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Multiple sclerosis: diagnosis and definitions

Many a chapter, monograph and paper on multiple sclerosis (MS) begins with the observation that the disease is the most common cause of neurological disability in young and middle-aged adults. While the emphasis for much of the nineteenth and twentieth centuries was on the neurological manifestations of the disease, since the mid 1980s clinicians, researchers and patients have become more aware of the associated behavioral changes. A burgeoning literature devoted to the neuropsychiatry of MS attests to this new found interest, although those with knowledge of the medical history of MS may find themselves a little surprised why it took so long for this enthusiasm to re-ignite. Descriptions of altered mentation in MS patients long predate the man credited with naming, describing and making the condition known, the French behavioral neurologist Jean-Martin Charcot (Charcot, 1868; see also Murray, 2005).

One cannot describe the psychiatric and cognitive changes associated with MS without first referring to the neurology and pathology of the disorder. This chapter, therefore, begins with a summary of the pathogenesis, pathology, signs and symptoms, diagnosis and differential diagnosis of MS. With the book's emphasis on mentation, this introduction will by design be brief and those seeking more detailed explanations are encouraged to consult the many texts specifically devoted to these aspects. This chapter will, however, discuss in depth the research guidelines for diagnosing MS and furnish clear definitions for terms that apply directly to the disease. These points are important for they will clarify at the outset many descriptive terms that appear in the MS research literature and are used throughout this book. The chapter will conclude with a discussion on rating disability and how behavioral changes may affect this assessment.

Epidemiology

In the UK, the lifetime risk for multiple sclerosis is 1:800, which translates into approximately 60 000 people with the disease (Compston, 1990). In the USA,

the figure is at least four times greater. There is a recognition that some cases of MS go undetected in life, appearing as a chance finding at postmortem (Gilbert and Sadler, 1983). Estimates that up to 20% of cases fall into this category (Mackay and Hirano, 1967) introduces a cautionary note in interpreting the epidemiological data. Generally, MS is seen with greater frequency as the distance from the equator increases in either hemisphere (Gonzalez-Scarano *et al.*, 1986; Skegg *et al.*, 1987). It is twice as common in women and, although it may occur at any age, the onset is typically in early adult life. The etiology is unknown and both genetic and environmental influences are considered important. The 31% monozygotic concordance rate, at six times the dizygotic rate (Sadovnik *et al.*, 1993), attests to the former, while evidence of environmental influences comes from three main sources. Migration studies have demonstrated that those who emigrate during childhood assume the risk of the country of adoption (Dean, 1967); disease epidemics have been reported in isolated communities such as the Faroe Islands (Kurtzke and Hyllested, 1979), and marked variations in prevalence have been found in genetically homogenous populations (Miller *et al.*, 1990).

Clinical features

The disorder may present with diverse neurological signs that vary considerably between patients. Initial symptoms, which reflect the presence and distribution of the plaques, commonly involve numbness or tingling in the limbs or weakness affecting one or more limbs, loss of vision or impaired visual acuity, diplopia, facial numbness, vertigo, dysarthria, ataxia, urinary frequency or urgency and fatigue. Prominent cortical signs (i.e. aphasia, apraxia, recurrent seizures, visual field loss, early dementia and extrapyramidal symptoms such as chorea and rigidity) are unusual and seldom define the clinical presentation (Noseworthy *et al.*, 2000). The course of the disease is variable and initially difficult to predict. Approximately 5–10% of patients show a steady progression of disability from the onset of the disease. The remainder run a relapsing–remitting course of which 20–30% never become seriously disabled and continue to function productively 20–25 years after symptom onset (Sibley, 1990). However, the largest group (almost 60%) enter a phase of progressive deterioration a variable number of years after symptom onset. Even within this group, there is considerable variability, with a patient's condition fluctuating between relapses, periods of stability and progressive deterioration. Recent longitudinal outcome data from a study of 2837 MS patients paints a more optimiztic picture than previously thought, with a median of 27.9 years elapsing before patients require a cane, at least, for walking (Tremlett *et al.*, 2006).

Pathology

Although the exact pathogenesis of MS is uncertain, there is firm evidence of an autoimmune-mediated inflammatory disorder affecting the central nervous system (CNS) (Lisak, 1986; ffrench-Constant, 1994). The target of the inflammatory response is myelin, a lipoprotein made by oligodendrocytes and investing the axons. Along the length of a nerve, the myelin sheaths are separated by gaps, the nodes of Ranvier. Nerve transmission is facilitated by impulses jumping from node to node in a process known as saltatory conduction. With damage to the myelin (i.e. demyelination), the conduction becomes impaired, transmission of nerve impulses is delayed or blocked completely and symptoms ensue.

Postmortem findings have further elucidated the neuropathological changes that occur (Allen, 1991). In patients severely affected by MS and who come to autopsy, the brain shows a mild degree of generalized atrophy with sulcal widening and dilatation of the ventricles. Plaques, which show histological evidence of demyelination, have a striking predilection for a bilateral periventricular distribution, particularly the lateral angles of the lateral ventricles, the floor of the aqueduct and the fourth ventricle. When viewed on sagittal section, the relationship of demyelination to the terminal veins may be seen. In some patients, the cerebrum is relatively spared, the main lesion load involving the optic nerves, brainstem and spinal cord (Allen, 1991). Cortical demyelination (Bruck and Stadelmann, 2005; Kutzelnigg and Lassmann, 2005; Merkler *et al.*, 2006) and cortical atrophy (Carone *et al.*, 2006; Prinster *et al.*, 2006) occur more often than previously thought, with the degree and type of pathological change correlating with the disease type. In a postmortem study of 52 MS patients of differing disease type (acute, relapsing–remitting, primary and secondary progressive; see p. 16), active and focal inflammatory demyelinating lesions in the white matter predominated in patients with acute and relapsing MS, whereas diffuse injury to white matter of normal appearance and cortical demyelination were characteriztic of primary and secondary MS (Kutzelnigg *et al.*, 2005). The latter changes reflected diffuse axonal injury with an underlying global inflammatory response affecting the whole brain and meninges. Significantly, the relationship between the focal white matter lesion load on the one hand and diffuse white matter injury or cortical demyelination, on the other, was either weak or absent. These data point to a clear temporal sequence of pathological events: MS beginning as a focal inflammatory disease with circumscribed white matter plaques giving way over time to a chronic picture of diffuse inflammatory changes, slowly progressive axonal injury and cortical demyelination.

The conventional view of neuropathological changes can be briefly summarized as follows. In the early stages of myelin breakdown, oligodendrocytes are still

recognizable. As disease progresses, the myelin becomes progressively attenuated, partially detached from the axon and ultimately phagocytosed by invading macrophages. The early, established lesion shows a characteriztic pattern of increased cells (macrophages, astrocytes), a mixture of intact and disintegrated myelin sheaths, perivascular inflammation (lymphocytes, plasma cells, macrophages), oligodendrocyte loss, relatively preserved axons and, within the gray matter, preservation of cell bodies. In non-acute but active plaques, there is hyperplasia of macrophages and astrocytes and lesions contain myelin lipid degradation products. Perivascular inflammation, although present, is sparse. While the edges of active lesions are hypercellular with evidence of normal and disintegrating myelin sheaths, the core of such lesions may resemble older, inactive plaques. As the lesion evolves from an active to non-active phase, signs of inflammation disappear. Chronic lesions, which generally make up the bulk of the large characteriztic periventricular lesions seen in magnetic resonance imaging (MRI) or at postmortem, are, therefore, hypocellular, demyelinated, gliosed and contain few oligodendrocytes. The small venules are not inflamed, as in acute lesions, but rather show thickened hyalinized walls (Allen, 1991).

More recent data from actively demyelinating lesions, however, suggest a picture of greater complexity. Lucchinetti *et al.* (2000) examined biopsy and autopsy material with an array of immunological and biological markers and found marked lesion heterogeneity. Four different types of demyelination were noted based on the degree of myelin protein loss, the site and size of plaques, the patterns of oligodendrocyte destruction and the immunopathological evidence of complement activation. The four types of lesion (type I, macrophage-mediated demyelination; type II, antibody-mediated demyelination; type III, distal oligodendrogliopathy and apoptosis; and type IV, primary oligodendroglia degeneration) are thought to differ with respect to pathogenesis, as their descriptors indicate (Lucchinetti *et al.*, 2000; Lassmann *et al.*, 2001).

Advances in neuropathology have also challenged the historical view of MS as primarily a demyelinating disease in which axons are relatively spared. Using an antibody against amyloid precursor protein as a proven marker of axonal damage, Ferguson *et al.* (1997) examined paraffin-embedded MS lesions of varying ages. The results revealed the expression of amyloid precursor protein in damaged axons within acute MS lesions and in the active borders of less acute lesions. Confirmatory evidence of early axonal damage was soon provided by Trapp *et al.* (1998). Immunohistochemistry and confocal microscopy revealed that transected axons were a consistent feature in MS brain lesions, correlating with the degree of inflammation within a lesion. Thus, the greatest frequency of transected axons (11 236/mm^3) was found in active lesions, the density falling in the hypocellular edges of chronic active lesions (3138/mm^3) and declining still further in the hypocellular center of chronic active lesions (875/mm^3).

Irrespective of the stage of the lesion, remyelination may affect the changes observed. Remyelination has been noted in acute MS lesions (Prineas *et al.*, 1993), giving rise to thin myelin sheaths in areas previously noted to be free of myelin. Newly formed as opposed to surviving oligodendrocytes are thought to be the source (Prineas *et al.*, 1989). In chronic lesions where not all the myelin is lost, demyelination and remyelination are thought to be occurring simultaneously. In MS, remyelination is not complete, perhaps because repaired areas are subject to repeated bouts of demyelination, leading to either a reduction in oligodendrocyte precursors (termed 02A progenitor cells) or the creation of an environment that inhibits their migration (ffrench-Constant, 1994).

Imaging studies during an acute attack have shown leakage of contrast-enhancing materials, indicative of a breakdown in the blood–brain barrier. The compromised barrier results in edema and the entry of immune mediators (antibodies and lymphocytes), which may contribute to myelin destruction. The leakage disappears spontaneously over 4–6 weeks (Miller *et al.*, 1988) and may be reversed temporarily by the administration of corticosteroids (Barkhof *et al.*, 1991). Postmortem studies have confirmed that lesions visualized by MRI and axial computed tomography (CT) correspond to MS plaques (Ormerod *et al.*, 1987). Furthermore, an in vivo study of MRI and histological parameters from six biopsy-proven cases of inflammatory demyelination of the CNS has shown that changes observed on MRI correlated with the evolving pattern of lesions (i.e. from acute to less active to chronic; Bruck *et al.*, 1997).

An important observation is that white matter that appears normal to the naked eye will more often than not show histological abnormalities. These include microscopic foci of demyelination; diffuse gliosis; perivascular inflammation; deposits of iron, lipofuscin and calcium; collagenization of small vessels; and axonal loss. Furthermore, this evidence of a more diffuse pathological process may occur in the absence of significant plaque formation. The clinical significance of these findings is that neuroimaging of the brain and spinal cord with standard sequences devised for plaque detection may mislead the observer into thinking the normal appearing white matter was indeed normal. Alternative imaging procedures for probing these more subtle changes have been devised, namely magnetic resonance spectroscopy, diffusion tensor and magnetization transfer imaging.

Diagnosis

The diagnosis of MS carries major implications for patients and their families. Uncertainty over the future, the ability to work, earn a living and live independently are all issues that readily come to mind. It is, therefore, imperative for the clinician to be clear about what symptoms and signs constitute a diagnosis

of MS. In addition, making an early, correct diagnosis has assumed added importance because, for the first time, the MS patient is facing a choice of treatment options.

The diagnosis of MS can be made on clinical grounds alone. This requires that a patient have at least two episodes of neurological disturbance implicating different sites in the central white matter. A number of investigations may help the clinician to establish the presence and site of white matter lesions, thereby facilitating a diagnosis. It is, however, important to realise that these investigations (neuroimaging, evoked potentials and cerebrospinal fluid [CSF] electrophoresis) are not specific for MS and should be viewed only as helpful adjuncts to the clinical presentation.

From a research perspective, correctly diagnosing MS is equally important. The need for researchers across sites to talk the same language has prompted serial attempts to develop a set of diagnostic guidelines. For many years those of Schumacher *et al.* (1965) sufficed, but in response to improved laboratory and clinical procedures these gave way to the Poser criteria (Poser *et al.*, 1983).

The Poser Committee's recommendations

The Poser Committee convened in Washington, DC in 1982 and comprehensively reviewed historical and clinical symptomatology in MS; immunological observations; CSF tests; a variety of neurophysiological, psychophysiological and neuropsychological procedures; neuroimaging procedures (CT and MRI); and urological studies of bladder, bowel and sexual function. They concluded that revisions to existing criteria were essential in order to conduct multicenter therapeutic trials, to compare epidemiological data, to evaluate new diagnostic procedures and to estimate disease activity (Poser *et al.*, 1983; Poser, 1984).

>Definitions and guidelines were provided for what constituted an MS attack (synonyms here included bout, episode, exacerbation, relapse), a remission, *clinical* evidence of a lesion, what constituted separate lesions, *paraclinical* evidence of a lesion (i.e. abnormalities on evoked potentials [Fig. 1.1], MRI [Fig. 1.2] and urological assessment) and *laboratory* support indicative of MS (i.e. increased production of immunoglobulin G (IgG) and the presence of CSF oligoclonal bands in the absence of such bands in the serum [Fig. 1.3]. The authors made it clear that MRI and evoked potential abnormalities were not considered *laboratory* evidence, but rather an extension of the *clinical* examination, hence the *paraclinical* label. Bringing together all these strands of evidence enabled the neurologist to arrive at one of four possible diagnoses: clinically definite MS, laboratory supported definite MS, clinically probable MS and laboratory supported probable MS. Of note was the committee's view that neuropsychological evidence of impaired

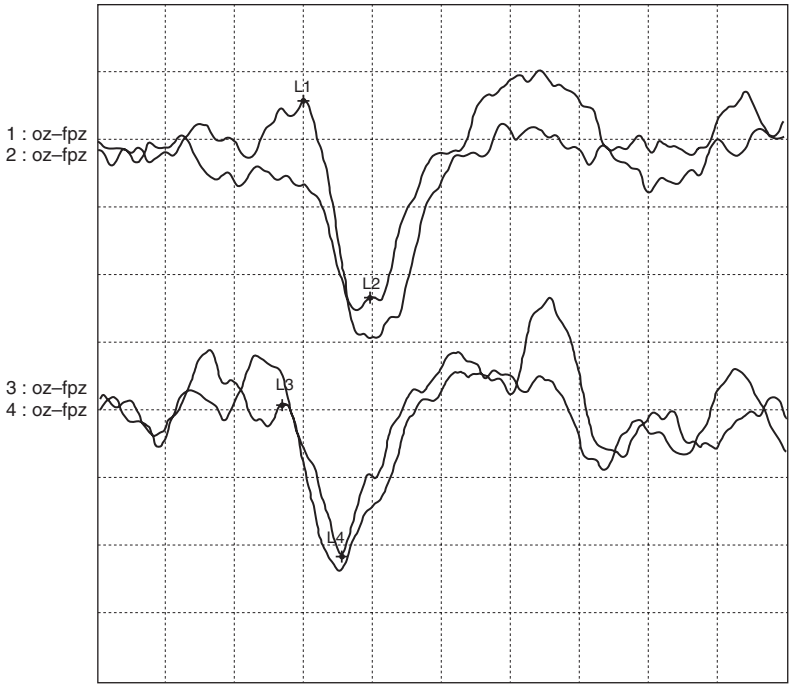

Fig. 1.1. Visual evoked potentials in a 33-year-old female with multiple sclerosis. Note the mildly delayed conduction in the right optic nerve (top) compared with left nerve (bottom); this is comparable with optic neuritis.

cognition in someone under 50 years, although suggestive of MS, was not specific enough to be considered diagnostic.[1]

In concluding, the committee acknowledged that there would always be patients who defied easy categorization. The experienced neurologist would have to rely on intuition and accumulated clinical skill in arriving at diagnoses for this group. The criteria outlined were primarily for research purposes. Furthermore, there was a recommendation that clinical trials and research protocols should be limited to patients in one of the two *definite* groups. The category of *probable* was designed for the purpose of prospectively evaluating new diagnostic methods. The Poser criteria would hold sway over the MS world for the next 18 years.

The McDonald Committee's recommendations

In 2000, the International Panel on the Diagnosis of MS was convened with the aim of setting out new diagnostic criteria to be used by clinicians and adapted, as necessary,

[1] This recommendation, which was made in 1983, predated the plethora of studies from later in the decade that unequivocally demonstrated the presence of clinically significant cognitive dysfunction in approximately 40% of community based MS patients (Rao *et al.*, 1991, McIntosh-Michaelis *et al.*, 1991).

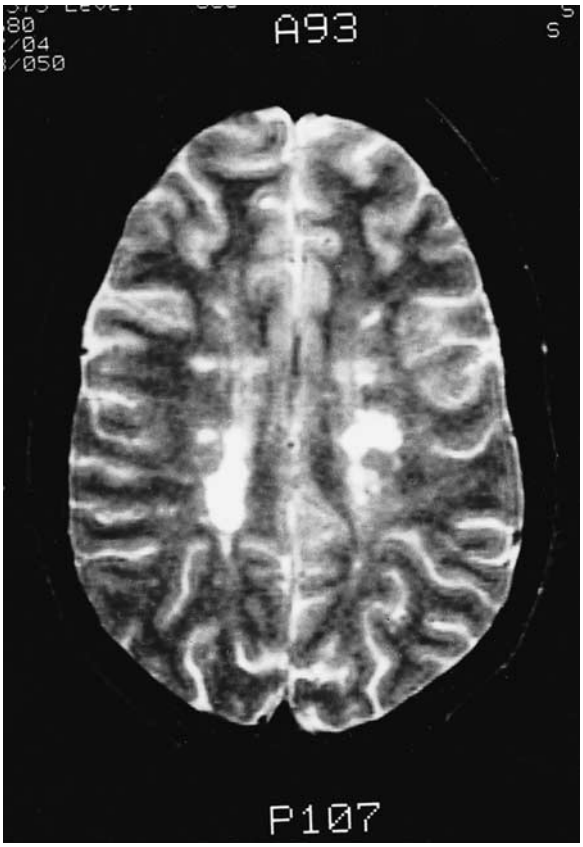

Fig. 1.2. Axial T_2-weighted (spin echo) scan demonstrating the extensive white matter lesions (multiple sclerosis plaques) in a typical periventricular distribution.

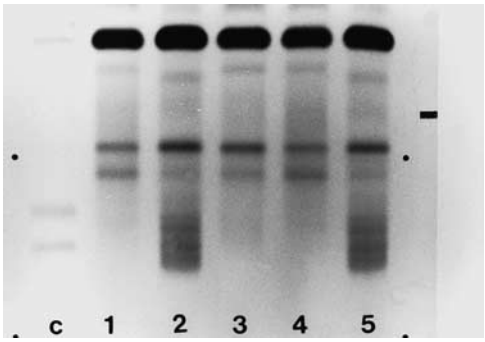

Fig. 1.3. Abnormal oligoclonal banding in patients 2 and 5, who both have a diagnosis of multiple sclerosis.

for clinical trials (McDonald *et al.*, 2001). Much had changed since the formulation of the Poser criteria, including significant advances in MRI technology, the advent of disease-modifying treatments such as the interferons beta-1a and beta-1b, and the recognition of a new disease course, namely primary progressive (see below).

The committee kept certain sacrosanct principles intact, namely that obtaining objective evidence of dissemination of lesions (typical of MS) in time and place was essential in making a secure diagnosis. Furthermore, while history taking was clearly informative, clinical evidence depended essentially on objectively determined neurological signs. A diagnosis of MS based purely on clinical grounds would, therefore, depend on objective evidence of lesions separated in time and space. Radiological and laboratory investigations retained their utility in the diagnostic process, but with some further caveats; For example, visual evoked potentials were still considered helpful but not somatosensory and brainstem readings, which were thought to contribute little to the diagnosis. Following a diagnostic evaluation, an individual was either deemed to have, or not to have, multiple sclerosis. While a category of *possible MS* was thought necessary (referring to a patient whose evaluation met some, but not all, of the necessary criteria), diagnostic categories such as clinically definite and laboratory supported MS were considered obsolete.

Definitions

Definitions from previous diagnostic criteria were reviewed and where needed refined and clarified.

Attack (exacerbation, relapse)

An attack referred to an episode of neurological disturbance (a subjective report *and* objective evidence) lasting at least 24 hours and not to be confused with a pseudo-attack, as might be caused by infection or change in core body temperature.

Time between attacks

In defining what constituted separate attacks, it was felt that a minimum of 30 days should separate the onset of the first event from the onset of the second.

Paraclinical abnormalities: what are they?

When Poser and his committee set out their criteria in 1982, MRI technology was in its infancy. Two decades later, the technique had substantially evolved and, given its pivotal role in assessing patients with MS, considerable attention was devoted to it by McDonald *et al.* (2001). A more detailed account of MRI abnormalities in MS appears in Chapter 10. Here it is sufficient to note that the McDonald criteria emphasised that MRI can provide evidence of dissemination of lesions in both time and space. A stringent procedure was adopted for

determining that MRI abnormalities were indicative of MS (Barkhof *et al.*, 1997; Tintoré *et al.*, 2000).

In keeping with the removal of the laboratory supported diagnostic label, the McDonald criteria incorporated CSF abnormalities under the paraclinical rubric. Analysis of CSF assumes greater importance if imaging results are equivocal or when the clinical presentation is atypical, but information from CSF cannot provide evidence of dissemination in time. As with the Poser definition, CSF significance pertains to the presence of oligoclonal IgG bands (distinct from such bands in the serum) and/or the presence of an elevated IgG index. Lymphocyte pleocytosis should be less than 50/mm^3.

Abnormal visual evoked potentials typical of MS (delayed but with well-preserved waveform) remained a useful adjunct to the clinical examination and could provide evidence of a second lesion providing that the sole clinical manifestation was not limited to the visual pathways.

The McDonald classification criteria revised

Four years after their publication, the McDonald criteria were revised (Polman *et al.*, 2005). New guidelines were provided to define what is meant by the dissemination of lesions in time, to clarify the significance of spinal cord lesions and to simplify the diagnosis of primary progressive MS. In the introduction to the revisions, the authors emphasised that the primary aim of the McDonald criteria was to help clinicians to make a valid and reliable diagnosis. This focussed on balancing the importance of arriving at an early, correct diagnosis with the need to avoid a false-positive diagnosis.

The committee acknowledged that the McDonald criteria had been derived from data largely pertaining to an adult Caucasian population. Therefore, the results from ongoing studies in Asian and South American groups were needed to validate the criteria more widely. Similarly, the applicability of the criteria to children was also questioned, with further work needed here. As with their predecessors, the committee made reference to the challenges posed by diseases that could mimic MS and the uncertainty over how best to classify disorders such as acute disseminated encephalomyelitis and neuromyelitis optica.

Give the central importance of these refined recommendations to any discussion of multiple sclerosis, the salient points are given here in greater detail.

Magnetic resonance imaging criteria to demonstrate brain abnormality and dissemination in space

Three of the following are required.

1. At least one contrast (gadolinium)-enhancing lesion or nine T_2 hyperintense lesions if there is no contrast-enhancing lesion.
2. At least one infratentorial lesion.