Multiple sclerosis

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Abstract
Multiple sclerosis (MS) is an inflammatory neurological condition that primarily affects young adults. The incidence is increasing. Most people with MS initially present with a clinically isolated syndrome; which is an initial subacute neurological deficit otherwise known as a relapse. Most are subsequently diagnosed with relapsing–remitting MS, the most common form of the disease. Some develop secondary progressive MS; primary progressive MS is the least common form. Treatments are based on immunomodulation or immunosuppression. There is an increasing emphasis on aggressive early management to prevent long-term disability. Increased awareness and knowledge among practising clinicians from all specialties is important to ensure appropriate investigation, diagnosis and management.

Keywords
Demyelination; multiple sclerosis; pregnancy; relapsing–remitting; secondary progressive

Key points

- Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system, which leads to disability in young adults
- Environmental risk factors such as smoking, obesity, low vitamin D, low ultraviolet B exposure and previous infection with Epstein–Barr virus may significantly increase its risk
- Pathologically, MS is characterized by the presence of demyelinating plaques
- Corticosteroids are used to treat relapses, but they do not change the natural history of the disease
- All women presenting with MS should have regular conversations about family planning and be advised that starting disease-modifying treatment early will not affect their fertility in later life

Definition

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS). It is the most common cause of non-traumatic disability in young adults in the UK. MS is thought of as an organ-specific autoimmune disorder affecting the CNS. It most commonly presents in early adulthood and, as with many other autoimmune diseases, is three times more common in women.

Incidence and prevalence, UK and worldwide

MS affects 2.2 million people worldwide. Approximately 130,000 people across the UK are affected, with 6700 being diagnosed each year.

Epidemiology and aetiology

Several factors appear to play a significant role in an individual's risk of developing MS, including polygenic susceptibility as well as Epstein–Barr virus (EBV) seropositivity, low vitamin D levels, smoking, obesity and low ultraviolet (UV)B exposure. These combine to significantly increase the risk of MS, although individuals may still develop MS in the absence of any known risk factors.

EBV seropositivity is strongly associated with MS. Late infection with EBV resulting in infectious mononucleosis doubles the risk of developing MS. Migration studies illustrate the effect of environmental risk factors, with children of migrants to Europe (i.e. second-generation migrants) being at high risk. The risk in first-generation migrants appears to depend on the age of migration. The latitudinal effect of MS – a greater prevalence in countries further from the equator – correlates with vitamin D levels and UVB exposure.

Family members of MS patients have an increased risk compared with the general population. Individuals heterozygote for HLA-DRB1*1501 have an odds ratio (OR) of around 3, and homozygous individuals an odds ratio of >6. Over 100 common genetic variants (single-nucleotide polymorphisms) have been identified in genome-wide association studies (GWASs) as contributing to overall MS risk, although the risk conferred by each individual variant is low (OR approximately 1.1).

Course of the disease

MS commonly initially presents as clinically isolated syndrome (CIS), the first clinical attack caused by focal demyelination, alternatively termed a first clinical relapse. It is possible to diagnose at least some patients presenting with CIS with MS at the time of initial presentation – those with multiple lesions on magnetic resonance imaging (MRI) and positive cerebrospinal fluid (CSF) oligoclonal bands (OCBs) meet the 2017 revisions of the diagnostic criteria. This is based on the high probability of these individuals having a second attack. New lesions on sequential MRI (generally accepted as 3 or more months apart) can be used as evidence of dissemination in both time and space even in the absence of a second clinical attack.

Patients undergoing MRI for an unrelated reason (e.g. headache) who are found to have lesions suggestive of demyelination may be diagnosed with radiologically isolated syndrome (RIS). The rates of progression from RIS to CIS or MS remain unclear as they depend on a number of factors including case definition and duration of follow-up; however, a significant proportion of individuals will develop clinically apparent disease.

Around 85% of patients have relapsing–remitting MS and experience clinical relapses followed by varying degrees of recovery. Of these patients, 50% enter a progressive phase, known as secondary progressive MS. Approximately 15% of patients have a clinical course that is progressive from the outset without relapses, known as primary progressive MS.

The nomenclature used to describe these different phases of MS is useful for categorizing the disease course but is thought to reflect a continuum within the disease rather than separate entities. Disability in MS is measured using the Expanded Disability Status Scale (Figure 1).

Pathogenesis and physiological mechanisms

MS is characterized pathologically by the presence of demyelinating plaques. These inflammatory lesions are caused by CNS invasion of inflammatory cells such as macrophages, CD8 T cells and, to a lesser extent, B cells and plasma cells.[1] This leads to disruption of myelin and axonal damage, causing delay or loss of neuronal signalling, which results in the disability seen clinically. Lesions found in relapsing–remitting disease appear to have greater lymphocytic inflammation, while in progressive MS, B lymphocytes and plasma cells form a greater proportion of the inflammatory infiltrate. As the disease progresses, axons and neurones are affected, leading to progressive, gradual neuroaxonal deterioration and resulting brain atrophy. It seems likely that this neuroaxonal loss starts early in the disease course, and it may have a different underlying aetiology from the inflammation visible on MRI.

Diagnosing MS

Diagnosis can be challenging because of the clinical and radiological heterogeneity found in MS. A summary of the most recent diagnostic guidelines is given in Table 1. When assessing a patient who might have MS, the first important step is identifying a clinical syndrome suggestive of MS. The symptoms and signs found usually depend on and correspond to the location of the lesion. Optic neuritis, brainstem syndromes such as internuclear ophthalmoplegia, cerebellar syndromes and transverse myelitis are considered typical, and should prompt further investigation.[1] Presentations involving higher cognitive function, hemiparesis or psychiatric illness are rare.

Key examination findings

Clinical signs that are often found in MS patients include the following: a relative afferent pupillary defect caused by optic nerve involvement; optic disc pallor secondary to previous optic neuritis; internuclear ophthalmoplegia; cerebellar ataxia; and signs suggestive of spinal cord involvement including spastic paraparesis, bladder dysfunction and sensory ataxia.

Investigations

Serology: initial blood tests should include testing for vitamin B_{12} and folate concentrations, antinuclear antibody, HIV, syphilis and thyroid function. Depending on the clinical presentation, it is important to consider other blood tests, as detailed in Table 2.

Cerebral spinal fluid: patients with suspected MS should have a lumbar puncture to check for OCBs unique to the CSF (i.e. not present in paired serum), which are present in 90% of MS patients. Rarely, OCBs are not present early in the disease course. The presence of OCBs can be used to show dissemination in time as part of the McDonald criteria. Raised CSF neurofilament levels can provide additional support for the diagnosis.

Imaging: MRI of the brain and spinal cord is essential to confirm lesions in keeping with MS and to rule out other possible diagnoses. Active lesions enhance with gadolinium contrast, and asymptomatic historical lesions may also be noted. Characteristic findings are listed in Table 2 and noted in Figure 2.

Electrophysiology: delayed conduction in visual, auditory and sensory evoked potentials, in addition to slowed central motor conduction time, can also help to provide evidence for dissemination in space in certain cases.

MS mimics

Table 3 highlights important differential diagnoses. Red flags for MS include bilateral or severe optic neuritis, in addition to fever or intractable vomiting; these are more common in neuromyelitis optica (NMO, Devic's disease). Sarcoidosis, NMO associated with aquaporin (AQ4) antibodies, anti-myelin oligodendrocyte glycoprotein (MOG)-associated myelitis, tumours, paraneoplastic disorders and

systemic rheumatological disease can present with transverse myelitis. Fever and high CSF pleocytosis in the presence of a transverse myelitis or optic neuritis should lead to investigations for another inflammatory cause or infectious process. Involvement of multiple cranial nerves may be more typical of neurosarcoid, particularly in the context of leptomeningeal enhancement on MRI. Systemic symptoms such as weight loss, night sweats, poor appetite and lethargy should prompt a search for an underlying malignancy, while features such as joint pain, rash and lethargy can point to a rheumatological cause.[3]

Management

Acute relapse

Relapses are defined as an acute episode of neurological decline lasting >24 hours. There should be no other explanation or evidence of 'pseudorelapse' (a deterioration in neurological symptoms not caused by new demyelination) triggered by infection. Mild sensory symptoms occurring in isolation are usually not treated unless they cause significant distress. Most patients presenting with a relapse require MRI, in order to aid decision-making around treatment and to provide a baseline for future MRI studies.

Oral treatment for relapses includes 500 mg of methylprednisolone per day for 5 days. Current evidence suggests that there is no difference in medium and long-term outcomes between patients given oral or intravenous steroids. However, if patients present with severe relapses, have diabetes mellitus or a history of depression or mania, or treatment with oral corticosteroids has failed, they may require admission for intravenous methylprednisolone. This is usually given at a dose of 1 g/day for 3 days.

Symptomatic treatment

Symptoms in MS that result from CNS dysfunction include fatigue, depression, cognitive impairment, spasticity, sexual dysfunction, paroxysmal symptoms such as trigeminal neuralgia and temperature dysregulation. Fatigue affects approximately 80% of patients with MS. Management of fatigue includes limiting sedating medicines, ruling out co-morbid depression, addressing obstructive sleep apnoea and in some cases giving a prescribed exercise regime.

Depression occurs in 30% of MS patients and should be screened for at annual reviews. Cognitive behavioural therapy and selective serotonin reuptake inhibitors or serotonin–noradrenaline (norepinephrine) reuptake inhibitors have been shown to improve symptoms. MS-specific symptomatic therapies include Sativex (an oral cannabis extract) for spasticity and fampridine (Fampyra, dalfampridine) for walking, however NHS prescribing of these is limited.

Disease-modifying treatment (DMT)

An emerging concept in MS therapy is 'NEDA', or 'no evidence of disease activity', as a treatment target for people with MS. This new description has encouraged the earlier use of highly effective treatments to prevent subclinical progression of the disease and associated long-term disability. NEDA describes a state in which a patient is no longer experiencing relapses or disability progression (NEDA 1 and 2, respectively) and does not have any new lesions on MRI (NEDA 3), brain atrophy (NEDA 4) or CSF biomarkers such as neurofilaments (NEDA 5).[4]

There are now 12 different types of DMT licensed for people with MS, with several in development or awaiting regulatory approval. These therapies target the immune system in different ways. Interferon-β preparations, glatiramer acetate and teriflunomide are immunomodulatory, while natalizumab, fingolimod and ocrelizumab are immunosuppressant. A new therapeutic approach has sought to introduce the early use of immune reconstitution therapies, such as cladribine, alemtuzumab and haemopoietic stem cell therapy, to provide long-term efficacy with interval treatment.

Table 4 lists DMTs that are currently licensed in the UK (with haemopoietic stem cell therapy available via specific regional referral pathways). With more aggressive therapies, there are in general greater risks, which can be affected by individual co-morbidities. Natalizumab (Tysabri) has

been associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a subacute neurological condition caused by JC virus infection and more commonly associated with HIV/AIDS and other causes of chronic immunosuppression.

Implications in pregnancy

The peak incidence of MS is in women of childbearing age. Considerations around the management of MS in pregnancy are therefore highly important. Recent guidelines have advised that women with MS should not defer DMT because they wish to have children in later life, and they should be reassured that pregnancy will not increase their risk of disability. Women with MS should be encouraged to discuss family planning with their MS team before trying to conceive as DMTs have different safety profiles in pregnancy.

Glatiramer acetate and interferon-β can be continued in pregnancy and while breastfeeding. There is increasing evidence supporting the cautious use of natalizumab during (at least) early pregnancy – stopping this medication before pregnancy has been associated with significant relapses that may lead to sustained disability. A washout period of 4 months after alemtuzumab, 6 months after cladribine and 12 months after ocrelizumab should be adhered to before conception.

The Medicines and Healthcare Products Regulatory Agency has issued a warning regarding fingolimod and an association with teratogenicity – women taking this medication must have a negative pregnancy test before starting the medication, use adequate contraceptive methods and have at least a 3-month washout before trying to conceive. Teriflunomide is teratogenic in animals, and there are relatively few data on human pregnancies. Teriflunomide can be detected in the seminal fluid of men taking the drug, and the implications of this for exposure of the female partner should be considered in men with MS who want to start a family.

Dimethyl fumarate has a short washout period, and there is currently no signal for teratogenicity associated with fetal exposure. However, it is not recommended for women with MS during pregnancy or breastfeeding.[5] It is important for MS clinicians to be informed as soon as possible in the event of an unplanned pregnancy. Clinicians should be aware that corticosteroids and plasma exchange can be still be used for relapses in pregnancy, that MRI is not contraindicated but that gadolinium should not be used.

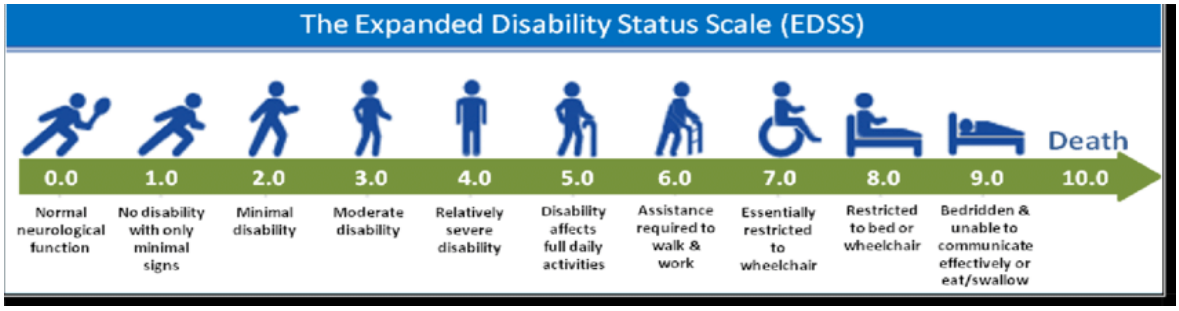

Figure 1. Expanded Disability Status Scale.
Source: Reproduced with permission from My-MS.org.

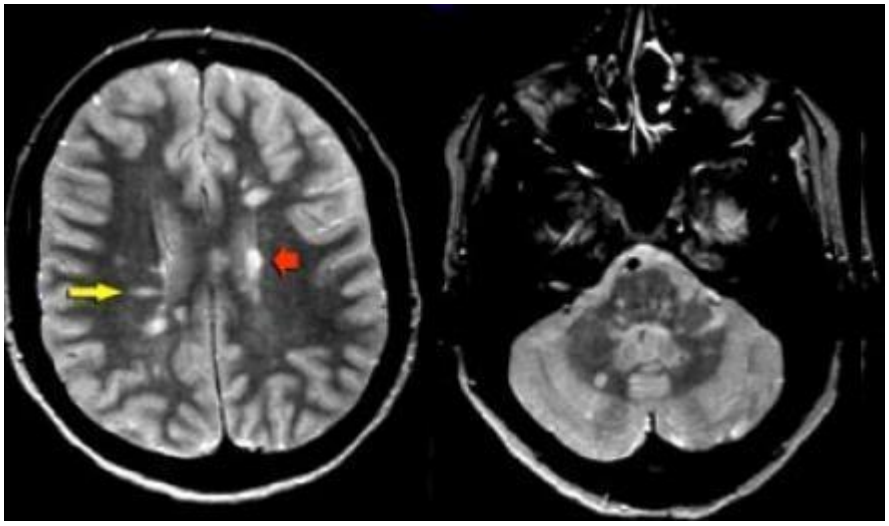

Figure 2. White matter lesions in a distribution typical of MS.
MRI showing periventricular lesions (red arrow) with Dawson's fingers (yellow) which are ovoid lesions perpendicular to the ventricle. Multiple brainstem and cerebellar lesions are shown in the MRI slice on the right.
Source: Reproduced with permission from radiologyassisstant.nl.

Summary of the 2017 McDonald Criteria for RRMS	
Dissemination in space	•Objective clinical evidence of 2 lesions ***or*** objective clinical evidence of 1 lesion with historical evidence of a prior attack involving a different CNS site ***or*** •≥1 T2 lesion in at least 2 of 4 of MS-typical areas of the CNS (infratentorial, juxtacortical, periventricular, spinal cord)
Dissemination in time	•≥2 attacks separated by at least 1 month ***or*** •Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time ***or*** •A new T2 or gadolinium-enhancing lesion on follow-up MRI irrespective of timing ***or*** •Presence of (2 or more) OCBs in CSF

Table 1

Source: Adapted from Thompson et al. (2018)[2] and Dobson and Giovannoni (2019).[4]

Investigations required in a patient presenting with CIS	
Baseline serology	Vitamin B_{12}, folate, antinuclear antibody, antineutrophil cytoplasmic antibodies, thyroid function, HIV, syphilis
Serology depending on presentation	Anti-aquaporin 4 (AQ4) antibody, anti-myelin oligodendrocyte glycoprotein (MOG) antibody – both for neuromyelitis optica Erythrocyte sedimentation rate, rheumatoid factor, complement Anti-double-stranded DNA, anti-cardiolipin, anti-phospholipid, Lyme disease – IgG/IgM Human T-cell lymphocytic virus 1 and 2 serology
Lumbar puncture	Presence of unmatched OCBs
MRI brain ± spinal cord ± gadolinium	New lesions enhance with gadolinium (for up to 1 month) **Typical brain lesions** •Periventricular Dawson's fingers (ovoid lesions perpendicular to ventricles) •Involvement of corpus callosum •Infratentorial lesions: peripheral lesions in the brainstem and cerebellum •Juxtacortical lesions (those touching the cortex) **Spinal cord lesions** •Less than two vertebral segments in height •Lesions are small and peripherally located
Visual and auditory sensory-evoked potentials	Delayed conduction times reflect areas of demyelination If normal, helps to exclude MS as diagnosis

Table 2

Differential diagnosis of relapsing and progressive MS				
Optic neuritis	**Isolated brainstem syndrome**	**Isolated spinal cord syndrome**	**Polysymptomatic**	**Progressive onset**
Ischaemic optic neuritis	Ischaemic/haemorrhagic (cavernous malformation)	Compression • Intervertebral disc • Tumour	Ischaemic event • Stroke • TIA • Small vessel disease • CADASIL	Compression • Disc • Tumour • Syrinx
Hereditary optic neuritis	Infiltrative	Ischaemia, infarction	Migraine	Progressive metabolic myelopathy
Inflammatory • NMO • Sarcoid • Lupus	Inflammatory • Sarcoid • Lupus • Brainstem encephalitis (Bickerstaff's) • CLIPPERS	Inflammatory • NMO • Sarcoid • Lupus • Sjögren's syndrome	Inflammatory • Sarcoid • Systemic autoimmune disease • Neuro-Behçet's disease	Genetic progressive spastic paraparesis/cerebellar ataxia • Hereditary spastic paraparesis • Spinocerebellar ataxia
Infection (syphilis, Lyme disease, viral, neuroretinitis)	Infection (syphilis, listeria, Lyme disease, viral)	Infection (syphilis, Lyme disease, viral, tuberculosis)	Primary CNS vasculitis	Leucodystrophies
Toxic/nutritional	Toxic/nutritional	Toxic/nutritional/metabolic • Vitamin B_{12} deficiency • Nitrous oxide toxicity • Copper deficiency	Susac's syndrome	Infectious causes • HIV • HTLV1
Infiltrative optic neuritis	Central pontine myelinolysis	Arteriovenous malformation	ADEM	
Retinal disorders	Neuromuscular Myasthenia gravis	Non-cord mimics • Guillain-Barré syndrome • Myasthenia gravis		

Table 3

ADEM, acute disseminated encephalomyelitis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; CLIPPER, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; TIA, transient ischaemic attack.

DMTs currently licensed or under investigation* in the UK			
	Trade name(s)	**Administration**	**Main adverse effects**
First-line injectables			
Interferon-β 1a and b	Avonex, Rebif, Extavia, Betaferon	Injectable; precise route variable according to brand	Injection site, flu-like symptoms, abnormal LFTs, leucopenia
PEG-IFN-β 1a	Plegridy	125 micrograms s.c. 2 weekly	Injection site, flu-like symptoms, abnormal LFTs, leucopenia
Glatiramer acetate	Copaxone Brabio (daily administration only)	20 mg s.c. daily or 40 mg s.c. three times a week (Copaxone only)	Injection site reactions, lipoatrophy, flushing
Oral immunomodulatory			
Dimethyl fumarate	Tecfidera (branded generic preparation also under evaluation)	120mg bd for first 2 weeks, maintenance dose 240 mg twice daily p.o.	Flushing, gastrointestinal symptoms, lymhopenia, abnormal LFTS, proteinuria, **PML**
Teriflunomide	Aubagio	14 mg daily p.o.	Hair thinning, gastrointestinal symptoms, abnormal LFTs, leucopenia
Oral immunosuppressive			
Fingolimod	Gilenya	0.5 mg daily p.o.	**Bradycardia (first dose)**, hypertension, bronchospasm, lymphopenia, abnormal LFTs, infections, **basal cell cancer**, **macular oedema**, opportunistic infections (**PML, cryptococcosis**)
Intravenous immunosuppressive			
Natalizumab	Tysabri	300 mg i.v. 4-weekly	Infusion reactions, **PML**
Ocrelizumab	Ocrevus	Initially 300 mg i.v., second dose 2 weeks later 300 mg i.v., subsequently 600 mg i.v. 6-monthly	
Immune reconstitution			
Alemtuzumab	Lemtrada	Year 1: 12 mg i.v. × 5 days Year 2: 12 mg i.v. × 3 days	Infusion reactions, opportunistic and other infections, leucopenia, secondary autoimmunity (thyroid, ITP, renal)

Cladribine	Mavenclad	Total dose of 3.5 mg/kg over 2 years (given as 2 courses 1 year apart)	Lymphopenia, infections (particularly herpes zoster)**PML**
*Autologous haemopoietic stem cell transplant		According to protocols	Adverse events as for those related to induction chemotherapy

Table 4

Bold type indicates serious adverse effects to be aware of.

ITP, idiopathic thrombocytopenic purpura; i.v., intravenously; LFT, liver function test; p.o., orally; s.c., subcutaneously.

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

QUESTION 1

A 27-year-old woman presented with a 2-day history of diplopia and blurring of vision on looking to the left. She had had some numbness in her right foot 6 months previously that had resolved before she sought medical attention.
On clinical examination, when asked to look to the left, she had failure of adduction to the left and horizontal nystagmus in the right eye on abduction.

What is the clinical sign?

A. Intranuclear ophthalmoplegia of the left eye
B. Intranuclear ophthalmoplegia of the right eye
C. Relative afferent pupillary defect of the left eye
D. Relative afferent pupillary defect of the right eye
E. Optic neuritis of the left eye

Correct answer: A.
Intranuclear ophthalmoplegia is a disorder of eye movement caused by damage to the medial longitudinal fasciculus, resulting in ipsilateral adduction failure with horizontal nystagmus in the unaffected eye on abduction. It results in blurring and double vision. A relative afferent pupillary defect is a condition in which the affected pupil becomes dilated when assessing direct response using the swinging flashlight test. Optic neuritis presents with painful visual loss in the affected eye which occurs over hours to days and may persist for weeks.

QUESTION 2

A 33-year-old woman presented with weakness of both legs (power 4/5), associated with tingling and numbness to the level of the umbilicus. She was finding it difficult to walk, but could manage to mobilise independently. She was known to have multiple sclerosis and was 20/40 weeks' pregnant. After discussion with her multiple sclerosis consultant, she had stopped taking her disease-modifying treatment prior to pregnancy. She had experienced similar symptoms during previous relapses of her multiple sclerosis. She had no dysuria or cough, and her inflammatory markers were normal.

What is the most appropriate management plan?

A. Urine dipstick, discuss with neurology team, consider MRI of the brain and spine either during or shortly after pregnancy, consider oral corticosteroids for management of acute relapse
B. CT of the brain and spine, start oral corticosteroids
C. Treatment with methylprednisolone intravenously
D. Restart disease-modifying treatment
E. Manage conservatively, refer to the multiple sclerosis specialist nurse

Correct answer: A.
Pregnant MS patients having a clinical relapse should be discussed with their MS team, or the neurology team if their MS team is not available. All people with MS having a possible relapse should have a urine dip performed, as UTI is a common cause of pseudorelapse. MRI is not contraindicated in pregnancy, but discussions about investigations and treatment of pregnant patients should be led by the neurology team. MRI is the investigation of choice in all MS patients presenting with

symptoms suggestive of a relapse with motor signs, and should be completed prior to initiating any therapy. Oral steroids for relapses impacting on function can be considered during pregnancy, but patients need to be carefully counselled. CT is not generally a useful investigation for MS relapses. Discussion with the neurology team is also important so that appropriate management and timely follow up can be ensured.

QUESTION 3

A 55-year-old man presented with his partner who reported that, over the past 3 months, she had been concerned that he had not been himself, had been irritable and had angered easily, which was unusual for him. In addition, he had seemed to have been a little clumsy over the previous week. He had previously been found to have relapsing–remitting multiple sclerosis but had been relatively stable since starting natalizumab. The last documented relapse had been a year before.

What is the appropriate next step in management?

A. Refer to psychiatry, consider starting antidepressants
B. Screen for urine infection and start corticosteroids, to attend for next natalizumab infusion as planned
C. Manage conservatively, review in the clinic in 4 months, with a multiple sclerosis specialist nurse review if needed
D. Admission for John Cunningham (JC) virus serology, urgent lumbar puncture for JCV viral load, MRI to rule out progressive multifocal leucoencephalopathy (PML). Withold natalizumab until above investigations performed.
E. Reassure his partner and refer him to outpatient physiotherapy.

Correct answer: D.

This patient has been treated with Natalizumab, a side effect of which can be the development of progressive multifocal leukoencephalopathy (PML) a rare but potentially fatal complication caused by reactivation of the JC virus. It usually develops over weeks to months and presents with features such as clumsiness, weakness, speech, visual and personality changes. It may mimic a relapse; however MRI and lumbar puncture should be performed as a matter of urgency. Early cessation of natalizumab and consideration of adjunct treatment is associated with improved outcomes, and so natalizumab should not be continued until PML is excluded.