Suspected cases of multiple sclerosis (MS) are usually young adults attending the neurology outpatient clinic. The onset of symptoms is rare before puberty or after the age of 60 years; however, being a relatively common neurological disease (1:800 in UK), both situations may be familiar to practising neurologists. MS will usually present with either a history of acute relapse(s) or with progressive neurological impairment.

**RELAPSING REMITTING DISEASE**

The most common presentation of MS is following a relapse. The peak age of the first episode is in the third decade; however, patients often present to the neurologist later with their second or third relapse or less commonly in the secondary progressive phase of illness. This form of MS is twice as common in women as in men.

The most common scenario is a patient of 20–40 years old referred fairly urgently to the outpatient clinic with a subacute onset of neurological disturbance, most commonly sensory symptoms, often resolving by the time they are seen. Because sensory symptoms may occur in the absence of clinical signs the neurological examination may be normal or near normal even when seen during relapse. The distribution of sensory loss is extremely variable but most commonly involves one or more limbs and usually represents a partial transverse myelitis with an evolving sensory level (which may be patchy or unilateral). Optic neuritis is also common but usually presents to the ophthalmology department. Other common presentations include a more extensive transverse myelitis with motor and bladder involvement, brain stem symptoms including diplopia (usually an internuclear ophthalmoplegia), cerebellar and vestibular disturbance, and Lhermitte's phenomenon. Less frequent but more specific are symptoms such as Uhthoff's phenomenon (the original description being reversible exercise induced symptoms, now more commonly referred to as heat induced symptoms), and paroxysmal stereotypic symptoms occurring many times a day for seconds at a time over a relapse time course. The latter may involve dystonic posturing of a limb or one side of the body. Fatigue and less frequently cognitive disturbance may present alongside other symptoms but are rare as isolated presentations.

A relapse has been defined for the purpose of clinical trials as lasting at least 24 hours in the context of a normal body temperature. It has been suggested that a period of 30 days should separate the onset of two events for them to be documented as separate attacks. The more typical time course is for symptoms to evolve over days to two weeks, stabilise for 1–2 weeks, and then improve over weeks. Partial recovery with persistent residual symptoms and longer recovery periods may occur, especially with more severe relapses.

The neurology outpatient clinic is full of people with a history of episodic neurological symptoms, particularly sensory disturbance. The decision to investigate will depend upon the specificity of symptoms for MS—that is, a reasonable distribution of sensory symptoms, maximal over a relapse time course, and which may be associated with other suggestive complaints. Anxious poly-symptomatic patients with normal neurological examination should not be primarily investigated for the possibility of MS.

Fatigue is another common non-specific symptom seen in the neurology clinic setting. “MS type” fatigue differs from depression associated fatigue in that it is associated with specific neurological symptoms, fluctuates with heat, exercise or as the day proceeds, and is alleviated by a short period of rest. Depression associated fatigue tends to be described as a non-specific generalised lack of energy and may be associated with other features of depression such as sleep disturbance. However, depression also commonly coexists in patients with organic disorders such as MS.

At present many neurologists jointly with their patients prefer not to investigate a single resolved attack, especially when no objective signs have been noted. However, if early treatment with disease modifying therapies is shown to reduce long term disability to a clinically useful degree then the threshold for investigating patients early will be lowered.
Primary progressive disease

The primary progressive form of MS (found in about 10% of MS patients) has an insidious and vague onset, which often predates referral to a neurologist by a number of years. Not only is the age of onset later than with the relapsing remitting form (mean around 40 years), but it is the most common form in older persons. Presentation of progressive disease may represent primary or secondary progressive MS, the latter not uncommonly associated with one or two, often poorly recollected, relapses many years previously.

Primary progressive MS usually presents to the neurology outpatient clinic with a request to evaluate a progressive gait disorder. Patients may underestimate their neurological impairment because of the slowness of deterioration in their walking, enabling them to adapt to maintain functional ability. Patients and their general practitioners frequently put the initial symptoms down to “age” or “arthritis”. By the time they are examined by a neurologist the examination is usually evidently abnormal with lower limb pyramidal dysfunction. Ataxia is also frequently seen. This presentation is in sharp contrast to the relapsing remitting form.

What investigations are available to help support the diagnosis of MS?

There are three main investigations that, because of their high specificity and sensitivity, are valuable in the diagnosis of MS: magnetic resonance imaging (MRI), evoked potentials; and cerebrospinal fluid (CSF) examination for the presence of oligoclonal bands (OCBs).

**Magnetic resonance imaging**

T2 weighted brain MRI is abnormal in about 95% of patients with clinically definite MS. The white matter lesions (WMLs) seen on such imaging correlate well with macroscopic plaques pathologically. Although WMLs are seen in other conditions the most frequently encountered differential is of ischaemic and age related changes. The useful distinguishing features are set out in table 1. Although these improve MS specificity, MRI is not a pathologically definitive investigation; also up to 4% of normal healthy controls have periventricular lesions indistinguishable from MS’ and caution must be exercised in using MRI alone to diagnose MS, especially in patients with atypical or non-specific histories. In these circumstances a reported “typical MS MRI” needs to be reviewed with a neuroradiologist and further clinical evaluation or additional investigations considered.

MRI of the brain is often less abnormal in primary progressive MS, possibly as a result of more spinal cord pathology and/or a different pathological spectrum (that is, a more generalised axonopathy).

Gadolinium enhancement is seen with new early active lesions due to blood brain barrier breakdown, and usually lasts 4–6 weeks. Ring enhancement and mass effect with acute lesions may be seen. New enhancing lesion activity is 5–10 times more frequent than the clinical relapse frequency, thus the tendency to deploy this technique as a surrogate outcome measure in clinical trials. The routine use of contrast is expensive and requires the need for cannulation of the patient. In fact gadolinium enhanced imaging rarely adds much useful information in clinical practice, except when differentiating from diseases which have an associated meningeal inflammation such as sarcoidosis. The demonstration of enhancing lesions six months after a monophasic illness indicates spatial and temporal dissemination, but most clinicians still prefer further clinical evidence before making a definite diagnosis.

Spinal cord lesions are common in MS and their detection is useful as a diagnostic tool in older patients. MS occasionally coexists with extrinsic cord compression, and spinal cord lesions often locate close to the site of compression. In patients presenting with progressive lower limb symptoms it is important but often difficult to distinguish between anatomically associated intrinsic ischaemic changes caused by compression from inflammatory demyelination. As a general rule MS lesions tend to locate at a level above whereas intrinsic ischaemic compression lesions locate at the site of maximum compression.

When brain MRI is used as diagnostic criteria for research studies the need for specificity predominates over sensitivity, and thus stricter criteria have been suggested including three, four or eight WMLs, lesions greater than 3 mm or 6 mm diameter, and various combinations of features as set out in table 1.

**Evoked potentials**

The rate of conduction and the amplitude of the nerve impulse (from site of stimulus to cortex) of the visual, auditory, sensory posterior column, and motor systems (cortex to muscle) can be measured using evoked potentials. Of these the visual evoked potentials (VEPs) contribute the most to the diagnosis of MS. Delay is indicative of demyelination in visual pathways. Reduction in amplitude can occur secondary to conduction block and dispersion, as well as from axonal damage, a major determinant of disability in MS. Using evoked potentials the level of initial delay or block can be determined, but further proximal sites of damage cannot be identified in number or position. It may be for this reason that although evoked potentials are more easily quantifiable than MRI their use in monitoring efficacy in treatment trials has been limited.

**Visual evoked potentials.**

Although reports of the long term conversion rate from optic neuritis to MS varies hugely, optic nerve involvement (even in the absence of a clinical episode) is extremely common in MS. Thus assessment of the visual system, particularly the anterior pathways, is useful. The frequency of abnormal VEPs in patients with clinically definite MS varies between
studies from 42–100% and is likely to depend on the time from disease onset when tested. A delay in the P100 (major positive deflection occurring at about 100 ms using the pattern reversal technique) is the typical abnormality inferring demyelination. However, asymmetry of the latencies between sides of more than 6 ms and central stimulation testing can increase the sensitivity to lesions of the optic nerve further. During the acute phase of optic neuritis the amplitude may be reduced or absent if the visual acuity is less than 6/24. VEPs are more sensitive than detailed clinical examination, including fields mapping and colour desaturation testing, and examination of the optic fundus and pupillary responses. In addition to the sensitivity, the usefulness of VEPs arises from the persistence of abnormality with clinical recovery from optic neuritis (80–90%), or even in the absence of a clinical event marking a clinically silent lesion. However, increasing age, lack of attention, drowsiness, and optic nerve compression also increase the latency. In patients with ocular disease causing a central scotoma, the VEPs arising from the paramacular regions will produce an increase in the latency. Refractive errors should be corrected where possible. Abnormal VEPs can occasionally occur in other conditions such as the hereditary ataxias, B12 deficiency, neurosyphilis, Parkinson’s disease, and metabolic disturbances. However, these disorders tend to cause symmetrical abnormalities.

Posterior visual pathway lesions can be identified using half field stimulation.

Somatosensory evoked potentials
After a brief electrical stimulus is applied to the median or posterior tibial nerves, recordings are made at several levels ending at the primary somatosensory cortex. The peripheral component is then subtracted to obtain a measure of central conduction. Abnormalities of sensory evoked potentials have been reported in around 80% of patients with clinically definite MS, many of whom have no relevant symptoms. Metabolic disorders such as B12 deficiency and focal lesions affecting the somatosensory pathway can disrupt conduction.

Brainstem auditory evoked potentials
This measures five waves of the short latency response from the time of auditory stimulus to the superior olivary complex, lateral lemniscus, and the inferior colliculus. This test is omitted in an evoked potential screen by many centres because of its lower sensitivity in MS. It is not specific either and detects pontine/lower midbrain lesions resulting from other causes. Brainstem auditory evoked potentials require greater technical expertise than the other evoked potentials to give reliable results. As with the other evoked potentials end organ damage may interfere with the response.

Magnetically evoked motor potentials.
A powerful brief magnetic stimulus is applied to the scalp overlying the primary motor cortex region on either side. This produces an electric current in the underlying cerebral cortex and causes primary motor neurones to discharge. Distal magnetically evoked potential recordings are made. This test is of low specificity—being impaired in a wide range of other neurological disorders—and reports of its sensitivity, especially in the absence of a clinically relevant lesion, vary.

Cerebrospinal fluid examination
Oligoclonal bands
Oligoclonal banding in the CSF not matched in the serum has high specificity and sensitivity for MS, although the former depends on the differential diagnoses being considered. Around 95% of patients with clinically definite MS are reported to have OCBs by isoelectric focusing. It is well recognised that many inflammatory diseases can be CSF OCB positive. Additionally about 4% of patients with non-inflammatory neurological diagnosis have been noted to produce OCBs in the CSF.

OCB patterns are remarkably stable within an individual with MS over many years, although the absolute concentrations of IgG may decrease. This observation supports the OCBs as representing a specific immunological reaction within the CSF rather than a non-specific bystander effect.

Figure 1 Flow chart showing the stages in the diagnosis of multiple sclerosis (MS) leading to a confirmed diagnosis. CSF, cerebrospinal fluid; EPs, evoked potentials; MRI, magnetic resonance imaging.
Table 2. Poser criteria for the diagnosis of clinically definite multiple sclerosis (MS) and laboratory supported MS (modified from Poser et al)³

<table>
<thead>
<tr>
<th>Clinical relapse</th>
<th>Clinical evidence (number of lesions)</th>
<th>Paraclinical lesions</th>
<th>CSF/OBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically definite MS</td>
<td>2* 2†</td>
<td>1 or more</td>
<td>None</td>
</tr>
<tr>
<td>Laboratory supported MS</td>
<td>1</td>
<td>2†</td>
<td>+</td>
</tr>
</tbody>
</table>

Clinical evidence means documented neurological signs relating to a lesion. Paraclinical lesions are lesions found by investigation that are distinct from clinical lesions.

*Two clinical relapses involve lesions at different times and different sites.
†Can substitute documented clinical signs of one episode with strong typical historical information.
‡Evidence of two different lesions separated in time (that is, not both present initially).
CSF, cerebrospinal fluid; OCBs, oligoclonal bands, NA, not available.

Other CSF components

The protein is usually normal but may be raised minimally. Mildly raised lymphocyte counts are common but it is rare for this to exceed 50 cells/mm³. Raised neutrophil counts are not seen in MS (but may be found in Devic’s disease).

The cell count and other specific CSF tests can be useful in differentiating between MS and other central nervous system inflammatory diseases.

How do you make the diagnosis of MS?

It must be emphasised that the diagnosis of relapsing remitting MS (fig 1) is primarily a clinical one and thus investigation should follow on from a suspect history. Because MRI can show abnormalities in healthy controls, performing tests to rule out the diagnosis may be misleading and can make subsequent management difficult. Additionally, all investigations have a false negative rate. The diagnosis of MS rests on the clinical (and paraclinical) evidence of typical lesions/events disseminated in time and place. The security of each clinical attack as an MS relapse does depend upon the pattern and distribution of symptoms and prior documentation of objective signs. In 1983 a committee devised diagnostic criteria for MS, the degree of certainty dependent on the evidence for MS relapses, investigations revealing clinically silent lesions, and CSF OCBs.³ Using such Poser criteria (table 2) the specificity for clinically definite MS is 94%.⁷ These criteria have recently been updated, incorporating the use of MRI in securing the diagnosis in monosymptomatic situations (table 3) and simplifying the diagnostic categories into “MS”, “not MS”, and “possible MS”.¹

Presentation with a second or more clinical relapse

This is the most straightforward situation. When a patient in their 20s or 30s presents with a second typical neurological episode supported by a characteristic brain MRI, most physicians would feel sufficiently confident to tell the patient that they have MS (even when they have not been seen and examined during the first attack).

Further tests help to identify the small number of MS patients in whom brain MRI is negative or borderline. Evoked potentials may identify extra paraclinical lesions in such circumstances, and typical abnormalities of CSF examination and brain MRI may not always coexist, thus lumbar puncture may further the diagnostic certainty.

Presentation at the time of the first clinical episode

A single clinical episode is insufficient for the diagnosis of clinically definite MS. The diagnosis of laboratory supported definite MS, however, includes patients with monophasic

Table 3. Recently proposed diagnostic criteria for multiple sclerosis (modified from McDonald et al)²

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Additional data needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 clinical relapses</td>
<td>None</td>
</tr>
<tr>
<td>Objective clinical evidence ≥ 2 lesions</td>
<td>Dissemination in space†</td>
</tr>
<tr>
<td>Objective clinical evidence 1 lesion</td>
<td>MRI dissemination in space*</td>
</tr>
<tr>
<td>1 clinical relapse with objective evidence</td>
<td>MRI dissemination in time† and space</td>
</tr>
</tbody>
</table>

Progressive picture

OCBs and Dissemination in space (MRI ± VEPs†) and Dissemination in time (MRI† or clinical)

*Dissemination in space: typical MRI (>3 of 4 criteria satisfied) or >2 MRI lesions (brain/spinal cord) + OCBs.
†Dissemination in time: Gd-enhancing lesion on 3 month single interval MRI or new 12 lesion on 6 month MRI not seen at 3 months.
‡Various combinations brain/spinal cord lesions and VEP abnormalities.

clinical presentations in the presence of CSF OCBs and evidence of two or more lesions.⁴

Around 60% of patients presenting with a typical “MS type” clinically isolated syndrome will have multiple white matter lesions (asymptomatic) on MRI. The presence of an abnormal brain MRI (one or more asymptomatic typical lesion) in this clinical setting is associated with an 83% risk of developing clinically definite MS after 10 years.⁹ Longer follow up periods and longitudinal studies of MRI and/or evoked potentials may increase this figure further. The updated guidelines now allow a diagnosis of MS to be made in such patients where longitudinal investigations show evidence of new lesions on MRI.¹

If one defines a brain MRI as “abnormal” when there is any number of definite white matter lesions, this investigation appears to be more sensitive than evoked potentials and CSF at predicting which patients develop MS at follow up. Increasing degrees of abnormality such as lesion number does not increase the sensitivity to conversion rates over 10 years but predicts worse disability (at five and 10 year follow up) and earlier time to conversion.³

Thus, in the clinical setting, brain MRI can indicate how likely a patient with a single typical neurological episode will progress to clinically definite MS in the future, and longitudinal studies have now been advocated to make the diagnosis. A negative scan can provide some reassurance—only 11% of such patients developed clinically definite MS by 10 years. However, these MRI data can only be extracted and used prognostically if the clinical picture is as secure as in the original study.

Presentation with a progressive picture

The diagnosis in patients presenting with progressive problems should be made only after other causes are ruled out: in particular spinal cord compression and other structural lesions of the spinal cord and brain. Other rarer differential diagnoses should be considered where appropriate and include: inflammatory conditions involving the central nervous system (for example, systemic lupus erythematosus, Sjögren’s syndrome, sarcoidosis); subacute combined degeneration of the cord, infection (for example, syphilis, HTLV-1); motor neurone disease in the absence of lower motor neurone abnormalities; and hereditary conditions (for example, familial spastic paraparesis, atypical Leber’s optic atrophy) (see article by Scolding on p i9).

Because of the delay from onset to presentation to a neurologist in primary progressive MS, the clinical picture of progressive deterioration is usually clear. Due to the older
age at presentation a larger proportion of patients will present after the age of 50 years and the usual confirmatory brain MRI appearances may be difficult to distinguish from age related and vascular WMLs commonly seen. The addition of spinal cord MRI contributes greatly in the investigation of such patients, not only because it is useful in eliminating other important differential diagnoses, but because spinal cord lesions are commonly seen in MS. Indeed one series found spinal cord lesions in all brain MRI negative patients. In contrast incidental spinal cord lesions are rare and do not occur as an age related feature.

Thus patients being investigated with a primary progressive form of MS are more likely to require spinal cord MRI, CSF examination, and evoked potentials in order to establish the diagnosis, than patients presenting with a relapsing remitting pattern.

Patients in whom the initial investigations are negative

Normal brain MRI is found in only 5% of MS patients using modern techniques. Half of such patients in one series consisted of patients with primary progressive disease, the majority of whom were severely disabled. In relapsing remitting disease normal imaging was associated with early or mild disease. All brain MRI negative patients had at least one lesion in the spinal cord using modern imaging techniques, 87% had OCBs, and 56% abnormal VEPs showing the added value of these additional investigations. Complete normality of all three investigations (when using optimum techniques) would thus seriously question the diagnosis of MS. In such patients with relapsing symptoms the majority have no objective signs and a non-organic diagnosis is the most common conclusion. However, a minority of patients with early relapsing remitting (often monophasic) symptoms who are initially negative upon investigation, go on to develop further problems and show abnormalities on repeat investigations. In patients with progressive disease alternative diagnoses should be considered.

What other diagnoses should be considered?

The differential diagnosis of MS is discussed in detail elsewhere (see article by Scolding on p ii9). Where appropriate a number of these conditions should be ruled out.

Discussing the diagnosis of MS with the patient

Initially in the outpatient clinic

The aims when initially discussing the diagnosis of MS are to reduce the initial shock when the term MS is first used and to give an optimistic picture of the prognosis. The patient’s perception of MS is usually worse than reality unless he or she has personal experience of someone with mild disease.

Discussing the possibility of the diagnosis (along with other possible suggestions—that is, “a viral illness”, “might not find an explainable cause”) at the initial consultation, when the clinical picture is suggestive but before investigations, leads the patient more gently into the MS label. This approach may increase anxiety in susceptible individuals during the wait for investigations and follow up appointment. Additionally the anxiety may prove unnecessary, thus one needs to take into account the personality of the patient and the degree of clinical suspicion. Breaking the news to the patient is best done in the presence of a partner, friend or family member, and it is easier to request that someone attends with them at follow up if the possibility of MS has already been raised. Inevitably MS will be discussed at the time the diagnosis is confirmed, many questions being led by the patient and companion, especially if forewarned about the possible diagnosis. Many centres have access to an MS nurse and patients are grateful to receive a contact number at an early stage. Good communication of previous discussions with the patient along with relevant copy letters should be sent to the nurse. It is preferable to arrange for the MS nurse to be present in the clinic (enabling them to gain a good grasp of the situation and an initial rapport) who can then arrange a further follow up session with the patient.

Follow up session with the MS nurse

Most patients and their relatives (who frequently have as many questions as the patient) find a formal counselling/educational session welcome. It is usefully given at an interval from the initial neurology consultation in order to allow them to collect their thoughts and write down their questions once the diagnosis has sunk in. Many patients find the unpredictability of MS difficult to cope with or prepare for and further sessions may be needed, especially when the level of anxiety is high. The availability of a phone line is also greatly reassuring and used with great variability. In many patients the emotional reaction is more disabling to the patient than the MS, and this is especially true in the first two years from the diagnosis.

Follow up by the neurologist

When patients are seen during an unresolved relapse or in the progressive phase of the disease it is reassuring for them to be given a further up appointment to see the neurologist. Although it is not possible to follow up all patients with chronic neurological disease, early support while they are coming to terms with the diagnosis may prevent the interpretation of disinterest that patients sometimes attribute to their consultant.

References


One of the earliest studies demonstrating the sensitivity of brain MRI in 114 patients with MS and also demonstrating that the MRI lesions correspond well with the plaques seen pathologically. They also note the usefulness for identifying silent lesions, and compare appearances with CNS diseases. Spinal cord imaging and longitudinal MRI changes were also studied.


A study of brain MRI mainly in healthy controls, MS, and hypertensive patients. Demonstrates not only the sensitivity and specificity of the white matter lesions but the small percentage of abnormal scans in healthy individuals under the age of 50 years.


A large study of 1007 patients showing the high sensitivity and specificity of isoelectric focusing for the detection of oligoclonal bands in MS.


A study of CSF electrophoresis in a large number of patients with MS and other inflammatory and non-inflammatory neurological diseases. Shows the high sensitivity in clinically definite MS, low positivity in patients with possible MS, and high specificity for MS. The study details the small percentage of non-MS conditions with OCBs.


The Poser criteria are the criteria used for classifying the “firmness” of the diagnosis of MS, as compiled at a workshop nearly 20 years ago. These are still widely used, although an updated version is in preparation to incorporate MRI information. Essential reading.


A classic neuropathological study examining 518 patients with clinically definite MS and showing the Poser criteria was correct in 94% of cases.


Much quoted trial showing the importance of the MRI appearances in predicting the risk of developing MS over the next 10 years, in patients presenting with a single episode of demyelination. Essential reading.


A useful study of brain MRI negative MS patients showing the usefulness of spinal cord MRI and the added value of evoked potentials and OCBs testing.


A study using a faster technique and thus shorter scan time to obtain high resolution images of the spinal cord showing high signal T2 lesions are not a feature of age related change as they are with brain imaging.