Multiple sclerosis

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Abstract | Multiple sclerosis (MS) is the most common chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system in young adults. This disorder is a heterogeneous, multifactorial, immune-mediated disease that is influenced by both genetic and environmental factors. In most patients, reversible episodes of neurological dysfunction lasting several days or weeks characterize the initial stages of the disease (that is, clinically isolated syndrome and relapsing–remitting MS). Over time, irreversible clinical and cognitive deficits develop. A minority of patients have a progressive disease course from the onset. The pathological hallmark of MS is the formation of demyelinating lesions in the brain and spinal cord, which can be associated with neuro-axonal damage. Focal lesions are thought to be caused by the infiltration of immune cells, including T cells, B cells and myeloid cells, into the central nervous system parenchyma, with associated injury. MS is associated with a substantial burden on society owing to the high cost of the available treatments and poorer employment prospects and job retention for patients and their caregivers.

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS). MS is a heterogeneous, multifactorial, immune-mediated disease that is caused by complex gene–environment interactions. The pathological hallmark of MS is the accumulation of demyelinating lesions that occur in the white matter and the grey matter of the brain and spinal cord. The clinical manifestations and course of MS are heterogeneous; in most patients, reversible episodes of neurological deficits (known as relapses) that usually last for days or weeks characterize the initial phases of the disease (that is, clinically isolated syndrome (CIS) and relapsing–remitting MS (RRMS); FIG. 1). Over time, the development of permanent neurological deficits and the progression of clinical disability become prominent (known as secondary progressive MS (SPMS); FIG. 1). A minority of patients have a progressive disease course from onset, which is referred to as primary progressive MS (PPMS); FIG. 1). Each subtype of MS can be classified as active or not active on the basis of clinical assessment of relapse occurrence or lesion activity detected using MRI[1]; moreover, patients with PPMS or SPMS, can be classified according to whether disability has progressed over a given time[1,2].

MS typically affects young adults, with an onset between 20 years and 40 years of age and has a higher prevalence in women, although some patients experience their initial demyelinating event during childhood or adolescence, typically with an RRMS form[3,4]. Diagnosis is based on the demonstration of the dissemination of demyelinating lesions to different regions of the CNS (dissemination in space (DIS)) and over time (dissemination in time (DIT)), which can be demonstrated using clinical evaluation or paraclinical tools once MS-mimicking disorders have been excluded. MRI has a high sensitivity for detecting disease-related abnormalities, including the presence of demyelinating lesions and, accordingly, the use of this imaging modality has substantially changed the diagnosis of MS. Additionally, MRI is helpful for monitoring disease activity and the response to disease-modifying treatments (DMTs). Combined with improved understanding of the immunological and neurobiological disease processes underlying MS, improvements in diagnosis have led to the development of many new treatments that can substantially reduce disease activity in many patients and delay, at least partially, the progression of MS.

In this Primer, we review current knowledge on the epidemiology and pathophysiology of MS and describe the clinical presentations and the classification of clinical phenotypes. The current diagnostic tools and their prognostic value are discussed, in addition to how treatment of the disease has evolved. Finally, key outstanding questions in the field are considered, including the identification of features specific to the pathological substrates of MS, the development of biomarkers sensitive to disease-related changes, the optimization of treatment at an individual patient level and the assessment of the impact of comorbidities.

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Epidemiology

MS is one of the most widely studied neurological diseases in terms of epidemiology and it is the primary cause of non-traumatic disability in young adults. RRMS typically has an onset between 20 years and 35 years of age, whereas PPMS typically begins at ~40 years of age, although up to 10% of patients experience their initial demyelinating event during childhood or adolescence[4]. Approximately 2.3 million people have MS[5] worldwide, and this disease is associated with a high societal economic burden, which has increased over time. The economic burden of MS was estimated as ~14.6 billion euros in 2010 within Europe and 4.3 billion dollars in the United States in 2013 (REFS[6,7]).

The prevalence of MS varies between countries (FIG. 2). MS is mainly found in individuals of European descent and is rare in Asian, black, Native Americans and Māori individuals[8]. Prevalence estimates range from 2 per 100,000 individuals in Asia to ~1 per 1,000 individuals in Western countries, although a prevalence of 1 per 400 individuals has been reported in some countries with a high latitude[9]. Indeed, in many studies, a higher latitude correlates with increased prevalence and incidence of MS, mainly in Europe and North America[9,10]. Genetic factors, in particular the distribution of the *HLA-DRB1* haplotype, might account in part for the latitudinal gradient, but environmental risk factors that vary with latitude might also be involved. Of these factors, low vitamin D levels owing to a lack of sun exposure is the most likely candidate (see Risk factors, below).

The prevalence of MS has increased since the 1950s, especially in women[9]; this finding might represent a true increase in disease burden but might also be attributed to improved access to medical facilities, better diagnostic accuracy and increased life expectancy owing to improved management. However, these reasons cannot explain the female preponderance. The female to male ratio of MS, which seems to decrease with higher latitude, has increased to ~3:1 in the 2010s from a 2:1 ratio in the 1950s, despite no difference in the incidence of disease in males and females in some regions (such as Norway, the United States and Italy)[9,11]. In 2008, a systematic review estimated an overall incidence of 3.6 per 100,000 person-years in women and 2.0 per 100,000 person-years in men[10] and demonstrated an increased female to male ratio over time from an estimated 1.4 in 1955 to 2.3 in 2000 (REF.[10]). The increased female preponderance of MS suggests a possible role of environmental risk factors that mainly affect women (for example, occupation, increased cigarette smoking, obesity, birth control and childbirth)[9,11].

MS symptoms are the main direct cause of death in >50% of patients with MS, although infections and suicide are substantially increased compared with the general population[12]. The life expectancy of patients is reduced by 7–14 years, but this decreased life expectancy is less evident in recent estimates[12]. Excess standardized mortality values are higher in men than women, in patients with PPMS than those with RRMS and in those with higher disability[13–16].

Risk factors

The causes of MS are still unknown, although this disease is known to result from interplay of genetic susceptibility and environmental risk factors.

Lifestyle and environmental factors. Many environmental factors can contribute to the risk of MS and might be present and therefore increase disease risk during a particular time frame. Substantial evidence supports a period of susceptibility to environmental risk factors for MS during adolescence[17] (TABLE 1), although exposure to some factors might be relevant during other phases of life (such as low vitamin D level during pregnancy)[18]. Identifying the role of lifestyle or environmental risk factors of MS is difficult and large prospective studies are, with few exceptions, rare. The most well-established risk factors are Epstein–Barr virus (EBV) infection in adolescence and early adulthood, tobacco exposure through active or passive smoking, a lack of sun exposure, low vitamin D levels and obesity during adolescence (TABLE 1). Other, less-established risk factors include night work, excessive alcohol or caffeine consumption and history of infectious mononucleosis[17].

Owing to the immune-mediated pathogenesis of MS, infectious diseases have been suggested as possible triggers for disease onset. Of the different pathogens investigated, EBV infection is the most consistently and robustly associated[17,19]. To this end, it is noteworthy that up to 100% of patients with MS are seropositive for EBV according to epidemiological studies[20]. The mechanism by which EBV infection increases the risk of MS is not clear, but molecular mimicry leading to the generation of cross-reactive T cells and antibodies has been proposed[17,19]. Despite data supporting an increased risk of MS with EBV infection, a direct causal relationship remains difficult to establish.

Smoking has been consistently demonstrated as a risk factor for MS and has an odds ratio (OR) of ~1.6 (REF.[17]). The risk of MS and smoking is dose-dependent: a higher amount of smoking and cumulative smoking are both associated with increased risk. Passive exposure to smoking has also been associated with increased risk of MS[17]. Moreover, smoking has also been linked to faster

disability progression and to higher risk of conversion from RRMS to SPMS[21]. A direct toxic effect of some smoke components (promoting lung irritation) and an indirect systemic effect (mediated by the peribronchial lymphatic tissue) have been proposed to explain the association.

Sun exposure, particularly exposure to ultraviolet-B radiation, is the major determinant of vitamin D levels and tends to decrease with increasing latitudes. Thus, vitamin D levels have been proposed to underlie the 'latitude effect' in MS prevalence. Several studies suggest an association between low vitamin D levels and increased risk of MS and an increased disease activity (in terms of clinical relapses and MRI activity)[17,22], suggesting a protective effect of normal vitamin D levels throughout the disease course. Although the mechanisms of action of vitamin D are not fully clear, some data suggest that the active form of vitamin D (1,25-dihydroxycholecalciferol) has a role in the modulation of immune function[17,22].

Interestingly, some of these risk factors, notably EBV infection, obesity during adolescence and smoking, can interact with genetic risk factors for MS, such as polymorphisms in genes encoding human leukocyte antigen (HLA), to confer a higher risk of MS. As some of the environmental factors are modifiable, preventive strategies might be possible in the future; this strategy might also be relevant after disease onset, as some of these risk factors have an influence on disease course and prognosis (see below).

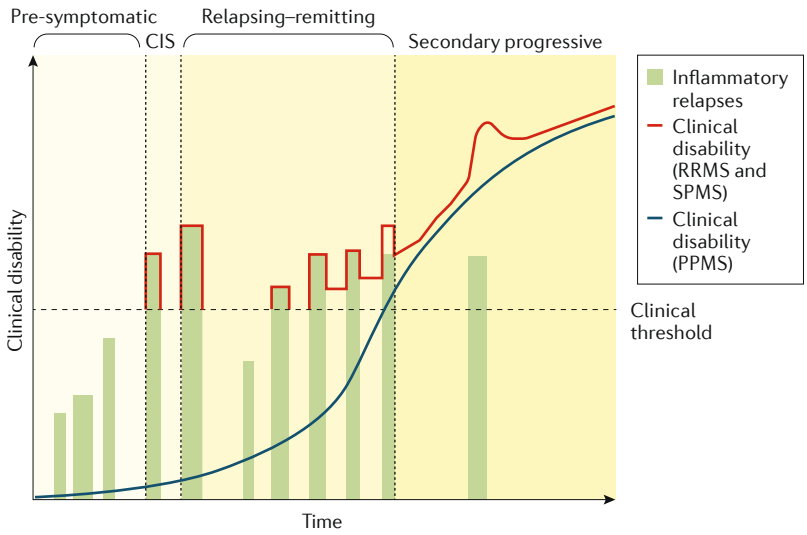


Fig. 1 | **Clinical course of MS.** The National Multiple Sclerosis Society Advisory Committee on Clinical Trials in multiple sclerosis (MS)[316] defined four clinical courses of MS: relapsing–remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS)[316]. RRMS accounts for ~85% of patients and is characterized by the occurrence of relapses at irregular intervals with complete or incomplete neurological recovery[133,317,318]; the average relapse frequency is ~1.1 per year early in the disease course but seems to decrease with advancing disease, increasing neurological dysfunction and age[319]. Most patients with RRMS will develop SPMS, which is characterized by progressive, irreversible disability that occurs independently of the presence of relapses[316]. Conversion to SPMS occurs in ~2–3% of patients per year[316]. Approximately 10–15% of patients present with PPMS, which is characterized by disease progression from the onset, resulting in gradual, progressive and permanent neurological deficits for >1 year without relapses[159,316]. PRMS is rare and is characterized by progressive disease from the onset, with acute relapses (with or without full clinical recovery) and periods of continuing progression between relapses[316]. A revision of these phenotypes has been proposed[1] and includes clinically isolated syndrome (CIS)[1] to denote those patients whose first clinical presentation has characteristics of inflammatory demyelination that could be MS but who do not fulfil its diagnostic criteria[1]. Within each subtype, disease can be classified as active or not active, which are defined by the occurrence of relapses or lesions detected using MRI. Another important modifier of the progressive stages is the inclusion of whether disability has progressed over a given time period.

Genetic factors

The prevalence of familial MS is ~13% for all MS phenotypes[23]. The risk of recurrence within families increases with the percentage of genetic sharing[24]; for example, the age-adjusted risk in monozygotic twins is 35%, as compared with 6% in dizygotic twins and 3% in siblings[24]. The heritability of MS is polygenic and involves polymorphisms in several genes, each of which is associated with a small increase in disease risk. Among these, polymorphisms in HLA class I and HLA class II genes convey the highest risk of MS[17,24].

Genome-wide association studies have identified >200 genetic risk variants for MS; each variant has a small effect on risk of disease, and different combinations of these variants likely contribute to genetic susceptibility in different patients[25]. Most of these variants encode molecules involved in the immune system (such as the *HLA* genes on chromosome 6, including *HLA-DRB1*15:01* polymorphisms, and polymorphisms in *IL2* and *IL7R*) and are associated with a higher risk of other systemic immune disorders. Polymorphisms in genes involved in T cell activation and proliferation (such as *IL2* and *IL7R*) are a major feature of the disease, together with polymorphisms in other components of adaptive and innate immunity (such as genes that modulate tumour necrosis factor (TNF))[26–28]. Risk genes of MS do not overlap with those of other neurodegenerative diseases, whereas mutations in only a few genes that have clear functions in the nervous system have been associated with an increased risk of MS (for example, *MANBA* and *GALC*). As previously mentioned, some polymorphisms, particularly those in *HLA* genes, might interact with environmental risk factors (TABLE 1). For example, the *HLA-DRB1*15:01* allele, which conveys an increased risk of MS, but not the protective *HLA-A*02* allele, confers a significantly higher risk of MS in smokers (OR 13.5)[29], in individuals with EBV infection (OR 16.0)[30] and in those with adolescent obesity (OR 16.2)[31]. Moreover, polymorphisms in genes involved in vitamin D metabolism (such as *GC* and *CYP24A1*)[32] are associated with an increased risk of MS[17]. Further efforts are required to elucidate how environmental risk factors interact with MS susceptibility genes to contribute to early disease mechanisms in the immune system and the CNS.

Mechanisms/pathophysiology

Pathology

The pathological hallmark of all MS phenotypes is focal plaques (also known as lesions), which are areas of demyelination that are typically located around postcapillary venules and are characterized by breakdown of the blood–brain barrier (BBB). The mechanisms of BBB breakdown are incompletely understood but seem

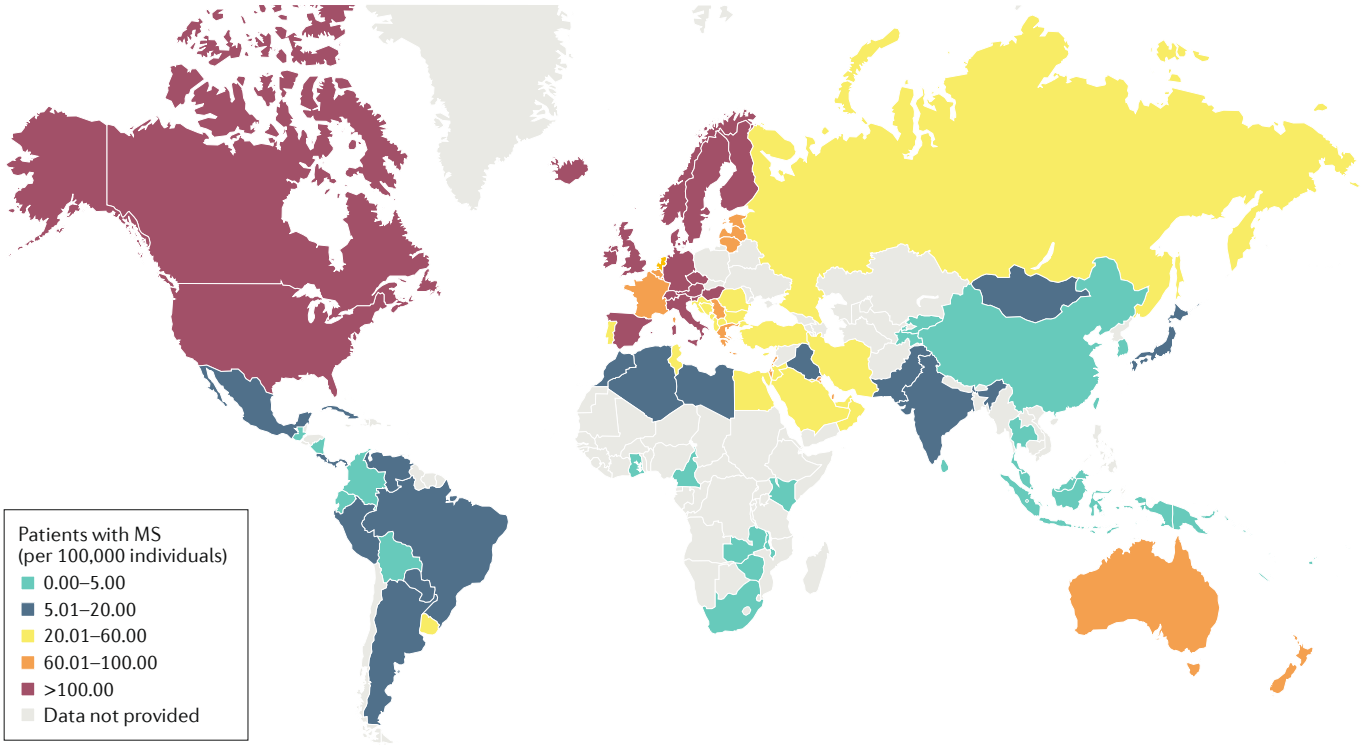


Fig. 2 | **Worldwide prevalence of MS.** The prevalence of multiple sclerosis (MS) varies between countries. In general, the prevalence of MS is higher in countries of higher latitude and in Western countries. The MS International Federation's Atlas of MS, 2013.

to involve direct effects of pro-inflammatory cytokines and chemokines (such as TNF, IL-1β and IL-6) produced by resident cells and endothelial cells, as well as indirect cytokine-dependent and chemokine-dependent leukocyte-mediated injury[33,34]. The dysregulation of the BBB increases the trans-endothelial migration of activated leukocytes, including macrophages, T cells and B cells, into the CNS, which leads to further inflammation and demyelination, followed by oligodendrocyte loss, reactive gliosis and neuro-axonal degeneration[35,36].

Plaques occur in both white matter and grey matter and are typically found throughout the CNS, including in the brain, optic nerve and spinal cord[37–39]. Although the anatomical location of white matter lesions is associated with specific clinical manifestations of MS, the total volume of these lesions is only moderately correlated with overall clinical disability and cognitive impairment[40,41] owing to the involvement of other pathophysiological mechanisms, such as the occurrence of grey matter lesions and normal-appearing brain tissue damage, which affect both grey matter and white matter.

White matter lesions

The earliest phases of MS (CIS and RRMS) are typically characterized by active demyelinating lesions. These lesions have heavy lymphocyte infiltration (mainly $CD8^+$ T cells and $CD20^+$ B cells, with fewer $CD4^+$ T cells), activated microglia (particularly at the lesion edge and containing myelin debris), macrophages (containing myelin debris) and large, reactive (sometimes multinucleated) astrocytes[42,43]. By contrast, active demyelinating plaques are less frequent in patients with PPMS and SPMS owing to a reduced frequency of inflammatory events in these patients. PPMS and SPMS are mainly characterized by inactive lesions. Inactive lesions are sharply circumscribed, hypocellular and have well-defined demyelination, reduced axonal density, reactive astrocyte gliosis, variable microglial activation only in the periplaque white matter (without macrophages) and a lower density of lymphocytes than active lesions[42–46]. However, inflammatory mechanisms still have a role in PPMS and SPMS[44,45,47–49]; indeed, active or mixed (inactive and active) lesions represented up to 57% of all lesions in patients with progressive MS in one study, and active lesions correlated with a more-severe disease course[49].

Other forms of plaques include chronic active plaques and slow expanding lesions. Chronic active plaques are more frequent in patients with MS with a longer disease duration and in SPMS and are characterized by macrophages at the edge of the lesion, with fewer macrophages in the lesion centre (FIG. 3). Slow expanding lesions, which are typically found in patients with SPMS, are characterized by an inactive centre with demyelination, activated microglia at the lesion edge and few macrophages containing myelin debris, but transected axons are also observed, suggesting a very slow rate of ongoing demyelination and axonal damage[42,44–46].

Normal-appearing white matter. In addition to the focal lesions typically observed in patients with MS, macroscopically normal white matter (that is, normal-appearing white matter (NAWM)) often shows signs

Table 1 | **Lifestyle and environmental risk factors for MS**

Risk factor	Odds ratio	*HLA* gene interaction	Combined odds ratio[a]	Effect during adolescence	Immune system implied	Level of evidence
Smoking	~1.6	Yes	14	No	Yes	+++
EBV infection (seropositivity)	~3.6	Yes	~15	Yes	Yes	+++
Vitamin D level <50 mM	~1.4	No	NA	Probable	Yes	+++
Adolescent obesity[b]	~2.0	Yes	~15	Yes	Yes	+++
CMV infection (seropositivity)	0.7	No	NA	Unknown	Yes	++
Night work	~1.7	No	NA	Yes	Yes	++
Low sun exposure	~2.0	No	NA	Probable	Yes	++
Infectious mononucleosis	~2.0	Yes	7	Yes	Yes	++
Passive smoking	~1.3	Yes	6	No	Yes	+
Organic solvent exposure	~1.5	Unknown	Unknown	Unknown	Unknown	+
Oral tobacco or nicotine consumption	0.5	No	NA	Unknown	Yes	+
Alcohol	~0.6	No	NA	Unknown	Yes	+
Coffee	~0.7	No	NA	Unknown	Yes	+

+, non-replicated observations that require further study; ++, case–control observations that have been replicated and/or supported by independent methods; +++, high level of evidence from large prospective studies or a case–control observation that is supported by Mendelian randomization studies; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HLA, human leukocyte antigen; MS, multiple sclerosis; NA, not applicable. [a]Combined odds ratio for the non-genetic factor and HLA allele. [b]Adolescent obesity defined as body mass index >27 at 20 years of age). Adapted from REF.[17], Springer Nature Limited.

of diffuse inflammation and neuro-axonal damage[45,50]. Abnormalities of NAWM have been observed in patients with RRMS but are more severe in those with progressive disease and include decreased fibre density owing to axonal degeneration and demyelination, small round cell infiltration (mainly lymphocytes), macrophage infiltration, widespread microglia activation and gliosis[50]. NAWM was previously considered secondary to the axonal damage within focal lesions, although these diffuse changes poorly correlate with the number, size, location and destructiveness of focal white matter lesions in the brain[50] and spinal cord, suggesting that they might occur independently[51].

Grey matter lesions. Extensive cortical demyelination is observed in the forebrain[50,52] and cerebellum[53] in patients with MS, occurs from the earliest phases of the disease (that is, also in patients with radiologically isolated syndrome[54] (see below) and CIS[55]) and is more widespread in patients with PPMS and SPMS, in extreme cases of which >60% of the cortex can be affected. Lesions can also occur within deep grey matter nuclei[56,57] and in the grey matter of the spinal cord, in which grey matter demyelination is more extensive and widespread than in the white matter[37,39]. Although the mechanisms underlying the differences in the extent of demyelination in the grey matter and white matter have not been clarified, it could be due to differences in the mechanisms of promoting demyelination and the presence of pro-demyelinating soluble factors in the cerebrospinal fluid[37,39].

Cortical lesions are predominantly found in cortical sulci and in deep invaginations of the brain surface and are often topographically related to inflammatory infiltrates in the meninges[58,59]. Moreover, their formation is supposed to be promoted by pro-inflammatory mediators released from the meninges or present in the cerebrospinal fluid[60]. Compared with white matter lesions, cortical lesions typically display less BBB breakdown, less oedema, a lower degree of inflammation (characterized by fewer infiltrating activated microglia and macrophages[61]) and more efficient myelin repair occurring after demyelination, suggesting that different mechanisms determine lesion formation in the white matter and the grey matter[62,63]. Cortical lesions are associated with variable degrees of transected neurites, neuronal apoptosis and loss of neurons, neuro-axons and glial cells, together with a substantial loss of synapses[61,64,65] (FIG. 3). Decreased synaptic density has also been described in the normal-appearing cortex in patients with MS without cortical lesions, suggesting that synaptic loss might be in part independent from focal demyelination in the cortex[65].

According to their location within the grey matter, four different types of cortical lesions have been identified in patients with MS[61,66]: type I lesions are located at the cortico-subcortical border and affect both the grey matter and the white matter; type II lesions are small perivenous intracortical lesions that do not affect white matter or the pial surface of the brain; type III lesions extend inward from the subpial layers of the cortex (subpial lesions); and type IV lesions extend through the whole width of the cortex but without passing the border between the cortex and the white matter. Type III cortical lesions are the most frequent in patients with MS and are characterized by subpial areas of demyelination, which involve the cortical ribbon of several gyri and are often related to meningeal inflammatory infiltrates[58,59] usually not extending beyond layers 3 and 4 of the cortex.

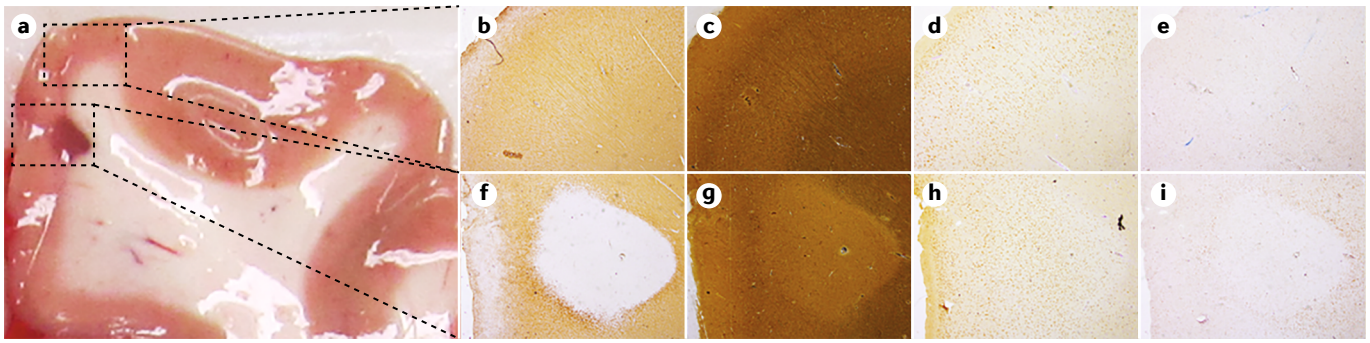


Fig. 3 | **Post-mortem histopathological findings in MS. a** | A tissue block from the superior frontal gyrus (SFG) showing normal-appearing grey and white matter (upper rectangle) and a macroscopically visible mixed grey and white matter lesion (lower rectangle) was obtained from a 70-year-old patient with secondary progressive multiple sclerosis (MS) with a disease duration of 33 years who died owing to euthanasia, with a post-mortem delay of 6 hours. **b**–**e** | Stained sections of normal-appearing grey and white matter are shown. **f**–**i** | Stainined sections of a mixed grey and white matter lesion are shown. Proteolipid protein labelling (parts **b**,**f**) to quantify myelin confirmed the presence of a mixed grey and white matter lesion (part **f**). In the same lesion, Bielschowsky (part **g**) and NeuN (part **h**) staining revealed axonal injury and neuronal shrinkage and loss, respectively. Compared with normal-appearing grey and white matter (part **e**), sections stained for ionized calcium binding adaptor molecule 1, a marker of microglia, showed a higher density of microglia in the rim of the lesion (part **i**), mainly in the white matter edge. The patient donor gave written informed consent for the use of his tissue and medical records for research purposes, and he was registered at the Netherlands Brain Bank, Amsterdam, Netherlands.

Remyelination and degeneration. Remyelination can occur in MS[62,63,67], has been suggested as a mechanism of clinical recovery after a relapse and could represent a target for future therapies[68]. Remyelination gives rise to the so-called shadow plaques that are characterized by global or patchy remyelination, a sharp demarcation from the surrounding NAWM and axons with thin myelin sheaths and shortened internodes[62,63,69,70]. The extent of remyelination is very heterogeneous, although it is generally limited and restricted to the lesion border or is patchy, and has been demonstrated in ~40–50% of white matter lesions and in up to 90% of grey matter lesions, although different values have been reported in some studies[62,63,67]. The variability in remyelination depends on several factors, including patients' age, disease duration, lesion location, the presence of oligodendrocyte progenitor cells and axonal integrity[48]; substantial remyelination is frequently observed during the earlier phases of MS and in younger individuals, whereas it is more sparse or absent in PPMS and SPMS[71].

Of the neuropathological findings in MS, neuro-axonal loss is of particular interest, as it corresponds to neurodegeneration. In MS, neurodegeneration occurs from the earliest phases of disease and might contribute to irreversible clinical disability[45]. Whether the degree of axonal loss correlates with the severity of MS is unknown and requires further study. Different mechanisms occurring at different stages of MS might drive neurodegeneration as a primary and/or secondary phenomenon[45,48].

Immune pathophysiology

Our understanding of the underlying immunopathophysiology of MS has evolved. The traditional view of T cell-mediated MS relapses has been altered to include the involvement of key bidirectional interactions between several immune cell types, including T cells, B cells and myeloid cells in the periphery, and resident cells of the CNS such as microglia and astrocytes[72]. Together with peripheral immune cells, CNS-resident cells secrete a range of inflammatory mediators that can recruit inflammatory cells into the CNS, lead to neuronal demyelination and induce inflammation within the CNS parenchyma. In addition, both peripheral and CNS-compartmentalized inflammatory mechanisms are involved in MS pathophysiology. In particular, CNS-resident cells that sense homeostatic disturbances, mainly microglia and astrocytes, can also produce neurotoxic inflammatory mediators (such as cytokines, chemokines and reactive oxygen species) that can promote and sustain neuro-axonal damage and neurodegeneration in MS[47] (FIG. 4). Despite the notion that CNS-compartmentalized inflammation likely contributes to CNS injury, it is poorly targeted by currently available treatments[73] and needs further study[48,74].

T cell involvement. The historical view of MS, on the basis of studies of patients and studies using the most commonly used animal model of MS (that is, experimental autoimmune encephalomyelitis (EAE)), is that relapses are principally mediated by aberrantly activated and/or insufficiently regulated pro-inflammatory CNS-specific effector T cells, including $CD4^+$ T cells and $CD8^+$ T cells, that traffic to the CNS parenchyma and cause perivascular demyelination, glial cell activation and neuro-axonal injury[47,75]. One potential cause of aberrant effector T cell activation is an insufficiency in the function of regulatory T (T_{reg}) cells and resistance of CNS-specific effector T cells to T_{reg} cell-mediated regulation[76,77]. Indeed, several abnormalities in circulating T_{reg} cells have been observed and implicated in MS, including decreased expression of forkhead box protein P3 (FOXP3) by T_{reg} cells and/or deficient regulatory capacity of FOXP3-expressing $CD25^{hi}CD127^{low}$ natural T_{reg} cells (which arise in the thymus and are a separate lineage to induced T_{reg} cells)[78–80]. In addition, decreased numbers or deficient regulatory responses have also been suggested for CD46-expressing

induced type 1 regulatory cells, CD39-expressing T_{reg} cells, IFNγ-expressing T_{reg} cells and follicular T_{reg} cells in blood in patients with MS, which could promote aberrant effector T cell function[81–83].

The most widely implicated pro-inflammatory effector T cells are IL-17-expressing $CD4^+$ T cells (known as T helper 17 cells (T_H17 cells)) and $CD8^+$ T cells that might be increased in the periphery and in the CNS in patients with MS. These cells are speculated to contribute to direct injury of oligodendrocytes and neurons (although the exact mechanisms that direct injury have not been defined) and to indirect tissue injury through the activation of other cells, such as macrophages[84–87]. Other effector T cell subsets with a role in MS include IFNγ-secreting $CD4^+$ T cells (T_H1 cells) and granulocyte–macrophage colony-stimulating factor (GM-CSF)-expressing $CD4^+$ and $CD8^+$ T cells; the role of GM-CSF is not fully defined in MS, but GM-CSF has been shown to activate myeloid cells and $CD8^+$ mucosal-associated invariant T (MAIT) cells in the EAE model[88–90].

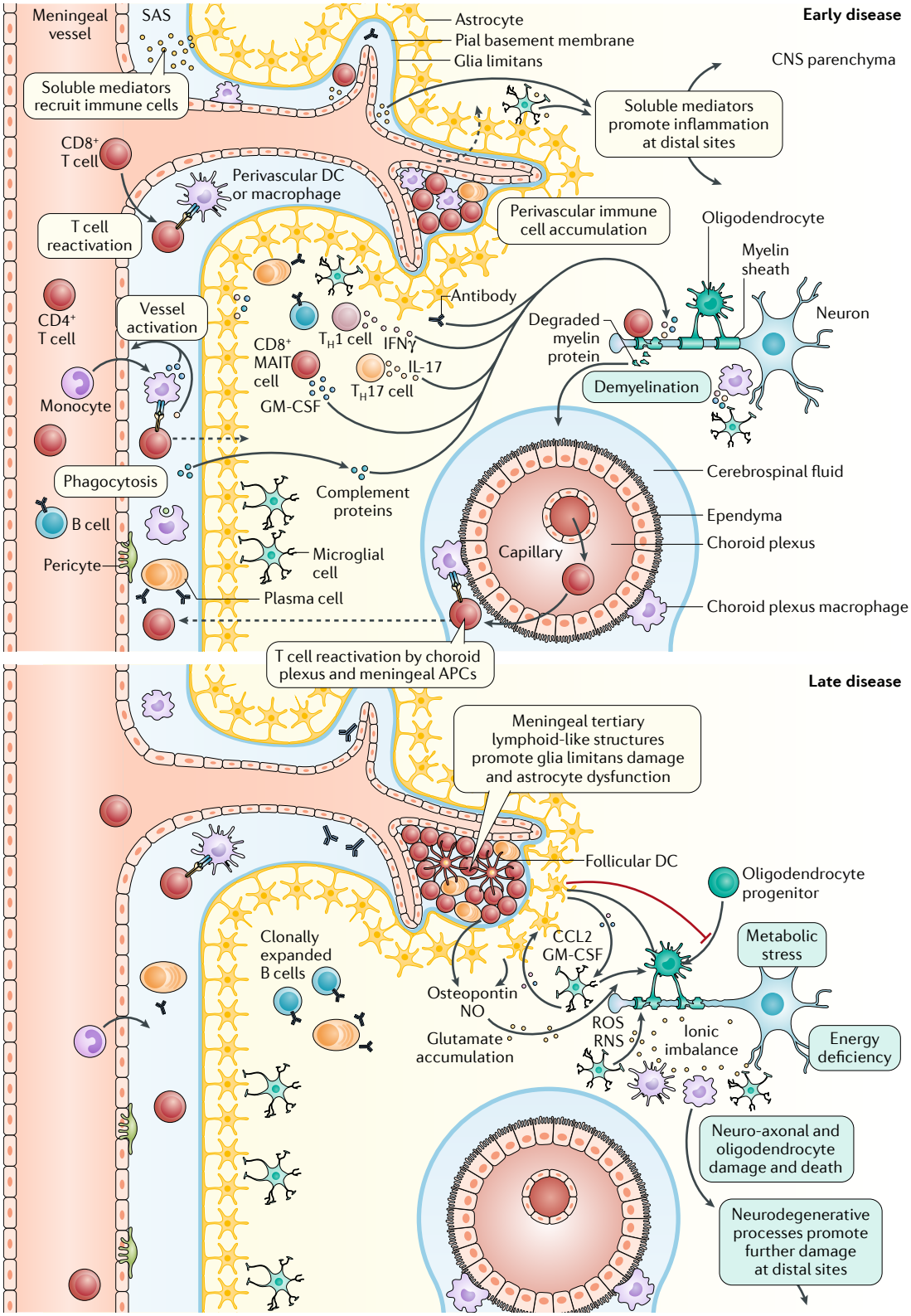
The aberrant T cell activation in MS requires antigen presentation to T cells by antigen-presenting cells (APCs) such as B cells and myeloid cells (macrophages, dendritic cells and microglia) in the periphery and the CNS, although the responsible antigens have not been routinely identified[91] (BOX 1). Myelin-related antigens are suspected to be involved, although there is no consensus, and some studies have suggested antigens on the neuronal or glial cell surface. Important bidirectional interactions between T cells and myeloid cells that can shape their effector responses (both pro-inflammatory or anti-inflammatory responses) have long since been recognized[75,92]. Pro-inflammatory APCs such as B cells and myeloid cells can drive T_H1 cell and T_H17 cell responses, which might have a role in immune cell interactions and the trafficking that underlies relapses in MS. To this end, circulating myeloid cells in patients with MS have an overly pro-inflammatory profile, including the expression of the microRNA miR-155 and pro-inflammatory cytokines such as TNF, IL-12, IL-6, IL-23 and IL-1β, which are involved in T_H1 cell and T_H17 cell differentiation[93–95].

How aberrantly activated immune cells access the CNS in MS is of ongoing interest and therapeutic importance. Despite the fact that the CNS was considered immune privileged, with the BBB thought to restrict entry of cells and macromolecules from the circulation, as previously mentioned, BBB breakdown has been observed in patients with MS, which is speculated to facilitate the migration of pro-inflammatory cells into the CNS parenchyma. In addition, a lymphatic drainage system has been demonstrated in the CNS[96]. The immune system can interact continuously with the CNS as part of normal immune surveillance and, in MS, bidirectional trafficking likely takes place during the course of disease[97,98]. After activation in the periphery, immune cells upregulate cell surface molecules such as chemokine receptors and adhesion molecules, which enables efficient tissue infiltration, including to the CNS. Indeed, chemokine receptors, such as CC-chemokine receptor 6 (CCR6), CCR2 and CCR5, and cell surface glycoprotein MUC18 (also known as MCAM) are thought to contribute to effector T cell trafficking from lymphoid structures and blood to the CNS in the EAE model and possibly in patients with MS[99,100]. In addition, junctional adhesion molecule-like (JAML) has a role in the migration of $CD8^+$ T cells and monocytes across the brain endothelium, whereas MUC18 is used by $CD8^+$ T cells and $CD4^+$ T cells to access the CNS, and ninjurin 1 is selectively implicated in the CNS migration of myeloid cells[99,101]. Also of note, in addition to the post-capillary venule BBB endothelial cells (which are the site of the classical perivascular MS lesions), immune cells might enter the CNS via the subarachnoid space and the blood–CSF barrier. Identifying the molecules that are involved in the trafficking of subsets of immune cells across distinct CNS barriers might guide development of more selective therapeutic targeting. The earliest molecular mechanisms underlying new inflammatory lesion formation in MS might involve abnormalities in these barriers, which enable immune cell infiltration from the periphery[102–104].

The biology underlying remission in MS is not well understood, but it is unlikely to merely represent a passive decline in the pro-inflammatory effector cell activity and is likely to involve mechanisms that downregulate immune responses, such as T_{reg} cell activity[76]. In addition, remission is likely to involve activation-induced cell death wherein activated pro-inflammatory cells might have upregulated surface molecules that make them more susceptible to killing by other immune cells[105]. Indeed, several studies have suggested that apoptosis of immune cells (such as myelin-reactive T cells) could exert positive effects by switching off CNS inflammation[106].

B cell involvement. A role for B cells in the development of MS relapses has emerged on the basis of impressive results of selective B cell-targeting therapies (such as anti-CD20 antibodies) in MS[107]. The role of a small subset of CD20-expressing T cells (which are also depleted with anti-CD20 therapy) remains of interest, although this subset has not been ascribed a particular pathogenetic function in MS[108].

Healthy individuals typically have low levels of antibodies in the CNS (the normal ratio is ~1:300 of CNS to periphery); patients with MS have an abnormally increased production of antibodies within the CNS, which can be detected, for example, as increased immunoglobulin synthesis rates and the presence of cerebrospinal fluid-restricted oligoclonal bands (OCBs). This finding was the basis for anti-B cell therapies in MS, although interestingly, the reduction in relapse rate with anti-CD20 therapy was associated with little or no change to the cerebrospinal fluid immunoglobulin profile in patients[109,110], suggesting an antibody-independent role of B cells in MS relapses. These antibody-independent functions are likely to be the contribution of B cells to cascades of cellular immune interaction in the periphery and/or their ability to attract and activate T cells and myeloid cells in the CNS[72]. Indeed, B cells from patients with MS have an abnormal propensity to produce pro-inflammatory cytokines (including IL-6, GM-CSF, TNF and lymphotoxin-α



(LTα)) and are deficient in regulatory cytokines such as IL-10 (REFS[111–116]). One subset of pro-inflammatory B cells, CD27+ GM-CSF-expressing memory B cells, which produce high levels of TNF and IL-6 but do not express IL-10, is found in increased numbers in the circulation of patients with MS and has an exaggerated response profile[112]. The abnormal cytokine response profile of B cells from patients with MS can induce aberrant T_H1 cell and T_H17 cell responses through TNF and IL-6 and can induce pro-inflammatory myeloid cell responses (principally through GM-CSF), which could contribute to the cellular immune cascades involved in relapses[111–116]. In line with this finding, anti-CD20 B cell-depleting therapy reduces the pro-inflammatory

◀ Fig. 4 | **Immune system dysregulation within the central nervous system in early and late MS.** Immune cells are believed to enter the central nervous system (CNS) in multiple sclerosis (MS) through the blood vessels of the blood–brain barrier (BBB), the subarachnoid space (SAS) and the choroid plexus (dashed arrows). In MS relapses, which are more prominent in the early phases of disease, underlying mechanisms involve the infiltration of cells of the innate and adaptive immune systems, such as $CD4^+$ and $CD8^+$ T cells, B cells and myeloid cells, into the CNS parenchyma with perivascular distribution around post-capillary venules of the BBB. These immune cells, together with resident activated microglia and astrocytes, are thought to contribute to oligodendrocyte injury, demyelination and neuro-axonal injury through cell contact-dependent mechanisms and the secretion of soluble factors. In later stages of the disease, the episodic infiltration of immune cells into the CNS is diminished. Mechanisms contributing to ongoing tissue injury (and the clinical manifestations of progressive disease) are thought to include neurodegeneration, in terms of neuro-axonal, astrocyte and oligodendrocyte damage, owing to acute or chronic oxidative stress promoted by innate and adaptive immune cell activation, mitochondrial dysfunction, extracellular free iron accumulation, loss of myelin trophic support, hypoxia, altered glutamate homeostasis and a pro-inflammatory environment, with possible involvement of cytotoxic factors and complement activation. Chronic inflammation is potentially mediated by ongoing CNS-compartmentalized inflammation involving meningeal immune cell infiltrates (for example, B cells) that can form lymphoid-like structures and by CNS-resident innate cells (for example, microglia). For example, CC-chemokine ligand 2 (CCL2) and granulocyte–macrophage colony-stimulating factor (GM-CSF) produced by astrocytes can promote microglia recruitment and activation, and astrocytes can limit remyelination by preventing the differentiation of oligodendrocyte progenitor cells into mature oligodendrocytes. APC, antigen-presenting cell; DC, dendritic cell; MAIT, mucosal-associated invariant T; NO, nitric oxide; RNS, reactive nitrogen species; ROS, reactive oxygen species; T_H1, T helper 1; T_H17, T helper 17. Adapted from REF.[47], Springer Nature Limited.

responses of T_H1 cells and T_H17 cells and reduces myeloid cell pro-inflammatory responses in the periphery of patients with MS[111,112]. By contrast, the (largely naive) B cells that re-emerge after discontinuation of anti-CD20 treatment[111,112,114] have reduced secretion of GM-CSF, IL-6 and TNF but increased IL-10 secretion; whether these cells have an immune-regulatory effect in a subset of patients that potentially contributes to the durability of the treatment effect and whether the treatment effect lasts until the re-emergence of pro-inflammatory memory B cells are of interest.

MS relapses might also be driven by alterations in the balance between pro-inflammatory and anti-inflammatory B cells. This is supported by the observation that, aside from anti-CD20 therapies, all other approved therapies for MS affect memory B cell responses (reviewed previously[72]). In addition, the finding that atacicept (a recombinant fusion protein that inhibits B cells) exacerbated MS relapses in clinical trials lends further support to this hypothesis[117]. Atacicept leads to selective loss of several subsets of B cells (including plasmablasts and plasma cells) but spares memory B cells, which might result in a more pro-inflammatory B cell profile, therefore, aggravating disease.

The antibody-independent functions of B cells do not preclude a role for antibodies in MS pathophysiology. However, antibody levels in the CNS do not substantially change following anti-CD20 treatment[118], suggesting that antibodies are unlikely to be critically involved in triggering relapses. It is possible that antibodies could persist in the CNS for a long period of time after treatment; however, if the antibodies were relevant, the effects of treatment would not be quick or substantial while the antibodies do not change. Studies of circulating antibodies in patients with MS, including antibodies directed against myelin antigens, such as myelin basic protein (MBP) or myelin-oligodendrocyte glycoprotein (MOG) and the inward rectifying potassium channel Kir4.1 (also known as KCNJ10)[119–121], have not led to the same pathogenetic implications for specific CNS-directed antibodies as those observed in other conditions, such as anti-aquaporin 4 antibodies in neuromyelitis optica spectrum disorders (NMOSDs) and anti-*N*-methyl-D-aspartate (NMDA) antibodies in NMDA encephalitis. In addition, the presence of circulating anti-MOG antibodies in a subset of patients with CNS inflammatory demyelinating disease, including NMOSD[122], has been associated with clinical and imaging features that are not typical of MS[123,124] (even if they have been also described in up to 5% of patients with MS), which are mainly characterized by severe brainstem and spinal cord involvement, a severe disease course with high relapse rates and failure in response to several DMTs[125].

Progressive MS. In addition to cascades of the cellular immune interactions in the periphery that contribute to MS relapses, ongoing inflammation in the CNS might contribute to the propagation of injury in patients with PPMS and SPMS (FIG. 4). In particular, inflammation may differ in individuals with progressive MS compared with RRMS and is characterized by a lower frequency of inflammatory relapses (waves of infiltration of activated immune cells into the CNS in a perivascular distribution). Additionally, a CNS-compartmentalized inflammation is evident, involving, for example, $CD8^+$ T cells and plasma cells that survive and persist in the CNS or surrounding meninges and possibly also involving microglia and astrocyte inflammatory responses[43,45,47,48]. $CD8^+$ T cells might be quiescent memory cells that promote further tissue damage when exposed to and activated by their target antigen[43]. The different inflammatory mechanisms in PPMS and SPMS might contribute to the lack of efficacy of DMTs, which typically have systemic anti-inflammatory activity[45,48].

Ongoing questions relate to how relapse biology is involved in the initiation and maintenance of CNS-compartmentalized inflammation, which, at least at some point in the disease process, is maintained in the absence of obvious relapses. The subpial demyelinating cortical injury that is present from the earliest phase of the disease and is more widespread in patients with progressive MS reportedly involves a graded pattern of neuronal loss and microglial activation[45,126,127], which could be consistent with a 'surface-in' process, such as that mediated by one or more toxic substances in the cerebrospinal fluid. In this regard, the extent of meningeal inflammation is associated with the extent of subpial cortical injury[126] and with higher levels of pro-inflammatory cytokines such as IFNγ, TNFα, LTα and IL-6 in the cerebrospinal fluid of patients[60]. The potential for meningeal immune cells to contribute to CNS injury has also been noted above in the context of cytotoxic $CD8^+$ T cells that may enter the CNS through the meninges to respond to local (potentially EBV-infected) B cells[60,128] (BOX 1). In addition, B cells from patients with MS can secrete unidentified factors that are toxic to oligodendrocytes and neurons in vitro[129,130]. The CNS inflammation in patients

might, in turn, foster B cell persistence and propagation of CNS-compartmentalized inflammation[131]. Future research will aim to elucidate whether and how bidirectional interactions between meningeal immune cells and underlying brain cells contribute to the propagation of non-relapsing inflammation and progressive injury to CNS structures adjacent to the cerebrospinal fluid and how such processes could interact with and/or respond to the degenerative mechanisms described above (reviewed previously[45]).

Despite occurring at early disease stages, neuro-axonal degeneration is common in progressive disease. The mechanisms of neuro-axonal degeneration include neuronal apoptosis owing to acute or chronic oxidative stress promoted by innate and adaptive immune cell activation, mitochondrial dysfunction and extracellular free iron accumulation, loss of myelin trophic support, hypoxia, altered glutamate homeostasis and a pro-inflammatory environment, with possible cytotoxic factors and complement activation[45,48].

Diagnosis, screening and prevention

Clinical presentation

The clinical presentation of MS is heterogeneous and depends on the location of demyelinating lesions within the CNS. Although no clinical findings are unique to MS, some are highly characteristic of the disease. Typically, the onset of MS is characterized by an initial clinical attack (defined as CIS) in ~85% of patients, which consists of an unpredictable episode of neurological dysfunction owing to demyelinating lesions in the optic nerve (leading to optic neuritis), spinal cord (leading to myelitis), brainstem or cerebellum (leading to brainstem and/or cerebellar syndromes) or the cerebral hemispheres (cerebral hemispheric syndrome; FIG. 5; TABLE 2). During the disease course of RRMS, further clinical episodes can occur (known as relapses); these episodes last for ≥24 hours and occur in the absence of fever, infection or clinical features of encephalopathy (for example, altered consciousness or epileptic seizures)[132]. Symptoms of a clinical attack typically show an acute or sub-acute onset, worsen over days or weeks, reach a peak severity within 2–3 weeks and remit to a variable degree, ranging from minimal resolution to complete recovery normally 2–4 weeks after reaching maximum deficit[133].

Optic neuritis is the first neurological episode in ~25% of patients and is associated with a conversion to clinically definite MS in 34–75% of patients between 10 years and 15 years after clinical onset[134–136]. Approximately 70% of patients with MS have optic neuritis during the course of the disease[134–136]. Optic neuritis is characterized by a partial or total visual loss in one eye with a central scotoma (a blind spot in the visual field), dyschromatopsia (deficiency of colour vision) and pain within the orbit that is worsened by eye movement[134–136] (TABLE 2). During fundus oculi examination using ophthalmoscopy, the optic nerve head appears normal if inflammation is limited to the retrobulbar portion of the nerve, but approximately one-third of patients might have inflammation of the optic disc (papillitis) and disc oedema owing to anterior optic neuritis. Patients without visual complaints with suspected MS should be evaluated for more subtle manifestations of optic neuritis, such as an afferent pupillary defect or abnormalities at paraclinical tests (for example, visual evoked potentials, optical coherence tomography (OCT) or MRI).

Sensory symptoms are the first clinical manifestation in up to 43% of patients with MS and are mainly caused by myelitis or brainstem syndromes[137]. Sensory symptoms include paresthesia (commonly described as numbness, tingling, pins-and-needles feeling, tightness, coldness and/or swelling of the limbs or trunk), Lhermitte sign[138] (a transient symptom described as an electric shock radiating down the spine or into the limbs with flexion of the neck), impairment of vibration and joint position sensation, and reduced pain and light touch perception. These symptoms can temporarily worsen with increased body temperature (known as Uhthoff phenomenon).

Motor manifestations are the initial symptoms in 30–40% of patients and affect almost all patients during the course of the disease[139]. Motor symptoms are characterized by pyramidal signs (such as Babinski sign, more-pronounced reflexes and clonus), paresis and spasticity. Brainstem and cerebellar symptoms are present in up to 70% of patients with MS[139], which include impairment in ocular movements (such as nystagmus (involuntary eye movement), oscillopsia (a visual phenomenon in which items in the visual field seem to move) and diplopia (double vision)), ataxia and gait imbalance, dysmetria (poor coordination) and decomposition of complex movements, slurred speech and dysphagia (difficulty swallowing). The extent of sphincter and sexual dysfunction often parallels the degree of motor impairment in the

Box 1 | **Autoantigens in MS**

The antigenic targets of the aberrant immune cell activation in multiple sclerosis (MS) remain incompletely defined. Historically, the focus of investigation was on myelin proteins that are commonly used to induce autoimmune encephalomyelitis (EAE) in experimental models, such as myelin basic protein (MBP), proteolipid protein and myelin-oligodendrocyte glycoprotein[75,92]. Indeed, several studies in patients support a role for myelin-reactive T cells in MS owing to the increased frequency, stability and/or pro-inflammatory response profiles of these cells in patients compared with controls[92,299]. However, most healthy individuals also have T cells (and B cells) that are reactive to the same myelin antigens as patients with MS, therefore, the mere presence of such autoreactive cells is insufficient to induce disease. Non-myelin antigens might be relevant in early MS pathogenesis, such as axo-glial apparatus molecules that have been implicated in paediatric-onset MS[300]. T cell activation by an infectious agent that has similarities with central nervous system (CNS) antigens (known as molecular mimicry) has been postulated as a mechanism for triggering MS and MS relapses. In particular, a strong epidemiological association has been demonstrated between Epstein–Barr virus (EBV) infection and risk of MS in the earliest phases of MS, close to its biological onset[301,302]; EBV shares a molecular sequence with MBP, and aberrant $CD4^+$ and $CD8^+$ T cell responses to EBV have been reported in patients with MS[303,304]. Moreover, EBV can transform and activate B cells in vivo, and it is plausible that, in patients with MS, EBV contributes to pro-inflammatory B cell activation in the periphery and, in turn, mediates aberrant activation of CNS-reactive T cells that are involved in MS relapses. In addition, some studies have demonstrated EBV-infected B cells and plasma cells in patients with MS, which are located adjacent to $CD8^+$ T cells expressing cytotoxic molecules, such as perforin and granzyme[128,305]. The process by which immune cell activation to additional CNS antigens might be triggered as a consequence of CNS injury and exposure of additional antigenic targets has been referred to as epitope spreading. This process is well demonstrated in EAE, with limited studies suggesting this might also occur in patients with MS[92,306].

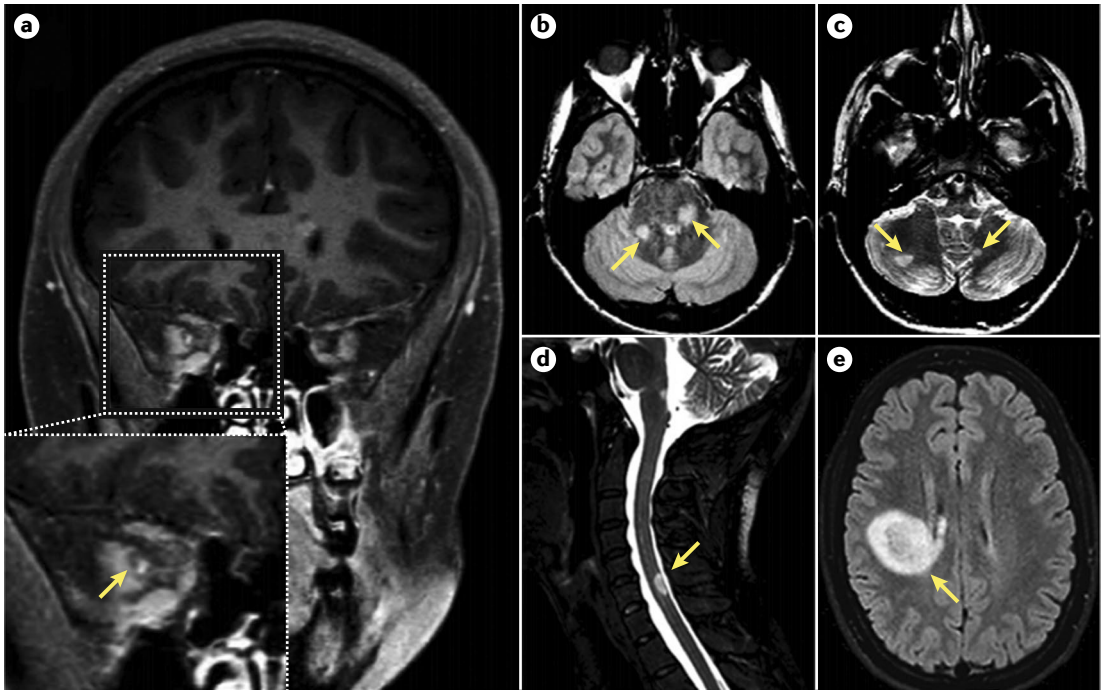


Fig. 5 | **Radiological examples of demyelinating events in MS.** 3T MRI sequences from five patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS), within 5 days from clinical onset, are shown. Focal lesions (arrows) can be observed in: the right optic nerve in a patient with acute optic neuritis (part **a**); the left pons and the right middle cerebellar peduncle in a patient with diplopia (part **b**); the cerebellar hemispheres in a patient with vertigo (part **c**); the cervical spinal cord in a patient with paresthesia and Lhermitte sign (part **d**); and the left cerebral hemisphere in a patient with right sensorimotor hemisyndrome (part **e**).

lower extremities, and the dysfunction usually becomes permanent late in the disease course, affecting 34–99% of patients[140]. The most common symptom of bladder dysfunction is urinary urgency, but hesitancy, frequency and urge incontinence can also occur[140]. Constipation is more common than faecal incontinence, and men with MS often have erectile dysfunction and impotence.

Other symptoms include cognitive impairment, fatigue and affective disturbance. Overall, 40–70% of patients with MS have cognitive impairment, which can start in the earliest phases of the disease[41]. Cognitive deficits can predict conversion to clinically definite MS in patients with CIS[141], are more frequent and more-pronounced in chronic progressive MS, worsen over time and affect patients' daily life activities[41]. Common cognitive symptoms include impairment in information processing speed, episodic memory, attention, efficiency of information processing and executive function[41]. Up to 95% of patients experience fatigue[142]. Several mechanisms have been suggested to promote the occurrence of fatigue in patients with MS. Fatigue can be associated with relapses and can persist after the attack has subsided, but it can also be a feature of daily life and can be present for years. Several strings of evidence support the hypothesis of a central origin of MS-related fatigue owing to a dysfunction of cortico-subcortical circuits, mainly involving structural damage in fronto-parietal regions and the basal ganglia[143]. Sleep disorders (for example, insomnia, obstructive sleep apnoea and restless legs syndrome) are found in up to 54% of patients with MS[144] and might also promote fatigue[145].

Affective disturbance occurs in up to two-thirds of patients, of which depression is the most common manifestation[146]. Pain is reported in up to 43% of patients and can include trigeminal neuralgia, dysesthetic pain, back pain, visceral pain and painful tonic spasms[147]. Typically, the prevalence and the severity of all clinical manifestations previously described are higher in patients with PPMS and SPMS than in those with RRMS.

Several qualitative and semi-quantitative scales have been proposed to grade the clinical manifestations of MS. Of these, the Expanded Disability Status Scale (EDSS)[148] is the most widely accepted measure of clinical disability. The EDSS is a scale that ranges from 0 (a completely normal neurological examination) to 10 (death owing to MS) and provides 8 subscale measurements (functional system scores) that include the main functional domains affected by MS, including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, mental and other domains.

Diagnostic criteria

The diagnosis of MS is primarily based on clinical criteria; in most patients, the occurrence of two or more clinically distinct episodes of CNS dysfunction with at least partial resolution is sufficient for diagnosis of RRMS. Although the diagnosis can be made on the basis of clinical criteria alone, MRI can support, supplement or replace some clinical criteria owing to the sensitivity and specificity of this imaging modality in demonstrating demyelinating lesions, as well as DIS and DIT[149] (BOX 2).

Table 2 | **Typical and atypical clinical presentations of MS**

Presentation	Typical or atypical presentation	Onset	Involvement	Signs or symptoms	Recovery
Optic neuritis	Typical	Sub-acute to chronic (hours to days)	Unilateral	• Afferent pupillary defect • Central visual blurring or scotoma • Reduced visual acuity • Dyschromatopsia (colour blindness) • Normal optic disc or optic disc swelling • Mild unilateral orbital pain that is worsened by eye movements	Gradual recovery within 2–4 weeks after reaching peak severity
	Atypical	Acute (seconds to minutes)	Bilateral	• Peripheral visual loss • Altitudinal visual loss • Retinal haemorrhages or exudates • Severe optic disc swelling • No light perception • No or severe orbital pain • Photophobia	Progressive worsening or no recovery
Brainstem and/or cerebellar syndromes	Typical	Sub-acute and/or chronic (hours to days)	Unilateral and localized	• Unilateral or bilateral internuclear ophthalmoplegia • Multidirectional nystagmus • Sixth cranial nerve palsy • Ataxia or gait imbalance • Vertigo • Facial numbness or sensory loss • Dysmetria and decomposition of complex movements • Dysarthria and slurred speech • Dysphagia • Hearing loss • Nausea	Gradual recovery starting within 2–4 weeks after reaching peak severity
	Atypical	Acute (seconds to minutes)	Alternating syndromes	• Vascular territory signs • Isolated trigeminal neuralgia • Fluctuating ocular or bulbar weakness • Fever • Meningism	Progressive worsening or no recovery
Myelitis	Typical	Sub-acute and/or chronic (hours to days)	• Incomplete transverse myelitis • Asymmetric involvement	• Sensory involvement: paresthesias (numbness, tingling, pins-and-needles feeling, tightness, coldness and/or swelling of the limbs or trunk), Lhermitte sign, impairment of vibration and joint position sense, decreased pain and light touch perception and Uhthoff phenomenon • Motor deficits: pyramidal signs (Babinski sign, bright reflexes and clonus), spastic paresis and/or weakness (asymmetric) and spasticity • Sphincter dysfunction: urinary urgency, hesitancy, urge incontinence, constipation and faecal incontinence • Sexual dysfunction: erectile dysfunction and impotence	Gradual recovery starting within 2–4 weeks after reaching peak severity
	Atypical	Acute (seconds to minutes)	• Complete transverse myelitis • Complete Brown-Séquard syndrome • Cauda equina syndrome • Anterior spinal artery territory lesion • Localized or radicular spinal pain	• Progressive and symmetrical spastic paraparesis • Progressive sensory ataxia (posterior column involvement) • Sharp level to all sensory modalities • Segmental loss of pain and temperature sensation • Areflexia and/or spinal shock • Acute urinary retention • Severe pain	Progressive worsening or no recovery
Cerebral hemispheric syndromes	Typical	Sub-acute and/or chronic (hours to days)	Unilateral	• Hemisyndrome (corticospinal tract involvement): hemiparesis and hemisensory deficits • Campimetric deficits (optic radiation involvement)	Gradual recovery starting within 2–4 weeks after reaching peak severity
	Atypical	Acute (seconds to minutes)	Bilateral	• Encephalopathy • Epilepsy • Cortical blindness • Headache • Intracranial hypertension	Progressive worsening or no recovery

MS, multiple sclerosis.

The original Schumacher diagnostic criteria required evidence based on clinical examination alone for DIS and DIT[150]. Although these criteria were developed before the introduction of MRI, they are still used as a reference tool for basic definitions of DIS, DIT and relapse. These criteria were subsequently modified to include laboratory diagnostic studies such as assessment of cerebrospinal fluid, evoked potentials and neuroimaging[151]. Cerebrospinal fluid findings supporting a diagnosis of MS include a normal or mildly raised white cell count and protein levels, increased immunoglobulin G (IgG) index and the presence of cerebrospinal fluid-specific IgG OCBs. Cerebrospinal fluid-specific OCBs were included in the latest revision of the MS diagnostic criteria[152] on the basis of their high prevalence in patients with MS (up to 88%)[153] and owing to their role in predicting evolution to clinically definite MS (see below)[154,155]. Evoked potentials, including sensory (visual, somatosensory and brainstem auditory) and motor evoked potentials, assess functionally relevant pathways and can identify clinically silent lesions in the CNS, which might be missed during standard routine clinical examination[156]. MRI was formally included in the diagnostic algorithm of patients with CIS and suspected MS in 2001 (REF.[157]). The original criteria have been revised for clarification and to simplify their use in the clinical setting[55,149,158,159], culminating in the latest revision of the MS diagnostic criteria (that is, the 2017 revision of the McDonald criteria)[152] (BOX 2; FIG. 6).

Box 2 | **The 2017 revised criteria for the diagnosis of MS**

Relapsing–remitting MS

- At least two clinical relapses and objective clinical evidence on neurological examination of at least two lesions with distinct anatomical location, or at least two clinical relapses and objective clinical evidence of one lesion and clear-cut historical evidence of a prior relapse involving a lesion in a distinct anatomic location
- At least two clinical relapses and objective clinical evidence of one lesion; in addition, DIS should be demonstrated by either a second clinical relapse implicating a different CNS site or using MRI[a]
- One clinical relapse and objective clinical evidence of two or more lesions; in addition, DIT should be demonstrated by a second clinical relapse, or using MRI[b] or demonstration of cerebrospinal fluid-specific OCBs
- One clinical relapse and objective clinical evidence of one lesion; in addition, DIS should be demonstrated by a second clinical relapse implicating a different CNS site or using MRI, whereas DIT should be demonstrated by a second clinical relapse, or using MRI or demonstration of cerebrospinal fluid-specific OCBs

Primary progressive MS

A disease course characterized by progression from onset, 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse and two of the following criteria:

- One or more T2-hyperintense lesions in at least one area in the brain characteristic of MS (periventricular, cortical and/or juxtacortical or infratentorial)
- Two or more T2-hyperintense lesions in the spinal cord with no distinction between symptomatic or asymptomatic lesions
- Demonstration of cerebrospinal fluid-specific OCBs

CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; MS, multiple sclerosis; OCB, oligoclonal band. [a]One or more T2-hyperintense lesions in at least two of four areas of the CNS (periventricular, juxtacortical (by combining cortical or juxtacortical lesions), infratentorial and spinal cord lesions), with the removal of the distinction between symptomatic and asymptomatic lesions. [b]Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time, with the removal of the distinction between symptomatic and asymptomatic lesions, or a new T2-hyperintense and/or gadolinium-enhancing lesion on follow-up MRI with reference to a baseline scan irrespective of the timing of the baseline MRI.

MRI. MRI has a high sensitivity for detecting macroscopic abnormalities in the brain and spinal cord in patients with MS. Abnormal MRI owing to the presence of focal lesions is observed in almost all patients with MS and in most patients with CIS. MS lesions have typical MRI signal and location characteristics, which aid in the diagnosis. Lesions usually appear as multifocal, ovoid areas of increased signal on T2-weighted images, with lesions commonly located in periventricular, juxtacortical and infratentorial regions of the brain and in the spinal cord (FIGS 5,6). The administration of gadolinium-based contrast agents and the acquisition of post-contrast T1-weighted images enable active lesions to be distinguished from inactive lesions; signal enhancement, which underlies active lesions, occurs owing to increased BBB permeability and corresponds to areas with ongoing inflammation. Lesions that persistently appear hypointense on post-contrast T1-weighted images (so-called black-holes) are associated with more severe tissue damage than that seen with lesions that do not appear dark on such images. This hypointensity is suggestive of demyelination and axonal loss[160]. Recommendations aimed at optimizing and standardizing the use of MRI of the CNS in clinical practice have been given[161].

In the diagnostic criteria for MS, MRI is used to confirm DIS or DIT for RRMS, and it has been included in the diagnostic criteria for PPMS (BOX 2; FIG. 6). The latest revision of the MS diagnostic criteria[152] included the count of symptomatic lesions for the definition of DIS and DIT, which enables the simplification of the application of MRI criteria without losing their accuracy[55] (BOX 2). The inclusion of cortical lesions as part of the diagnostic criteria is also relevant, as these lesions are specific for MS, although improvement in their detection is still necessary. At present, ~18% of cortical lesions confirmed by pathological studies can be detected using MRI, most of which are type I lesions, whereas type III lesions (subpial) are difficult to detect even with advanced MRI techniques.

The growing application of MRI has substantially increased the identification of asymptomatic individuals with brain MRI abnormalities suggestive of MS, which is referred to as radiologically isolated syndrome (RIS)[162]. Up to 34% of patients with RIS have a clinical attack within 5 years. Male sex, younger age and the presence of spinal cord lesions increase the risk of having a first clinical event[163]. More studies are necessary to further define RIS and the differential diagnosis of this disorder and to develop recommendations to monitor and eventually treat these patients.

Aside from use in diagnosis, MRI has also gained a fundamental role in monitoring treatment efficacy (use in monitoring inflammation and/or neurodegeneration) and in the early recognition of treatment-related adverse effects (for example, progressive multifocal leukoencephalopathy (PML) and other opportunistic infections)[164].

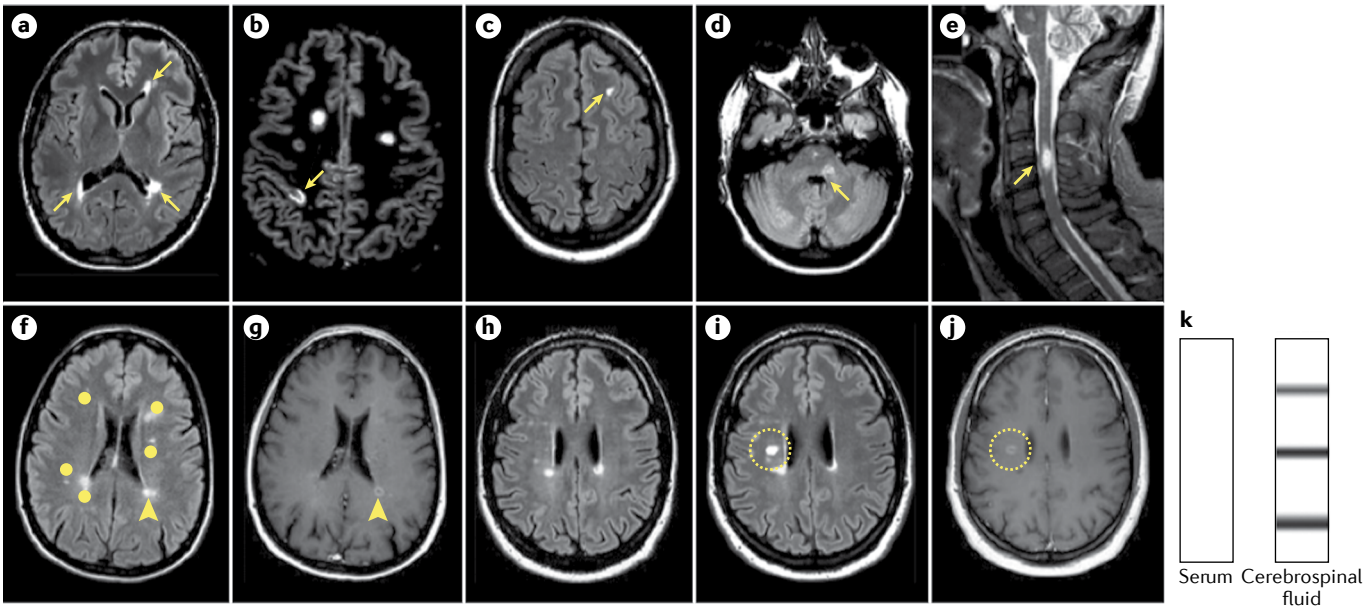


Fig. 6 | **2017 McDonald Criteria for demonstration of DIS and DIT in a patient with CIS suggestive of MS.** **a**–**e** | Dissemination in space (DIS) can be demonstrated by one or more T2-hyperintense lesions in two or more of four typical areas of the central nervous system (arrows), with the removal of the distinction between symptomatic and asymptomatic lesions. Periventricular lesions are shown in part **a**. Cortical or juxtacortical lesions to define juxtacortical involvement are shown in parts **b** and **c**. Infratentorial lesions are shown in part **d**. A spinal cord lesion is shown in part **e. f**–**j** | Dissemination in time (DIT) can be demonstrated by a simultaneous presence of gadolinium-enhancing and non-enhancing lesions (parts **f**,**g**) at any time and with the removal of the distinction between symptomatic and asymptomatic lesions, a new T2-hyperintense and/or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan (parts **h**–**j**), irrespective of the timing of the baseline MRI, or the presence of cerebrospinal fluid-specific oligoclonal bands (OCBs), which are not visible in the serum (part **k**). Several white matter lesions are visible on the fluid-attenuated inversion recovery (FLAIR) sequence (part **f**); one showed gadolinium-enhancement (arrowhead) on the post-contrast sequence (part **g**), whereas the majority were non-enhancing (dots). Compared with the baseline FLAIR sequence (part **h**), a new T2-hyperintense and gadolinium-enhancing lesion (circled) is visible on follow-up FLAIR (part **i**) and on post-contrast sequences (part **j**). CIS, clinically isolated syndrome; MS, multiple sclerosis.

Biomarkers and prognostic factors

Several biomarkers and prognostic factors associated with conversion from CIS to MS and with disability progression in patients with CIS and early RRMS have been identified, including environmental, genetic, clinical, laboratory and MRI features[132] (TABLE 3). Patients with CIS and brain lesions at MRI (including patients with one lesion only) have a >80% chance of developing MS within 20 years[165,166]. Although predicting the long-term clinical outcome of patients with MS, including the severity of disability, is more difficult than predicting conversion to MS in patients with CIS, several risk factors have been identified (TABLE 3). A progressive disease from the onset and a faster rate of disability accumulation in the first 2–5 years are predictors of poor outcomes in PPMS[132,167].

Differential diagnosis

The range of diseases that mimic the clinical manifestations and MRI features of MS is wide (BOX 3), and therefore, careful exclusion of other neurological disorders is essential during the diagnostic work up for MS. The identification of clinical and paraclinical features that are not suggestive of MS might reduce the chance of a false positive diagnosis. On this basis, MRI red flags have been identified in individuals with clinically suspected MS that alert clinicians to reconsider the differential diagnosis in more detail. These red flags include longitudinal extensive transverse myelitis extending over three spinal cord segments (suggesting a diagnosis of NMOSD) and the presence of bleeds or infarcts, which might suggest a cerebrovascular aetiology[168,169].

Prevention

As previously discussed, MS is a complex disease that is caused by the possible interactions between genetic and environmental factors; some of these factors are modifiable and, therefore, represent a promising basis for MS prevention[170]. Up to 80% of the population that is at risk of MS (particularly in Western countries) have suboptimal low serum vitamin D levels; available data suggest that the risk of MS is reduced if serum 25-hydroxy vitamin D levels are >100 nmol per litre. Accordingly, vitamin D supplementation might reduce MS incidence and promote potential benefits for the prevention of other systemic diseases, like osteoporosis[170]. In line with this, studies are ongoing to evaluate the effect of vitamin D supplementation alone or in addition to DMTs to reduce MS-related disease activity (that is, occurrence of relapses and formation of new white matter lesions at MRI) and disability progression[171].

In addition, smoking is associated with an increased risk of MS and poorer prognosis, therefore, promoting smoking cessation might be a straightforward intervention to reduce MS incidence, disability progression and the risk of comorbidities[170]. Overweight and obesity are associated with a twofold to threefold increased risk of MS and have a negative effect on clinical and MRI disease-related outcomes and with several comorbidities; to this end, educational interventions aiming to reduce body mass index (BMI) and to promote more healthy lifestyles (through, for example, reduction of food intake and increased physical activity) are strongly suggested for people at risk of developing MS (especially adolescents and young adults)[170]. Finally, on the basis of the evidence on the role of EBV in MS, research aiming to develop specific treatments (including antiviral therapies, prophylactic and therapeutic EBV vaccines and viral neutralization antibodies), which could be used for MS prevention, is ongoing[170].

Table 3 | **Features of CIS and early MS predicting conversion to definite MS and disability progression**

Factor	Association with conversion to MS	Association with disability progression	Refs
Environmental and lifestyle factors			
Smoking	Higher risk	Poor prognosis	21,320
Low vitamin D levels	Higher risk	Unknown	155,321
EBV infection	Higher risk	Unknown	304
Obesity (particularly in childhood and adolescence)	Higher risk	Poor prognosis	322,323
Genetic factors			
*HLA-DRB1*1501*	Higher risk	Unknown	324,325
Clinical factors			
Non-white ethnicity	Higher risk	Poor prognosis	326,327
Female sex	Higher risk	Good prognosis	328
Male sex	Lower risk	Poor prognosis	329
Older age	Lower risk	Poor prognosis	330,331
Younger age	Higher risk	Good prognosis	326,329
Onset with optic neuritis or somatosensory disturbances	Lower risk	Good prognosis	332,333
Onset affecting efferent pathways (for example, motor)	Higher risk	Poor prognosis	332
Monofocal onset[a]	Lower risk	Good prognosis	334,335
Multifocal onset[b]	Higher risk	Poor prognosis	334,335
Cognitive impairment	Higher risk	Poor prognosis	141
Higher relapse rate in the first 2–5 years from disease onset	NA	Poor prognosis	167,329,336
Incomplete recovery after a relapse			329
Higher disability accumulation in the first 2–5 years from disease onset			167,329,336
Shorter time to conversion to SPMS			329
Laboratoristic factors			
Presence of cerebrospinal OCBs	Higher risk	Poor prognosis	153,155,333
High level of neurofilament light subunit	Higher risk	Poor prognosis	251,254,337
Neuroradiological factors			
Higher number and volume of T2-hyperintense lesions	Higher risk	Poor prognosis	155,165,166,333
Lesions in infratentorial regions	Higher risk	Poor prognosis	338,339
Spinal cord lesions	Higher risk	Poor prognosis	340–342
Presence of gadolinium-enhancing lesions	Higher risk	No data	155
New T2 lesions formation in the first 5 years	Higher risk	Poor prognosis	165,166
Optical coherence tomography factors			
Lower ganglion cell and inner plexiform layer thickness	Higher risk	No data	266

CIS, clinically isolated syndrome; EBV, Epstein–Barr virus; MS, multiple sclerosis; NA, not applicable; OCBs, oligoclonal bands; SPMS, secondary progressive multiple sclerosis. [a]Involvement of a single functional system (for example, motor, somatosensory, visual, cerebellar or brainstem). [b]Two or more functional systems involved simultaneously.

Box 3 | **Common and relevant differential diagnoses of MS**

Infectious diseases[168,169]**:**
- Meningitis
- Encephalitis (including progressive multifocal leukoencephalopathy)
- Lyme neuroborreliosis
- Intracerebral abscess

Genetic disorders[307,308]**:**
- Leukodystrophies (for example, adrenoleukodystrophies)
- Leber hereditary optic neuropathy
- Fabry disease

Metabolic disorders[168,309]**:**
- Vitamin B_{12} deficiency
- Copper deficiency

Vascular disorders[169,310]**:**
- Cerebral small-vessel disease
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Susac syndrome
- Primary angiitis of the central nervous system
- Dural arteriovenous fistula

Systemic immune-mediated diseases[169]**:**
- Systemic lupus erythematosus
- Behçet disease
- Sarcoidosis
- Sjögren syndrome

Non-MS idiopathic inflammatory demyelinating diseases[311–314]**:**
- Neuromyelitis optica spectrum disorders
- Myelin-oligodendrocyte glycoprotein (MOG) encephalomyelitis
- Acute disseminated encephalomyelitis (especially in paediatric patients)
- Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

Variants of multiple sclerosis (MS)[168,315]**:**
- Balo concentric sclerosis
- Schilder disease
- Marburg MS

Headache
- Migraine[169]

Management

The treatment of MS can be divided into DMTs that are used to reduce inflammatory disease activity and its long-term clinical consequences, the management of MS relapses and symptomatic treatments used for short-term amelioration of MS symptoms such as fatigue, pain and spasticity. Several DMTs are available for the treatment of RRMS, whereas only one DMT is approved for PPMS. Additional DMTs are now in clinical trials for RRMS, PPMS and SPMS, and intense efforts are being made to identify novel therapeutic targets.

Current standard of care

Disease-modifying treatments for RRMS. A DMT should be prescribed as soon as a patient has been diagnosed with RRMS or CIS to reduce the risk of disease progression. Injectable DMTs, such as IFNβ or glatiramer acetate, have been the main first-line treatment options for two decades mainly because of their excellent safety profiles but also owing to their lower cost than newer drugs. However, although these therapies have very low risk of severe adverse drug reactions, they have only moderate clinical effectiveness and often poor tolerability owing to injection-related adverse effects, such as flu-like symptoms with IFNβ and injection site inflammation with both IFNβ and glatiramer acetate, which frequently prompt treatment switches[172] (TABLE 4). The increasing number of approved DMTs improves the possibility of tailoring therapy to individual patient needs with regard to efficacy, safety aspects and patients' preferences. Although caution should be applied when comparing across studies owing to the heterogeneity of patient cohorts and the lack of reliable comparative studies among treatments, approximate measures of clinical efficacy can be deduced from some parameters typically evaluated in randomized clinical trials (RCTs), including the relative reduction in annual relapse frequency and the number of patients needed to treat (the number of patients you need to treat to prevent one additional bad outcome, typically a relapse or disability progression)[173,174] (TABLE 4).

The dominant current treatment strategy for RRMS, called escalation therapy, is endorsed by the European[175] and American[176] guidelines and is, in part, dictated by the label of different DMTs and public or insurance-based regulations. The basis of escalation therapy is to start with a safe but moderately effective DMT, typically IFNβ, glatiramer acetate, teriflunomide or dimethyl fumarate, and switch to another first-line DMT in patients with intolerable adverse effects or to a more effective DMT (second-line or third-line therapies) in those with new relapses or MRI lesions. In patients with severe disease who do not respond to traditional DMTs, autologous haematopoietic stem cell transplantation might be effective[177]. However, owing to the availability of more effective DMTs, such treatment failures are increasingly rare, and in general, <1% of patients with RRMS are candidates for transplantation[177,178].

Another treatment strategy, known as induction therapy, has been introduced on the basis of the availability of more-effective drugs and of the evolving concept of treating patients earlier with more-effective drugs (such as alemtuzumab or ocrelizumab) to prevent the accumulation of irreversible CNS damage and clinical disability. Induction therapy refers to a strong immunointervention that is started soon after a confirmed diagnosis in a patient with negative prognostic factors (that is, a higher disease activity (severe and frequent relapses and a higher number of lesions at MRI) and an accumulation of disability) (TABLE 3). This approach enables a rapid reduction in disease-associated inflammation by removing T cells, B cells and myeloid cells and possibly shifting towards a more tolerogenic condition owing to a reset of the immune system, which can be followed by use of less-aggressive therapies as maintenance if needed[179]. One or more cycles of induction therapy can be performed, followed by a possible de-escalation therapy. However, when treatment with a high-efficacy drug is stopped, a careful evaluation of further treatment selection is needed; particularly for therapies that do not

exert a substantial immune reset (such as natalizumab or fingolimod), another high-efficacy treatment should be started to prevent potential disease reactivation[175].

However, despite the benefits of induction therapy, an important reason to restrict the use of more-effective DMTs, such as second-line or third-line treatments, is their risk profile. Collectively, older injectable DMTs have the lowest risk of more-serious adverse effects, although these therapies have more-frequent but less-serious adverse effects that affect tolerability[179]. By contrast, more-recent DMTs typically have a better tolerability but are associated with increased risks of severe adverse effects, especially infections[179] (TABLE 4). These effects include respiratory and urinary tract infections, herpesvirus reactivation and PML. In particular, PML, which is an opportunistic infection affecting the brain owing to John Cunningham virus, has been described in patients who received natalizumab, dimethyl fumarate and fingolimod treatment. For natalizumab, the risk of PML can be determined by testing patients for John Cunningham virus antibodies. In addition, newer DMTs have substantial immunosuppressive activity, which has been suggested to increase risk of long-term malignancy, although the precise risk of this is still uncertain[180]. Alemtuzumab treatment has been associated with autoimmune diseases[181–183]; of these, thyroid disease is the most common autoimmune adverse effect associated with alemtuzumab and is found in up to one-third of patients, although more-rare, serious autoimmune reactions, including immune thrombocytopenic purpura, Goodpasture disease, neutropenia, haemolytic anaemia, agranulocytosis and acquired haemophilia, have also been observed. In addition, before starting a DMT, the teratogenic risks associated with the treatment must be considered in women planning pregnancy. Of the treatments currently available, glatiramer acetate is the only DMT considered safe to use during pregnancy.

One of the limitations of data derived from RCTs is that trials include a selected group of mostly treatment-naive patients who do not have substantial comorbidities and relevant DMT comparators, which means that we have an imprecise evidence base for tailoring DMT strategies in these patient groups, therefore, careful monitoring of patients with MS is constantly needed[184]. Also, carrying out an individualized risk–benefit assessment for MS therapies is important, as the relative benefit of individual DMTs differs between patients and all DMTs are associated with adverse effects of varying severities (TABLE 4). For example, younger age and a more-active disease (in terms of relapse frequency and MRI activity) are associated with increased benefit regarding treatment-associated long-term protection of neurological functions. As the risk–benefit ratio of therapy can change over time, studies addressing the contexts in which DMTs can safely be discontinued are also needed, even if current guidelines suggest continuing a DMT if a patient is stable and shows no safety or tolerability issues[175]. Furthermore, the possible effect of combined therapies (the simultaneous treatment with two or more DMTs) should be further explored even though, at present, there is no convincing data suggesting that combinations of DMTs would provide an added benefit in terms of efficacy.

Disease-modifying treatments for progressive disease. DMTs that are used for the treatment for RRMS cannot prevent disease worsening in patients with PPMS and SPMS[173]. Mitoxantrone, a cytostatic drug, was approved by the US FDA for SPMS in 2000, but its use is limited by cardiotoxic and mutagenic adverse effects[185]. Fingolimod and natalizumab have been tested in patients with PPMS[186] or SPMS[187], respectively, but did not demonstrate superiority over placebo. More promising data emerged from a placebo-controlled study with rituximab in PPMS, in which the risk of disability progression was reduced in younger patients with signs of active inflammation on the baseline MRI scan[188]. A beneficial effect of anti-CD20 agents in PPMS was substantiated in a larger study with ocrelizumab, which significantly reduced the risk of disability progression compared with placebo and led to the first approval of a DMT for PPMS[189]. Notably, the patients in this study were young (mean 44.6 years of age), and 27% of patients had signs of active inflammation on baseline MRI, suggesting that earlier phases of the disease might be more responsive to treatment. Collectively, data indicate that DMTs that act mainly on the adaptive immune system have a reduced efficacy in progressive disease compared with in RRMS but that treatment with anti-CD20 DMTs such as ocrelizumab or rituximab should be considered, especially in patients with shorter disease duration and/or signs of active inflammation on MRI.

Relapses. The most established treatment for the acute management of MS relapses is high-dose corticosteroids. These drugs are associated with a faster functional recovery and protect against the occurrence of more severe deficits in the first weeks after treatment but have unclear long-term benefits. Current protocols typically include 3–5 days of intravenous methylprednisolone with or without oral tapering with prednisone. Intramuscular administration of dexamethasone and oral administration of high-dose methylprednisolone have an equivalent efficacy to intravenous administration. Relapses that do not respond to corticosteroids can be treated with plasma exchange (3–5 courses) or intravenous immunoglobulin.

Symptomatic treatments. Several different pharmacological agents are used to treat the symptoms of MS, such as impaired walking capability, spasticity, pain, loss of bladder and bowel control and neuropsychiatric symptoms[190,191]. However, for most therapies, the evidence base for clinical efficacy in patients with MS is weak.

Only two symptomatic treatments have undergone more extensive testing in MS: nabiximols for the treatment of spasticity and dalfampridine for walking ability. Nabiximols can ameliorate spasticity in patients with MS[192,193], and empirical evidence supports the use of baclofen, dantrolene, tizanidine and botulinum toxin A injections for the treatment of spasticity in restricted muscle groups. Dalfampridine is a voltage-dependent potassium channel blocker that improves the transmission of nerve signals in demyelinated axons and improves the walking ability of people with MS[194,195]. In addition to medical treatments, walking aids such as

Table 4 | **Relapse rates and the main adverse effects of DMTs in relapsing–remitting MS**

DMT	Type	Reduction of annualized relapse rate[a]	Adverse effects	Refs
First line				
Glatiramer acetate	s.c. mixture of synthetic polypeptides	30%	• Injection site reactions (erythema, inflammation, induration or pain at injection site) • Flushing • Chest tightness or pain • Palpitations • Anxiety • Trouble breathing	343
IFNβ1a	s.c. recombinant protein	32%	• Injection site reactions (erythema, inflammation, induration or pain at injection site) • Flu-like symptoms • Leukopenia (neutropenia or lymphopenia) • Thrombocytopenia • Anaemia • Infections • Thyroid dysfunction (hypothyroidism or hyperthyroidism) • Liver damage (transaminase increase) • Fatigue • Mood disturbances (depressive symptoms)	344
IFNβ1a	i.m. recombinant protein	32%		345
IFNβ1b	s.c. recombinant protein	34%		346
Pegylated IFNβ1a	s.c. pegylated recombinant protein	35%		347
Teriflunomide	Oral pyrimidine synthesis inhibitor	34%	• Headache • Diarrhoea • Hair thinning or loss • Liver damage (transaminase increase) • Increased blood pressure • Paresthesia • Leukopenia (neutropenia or lymphopenia) • Infections	348,349
Dimethyl fumarate	Oral NRF2 agonist	49%	• Flushing • Liver damage (transaminase increase) • Gastrointestinal disturbances (abdominal pain, nausea and vomiting) • Leukopenia (mainly lymphopenia) • Infections • PML • Allergic reactions	350,351
Second line				
Fingolimod	Oral S1P inhibitor	54%	• Reduced heart rate • Increased blood pressure • Leukopenia (mainly lymphopenia) • Infections • Liver damage (transaminase increase) • Macular oedema • PML • Skin cancer (basal and Merkel cell carcinoma) and melanoma	352,353
Daclizumab (withdrawn)	i.v. monoclonal anti-CD25 antibody	44%[b]	• Liver damage (transaminase increase) • Gastrointestinal disturbances (abdominal pain, nausea and vomiting) • Allergic reactions • Infections • Immune-mediated encephalitis	354
Alemtuzumab	i.v. monoclonal anti-CD52 antibody	52%	• Infusion-related reactions • Leukopenia (mainly lymphopenia) • Infections • Autoimmune reactions (immune thrombocytopenia, immune thyroiditis and immune glomerulonephritis) • Cancers (thyroid cancer, melanoma and lymphoproliferative disorders)	355,356
Cladribine	Oral purine analogue	58%	• Leukopenia (neutropenia or lymphopenia) • Infections • Rash • Alopecia • Cancers	357

Table 4 (cont.) | **Relapse rates and the main adverse effects of DMTs in relapsing–remitting MS**

DMT	Type	Reduction of annualized relapse rate[a]	Adverse effects	Refs
Second line (cont.)				
Ocrelizumab	i.v. monoclonal anti-CD25 antibody	45%[b]	• Infusion-related reactions • Leukopenia (mainly lymphopenia) • Decreased blood immunoglobulin • Infections • Cancers	107
Natalizumab	i.v. monoclonal anti-VLA4 antibody	69%	• Infusion-related reactions • Allergic reactions • Infections • Progressive multifocal leukoencephalopathy	358,359

DMT, disease modifying treatment; i.m., intramuscular; i.v., intravenous; MS, multiple sclerosis; NRF2, nuclear factor erythroid 2-related factor 2; PML, progressive multifocal leukoencephalopathy; S1P, sphingosine-1-phosphate; s.c., subcutaneous; VLA4, very late antigen 4. [a]Compared with placebo unless otherwise stated. [b]Compared with IFNβ1a.

orthoses, crutches or walkers are important to improve ambulation capacity. Traditional or electrical wheel chairs and other mobility devices constitute important means to preserve independence of movement among patients with more-advanced disease.

Damage to sensory nerve tracts in MS leads to chronic neuropathic pain conditions for which gabapentinoids (such as gabapentin and pregabalin), tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors are first-line treatments. Opioids such as tramadol or codeine are second-line treatments for moderate to severe pain. In some countries, cannabinoids in the form of medical marijuana or synthetic drugs are recommended as a possible third-line option[196]. The management of lower urinary tract symptoms consists of oral antimuscarinic drugs, administered alone or in combination with intermittent self-catheterization, and the use of botulinum toxin A bladder instillations, neuromodulation, indwelling catheters and surgery in patients with more-severe symptoms[197].

Despite the high prevalence and clinical relevance of cognitive impairment in patients with MS, effective treatments options are still lacking. The effects of symptomatic therapies such as modafinil and donepezil are inconsistent; however, some DMTs (such as IFNβ, fingolimod and natalizumab) in combination with cognitive rehabilitation might improve or at least stabilize cognitive performances[198]. Fatigue and psychiatric comorbidities are important contributors to loss of working ability and social participation of patients with MS[199,200]. The off-label prescription of alertness-improving drugs such as modafinil and amphetamine is common even though evidence supporting the efficacy of these therapies in MS is poor or absent[201,202]. However, several smaller studies suggest that novel approaches to treat fatigue, including alfacalcidol (a vitamin D analogue)[203], physical exercise[202], cognitive behavioural therapy[202,204], deep transcranial magnetic stimulation[205] and fatigue management courses[202], give some clinical benefit.

Considering the high prevalence of sleep disorders in patients with MS, the treatment of an underlying sleep disorder (continuous positive airway pressure for obstructive sleep apnoea, drug therapy and cognitive behavioural therapy for insomnia and drug therapy for restless leg syndrome) significantly reduced fatigue and might exert positive effects on the quality of life (QOL) of patients with MS[206]. Anxiety and depression, as well as suicide, rates are elevated in MS, but studies addressing the efficacy of pharmaceutical and non-pharmaceutical interventions specifically in MS are rare, therefore, treatment guidelines largely rely on data from non-MS populations and include the use of selective serotonin or noradrenergic reuptake inhibitors and/or cognitive behavioural therapy[207,208]. As a whole, offering patients with MS comprehensive rehabilitation programmes to address the wide range of MS-associated symptoms, with the aim of alleviating burdensome symptoms through increasing the levels of physical activity, is important[209].

Biomarkers for drug response

MRI is the only tool that can reliably assess disease activity in MS[164]. In general, MRI can identify the degree of inflammation (demonstrated by the quantification of contrast-enhancing lesions and new T2 lesions forming over time) and the degree of neurodegeneration (demonstrated by atrophy of the brain and spinal cord). Newly appearing T2-hyperintense MRI lesions are a valid surrogate marker of treatment efficacy in phase II DMT studies and correlate with relapse frequency[210]. To this end, regular brain MRI scans are recommended in patients with MS to verify treatment effects owing to the frequent subclinical disease activity. However, some studies have suggested the deposition of gadolinium-based contrast agents in the basal ganglia and in the dentate nucleus of patients who underwent serial MRI acquisitions[211]. Although significant clinical consequences of these deposits have not been demonstrated, further studies are required to better understand the potential long-term biological and clinical effects of gadolinium administration[211].

In patients with MS, the development of long-term disability correlates with brain atrophy measures[212], although these measurements have not been widely introduced into the clinical routine for several reasons. For example, the quantification of atrophy is still challenging because high-quality MRI sequences are necessary, several factors (for example, BMI, genetic factors, alcohol consumption, and so on) can influence the measurement of atrophy, particularly longitudinally, and its application for single patient monitoring still

needs to be validated[213]. Although the time to detect the effects of MS treatments on brain atrophy is longer than that for the accumulation of lesions, one meta-analysis demonstrated that the treatment effect on brain atrophy correlated with the effect on disability progression[214]. In addition to radiographic imaging, soluble biomarkers that are present in different body fluids have been proposed as markers of treatment effects in MS, but so far, none have been validated[215].

Treatments currently under development

Several novel drugs that have similar mechanisms of action to existing DMTs are in late-stage clinical trials, such as the sphingosine-1-phosphate (S1P) inhibitors siponimod, ponesimod and ozanimod, as well as the anti-CD20 monoclonal antibody ofatumumab[216,217]. The development of antigen-specific therapies is a major future goal and would alleviate the problems, such as infections, associated with long-term immunosuppression. In fact, small trials reporting beneficial effects suggest that this may become feasible[218,219]. Progress has also been made in identifying therapeutic agents with potential neuroprotective or remyelinating effects, in part by re-purposing older drugs used in other contexts. For example, phenytoin (an anti-epileptic drug) has shown promising neuroprotective effects in preserving nerve fibres in acute optic neuritis[220], and the anti-allergy drug clemastine increases optic nerve conduction in MS-associated optic neuropathy[221]. Similarly, the cholesterol-lowering drug simvastatin reduced the rate of brain atrophy in SPMS[222]. Newly developed drugs aimed at increasing remyelination, such as the monoclonal antibody opicinumab, are also in clinical testing[223,224].

Recently, different dietary-based treatment strategies have been proposed in patients with MS[225]. Among them, the oral supplementation of biotin (vitamin B_7) was shown to improve or at least stabilize disability in patients with PPMS or SPMS compared with placebo, and an RCT in SPMS is ongoing[225].

Quality of life

Symptoms of MS can negatively affect patient daily functioning, relationships, work and leisure activities and ultimately lead to reduced QOL[226,227]. Patient-reported outcome measures are increasingly used to overcome the limitations of clinician-reported measures (such as the EDSS) in fully capturing the patient's experience of the disease. Patient-reported outcomes typically address symptoms, functioning, satisfaction with care, treatment adherence and perceived value of treatment. In addition to being patient reported, QOL measures are multidimensional: at a minimum, they assess the consequences of the disease and treatments on the physical, psychological and social domains of patients' lives. One major driver of the development of QOL measures for MS was the recognition by the regulatory agencies of the importance of this construct as an outcome measure for clinical trials, provided that QOL inventories are targeted to the specific patient population[228,229]. The oldest MS-specific QOL instruments are the 54-item MS QOL (MSQOL-54) and the Functional Assessment of MS (FAMS)[230,231]. The FAMS was produced using a combination of the classical test theory and the Rasch model. The latter is a prescriptive psychometric approach which rests on the assumption that a scale has the basic property of unidimensionality and meets the fundamental measurement requirements, enabling arithmetic operations such as addition and subtraction[232]. Two MS-specific unidimensional QOL inventories were produced in the United Kingdom using the Rasch model: the Leeds MS QOL (LMSQOL) and the Patient-Reported Outcome Indices for MS (PRIMUS) QOL[233,234].

For other patient-reported outcome measures, linguistically validated versions are needed to appropriately compare data from different populations and to use QOL as an outcome measure in international trials[228,229]. The only example of an MS-specific QOL instrument concurrently developed in 14 languages is the MS International QOL Questionnaire (MusiQOL)[235]. Other inventories were developed in US English[230,231] or UK English[234] and linguistically validated in other languages. Another QOL scale property that is key for use as an outcome measure in clinical trials is responsiveness (the ability of an instrument to measure a meaningful clinical change)[228,229], which remains insufficiently assessed in the MS population[236–240].

Although the measurement and reporting of MS QOL data have evolved considerably, translation to clinical practice has been limited. Questionnaire length and complexity of score calculation and interpretation are recognized as major barriers to the use of QOL and other patient-reported inventories in clinical practice[227]. Questionnaire length can be particularly challenging for patients with fatigue, which is common in patients with MS. The 29-item MS QOL (MSQOL-29) was recently produced from the MSQOL-54 using Rasch analysis[239]. A further step is the development of computerized adaptive testing, which would present questions that are most relevant for an individual patient, reducing the questionnaire length and exposure to items that are not relevant or appropriate[241]. A multidimensional computerized adaptive version of the MusiQOL has recently been devised[242].

Outlook

Key outstanding questions in MS include the following: the identification of paraclinical features (for example, laboratory, neuroradiological or neurophysiological) that are more specific to the pathological substrates of MS, which might increase diagnostic specificity and reduce the risk of misdiagnosis; the development of biomarkers that are more sensitive to disease-related changes (such as inflammatory activity or disease progression); the optimization of treatment at an individual patient level; and an assessment of the effect of comorbidities.

Improving specificity in the diagnosis

An awareness of an increased risk of misdiagnosis[243] owing to an oversimplification of the diagnostic criteria and their incorrect application was one of the motivating factors for the 2017 revision of the McDonald criteria[152]. The identification of distinctive MRI features of MS might help to reduce the risk; for example, the consistent identification of lesions around small vessels in MS and

accordingly the MRI detection of a vein centrally inside white matter lesions have been proposed as biomarkers of inflammatory demyelination. Indeed, the proportion of lesions with a central vein is higher in MS[244] than in other conditions, including NMOSD[245], CNS inflammatory vasculopathies[246] and vascular diseases[247]. In addition, the detection of a central vein in three white matter lesions has good specificity, sensitivity and inter-rater reliability for the differential diagnosis of MS in patients with MS with or without comorbidities, patients with migraine and others with a misdiagnosis of MS[248]. Future work is required to assess the predictive value of the central vein sign for the development of MS in individuals with CIS and to define a standardized imaging protocol and to identify criteria for the clinical implementation of central vein assessment[244].

Novel biomarkers

Several novel biomarkers are currently being investigated in an attempt to improve MS diagnosis and monitoring. Among them, neurofilaments, OCT and measures of grey matter damage are receiving the most attention.

Neurofilaments. Neurofilaments are major components of the axonal cytoskeleton, consisting of light (NfL), intermediate and heavy chains that are released from damaged neurons and axons in neurological disorders[249]; these neurofilament chains can be quantified in the blood and cerebrospinal fluid as a marker for neuroaxonal damage in MS[215,250]. Several studies have demonstrated that levels of NfL in cerebrospinal fluid are higher in individuals with CIS who convert to MS than in individuals who do not convert[250,251] and also in patients with RIS who develop a first clinical attack than in those who do not[252]. In addition, higher levels of NfL are associated with greater disability[253], more frequent relapses[254], higher numbers of T2-hyperintense and gadolinium-enhancing lesions on MRI[255,256] and more severe brain atrophy[256,257]. In patients with RRMS, higher levels of NfL predicted more severe disability and evolution to SPMS after 14 years of follow-up[258], whereas in patients with PPMS or SPMS, levels of NfL predicted the annual EDSS increase[259]. Levels of NfL in cerebrospinal fluid or serum could be used to monitor treatment effects, as demonstrated by the reduction of NfL levels seen after treatment start with natalizumab[260] or fingolimod[261,262], although further studies are still necessary before using this quantification in the clinical setting.

Optical coherence tomography. OCT can generate high-resolution images of the retina in a non-invasive, rapid and reproducible manner and in a multicentre setting[263]; specific consensus guidelines for performing and reporting OCT results have also been defined[264,265]. Unlike time-domain OCT (TD-OCT), spectral-domain OCT (SD-OCT) enables visualization of individual retinal layers and, accordingly, the advent of SD-OCT has marked a substantial leap forward in image resolution and acquisition speed.

In MS, OCT might show asymptomatic optic nerve involvement in patients with CIS and might predict conversion to MS[266]; the combined ganglion cell-inner plexiform layer and the retinal nerve fibre layer (RNFL) have been the two most frequently studied layers of the retina in patients with MS. In patients with acute optic neuritis, dynamic modifications of RNFL thickness, characterized by an initial increase owing to acute inflammatory oedema followed by atrophy within the subsequent 3–6 months, have been detected, therefore, the occurrence of substantial and irreversible damage is detectable only after 6 months[267]. Meta-analyses of TD-OCT and SD-OCT studies have demonstrated RNFL thinning to be most marked in the temporal quadrant, which is the receiving region for the macular fibres[268,269]. In addition to the RNFL, technological advances in OCT have allowed the segmentation of other retinal layers, such as the ganglion cell layer (GCL), which has been shown to have a different response to optic neuritis attacks, as this layer has a faster onset of thinning without any acute-phase oedema. For this reason, macular GCL thickness has been proposed as a superior early indicator of neural changes following optic neuritis[270]. RNFL thinning has been shown in all MS phenotypes and can start in patients with CIS[271]. RNFL is more severe in patients with SPMS[272] than in those with RRMS independent of a history of previous optic neuritis[268,273]. Progression of RNFL and GCL thinning correlates with visual deficits and worsening disability[274]. In addition, correlations between OCT parameters and atrophy of the whole brain[275] and grey matter as detected using MRI have been observed[276]. As discussed previously[274], evidence for the utility of OCT in monitoring therapeutic response in MS is accumulating.

The role of OCT has now expanded beyond the detection of damage owing to optic neuritis[269]. Assessment of the afferent visual pathway has been proposed as a model of acute demyelinating events of the optic nerve and of the chronic effects of MS. The latter derives from the particular structure of retinal ganglion cells, which lack myelination in the retina. As a consequence, their thinning may reflect a cascade from optic neuritis or an overall process of neurodegeneration[277].

Grey matter damage. Improvements in MRI techniques have enabled the measurement of grey matter pathology in vivo, including focal lesions, tissue loss and neuronal abnormalities. Even though correlative MRI pathological studies have demonstrated that only a small part of grey matter lesions is detected by current technologies[278], this seems to be sufficient to provide clinically relevant information. Focal lesions in the cortex are a distinctive feature in patients with MS, and the presence of at least one cortical lesion (FIG. 6) identifies patients with CIS at higher risk of developing MS[55]. Cortical lesions are highly specific for MS, as they have not been detected in other neurological disorders that can mimic MS so far, such as NMOSD[279] or migraine[280]. The presence of both cortical lesions and grey matter atrophy are more pronounced in patients with progressive MS and correlates with more severe disability[281]. In addition, the quantification of cortical lesions and grey matter atrophy enables the long-term prognostication of worsening of disability and cognitive dysfunction[212,282].

Evaluation of grey matter damage might also be useful for assessing the effects of specific treatments[283]. However, the standardization of acquisition and analysis procedures for the assessment of grey matter involvement, particularly in a longitudinal setting, is lacking. Further studies with large sample sizes and a longitudinal setting are necessary to define reliable approaches for quantification of grey matter damage and to establish normative values for grey matter volume changes in both healthy individuals and patients with MS[282].

Optimizing treatment decisions at an individual level

The greater complexity of MS treatment scenarios owing to the greater availability of DMTs has increased uncertainty in daily treatment decisions both in terms of the initial type of treatment and when to switch between different treatments. In real-world practice, it is often difficult to apply criteria derived from RCTs, which are typically run in standardized and controlled situations. Also, RCTs typically have a short duration, and the long-term effectiveness and safety of a given treatment cannot be assessed. The growing number of observational real-world studies is providing insights into predictors of MS treatment response, the comparative effectiveness of DMTs and long-term treatment effectiveness, therefore assisting in decision-making for individuals in daily clinical practice[284]. For example, an analysis of data entered in the MSBase, a global MS cohort study including thousands of patients with MS[285], has enabled the identification of demographic, clinical and paraclinical information that is helpful in predicting individual response to DMTs at the time of their commencement.

Regarding the monitoring of disease activity after starting a given treatment, it is now accepted that disease activity should be judged using combined models based on the integration of clinical and paraclinical information. No evidence of disease activity (NEDA), a combined measure including MRI data (such as no new T2-hyperintense or gadolinium-enhancing lesions) and clinical measures (the absence of relapses or disability progression), has been proposed for a more comprehensive evaluation of treatment effects[286]. NEDA has been assessed in clinical trials and observational studies[287,288], which have suggested that, even though a substantial proportion of patients maintained NEDA status during the first 1–2 years of treatment, only a few patients sustained NEDA status over several years with newer DMTs[289,290].

The current definition of NEDA (NEDA-3) is strongly weighted towards inflammatory activity, whereas other relevant aspects of the disease, such as neurodegeneration, cognitive impairment, fatigue and QOL, are not considered[291,292]. As brain atrophy occurs faster in patients with MS than in healthy individuals and this atrophy is clinically relevant[213], it has been suggested that atrophy evaluation (NEDA-4) should also be included in the monitoring of patients with MS[293]. The integration of neuropsychological and blood or spinal fluid NfL levels, or patient-reported outcomes and QOL measures, has also been proposed[287]. However, before including any of these measures in clinical practice, it is crucial to define the cut-off values that separate normal physiological changes from pathological changes[213,287].

Tackling comorbidities

The comorbidities of patients with MS have only recently begun to receive attention[294,295]. As is the case for many chronic diseases, physical and mental comorbidities as well as adverse lifestyle or health factors, such as smoking and obesity, are common and can affect the course of disease by modulating biological pathways that promote inflammation and immune responses, influencing disability, the diagnostic delay between symptom onset and diagnosis, cognition, mortality and QOL[295]. Additionally, the presence of such comorbidities is likely to affect treatment decisions and treatment response.

A perceived knowledge gap in the estimates of the incidence and effects of such comorbidities is apparent, and recommendations have been formulated by experts to address this gap[296]. The prevalence of physical comorbidities in patients with MS, including diabetes mellitus, hypertension, hyperlipidaemia, ischaemic heart disease, fibromyalgia and irritable bowel syndrome, increases with age, whereas a similar increase is not seen for psychiatric comorbidities (for example, depression and anxiety)[295]. Patients with comorbidities are usually excluded from clinical trials[297], thereby limiting understanding of the treatment effects (and adverse effects) in patients with MS who have concomitant comorbidities. A retrospective population study found a reduced use of DMTs with increasing number of comorbidities[298].

Notably, some of the measures that are usually applied to monitor MS can be modified by the presence of comorbidities. For example, this is the case for the extent of T2-hyperintense lesions, whose number and burden are influenced by hypertension and vascular disease, or brain atrophy, which is accelerated by smoking. Consequently, incorporating the assessment, prevention and management of comorbidities into the care of patients with MS is required[213].

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Author contributions

Introduction (M.F.); Epidemiology (S.V.); Mechanisms/pathophysiology (P.P. and A.B.-O.); Diagnosis, screening and prevention (P.P. and M.A.R.); Management (F.P.); Quality of life (A.S.); Outlook (all authors); Overview of Primer (M.F.).

Competing interests

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