Chapter 2
What Is Disease Progression?

Stanley Hawkins and Alastair Wilkins

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2.1  General Introduction

The clinical course of multiple sclerosis (MS) represents a spectrum. The subdivision of MS, according to the clinical course, has become increasingly important in recent years, since therapeutic clinical trials have shown demonstrable reductions in the frequency of clinical relapses and of inflammatory lesions as demonstrated on magnetic resonance imaging (MRI). Measures of disease progression are more resistant to change and in patients with progressive MS, it has been more difficult to demonstrate positive benefits from therapeutic interventions.

It has long been recognized that although patients may essentially share the diagnostic label of MS, there is considerable variation across a spectrum in terms of clinical phenotype, prognosis, MRI appearances, immunological characteristics, and pathology. The nature of the clinical course may also determine the response to disease-modifying therapy and the course itself may be influenced by underlying genetic heterogeneity.

In approximately 85–90% of cases, the onset of MS is marked by relapses and remissions—relapsing–remitting MS (RRMS). With time, an increasing proportion
of these patients enter a secondary progressive phase (SPMS), 40% within 10 years and 65% within 25 years. SPMS represents a phase during which there are generally fewer relapses. It is characterized by gradual progression in disability. A minority of patients, 10–15%, do not have relapses at the onset of the disease, but rather, steadily accumulate disability over time [1]. This has come to be described as primary progressive MS (PPMS) [2].

How does the clinician know whether a patient with MS has progressive disease? In a similar way to the initial diagnosis of MS, although paraclinical measures and biomarkers (imaging and otherwise) can help, the diagnosis of progressive disease still remains firmly a clinical one. Neurologists will usually be able to classify the disease subtype of an individual patient based on clinical history and examination, although patients experiencing transition from relapsing–remitting MS to secondary progressive MS may be difficult to fully classify, as will patients experiencing significant numbers of relapses. In reality, disease progression is often not confidently diagnosed until time has passed in these patients and, thus, defining onset of disease progression is often a retrospective exercise.

2.2 Clinical Diagnosis of Progressive MS and Differential Diagnosis

The typical patient with relapsing–remitting MS will usually not present too many diagnostic difficulties. Such a “typical” patient will often be a young woman with a history suggestive of more than one episode of neurological dysfunction involving separate anatomical domains, thus satisfying the concept of “dissemination in time and space” [3]. Paraclinical investigations, such as MRI scanning and spinal fluid analysis are used to seek alternative explanations or to confirm the clinical suspicion of MS. Diagnosis of progressive disease, however, may be more challenging. In particular, the diagnosis of MS in those with a history suggestive of PPMS may be demanding. Furthermore, the question patients sometimes ask concerning whether they have entered the progressive phase of the disease after a period of relapsing and remitting disease is, again, often a difficult one to provide a definitive answer to.

In this section, a description of the diagnosis and differential diagnosis of MS that is progressive from outset and a discussion of the clinical diagnosis of secondary progression will be presented.

2.2.1 Primary Progressive MS

2.2.1.1 Definition of PPMS

That patients with MS can follow a progressive as well as a relapsing course has been recognized since the nineteenth century, but almost a century passed before a
What Is Disease Progression?

A clear distinction was made between those in whom the disease is progressive from onset (primary progressive) and those who have progressive deterioration with or without superimposed relapses, following an initially relapsing and remitting course (secondary progressive disease) [4]. It was more recently still that the clinical category of primary progressive MS was clearly defined [2].

Up to the late 1990s, the term “chronic progressive MS” was widely used in the literature. No clear distinction was made between cases that were progressive from the onset and those in whom progression of disability followed clear, distinct clinical bouts, exacerbations or relapses followed by improvement or remission. Over the years, primary progressive patients were undoubtedly included under the heading “chronic progressive” [5], while some have included those having “periods of general deterioration resembling relapses” [6] and “no or relatively few attacks” [7] within the category of PPMS. Some cases that have a steady progressive course at the outset have superimposed clinical relapses, and have been called progressive–relapsing and relapsing–progressive. The picture has been further complicated by the addition of another subcategory termed “transitional MS” [8]. This term has been used in two different settings. The first is to indicate that patients at a certain level of disability will probably become dependent on walking aids before long. The second is what has been referred to as “single attack progressive MS” (SAPMS) [9]. In this latter category, patients experience a single relapse and/or remission and then enter a phase of steady progression without superimposed relapses.

A clear framework was brought to the nomenclature in 1996 with the consensus document produced by Lublin and Reingold [2]. They undertook a survey of 125 members of the international MS clinical research community with the twin aims of standardizing terminology and facilitating a broader understanding of the recruitment parameters in MS therapeutic trials. Based on the replies received, PPMS was defined as disease progression from onset with occasional plateaus and temporary minor improvements, the essential element being a gradual, nearly continually worsening baseline with minor fluctuations, but no distinct relapses. The consensus of the vast majority of respondents at that time, including those with MRI expertise, was that MRI evidence was not required in distinguishing this clinical category. The terms “relapsing–progressive” and “chronic progressive” were considered redundant, the former for not corresponding to a clearly defined population and the latter for being vague. The term “transitional MS” appears not to have been considered although “progressive–relapsing” has been recognized as applying to a small group of patients with progressive disease from onset, but who have clear acute relapses, with or without full recovery. Some clarity regarding the prognosis of MS has been described in the literature over the last 10 years, in particular between the two major groups—primary progressive and secondary progressive MS.

The consensus guidelines have not been universally welcomed [10] and some groups have suggested, on the basis of analysis of their own considerable data, that progressive–relapsing patients and PPMS patients were so phenotypically and prognostically similar as to make their separation unnecessary [11, 12].
2.2.1.2 Diagnostic Criteria of PPMS

Clarification of the definition of PPMS has clearly been important, but a range of progressive neurological diseases may present in a similar way. This necessitates the application of relevant diagnostic criteria. Over the past 50 years, several diagnostic criteria have been formulated in MS, including those of Allison and Millar [13], Schumacher et al., [14] and McDonald and Halliday [15]. From 1983, for 20 years, the Poser criteria [16] were the most widely accepted and applied. The diagnosis of clinically definite MS (CDMS) by these criteria requires the occurrence of at least two attacks. Since PPMS patients, by definition, have a progressive course without relapse or remission, designation of such patients as having CDMS is impossible. Indeed, the absence of attacks also excludes PPMS patients from another of the Poser categories, that of laboratory-supported probable MS.

The limitations of the Poser criteria were highlighted in a study of 111 PPMS patients [17]. Applying the criteria in that population resulted in 37% of patients being considered to have laboratory-supported definite MS, 46% having clinically probable MS, and 17% being unclassifiable. This problem was addressed by a consortium led by Thompson with the publication in 2000 of a position paper setting out specific diagnostic criteria for PPMS [18].

Formulated by a panel of investigators involved in a multicenter, serial, clinical, and MRI study of PPMS, three categories of PPMS have been proposed. Definite PPMS represents cases where there is adequate clinical and investigative evidence to render the diagnosis definite enough for inclusion in research protocols and clinical trials; probable PPMS reflects cases where there is strong clinical suspicion of the diagnosis, but insufficient evidence to be definite; and possible PPMS, which reflects the existence of only limited evidence to suggest the diagnosis.

The panel recommended a minimum period of clinical progression of at least 12 months and suggested that there should be documented evidence of progression as may be reflected in the Kurtzke Extended Disability Status Scale [19] or on timed walk recordings. It is presumed that other potential mimics of PPMS will have been excluded by thorough investigation. Age limits of 25–65 years have been set for age at onset, in order for the criteria to be applied, the upper limit being higher than that established by the Poser criteria (59 years). In the new criteria, great importance is placed on the identification of abnormal intrathecal synthesis of IgG. Although it might be argued that a patient with a progressive course, compatible MRI, and delayed visual evoked responses could scarcely have anything other than PPMS, justification for the cautious approach is derived from studies of oligoclonal band (OCB)-negative presumed MS, where other diagnoses have become apparent on prolonged follow-up [20]. The minimum number of brain lesions required on T2-weighted images is set at nine although if there is at least one lesion seen on spinal MRI, only between four and eight brain lesions are necessary.

In the position paper, the authors applied their proposed criteria to a database of 156 PPMS patients, 64% had definite PPMS, 35% had probable PPMS, and just 1%
had possible disease [18]. Just how typical this population is of PPMS, in general, remains to be seen, given its relatively youthful profile (average age of 40 years) and earlier age at onset (29 years) than is usually typical for this subgroup of patients. As the authors recommend, validation of these criteria is required both in a prospective cohort and with postmortem examination.

The recommendations laid out in the position paper of Thompson and colleagues were incorporated in the 2001 McDonald Criteria [21]. There have been further revisions in 2005 [22] and 2011 [3].

In 2005, the panel recommended revising the McDonald Criteria for diagnosis of primary progressive multiple sclerosis (PPMS) to require, in addition to 1 year of disease progression, two of the following three findings: positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP); positive spinal cord MRI (two focal T2 lesions); or positive CSF (the identification of abnormal intrathecal synthesis of IgG). These criteria reflected the special role of both CSF examination and spinal cord MRI in PPMS, have been found to be practical and are generally well accepted by the neurological community, and have been used as inclusion criteria for PPMS clinical trials. To harmonize MRI criteria within the diagnostic criteria for all forms of MS, while recognizing the special diagnostic needs for PPMS, the 2010 revision panel recommended that the McDonald Criteria requirement of fulfilling two of three MRI or CSF findings be maintained for PPMS, with replacement of the previous brain imaging criteria with the new MAGNIMS brain imaging criteria for DIS (two of three of the following: ≥1 T2 lesions in at least one area characteristic for MS [periventricular, juxtacortical, or infratentorial]; ≥2 T2 lesions in the cord; or positive CSF [isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index]). This consensus-based recommendation is justified by comparing diagnostic criteria for PPMS and by a subsequent reanalysis of these data by Montalban et al. [23]. These two revisions removed the absolute requirement for CSF abnormalities.

2.2.1.3 Clinical Features of PPMS

Patients with PPMS differ significantly in terms of their mode of presentation when compared with initially relapsing–remitting patients. In the Belfast cohort of 111 PPMS patients, progressive myelopathy manifesting as motor disturbance occurred in 67.6%, whereas visual loss at onset was uncommon (3.6%) [1]. This contrasts with the initially relapsing–remitting group, where, although the range of symptoms is obviously similar, the relative frequency of motor symptoms at onset is much less and visual symptoms are much more common (16.8% with motor disturbance at onset and 22.3% with visual disturbance at onset). Similar results have been found elsewhere. One study found that 61% of PPMS patients had pyramidal signs and symptoms at onset, while only 19% of an RRMS group did so [24]. In another study, 79% of primary progressive patients had motor weakness at onset, whereas just 16.5% of relapsing–remitting or secondary progressive cases presented likewise [25]. Other recent studies have concurred with the observation that motor symptoms at onset occur in the majority of PPMS patients [11, 26].
Clinical presentations other than progressive myelopathy occur in PPMS, although with much lower frequencies. The neurological domains in which disease progression may occur are similar to those occurring in SPMS (see Table 2.3 below).

2.2.1.4 Differential Diagnosis of PPMS

As indicated, the commonest presentation of PPMS is with progressive lower limb dysfunction and signs suggestive of a spastic paraparesis. The differential is large and initial investigations in such patients will be aimed at determining whether there is evidence of any structural lesions causing spinal cord compromise or evidence of intrinsic cord lesion(s). Associated symptoms of spinal cord dysfunction, such as urinary dysfunction (urgency, frequency, nocturia, etc.), are common but often do not helpfully discriminate from other differential diagnoses of a spastic paraparesis. Sensory changes are common, but often not as marked as the motor dysfunction, and a discrete sensory level is usually absent in MS and may help differentiate from a structural compressive spinal cord lesion. Similarly, the absolute absence of any sensory symptoms may prompt a more extensive search for an alternative diagnosis, such as amyotrophic lateral sclerosis (ALS) or primary lateral sclerosis (PLS) [27]. However, studies have shown that a large proportion of patients presenting with a progressive myelopathy will have an eventual diagnosis of MS [28].

Inflammatory cord lesions may also arise from systemic disorders such as sarcoidosis, systemic lupus erythematosus, and Sjogren’s syndrome. Importantly, neuromyelitis optica (Devic’s disease) may present with an inflammatory cord lesion (typically longitudinally extensive over three or more vertebral segments) [29]. Diagnostic criteria have been developed for this condition and differentiating neuromyelitis optica from MS is of importance since prognosis and therapies differ [30].

Of particular note, female carriers of the X-linked adrenoleukodystrophy (X-ALD) gene may manifest as a progressive spastic paraparesis, often in third or fourth decade, and family history of leucodystrophy should warrant further investigations with very long-chain fatty acid analysis or genetic testing in this setting [31, 32]. The differential diagnosis of a progressive spastic paraparesis of adult onset is given in Table 2.1.

Clinical presentations other than spastic paraparesis occur in PPMS, although with much lower frequencies. The neurological domains in which disease progression may occur are similar to those occurring in SPMS (see Table 2.3 below). Progressive visual loss should raise suspicion of Leber’s hereditary optic neuropathy (LHON) and lead to mitochondrial DNA testing [33]. Progressive ataxia occurs as a presenting feature in some patients, although may often be associated with features of a spastic paraparesis. The differential diagnosis is broad and a search for other causes of cerebellar dysfunction (including metabolic disturbances (such as alcohol excess), vascular disease, a structural lesion within the posterior fossa, paraneoplastic disease, or one of the inherited ataxias) must be undertaken. The differential diagnosis of progressive ataxia in adults is given in Table 2.2.
In a similar vein, cognitive dysfunction occurs in PPMS, although, again, usually accompanied by other neurological manifestations. Disturbances in verbal memory, attention, verbal fluency, and spatial reasoning have been documented in populations of patients with PPMS [34, 35]. Differences between cognitive function in PPMS and SPMS patients have been noted, although the significance of these observations remains unclear [36–38].
2.2.2 Clinical Diagnosis of Secondary Progressive Disease

Secondary progression follows the RRMS in the majority of cases and it is likely that over 80% of RRMS patients will eventually enter a secondary progressive phase, with risk of progression increasing incrementally dependent on the length of
time since diagnosis (see Chap. 3) [39–41]. Natural history studies regarding risk of progression have been hugely informative and rely upon the use of defining disability using specific scales (see below). The epidemiology of progressive MS gleaned from these studies will be further discussed in subsequent chapters.

Away from large-scale epidemiological studies, when faced with deterioration in an individual patient, it is useful to make a clinical diagnosis of disease stage in order to prognosticate, plan for long-term care and, importantly, decide on the suitability of disease-modifying therapy. Most physicians seeing patients with an initial diagnosis of RRMS would define secondary progression as period of sustained deterioration in neurological function without remission [2]. Once a given level of disability has been sustained for 6 months, the likelihood of reversibility (in treatment-naive patients) is likely to be negligible [42]. Deterioration may occur as a result of relapse activity and delineating relapse from progression at the point of onset of neurological worsening may be difficult. The speed of change in neurological function may give a clue to the onset of progression: if deterioration in neurological status is rapid, this suggests a relapse; whereas slow deterioration would generally be regarded as disease progression [43]. Another important observation on disease progression in MS is that for a given patient, progression of the disease appears to occur at a steady rate [44]. Furthermore, in patient populations, once progression has “set in,” further rates of progressive decline appear to happen in a uniform (and slowly progressive) way, and in a way that appears independent of previous clinical disease course [45–47]. Thus, the pattern of deterioration is highly indicative of progression and may delineate from relapse. However, the course of the disease may only become clear over time and may only become apparent after a period of retrospective analysis.

Progressive clinical deterioration can occur in a number of neurological domains (see Table 2.3), some of which will be discussed in more detail below. Usually, a fairly stereotyped clinical pattern emerges of an “upper motor neuron syndrome” causing impaired ambulation and spasticity, with variable degrees of superimposed ataxia and cognitive impairment. In addition, bladder and bowel dysfunction, fatigue, mood disturbance, and paroxysmal symptoms such as trigeminal neuralgia often occur. These will also be discussed further in Chap. 8 with a description of symptomatic therapies.

2.2.2.1 Progressive Motor Dysfunction in SPMS

The clinical diagnosis of disease progression rests heavily on observing changes in motor function and the commonly used disability scales reflect this [19]. Undoubtedly, the reason for this is that motor deficits are more straightforward to document and are picked up during a standard neurological examination. The use of natural history studies employing the Expanded Disability Status Scale (EDSS) has provided information on mean levels of motor dysfunction progression within MS populations (see below).

A common manifestation in disease progression is reduced ambulation. Natural history studies often define ambulation difficulties in terms of: limited walking but
without aid (correlating to EDSS 4); walking with unilateral aid (stick/cane; correlating to EDSS 6); and wheelchair bound (correlating to EDSS 7). Time to reach these milestones has been studied in some detail in population databases [48]. Of note, progression through disability milestones occurs at a slow rate. For instance, in the Lyon Multiple Sclerosis Cohort, median times from EDSS 4 to reach EDSS 6 and EDSS 7 were 5 and 12 years, respectively, and from EDSS 6, median time to reach EDSS 7 was 4 years [40, 49]. Furthermore, reaching a disability milestone appears, to some extent, to be dependent on age at onset of the disease, such that those with earlier onset of disease tend to reach fixed levels at an earlier age [50]. Further discussions of the natural history studies utilizing EDSS measurements will be presented in Chap. 3.

2.2.2.2 Progressive Cognitive Dysfunction in SPMS

Progressive deficits in domains other than motor function are common, including cognition, ataxia, fatigue, and sphincter function. Clinical assessment of these domains may provide useful diagnostic information. Of these, cognitive dysfunction is common in progressive MS and is an important predictor of quality of life in the disease [51].

Cognitive dysfunction has been particularly noted in progressive MS and occurs at higher frequency than in RRMS [36, 52]. Domains of cognition relating to learning and recall of new information, as well as working memory appear to be particularly affected [53]. The prevalence rates of memory difficulties in MS appear to be in the region of 40–65% [54]. Other changes in cognition such as executive function, semantic memory, visuospatial skills, and language function also occur [55, 56]. Importantly, cognitive defects negatively impact significantly on rehabilitation potential in MS [57]. As with cognitive deficits in all neurological diseases, a thorough history is required to determine whether depression is a contributing factor, since depression commonly causes defects in memory and attention [58]. Depression is the most frequent psychiatric manifestation of MS with a prevalence of 40–60%, and therapeutic intervention may lead to considerable improvements [59, 60]. In addition, fatigue impacts upon cognitive ability in MS, although the precise relationship of fatigue to specific cognitive domains is unclear [61].

Detailed assessment of cognitive profiles in patients with MS may be best performed by neuropsychologists. Of the cognitive batteries available, the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery may be of particu-
lar use [62]. MACFIMS is composed of seven neuropsychological tests, assessing five cognitive domains commonly impaired in MS (processing speed/working memory, learning and memory, executive function, visual–spatial processing, and word retrieval), supplemented by a measure of estimated premorbid cognitive ability [53, 63].

### 2.2.2.3 Progressive Ataxia in SPMS

Ataxia occurs commonly in SPMS and causes significant disability [64]. Changes in cerebellar architecture are seen in autopsy brain specimens of patients with a history of chronic SPMS, with widespread demyelination and changes in Purkinje cell phenotype [65, 66]. In addition, MRI studies have confirmed extensive cerebellar involvement in progressive MS [67, 68]. Persistent cerebellar dysfunction has been linked with magnetic resonance spectroscopy markers of axonal loss [69]. Interestingly, some researchers have suggested that cerebellar dysfunction in MS may be linked to an acquired channelopathy, since changes in sodium channel subtypes have been observed [70]. This observation has been the basis of the suggestion that modulation of cerebellar ion channels may ameliorate ataxic symptoms in MS [71].

### 2.3 Defining Disease Progression: Trial Perspective

In order to determine whether a particular therapeutic agent is effective in preventing or slowing disease progression, outcome measures which will reflect disability are required. Several disability scales are in common usage. While many have their own individual benefits, several problems are linked to their use and some remain unvalidated. The short-term nature of many clinical trials may also make the use of disability scales difficult to interpret. A number of disability scales of relevance to MS will be discussed here. Further discussions on the use of disability scales in epidemiological studies will be provided in Chap. 3 and the results of treatment trials using disability scales in Chap. 9.

#### 2.3.1 Disability Scales

##### 2.3.1.1 Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) remains the most commonly used method of quantifying disability in MS (Table 2.4) [19]. It was developed from the earlier Disability Status Scale (DSS) by dividing into two each step from DSS 1–9.
and thus effectively creating a 20-point scale [72]. It encompasses a complementary set of scales for eight functional systems (FS; pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and “others”; Table 2.5). When performing the EDSS, the clinician grades according to history and neurological

<table>
<thead>
<tr>
<th>Table 2.4 Expanded disability status scale</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1.0</td>
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<td>1.5</td>
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<td>9.0</td>
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<tr>
<td>9.5</td>
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<tr>
<td>10.0</td>
</tr>
</tbody>
</table>

Adapted from [19]
### Table 2.5 Functional systems used in assessing EDSS

<table>
<thead>
<tr>
<th>Pyramidal systems</th>
<th>Visual functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal</td>
<td>0 Normal</td>
</tr>
<tr>
<td>1 Abnormal signs without disability</td>
<td>1 Disc pallor and/or mild scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)</td>
</tr>
</tbody>
</table>

2 Minimal disability: patient complains of fatigability or reduced performance in strenuous motor tasks and/or MRC grade 4 in one or two muscle groups

3 Mild-to-moderate paraparesis or hemiparesis: usually MRC grade 4 in more than two muscle groups or MRC grade 3 in one or two muscle groups; movements against gravity are possible; severe monoparesis: MRC grade 2 or less in one muscle group

4 Marked paraparesis or hemiparesis: usually MRC grade 2 in two limbs; moderate tetraparesis: MRC grade 3 in three or more limbs; monoplegia: MRC grade 0 or 1 in one limb

5 Paraplegia: MRC grade 0 or 1 in all muscle groups of the lower limbs; hemiplegia; marked tetraparesis: MRC grade 2 or less in three or more limbs

6 Tetraplegia: MRC grade 0 or 1 in all muscle groups of the upper and lower limbs

<table>
<thead>
<tr>
<th>Cerebellar systems</th>
<th>Brainstem functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal</td>
<td>0 Normal</td>
</tr>
<tr>
<td>1 Abnormal signs without disability</td>
<td>1 Signs only</td>
</tr>
<tr>
<td>2 Mild ataxia</td>
<td>2 Moderate nystagmus or other mild disability</td>
</tr>
<tr>
<td>3 Moderate truncal or limb ataxia</td>
<td>3 Severe nystagmus; marked extraocular weakness or moderate disability of other cranial nerves</td>
</tr>
</tbody>
</table>

4 Severe truncal ataxia and severe ataxia in three or four limbs

5 Unable to perform coordinated movements due to ataxia

X pyramidal weakness (MRC grade 3 or worse in limb strength) interferes with cerebellar testing

<table>
<thead>
<tr>
<th>Sensory function</th>
<th>Bowel and bladder function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal</td>
<td>0 Normal</td>
</tr>
<tr>
<td>1 Vibration or figure-writing decrease only, in one or two limbs</td>
<td>1 Mild urinary hesitancy, urgency, and/or retention</td>
</tr>
<tr>
<td>2 Mild decrease in touch or pain or position sense and/or moderate decrease in vibration in one or two limbs, mild vibration or figure-writing decrease alone in three or four limbs</td>
<td>2 Moderate urinary hesitancy and/or urgency, and/or rare urinary incontinence</td>
</tr>
</tbody>
</table>

(continued)
examination in the appropriate grades of the FS. An overall score is assigned by combining the different FS grades with the ability to walk. As such, up to 3.5, the scale is largely dependent on impairment in functional systems, whereas disability in the higher grades is mainly determined by ambulation. EDSS steps 1.0–4.5 refer to people with MS who are ambulatory. EDSS steps 5.0–9.5 are defined by the impairment to ambulation.

Although used for the majority of epidemiological studies and treatment trials, it is not without its limitations. The scale relies on some degree of subjectivity, particularly in relation to ambulation and bladder or bowel function, and the ability to define whether the patient is able to walk specific distances often relies upon estimations, since accurately assessing a patient’s ability to walk 500 m in a clinic may not be possible [73]. Inter-rater reliability is highly important, that is, whether two independent examiners ascribe the same score to a patient, and some studies have suggested this to be rather low [74–76]. One of these studies estimated that 95% of the independent observers would score within 1.5 EDSS units of the “correct” value. Since treatment trials often use primary outcome measures of an EDSS change of half or one point (sustained for 3 months), inter-rater reliability and precision in allocating scores become hugely important and may be a major component in the “failure” of certain trials (see Chap. 9).

Table 2.5 (continued)

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Moderate decrease in touch or pain or position sense and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs</td>
</tr>
<tr>
<td>4</td>
<td>Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs</td>
</tr>
<tr>
<td>5</td>
<td>Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head</td>
</tr>
<tr>
<td>6</td>
<td>Sensation essentially lost below the head</td>
</tr>
</tbody>
</table>

**Cerebral (or mental) functions**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Mood alteration (depression and/or euphoria) alone (does not affect EDSS step)</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in mentation</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in mentation</td>
</tr>
<tr>
<td>4</td>
<td>Marked decrease in mentation (Chronic brain syndrome moderate)</td>
</tr>
<tr>
<td>5</td>
<td>Dementia or chronic brain syndrome – severe or incompetent</td>
</tr>
</tbody>
</table>

Adapted from [19]
The scale also mixes measurement in different domains of disability and that which is measured at one end of the scale is different to the other end of the scale. In addition, some domains of disability are poorly represented, such as cognition. Progression in the EDSS is also not linear, and progression from 1 to 5 occurs much more quickly than from 5 to 7, which, again, may have implications for trial design [77]. Despite this, the EDSS has clinical use, since a particular score is able to convey a description of disability in a similar way that the Medical Research Council (MRC) grade of muscle strength does in a standardized and universally accepted manner.

### 2.3.1.2 Other Disability Scales and Outcome Measures

A variety of other assessment scales are in use. Of these, the Multiple Sclerosis Functional Composite (MSFC) was used in the International MS Secondary Progressive Avonex Controlled Trial (IMPACT) as a primary outcome measure for disease progression [78]. The MSFC was developed in order to address some of the limitations of the EDSS and to move away from the emphasis this scale puts on ambulation as a marker of disability. The MSFC consists of three items: a timed walk of 25-ft (T25FW; measuring ambulation); a 9-hole peg test (measuring upper limb function); and a paced auditory serial addition test at 3-s intervals (used as an indicator of cognitive function) [79, 80]. Component scores are transformed into \( z \)-scores by standardizing to a reference population and the individual scores are averaged to create the composite score. Scores for individual items may be used or the composite. The MSFC has the advantage that it is easy to administer and can usually be performed more quickly than the EDSS. The MSFC was designed specifically for use as an outcome measure for clinical trials and validation against EDSS, quality of life measures (QoL), and MRI markers has demonstrated its validity, reliability, and sensitivity to change [81–85]. The MSFC has also been used as a secondary outcome measure for a number of disease-modifying drug trials [86–90]. Recently, the T25FW component of the MSFC was used as an outcome measure for studies of fampridine in progressive MS (see Chap. 8) [91].

The importance of evaluating treatments using measurements that are important to patients has led to the development of patient-based outcome measures, notably, for multiple sclerosis, the MSIS-29 [92]. The 29 items in the questionnaire-based scale measure 20 physical items (e.g., In the past 2 weeks, how much have you been bothered by difficulties using your hands in everyday tasks?) and nine psychological items (e.g., In the past 2 weeks, how much have you been bothered by worries relating to your MS?). Patients respond with a subjective assessment of how their illness affects them on a scale of 1 (not at all) to 5 (extremely).

The Multiple Sclerosis Severity Score (MSSS) was developed to attempt to integrate disability and disease duration in order to give an indication of disease severity [93]. In this system, a patient with a high EDSS after a short disease duration would be classified with a higher MSSS score (and by implication a more “severe” disease), compared to a patient with the same EDSS but a much longer disease
duration. It is useful as a “single assessment” indicator of disease severity and may have a number of research applications, such as genetic studies analyzing the link between susceptibility genes and disease phenotypes [94], as well as epidemiological studies in the disease [95].

2.3.2 Outcome Measures for Clinical Trials

The search for reliable, reproducible, and sensitive outcome markers for trials in progressive MS continues. Despite refinements and the generation of new scales, many outcome measures used in clinical trials may be difficult to interpret and may lead to spurious results [96]. Optimal clinical outcome measures for MS trials are discussed in detail elsewhere [77, 84, 97, 98]. A major problem in MS research has been that many trials have used similar outcome measures for RRMS trials and SPMS/PPMS trials, which may not truly reflect specific pathophysiological processes in different phases of the disease. This is of particular importance in a disease such as MS which is characterized by episodic deterioration (relapses) causing fluctuations in disability scores which may not be indicative of permanent disability progression. Indeed the “best” outcome measure for MS treatment trials has been relapse rate reduction, which reflects the relative ease of identifying and defining a clinical relapse. Similarly, chronic MS is subject to day-to-day variability and changes in symptoms and functional levels vary with environmental factors (e.g., Uhthoff’s phenomenon). Coupled to this, the problems with inter-rater reliability mentioned above mean that a true measurement of disability is difficult to obtain. These considerations have driven the search for reliable biomarkers in the disease (either biological samples or imaging surrogates) which are discussed in Chaps. 6 and 7.

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