

The clinical neuropsychiatry of

multiple sclerosis

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Multiple sclerosis: diagnosis and definitions

Many a chapter, monograph and paper on multiple sclerosis begins with the observation that MS is the commonest disabling neurological disease affecting young and middle-aged adults. Since the first clinical description of the disease in the late 1830s, attention has largely focused on neurological manifestations and it is only over the past decade that clinicians, researchers, and indeed the patients themselves, have become more aware of the behavioural changes that may accompany MS. 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 perplexed as to why it has taken so long for this interest to ignite. Descriptions of altered mentation in MS patients predate the writings of the man first credited with naming the condition over a century ago, the French behavioural neurologist Jean-Martin Charcot (Stenager, 1991).

Before describing the psychiatric and cognitive changes associated with MS, reference will be made 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 multiple sclerosis. 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 behavioural changes may affect this assessment.

Epidemiology

In the United Kingdom the lifetime risk is 1:800, which translates into approximately 60 000 people with the disease (Compston, 1990). In the United States, the figure is at least four times that. 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 as in men and, although may occur at any age, onset in early adult life is commonest. The etiology is unknown, and both genetic and environmental influences are considered important. The 25% monozygotic concordance rate (Ebers and Bulman, 1986) 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 homogeneous 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, dysathria, ataxia and urinary frequency or urgency and fatigue. As MS is predominantly a white matter disease, symptoms referable to cortical (grey) matter involvement are considered rare. Thus, dementia, aphasia, seizures, pain, abnormal and involuntary movement, muscle atrophy and fasciculations although possible, are so unusual they may cast doubt on the diagnosis (Rolak, 1996). The course of the disease is variable and initially impossible 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.

Pathology

Although the exact pathogenesis of MS is uncertain, there is firm evidence of an autoimmune mediated inflammatory disorder affecting the central ner-

vous system (Lisak, 1986; French-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 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. While plaques may also be scattered throughout the white matter, immediate subcortical myelin is usually spared and the cortex only rarely involved. 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, brain stem and spinal cord (Allen, 1991). Such a constellation of plaques has major implications for the presence and nature of behavioural and cognitive changes and will be more fully discussed in Chapters 2 and 9.

What exactly occurs in the early stages of demyelination is unclear, and it is the subject of debate whether demyelination can occur *de novo* without an observed immune response and increased cellularity, e.g. an influx of lymphocytes associated with perivascular inflammation. 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 characteristic pattern of increased cells (macrophages, astrocytes), a mixture of intact and disintegrated myelin sheaths, perivascular inflammation (lymphocytes, plasma cells, macrophages), oligodendrocyte loss, preserved axons, and within the grey 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 characteristic periventricular lesions seen on MRI or at post-mortem, are

thus hypocellular, demyelinated, gliosed and contain few oligodendrocytes. The demyelinated axons are separated by a heavy concentration of astrocytic processes (French-Constant, 1994). The small venules are not inflamed, as in acute lesions, but rather show thickened hyalinized walls (Allen, 1991). Although considered a disease primarily affecting myelin, there is evidence that axons denuded of myelin are also susceptible to damage (Paty, 1997).

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 O2A progenitor cells), or the creation of an environment that inhibits their migration (French-Constant, 1994).

Imaging studies during an acute attack have shown leakage of contrast enhancing materials, indicative of a breakdown in the blood-brain barrier (BBB). The compromised BBB results in edema and the entry of immune mediators (i.e. antibodies), 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 on magnetic resonance imaging and computerized axial tomography 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 central nervous system, has shown that changes observed on MR imaging correlate 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, which appears normal to the naked eye (NAWM) will, more often than not, show histological abnormalities. These include microscopic foci of demyelination, diffuse gliosis, perivascular inflammation, deposits of iron, lipofuscin and calcium and collagenization of small blood vessels (Allen, 1991). Furthermore, this evidence of a more diffuse lesion 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, and T_1 and T_2 relaxation times, and are discussed in Chapter 9.

Diagnosis

The diagnosis of multiple sclerosis (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 is assuming added importance because, for the first time, the MS patient is facing a choice of treatment options.

The diagnosis of MS is essentially a clinical one and requires that a patient of an appropriate age has had at least two episodes of neurological disturbance, implicating different sites in the central white matter. A number of investigations may help the clinician establish the presence and site of white matter lesions, thereby facilitating a diagnosis. It is, however, important to realize that these investigations (neuroimaging, evoked potentials and cerebrospinal fluid electrophoresis) are not specific for multiple sclerosis and should thus be viewed only as helpful adjuncts to the clinical presentation.

From a research perspective, correctly diagnosing MS is equally important. Researchers across sites need to talk the same language and, while well-defined clinical criteria are essential, they cannot stand apart from advances in technology. A recognition of the need to bring coherence, to what may be widely divergent neurological presentations, has prompted researchers over the years to come up with a series of diagnostic guidelines. For many years those of Schumacher (1965) sufficed, but in response to improved laboratory and clinical procedures these have given way to revised criteria (Poser et al., 1983).

The Poser Committee's Recommendations

The Poser Committee that convened in Washington, DC in 1982 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 multicentre, therapeutic trials, to compare epidemiological data, to evaluate new diagnostic procedures and to estimate disease activity (Poser et al., 1983; Poser, 1984). It was also clear to Poser and his committee that physicians differed in their use of MS-related terminology (e.g. relapse, remission, etc.), so new definitions were included with the diagnostic criteria. They are still used today. Given the pivotal place they have assumed in MS

research, and because they define concepts and categories that occur throughout this book, a detailed description follows.

Definitions

Age

For research purposes, age was limited to 10–59 years in order to minimize contamination by patients suffering from other disorders. However, it is recognized that patients may present outside this range, although such occurrences are rare.

Attack (bout, episode, exacerbation, relapse)

This was defined as the occurrence of a symptom or symptoms of neurological dysfunction, with or without objective confirmation, lasting more than 24 hours. The completely subjective nature of the symptoms were stressed, although it was acknowledged that medical corroboration would strengthen the case. Individual symptoms that were transient, such as Lhermitte's sign, i.e. sudden paresthesia following neck flexion, or vertigo lasting a few seconds, were not considered evidence of an attack.

Clinical evidence of a lesion

This refers to the demonstration of abnormal signs on examination by a competent clinician. These signs are acceptable, even if no longer present, provided they were elicited and recorded earlier by an examiner.

Paraclinical evidence of a lesion

Procedures, other than the clinical examination, that can demonstrate the existence of a lesion in the CNS are termed paraclinical evidence. The lesion may or may not have produced symptoms and signs of neurological dysfunction in the past. The procedures include evoked potential studies (Fig. 1.1), neuroimaging, most notably magnetic resonance imaging (MRI) (Fig. 1.2), and expert urological assessment.

Typical of multiple sclerosis

Certain sites within the CNS are more likely to be affected by demyelination than others, with the result that symptoms related to these sites occur more frequently. Grey matter lesions producing symptoms such as aphasia, seizures and alterations in consciousness should not be considered in making the diagnosis. However, the presence of these symptoms, in the presence of a typical clinical presentation of MS, should not invalidate the diagnosis.

Remission

A definite improvement in signs, symptoms or both that have been present

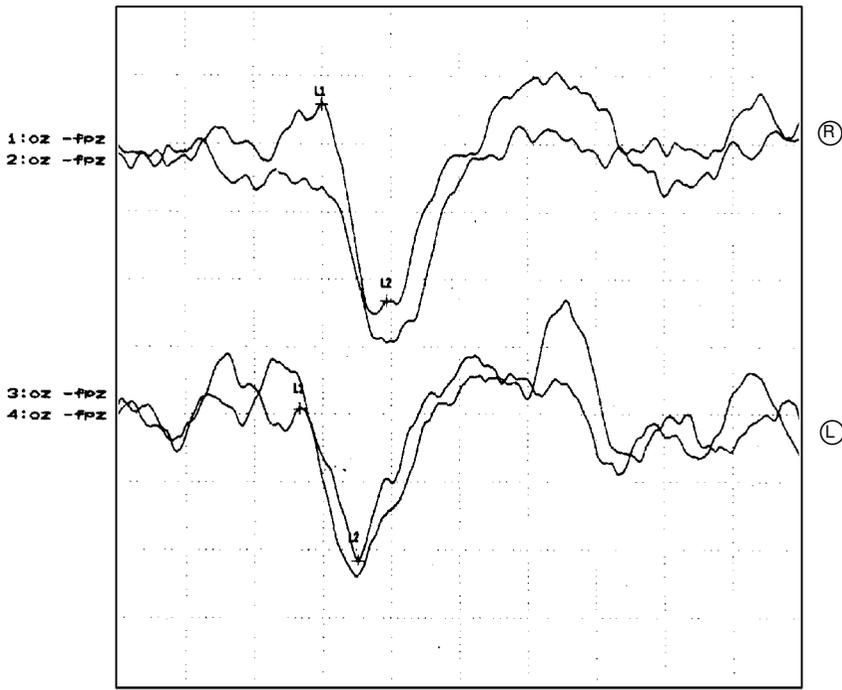


Fig. 1.1. Visual-evoked potentials in a 33-year-old female with clinically definite MS. Note the mildly delayed conduction in the right optic nerve, compatible with optic neuritis.

for at least 24 hours is called a remission. For this to be considered clinically significant, the remission should last for a period of at least 1 month.

Separate lesions

Separate signs or symptoms cannot be accounted for by a single lesion. An example given is brainstem infarction, which may give rise to the simultaneous presentation of internuclear ophthalmoplegia, facial weakness and signs of corticospinal tract involvement. Similarly, optic neuritis affecting both eyes simultaneously is excluded. Should the second eye become involved within 15 days of the other, then convention holds that it is still regarded as a single lesion. Thus, only lesions involving distinctly different parts of the CNS satisfy the criterion.

Laboratory support

This refers only to immunological abnormalities detected in the CSF, namely increased production of immunoglobulin G (IgG) and the presence of oligoclonal bands in the absence of such bands in the serum (Fig. 1.3).

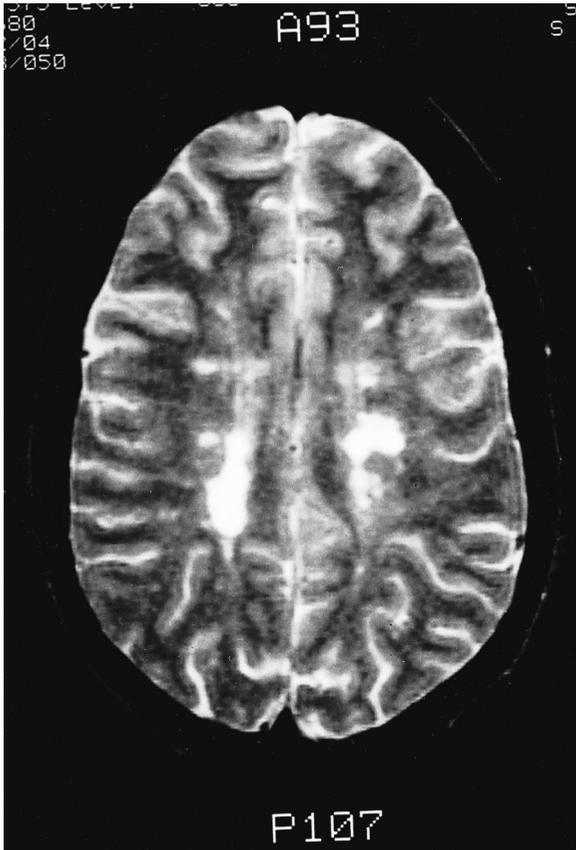


Fig. 1.2. Axial T_2 -weighted (spin echo) scan, demonstrating the extensive white matter lesions (MS plaques) in a typical periventricular distribution.

Procedures such as neuroimaging and evoked potential studies are not regarded as laboratory evidence, but rather are considered as an extension to the clinical examination (paraclinical evidence).

Associations between paraclinical and laboratory supported indices

A number of studies have investigated the degree with which the paraclinical and laboratory data are in concordance. In a study of 62 patients with clinically definite MS, Baumhefner et al. (1990) noted brain MRI abnormalities in 97% of patients, and positive oligoclonal bands in all but one of the subjects. Not all reports have yielded such strongly positive associations, however, with Pirttila and Nurmiko (1995) noting a more modest concordance rate approaching two-thirds of cases. Exploring the strength of an association between the two main paraclinical modalities, MRI abnormalities

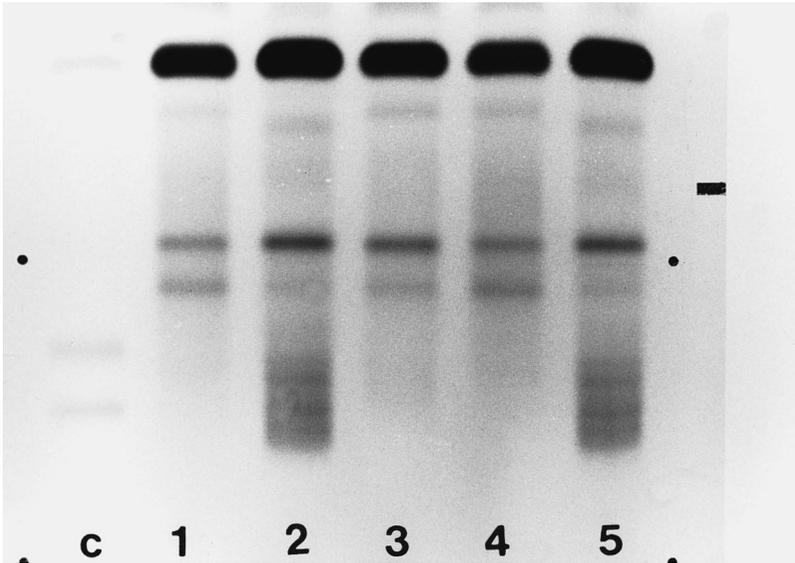


Fig. 1.3. Abnormal oligoclonal banding in patients 2 and 5, who both have a diagnosis of laboratory supported definite multiple sclerosis.

in the brainstem have been found to correlate significantly with abnormal auditory-evoked potentials (Hendler et al., 1996), while significant correlations have also been noted between total brain MRI lesion area and delayed conduction in visual evoked potentials (Baumhefner et al., 1990).

The Poser Classification Criteria

The criteria, designed specifically for research purposes, divides MS patients into two broad groups, *definite* and *probable*, each of which may be subdivided into *clinical* and *laboratory supported*.

Clinically definite MS (CDMS)

- (i) Two attacks and clinical evidence of two separate lesions.
- (ii) Two attacks; clinical evidence of one lesion and paraclinical evidence of another, separate lesion.

The two attacks must involve different parts of the central nervous system, each must last a minimum of 24 hours and be separated by a period of a month. In some cases, symptoms if considered reliable and adequate to localize a lesion typical of MS, may be accepted in lieu of clinical evidence, e.g. Lhermitte's sign in any person under 50 years of age, who does not have radiological evidence of an independent cause. Symptoms on their own must,

however, only be considered with extreme caution and, if possible, corroboration from friend or relative should be sought if the attack was not recorded by a physician.

Paraclinical evidence that aids in diagnosis includes CT and MRI, evoked potentials, hyperthermia challenge and specialized urological studies. Of note is the recommendation that neuropsychological evidence of impaired cognition in someone under 50 years, although suggestive of MS, was not specific enough to be considered diagnostic. 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., 1991a; McIntosh-Michaelis et al., 1991). To date, however, impaired cognition is still not one of the acceptable paraclinical signs.

Laboratory-supported definite MS (LSDMS)

Laboratory support comes from increased IgG in the CSF, with normal levels in the serum or oligoclonal bands in the CSF, but not in the serum.

- (i) Two attacks; either clinical or paraclinical evidence of one lesion and CSF IgG or oligoclonal bands.
- (ii) One attack; clinical evidence of two separate lesions; and CSF IgG or oligoclonal bands.
- (iii) One attack; clinical evidence of one lesion and paraclinical evidence of another separate lesion; CSF IgG or oligoclonal bands.

The two attacks must involve different parts of the CNS, each must last 24 hours and be separated by a month. One of the episodes must involve a part of the CNS distinct from that demonstrated by the clinical or paraclinical evidence. Unlike CDMS, historical information cannot be substituted for clinical evidence. Whether the evidence is clinical or paraclinical, both lesions must not have been present at the time of the first examination and must be separated by at least a month. This time factor is to reduce the possibility of including a case of acute disseminated encephalomyelitis.

In patients with progressive MS from symptom onset, clinical or paraclinical evidence of the second lesion should not have been present at the time of symptom onset. If the second lesion was present, the patient can only be deemed to have had MS once symptom progression had taken place for 6 months.

Clinically probable multiple sclerosis (CPMS)

- (i) Two attacks and clinical evidence of one lesion.
- (ii) One attack and clinical evidence of two separate lesions.
- (iii) One attack; clinical evidence of one lesion and paraclinical evidence of another separate, lesion.

The two attacks must involve separate parts of the CNS. Historical information cannot replace clinical evidence, and the restrictions discussed under *laboratory supported definite multiple sclerosis* also apply.

Laboratory supported probable multiple sclerosis (LSPMS)

(i) Two attacks and CSF IgG or oligoclonal bands.

The two attacks must involve different parts of the CNS, must be separated by a minimum of a month and each must have lasted 24 hours.

In summary, the Poser committee acknowledge that there will always be patients who defy easy categorization. The experienced neurologist will have to rely on intuition and accumulated clinical skill in arriving at diagnoses for this group. The criteria as outlined above are primarily for research purposes. Furthermore, there is 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.

Clinically isolated lesions

Patients with clinically isolated lesions (CIL) are of particular interest as they are frequently the forerunners of MS. In attempting to describe the natural history of psychiatric and cognitive abnormalities in MS, the study of such patients affords a valuable opportunity to document the earliest evidence of dysfunction before patients progress to the full syndrome. Throughout the book, reference will be made to patients with CIL and a brief description of these conditions is therefore given.

Optic neuritis

Acute unilateral optic neuritis (ON) in adults is the presenting feature of MS in 20% of cases, over three-quarters of patients going on to develop MS (Francis et al., 1987). It is characterized by the rapid development of visual loss, usually accompanied by pain with symptoms progressing for 3–4 weeks and then resolving over 2–3 months, recovery to 6/9 vision occurring in greater than 90% of patients (McDonald, 1983). MRI with contrast enhancement may reveal lesions within the optic nerves (Fig. 1.4). In addition, 60% of adults presenting with clinically isolated optic neuritis display one or more asymptomatic white matter brain lesions on MRI which appear indistinguishable from those seen in MS (Ormerod et al., 1987). The presence of these lesions is associated with a high risk of progression to clinically definite MS within 5 years (Miller et al., 1992), but MS should still not be diagnosed at

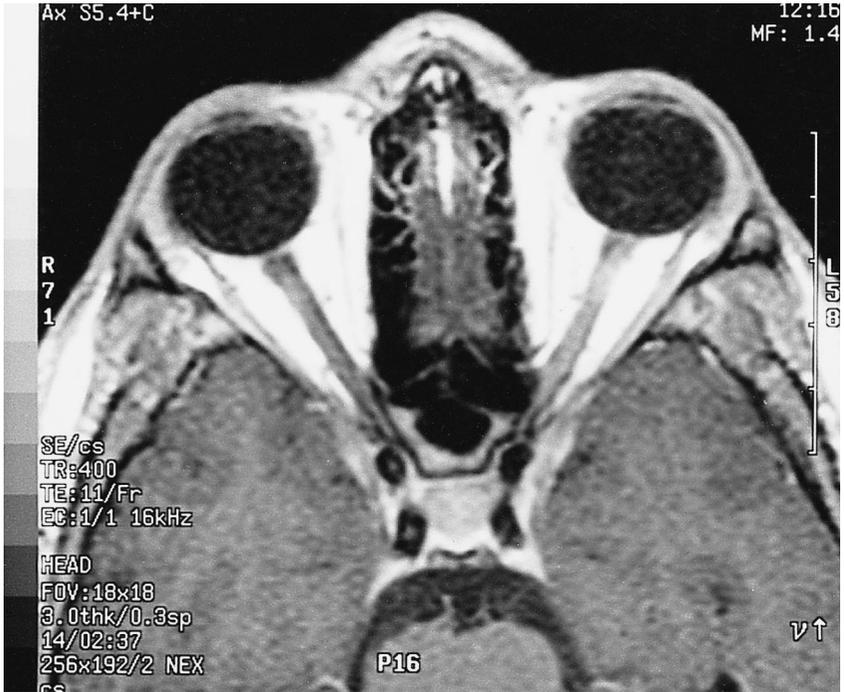


Fig. 1.4. T_1 -weighted, contrast (gadolinium-DTPA)-enhanced MRI, showing pathological changes in the optic nerve in a patient with clinically definite MS.

presentation because the criterion of dissemination in space has not been satisfied.

Brainstem and spinal cord syndromes

Acute brainstem disturbance (e.g. vertigo, diplopia) is the presenting feature of MS in approximately 15% of patients, while twice as many will present with spinal cord symptoms (sensory, motor and sphincter disturbance). The percentage that go on to develop MS is probably similar to that of optic neuritis (Miller et al., 1992).

Differential diagnosis

Given the broad array and often subtle nature of neurological signs and symptoms that may herald the onset of MS, the list of conditions that make up a differential diagnosis is potentially formidable (Rolak, 1996). These include somatization disorder (hysteria), postviral demyelination (acute dis-

seminated encephalomyelitis), vasculitis affecting the CNS (either primary or secondary conditions such as lupus erythematosus), retroviral infections such as acquired immune deficiency syndrome (AIDS), cerebrovascular accidents (stroke), metachromatic leukodystrophy and tumours (metastases, lymphoma).

To the neuropsychiatrist, dealing primarily with the behavioural sequelae of MS, the somatizing patient masquerading with MS-like symptoms can present a considerable therapeutic challenge (Aring, 1965). A follow-up of 400 patients, referred to neurologists and subsequently found not to have MS, revealed 14 with primarily psychiatric problems (Murray and Murray, 1984). These patients were more likely to be female, hospital employees or have a friend with MS and suffer from anxiety, depression and somatization disorder, the latter formerly called hysteria. Conversely, there are patients with MS, who may be incorrectly dismissed as 'hysterical'. Skegg et al. (1988) were able to identify 91 patients with MS (a point prevalence of 0.08%), of whom 16% had been referred to a psychiatrist between the onset of neurological symptoms and the diagnosis of MS. Although neurological symptoms were present at the time in the majority of patients, these had been overlooked by the psychiatrist in all but two cases. Instead, patients were given diagnoses, such as hysterical personality disorder or conversion disorder.

The clinical course of multiple sclerosis

In describing the clinical course of MS, difficulties have also been present with respect to terminology (Whitaker et al., 1995), the situation proving analogous to the imprecision that surrounded the diagnosis of MS and the definition of terms such as relapse, remission, etc. While there is general recognition that the course of MS shows individual variability, and that physical disability usually follows either a relapsing–remitting or steadily progressive course, what is meant by these terms has demanded clarification. A tightening up of terminology is not only important from a research perspective, where clear definitions of patient subgroups are essential for valid data interpretation, but also for correctly assigning patients to particular treatments. The question of which patients would benefit from which treatments is one of crucial importance to physicians looking for clear guidelines in their clinical practice.

Differences amongst researchers and clinicians in defining terms that describe the course and severity of MS have stemmed from a reliance on verbal descriptors as opposed to biological markers. This recognition led to an international survey of MS researchers, with the aim of assessing agreement pertaining to the various descriptive terms currently in use (Lublin

and Reingold, 1996). The survey supplied definitions of the following disease courses and types: relapsing–remitting (RR), relapsing–progressive (RP), primary progressive (PP), secondary progressive (SP), benign and malignant. Definitions of each of these terms were included in the survey, but space was also made available for researchers to provide their own definitions if they disagreed with those enclosed. Of the 215 surveys mailed out, 125 (58%) were returned. The results led to the National Multiple Sclerosis Society (USA) providing a set of consensus definitions, which are given below.

Clinical course definitions

Relapsing–remitting (RR) MS

The consensus definition refers to clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; the periods between disease relapses characterized by a lack of disease progression. The defining characteristics of this course are the acute episodes of neurological deterioration with variable recovery, but a stable course between attacks (Fig. 1.5(a),(b)).

Primary–progressive (PP) MS

The consensus definition refers to disease progression from symptom onset, with occasional plateaux and temporary minor improvements allowed. The cardinal feature here is a gradual, nearly continuous worsening of neurological function from the first presentation, with some minor fluctuations but no discrete relapses (Fig. 1.6(a), (b)).

Secondary–progressive (SP) MS

This defines a course that is initially relapsing–remitting followed by a progression, with or without occasional relapses, minor remissions and plateaux. SP–MS is viewed as the long-term outcome of patients who initially show a RR–MS course. What characterizes the switch from one to the other is when the baseline between relapses begins to worsen (Fig. 1.7 (a), (b)).

Relapsing–progressive (RP) MS

There was no consensus amongst those surveyed, which was due largely to the overlap between this term and some of the other categories. The recommendation was for the term to be abandoned.

Progressive–relapsing (PR) MS

The generally agreed definition was of progressive disease from symptom onset, with clear, acute relapses, with or without full recovery; the periods between relapses were marked by continuing disease progression. PR–MS

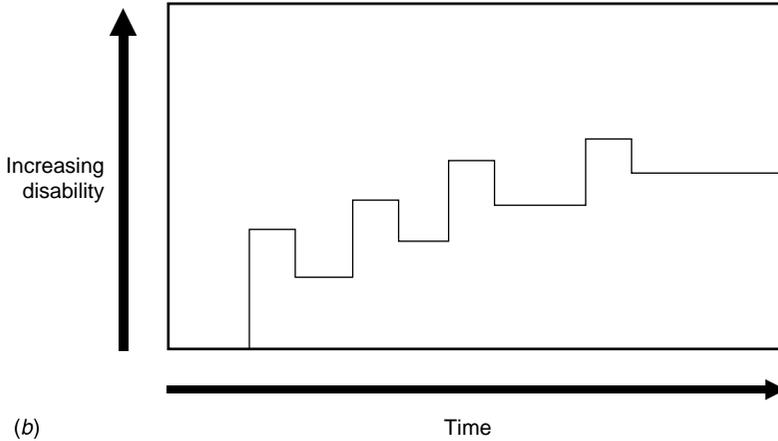
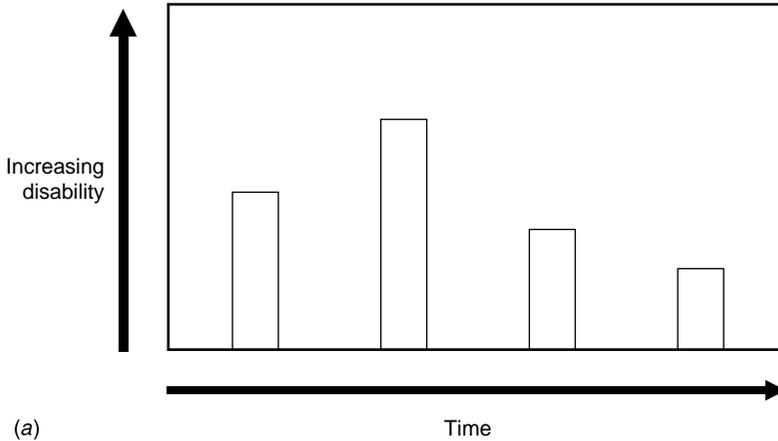


Fig. 1.5. Relapsing–remitting (RR) MS is characterized by (a) clearly defined acute attacks with full recovery (b) with sequelae and residual deficit upon recovery. Periods between disease relapses are characterized by lack of disease progression. (Lublin & Reingold, 1996). (By permission of the American Academy of Neurology.)

was considered an additional, but rare, clinical course that warranted a separate definition (Fig. 1.8 (a), (b)).

Clinical severity definitions

The merits of defining severity according to two terms, ‘benign’ or ‘malignant’ were surveyed, and the results indicated a lack of uniformity amongst

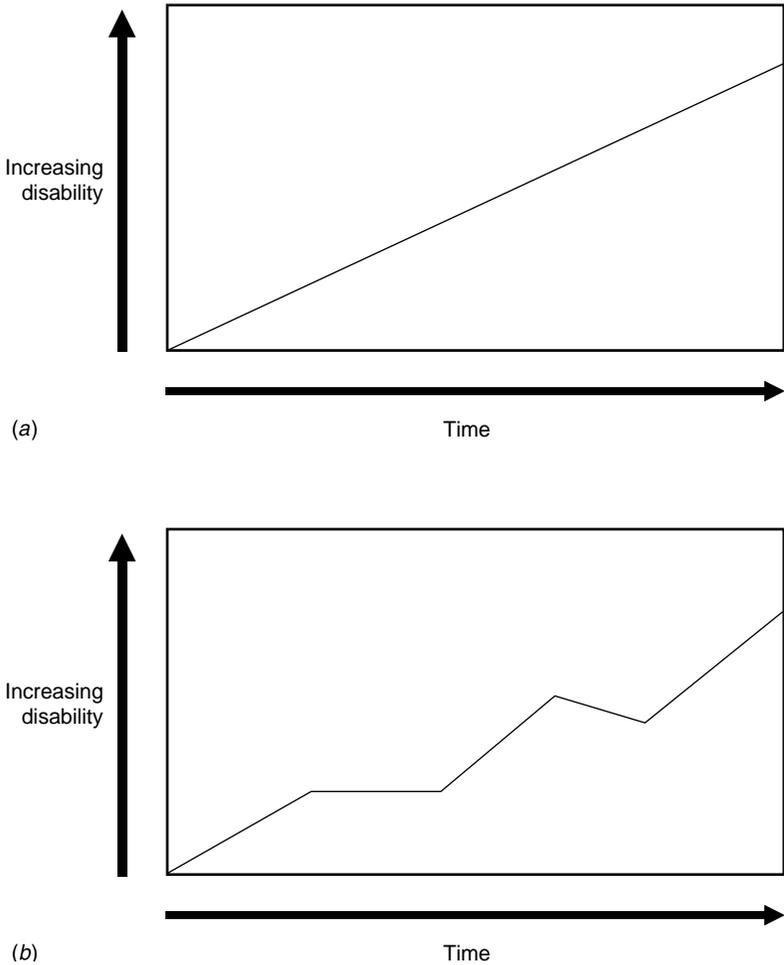
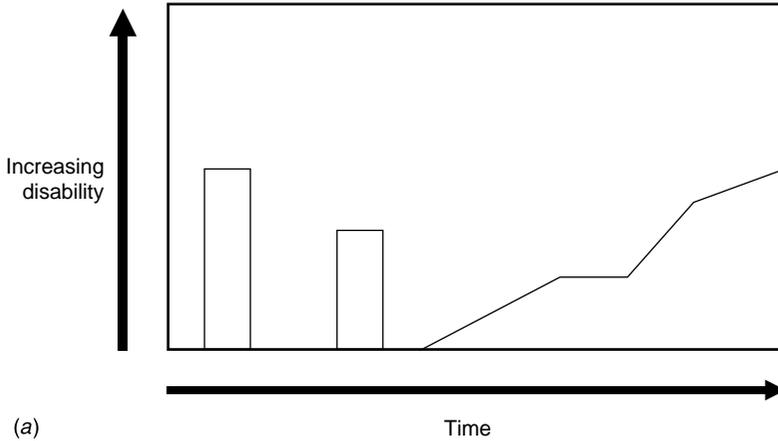
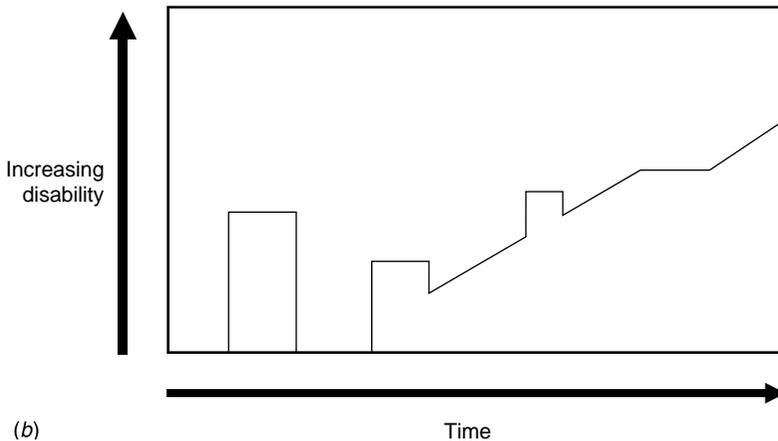


Fig. 1.6. Primary–progressive (PP) MS is characterized by disease showing progression of disability from outset (a) without plateaux or remissions or (b) with occasional plateaux and temporary minor improvements (Lublin & Reingold, 1996). (By permission of the American Academy of Neurology.)

researchers. The disagreement was greater for what constitutes benign as opposed to malignant MS. Many respondents believed that precise definitions were not needed or useful. There was, however, agreement that the terms should not be defined according to scores on the Expanded Disability Status Scale (EDSS)(Kurtzke, 1983), the most widely used rating scale to assess physical disability in MS, as this would be too restrictive. In the end, definitions were provided with the proviso they be used primarily in a research setting.



(a)



(b)

Fig. 1.7. Secondary-progressive (SP) MS begins with an initial RR course, (a) followed by progression of variable rate; (b) that may also include occasional relapses and minor remissions (Lublin & Reingold, 1996). (By permission of the American Academy of Neurology.)

Benign MS

The consensus definition was of disease in which the patient remains fully functional in all neurologic systems at least 15 years after disease onset.

Malignant MS

The consensus definition was of disease with a rapidly progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

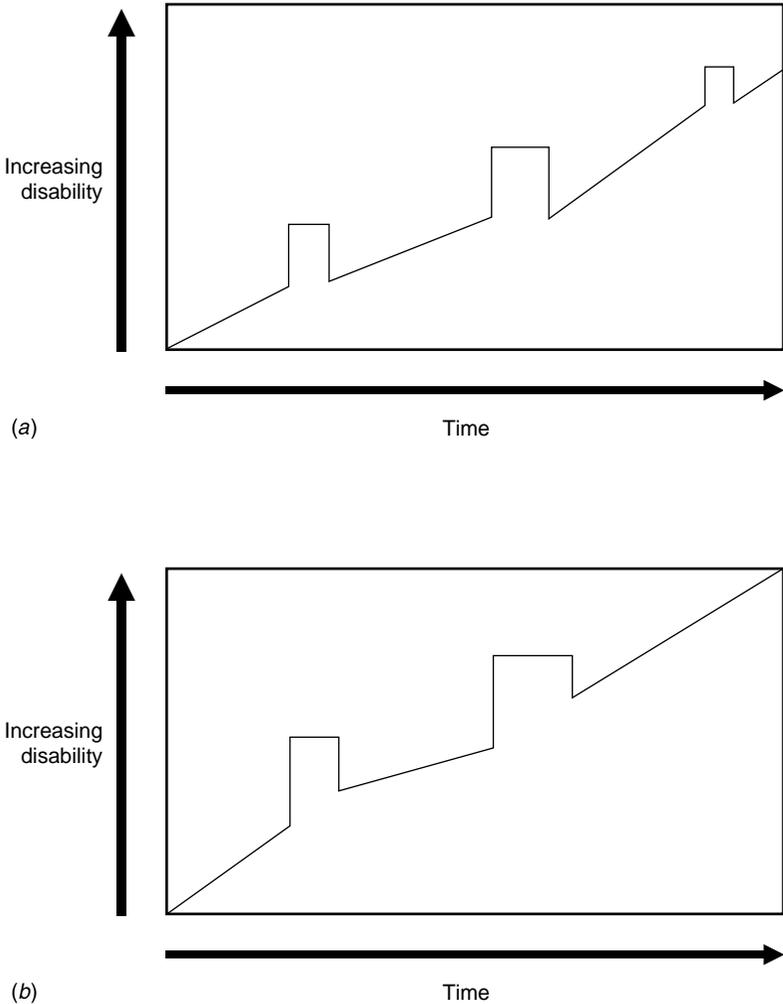


Fig. 1.8. Progressive-relapsing (PR) MS shows progression from outside (a) with clear acute relapses (b) without full recovery (Lublin & Reingold, 1996). (By permission of the American Academy of Neurology.)

In summarizing their results, Lublin and Reingold (1996) emphasized their definitions are purely clinically based and descriptive. While acknowledging the usefulness of investigations such as MRI, they concluded that current knowledge was too imprecise at this stage to allow for the course of the illness to be defined or influenced by the neuroimaging data.

In addition, the recommendations did not define what they meant by a relapse. A reason for their hesitancy in this regard was their recognition of the discordance between clinical evidence of a relapse, on the one hand, and MRI

and neuropathological signs of relapse on the other. Nevertheless, the term is used repeatedly throughout their definitions, and they therefore advise that, for the purpose of a clinical trial, what is meant by relapse will need to be defined by consensus amongst investigators as part of the protocol. This view represents a clear departure from the clinical guidelines laid out by Poser et al. (1983) and illustrates a recognition that procedures such as MRI have, over the intervening 15 years, reached a level of sophistication sufficient to influence how researchers view the dynamic nature of the MS lesion.

Welcome as these guidelines are, the difficulty is assigning disease course to patients relates, in part, to the changes in neurological state that occur with time. Goodkin et al. (1989) prospectively followed a group of 254 MS patients over a 1 to 5-year-period (mean 2.6 years). They reported that adherence to the initial assigned disease course varied considerably. Thus, 30% of patients with chronic–progressive disease had become stable, 32% with stable disease had become chronic–progressive, 20% of relapsing–remitting patients had stabilized, while a similar percentage had deteriorated to a chronic–progressive phase. Furthermore, patients with either stable or relapsing–remitting (44%) disease switched as frequently to a chronic–progressive phase as patients with the latter reverted to a stable or relapsing–remitting state. The former would now be called secondary progressive disease, but the study was completed before the subdivisions of primary and secondary entered the lexicon. The implications of this study are considerable for, given the dynamic nature of the disease process, they beg the question of how valid is the assignment of disease course? Patients who qualify for interferon beta-1b therapy by virtue of having relapsing–remitting MS, may in fact have had a secondary–progressive course a few months back. Are these patients any different from those relapsing–remitting patients who have not shown a similar transformation? If so, what are the implications for treatment? The answer to these conundrums are not yet known. There is, however, an awareness that the disease is seldom static. Clearly defined definitions that carry broad agreement will ensure that if, and when, change occurs, those treating and researching multiple sclerosis patients continue to speak the same language.

Rating neurological impairment in multiple sclerosis

The yardstick by which neurological disability is rated in MS patients is the Expanded Disability Status Scale (EDSS)(Kurtzke, 1983). The scale, routinely used in clinical and research settings, represents a refinement of earlier methods devised to assess physical disability in MS (Kurtzke, 1955; Kurtzke, 1970). The scale consists of eight ‘functional systems (FS)’, namely pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental) and a miscellaneous category termed ‘other’. Each of these

Table 1.1. Expanded Disability Status Scale (EDSS)

0	Normal neurologic exam (all grade 0 in functional systems (FS). Cerebral grade 1 acceptable.
1.0	No disability, minimal signs in one FS (i.e. grade 1 excluding cerebral grade 1)
1.5	No disability. minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory, but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 metres.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 metres.
5.0	Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (eg. to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)
5.5	Ambulatory without aid or rest for about 100 metres; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0.)
6.0	Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk about 100 metres with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
6.5	Constant bilateral assistance (canes, crutches or braces) required to walk about 20 metres without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)
7.0	Unable to walk beyond 5 metres even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self, but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)