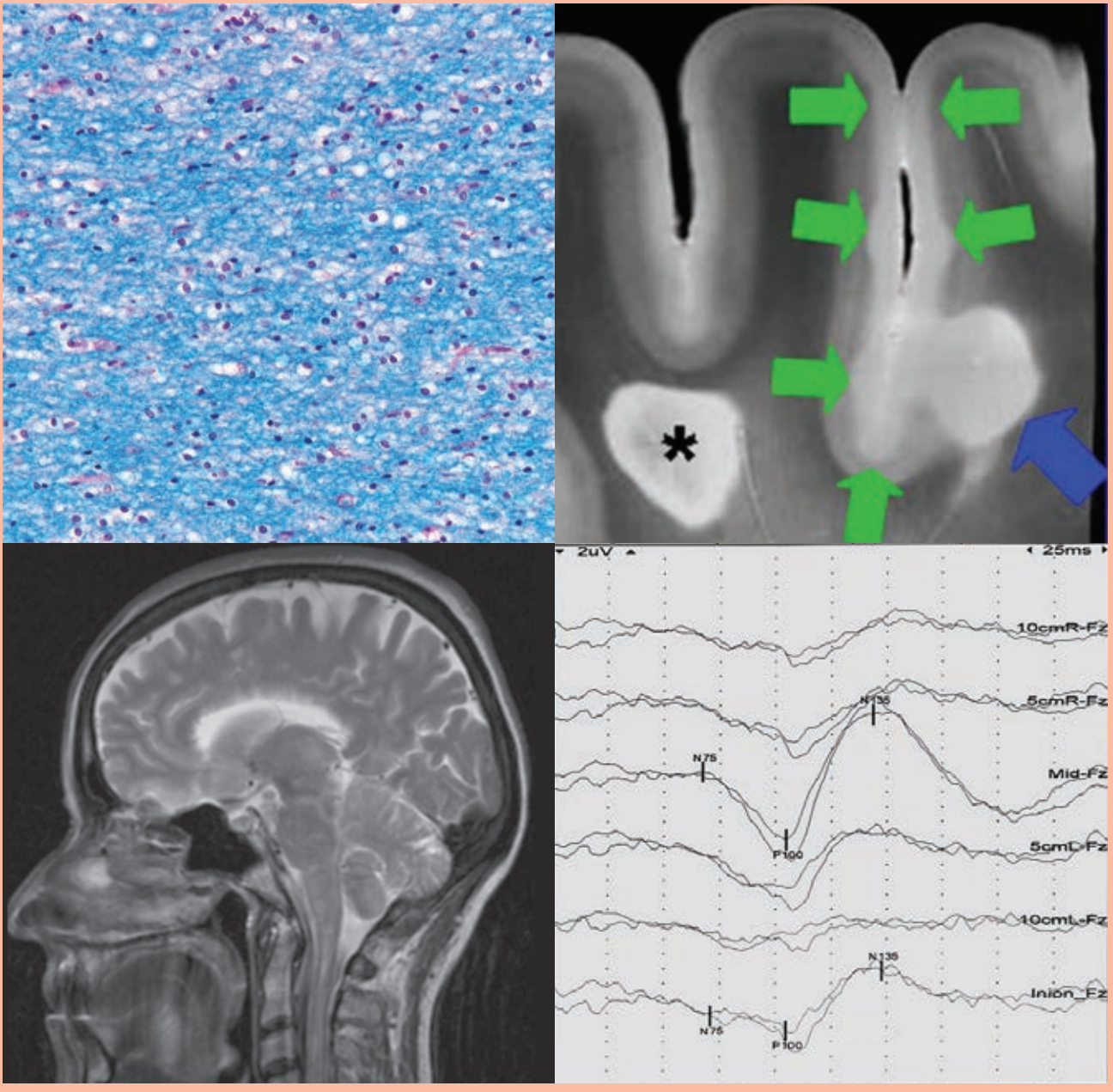
Visual Guide for Clinicians

MULTIPLE SCLEROSIS

R Dobson
G Giovannoni



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MULTIPLE SCLEROSIS

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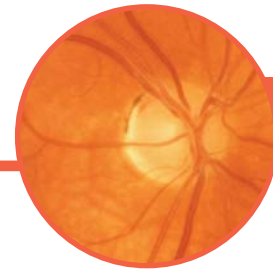
Abbreviations

ADEM	acute disseminated encephalomyelitis
BBB	blood–brain barrier
CMCT	central motor conduction time
DMD	disease-modifying drug
DWI	diffusion-weighted image
EAE	experimental autoimmune encephalomyelitis
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Score
FAMS	Functional Assessment in MS
FLAIR	fluid attenuated inversion recovery
GA	glatiramer acetate
Gd+	gadolinium enhancing
HLA	human leucocyte antigen
IFN	interferon
IM	infectious mononucleosis
IV	inverse variance
JCV	JC (after John Cunningham) virus
LVEF	left ventricular ejection function
MS	multiple sclerosis
MSCF	Multiple Sclerosis Functional Composite
MSIS-29	MS Impact Scale 29
MSQL-54	MS Quality of Life-54
MUGA	multiple gated acquisition scan
MUS	medically unexplained symptoms
Nab	neutralizing antibody
OCB	oligoclonal band
ON	optic neuritis
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
RF	radio-frequency
RNFL	retinal nerve fibre layer
RRMS	relapsing–remitting multiple sclerosis
S1P	sphingosine-1-phosphate
SPMS	secondary progressive multiple sclerosis
SSEP	somatosensory evoked potential
T	Tesla
VEP	visual evoked potential
WBC	white blood cell



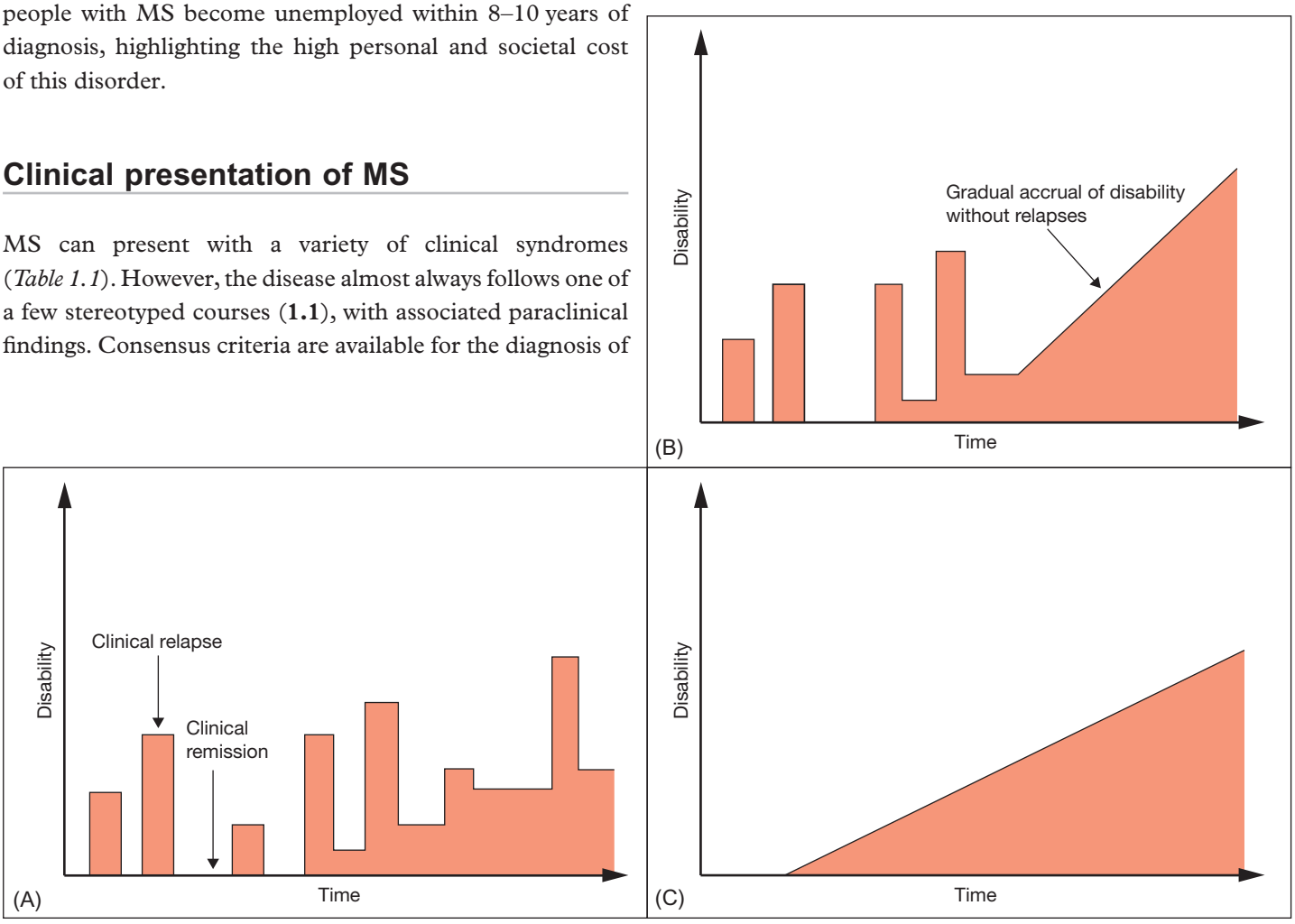
Diagnosing multiple sclerosis

Ruth Dobson, Angharad Davis and Ben Turner

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) and the most common non-traumatic cause of neurodisability in the young.[1] The average age at diagnosis is approximately 30 years. Up to 50% of people with MS become unemployed within 8–10 years of diagnosis, highlighting the high personal and societal cost of this disorder.

Clinical presentation of MS

MS can present with a variety of clinical syndromes (*Table 1.1*). However, the disease almost always follows one of a few stereotyped courses (**1.1**), with associated paraclinical findings. Consensus criteria are available for the diagnosis of MS (*Table 1.2*). A number of 'red flags' prompt the physician to consider an alternative diagnosis (*Table 1.3*).



1.1 Subtypes of multiple sclerosis. (A) Relapsing–remitting MS is characterized by episodic neurological symptoms (relapses), lasting days to weeks, followed by complete or partial recovery. (B) Following relapsing–remitting MS, many patients go on to develop secondary progressive MS, with gradual accrual of disability independent of relapses. (C) Primary progressive MS is characterized by the absence of relapses and the gradual accrual of disability from disease onset.

Table 1.1 Presenting symptoms in MS

Symptom/sign	Frequency (%)
Long tract symptoms (i.e. those arising from brain or spinal cord)	52
Multifocal symptoms	21
Optic neuritis	18
Brainstem symptoms	9

Adapted from Confavreux *et al*.[5]

Table 1.3 'Red flags' indicating that an alternative diagnosis to MS should be sought

- Age >60 years
- Hyperacute onset suggestive of vascular aetiology
- Lower motor neuron features, amyotrophy
- Significant nerve root pain
- MRI not in keeping with MS
- Features suggestive of an alternative multisystem disorder involving the CNS, such as aphthous ulcers, photosensitive rash

Table 1.2 McDonald criteria for the diagnosis of MS (2010)[6]

Clinical presentation	Additional data needed for MS diagnosis	
• ≥2 attacks AND objective clinical evidence of ≥2 lesions; OR • Objective clinical evidence of 1 lesion AND reliable history of ≥1 previous attack	None	
• ≥2 attacks AND objective clinical evidence of 1 lesion	Dissemination in space	• ≥1 T2 lesion in at least 2 of 4 'MS-typical' regions of the CNS (periventricular, juxtacortical, infratentorial or spinal cord); **OR** • Await a further clinical attack implicating a different site
• 1 attack AND objective clinical evidence of ≥2 lesions	Dissemination in time	• Simultaneous presence of gadolinium-enhancing and non-enhancing lesions on a single scan; **OR** • A new T2 and/or new gadolinium-enhancing lesion on a follow-up MRI; **OR** • Await a second clinical attack
• 1 attack AND objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in time and space	• Dissemination in **time**: simultaneous presence of gadolinium-enhancing and non-enhancing lesions on a single scan, or a new T2 and/or new gadolinium-enhancing lesion on a follow-up MRI; **AND** • Dissemination in **space**: ≥1 T2 lesion in at least 2 of 4 'MS-typical' regions of the CNS (periventricular, juxtacortical, infratentorial or spinal cord); **OR** • Await a second clinical attack implicating a different site
• Insidious neurological progression suggestive of MS (primary progressive MS)	1 year of disease progression (prospective or retrospective)	• Evidence of dissemination in space on MRI of brain and/or spinal cord • Positive CSF oligoclonal bands and/or elevated IgG index

CNS, central nervous system; CSF, cerebrospinal fluid; IgG, immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis.

Approximately 85% of people with MS present with a relapse, defined as acute deterioration in neurological function, followed by partial or total recovery (remission). The symptoms experienced during a relapse are dependent on the site of the lesions, although certain presentations are more common (*Table 1.1*). The first clinical event is described as a clinically isolated syndrome.

If a patient has a second relapse or shows magnetic resonance imaging (MRI) evidence of active disease then they fulfil the criteria for clinically definite relapsing–remitting MS (RRMS). The probability of progression from clinically isolated syndrome to clinically definite MS is highly dependent on MRI and cerebrospinal fluid (CSF) findings.[2] Patients may have relapses for a number of years, and may accrue fixed disability with each relapse.

After disease duration of 10–25 years, patients with RRMS may begin to accrue disability independent of relapses. They are then described as having secondary progressive MS (SPMS). Patients with SPMS may or may not continue to have relapses.

A significant minority of patients (10–15%) present with a progressive course from the outset without relapses. These patients are described as having primary progressive MS (PPMS). Rarely, a patient with a PPMS course has superimposed relapses and this is then referred to as progressive relapsing MS.

If a patient has been diagnosed with MS for 15 years and remains independently mobile, then they are referred to as having 'benign MS'. This diagnosis can only be made in retrospect.

Common clinical presentations

Although patients with MS may present with any number of neurological deficits, there are a few clinical presentations that are particularly common and worthy of further discussion.

Optic neuritis

Approximately 20% of patients who go on to develop MS present with optic neuritis (ON). Not all patients with ON go on to develop MS, but the overwhelming majority of patients with MS have at least one episode of ON.

The diagnosis of ON is predominantly a clinical one. Patients complain of unilateral visual blurring and/or colour desaturation. This is typically associated with retro-orbital eye pain, which is exacerbated by eye movements. Symptoms develop over days, and an ongoing deterioration in vision after 2 weeks suggests an alternative diagnosis. In ON associated with MS, total visual loss is rare, and suggests an alternative underlying aetiology.

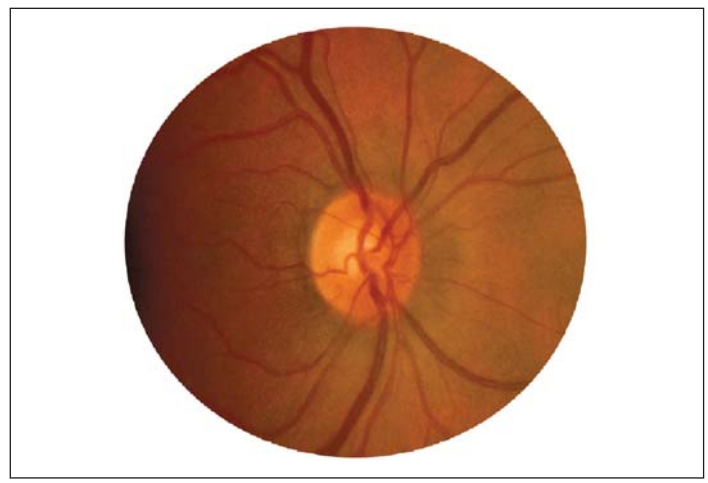
Examination of the fundus may reveal normal findings (**1.2**), or swelling of the disc, if the site of inflammation is anterior. The latter is referred to as papillitis and is seen in approximately 30% of patients presenting with ON (**1.3**). An afferent pupillary defect or relative afferent pupillary defect is commonly found, although this may be subtle in mild cases. Following resolution of an acute attack of ON, optic atrophy can be seen (**1.4**). MRI during an acute attack of ON may show gadolinium enhancement of the optic nerve sheath (**1.5**).

Treatment of an acute attack of ON is with intravenous steroids (most commonly methylprednisolone, 1 g/day for 3 days). This hastens recovery, but does not have any effect on long-term visual outcome.[3]

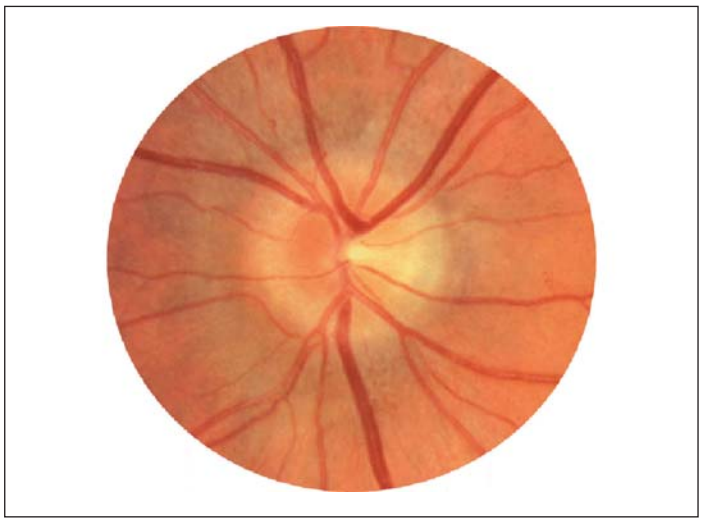
Transverse myelitis

There are a large number of causes of acute transverse myelitis, of which MS is only one. The clinical history tends to be that of evolution of weakness and/or sensory symptoms over days. Patients may have loss of pain, temperature and vibration sensation with a clear sensory level. Bladder and bowel function may also be affected.

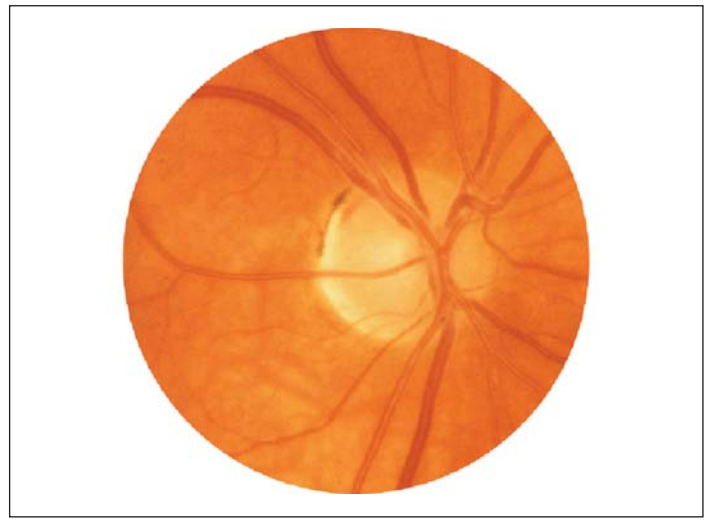
Lhermitte's syndrome, in which neck flexion results in paraesthesia down the spine and in the upper and/or lower limbs has classically been associated with a demyelinating lesion in the cervical spinal cord. However, this sign is not pathognomonic of MS, and may be seen in other conditions such as compressive myelopathies. A rare manifestation



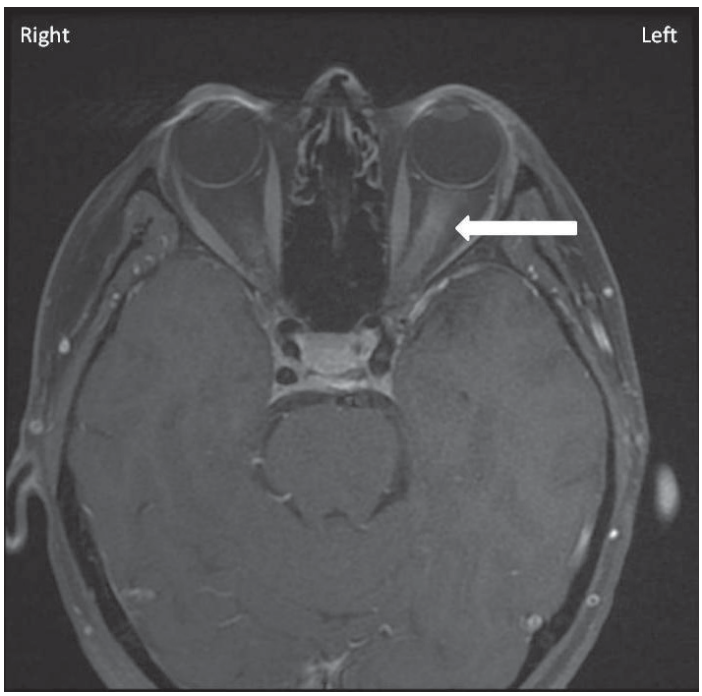
1.2 Normal optic disc.



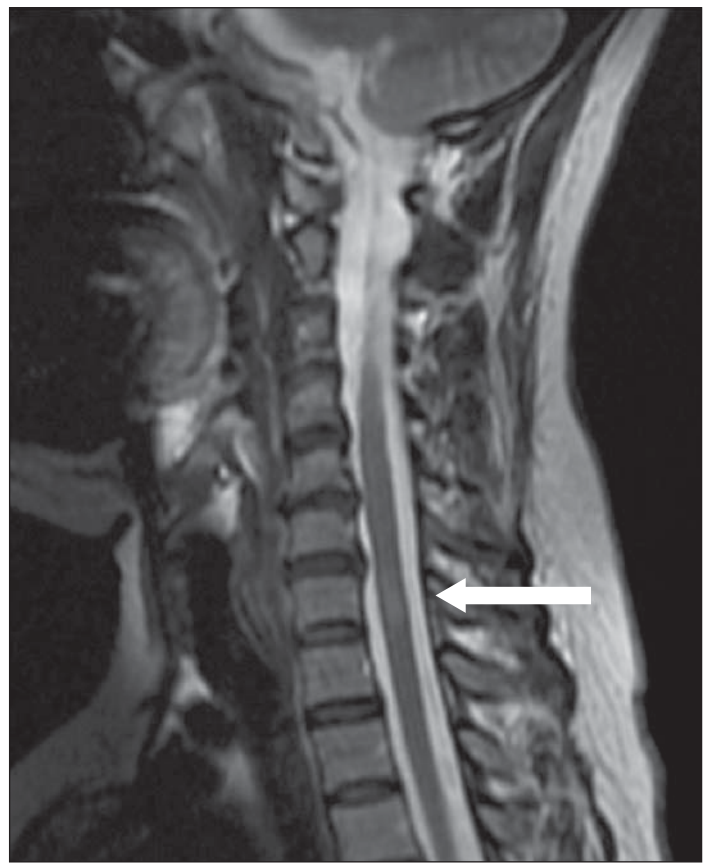
1.3 Acutely inflamed disc (papillitis) in optic neuritis.



1.4 Optic atrophy.



1.5 MRI showing gadolinium enhancement of the left optic nerve (*arrowed*) in keeping with acute optic neuritis.



1.6 Typical image of a T2-hyperintense lesion within the spinal cord in keeping with transverse myelitis (*arrowed*).

is flexor spasms due to spontaneous activation of motor pathways. The spasms are usually self-limiting, resolve within 4–6 weeks, and they respond to sodium channel blockers (e.g. carbamazepine).

The diagnostic modality of choice for acute transverse myelitis is MRI. This may show a signal change within the spinal cord on T2-weighted sequences, with or without cord swelling (**1.6**). In MS, this signal change is typically asymmetric, and rarely exceeds two vertebral segments in length. Lesions longer than this are referred to as longitudinally extensive transverse myelitis and are more common in the MS mimic neuromyelitis optica (Devic's disease). In transverse myelitis associated with MS, lesions typical for MS may be seen elsewhere in the CNS.

Brainstem symptoms

Approximately 1 in 10 patients with MS will present with a brainstem syndrome. Common presentations include internuclear ophthalmoplegia, which can be bilateral (caused by bilateral lesions affecting the medical longitudinal fasciculi), ataxia with nystagmus, sixth nerve palsy and facial numbness.[4] Less commonly, facial palsy, trigeminal neuralgia, hemifacial spasm, facial myokymia and other ophthalmoplegias may be seen.

A number of brainstem syndromes are not commonly associated with MS. These include complex and complete external ophthalmoplegia, third nerve palsy, progressive trigeminal neuralgia and focal dystonia with or without torticollis. Multiple cranial neuropathies should prompt the search for an alternative diagnosis.[4]

Investigation findings

Blood tests

Routine blood tests are usually normal in MS. The role of blood tests is, therefore, predominantly in the elimination of other potential diagnoses, which are discussed in more detail in Chapter 5.

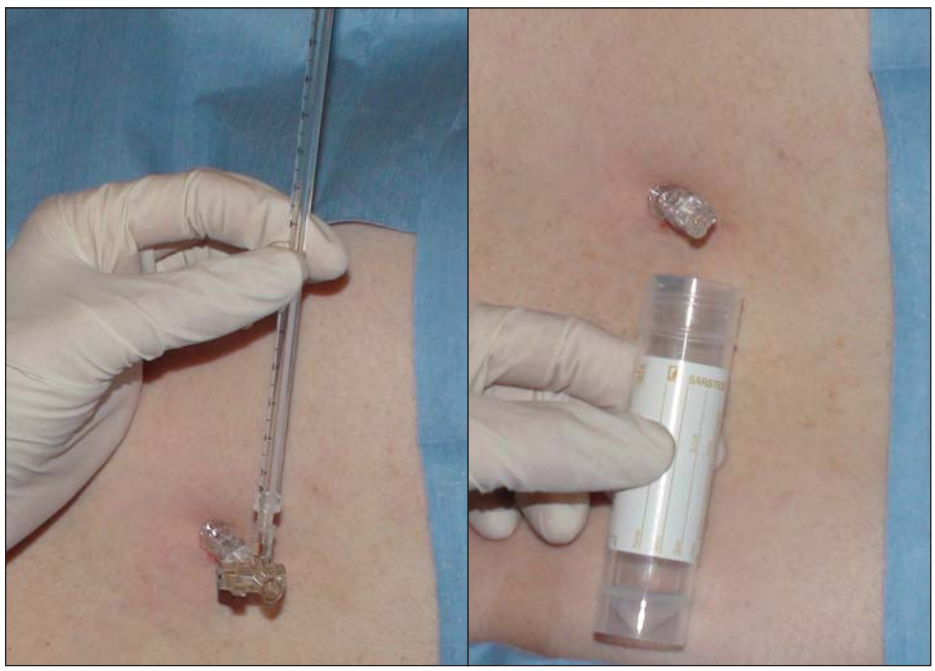
Cerebrospinal fluid

The majority of patients diagnosed with MS will have CSF analysis performed. Typical findings are described in *Table 1.4*. Although CSF analysis is only included in the diagnostic criteria for PPMS, it is often examined in cases where RRMS is suspected. CSF examination is important in suspected MS as it can both support the diagnosis of MS and exclude alternative diagnoses.

Table 1.4 Typical CSF findings in MS

- CSF may show mild pleocytosis (<50×106 leucocytes/l), predominantly neutrophils
- Unmatched oligoclonal bands unique to cerebrospinal fluid
- Raised CSF IgG index indicating central nervous system production of IgG
- Protein typically normal or slightly raised
- Glucose typically normal

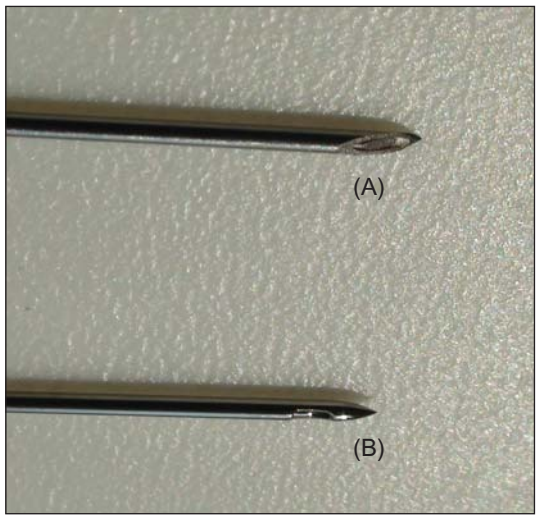
CSF samples are obtained via lumbar puncture (**1.7**). While this has traditionally been performed using cutting needles (otherwise known as traumatic or Quinke needles),



1.7 Performing a lumbar puncture. The patient is in the left lateral position, and the L3/4 interspace identified. The area is infiltrated with local anaesthetic and the spinal needle inserted. A manometer is used to measure CSF pressure before CSF collection. Reference 7 is a good online video on how to perform a lumbar puncture.

there is a move towards the use of atraumatic needle systems (Sprotte) (**1.8**). These have been shown to reduce the rates of post-lumbar puncture headache in those undergoing diagnostic lumbar puncture.

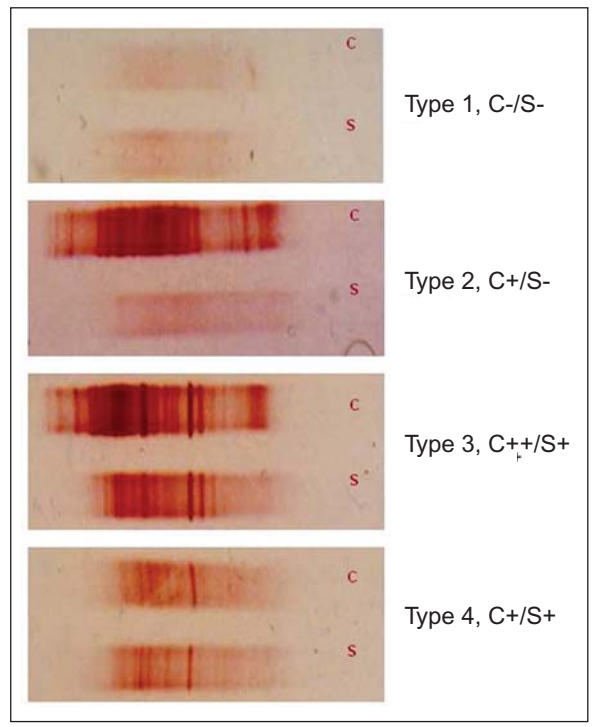
CSF should be collected in a polypropylene tube (**1.9**). Basic CSF parameters (protein and glucose) are usually normal. Although there may be a slight elevation in the CSF white cell count, particularly in the context of an acute relapse, this tends not to be marked.



1.8 (A) Traumatic (Quincke) and (B) atraumatic (Sprotte) needle systems used in lumbar puncture. The 'pencil-point' tip of the atraumatic needle system can clearly be seen. This prevents the formation of a persistent dural flap with CSF leak, which is thought to be responsible for the occurrence of post-lumbar puncture headache.

1.9 Clear and colourless CSF collected in a polypropylene tube.

The hallmark of MS is the presence of CSF oligoclonal IgG bands (**1.10**), which are present in more than 90% of patients. These represent the intrathecal synthesis of oligoclonal immunoglobulin G (IgG), which is unique to the CSF, and not present in a paired serum sample. Oligoclonal bands are detected using isoelectric focusing with immunofixation. It must be noted that oligoclonal bands are not specific for MS, as they may be present in a number of conditions, including CNS infections, CNS lupus and other autoimmune disease (e.g. paraneoplastic syndromes). Their presence is therefore merely supportive of a diagnosis of MS and should be interpreted alongside clinical history. The absence of oligoclonal bands is very useful in excluding a diagnosis of MS (i.e. their negative predictive value).



1.10 Oligoclonal bands unique to the CSF detected by CSF isoelectric focusing; the oligoclonal bands present are due to IgG. There are four common patterns: type 1, no bands in CSF and serum (S); type 2, oligoclonal IgG bands in CSF, not in the S sample, indicative of intrathecal IgG synthesis; type 3, oligoclonal bands in CSF (like type 2) and additional identical oligoclonal bands in CSF and the S sample – the unique CSF bands are indicative of intrathecal IgG synthesis; type 4, identical oligoclonal bands in CSF and the S sample illustrative of a systemic rather than intrathecal immune reaction, with a leaky or normal or abnormal blood–CSF barrier and oligoclonal bands passively transferred in the CSF.

Magnetic resonance imaging

The typical MRI finding seen in MS is multifocal demyelination. This is visualized as T2-weighted hyperintensities seen on unenhanced MRI (**1.11**). Acute lesions may enhance after administration of gadolinium. The MRI findings in MS are discussed in more detail in Chapter 3.

Neurophysiology

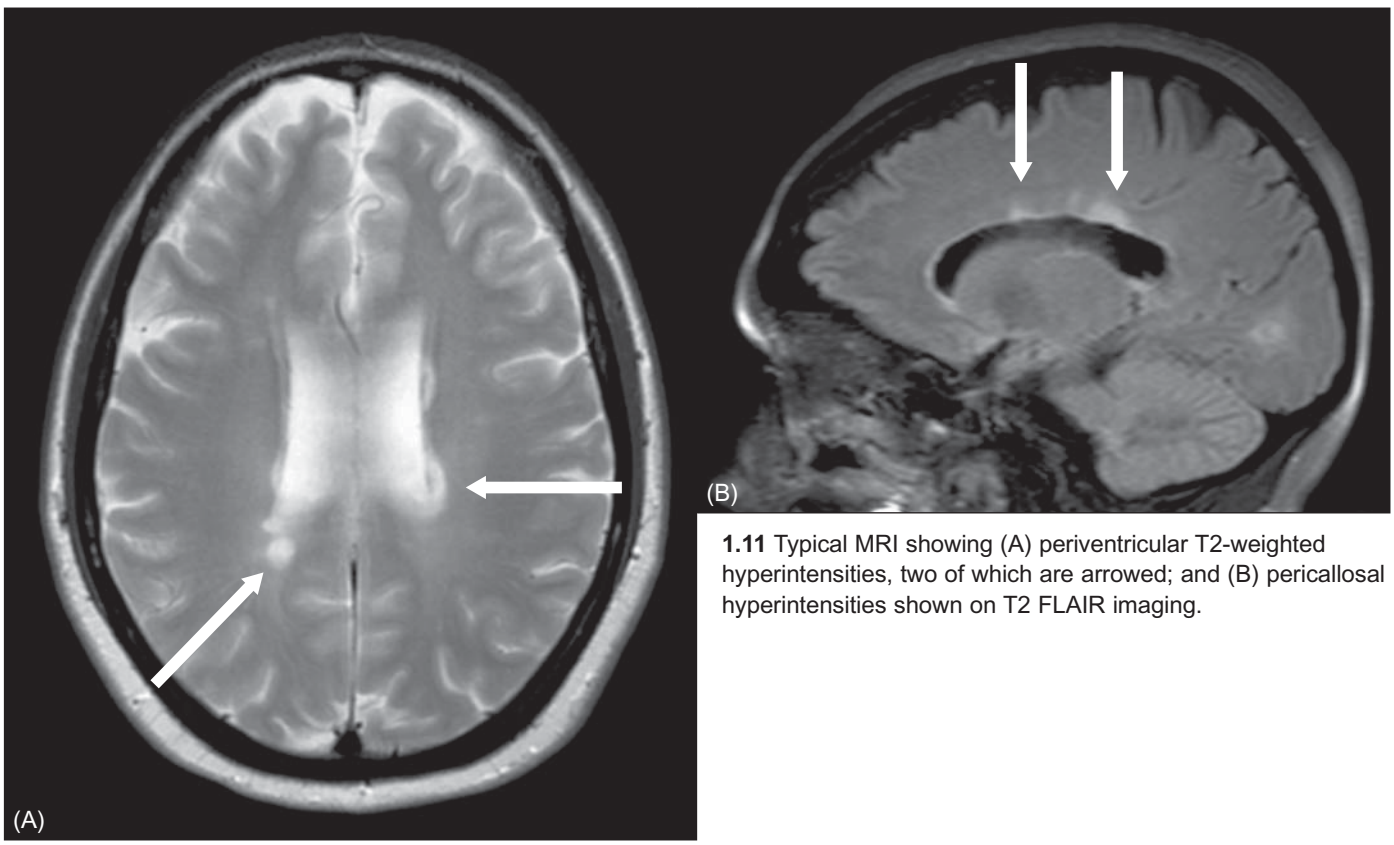
The role of neurophysiology in the diagnosis of MS will be discussed more in Chapter 4. Suffice to say, the main value of neurophysiology is to show central conduction slowing, which is pathognomonic of demyelination. Conduction slowing is useful to show subclinical involvement of specific pathways, which often helps to show dissemination of lesions in space.

Differential diagnosis

An accurate diagnosis of MS is dependent on both the exclusion of plausible alternative diagnoses, the range of which may depend on presenting symptoms and signs, as well as a clinical picture in keeping with MS. The differential diagnosis of MS is covered in more detail in Chapter 5.

Online resources for patients and practitioners

Online resources can be a valuable source of information and support for both patients and practitioners. A number of websites are particularly recommended (*Table 1.5*).



1.11 Typical MRI showing (A) periventricular T2-weighted hyperintensities, two of which are arrowed; and (B) pericallosal hyperintensities shown on T2 FLAIR imaging.

Table 1.5 Online resources for people with MS, and those with an interest in MS

Resource	Web address
MS Society of Great Britain and Northern Ireland	www.mssociety.org.uk/
MS Trust	www.mstrust.org.uk/
Shift MS – for young people with MS	http://shift.ms/
Multiple Sclerosis blog	www.multiple-sclerosis-research.blogspot.co.uk/
Multiple Sclerosis Resource Centre	www.msrc.co.uk/
National MS Therapy Centres	www.msntc.org.uk/
National MS Society (North America)	www.nationalmssociety.org
Multiple Sclerosis International Federation (MSIF)	www.msif.org/en/

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