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Practical management of multiple sclerosis

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Patients with multiple sclerosis often require high levels of medical input from their GP and treating neurologist. GPs are often their first point of contact regarding symptoms or complications of their disease or its treatment.

Key points

- **The diagnosis of multiple sclerosis (MS) is based on the principle that MS plaques develop on more than one occasion (dissemination in time) and in more than one part of the CNS (dissemination in space).**
- **MS cannot be diagnosed with MRI alone; clinical signs and symptoms must also be present.**
- **As a general rule, initiation of therapy in MS is a decision for the neurologist. The GP has a pivotal role in co-management.**
- **Immunomodulatory therapies cannot alleviate already existing MS symptoms. They merely prevent the development of acute relapses.**
- **Symptoms can influence each other in a negative way: for example, depression negatively affects cognition, and increased effort to overcome a higher muscle tone in spasticity may increase fatigue.**

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that affects an estimated 25,000 individuals in Australia, or about 0.1% of the population. The disease typically starts in early adulthood, and affects females approximately twice as often as males. In young adults, MS is the most common cause of neurological disability. The aetiology of MS is unknown; however, genetic as well as environmental factors such as infections, low sunlight exposure and vitamin D deficiency might be involved. Also, there is now unequivocal evidence for the deleterious effects of cigarette smoking on MS (it has been shown to increase the rate of progression of MS by 3.6 times).

Due to the high prevalence of the disease, GPs are likely to be confronted with these patients on a regular basis. They therefore play an important role in the management of these patients, including early diagnosis of the condition and referral of patients to a neurologist. The GP also serves as the first contact point and source of information for patients with MS. Daily problems, most of which are consequences of long-standing disease (e.g. spasticity, incontinence, pain, depression) are largely managed by the GP alone. Furthermore, the GP must be aware of the side effects and complications of the disease-modifying therapies used to treat MS.

This article focuses on the diagnosis of MS and also provides an overview on the presently available therapies and their side effects. Clinical and MRI presentations of MS and its pathology are also discussed.

HOW DO PATIENTS WITH MS PRESENT?

The plaques of MS can occur anywhere in the CNS, and therefore MS may present with a wide range of symptoms. These can include disturbed vision (if the plaque is in the optic nerve), loss of balance (due to a plaque in the cerebellum), and numbness, weakness or incontinence (caused by a plaque in the spinal cord). Most plaques are asymptomatic, with only about one in 15 causing clinical symptoms.

The clinically isolated syndrome, CIS

The first clinical episode in which a previously healthy person has symptoms and signs suggestive of MS is called a 'clinically isolated syndrome, or CIS. It usually occurs in young adulthood and the most commonly affected areas are the optic nerves, brainstem, cerebellum

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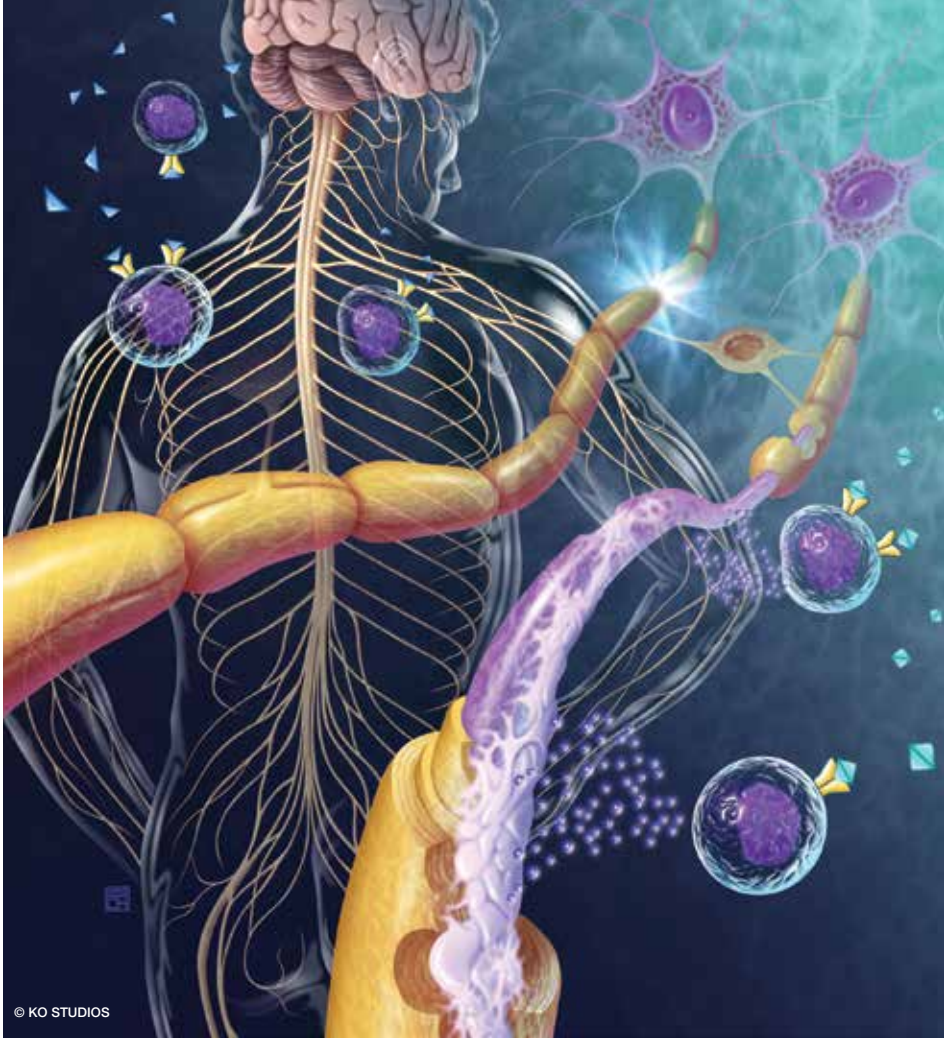
and spinal cord; the cerebral hemisphere is less often affected. The characteristics of a CIS are that the episode has an acute or subacute onset, lasts for at least 24 hours and occurs in the absence of fever or infection. Typically, patients recover from the symptoms after they reach their peak within two to three weeks. Usually a CIS is isolated in space (i.e. monofocal), which means that the patient has signs indicative for a lesion in a single area, and not in multiple areas. The features of a CIS suggestive of MS (typical features) and those for which other diagnoses should be considered (atypical features) are summarised in Table 1.



THE DISEASE COURSE

- *A relapse is caused by a newly developing MS plaque and is defined as a period of neurological worsening that lasts for at least 24 hours and occurs in the absence of fever or infection.*

Some patients with CIS never have a second area of demyelination, but if an episode subsequently occurs anywhere in the CNS then that is a defining event for the development of MS. Although the clinical course of MS varies considerably between patients, in the majority (about 85%) of those with the condition, the two phases described below and in Figure 1 can be distinguished.

The relapsing–remitting phase (RR–MS). This phase, which occurs at the beginning of the disease, is characterised by episodes of neurological disability (so-called exacerbations, relapses or attacks) separated by periods of recovery. In other words, disability due to the relapses resolves partly or completely in this phase. Relapses happen at random intervals, and occur on average about once per year, and steadily decrease thereafter.

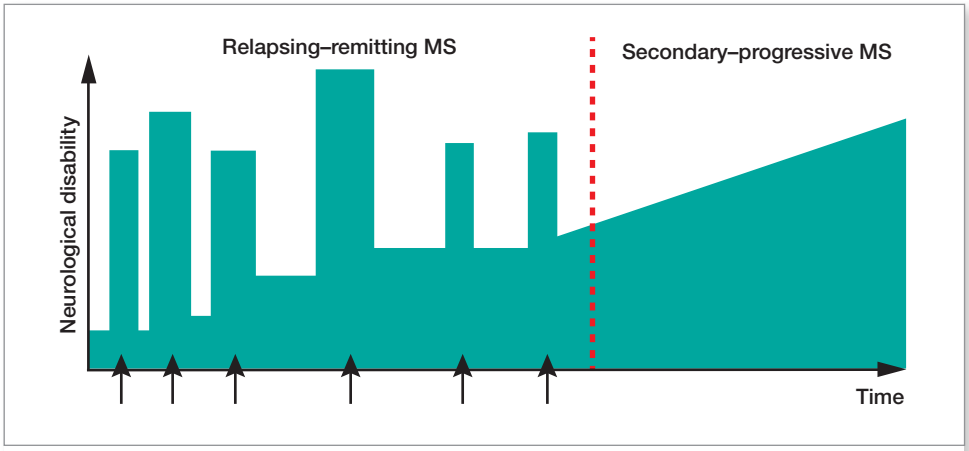


Figure 1. Disability due to relapses of MS is likely to resolve in the relapsing–remitting phase of the disease. Permanent and irreversible disability predominantly occurs in the secondary–progressive phase. Arrows indicate relapses.

TABLE 1. FEATURES OF CIS TYPICAL AND ATYPICAL FOR MULTIPLE SCLEROSIS

Typical for MS*	Atypical for MS†
All cases of CIS	
• Acute or subacute onset • Last at least 24 hours • Symptoms reach peak after three weeks • Partial or complete recovery beginning after three weeks • Most often monofocal	• Chronic/progressive onset • Symptoms last less than 24 hours (e.g. minutes, seconds) • Absence of recovery • Symptoms in setting of fever or infection
Optic nerve	
• Optic neuritis in one eye, characterised by: – mild pain on eye movement – reduced visual acuity and colour vision – normal or only mild disc swelling – improvement within three weeks from onset	• Optic neuritis in both eyes at the same time, characterised by: – complete loss of vision – no recovery – chronic blurry vision – painless or severe pain with visual loss – scintillating scotoma for minutes – photophobia
Brainstem/cerebellum	
• Loss of balance • Gaze evoked nystagmus • Often more than one symptom (e.g. vertigo and facial numbness) • Disturbed eye movements (weakness of eye muscles), double vision	• Fluctuating weakness of eye muscles (fluctuating double vision) • Isolated facial pain • Movement disorders (twitching eyelids, or forced closure of eye)
Spinal cord	
• Lhermitte's symptom • Urinary or faecal incontinence • Asymmetric weakness of limbs • Altered sensation on one side of trunk or both legs	• Tingling everywhere • Lateralised, marching tingling • Numb hands at night • Sharp level to sensory loss • Areflexia
Cerebral hemispheres	
• Hemiparesis • Hemisensory distubance	• Isolated fatigue • Isolated cognitive disturbance • Isolated depression • Generalised weakness • Epilepsy • Confusion • Chronic headache • Blindness in both eyes

Modified from Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. Lancet Neurol 2012; 11: 157-169.
ABBREVIATIONS: CIS = clinically isolated syndrome; MS = multiple sclerosis.
* These features of CIS are typical of an inflammatory demyelinating disorder of the CNS, such as MS.
† These features of CIS are not typical of an inflammatory demyelinating disorder of the CNS and other diagnoses should be considered.

The secondary–progressive phase (SP–MS). About 90% of patients with RR–MS progress to SP–MS within 25 years. This phase is characterised by steady neurological worsening without recovery. Typically, relapses do not occur during this phase. Patients in this phase lose their ability to walk independently and eventually become wheelchair or bed bound. Also, cognitive problems become more prominent.

Other phases

A small group of patients with MS (10%) follow a primary progressive disease course (PP–MS), which is characterised by steady decline in neurological functioning from the beginning. These patients usually present with a gait disorder and never experience relapses.

About 5% of patients with MS suffer from a progressive disease course accompanied by acute attacks with or without recovery, which is referred to as progressive–relapsing MS (PR–MS).

WHAT CAUSES DISABILITY?

- *Axonal loss is the major cause of progressive and irreversible neurological deficit in MS.*

The relapsing–remitting phase of MS is characterised by the development of acute MS plaques, which typically form in the corpus callosum, optic nerves, periventricular region, juxtacortical region and the spinal cord. The cerebellum and brainstem may also be affected. In addition, MS plaques frequently develop in the grey matter, although MRI has a low sensitivity for these lesions. The acute plaque consists of an accumulation of lymphocytes and macrophages, in close proximity to degenerating myelin, leaving 'nude' nerve fibres (axons) in the affected area. During this process, variable numbers of axons are also damaged. This phase is followed by a reactive astrocytic scar formation, and after the inflammation subsides a 'chronic inactive' MS plaque develops. Both axonal damage and scar formation are irreversible and, furthermore, axonal loss continues

after the acute inflammation subsides. Acute plaques cause a relapse if they develop in an eloquent area of the CNS; otherwise they stay clinically silent. A lesion is shown in Figure 2.

In the early stages of the disease, the brain is able to compensate for the damage of MS plaques and also variable remyelination occurs. In this phase, patients partly or completely recover from the symptoms of relapses. With increasing damage, the compensatory mechanisms become exhausted and progressive and irreversible neurological deficits develop; the patient has entered the progressive phase of the disease. In this phase, acute lesions become less common and global change in the white matter, with diffuse axonal loss and inflammation, becomes the prominent feature of the disease. As a consequence of longstanding disease and axonal loss, the brain 'shrinks'. Atrophy affects both the white matter and the grey matter, most likely has onset at the earliest stages of the disease, and is evident in later disease by the presence of wide sulci and ventricles and decreasing brain weight.

Figure 2. Brain slice with a macroscopically visible lesion in the subcortical white matter. The hallmark of MS are multiple, sharply demarcated 'sclerotic' plaques in the white matter. Some MS plaques can be seen with the naked eye. The lesions feel hard when touched, which is a consequence of the scar formed by astrocytes. This gave the disease its name: 'sclerosis' originates from the Greek word meaning 'hard'.

STILL CIS OR ALREADY MS? HOW IS MS DIAGNOSED?

- *The diagnosis of MS is based on the principle that MS plaques develop:*
  - *on more than one occasion, i.e. dissemination in time*
  - *in more than one part of the CNS , i.e. dissemination in space.*

Patients with CIS usually present with one episode in one part of the CNS – for example, the presenting symptom might be blurred vision due to a plaque in the optic nerve. The diagnosis of MS cannot be made until it is proven that the patient has had another MS plaque/episode in a different part of the CNS. If the same patient develops weakness due to a lesion in the cerebral hemispheres and at least 30 days between the onset of the weakness and optic neuritis can be distinguished

DIAGNOSING MULTIPLE SCLEROSIS

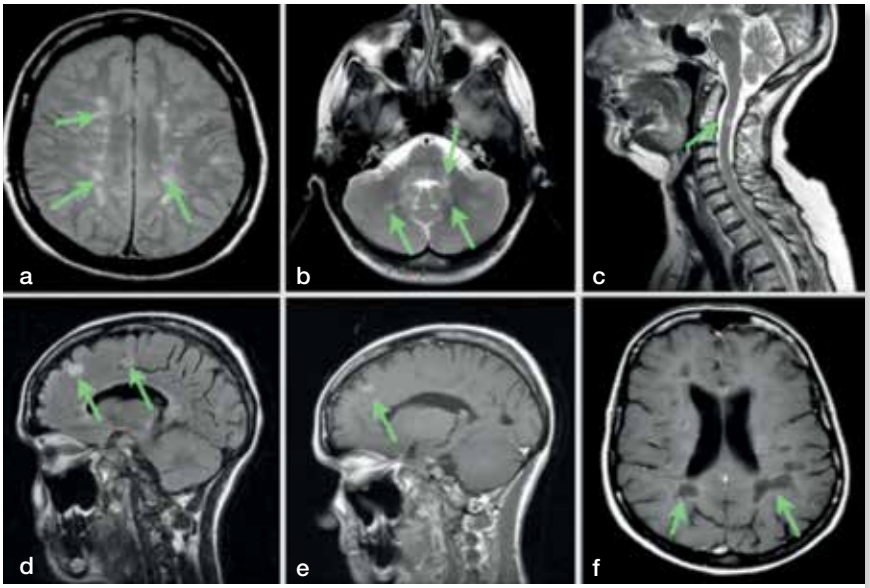
For the diagnosis of MS, lesions or symptoms have to show dissemination in space (DIS) and time (DIT), as summarised below and in the Table:

- if a patient has at least two clearly distinguishable episodes in two different anatomical locations of the CNS, a diagnosis of relapsing-remitting MS can be made
- if a patient has only one episode affecting one site, either the presence of both DIS and DIT on MRI is necessary to confirm the diagnosis or a second attack has to be awaited.

TABLE. WHAT IS NEEDED TO CONFIRM A DIAGNOSIS OF MS?

Number of episodes	First clinical episode	Subsequent clinical episode	Needed to confirm diagnosis		
			N	DIT	DIS
One episode 	One site affected	None		Yes	Yes
	Two or more sites affected	None		Yes	
Two episodes 	One site affected	Different site affected	Yes		
	One site affected	Same site affected			Yes

ABBREVIATIONS: DIS = dissemination in space; DIT = dissemination in time; N = no need for further confirmation.



Figures 3a to f. Typical MS lesions are round to ovoid in shape, from a few millimetres to more than a centimetre in diameter. a (top left). Multiple periventricular lesions, typically orientated perpendicular to the lateral ventricles (axial PD-weighted image). b (top centre). Infratentorial lesions (axial T2-weighted image). c (top right). Lesion in the dorsal aspect of the cervical spine. Typical spinal cord lesions are cigar shaped and eccentrically located, and do not involve the entire diameter of the medulla (sagittal T2-weighted image). d (bottom left). Juxtacortical lesions (sagittal FLAIR image). e (bottom centre). Contrast-enhanced active, juxtacortical lesion. Enhancement may be detectable up to eight weeks after formation of a new lesion (sagittal T1-weighted image with gadolinium). f (bottom right). Hypointense (dark) lesions on T1-weighted images are called 'black holes'. They are characteristic for MS and if they persist longer than six months correspond to severe tissue damage and axonal loss (axial T1-weighted image).

MRI CRITERIA FOR MULTIPLE SCLEROSIS

Dissemination in space

- One or more asymptomatic T2 lesions in at least two of the following four locations: juxtacortical, periventricular, infratentorial and spinal cord

Dissemination in time

- A new lesion visible on a follow-up scan when this is compared to a previous scan obtained at any time after the onset of CIS
- A scan showing both gadolinium-enhancing and non-enhancing lesions that do not cause clinical signs

DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS

Other demyelinating diseases of the CNS

Including:

- Acute disseminated encephalomyelitis
- Neuromyelitis optica
- Idiopathic transverse myelitis

Inflammatory nondemyelinating diseases of the CNS

Including:

- Sarcoidosis
- Vasculitis
- Systemic lupus erythematosus

Noninflammatory CNS diseases

Including:

- Small vessel disease
- Ischaemia/infarction
- Metabolic disorders

then dissemination in time and in space is present and the diagnosis of RR–MS can be made (see the box on page 19).

Magnetic resonance imaging (MRI)

- *MS cannot be diagnosed with MRI alone; clinical signs and symptoms must also be present.*

The imaging technique MRI is the modality of choice for the assessment of patients with suspected MS. CT has a very limited sensitivity to detect MS lesions and is therefore not used. MS lesions in typical locations are seen as hyperintense (bright compared with surrounding tissue) lesions on T2-weighted (including PD and FLAIR) magnetic resonance images. New so-called 'active' lesions typically enhance after the administration of gadolinium-based contrast agents, and appear 'bright' on T1-weighted images (Figures 3 a to f).

MRI may provide an earlier and more confident diagnosis in patients with CIS and can provide evidence for dissemination in time and space. More than half of adults with CIS have multiple asymptomatic brain lesions suggestive of MS. If lesions are present, gadolinium-enhanced MRI may be useful to demonstrate dissemination in time. The MRI criteria for multiple sclerosis are shown in the box on this page.

DIFFERENTIAL DIAGNOSIS

- *Spinal cord MRI is often useful for:*
  - *confirmation of dissemination in space*
  - *exclusion of structural lesions in patients presenting with a cord syndrome*
  - *clarification of the diagnosis in patients with an equivocal MRI of the brain.*

Asymptomatic white matter lesions detected as T2 hyperintense lesions are very frequent in a wide range of diseases, including some that may mimic MS (see the box above). The MS

TABLE 2. IMMUNOMODULATORY THERAPIES FOR MULTIPLE SCLEROSIS

Drug	Dosing	Adverse effects	Precautions
Interferon beta-1a	Intramuscular injection: 30 µg IM once a week Subcutaneous injection: 44 µg SC three times a week	Leukopenia, LFT abnormalities	Baseline and follow-up LFTs and full blood count
Interferon beta-1b	8 mIU SC every other day	Leukopenia, LFT abnormalities	Baseline and follow-up LFTs and full blood count
Glatiramer acetate	20 mg SC daily	Injection site reactions, systemic reactions	–
Natalizumab	300 mg IV once a month	Progressive multifocal leuko-encephalopathy	Immunodeficiency, JC virus positivity, cancer
Fingolimod	0.5 mg orally once daily	Bradycardia with first dose, macular oedema, decreased forced expiratory volume, LFT abnormalities	Immunodeficiency, infections, cancer, diabetes, asthma, cardiac disease, hypertension, varicella zoster virus immunity
Teriflunomide	14 mg orally once daily	Liver failure, neuropathy, leukopenia	Pregnancy, LFTs, basal cell carcinoma
Dimethyl fumarate	240 mg orally twice daily	Flushing, gastrointestinal symptoms	Baseline and annual full blood count

ABBREVIATIONS: IM = intramuscular; IV = intravenous; LFT = liver function test; SC = subcutaneous.

MRI criteria should therefore only be used in the clinical context of suspected MS or CIS. Nonspecific lesions, particularly those that are small and subcortical, are frequently seen in otherwise normal healthy people. Because of the nonspecific nature of these lesions, 'possible demyelination' is often mentioned in radiological reports, which can lead to an inappropriate and potentially harmful diagnosis of MS.

Other investigations, such as lumbar puncture and evoked potentials, are not mandatory for the diagnosis of RR–MS but can help to exclude other diseases or confirm the diagnosis of demyelination. Routine blood tests are normal in patients with MS, but an autoimmune screen or investigations for infections are often necessary to exclude MS mimics.

THE THERAPY OF MS

As a general rule, initiation of therapy in patients with MS is a decision for the neurologist. However, the GP has a pivotal role in co-management.

If treatment of relapses is warranted, corticosteroids are used as the first-line therapy, followed by immunomodulatory therapies as necessary.

Corticosteroids

Corticosteroids are used for the first-line treatment of relapses in patients with MS. Not every relapse mandates treatment, however, and if the patient's symptoms are mild (e.g. paraesthesias), a watchful waiting period is usually appropriate. More significant symptoms (e.g. motor weakness or vision loss) may warrant the use of high-dose corticosteroid therapy. Most frequently, 1000 mg intravenous methylprednisolone is used for three to five days.

These drugs are potent anti-inflammatory agents that reduce oedema, stabilise the blood–brain barrier and may repair the regulatory function of immune cells. They accelerate recovery from the acute attack, but data on their effects on subsequent relapse and atrophy are lacking.

Immunomodulatory therapies

Immunomodulatory or disease-modifying therapies are used as monotherapies in patients with relapsing MS to reduce the frequency and severity of clinical attacks. So far, no therapy has been proven effective for the purely progressive forms of MS.

The treatments with the longest history (interferon beta and glatiramer acetate) have understandably been the most often used treatments for MS. Their advantage is their excellent safety profile; their disadvantage, their incomplete efficacy in some patients. In addition, compliance may be poor in some patients, usually secondary to poor tolerance.

More recently introduced drugs (e.g. mitoxantrone, teriflunomide, fingolimod, natalizumab and dimethyl fumarate) may show greater efficacy in some patients but also possess greater safety concerns. Ideally, the optimal treatment would be the one with highest efficacy and least 'treatment burden' (i.e. side effects, tolerability, convenience and safety). In practice, a

compromise between efficacy and treatment burden has to be accepted.

The dosage, adverse effects and precautions for use of the immunomodulatory therapies currently available are summarised in Table 2.

Interferon beta

Interferon beta was the first approved medication for MS and has an extensive clinical trial evidence base. It reduces the frequency of relapses by about one-third. In addition, patients treated with interferon early in the course of the disease show a significant delay in time to disease progression.

Interferon beta-1a is administered by intramuscular injection weekly or subcutaneous injection three times per week, and interferon beta-1b by subcutaneous injection every other day. Common adverse effects include 'flu-like' symptoms (myalgia and fever), injection site reactions and, possibly, aggravation of depression. These side effects may be minimised with dose titration when commencing the drug and the use of antipyretics such as NSAIDs. Side effects decline over time. Haematological abnormalities (e.g. leucopenia, thrombocytopenia) and liver enzyme elevation are well documented but are usually transient in nature. Baseline liver function tests (LFTs) and full blood count should be performed, with follow-up testing typically at one, three and six months after interferon initiation.

Glatiramer acetate

Glatiramer acetate has comparable clinical efficacy to interferons for the treatment of MS. It does not require regular blood monitoring. The most common side effects are injection site reactions (itching, bruising and lipoatrophy), and about 10% of patients develop infrequent systemic reactions, which usually occur after several months of treatment, are self-limited, develop within 15 minutes of the injection and are characterised by flushing, tachycardia, tachypnoea and anxiety.

The exact mechanisms of action of the interferon therapies and glatiramer acetate in MS are not known.

Natalizumab

Natalizumab is the only monoclonal antibody approved for the treatment of MS at present, and in Australia a neurologist must initiate its use. It blocks adhesion molecules on lymphocytes and thereby prevents their migration into the brain. It reduces the relapse rate by 67% compared with placebo, and overall is very well tolerated.

Natalizumab has been associated with an increased risk of developing progressive multifocal leucoencephalopathy (PML), a rare opportunistic infection of the brain caused by the JC virus (JCV). Infection with JCV in childhood is common (seroprevalence of 50 to 57% in the general population) and mostly asymptomatic, with the virus remaining latent in the gastrointestinal tract, the kidneys and the CNS. PML most often presents with cognitive or behavioural symptoms (e.g. personality change), alone or in association with motor, language or visual symptoms. The risk for PML in patients treated with natalizumab ranges from less than one in 10,000 to one in 100 and increases with duration of treatment beyond two years, previous immunosuppressant therapy and a positive result with the proprietary Stratify JCV test. Therefore, the risks and benefits of treatment with natalizumab should be carefully considered in patients who have all three risk factors. On the other hand, patients who are Stratify JCV-negative have a very low risk of PML irrespective of duration of treatment and immunosuppressant use. Regular clinical and MRI follow up of patients with the neurologist is mandatory for therapy to continue. Practice points on the use of natalizumab are listed in the box on this page.

Mitoxantrone

Mitoxantrone is a cytotoxic agent that was used for patients with rapidly worsening relapsing–remitting MS or secondary–progressive MS. Its use has been superseded by newer agents such as natalizumab. It is recommended that all patients who have received mitoxantrone be monitored for late development of cardiac failure and haematological malignancy.

NATALIZUMAB PRACTICE POINTS

Before commencement

- Perform Stratify JC virus (JCV) antibody test
- Obtain baseline MRI of brain
- Perform clinical assessment
- Take history (including whether there has been immunosuppressive therapy in the past)

During treatment

- Monitor for signs typical of progressive multifocal leucoencephalopathy (PML)
- Perform Stratify JCV antibody test every six months if negative
- Perform clinical assessment at least every six months
- Perform MRI at intervals
- Reassess risk/benefits after two years

High PML risk

The risk of PML is high in patients with the following features:

- have been treated with natalizumab for longer than two years
- are Stratify JCV antibody-positive
- have had previous immunosuppressant therapy

Fingolimod

Fingolimod is an oral immunomodulatory agent approved for relapsing forms of MS. It blocks lymphocyte egression from lymph nodes, reducing the number of lymphocytes in the peripheral blood and therefore their migration into the CNS. The effects on circulating lymphocytes are reversible, and cell counts return to normal within four to six weeks after cessation of treatment. In the pivotal trial of fingolimod, the drug reduced the annualised relapse rate by 54% compared with placebo.

Fingolimod is generally well tolerated, but adverse effects may include bradycardia and atrioventricular block, and monitoring for these is required for six hours after the first dose. Other adverse effects include reversible asymptomatic elevations of liver enzymes, macular oedema, reduction in forced expiratory

FINGOLIMOD PRACTICE POINTS

Before commencement
- Perform baseline ophthalmologic examination
- Perform baseline liver function tests and complete blood count
- Start contraception if applicable
- Perform ECG
- Perform varicella zoster virus serology (to confirm immunity)

First dose
- Observe patient for six hours for adverse events such as bradycardia and atrioventricular block

During treatment
- Do not administer any live attenuated vaccines
- Perform ophthalmological examination three months after first dose
- Perform spirometric evaluation if clinically indicated
- Monitor blood pressure
- Follow up liver function tests and complete blood count

volume and an increased risk of infections due to marked peripheral lymphopenia. Nonimmunity to varicella zoster virus (VZV) is an absolute contraindication and VZV antibody testing must be performed prior to fingolimed's commencement. Other contraindications include myocardial infarction, unstable angina, stroke or transient ischaemic attack in the past six months, QTc interval longer than 500 msec and concomitant treatment with class Ia or III antiarrhythmics. Caution must be exercised in patients with diabetes, hypertension and asthma. Practice points regarding the use of fingolimod are summarised in the box on this page.

Cladribine

Cladribine is approved in Australia for the treatment of MS but has been withdrawn from the market by the manufacturer. It causes lymphocyte depletion and long-lasting lymphopenia and its parenteral formulation is used for the treatment of hairy cell leukaemia and B-cell chronic lymphocytic leukaemia.

Teriflunomide

Teriflunomide was approved in 2012 for the treatment of relapsing forms of MS. It is relatively well tolerated and is chemically closely related to leflunomide. It suppresses the proliferation and effector functions of activated B and T lymphocytes. It has been recommended for PBS listing by the Pharmaceutical Benefits Advisory Committee (PBAC) and a Patient Familiarisation Program has been under way for many months.

Patients taking teriflunomide require ongoing blood monitoring, and adverse effects include liver failure, neuropathy and leucopenia. Importantly, there is extensive enterohepatic circulation of this drug and if rapid drug clearance is required then active specific intervention is necessary. It is rated category X for pregnancy, and men too must stop taking the drug if they wish to father a child.

Dimethyl fumarate

Dimethyl fumarate is a new oral therapy that was recently approved by the TGA for use in patients with relapsing MS to reduce the frequency of relapses and to delay the progression of disability. It has been recommended for PBS listing by the PBAC and a Patient Familiarisation Program commenced in Australia in October 2013.

Dimethyl fumarate has been shown to significantly reduce MS disease activity, including relapses and development of brain lesions, as well as to slow disability progression over time. It has a favourable safety and tolerability profile, the most common adverse reactions being flushing, mostly mild to moderate in nature, and gastrointestinal symptoms (diarrhoea, nausea, abdominal pain). These events are most common at the start of therapy, and usually decrease over time. Dimethyl fumarate may decrease lymphocyte counts. A full blood count should be performed before initiation and repeated annually or as clinically indicated.

Vitamin D

Vitamin D supplementation is often recommended to patients with MS, although strong evidence for benefit has not been accumulated. Observational studies have shown an association between low serum vitamin D concentrations and an increased incidence of MS, as well as increased MS activity. The true relation between serum vitamin D concentrations and MS has yet to be fully elucidated. Serum vitamin D concentrations greater than 75 nmol/L are recommended, and doses of 1000 IU up to 5000 IU daily may be necessary to maintain the desired serum levels. The possible benefits of vitamin D are being studied in Australia by the PrevANZ study, which commenced in 2012.

During vitamin D supplementation, patients should be monitored for signs of toxicity as well as serum levels.

Immunomodulatory treatments in development

Several immunomodulatory treatments for MS have shown positive effects in clinical trials and are likely to be introduced in the future. These treatments include oral therapies (laquinimod), as well as monoclonal antibody therapies (alemtuzumab, daclizumab and ocrelizumab).

SYMPTOM MANAGEMENT

- *Immunomodulatory therapies cannot alleviate already existing MS symptoms. They merely prevent the development of acute relapses.*

Immunomodulatory therapies reduce the number of relapses in MS and reduce clinical progression, but cannot relieve existing symptoms (e.g. pain, spasticity and cognitive problems) that the disease has already caused. Therefore, symptomatic treatments are of major importance for patients with MS. In many parts of Australia, the local chapter of the MS Society provides numerous patient services, including counselling, immunotherapy support, physiotherapy,

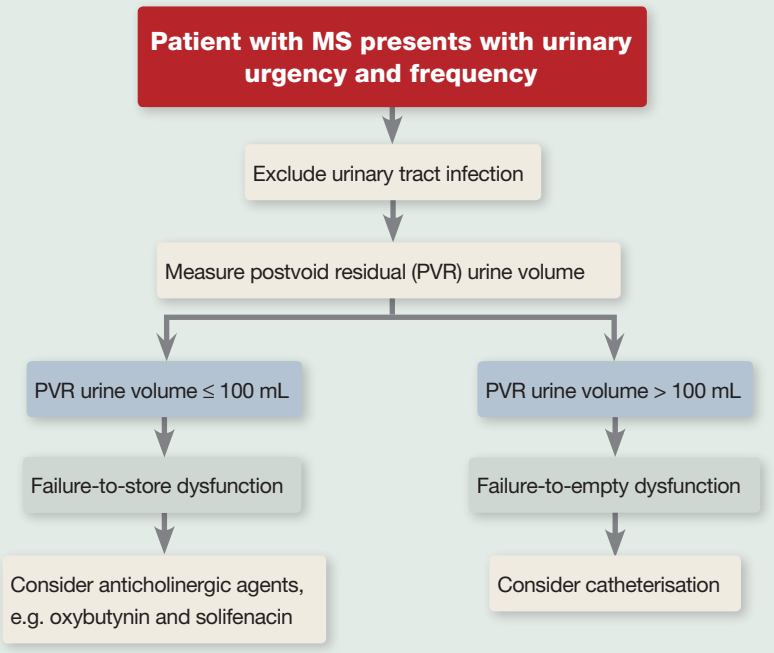
occupational therapy, continence support and home services, and has appropriately trained and experienced allied health staff. The multidisciplinary input they are able to provide can be of great assistance to the medical practitioner caring for patients with this disease.

Bladder problems

Bladder problems are present in more than 70% of patients with MS. Patients most often complain about urinary urgency, frequency, incontinence, urinary hesitancy and a sensation of bladder fullness after voiding. In all patients presenting with bladder problems, a urinary tract infection should be excluded as the first step. Then the bladder dysfunction should be categorised as either a failure-to-store or a failure-to-empty abnormality. Determination of postvoid residual (PVR) urine volume by ultrasound can help to distinguish between a failure-to-empty (PVR urine volume > 100 mL) and a failure-to-store (PVR urine volume ≤ 100 mL) dysfunction (see the flowchart on this page). Many patients have a mixture of both problems.

Failure-to-store bladder disorders may be treated with anticholinergic agents, such as oxybutynin and solifenacin. Intranasal desmopressin may be used to reduce nocturia but patients taking this require monitoring for hyponatraemia by measurement of serum osmolality. Failure-to-empty bladder dysfunctions are best treated with intermittent catheterisation. An α-adrenergic medication, such as tamsulosin, can reduce PVR urine volume, and may be effective in some patients. Patients with both failure-to-store and failure-to-empty bladder dysfunction may benefit from a combination of catheterisation and anticholinergic agents. More complex symptoms and/or no improvement may require an accurate diagnosis of the type of bladder or sphincter dysfunction, including urodynamics and urological referral. Intravesical injection of botulinum toxin by a urologist may be useful to treat refractory spastic bladder symptoms.

AN APPROACH TO BLADDER PROBLEMS IN PATIENTS WITH MULTIPLE SCLEROSIS



Bowel problems

Bowel dysfunction, including constipation or faecal incontinence, may occur in patients with MS. Constipation can be worsened by anticholinergic medication used for bladder problems, and also by antispasticity and antidepressant agents.

Pain

It is important to distinguish between primary pain due to the demyelinating process itself, and secondary musculoskeletal pain.

- Primary pain is characterised by a burning discomfort, or has a gnawing or shooting quality. Tricyclic antidepressants (such as amitriptyline and dothiepin) may be used as first-line treatment, but may exacerbate bladder dysfunction. The anticonvulsants gabapentin and pregabalin and the serotonin and noradrenaline reuptake inhibitors duloxetine and venlafaxine may also be used. First-line treatment for trigeminal neuralgia is carbamazepine, with other drugs being relatively ineffective.
- Secondary pain can arise due to poor posture, poor balance or the abnormal use of muscles and joints as a result of spasticity. Musculoskeletal pain is treated as in patients who do not have MS.

Spasticity

Besides pain, spasticity can lead to contractures and decubitus. The therapeutic approach should include physical and occupational therapy, stretching and exercise in addition to pharmacotherapy.

The first-line drug is the muscle relaxant baclofen, which must be slowly titrated from 10 mg to 140 mg per day in three to four divided doses. Side effects include sedation and increased muscle weakness, which may negatively affect gait.

Second-line agents include benzodiazepines, such as diazepam and clonazepam. Additional treatments for more severe spasticity management include intramuscular botulinum toxin injection and intrathecal baclofen pump placement. Controlled release fampridine may also benefit patients

with spasticity, improving their walking speed and reducing fatigue. Fampridine is not currently subsidised by the PBS and its cost may be prohibitive for many patients.

Fatigue

- *Increased effort to overcome a higher muscle tone in spasticity may increase fatigue.*

Fatigue is an overwhelming sense of tiredness and lack of energy, and is difficult to measure objectively. Nearly every patient with MS experiences fatigue to some degree, and one-third of them consider fatigue as the most troublesome of all symptoms. Fatigue can be the leading cause of inability to work and disruption of family and social life.

There is an overlap between the fatigue of MS and affective disorder, and many patients will benefit from the use of a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine or escitalopram. Amantadine may also be used on an empirical basis.

Depression

- *Symptoms can influence each other in a negative way – for example, depression negatively affects cognition.*

Major depression is the most common mood disorder associated with MS, and approximately 50% of patients with the disease are treated for depression at some stage. The GP must remain vigilant for depression in patients with MS. SSRIs are used as first-line agents.

Cognitive dysfunction

Cognitive impairment is frequent in patients with MS. It may already be present in the early disease stages, and may occur in the absence of significant physical disability. Cognitive problems mainly affect attention, concentration, short-term memory, information processing, visuospatial perception and verbal fluency. Although cognitive impairment can have significant impact on activities of daily life (driving, cooking, work performance), it often remains unrecognised. Cognitive dysfunction is one of the major causes for loss of employment and, along with affective disorder, is a significant factor in family breakdown.

MS CONTROVERSIES

Patients with MS frequently ask about or actively pursue unscientific and sometimes fraudulent putative therapies, and they are vulnerable to exploitation.

CCSVI

Patients may ask about 'CCSVI' (chronic cerebrospinal venous insufficiency) and MS. There is no scientific evidence for the efficacy of widening the cerebrospinal veins with angioplasty in patients with MS, and no reproducible randomised scientific evidence is able to associate these putative venous abnormalities with the occurrence, severity or progression of MS. Indeed, the converse is true.

Low-dose naltrexone

Similarly, there is no validated or randomised evidence to support the use of low-dose naltrexone in MS. Also, this drug is not licensed for MS and its use is not without hazard.

Diet

The evidence for the role of diet in MS is complex and unclear. Some uncontrolled observational studies have suggested that a low-fat diet may be beneficial, but careful case-control studies have not shown such a link. Some authors have proposed a high-fat so-called 'caveman diet'. The potential for significant confounders in the analysis of the relation between diet and MS is enormous, and until further evidence is available a healthy balanced diet remains appropriate advice.

CONCLUSION

The GP plays a pivotal role in the management of patients with MS and is usually the first point of contact when patients have symptoms or complications of either the disease or its treatment. Patients with MS often require high levels of medical input from both their GP and their treating neurologist. Knowledge of MS, its symptomatic therapies and the various disease-modifying therapies are pivotal in understanding the problems that patients with MS may encounter, and also facilitates effective communication between the patient, GP and neurologist. MT

FURTHER READING

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