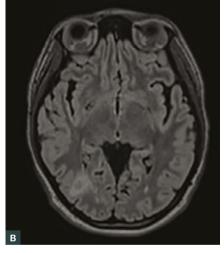
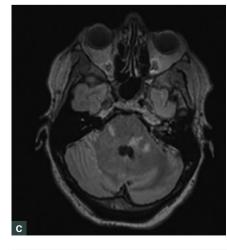After 10 years of follow up, the probability of a patient with RIS developing a first clinical event is 51%.[9] Risk factors for conversion to relapsing clinical disease are similar to that for CIS.

Relapsing remitting MS
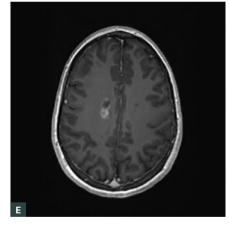Relapsing remitting MS (RRMS) is defined by episodes of CNS demyelination separated by time and by space (ie lesions in more than one region of the CNS). In untreated patients, ongoing neuro-inflammation results in accelerated brain atrophy of 0.5–1.4% per year,[10] and relapses occur erratically, with a mean rate of 0.65 clinical attacks per year.[11] Subclinical disease activity, which is the development of new lesions on imaging without clinical correlate, occurs more commonly.

An MS relapse is defined as symptoms or objective signs typical of an acute inflammatory CNS demyelinating event lasting at least 24 hours. They are caused by either a new focal lesion or reactivation of an old lesion.[12] Complete symptomatic resolution from a relapse often occurs; however, mild residual signs may persist in some patients. Hyperacute onset over seconds to minutes is unusual and should prompt investigation for other causes.

Pseudorelapse occurs when other medical conditions, particularly infections, cause transient neurological worsening related to historical demyelinating damage. Relapse may be distinguished from pseudorelapse by a lack of a trigger and by symptoms localising to a previously unaffected region in the CNS.

Progressive MS
Progressive MS describes an insidious deterioration of neurological function associated with new symptoms and signs, progressing for at least one year. It is predominantly driven by neurodegeneration, with widespread neuroaxonal loss in the white and grey matter.[7,13] Patients do not progress in a uniform manner, and the disease can remain relatively stable over periods of time.[13] Diagnosis is made retrospectively.

Secondary progressive MS (SPMS) describes a previously relapsing remitting disease course transitioning to progressive disability. The underlying mechanism that drives transition from RRMS to SPMS is not well established.[13] DMT helps to slow or prevent this transition. There is often a period of uncertainty regarding when patients transition from RRMS to SPMS.[13]

A small proportion of patients with MS have a progressive course from disease onset; this is termed primary progressive

Figure 1. Typical multiple sclerosis magnetic resonance imaging findings, sourced from multiple patients

A. Periventricular lesions (FLAIR sequence);
B. Juxtacortical lesion in the right parieto-occipital region (FLAIR sequence); **C.** Brainstem and cerebellar lesions (FLAIR sequence);
D. Spinal cord lesions in the thoracic cord (T2-weighted turbo spin echo sequence);
E. Gadolinium-enhancing lesion (T1-weighted sequence)

FLAIR, fluid attenuated inversion recovery

MS (PPMS). The most common presentation is with a gradual onset spastic paraparesis, followed by cerebellar or hemiplegic symptoms. It remains unclear whether PPMS is a separate entity from SPMS, or if it follows an unrecognised or subclinical inflammatory phase.[7,13]

Although patients are classified as having either relapsing or progressive MS, the driving pathology is thought of as a spectrum. Autopsies of patients with RRMS have shown widespread grey matter atrophy from early in the disease course,[13] and patients with progressive disease may continue to have new enhancing lesions on MRI (called active progressive MS).

Treatment

Acute relapses
Corticosteroids are the mainstay treatment for acute relapses. Intravenous methylprednisolone is generally used, although oral methylprednisolone has been shown to have similar efficacy.[14] Other options include adrenocorticotropic hormone or plasma exchange. Medical treatment is only necessary if the relapse symptoms have a significant impact on quality of life, as treatment may hasten the recovery from a relapse but not the likelihood of recovery or permanent disability.[14]

In cases of pseudorelapse, treatment should be targeted towards the exacerbating disease, with no role for steroids.

Disease-modifying therapies
The range of DMTs for MS continues to grow. The agent chosen is based on a combination of patient factors (age, comorbidities, plans for pregnancy), disease factors (number and location of lesions) and patient preferences (medication side effects versus efficacy). In all cases, DMTs should be initiated or modified under neurologist guidance. One DMT is used at a time – there have been no proven benefits to combination therapy. The Pharmaceutical Benefits Scheme (PBS) only covers DMTs for RRMS and a single agent for SPMS, with no agents covered under the scheme for CIS, RIS or PPMS. DMTs are assessed in trials for their effect on annualised relapse rate (ARR),

disability worsening, radiological lesion load and brain volume measurements. A summary of currently available DMTs is provided in Table 2.

There are two general approaches to initiating DMTs. In the step-up approach, a modestly effective initial agent is commenced; if disease progression occurs, then a more efficacious medication is substituted. A step-down approach involves starting with a high-efficacy treatment, which may be stepped back following a period of disease stability. Which strategy more effectively balances the risk of side effects with that of reduced future disability is the subject of active research.[15]

Subcutaneous and intramuscular DMTs
Interferon beta and glatiramer acetate are the longest established medications used for treatment of RRMS, giving them the greatest depth of safety data.[16] ARR is approximately 30% reduced when compared with placebo for each agent.[17,18]

Oral DMTs
Teriflunomide reduced ARR by 31% when compared with placebo, and significantly affected several MRI parameters.[19] It is teratogenic, so reliable contraception is required for women of reproductive age.

Dimethyl fumarate reduced ARR by 44% when compared with placebo.[20] Common adverse effects are flushing and gastrointestinal upset, which can be limited by aspirin use and taking medications with full meals.

Fingolimod, siponimod and ozanimod are oral sphingosine-1-phosphate receptor modulators. In their pivotal trials, fingolimod reduced ARR by 54% when compared with placebo,[21] and ozanimod reduced ARR by 49% when compared with interferon beta-1a.[22] Siponimod modestly slowed disability accumulation in patients with SPMS, especially those with relapses within two years of beginning treatment.[23] First-dose electrocardiography monitoring in hospital is required for all patients starting fingolimod because of the risk of symptomatic bradycardia, but it is only required for those with pre-existing cardiac conditions for siponimod and ozanimod. Ophthalmology review prior to

and 3–4 months after the commencement of fingolimod is required to exclude macular oedema.

Cladribine is given as two courses of treatment with a one-year gap between courses, with no planned ongoing treatment following this. ARR is reduced by 57% when compared with placebo.[24]

Intravenous DMTs
Natalizumab reduced the rate of disability progression, the ARR and the number of new gadolinium-enhancing lesions by 54%, 68% and 92%, respectively, when compared with placebo.[25] The most serious adverse effect is progressive multifocal leukoencephalopathy, a life-threatening opportunistic brain infection caused by the John Cunningham virus (JCV). This risk is less than 0.07 per 1000 patients if JCV antibodies are negative, rising to 1.7–2.7% over six years with positive antibodies.[26] For this reason, antibody levels are tested every 6–12 months.

Ocrelizumab is given every six months and reduced ARR by 46% when compared with interferon beta-1a.[27] In addition, it is the only DMT to have shown positive effects in a patient cohort with PPMS, with minor improvements in walking speed, brain lesions and brain volume loss.[28] Ofatumumab has a similar mechanism of action and efficacy as ocrelizumab but is delivered by a subcutaneous route monthly, avoiding hospital admissions for infusions.[29]

Alemtuzumab is given as two cycles of infusions one year apart. It reduced ARR by 55% when compared with interferon beta-1a.[30] However, it may induce significant autoimmune adverse effects including idiopathic thrombocytopenic purpura, nephropathy and thyroid dysfunction. Strict laboratory monitoring is required for five years after treatment.

Emerging options and future directions
Autologous haematopoietic stem cell transplant shows great promise for the management of treatment-refractory disease.[31] Treatment-related toxicity, including possible autoimmunity and infertility, is a limiting factor, so patient selection is very important. Other areas of investigation include remyelination

Table 2. Disease-modifying therapies for multiple sclerosis[14]

Medication	Mode of action	Route and recommended dose	Monitoring	Notable adverse effects	Other comments
Interferon beta-1a	Immunoregulatory actions including antagonism of interferon gamma, reduction of cytokine release and augmentation of suppressor T cell function	Avonex: IMI, 30 μg weekly Rebif: SC, 44 μg three times a week	FBE and LFTs at one, three and six months after initiation, then annually	Injection-site reactions, influenza-like illness	Dose titration recommended Paracetamol may reduce influenza-like symptoms Presence of neutralising antibodies may reduce response
Peginterferon beta-1a		SC, 125 μg fortnightly			
Interferon beta-1b		SC, 62.5–250 μg every two days			
Glatiramer acetate	Synthetic polypeptide; possibly blocks presentation of myelin antigens to T lymphocytes	SC, 40 mg three times a week	None	Injection-site reactions, post-injection systemic reactions	Antibodies to glatiramer develop in all patients and are not associated with adverse effects or decreased efficacy
Teriflunomide	Prodrug of leflunomide; inhibits pyrimidine synthesis in leucocytes	Orally, 14 mg daily	FBE and LFTs, monthly for six months, then every 8–4 weeks Blood pressure regularly	Nausea, diarrhoea	Teratogenic – highly effective contraception must be in place In case of toxicity or pregnancy, washout procedure with colestyramine can be used
Dimethyl fumarate	Antioxidative, immunomodulatory and anti-inflammatory effects via activation of the nuclear factor (erythroid-derived 2)-like 2 transcriptional pathway	Orally, 120 mg daily then weekly uptitration to maintenance dose of 240 mg bd	FBE every 3–6 months, LFTs every 6–12 months Urinalysis annually	Flushing, nausea, vomiting, diarrhoea, abdominal pain	Gastrointestinal upset and flushing are common and tend to improve with time.
Fingolimod	Sphingosine 1-phosphate receptor modulators; prevent lymphocyte trafficking through the lymph node and cause a reversible lymphopaenia	Orally, 0.5 mg daily	Lymphocyte count, LFTs, blood pressure periodically Visual acuity periodically Skin cancer screen annually	First-dose bradycardia, macular oedema	In-hospital cardiac monitoring required for first dose
Siponimod		Orally, 2 mg daily after initial uptitration		Similar to fingolimod	Cardiac monitoring in patients at risk for first dose
Ozanimod		Orally, 0.92 mg daily after initial uptitration			Cardiac monitoring in patients at risk for first dose
Cladribine	Synthetic adenosine analogue, interferes with DNA synthesis, reduces circulating lymphocytes	Two courses 12 months apart – total oral dose 1.75 mg/kg per course, half over five days in week 1, remainder in week 5	Lymphocyte counts at two and six months after starting treatment	Lymphopaenia, leukopenia, neutropenia, infection, hypersensitivity, headache, rash, alopecia	If lymphocytes <500 cells/mm^3, monitor closely for infection; if <200 cells/mm^3, consider herpes virus prophylaxis
Natalizumab	Recombinant humanised monoclonal antibody to α4-integrins, inhibiting leucocyte migration from blood to CNS	IV, 300 mg over one hour, given every four weeks (some circumstances can be given every six weeks)	MRI brain every 6–12 months JCV antibody testing every six months	PML	Persistent neutralising antibodies associated with reduced efficacy and increased risk of allergic reactions

Table continued on the next page.

Table 2. Disease-modifying therapies for multiple sclerosis[14] (Cont'd)

Medication	Mode of action	Route and recommended dose	Monitoring	Notable adverse effects	Other comments
Ocrelizumab	Humanised monoclonal antibody to CD20, depletes B lymphocytes	IV, 600 mg over several hours, every six months	None	Hypersensitivity and infusion reactions, infection, neutropenia Rare: PML	Long-term risks are not fully known, but there is a long-term risk of hypogammaglobulinaemia
Ofatumumab	Fully human monoclonal antibody to CD20	SC, 20 mg monthly	None	Hypersensitivity and infusion reactions, infection, neutropenia	Long-term risks are not fully known
Alemtuzumab	Humanised monoclonal antibody to CD52 (present on B and T lymphocytes)	Two courses 12 months apart; IV infusion over four hours, 12 mg daily for five days on the first course and three days on the second	Enrolment in a monitoring program with monthly blood tests and urinalysis Annual skin cancer screening	Infusion-related reactions, autoimmune disorders	Autoimmune disorders may be induced – thyroid dysfunction (30–40%), immune thrombocytopenic purpura, cytopenias, nephropathies, autoimmune hepatitis Herpes virus prophylaxis recommended from the start of each treatment for 1–2 months

bd, twice per day; CNS, central nervous system; FBE, full blood examination; IMI, intramuscular injection; IV, intravenous; JCV, John Cunningham virus; LFTs, liver function tests; MRI, magnetic resonance imaging; PBS, pharmaceutical benefits scheme; PML, progressive multifocal leucoencephalopathy; SC, subcutaneous injection

therapies to repair damaged neurons and various neuroprotective methods to prevent degeneration of previously demyelinated nerves.

Supplements and dietary modification

Low serum vitamin D levels are associated with higher disability in patients with MS.[32] Serum vitamin D should be checked regularly, with patients starting oral supplementation when levels drop below 100 nmol/L.

Altered gut bacteria and their short-chain fatty acid production have been suggested as part of MS pathogenesis. Early studies on short-chain fatty acid supplementation are promising,[33] but more data are required. The Mediterranean diet has shown a non-significant trend towards improved outcomes.[34] Other diets have been assessed in multiple studies with conflicting results.[32] Biotin supplementation showed early promise to slow disability in progressive MS, but

a recent phase III trial failed to show any benefit.[35]

Monitoring of treatment efficacy and treatment complications

Routine monitoring with MRI for subclinical radiological activity is often performed annually, and it may be performed more frequently when a risk of serious treatment-related adverse effects exists.[2] Patients should also have an MRI scan after a suspected MS relapse. Ideally, imaging comparisons are made on scans performed using comparable MRI field strength and imaging protocols, as variations may limit image interpretation or require a new baseline scan. Spinal cord MRI is not as sensitive to changes as MRI of the brain and is not always performed after the baseline scan. Gadolinium contrast allows increased detection of active demyelination and is given when relapse or treatment failure is suspected. Each DMT has different additional monitoring requirements, listed in Table 2.

Pregnancy and breastfeeding considerations

The risk of MS relapse is reduced during pregnancy when compared with the pre-pregnancy period;[36] however, the risk increases to greater than baseline in the first six months postpartum. Breastfeeding may slightly reduce this rate.[36] The most important factor affecting relapses during pregnancy is pre-pregnancy disease activity.

Any patient considering pregnancy should receive expert preconception planning regarding management of their DMT through the pregnancy and postpartum to balance DMT risks with that of disease recurrence. Expert opinion may allow the use of particular DMTs during some stages of pregnancy, or with a gap between DMT use and conception.[37]

COVID-19 and other vaccines

As a result of their immunosuppressed state, patients with MS on certain DMTs may be at higher risk of complications from COVID-19. Vaccination against

COVID-19 is recommended by both international and Australian MS medical societies for all patients with MS; however, the patient's DMT may influence the recommended timing of vaccination, and specialist advice from the treating neurologist should be sought.

Similarly, all patients with MS are recommended to complete the routine vaccination schedule. An exception is live vaccines, as these may present a particular risk, and expert opinion should be sought prior to administration. As advice in this area is rapidly evolving, it is recommended that readers follow updated advice on this topic on the MS Australia website (www.msaustralia.org.au/covid-19-vaccination-guidance-for-people-with-ms-2).

Prognosis of established MS

The outlook for patients with MS has improved substantially over the past few decades with improved DMTs. It is difficult to accurately forecast expected outcomes for patients on DMTs, as the long-term effects of these agents on prognosis and disease progression are only now being seen. A recent review over a 16-year period showed 18% of patients with RRMS progressed to SPMS, and 11% acquired sufficient disability to require a walking aid.[38] Increased morbidity is present, with an estimated 13.1 quality-adjusted life years lost per patient.[39] Modifiable risk factors that have a proven association with disease progression are low vitamin D level and current smoking.[32] Table 3 lists

non-modifiable factors associated with RRMS prognosis.

The progressive forms of MS have significantly earlier onset of irreversible disability, and most patients have mild-to-moderate disability by the time of diagnosis.[11] Risk factors associated with progression from RRMS to SPMS include older age at MS onset, male sex, high relapse frequency early in the disease, longer disease duration, higher baseline disability score, higher lesion burden on imaging, spinal cord involvement and lower brain volume.[13] Despite the advancements in RRMS treatment, options for progressive disease remain limited.

The largest international registry (MSBase) to track MS prognosis is ongoing and is being performed by Australian clinicians.[40]

Conclusion

MS is a clinical and radiological diagnosis based on the 2017 McDonald criteria. The range and effectiveness of treatment options have greatly improved over the past several decades, which has significantly improved the prognosis of MS in the modern era.

Resources

- MS Australia – information sheets for health professionals, www.msaustralia.org.au/about-ms/ms-practice
- MS Brain Health, www.msbrainhealth.org/healthcare-professionals

Table 3. Early clinical and imaging features affecting prognosis in multiple sclerosis[1,6]

Better prognosis	Poor prognosis
• Optic neuritis or isolated sensory symptoms as the initial presentation	• High relapse rate in first 2–5 years
• Complete recovery from the first neurological episode	• Substantial disability after five years
• Long interval to second relapse	• Abnormal initial MRI with large lesion load
• No disability after five years	• Infratentorial or spinal lesions on MRI
• Normal initial MRI	
• Older age at disease onset	

MRI, magnetic resonance imaging

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References

1. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17(2):162–73. doi: 10.1016/S1474-4422(17)30470-2.

2. Wattjes MP, Rovira À, Miller D, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis – Establishing disease prognosis and monitoring patients. Nat Rev Neurol 2015;11(10):597–606. doi: 10.1038/nrneurol.2015.157.

3. Magliozzi R, Cross AH. Can CSF biomarkers predict future MS disease activity and severity? Mult Scler 2020;26(5):582–90. doi: 10.1177/1352458519871818.

4. Solomon AJ, Bourdette DN, Cross AH, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. Neurology 2016;87(13):1393–99. doi: 10.1212/WNL.0000000000003152.

5. Wang ML, Zhang XX, Yu MM, Li WB, Li YH. Prevalence of white matter hyperintensity in young clinical patients. AJR Am J Roentgenol 2019;213(3):667–71. doi: 10.2214/AJR.18.20888.

6. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: A consensus approach. Mult Scler 2008;14(9):1157–74. doi: 10.1177/1352458508096878.

7. Allen CM, Mowry E, Tintore M, Evangelou N. Prognostication and contemporary management of clinically isolated syndrome. J Neurol Neurosurg Psychiatry 2020:jnnp-2020-323087. doi: 10.1136/jnnp-2020-323087.

8. De Stefano N, Giorgio A, Tintoré M, et al. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. Mult Scler 2018;24(2):214–21. doi: 10.1177/1352458517717808.

9. Lebrun-Frenay C, Kantarci O, Siva A, et al. Radiologically isolated syndrome: 10-Year risk estimate of a clinical event. Ann Neurol 2020;88(2):407–17. doi: 10.1002/ana.25799.

10. Andravizou A, Dardiotis E, Artemiadis A, et al. Brain atrophy in multiple sclerosis: Mechanisms, clinical relevance and treatment options. Auto Immun Highlights 2019;10(1):7. doi: 10.1186/s13317-019-0117-5.

11. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: A geographically based study 10: Relapses and

long-term disability. Brain 2010;133(Pt 7):1914–29. doi: 10.1093/brain/awq118.

12. Confavreux C, Vukusic S. The clinical course of multiple sclerosis. Handb Clin Neurol 2014;122:343–69. doi: 10.1016/B978-0-444-52001-2.00014-5.

13. Cree BAC, Arnold DL, Chataway J, et al. Secondary progressive multiple sclerosis: New insights. Neurology 2021;97(8):378–88. doi: 10.1212/WNL.0000000000012323.

14. Berkovich R. Treatment of acute relapses in multiple sclerosis. Neurotherapeutics 2013;10(1):97–105. doi: 10.1007/s13311-012-0160-7.

15. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. Lancet Neurol 2019;18(10):973–80. doi: 10.1016/S1474-4422(19)30151-6.

16. Australian Medicines Handbook. Australian Medicines Handbook 2020 [online]. Adelaide, SA: Australian Medicines Handbook, 2020.

17. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. Neurology 1995;45(7):1277–85.

18. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996;39(3):285–94. doi: 10.1002/ana.410390304.

19. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365(14):1293–303. doi: 10.1056/NEJMoa1014656.

20. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367(12):1087–97. doi: 10.1056/NEJMoa1206328.

21. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362(5):387–401. doi: 10.1056/NEJMoa0909494.

22. Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): A multicentre, randomised, minimum 12-month, phase 3 trial. Lancet Neurol 2019;18(11):1009–20. doi: 10.1016/S1474-4422(19)30239-X.

23. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): A double-blind, randomised, phase 3 study. Lancet 2018;391(10127):1263–73. doi: 10.1016/S0140-6736(18)30475-6.

24. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010;362(5):416–26. doi: 10.1056/NEJMoa0902533.

25. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354(9):899–910. doi: 10.1056/NEJMoa044397.

26. Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: A retrospective analysis of data from four clinical studies. Lancet Neurol 2017;16(11):925–33. doi: 10.1016/S1474-4422(17)30282-X.

27. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376(3):221–34. doi: 10.1056/NEJMoa1601277.

28. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376(3):209–20. doi: 10.1056/NEJMoa1606468.

29. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med 2020;383(6):546–57. doi: 10.1056/NEJMoa1917246.

30. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. Lancet 2012;380(9856):1819–28. doi: 10.1016/S0140-6736(12)61769-3.

31. Moore JJ, Massey JC, Ford CD, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. J Neurol Neurosurg Psychiatry 2019;90(5):514–21. doi: 10.1136/jnnp-2018-319446.

32. Hempel S, Graham GD, Fu N, et al. A systematic review of modifiable risk factors in the progression of multiple sclerosis. Mult Scler 2017;23(4):525–33. doi: 10.1177/1352458517690270.

33. Duscha A, Gisevius B, Hirschberg S, et al. Propionic acid shapes the multiple sclerosis disease course by an immunomodulatory mechanism. Cell 2020;180(6):1067–80.e16. doi: 10.1016/j.cell.2020.02.035.

34. Katz Sand I, Benn EKT, Fabian M, et al. Randomized-controlled trial of a modified Mediterranean dietary program for multiple sclerosis: A pilot study. Mult Scler Relat Disord 2019;36:101403. doi: 10.1016/j.msard.2019.101403.

35. Cree BAC, Cutter G, Wolinsky JS, et al. Safety and efficacy of MD1003 (high-dose biotin) in patients with progressive multiple sclerosis (SPI2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2020;19(12):988–97. doi: 10.1016/S1474-4422(20)30347-1.

36. Alhomoud MA, Khan AS, Alhomoud I. The potential preventive effect of pregnancy and breastfeeding on multiple sclerosis. Eur Neurol 2021;84(2):71–84. doi: 10.1159/000514432.

37. Krysko KM, Bove R, Dobson R, Jokubaitis V, Hellwig K. Treatment of women with multiple sclerosis planning pregnancy. Curr Treat Options Neurol 2021;23(4):11. doi: 10.1007/s11940-021-00666-4.

38. Cree BA, Gourraud PA, Oksenberg JR, et al. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 2016;80(4):499–510. doi: 10.1002/ana.24747.

39. Palmer AJ, van der Mei I, Taylor BV, Clarke PM, Simpson S Jr, Ahmad H. Modelling the impact of multiple sclerosis on life expectancy, quality-adjusted life years and total lifetime costs: Evidence from Australia. Mult Scler 2020;26(4):411–20. doi: 10.1177/1352458519831213.

40. Kalincik T, Butzkueven H. The MSBase registry: Informing clinical practice. Mult Scler 2019;25(14):1828–34.

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