

# Clinical features

## Clinical manifestations

The wide range of symptoms and signs of multiple sclerosis (MS) reflect multifocal lesions in the central nervous system (CNS), including in the afferent visual pathways, cerebrum, brainstem, cerebellum, and spinal cord (Figure 2.1). In general, the range and severity of manifestations in an individual at a particular time reflect the extent of lesions, their location, the severity of tissue damage, and the rate of accumulation. However, the correlation between lesions, as visualized on standard magnetic resonance imaging (MRI), and clinical manifestations is only approximate. This may be because repair and neural plasticity may compensate for damage and residual function may not parallel changes on MRI images. In addition, recent work showed there is pathology in both white and gray matter not visible on standard MRI. A number of MS manifestations are frequently underappreciated, including cognitive impairment, psychiatric disorders, pain, and fatigue, but often are major contributors to disability.

## Course

As summarized in Figure 2.2, the course of MS is categorized based on how clinical manifestations develop over time and on the severity and tempo of the disease [1].

Typical clinical manifestations of MS	
Category	Description
Vision	Visual loss – monocular (pre-chiasmatic) or homonymous (post-chiasmatic)
	Double vision
	Oscillopsia
Vestibular symptoms	Vertigo
	Imbalance
Bulbar dysfunction	Dysarthria
	Swallowing dysfunction
Motor	Weakness
	Spasticity
	Incoordination
	Tremor
Abnormalities of sensation	Sensory loss – any modality or distribution
	Positive sensory phenomena – paresthesias, dysesthesias, neuropathic pain
Gait impairment	Varying contributions from visual impairment, vestibular symptoms, weakness, spasticity, ataxia, imbalance, sensory loss, pain, and fatigue
Urinary symptoms	Urgency
	Frequency
	Hesitancy
	Retention
	Incontinence
Bowel symptoms	Frequent urinary tract infections
	Constipation
	Urgency
	Incontinence
Sexual dysfunction	Decreased libido
	Erectile dysfunction
	Anorgasmia
Cognitive impairment	Poor concentration or attention
	Slowed thinking
	Poor memory, particularly short-term
	Impaired executive function
Mood disorders	Depression
	Anxiety
	Affective release

Figure 2.1 Typical clinical manifestations of MS (continues opposite).

Typical clinical manifestations of MS (continued)	
Category	Description
<b>Fatigue</b>	Handicap fatigue – increased effort to perform routine tasks
	Motor fatigue – decreased performance or endurance with sustained effort
	Heat intolerance – worsening sensory or motor symptoms/signs with increased body temperature
	Systemic fatigue – persistent lassitude
<b>Pain</b>	Chronic neuropathic pain, paresthesias, dysesthesias
	Paroxysmal sensory symptoms (eg, neuralgic pain, Lhermitte's phenomenon, pseudoradiculopathy)
	Spasticity (eg, spasms, uncomfortable increased muscle tone)
	Paroxysmal motor phenomena (eg, tonic spasms, paroxysmal dystonia)
	Pain associated with acute inflammatory lesions and irritation of adjacent meninges (eg, optic neuritis, transverse myelitis)
	Chronic photophobia following optic neuritis
	Bladder spasms
	Mechanical back or joint pain from immobility
<b>Paroxysmal phenomena</b>	Compression fractures
	Epileptic seizures
	Nonepileptic paroxysmal motor phenomena (eg, paroxysmal dystonia, hemifacial spasm)
	Nonepileptic paroxysmal sensory phenomena (eg, Lhermitte's phenomenon)
	Uthoff's phenomenon

**Figure 2.1 Typical clinical manifestations of MS (continued).**

The typical course of MS is depicted in Figure 2.3. In 70–80% of patients MS begins with a relapsing–remitting (RR) course. A relapse (also known as an exacerbation or attack) [2,3] is defined as:

- new, worsening, or recurrent neurologic symptoms consistent with those caused by MS;
- typically developing over days to weeks;
- lasting at least 24–48 hours; and
- accompanied by an objective change on the neurologic examination corresponding to the patient's symptoms.

Even without treatment, most relapses recover partially or completely over weeks to months, particularly early in the disease. However, not all relapses recover completely, and early in the disease most impairment/disability accrual is the result of incomplete relapse recovery [4]. Relapses are heterogeneous within and between patients in terms of

Clinical categories of MS	
Category	Description
Clinically isolated syndrome (CIS)	One episode of inflammatory CNS demyelination Patients with a CIS are at increased risk of developing RR MS if there are multiple additional lesions on MRI or evidence of intrathecal antibody production in CSF
Relapsing–remitting (RR) MS	Recurrent episodes of inflammatory CNS inflammation with stable clinical manifestations between episodes (the initial course in ~70–80% of patients)
Secondary progressive (SP) MS	Gradual neurologic deterioration, with or without superimposed relapses, in a patient with prior RR MS
Primary progressive (PP) MS	Gradual neurologic deterioration from onset without superimposed relapses (~15–20% of patients)
Progressive-relapsing MS	Gradual neurologic deterioration from onset with subsequent superimposed relapses (~5% of patients)
Fulminant	Severe MS with frequent relapses and/or rapid disability progression (~5% of patients)
Benign	MS that remains mild over a prolonged course with rare relapses and minimal disability accumulation (~10–20% of patients)

Figure 2.2 Clinical categories of MS. CNS, central nervous system; CSF, cerebrospinal fluid.

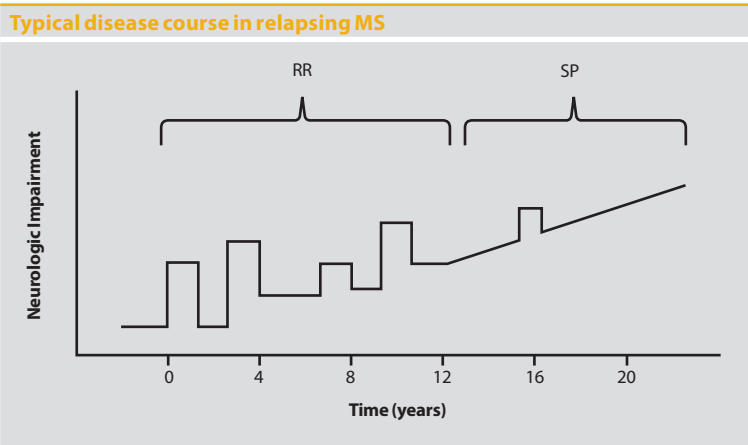


Figure 2.3 Typical disease course in relapsing MS. In 70–80% of patients, MS begins with a RR course. The initial relapse is a CIS. The diagnosis of RR MS is confirmed when a second clinical or MRI event occurs. In RR MS disability accrues from incomplete recovery from relapses. Relapses vary in neurologic manifestations, frequency, severity, and degree of recovery. Most patients with RR MS evolve into a SP course 10–15 years after onset. The transition from RR to SP MS is indistinct, with decreasing relapse frequency and onset of gradual worsening between relapses. Late in the disease, there is gradual progression without relapses. CIS, clinically isolated syndrome; RR, relapsing–remitting; SP, secondary progressive.

neurologic manifestations, frequency, severity, and degree of recovery. In practice, relapses may be indistinct or equivocal. Indeed, although a relapse is a clinical event, MS disease activity, as indicated by MRI lesion activity, can occur without clinical manifestations (ie, an MRI relapse). When a patient has had only a single relapse, the initial event is called a clinically isolated syndrome (CIS). The diagnosis of RR MS is confirmed when a recurrent CNS inflammatory event occurs, either a second relapse or new MRI lesion activity.

Patients with MS often experience worsening of pre-existing symptoms or reappearance of previous symptoms in the setting of infection or other intercurrent illness. These “pseudo-relapses” must be distinguished from bona fide relapses because they may indicate a condition that requires treatment and their ramification for long-term MS treatment differs. Acute relapses also must be distinguished from the transient fluctuations in manifestations that patients with MS frequently experience: transient worsening associated with increased body temperature (Uthoff’s phenomenon), single paroxysmal symptoms (eg, Lhermitte’s phenomenon or trigeminal neuralgia), or gradual worsening over months (ie, progression).

After 10–15 years most patients with RR MS exhibit gradual worsening of disability, known as the secondary progressive (SP) phase [5]. Sometimes there are continued superimposed relapses initially during the transition from RR to SP MS, but eventually there is continued progression in the absence of relapses and new MRI lesion activity.

Approximately 15% of patients with MS demonstrate gradual worsening disability from onset, known as have primary progressive (PP) MS. The clinical manifestations of PP MS frequently include a myelopathy (pyramidal manifestations in the legs and arms), or, less often, cerebellar, afferent visual, or cognitive symptoms. Patients with PP MS tend to be older at onset than those with relapsing forms of MS and there is less of a female predominance. A small proportion of patients with gradual worsening at onset experience subsequent superimposed relapses, called progressive-relapsing MS.

The biologic distinction between PP MS and relapsing forms of MS is not known. Similarly, the mechanisms that underlie the transition from RR

to SP MS and gradual worsening in purely progressive MS (ie, late SP MS and PP MS) are poorly understood. It is thought that the accumulation of irreversible axonal damage and the possible development of a degenerative process are important.

Prognosis

As for other chronic diseases, severity varies among patients with MS. Decisions regarding treatment, career, and family planning are based on prognosis. Ultimately, however, it is difficult to make accurate prognostic predictions in individual patients early in the disease when these decisions need to be made. Approximately 5% of patients have fulminant MS with frequent relapses and/or rapid disability progression. Conversely, 10–20% of patients have benign MS that remains mild over a prolonged course with rare relapses and minimal disability accumulation. Clinicians must be careful not to prematurely reassure patients that they have benign disease early in the course or to miss disabling cognitive impairment in patients who have mild physical manifestations.

Several features are potentially prognostic of a good or bad course in MS and are listed in Figure 2.4. The presence of multiple MRI lesions at the time of CIS, and to a lesser extent intrathecal antibody production in the cerebrospinal fluid (CSF), indicate increased risk of subsequent clinical or MRI events that will lead to the diagnosis of RR MS [6].

Prognostic factors in MS	
Factors suggesting a more favorable prognosis	Factors suggesting an unfavorable prognosis
Female sex	Male sex
Predominantly sensory symptoms	Predominantly pyramidal, cerebellar, or cognitive symptoms
RR course	Progressive course
Infrequent, mild relapses with good recovery	Frequent, severe relapses with poor recovery
Prolonged time to onset of progressive course and/or accumulation of disability	Short time to onset of progressive course and/or accumulation of disability
Modest MRI lesions activity, mild T2-hyperintense and T1-hypointense lesion burden and atrophy, with slow MRI progression	Prominent and persistent MRI lesion activity, extensive T2-hyperintense and T1-hypointense lesion burden and atrophy, and rapid MRI progression

Figure 2.4 Prognostic factors in MS. RR, relapsing–remitting.

Furthermore, several features in the early course of MS predict overall prognosis in MS [7]. Nevertheless, although the presence of worrisome features often indicates poor prognosis, some patients show spontaneous improvement. More importantly, the absence of poor prognostic features may be misleading.

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