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CORE TRAINING FOR DOCTORS

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Epidemiology and diagnosis of multiple sclerosis

Introduction

Multiple sclerosis is an inflammatory disease of the CNS. The disease is predominantly diagnosed in young adults, with long-term implications for both their personal and professional lives. The economic impact of the condition is particularly significant as the majority of patients are of working age, costing the UK economy approximately £1.4 billion (McCrone et al, 2008).

Despite a wide range of potential clinical presentations, the disease exhibits relatively stereotyped clinical, radiological and histopathological features. The commonest clinical sub-type presents as a relapsing remitting disorder, with neurological events (relapses) interspersed by periods of neurological recovery and relative stability (remissions). Over subsequent years, this sequence then frequently develops into progressive worsening of disability without relapses (secondary progression). A smaller group of patients do not experience true relapses or, importantly, remissions from the onset of their neurological symptoms, and these patients are termed as having 'primary progressive multiple sclerosis' (*Figure 1*).

The disease is a common neurological condition, encountered by a wide variety of health professionals. This review summarizes the key features of the epidemiology and diagnosis of multiple sclerosis, highlighting the relevance to clinicians at all stages of training. The second part of this article will look at the management and prognosis.

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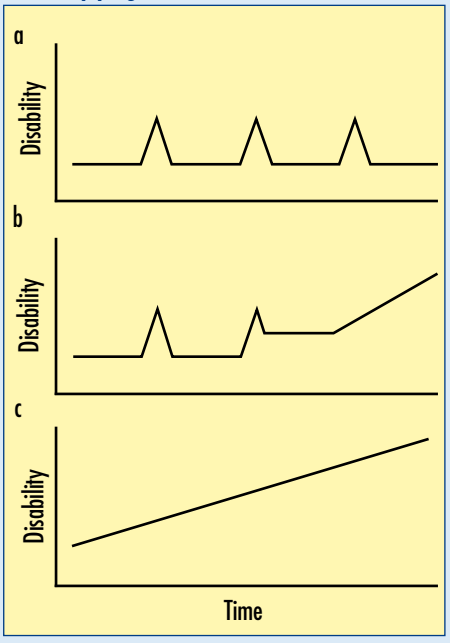
Epidemiology

The mean age of onset is approximately 30 years, with 70% of patients presenting symptoms between the ages of 20 and 40 years (O'Connor and the Canadian multiple sclerosis working group, 2002). Disease onset is rare before the age of 10 years and after 60 years, forming a unimodal, age-specific onset curve. Between 80 000 and 100 000 patients in the UK have been diagnosed with multiple sclerosis, with approximately 2500 people newly diagnosed each year (Multiple Sclerosis Trust, 2011).

The distribution is not geographically uniform – the greatest incidence tends to be at the extremes of latitude in both northern and southern hemispheres. For example, the prevalence rate in England and Wales is approximately 100 per 100 000, while the northern areas of

Figure 1. Clinical course for multiple sclerosis. a. Relapsing-remitting. b. Secondary progressive. c. Primary progressive.



Scotland have a prevalence approaching 200 per 100 000. This distribution is mirrored south of the equator, with high rates in the southernmost areas of New Zealand and lower rates in the north (Skegg et al, 1987). This strong latitudinal risk may be related to sunlight exposure, and a potential mediator of this is postulated to be vitamin D (see below).

Women are two to three times more likely to develop multiple sclerosis than men. Despite extensive research, the reason for this difference is unclear, beyond the standard observations that women are generally more susceptible to autoimmune conditions, and that this predisposition may therefore be hormonally related. The genetic influences on multiple sclerosis are clearly seen in twin studies, where the concordance rate for multiple sclerosis in monozygotic twins is as high as 30% compared to 5% for dizygotic twins (Willer et al, 2003). The risk of developing multiple sclerosis in first-degree relatives is about 1 in 40, which is 20 times higher than in the general population. For second degree relatives (cousins, uncles, aunts, nephews and nieces) the risk falls to around 1 in 100, still approximately 10 times higher than the background rate. Genetically unrelated family members living in the same environment, however, exhibit the same risk as the background population.

Further studies, initially using serological approaches and subsequently genetic linkage analysis studies (International Multiple Sclerosis Genetics Consortium, 2007), have found an association between multiple sclerosis and specific human leukocyte antigen (HLA) variants, coded within the major histocompatibility complex. This highly polymorphic region located on chromosome 6 encodes a range of proteins with important functions in regulating immune cell function, particularly in antigen presentation.

The best described association is with the HLA haplotype DR2 (HLA-DRB1*1501) (Lincoln et al, 2005). Despite this link the relative risk of an individual HLA-DR2 positive individual developing multiple sclerosis remains low, given that 35% of the general population are DR2 positive compared with 60–70% of multiple sclerosis patients. Further genetic studies, including several genome-wide association studies, have found sixteen or more genes with associated susceptibility, but none are as significant as the HLA linkage. At present it remains impossible to accurately assess the risk of developing multiple sclerosis on the basis of genetic susceptibility alone.

Environmental factors

There are numerous studies investigating links between specific environmental factors and multiple sclerosis, often with contradictory results and conclusions. These studies are particularly difficult to perform and interpret, as migration studies have highlighted that the movement of individuals from a high-risk to a low-risk area before puberty confers a degree of protection from developing the disease. This suggests that the timing of exposure to environmental factors may also be critical in determining subsequent risk – the so-called 'age-of-vulnerability' hypothesis.

Despite this, reproducible evidence links Epstein–Barr virus exposure, smoking and vitamin D levels to the development of multiple sclerosis and these are the current 'best established' environmental risk factors.

Epstein–Barr virus

A wide range of infectious agents have been examined for a potential link with multiple sclerosis, but the only consistently reported factor is Epstein–Barr virus, with more than 99% of patients with multiple sclerosis seropositive for Epstein–Barr virus. Confirming and investigating this link is complicated by the high background rates of infection (as high as 95%) in the general population.

There is dispute over the potential pathogenetic mechanisms involved in the association of Epstein–Barr virus with multiple sclerosis. Immortalization of autoreactive B cells, molecular mimicry with the CNS as the autoimmune target and modification of the 'hygiene hypothesis' with respect to Epstein–Barr virus have all been suggested as possibilities (Levin et al, 2005).

Smoking

Three studies – the Nurses' Health Studies (Hernán et al, 2001), the Tasmanian MS study (Pittas et al, 2009) and the Swedish MS study (Hedström et al, 2009) – have all confirmed that smoking roughly doubles the risk of developing multiple sclerosis. The possible mechanism for this association is not clear.

Vitamin D

Lower serum levels of vitamin D have been associated with increased risk of multiple sclerosis and correlate with disability and brain atrophy (Weinstock-Guttman et al, 2010). The previously described latitudinal gradient observed in multiple sclerosis natural history studies may be a consequence of lower serum vitamin D levels further away from the equator. Vitamin D appears to have immunomodulatory effects in experimental models but the exact mechanism through which it acts remains unclear (Ramagopalan et al, 2009).

Pathogenesis

Multiple sclerosis is thought to be an autoimmune demyelinating disease of the CNS, with autoreactive T-cells driving the disease once primed by a myelin-like antigen in the periphery. Activated T-cells then migrate through the blood–brain barrier, infiltrate the CNS and initiate selective cytokine and macrophage-mediated injury against oligodendrocytes and axons. Continuing inflammation leads to axonal damage, which is thought to be ultimately responsible for the disability seen in secondary progressive disease (Costantino et al, 2008). This pattern is evident pathologically in animal models of multiple sclerosis in which rodents are inoculated with myelin-associated proteins such as myelin basic protein or by adoptive transfer of autoreactive T cells, subsequently developing a disease similar to multiple sclerosis.

This model is likely to be a gross oversimplification of the true pathogenic processes in both human and animal models of multiple sclerosis (Batoulis et al, 2010). Ongoing research highlights the complexity of the immunological response in multiple sclerosis, including the role of B cells and cytokine networks (Hauser et al, 2008). The role of oligodendrocytes and the remyelinating capacity of the CNS are also increasingly recognized as critically important features in disease initiation and development (Watzlawik, 2010).

Clinical presentation

Clinically isolated syndrome

Approximately 85% of patients present with a neurological event which is followed

by recovery (typically over weeks), and then a period of relative neurological stability (*Figure 1*). The first neurological event (which is analogous to subsequent relapses in relapsing remitting multiple sclerosis) is termed a clinically isolated syndrome. The presenting neurological events are highly variable; one large study (Miller et al, 2005) found that 46% of patients with clinically isolated syndrome presented with long-tract symptoms and signs, 21% with optic neuritis, 10% with a brainstem syndrome and 23% with multifocal abnormalities (see below).

Relapsing-remitting multiple sclerosis

Once the patient experiences a second neurological event, he/she fulfils the criteria for relapsing-remitting multiple sclerosis, hence the term 'dissemination (of relapses) in time', with relapses interspersed by remissions. A relapse is defined specifically as (current or historical) patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, with duration of at least 24 hours in the absence of fever or infection (Polman et al, 2011).

Although it is preferable for acute relapses to be documented contemporaneously with objective abnormalities on clinical examination, historical events with symptomatology and evolution typical of multiple sclerosis (but for which no objective findings are found at the time of assessment) can provide reasonable evidence of a prior demyelinating event – see below.

Primary progressive multiple sclerosis

In contrast to relapsing-remitting multiple sclerosis, a proportion of patients never actually experience true relapses or remissions, but instead become gradually disabled over time; for example presenting with progressive limb spasticity and weakness. They constitute 15–20% of the multiple sclerosis population and are usually slightly older at presentation, atypically around 40 years of age.

Secondary progressive multiple sclerosis

Over time, typically 10–25 years, a large proportion of patients (around 65%) (Scalfari et al, 2010) with established relapsing-remitting multiple sclerosis find that their relapses become less frequent or even cease. Instead, they note a slowly progressive increase in their disability, usually with worsening gait or mobility either as a result of predominant ataxia, spasticity or a combination of both. These patients are termed as having entered the secondary progressive phase of multiple sclerosis. Regardless of the initial multiple sclerosis phenotype, patients manifest progressive disease at approximately 40 years of age (Leray et al, 2010). It is unclear whether early therapeutic intervention to reduce relapses in early disease alters the development of secondary progression (see below).

Symptomatic presentation

Lhermitte's sign

This is a context-specific phenomenon, whereby neck flexion or extension produces an 'electric-shock' sensation running down the spine and the limbs. The pathology is classically associated with cervical cord demyelination (either acute or chronic). The phenomenon is not specific to multiple sclerosis, and can be produced in compressive myelopathies, for example.

Uhtoff's phenomenon

This describes the worsening of neurological symptoms, e.g. limb weakness, when the body becomes heated, such as in the bath, in hot weather or during exercise. This can be differentiated from a true relapse as the symptoms are context-specific and improve on normalization of body temperature. This is because demyelinated axons are thought to be particularly vulnerable to conduction block in a temperature-dependent manner.

It is important to reassure patients experiencing either Lhermitte's or Uhtoff's phenomena that, unless the changes are accompanied by sustained neurological deficit (lasting more than 24 hours), it is unlikely that they are representative of an acute relapse.

Borderline multiple sclerosis diseases

Acute tumefactive multiple sclerosis (Marburg's), Balo's concentric sclerosis, Schilder's diffuse sclerosis (paediatric) and acute disseminated encephalomyelitis are sometimes termed 'borderline multiple sclerosis diseases', and display different clinicopathological features than more conventional multiple sclerosis. They are uncommon and detailed descriptions are beyond the scope of this review.

It is worth highlighting neuromyelitis optica, which can share some clinical and radiological features of multiple sclerosis, but – unlike multiple sclerosis – is frequently associated with serum aquaporin-4 antibodies. Neuromyelitis optica presents with a relatively characteristic disease phenotype of optic neuritis which can be bilateral and severe, and longitudinally extensive spinal cord inflammatory lesions (typically three or more spinal cord vertebral segments), features which are atypical for multiple sclerosis. The disease course of neuromyelitis optica is often more aggressive and prolonged immunosuppression may be required.

Diagnosis

Technically, multiple sclerosis can be diagnosed purely on clinical parameters, provided there is objective evidence of lesions disseminated in both time and space (Poser et al, 1983). For example, a patient presenting to hospital with clinical evidence of transverse myelitis but who also reports an episode a few years ago of visual loss consistent with optic neuritis, would fulfil criteria for dissemination in time and dissemination in space as two different neurological systems (spinal cord and optic nerve respectively) were affected at two different points in time (*Table 1*).

The diagnostic criteria for multiple sclerosis have always highlighted the need to consider alternative causes for the clinical presentation (sometimes phrased as 'there must be no better explanation for the clinical picture'). Paraclinical (particularly magnetic resonance imaging) tests are therefore important. The diagnostic criteria are the subject of ongoing reviews and revisions, with validity tested in clinical practice. Certain features, such as an absence of typical magnetic resonance imaging changes or negative oligoclonal bands, in addition to other red flags should alert the clinician to consider alternative diagnoses (*Tables 2* and *3*).

Magnetic resonance imaging

Ideally, a clinical diagnosis of multiple sclerosis be confirmed histopathologically, but this occurs extremely rarely in clinical practice. Magnetic resonance imaging has radically altered our appreciation of the neuropathological events occurring in vivo. Magnetic resonance imaging changes are characterized by high signal white matter lesions on FLAIR/T2-weighted sequences, in regions typical for multiple sclerosis (*Figure 2*). Several sets of magnetic resonance imaging diagnostic criteria have been validated in clinical practice, notably the McDonald criteria (McDonald et al, 2001; Polman et al, 2005), with the most recent update published this year (Polman et al, 2011).

Thus, it is now possible to identify disseminated in time and disseminated in space in order to diagnose multiple sclerosis after one clinical event, with appropriate ancillary magnetic resonance imaging evidence. Disseminated in space can be demonstrated with at least one T2 lesion in at least two of four locations characteristic for multiple sclerosis: juxtacortical, periventricular, infratentorial and spinal cord. Disseminated in time can be demonstrated by:

1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up magnetic resonance imaging, with reference to any baseline scan irrespective of its timing
2. Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.

Diagnostic criteria for primary progressive multiple sclerosis were also reviewed and defined as progression over 1 year in addition to two of three of the following:

1. Evidence of disseminated in space in the brain
2. Spinal cord
3. Positive CSF (*Table 2*).

These criteria do not typically require CSF analysis or neurophysiology to make the diagnosis.

Table 1. McDonald diagnostic criteria for clinically definite multiple sclerosis

Clinical presentation		Additional data needed for multiple sclerosis diagnosis	
Two or more attacks	Objective clinical evidence of two or more lesions	None	
	Objective clinical evidence of one lesion with reasonable historical evidence of prior attack	None	
Two or more attacks	Objective clinical evidence of one lesion	Dissemination in space	More than one T2 lesion in two or more of four multiple sclerosis-typical regions of CNS
			Or await further clinical attack implicating different CNS site
One attack	Objective clinical evidence of two or more lesions	Dissemination in time	Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time
			Or a new T2 and/or gadolinium-enhancing lesion on follow-up magnetic resonance imaging, irrespective of its timing in relation to baseline scan
			Or await second clinical attack implicating different CNS site
One attack	Objective clinical evidence of one lesion (clinically isolated syndrome)	Dissemination in space	More than one T2 lesion in two or more of four multiple sclerosis-typical regions of CNS
			Or await further clinical attack implicating different CNS site
		Dissemination in time	Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time
			Or a new T2 and/or gadolinium-enhancing lesion on follow-up magnetic resonance imaging, irrespective of its timing in relation to baseline scan
			Or await second clinical attack implicating different CNS site
Insidious neurological progression suggestive of primary progressive multiple sclerosis		1 year of disease progression (retrospectively or prospectively)	
		Plus two of three following criteria	Evidence of dissemination in space in brain in multiple sclerosis-typical regions
			Evidence of dissemination in space in spinal cord based on two or more T2 lesions in cord
			Positive CSF oligoclonal bands

From Polman et al (2011)

Table 2. Red flags

Age: <10 years or >60 years old
Hyperacute onset suggestive of vascular aetiology
Co-existence of other autoimmune disease
Strong family history
Lower motor neuron features: nerve root pain, segmental amyotrophy
Absence of magnetic resonance imaging changes

CSF

Basic CSF parameters are usually normal – with protein and glucose levels within the normal range. A minority of patients may exhibit a lymphocytic pleocytosis (up to 10 cells/mm^3), but CSF cell counts are usually normal. More strikingly, over 90% of multiple sclerosis patients will be positive for oligoclonal bands, which are CSF-specific gamma globulin proteins which migrate in agarose electrophoresis as abnormal distinct populations, and are not identifiable in the peripheral blood. Oligoclonal bands are occasionally present in other, rarer, neurological conditions including syphilis, Lyme disease and subacute sclerosing panencephalitis although the clinical picture would usually distinguish these conditions.

Electrophysiological findings

Visual evoked potentials are produced by sensory stimulation of the patient's visual field and the corresponding electrical

Table 3. Differential diagnosis of multiple sclerosis

Differential diagnosis	Distinguishing features from multiple sclerosis
Vitamin B_{12} deficiency	Dietary history, e.g. vegetarian Classically dorsal column abnormalities with or without dementia Low serum levels of vitamin B_{12}
Post-infectious encephalomyelitis	Preceding viral infection
Primary CNS vasculitis	Severe headaches, confusion and sudden stroke-like episodes High CSF protein levels +/- high white cell count and high serum erythrocyte sedimentation rate Abnormal angiography of cerebral vessels
Lyme disease	Lower motor neuron facial weakness (VII nerve palsy), occasionally bilateral History of tick bites, rashes and arthralgia Presence of Lyme titre and/or a Lyme polymerase chain reaction in the CSF
Systemic lupus erythematosus	Stroke-like episodes Systemic abnormalities, e.g. elevated antinuclear antibody, dsDNA antibody, leukopaenia, haematuria and elevated erythrocyte sedimentation rate Rarely, the two disorders co-exist
Tropical spastic paraparesis	Retroviral disease caused by human T-lymphotropic virus-1, detectable in serum and CSF Seen most frequently in those residing around the Caribbean Sea basin
Behçet's syndrome	Classically affects individuals with Middle Eastern or Asian ancestry Systemic features: oral and genital ulcers, uveitis, in addition to possible involvement of lungs, joints, gastrointestinal tract and heart High-risk of thrombotic events, including cerebral venous thrombosis
Sarcoidosis	Multisystem granulomatous disease on biopsy, associated with raised serum angiotensin-converting enzyme levels Systemic features: pulmonary or cutaneous abnormalities
Sjögren's syndrome or Sicca syndrome	Systemic features: autoimmune destruction of the exocrine glands that produce tears and saliva Can be secondary to other connective tissue diseases
Tertiary syphilis	Risk factors for sexually transmitted disease Classically dorsal column abnormalities with dementia Venereal Disease Research Laboratory or *Treponema pallidum* particle agglutination antibodies in CSF and serum
Adult leukodystrophies*	Magnetic resonance imaging: diffuse white matter involvement
Progressive multifocal leukoencephalopathy	Probably reflects re-activation of latent JC virus in immunocompromised patients Commences insidiously but, unlike multiple sclerosis, leads to rapidly progressive neurological dysfunction and death unless immunocompromised state is alleviated, e.g. cessation of natalizumab therapy Magnetic resonance imaging: white matter lesions can coalesce into large areas with ill-defined borders, most often seen in the parieto-occipital and frontal lobes

* e.g. metachromatic leukodystrophy, Krabbe's disease, X-linked recessive adrenoleukodystrophy

response in the occipital cortex can be observed using electroencephalography. The resulting waveform produced on the electroencephalogram has characteristic features, and a prolongation of the latency can demonstrate conduction delay in the visual pathways, thought to reflect demyelination. Abnormalities in conduction may be detected despite normal visual assessment or in patients who do not recall an episode of optic neuritis in the past. This test can therefore provide a useful historical marker of a previous neurological event.

Brainstem auditory evoked potentials measure the speed of impulses along the auditory portion of cranial nerve VIII. This nerve arises in the pontine region of the brainstem and therefore prolonged latencies may indicate lesions here. Somatosensory evoked potentials involve strapping an electrical stimulus around an arm or leg. The current is switched on for a few seconds and electrodes over the spine and skull measure the response at particular junctions. Again, prolonged latency between the brain and spinal segments may support demyelination in the appropriate clinical context.

Differential diagnosis of multiple sclerosis

As previously highlighted, multiple sclerosis diagnostic criteria are appropriate only if there is no better explanation for the clinical picture. Detailed history-taking is therefore critical to expose differential diagnoses (*Table 3*).

Conclusions

Multiple sclerosis is a complex disease, predominantly diagnosed in early adulthood, with lifelong implications. Accurate diagnosis and exclusion of multiple sclerosis-mimics is critical, and pivotal advances in neuroradiology in particular, have shaped our understanding and classification of the disease. Greater insight into potential risk factors and disease pathogenesis will enable us to develop more effective therapies, which will be discussed in the second part of this article. BJHM

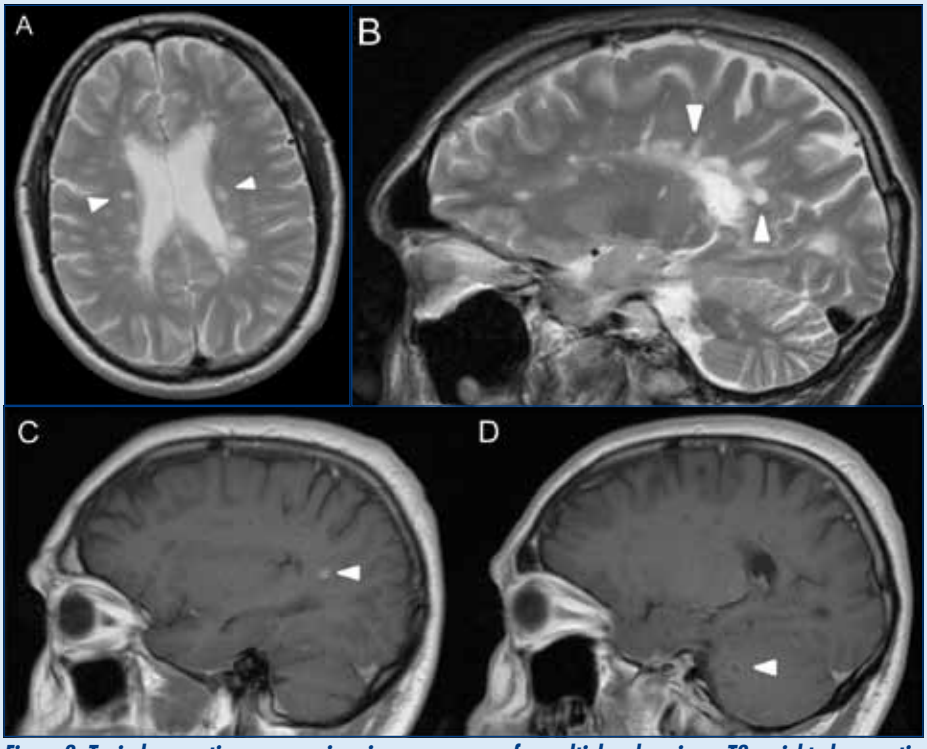


Figure 2. Typical magnetic resonance imaging appearances for multiple sclerosis. a. T2 weighted magnetic resonance imaging scan, with axial views demonstrating periventricular white matter lesions. b. T2 weighted magnetic resonance imaging scan demonstrating involvement of the corpus callosum, forming a distribution referred to as 'Dawson's fingers'. c. Contrast-enhanced T1 weighted magnetic resonance imaging scan, demonstrating contrast-enhancing lesion. d. Contrast-enhanced T1 weighted magnetic resonance imaging scan demonstrating a ring appearance.

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KEY POINTS

- The UK prevalence of multiple sclerosis is 1:1000 and is the commonest chronic brain disorder affecting young people.
- The risk of developing multiple sclerosis is 30% in monozygotic twins, 5% in dizygotic twins, 2.5% in first degree relatives and 1% in second degree relatives.
- Clinical features manifest CNS pathology only, unless cranial nerve nuclei are involved.
- Clinical features, CSF changes and radiological appearances are often stereotyped.
- Multiple sclerosis mimics can usually be identified by thorough history taking, examination, and ancillary laboratory testing revealing evidence of systemic disease.