

Early accurate diagnosis crucial in multiple sclerosis

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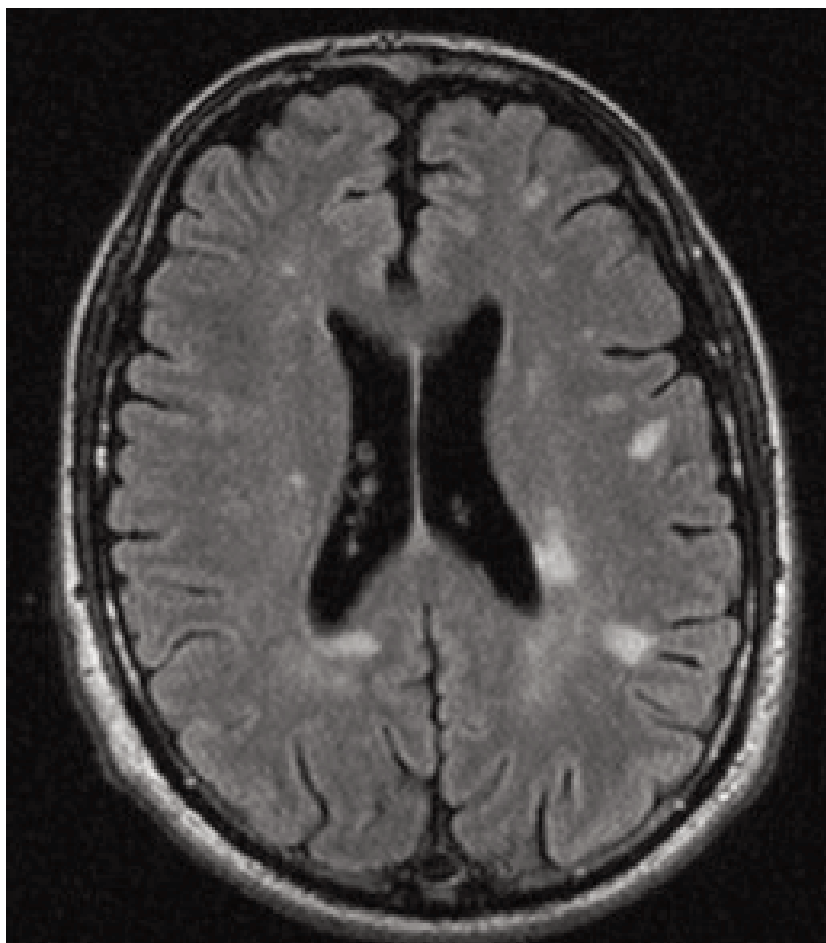
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FIGURE 1

Axial FLAIR image that shows typical MS lesions: small and ovoid hyperintensities in T2-weighted sequences. Here they are located in the periventricular white matter and juxtacortical white matter



MULTIPLE SCLEROSIS (MS) IS AN INFLAMMATORY-DEMYELINATING DISEASE OF THE CNS.

It is the most frequent disabling neurological disease among young adults, affecting 2.3 million people worldwide.¹ Around 100,000 people² in the UK have MS, giving an average prevalence of 1.5/1,000 (varying from 1.2/1,000 in England and Wales to 1.9/1,000 in Scotland).³

In about 85% of cases, MS starts with an acute neurological episode, a clinically isolated syndrome (CIS), considered to be the first clinical episode of relapsing-remitting MS (RRMS). It is characterised by the presence of acute relapses, after which there is normally a good functional recovery.⁴

About 15-20 years after symptom

onset, most patients develop secondary progressive MS (SPMS), characterised by a gradual and irreversible neurological decline.⁵ Although relapses can still be present in SPMS, the accrual of disability is typically independent of any relapses. In about 15% of cases, MS starts with progressive neurological deterioration, i.e. primary progressive MS (PPMS).⁶

MS affects women more frequently than men, with a ratio of 2-3:1.^{7,8} Age at disease onset varies depending on the type of MS. In RRMS the disease generally starts in the late 20s. Symptom onset in those with PPMS occurs around the age of 40.^{5,8} Once progression starts, the overall rate of neurological decline is similar for both SPMS and PPMS. Yet this progression rate may vary greatly between individuals and predicting

What are the different types of MS?

How should MS be diagnosed?

What are the management approaches?

which patients will follow a more rapid accrual of disability is still a challenge.

Recently, the International Advisory Committee on Clinical Trials in Multiple Sclerosis has re-examined the MS disease phenotypes.⁹ Although the main phenotype categories have not changed, these are now described in terms of the amount of disease activity observed, either inflammatory activity, i.e. presence of relapses and/or active lesions on MRI or neurodegenerative activity, i.e. disease progression. The goal of treatment in MS should be to prevent all disease activity.

The cause of MS is unknown. It is believed that a combination of risk factors can trigger an autoimmune response against the CNS leading to the development of MS. Risk factors can be either genetic or environmental and »

include a past history of infection by Epstein-Barr virus,¹⁰ high latitude/low solar exposure and low vitamin D levels,¹¹ smoking,¹² and obesity in adolescence.¹³

Clinical guidelines have been published by NICE,³ and the Association of British Neurologists (ABN) has produced guidance on the use of disease-modifying treatments in MS.¹⁴

PRESENTATION

Symptoms in relapsing-remitting MS

Clinical relapses reflect acute inflammation in the CNS, resulting in specific clinical syndromes:

Optic neuritis (ON): Acute inflammation of the optic nerve, generally unilaterally, presents with retroocular pain on eye movements, blurred vision, and colour vision impairment, i.e. dyschromatopsia. Recovery of visual function after ON may be incomplete and does not directly depend on the severity of initial visual loss.¹⁵

Myelitis: Acute inflammation of the spinal cord generally presents with

unilateral sensory or motor symptoms in one or two limbs. It can also present with a sensation of 'an oppressive band' in the trunk or an acute pain of neuropathic nature throughout the back triggered by cervical flexion (Lhermitte's sign). Bladder and bowel disturbances such as urge incontinence may also be present.⁴

Brainstem/cerebellum syndrome: Acute inflammation of the mesencephalon, pons, medulla oblongata, or cerebellum. Usual presentations include: diplopia, dysarthria, facial weakness or hypoesthesia, trigeminal neuralgia, lack of coordination in the upper limbs, or balance problems. Paroxysmal symptomatology, such as paroxysmal dysarthria, due to (aberrant) ephaptic transmission, can also occur in brainstem syndromes.⁴

Supratentorial syndrome: Less commonly, acute inflammation of the cerebral hemispheres may present with aphasia or cognitive dysfunction if the lesion involves the cortex, or, more frequently, with a hemimotor/ hemisensory

syndrome secondary to a subcortical lesion. Characteristically, only large supratentorial lesions will result in clinical symptoms, as opposed to lesions in other parts of the CNS.⁴

Symptoms in progressive MS (SPMS and PPMS)

Progression generally presents with gradual loss of power in the lower limbs, which may be asymmetric. It is often accompanied by sensory disturbances in the lower limbs, bladder and bowel symptoms. Upper limbs are generally affected at a later stage. Progressive loss of coordination in the lower or upper limbs can also occur. In the later stages of the condition, progressive dysarthria and difficulty swallowing may occur, the latter being potentially life-threatening if not managed effectively.¹⁶ Finally, there are all pervasive, interactive symptoms that can appear at any stage, notably fatigue, depression, pain and cognitive dysfunction.^{4,16,17}

When a patient presents with a clinical syndrome compatible with a CIS, they should be referred promptly to a

Table 1

Differential diagnoses in multiple sclerosis²⁷

	Signs that raise doubts about the diagnosis of MS	Assess for alternative diagnoses
Clinical (general)	Myopathy	Mitochondrial encephalomyopathy; Sjögren's syndrome
	Retinopathy	Mitochondrial encephalomyopathy; Susac and other vasculopathies (retinal infarction)
	Mucosal ulcers	Behçet's disease
	Recurrent spontaneous abortion or thrombotic events	Antiphospholipid antibody syndrome; thrombotic thrombocytopenic purpura; metastatic cancer with hypercoagulable state
	Arthritis, polyarthralgias, myalgias	Systemic lupus erythematosus; Lyme disease
Clinical (neurological)	Multiple cranial neuropathies, polyradiculopathy	Chronic meningitis in the context of sarcoidosis and tuberculosis; Lyme disease
	Peripheral neuropathy	B12 deficiency; adrenoleukodystrophy; metachromatic leukodystrophy; Lyme disease
	Extrapyramidal features	Whipple's disease; multisystem atrophy; Wilson's disease
	Cerebral venous sinus thrombosis	Behçet's disease; vasculitis; chronic meningitis, antiphospholipid or anticardiolipin antibody syndromes
MRI	Cortical infarcts	Embolic disease; thrombotic thrombocytopenic purpura; vasculitis
	Haemorrhages or microhaemorrhages	Amyloid angiopathy; Moyamoya disease; CADASIL; vasculitis
	Meningeal enhancement	Chronic meningitis; sarcoidosis; lymphomatosis; CNS vasculitis
	Lacunar infarcts	Hypertensive ischaemic disease; CADASIL; Susac syndrome
	Persistent Gd-enhancement and continued enlargement of lesions	Lymphoma; glioma; vasculitis; sarcoidosis
	Large and infiltrating brainstem lesions	Major Behçet's disease; pontine glioma
	Predominance of lesions at the cortical/subcortical junction	Major embolic infarction; vasculitis; progressive multifocal leukoencephalopathy

CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Gd = gadolinium; T1 = observed in MRI sequences that are weighted in T1; T2 = observed in MRI sequences that are weighted in T2

neurologist. An accurate and early diagnosis of MS is a priority for patients with this condition.¹⁸

Investigations need to:

- Rule out conditions that can mimic an inflammatory-demyelinating disease of the CNS
- Determine the presence of dissemination in space (DIS) and dissemination in time (DIT) of the inflammatory-demyelinating disease, the mainstays of the diagnosis of MS.¹⁹

MRI of the brain and spinal cord:

MS lesions are typically located in the

periventricular and juxtacortical white matter regions, brainstem, cerebellum, and spinal (preferentially cervical) cord. MS lesions tend to be small and ovoid in shape, see figure 1, p21). Gadolinium (Gd) contrast may be administered to assess disruption of the blood-brain barrier, which reflects acute inflammation. High lesion loads are associated with a greater risk of having a second relapse (in patients with a CIS), and a greater risk of future progression of disability.⁷

CSF examination: In MS, there is typically production of immunoglobulins within

the CNS, known as oligoclonal bands (OB). Normally, these OB are absent in peripheral blood, causing a blood-CNS mismatch, relatively specific to this disease, although it can be seen in quite a few other immunological conditions. The presence of OB in the CNS (together with their absence in serum) has been associated with a worse prognosis.^{7,20}

Visual, sensory, and brainstem evoked potentials:

Prolonged latencies in evoked potentials (and other neurophysiology tests) are indicative of demyelinating damage in the pathway explored. Visual evoked potentials (VEPs) are the most robust and clinically useful. Abnormally prolonged latencies in VEPs have been strongly associated with the presence of demyelination,²¹ have been used to support the diagnosis of MS,^{22,23} and are related to a worse prognosis.²⁴

FIGURE 2

Algorithm for the diagnosis of RRMS after a CIS.

The diagnosis of RRMS can only be made if: dissemination in space (DIS) and dissemination in time (DIT) are demonstrated. The presence of DIS and DIT indicate greater probability of a chronic inflammatory-demyelinating disease of the CNS such as MS, rather than a monophasic episode

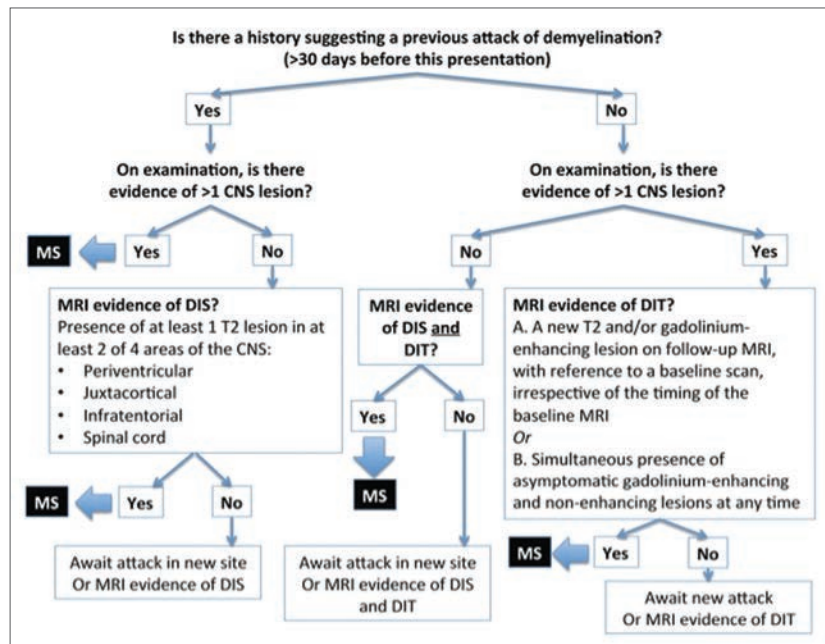
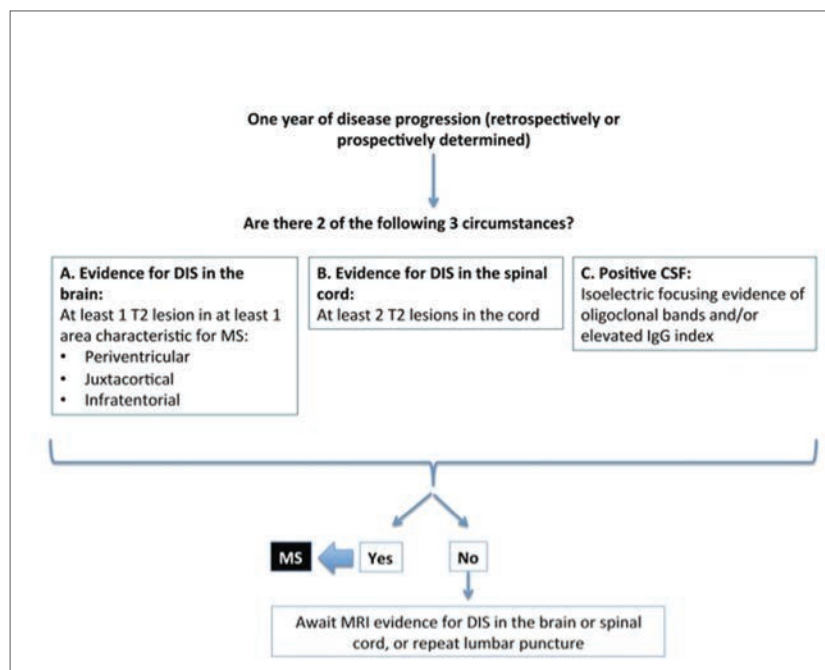


FIGURE 3

Algorithm for the diagnosis of PPMS.

For the diagnosis of PPMS the following need to be demonstrated: dissemination in space (DIS) in the brain and spinal cord, and dissemination in time (DIT), reflected by the presence of progression of disability for at least one year, which is mandatory for the diagnosis. The presence of oligoclonal bands in the CSF may support incomplete evidence of DIS



DIAGNOSIS

There is no confirmatory test for MS and it remains essentially a clinical diagnosis. Yet the exclusion of other conditions²⁵ (see table 1, p22) together with the fulfilment of current diagnostic criteria¹⁹ (see figures 2 and 3, left) allows the diagnosis of MS to be made with relative certainty. However, the diagnosis must always be revisited if unexpected symptoms appear.²⁵ In these cases, it may be that this is an unusual symptom for MS, the underlying condition is not MS or the patient has an additional condition.

A recent systematic review has shown that some conditions, such as meningiomas, possibly urinary system cancers, inflammatory bowel disease, irritable bowel syndrome, epilepsy, and several psychiatric conditions may be more frequent in those with MS than in the general population.²⁶ MS may reduce longevity, possibly in relation to the presence of comorbidities, especially psychiatric disorders.²⁷

MANAGEMENT

Management in MS is based on education, prevention, a multidisciplinary approach and self-management. Education is key as without a firm knowledge and understanding of their condition, patients will not be empowered to play an active role in its management. Patients should be encouraged to take regular exercise and adhere to a healthy diet. Regular exercise is particularly important for long-term mobility in MS.³

NICE guidelines do not recommend omega-3 or omega-6 fatty acid

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supplements, which had been suggested to be associated with better outcomes in MS, as there is insufficient evidence of their benefit. Similarly, there is not enough evidence that vitamin D supplements can improve relapses or disability in MS. Some studies have recently suggested that sodium chloride in the diet may worsen MS pathology,²⁸ although no recommendations have yet been made. There is increasing evidence supporting a harmful effect of smoking on progression of disability in MS, and there is a clear recommendation to advise patients not to smoke.³

Disease modifying drugs

Preventing worsening in MS includes strategies to change the disease course, i.e. disease modifying drugs (DMDs), which should be preceded by an accurate and early diagnosis. It may also include strategies to address specific symptoms in MS.²⁹ DMDs can only be prescribed in relapsing forms of MS (RRMS and SPMS with the presence of relapses), since they have only proved effective in reducing the number of relapses.

No treatment has proved effective in delaying, let alone stopping, the gradual neurological decline that characterises progressive MS.

Recently, the range of DMDs has broadened and they are usually divided into first- and second-line treatments.

First-line DMDs: These include beta-interferon (administered sc every other day or im weekly), and sc glatiramer acetate (daily or three times per week).³⁰

The new oral drugs BG-12 (dimethyl fumarate, twice daily)^{31,32} and teriflunomide (once daily)^{33,34} are also considered first-line DMDs.

They have all proved effective in reducing the number of relapses, around 30% for the interferons and glatiramer acetate,³⁵ and around 40-50% for the new oral drugs.³¹⁻³⁴

Importantly, beta-interferons, glatiramer acetate, and teriflunomide are able to delay a second attack if given to CIS patients at high risk of a further attack (i.e. high lesion load).^{36,37} At present, NHS England, based on the criteria outlined in the ABN guidelines,³⁸ recommends first-line DMDs for RRMS with at least two relapses over the past two years.³⁰

Beta-interferons can be prescribed within the first two years after a CIS if there is a high risk of developing further relapses, i.e. high lesion load and evidence of continuing disease activity on MRI.³⁰

The main side effects of first-line DMDs include:

- Flu-like symptoms (beta-interferon)
- Immediate post-injection reaction including vasodilatation, chest pain, dyspnoea, palpitations, and tachycardia (glatiramer acetate)
- Mild-moderate lymphopenia and elevated liver enzymes (beta-interferon, dimethyl fumarate, and teriflunomide)
- Flushing and gastrointestinal events (dimethyl fumarate)
- Hair loss, peripheral neuropathy, and elevated blood pressure (teriflunomide).

Second-line DMDs: These generally include iv natalizumab (administered monthly),^{39,40} oral fingolimod (daily),^{41,42} and iv alemtuzumab (for five consecutive days initially, and for three consecutive days one year later).⁴³⁻⁴⁵ They have all proved effective in reducing the number of relapses by around 55-70%.

Usually, second-line DMDs are recommended when, despite the use of DMDs, the relapse rate is equal to, or higher than, that prior to DMD treatment. In particular, the presence of at least two relapses over the previous year together with MRI evidence of inflammatory activity while on first-line treatment indicates the need to consider a second-line option.³⁰

However, all three drugs may be prescribed first line under certain circumstances. Natalizumab and alemtuzumab can be prescribed in patients with active MS, also called rapidly evolving severe relapsing remitting MS, i.e. if they have had at least two relapses over the past year together with MRI evidence of disease activity, even if they are not on any DMD.³⁰ Oral fingolimod, can be prescribed as an alternative to natalizumab in patients at high risk of progressive multifocal leukoencephalopathy (PML).^{30,46} »

FOOTNOTES

(a): start with very low dose and continue until optimum dose/maximum dose that can be tolerated; (b): when individual drugs do not provide adequate relief or it is not possible to increase the dose of individual drugs due to side effects; (c): potentially very useful for nocturnal spasms; (d): the use of fampridine to treat lack of mobility is not recommended because it is not a cost-effective treatment; (e): consider this for patients who have fatigue or mobility problems associated with limited standing balance; (f): not specifically named in the NICE guidelines for this purpose; (g): a randomised clinical trial has recently shown that pelvic floor muscle training alone or in combination with intravaginal neuromuscular electrostimulation or transcutaneous tibial nerve stimulation may be effective for female sexual dysfunction⁴⁸

Table 2

Symptomatic management in multiple sclerosis

Symptom	Assess for possible underlying cause/trigger
Spasticity	Urinary tract or other infections Constipation Inappropriately fitted mobility aids Pressure ulcers Pain
Reduced mobility	Infections Relapse Accrual of disability within the context of progressive MS
Fatigue	Depression, anxiety Pain Sleep disturbances Heat Medications Infections Medical problems
Emotional lability and depression	Anxiety, frustration Pain Medical problems
Cognitive dysfunction	Depression, anxiety Sleep disturbances Medications
Ataxia and tremor	
Visual problems (usually oscillopsia)	
Bladder dysfunction	Urinary tract infection Post-micturition bladder volume
Sexual dysfunction	Depression, anxiety Medications Pain, spasms
Bowel/anal sphincter dysfunction	Medications
Pain	Type of pain: neuropathic vs musculoskeletal pain Possible causes of musculoskeletal pain Depression
Dysarthria	Medications
Swallowing problems	
Pressure sore	Formal risk assessment Nutritional status Loss of sensation Cognitive status Handling techniques if wheelchair- or bed-bound Equipment deficiencies

Pharmacological treatment ³	Non-pharmacological treatment ³
First line (a): baclofen, gabapentin, or a combination of both (b) Second line: tizanidine or dantrolene Other drugs: pregabalin, clonazepam/benzodiazepines (c)	Physiotherapy and exercise Other interventions: Vibration, mid thoracic magnetic stimulation
Fampridine: not recommended (d)	Physiotherapy Supervised exercise programmes Vestibular rehabilitation (e) Continued regular exercise
Amantadine Other treatments (vitamin B12 injections) are not recommended	Aerobic exercise Energy conservation techniques Cognitive behaviour therapy (CBT) Supervised exercise programmes Vestibular rehabilitation (e) Continued regular exercise
If emotional lability: amitriptyline If depression: antidepressants	CBT for depression Liaison with psychiatrist
	Explain to patients that MS may affect cognitive abilities Assessment by occupational therapist and neuropsychologist
Isoniazid Other drugs: gabapentin is sometimes used (f)	Physiotherapy Consider neurosurgery if severe
First line: gabapentin Second line: memantine	Assessment by ophthalmologist
If overactive bladder: antimuscarinic drugs (oxybutynin); botulinum toxin A bladder wall injection; desmopressin if nocturia	If difficulty emptying: intermittent self-catheterisation; indwelling catheter; suprapubic catheter
If erectile and/or ejaculatory dysfunction in men: oral sildenafil. If sildenafil fails, intraurethral alprostadil	Physiotherapy of pelvic floor (g) CBT if underlying depression
If constipation: laxatives, rectal stimulants (suppositories, enemas), transanal irrigation	Assessment by continence advisor/physiotherapist If constipation: increase level of exercise, abdominal massage If incontinence: physiotherapy of pelvic floor, biofeedback retraining
For neuropathic pain (except trigeminal neuralgia): First line: either amitriptyline, duloxetine, gabapentin, or pregabalin Second line: tramadol; capsaicin cream if localised neuropathic pain For trigeminal neuralgia: First line: carbamazepine Second line: oxcarbazepine, lamotrigine, gabapentin, pregabalin, baclofen For musculoskeletal pain: Common analgesia	Assessment by pain specialists Physiotherapy Assessment by orthopaedic surgeon/rheumatologist if needed (musculoskeletal pain)
	Assessment by speech and language therapists Assessment by speech and language therapists Hygiene measures: improve seating, avoid food with mixed textures, add thickeners to liquids Swallowing/chest physiotherapy Consider NGT or PEG if severe
Nutritional supplements and hydration	Debridement if necessary Antibiotics/antiseptics Change position regularly Pressure relieving mattresses Regular skin inspections Referral to palliative care services if/when appropriate ³

The main side effects of second-line DMDs include the following:

Fingolimod: Bradycardia and other heart conduction abnormalities, lymphopenia, macular oedema, elevated liver enzymes, and elevated blood pressure.

Natalizumab: Immunogenicity (antibodies against the drug) and PML – the risk increases if the patient has received immunosuppressants in the past, has been on natalizumab treatment for more than two years, and has prior exposure to the John Cunningham virus.

Alemtuzumab: Marked perfusion reaction with nausea and vomiting, marked lymphopenia, high risk of viral infections, and secondary autoimmunity, especially affecting the thyroid, platelets and kidneys.

Recently, the ABN has suggested that all DMDs be divided into two broad categories, based on their efficacy.¹⁴

Category 1 drugs (moderate efficacy) include sc and im beta-interferon, sc glatiramer acetate, oral teriflunomide, oral dimethyl fumarate, and oral fingolimod.

Category 2 drugs (high efficacy) include iv natalizumab and iv alemtuzumab.

In general, the most recent recommendations by the ABN are similar to those currently proposed by NHS England, although the ABN encourages early treatment.¹⁴

With respect to SPMS, the treatment criteria for those relapsing forms would be similar to RRMS. For non-relapsing SPMS, as for PPMS, no treatment has been recommended.

DMD stopping criteria are not as straightforward as starting criteria, since it is extremely difficult to know when a treatment is not helping any more in a particular case. In general, it is accepted that the presence of intolerable side effects, the development of SPMS without relapses, and the confirmation of a pregnancy are situations where DMDs should be stopped. In some cases though, a neurologist may suggest that a woman with MS remains on DMD therapy throughout pregnancy.

Men receiving any of the DMDs whose partners are trying to conceive should discuss this with their MS nurse or neurologist.

MONITORING

Safety monitoring for DMDs must be carried out in specialised MS centres. In general, it includes regular blood tests and other investigations aimed at ruling out drug-specific side effects. Annual MRI brain scans are generally

recommended as well, to monitor both safety and treatment efficacy.¹⁴

If a patient with MS presents to their GP with symptoms suggestive of a relapse, it is important to check the concomitant presence of an infection, such as urinary tract infection or chest infection, and treat it if necessary.

Steroid treatment (usually 0.5 g oral methylprednisolone per day for five consecutive days, or 1 g iv methylprednisolone per day for three-five consecutive days) may be administered when there is a disabling clinical relapse. Steroids may shorten the recovery time but there is no firm evidence that they improve outcomes.³

Symptomatic treatment includes both pharmacological and non-pharmacological approaches.²⁹ Over time, the number of interacting symptoms tends to increase. NICE guidelines recommend comprehensive annual assessments by healthcare professionals with expertise in MS, focusing on mobility and balance, including falls, the need for mobility aids, including wheelchair assessment, use of arms and hands, and muscle spasms and stiffness.³

NICE also recommends the use of coordinated multidisciplinary approaches that involve consultant neurologists, MS nurses, physiotherapists and occupational therapists, speech and language therapists, psychologists, dietitians, social care and continence specialists, and GPs.³ Self-management strategies are vital and the patient should be at the centre of all decision making.

As regards pregnancy, there is no contraindication to pain relief or caesarean delivery, and MS is not thought to be associated with an elevated risk for any pregnancy complications, with the exception perhaps of low birthweight babies in women on beta-interferon (for newer drugs, i.e. fingolimod, natalizumab, teriflunomide, dimethyl fumarate and alemtuzumab, the information is limited).⁴⁷

Women with MS should discuss with their healthcare professional the increased risk of relapses at three-six months after childbirth, although it should be made clear that the risk of progression of disability is not increased in women who have children. Other general aspects must also be discussed, including long-term prospects in relation to overall MS prognosis.⁵

THE ROLE OF THE GP

GPs have a crucial role in referring patients with symptoms suggestive of MS to specialised MS centres. This can lead to early diagnosis and treatment. A recent survey by the MS Society suggests that there is still a lot to be done to raise awareness of the condition.¹⁸

Once the disease has been diagnosed, GPs should encourage patients to adopt a healthy lifestyle and to develop self-management strategies. NICE recommends regular comprehensive assessments, and GPs should be able to liaise with reference MS teams and to identify new needs, of any kind, that the patient with MS may have. GPs may play a key role in MS drug compliance, together with MS specialist nurses.

Organisations such as the MS Society and MS Trust (see Useful information box, p27) can provide valuable resources for both GPs and patients. Greater participation of the patient in the management of their condition increases their chances of successfully coping with the disease.

REFERENCES

- 1 Browne P, Chandraratna D, Angood C et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 2014;83:1022-24
- 2 Mackenzie IS, Morant SV, Bloomfield GA et al. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry* 2014;85:76-84
- 3 National Institute for Health and Care Excellence. CG186. Multiple Sclerosis: Management of multiple sclerosis in primary and secondary care. NICE. London. 2014
- 4 Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. *Lancet Neurol* 2012;11:157-69
- 5 Compston A, Coles A. Multiple sclerosis. *Lancet* 2008;372:1502-17
- 6 Thompson AJ, Montalban X, Barkhof F et al. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. *Ann Neurol* 2000;47:831-35
- 7 Tintore M, Rovira A, Rio J et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015;138:1863-74
- 8 Scalfari A, Neuhaus A, Daumer M et al. Age and disability accumulation in multiple sclerosis. *Neurology* 2011;77:1246-52
- 9 Lublin FD, Reingold SC, Cohen JA et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014;83:278-86
- 10 Lucas RM, Hughes AM, Lay ML et al. Epstein-Barr virus and multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2011;82:1142-48
- 11 Simpson S Jr, Blizzard L, Otahal P et al. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *J Neurol Neurosurg Psychiatry* 2011;82:1132-41
- 12 Hernan MA, Olek MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. *Am J Epidemiol* 2001;154:69-74
- 13 Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology* 2009;73:1543-50
- 14 Scolding N, Barnes D, Cader S et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015;15:273-79
- 15 Toosy AT, Mason DF, Miller DH. Optic neuritis. *Lancet Neurol* 2014;13:83-99
- 16 Rovaris M, Confavreux C, Furlan R et al. Secondary progressive multiple sclerosis: current knowledge and future challenges. *Lancet Neurol* 2006;5:343-54
- 17 Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol* 2007;6:903-912
- 18 MS Society. MS Priority Setting Partnership. Voting survey results 2013
- 19 Polman CH, Reingold SC, Banwell B et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the

key points

SELECTED BY

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In around 85% of cases, multiple sclerosis (MS) starts with an acute neurological episode, a clinically isolated syndrome, which is considered to be the first clinical episode of relapsing-remitting MS (RRMS). It is characterised by the presence of acute relapses, after which there is normally good functional recovery. About 15-20 years after symptom onset, most patients develop secondary progressive MS, characterised by a gradual and irreversible neurological decline.

MS affects women more frequently than men, with a ratio of 2-3:1. Age at disease onset varies depending on the type of MS. In RRMS the disease generally starts in the late 20s. Symptom onset in those with primary progressive MS occurs around the age of 40.

The cause of MS is unknown. It is believed that a combination of risk factors can trigger an autoimmune response against the CNS leading to the development of MS. Risk factors can be either genetic or environmental and include: a past history of infection by Epstein-Barr virus; high latitude/low solar exposure and low vitamin D levels; smoking; and obesity in adolescence.

Clinical relapses in RRMS reflect acute inflammation in the CNS, resulting in specific clinical syndromes including optic neuritis, myelitis, brainstem/cerebellum syndrome and supratentorial syndrome. In progressive MS, progression generally presents with gradual loss of power in the lower limbs, which may be asymmetric. It is often accompanied by sensory disturbances in the lower limbs, bladder and bowel symptoms.

Investigations need to rule out conditions that can mimic an inflammatory-demyelinating disease of the CNS and determine the presence of dissemination in space and dissemination in time of the inflammatory-demyelinating disease. There is no confirmatory test for MS and it remains essentially a clinical diagnosis.

Management is based on education, prevention, a multidisciplinary approach and self-management. Preventing worsening in MS includes strategies to change the disease course, i.e. disease modifying drugs, which should be preceded by an accurate and early diagnosis.

If a patient with MS presents to a GP with symptoms suggestive of a relapse, it is important to check for the concomitant presence of an infection, such as urinary tract infection or chest infection, and treat it if necessary. Steroid treatment may be administered when there is a disabling clinical relapse.

McDonald criteria. *Ann Neurol* 2011;69:292-302

20 Kuhle J, Disanto G, Dobson R et al. Conversion from clinically isolated syndrome to multiple sclerosis: A large multicentre study. *Mult Scler* 2015;21:1013-24

21 Asselman P, Chadwick DW, Marsden DC. Visual evoked responses in the diagnosis and management of patients suspected of multiple sclerosis. *Brain* 1975;98:261-82

22 McDonald WI, Compston A, Edan G et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50:121-27

23 Polman CH, Reingold SC, Edan G et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58:840-46

24 Fuhr P, Borggreffe-Chappuis A, Schindler C, Kappos L. Visual and motor evoked potentials in the course of multiple sclerosis. *Brain* 2001;124:2162-68

25 Miller DH, Weinshenker BG, Filippi M et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler* 2008;14:1157-1174

26 Marrie RA, Cohen J, Stuve O et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. *Mult Scler* 2015;21:263-81

27 Scalfari A, Knappertz V, Cutter G et al. Mortality in patients with multiple sclerosis. *Neurology* 2013;81:184-92

28 Kleinewietfeld M, Manzel A, Titze J et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature* 2013;496:518-22

29 Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. *Lancet Neurol* 2010;9:1182-99

30 NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis. 2014

31 Gold R, Kappos L, Arnold DL et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098-1107

32 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;367:1087-97

33 O'Connor P, Wolinsky JS, Confavreux C et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;365:1293-1303

34 Confavreux C, O'Connor P, Comi G et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:247-56

35 National Institute for Health and Clinical Excellence CG32. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. NICE. London. 2002

36 Tintore M. Rationale for early intervention with immunomodulatory treatments. *J Neurol* 2008;255 Suppl 1:37-43

37 Miller AE, Wolinsky JS, Kappos L et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:977-86

38 Association of British Neurologists. Revised (2009) Guidelines for Prescribing in Multiple Sclerosis. 2009

39 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;354:899-910

40 Miller DH, Khan OA, Sheremata WA et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;348:15-23

41 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;362:387-401

42 Cohen JA, Barkhof F, Comi G et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402-15

43 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;380:1819-28

44 Coles AJ, Fox E, Vladic A et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurol* 2011;10:338-48

45 Coles AJ, Twyman CL, Arnold DL et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012;380:1829-39

46 Tur C, Montalban X. Natalizumab: risk stratification of individual patients with multiple sclerosis. *CNS Drugs* 2014;28:641-48

47 Amato MP, Portaccio E. Fertility, pregnancy and childbirth in patients with multiple sclerosis: impact of disease-modifying drugs. *CNS Drugs* 2015;29:207-20

48 Lucio AC, D'Ancona CA, Lopes MH et al. The effect of pelvic floor muscle training alone or in combination with electrostimulation in the treatment of sexual dysfunction in women with multiple sclerosis. *Mult Scler* 2014;20:1761-68

Useful information

MS Society
www.mssociety.org.uk

MS Trust
www.mstrust.org.uk
The organisation also has a website to aid patients in decision making
www.msdecisions.org.uk

NICE
CG186. Multiple Sclerosis. Management of multiple sclerosis in primary and secondary care
www.nice.org.uk

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