Multiple sclerosis

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Multiple sclerosis continues to be a challenging and disabling condition but there is now greater understanding of the underlying genetic and environmental factors that drive the condition, including low vitamin D levels, cigarette smoking, and obesity. Early and accurate diagnosis is crucial and is supported by diagnostic criteria, incorporating imaging and spinal fluid abnormalities for those presenting with a clinically isolated syndrome. Importantly, there is an extensive therapeutic armamentarium, both oral and by infusion, for those with the relapsing remitting form of the disease. Careful consideration is required when choosing the correct treatment, balancing the side-effect profile with efficacy and escalating as clinically appropriate. This move towards more personalised medicine is supported by a clinical guideline published in 2018. Finally, a comprehensive management programme is strongly recommended for all patients with multiple sclerosis, enhancing health-related quality of life through advocating wellness, addressing aggravating factors, and managing comorbidities. The greatest remaining challenge for multiple sclerosis is the development of treatments incorporating neuroprotection and remyelination to treat and ultimately prevent the disabling, progressive forms of the condition.

Introduction

Multiple sclerosis is a complex condition but some of the fundamental questions relating to causation and susceptibility have been answered. It predominantly affects individuals in their early adult life, and has a huge impact functionally, financially, and on quality of life. Costs are considerable and rise with increasing disability.[1]

This Seminar will focus on major developments in our understanding of the development and management of multiple sclerosis. There is an improved understanding of the genetic (eg, HLA DRB1*15:01), environmental (eg, vitamin D), and lifestyle (eg, cigarette smoking) factors that contribute to the development of the disease, with environmental, rather than genetic, factors playing a bigger part in susceptibility. Both the innate and adaptive immune systems, with their effector cells (eg, microglia, activated macrophages, B and T lymphocytes), are known to influence the pathogenesis of multiple sclerosis, and the discovery that B cells are major contributors to the disease has led to new treatment targets.

The increase in the number of disease-modifying treatments available for the most common form of the condition, relapsing remitting multiple sclerosis, is another major development;[2] however, this advance is in contrast to the paucity of effective treatments for the progressive forms of the condition. Treatment guidelines that place the patient at the centre of the decision-making process have been developed to improve management of multiple sclerosis. The emergence of effective treatments has created an impetus to diagnose as early as possible. Diagnostic criteria in patients with clinically isolated syndrome have been revised to put more emphasis on exclusion of disorders that mimic multiple sclerosis, and the introduction of cerebrospinal fluid (CSF) findings. The use of disease-modifying treatments might have contributed to the improved longevity in multiple sclerosis,[3] and reduced rates of worsening and evolution to secondary progressive multiple sclerosis when compared with early natural history cohorts.[4] The plethora of new agents poses challenges in selecting the right drug for the right person at the right time, and so current research aims to provide the evidence and tools for personalised medicine in multiple sclerosis.[5] Finally, when considering the overall management of the disease, there is increasing awareness of the effect of age on the pathophysiology and clinical manifestations of the condition.[6] The aim of this Seminar is to provide clinicians and researchers with a comprehensive review of the latest developments and discoveries in multiple sclerosis research, by emphasising those that have an implication for care and an impact on patient management and treatment.

Search strategy and selection criteria

Resource publications for this Seminar were identified through searches of PubMed and MEDLINE, and references from selected articles, using "multiple sclerosis" as search terms relevant to each, and a filter for publication date (up to Dec 31, 2017). Studies chosen for this Seminar describe the most recent advances in research, were published in high-impact, peer-reviewed journals, and showed results based on satisfactory numbers of study participants, covering a relevant population. Only articles in English were chosen.

Epidemiology

With a prevalence of 50–300 per 100 000 people, about 2·3 million people are estimated to live with multiple sclerosis globally (figure 1),[7] although this is likely to be an underestimate given the relative lack of data from large populations including India and China. The global distribution of multiple sclerosis generally increases with increasing distance from the equator, although there are exceptions.[7] In addition, while the disease is common in regions populated by people from northern Europe, this effect is modified according to where these individuals live in early life. Migration studies since the 1970s[8] indicate that migration from low-risk to high-risk regions in childhood is associated with a low risk of developing multiple sclerosis and vice versa. However, the precise

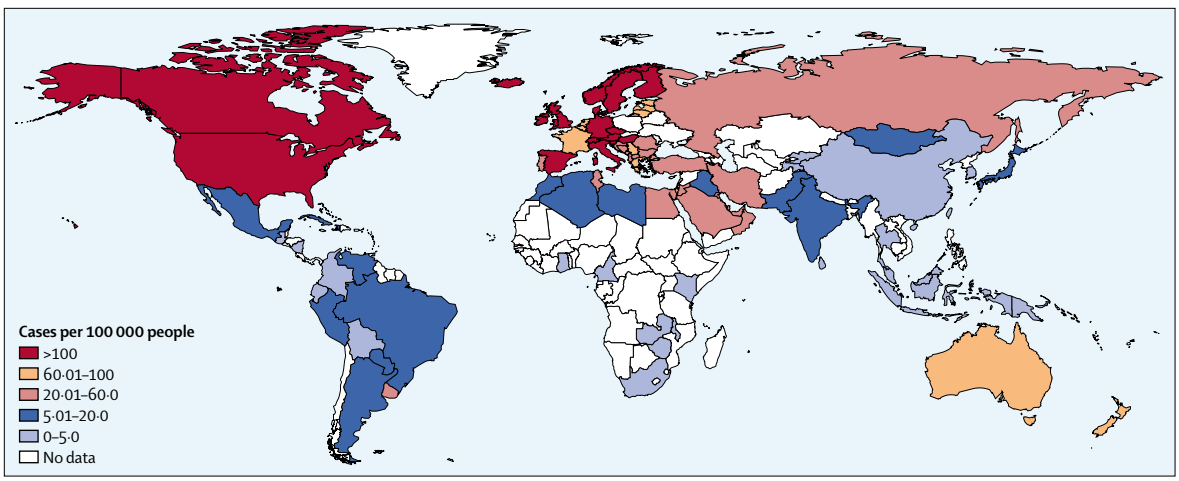

Figure 1: **Global prevalence of multiple sclerosis**
Source: Reproduced with permission from Atlas of MS 2013, MS International Federation.

For the **Atlas of MS** see http://www.atlasofms.org

cutoff is less clear and the risk of exposure could span a wider range than was initially thought.[9] Minorities in the USA, such as Hispanic Americans and black Americans, experience faster disease progression than do white Americans.[10]

The female to male sex ratio has increased markedly because of increased incidence of multiple sclerosis in women.[11] Most patients present in early adult life but there is increased awareness of presentation in childhood.[12] Most, but not all, patients presenting in later life (over the age of 60 years) are progressive from onset.[13]

Comorbidities are frequent in multiple sclerosis and have an adverse influence on outcome and adherence to treatment[14] and, therefore, should be recognised and managed appropriately.[15]

Causes

Environmental, genetic, and epigenetic factors have a causal role in multiple sclerosis and potentially interact with modifiable risk factors.[16] Current research is focused on the identification of new risk factors and the extent to which they contribute to multiple sclerosis aetiology.

Environmental risk factors

Environmental risk factors such as vitamin D deficiency (related to reduced exposure to sunlight and decreased natural production from sun exposure in ethnic groups with dark skin), diet, obesity in early life, and cigarette smoking are known to play a part in the development of multiple sclerosis.[17] Chief among these are low vitamin D levels and cigarette smoking.[18–21] Therefore, correction of vitamin D insufficiency could be important for prevention of multiple sclerosis, although there is no evidence of an association between neonatal vitamin D levels and disease risk.[22] The risk associated with cigarette smoking increases with duration and intensity, and is stronger in men than in women. Obesity in early life is associated with a twofold increase in risk in men and women, which could be due, in part, to lower vitamin D levels in obese individuals. In addition, exposure to infectious agents might affect the risk of developing conditions involving the immune system such as multiple sclerosis; the hygiene hypothesis postulates that multiple infectious exposures in early childhood, as is often the case in tropical and subtropical areas, reduces the risk of developing autoimmune and allergic diseases.[23] Conversely, the development of multiple sclerosis can also be associated with specific infections; for example, late infection as a young adult with Epstein-Barr virus increases the risk of subsequently developing the disease (relative risk 3·0).[24]

Genetics

The increased heritability within families, and the directly proportional decrease in risk with degree of relatedness, provide evidence that genetic factors have a prominent role in the development of multiple sclerosis. The HLA region of chromosome 6 has been implicated in the development of hundreds of human diseases, including most autoimmune diseases.[25] In multiple sclerosis, an association with the serotype DR2 (now preferentially covered by HLA-DR15 and HLA-DR16 serotype group) has been known since the 1970s[26] and consistently replicated. Carriers of the HLA DRB1*15:01 allele are about three times more likely to develop multiple sclerosis than are non-carriers.[27] Additional HLA and non-HLA risk and protective alleles have been reported.[27] A genome-wide association study (GWAS) from 2017,[28] identified 31 independent associations within the extended MHC region, including some within class I genes and the non-classical HLA region. The HLA locus accounts for 20–30% of the genetic susceptibility in multiple sclerosis,[29] as estimated from the values of HLA allele sharing by descent in sibships.

In addition, GWAS have led to the identification of genetic variants with minor effects including genes in *IL2RA* and *IL7RA*, the first two non-HLA associations.[30]

Subsequent GWAS and a meta-analysis[31] identified another dozen associations including the regions of *CD58*, *TYK2*, *STAT3*, and *TNFRSF1A*. Overall, GWAS data support the long-held idea that susceptibility to multiple sclerosis is affected by the action of common (ie, those with a risk allele frequency >5%) sequence allelic variants in multiple genes.[32] Meta-analysis has now brought the total number of associations to more than 200.[28] The sum of each multiple sclerosis-associated allele (weighted by its effect size) is defined as multiple sclerosis genetic burden and can be calculated for each individual.[33,34] A similar measure has also been computed to quantify risk at the HLA region; a high HLA-genetic burden is associated with a few demographic (young age at onset) and imaging characteristics,[35] although findings of associations with clinical and MRI measures are not always in agreement.[36] These data provide the genetic architecture of the disease, and suggest a key role of the immune system. In addition, environmental factors have been shown to interact with genetic risk loci (eg, smoking and HLA), therefore increasing the risk of developing multiple sclerosis.[16]

The next generation of genetic studies will probably focus on the identification of determinants of disease progression and on how individual information can be used to personalise treatment and follow-up, to provide more comprehensive and integrative care for patients with multiple sclerosis.

From immune responses to pathology

Genetic and pathological studies[37,38] point towards the adaptive immune system, which consists of T cells and B cells, as a key player in the pathogenesis of multiple sclerosis. Inflammation in multiple sclerosis only affects the central nervous system (CNS), strongly suggesting that T cells and B cells are selectively recruited by specific target antigens (probably autoantigens) that are only expressed in the CNS. Although several candidate antigens have been proposed, none has been confirmed.[39,40]

Why immune responses are initiated against CNS antigens and maintained in multiple sclerosis is unclear. Generation of specific T cell and B cell responses, which involves the expansion of large numbers of antigen-specific lymphocytes from few precursor cells in the lymph node, requires professional antigen presenting cells (APCs), such as dendritic cells. Autoreactive lymphocytes, which harbour the potential to induce CNS autoimmunity, are part of the normal lymphocyte repertoire. The pathogenic immune responses to CNS autoantigens might be initiated[41] in two ways: first, the CNS intrinsic model hypothesises that the initial event takes place in the CNS, which leads to the release of CNS antigens to the periphery (either by drainage to the lymph nodes or active carriage by APCs). In the context of a proinflammatory environment, an autoimmune response is generated that eventually targets the CNS. Second, by contrast, the CNS extrinsic model hypothesises that the initial event takes place outside the CNS (eg, in the context of a systemic infection) and leads to an aberrant immune response against the CNS. Several mechanisms (eg, reactivity between microbial antigens and autoantigens, or priming autoimmune responses by a strong inflammatory stimulus) might account for the initiation of autoimmune responses. Both scenarios will flow into a detrimental circle of events: tissue damage leads to release of antigens to the periphery, which primes new immune responses in the lymphoid tissue, followed by the invasion of lymphocytes into the CNS.

The innate immune system, mainly consisting of phagocytic cells, also has an important role in the initiation and progression of multiple sclerosis. Macrophages promote the proinflammatory response of T cells and B cells which causes tissue damage. Early microglial activation might be one of the initial events in the development of multiple sclerosis lesions. When activated, microglial cells could contribute to disease pathology through several possible mechanisms, including secretion of proinflammatory cytokines, chemokines, free radicals, and increased release of glutamate.

During the progressive phase of the disease, the contribution of the peripheral immune system decreases and immune responses are thought to be confined to the CNS compartment. CNS pathology changes from focal to diffuse white matter injury associated with microglia activation and diffuse lymphocytic and monocytic infiltrates,[42] and increasing cortical involvement, which is thought to be associated with lymphoid-like follicles in the meninges.[43] In progressive multiple sclerosis, diffuse tissue injury is also caused by mechanisms other than the compartmentalised immune response, including degeneration of chronically demyelinated axons,[44] damage or dysfunction of astrocytes,[45,46] and microglia activation.[47]

The hallmarks of multiple sclerosis pathology are axonal or neuronal loss, demyelination, and astrocytic gliosis. Among these neuropathological characteristics, axonal or neuronal loss (referred to as neurodegeneration) is particularly relevant because it is the main underlying mechanism of permanent clinical disability. Axonal loss occurs acutely in new inflammatory lesions, but also more slowly over time in chronically demyelinated lesions. The mechanisms that lead to axonal loss are becoming clearer. Some, such as the neuronal energy deficit linked to mitochondrial dysfunction, might occur in both the acute and chronic phases, while others, such as the loss of myelin trophic support, which leads to progressive swelling and cytoskeletal disorganisation of chronically demyelinated axons, could be unique to the chronic phase.

Pathogenic events, including inflammation, demyelination, axonal loss, and gliosis, can be studied in vivo using both conventional and advanced imaging techniques (figure 2). As mentioned previously, the consequence of

the cascade of pathogenic events is neuronal and axonal loss, which is observed in vivo as reduced brain volume (or brain atrophy) by volumetric MRI. Whole brain atrophy in multiple sclerosis occurs at rates of 0·5–1·5% per year, and faster rates could be seen in the progressive phases of the disease and in the deep grey matter structures.[48] Despite the mismatch between the scale of the microscopic event and the image resolution, technical advances have led to the identification of structural, metabolic, and molecular imaging biomarkers[49,50] that reflect underlying pathological abnormalities, correlate with clinical changes, and can be used in clinical trials to monitor the efficacy of treatments.

From pathology to clinical features

Early multiple sclerosis is usually characterised by acute episodes of neurological deficits known as relapses, that depend on both the location of the CNS region affected by the acute inflammatory demyelinating lesions and the extent of the inflammatory process. For example, the development of an acute inflammatory lesion in the optic nerve leads to optic neuritis, which is characterised by visual impairment and pain on eye movements. Here we use optic neuritis as a model to illustrate the mechanisms that link pathological abnormalities to clinical symptoms.

Proinflammatory cytokines and nitric oxide in the optic nerve lesion, together with demyelination, are considered to be the major determinants of the complete or intermittent conduction block that is responsible for visual loss typical of optic neuritis.[51] Demyelinated axons can become hyperexcitable and spontaneously generate impulses that translate into positive symptoms, such as the perception of flashing light or other phosphenes upon eye movements.

Longitudinal studies done in patients following an episode of optic neuritis have shown that acute and persistent optic nerve demyelination is associated with increased vulnerability of axons. This process predicts the development of axonal loss after 6 months, as reflected by MRI and optic coherence tomography.[52] These findings support the hypothesis that a lack of myelin-derived trophic support[53] and mitochondrial dysfunction[54] contribute to the degeneration of chronically demyelinated axons responsible for irreversible disability in the progressive phase of the disease.[55]

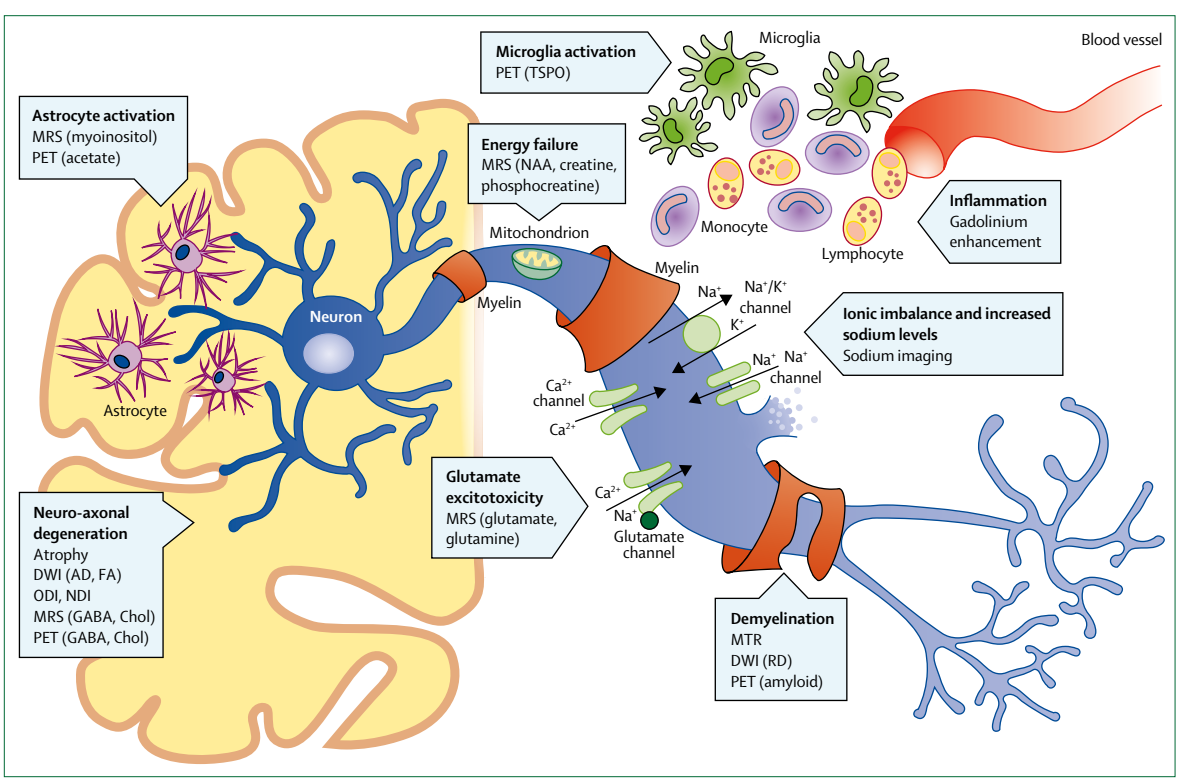

Figure 2: **Pathogenic mechanisms of multiple sclerosis and their imaging targets**
Inflammation is generally studied by counting gadolinium-enhancing areas on T1-weighted images. Neuroaxonal degeneration is measured by determining whole brain atrophy and compartment-specific atrophy (eg, white, grey, and deep grey matter). Demyelination is quantified with MTR. Microstructural changes involving neurons and axons are measured with DWI, ODI, and NDI. Specific molecular PET and metabolic MRS targets for astrocyte activation, neuroaxonal degeneration, microglia activation, energy failure, glutamate excitotoxicity, and demyelination have been developed. Sodium imaging quantifies intracellular and extracellular sodium content. MRS=magnetic resonance spectroscopy. PET=positron emission tomography. DWI=diffusion-weighted imaging. AD=axial diffusivity. FA=fractional anisotropy. ODI=orientation dispersion index. NDI=neurite density index. GABA=γ-aminobutyric acid. Chol=choline-containing compounds. TSPO=translocator protein. NAA=*N*-Acetyl-aspartate. MTR=magnetisation transfer imaging. RD=radial diffusivity.

Tissue repair, plasticity, and clinical recovery

Clinical deficits caused by acute inflammatory demyelination could be reversible via restoration of nerve conduction. The restored nerve conduction is more continuous than saltatory, and is achieved because the demyelinated axonal membrane shows several changes following demyelination, such as an increase in sodium channels. In addition, remyelination leads to new myelinated internodes, although these are shorter and thinner than normal.[56] These changes lead to increased energy demand, which in turn might induce changes in the size and number of mitochondria.[54]

Particular attention has been paid to the spontaneous phenomenon of remyelination, which is overall sparse in chronically demyelinated multiple sclerosis lesions, despite the presence of axons and oligodendrocyte precursors in some of them.[56] Remyelination could promote both axonal survival and restoration of nerve conduction.[53]

In addition to these structural changes, the recovery of clinical symptoms could also be secondary to cortical plasticity,[57] which consists of a reorganisation of the functional activation of cortical regions to maintain clinical function. In the case of optic neuritis, early neuroplasticity in higher visual areas is an important determinant of recovery, independent of tissue damage in the anterior or posterior visual pathway.[58] At the synaptic level, long-term potentiation of synaptic transmission might functionally compensate for neuronal loss.[59]

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands‡
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands‡

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. CSF=cerebrospinal fluid. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. There must be no better explanation for the clinical presentation and objective evidence must be present to support a diagnosis of multiple sclerosis. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure. Reproduced with permission from Elsevier.[62]

Table 1: **The 2017 McDonald Criteria for diagnosis of MS in patients with an attack at onset**

Diagnosis

The diagnosis of multiple sclerosis is based on the integration of clinical, imaging, and laboratory findings. Clinical expertise is necessary to demonstrate evidence of dissemination in time and space and, importantly, to exclude other neurological conditions. MRI can provide this evidence and assist in excluding other conditions, allowing earlier diagnosis with increased certainty with successive versions of the diagnostic criteria.[60] The diagnostic criteria, known as the McDonald Criteria,[61,62] have evolved as technology has improved to refine definitions, become simpler, and more accessible and applicable to a larger proportion of the population while maintaining specificity and sensitivity.[61,62] The 2017 revision[62] implemented changes that were evidence-based and arrived at by consensus and reinstated the role of abnormalities of the CSF (table 1). Standardised MRI protocols for the evaluation of patients with suspected or clinically definite multiple sclerosis have been suggested for baseline and follow-up scans, and for brain and spinal cord imaging.[63]

The diagnostic criteria should be applied to diagnose patients who present with symptoms typical of multiple sclerosis and in whom the disease is suspected, and not to differentiate multiple sclerosis from other neurological disorders. Inappropriate application of diagnostic criteria to patients with symptoms atypical for demyelination is the main contributor to misdiagnosis.[64] A combination of MRI and serological testing, in association with clinical features and history, should be used to navigate through the differential diagnosis of idiopathic inflammatory disorders, including neuromyelitis optica spectrum disorder,[65] and other relapsing disorders that can mimic multiple sclerosis (table 2).

Phenotype

The overwhelming majority of patients who develop multiple sclerosis begin with a single episode, termed a clinically isolated syndrome, that involves the optic nerve, brainstem, or spinal cord, and resolves over time. The concept of a clinically isolated syndrome is now well established[66] and is being incorporated into the WHO International Classification of Diseases, version 11. Most patients who have experienced a clinically isolated syndrome and have an abnormal MRI scan will have a second episode (or relapse), which marks the onset of clinically definite multiple sclerosis. Patients who have at least two relapses are described as having relapsing remitting multiple sclerosis. Studies[67] have reported that the percentage of patients with this form of the disease who develop progressive disability, with or without superimposed relapses (described as secondary-progressive multiple sclerosis) could be between 15%[4] and 30% over a

long-term follow-up. These percentages are lower than previously reported, and could reflect changes in the natural history of the disease and the effect of disease-modifying treatments. About 15% of patients develop progressive onset multiple sclerosis from the outset, described as primary progressive multiple sclerosis.[68] There has been a focus on the earliest stages of the condition. Patients with incidental MRI findings consistent with multiple sclerosis, known as radiologically isolated syndrome,[69] have been described and indicators for patients more likely to demonstrate clinical symptoms of the disease and further MRI abnormalities over time are emerging.[70] In addition, the development of primary progressive multiple sclerosis in patients with radiologically isolated syndrome is becoming better understood.[71] Finally, there has been further exploration of the two forms of progressive multiple sclerosis (primary progressive and secondary progressive), which have been shown to be more similar than different—ie, the differences between them are relative rather than absolute.[72]

The standardised definitions of the clinical courses of multiple sclerosis (relapsing-remitting, primary progressive, and secondary progressive) were proposed in 1996;[73] however, the definitions are purely descriptive and do not provide information about the underlying pathophysiology of the disease. This terminology has therefore evolved to describe the presence or absence of activity, including relapses and progression and, on MRI, new lesions indicating inflammatory activity, and atrophy suggesting ongoing neurodegeneration.[74] Linking phenotype firmly to pathophysiology is crucial for the effective selection of disease-modifying treatments.[75]

	Neurological features	MRI features	Blood test and CSF findings
Acute disseminated encephalomyelitis (typically found in children)	Similar to multiple sclerosis symptoms but encephalopathy is typical; also multifocal symptoms	Large spectrum from small punctate lesions to tumefactive lesions with mass effect, in the supratentorial or infratentorial white matter, bilateral, and asymmetrical; involvement of cerebral cortex, deep grey matter, brainstem and spinal cord; enhancement	CSF pleocytosis; serum antibody to myelin oligodendrocyte glycoprotein
Neuromyelitis optica spectrum disorder	Concomitant or concurrent (severe) optic neuritis and transverse myelitis; nausea and vomiting; paroxysmal tonic spasms	Longitudinally extensive spinal cord lesion (>3 vertebral segments); optic chiasmal involvement; pencil-thin ependymal enhancement and cloud-like enhancement	Serum antibody to aquaporin-4 and to myelin oligodendrocyte glycoprotein; sometimes mild pleocytosis; CSF oligoclonal bands infrequent
Neurosarcoidosis	Cranial nerve involvement (primarily facial and optic nerve); headache; raised intracranial pressure; meningitis; seizures; myelopathy	Meningeal enhancement with pituitary, hypothalamic and cranial nerve involvement; brain white matter lesions; simultaneous enhancement of all lesions	Raised serum and CSF ACE (not sensitive or specific for sarcoidosis); CSF oligoclonal bands sometimes present
CNS vasculitis	Confusion, headache, personality change; seizures; stroke-like symptoms	Ischaemic, multiple lesions; predominance of lesions at the cortico-subcortical junction; intracranial haemorrhage; meningeal enhancement; simultaneous enhancement of all lesions; microbleeds	Serum anti-neutrophil cytoplasmic antibodies; CSF oligoclonal bands sometimes present
Susac's syndrome	Visual loss; sensorineural hearing loss; encephalopathy; headache; memory loss; behavioural disturbances	Focal and small lesions in supratentorial and infratentorial regions (both white matter and grey matter); involvement of corpus callosum (snowball lesions); leptomeningeal enhancement	CSF oligoclonal bands usually absent
Hypoxic-ischaemic vasculopathies (in particular small vessel disorder)	Stroke events; cognitive decline; focal neurological signs; gait disturbance	Punctuate and peripheral white matter lesions, sparing U-fibres; symmetrical and confluent, periventricular lesions; lacunar infarcts; involvement of central transverse fibres in the pons; microbleeds	Serum testing for vascular risk factors (diabetes, hypercholesterolaemia); CSF oligoclonal bands absent
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)	Migraine; stroke events; psychiatric problems and dementia	Temporal pole lesions; external capsule and U-fibre lesions; microbleeds	CSF oligoclonal bands absent; testing for *NOTCH3* gene mutation
Connective tissue disorders (systemic lupus erythematosus, Sjögren syndrome, antiphospholipid antibodies syndrome)	Optic nerve, brain, and spinal cord involvement; neuropsychiatric symptoms; seizures; ischaemic episodes	Brain infarcts and haemorrhage; basal ganglia lesions; punctate (subcortical) lesions; spinal cord lesions; cerebral venous sinus thrombosis; parotid gland involvement in Sjögren syndrome	Serum antinuclear antibody; extractable nuclear antigens (in particular, anti SS-A(Ro) and SS-B(La) antibodies for Sjögren syndrome, and anti-Sm for systemic lupus erythematosus); CSF oligoclonal bands usually absent
Neuro-Behçet's disease	Brainstem syndrome; myelopathy; meningoencephalitis	Large brainstem lesions; basal ganglia, subcortical white matter, and spinal cord lesions; gadolinium enhancement; cerebral venous sinus thrombosis	HLA-B5; CSF pleocytosis; CSF oligoclonal bands usually absent
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)	Cranial nerve dysfunction and long tracts signs; symptoms referable to brainstem or cerebellar dysfunction; spinal cord syndrome; cognitive dysfunction	Multiple punctate, patchy, and linear regions of gadolinium enhancement relatively confined to the pons; lesions also involving cerebellum, basal ganglia, supratentorial white matter, brainstem, and spinal cord	CSF oligoclonal bands sometimes present
Fabry disease	Stroke events; vertigo	Posterior infarcts; multiple white matter lesions with pulvinar involvement (T1 hypointense lesions)	Reduced activity of the GLA enzyme; analysis of *GLA* gene

Infectious diseases are not included in this table but should be considered, especially in cases of atypical demyelinating lesions. CSF=cerebrospinal fluid. ACE=angiotensin-converting enzyme. GLA=α galactosidase A.

Table 2: **Differential diagnosis of multiple sclerosis: clinical, MRI, and serological findings of the main disorders that can resemble relapsing-remitting disease**

	Generic name	Mechanisms of action	Efficacy on relapses*	Route of administration and dose	Common side-effects	Less common but serious side-effects	Monitoring in clinical practice	
							Before	During
Avonex†	Interferon β-1a	Reduces antigen presentation and T cell proliferation, alters cytokine expression, restores suppressor function	32%	Intramuscular, once a week	Influenza-like symptoms; injection site reactions; increased liver enzymes	Very rare liver toxicity	Blood test (blood cell counts and liver function)	Blood test (blood cell counts and liver function)
Rebif†	Interferon β-1a	Reduces antigen presentation and T cell proliferation, alters cytokine expression, restores suppressor function	33%	Subcutaneous, three times a week	Influenza-like symptoms; injection site reactions; increased liver enzymes	Rare liver toxicity	Blood test (blood cell counts and liver function)	Blood test (blood cell counts and liver function)
Betaferon†	Interferon β-1b	Reduces antigen presentation and T cell proliferation, alters cytokine expression, restores suppressor function	34%	Subcutaneous, every other day	Influenza-like symptoms; injection site reactions; increased liver enzymes	Very rare liver toxicity	Blood test (blood cell counts and liver function)	Blood test (blood cell counts and liver function)
Extavia†	Interferon β-1b	Reduces antigen presentation and T cell proliferation, alters cytokine expression, restores suppressor function	34%	Subcutaneous, every other day	Influenza-like symptoms; injection site reactions; increased liver enzymes	Very rare liver toxicity	Blood test (blood cell counts and liver function)	Blood test (blood cell counts and liver function)
Plegridy†	Peginterferon β-1a	Reduces antigen presentation and T cell proliferation, alters cytokine expression, restores suppressor function	30%	Intramuscular, once every 2 weeks	Influenza-like symptoms; injection site reactions; increased liver enzymes	Very rare liver toxicity	Blood test (blood cell counts and liver function)	Blood test (blood cell counts and liver function)
Copaxone†	Glatiramer acetate	Alters T cell differentiation inducing proliferation of anti-inflammatory lymphocytes	29%	Subcutaneous, every day or two preparations three times a week	Injection-site reactions; lipoatrophy; post-injection general reaction	None	None	None
Tecfidera†	Dimethyl fumarate	Reduces the release of inflammatory cytokines and activates antioxidant pathways	51%	Oral, twice a day	Flushing; gastrointestinal symptoms; lymphopenia	PML (1:50 000 [as of February, 2018])	Urine and blood test (blood cell counts, liver and kidney function), recent MRI scan	Urine and blood test (blood cell counts, liver and kidney function), MRI scan
Aubagio†	Teriflunomide	Active metabolite of leflunomide, which inhibits the proliferation of autoreactive B and T cells and induces a shift to an anti-inflammatory profile	35%	Oral, once a day	Nausea; diarrhoea; hair thinning; skin rash	None, but teratogenic	Blood test (blood cell counts and liver function)	Blood test (liver function)
Gilenya	Fingolimod	Functional antagonist of sphingosine 1-phosphate receptors, which inhibits egress of lymphocytes from lymph nodes and their recirculation	52%	Oral, once a day	Bradyarrhythmia, heart block; increased risk of infections; lymphopenia; liver dysfunction	PML (1:12 000 [as of February, 2018]); macular oedema; VZV; herpes encephalitis	Blood test (blood cell counts and liver function), blood pressure and pulse, VZV antibody test, eye and skin examinations, recent MRI scan	Blood test (blood cell counts and liver function), blood pressure and pulse, eye and skin examinations, MRI scan
Tysabri‡	Natalizumab	Humanised monoclonal antibody acting as α-4 integrin blocker, which prevents lymphocytes from entering the CNS across the blood–brain barrier	68%	Intravenous, once every 4 weeks in hospital clinic	Dizziness; nausea; itchy skin; rash; shivering; increased risk of infection	PML (4·19 per 1000 patients [as of Nov 30, 2017]); hypersensitivity reactions	Urine and blood test (blood cell counts, liver and kidney function), JCV antibody test (including index value), recent MRI scan	Urine and blood test (blood cell counts, liver and kidney function), JCV antibody test (including index value), MRI scan
Mavenclad	Cladribine	Synthetic deoxyadenosine analogue, which depletes B and T cells	58%	Oral, two courses 12 months apart	Lymphopenia; increased risk of infection; headache	Possibly teratogenic; pulmonary tuberculosis; malignancy; PML (in hairy cell leukaemia at a different dose)	Blood test (blood cell counts and liver function), tuberculosis screening, HIV screening, hepatitis B screening, VZV antibody test, recent MRI scan.	Blood test (blood cell counts)

(Table 3 continues on next page)

	Generic name	Mechanisms of action	Efficacy on relapses*	Route of administration and dose	Common side-effects	Less common but serious side-effects	Monitoring in clinical practice	
							Before	During
(Continued from previous page)								
Lemtrada‡	Alemtuzumab	Humanised monoclonal antibody against the lymphocyte and monocyte surface antigen CD52, which depletes B and T cells	52%§	Intravenous, two courses 12 months apart	Infusion reactions; increased risk of infection; thyroid problems (40%), blood clotting disorder (1:5)	ITP; kidney problems; lysteria encephalitis; other infections (cytomegalovirus, VZV, nocardiosis)	Urine and blood test (blood cell counts, kidney and thyroid function), VZV antibody test, HPV screening, tuberculosis screening, hepatitis screening, recent MRI scan	Urine and blood test (blood cell counts, kidney and thyroid function), MRI scan
Ocrevus‡	Ocrelizumab	Humanised monoclonal antibody against the B cell surface antigen CD20	47%§	Intravenous, four courses 6 months apart	Infusion reactions; chest infection; herpes infection	One case of PML (after natalizumab); increased risk of malignancy	Blood test (blood cell counts), hepatitis B screening	Blood test (blood cell counts and liver function), MRI scan

VZV=varicella zoster virus. JCV=JC virus. ITP=idiopathic thrombocytopenic purpura. HPV=human papillomavirus. PML=Progressive multifocal leukoencephalopathy. *Results of unrelated and independent clinical trials that tested the disease-modifying treatment, either versus placebo, or versus active comparator; therefore, comparisons between efficacy should be viewed with caution. If more than one trial has been done, efficacy is reported as the mean of all trials. †Drugs used as first-line treatments in the escalation strategy. ‡Drugs used in the induction strategy. §Disease-modifying treatment compared with interferon.

Table 3: **Licensed disease-modifying treatments**

Predicting clinical course

Age, sex, spinal cord lesions, and extent of brain abnormalities on MRI are predictors of outcome across all phenotypes of multiple sclerosis. 34% of patients with radiologically isolated syndrome develop a first acute clinical event consistent with clinically isolated syndrome or multiple sclerosis within 5 years;[76] risk factors for developing a first symptomatic event include male sex, younger age at the time of radiologically isolated syndrome diagnosis (<37 years), and presence of spinal cord lesions.[76] Spinal cord lesions and male sex predicted development of primary progressive multiple sclerosis from radiologically isolated syndrome, which had a prevalence of 12% in a large, multicentre cohort.[71] In patients with clinically isolated syndrome, the demographic (female sex and younger age) and topographic characteristics (non-optic neuritis presentations) are low-impact prognostic factors, the presence of oligoclonal bands is a medium-impact prognostic factor, and the presence of ten or more brain lesions on brain MRI is a high-impact prognostic factor for conversion to clinically definite multiple sclerosis and disability.[77] In addition to baseline lesion number, the increase in lesion volume during the first 5 years following a clinically isolated syndrome is associated with greater disability after 20 years.[78] In patients with clinically isolated syndrome and non-spinal presentation, the presence of spinal cord lesions predicts a second clinical event.[79] In primary progressive multiple sclerosis, combining imaging with clinical measures allows early prediction of worsening disability.[80] Receiving a disease-modifying treatment before the second attack is associated with a lower risk of reaching moderate disability.[77] Exposure to disease-modifying treatments provides the most protection against events that worsen disability in paediatric clinically isolated syndrome.[81] Clinical outcomes, including disease activity and neuropsychological tests, suggest a persistent long-term benefit of early treatment at onset of the syndrome.[82] In patients with clinically isolated syndrome on disease-modifying treatments, vitamin D levels predict disease activity and prognosis.[19]

Once multiple sclerosis diagnosis is confirmed, older age, male sex, higher disability at baseline, and greater brain atrophy (mainly in the deep grey matter nuclei) are predictors of disability accumulation.[48,83] Because of several technical issues relating to MRI techniques and methodology, brain atrophy cannot yet be used in clinical practice for diagnosis or prediction of prognosis.[63] Women have a higher relapse rate than do men throughout the course of the disease.[84] Overall, active management of multiple sclerosis with disease-modifying treatments is associated with a favourable clinical outcome, as shown by only 11·3% of patients with the disease transitioning to secondary progressive multiple sclerosis during 10-year follow-up.[4] By contrast, patients with multiple sclerosis who experience relapses when on disease-modifying treatments have a poorer prognosis than do those who do not relapse.[85]

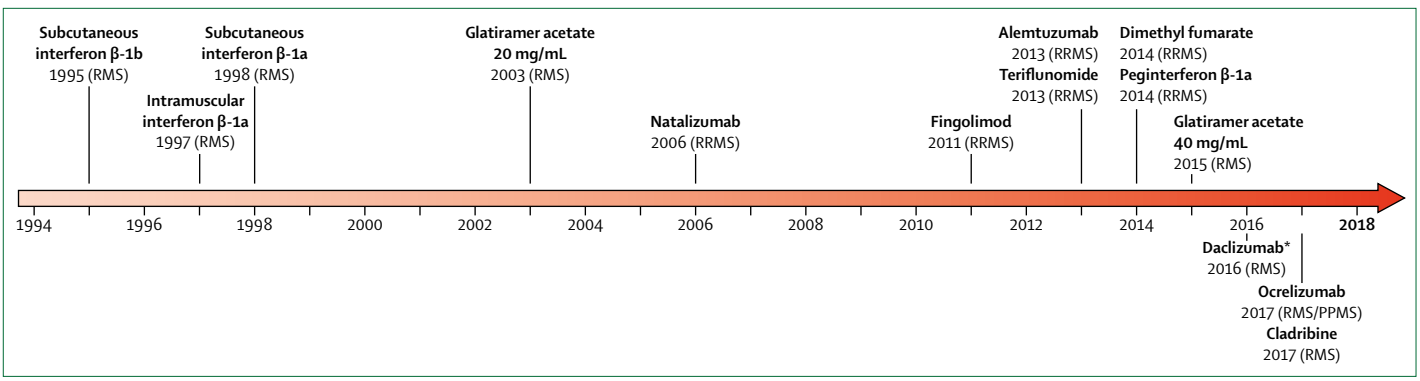

Figure 3: **Disease-modifying treatments for multiple sclerosis and their year of discovery or licensing**
RMS=relapsing multiple sclerosis. RRMS=relapsing remitting multiple sclerosis. PPMS=primary progressive multiple sclerosis. *Daclizumab was withdrawn for use in the treatment of multiple sclerosis in March, 2018, because of reports of adverse events including inflammatory encephalitis and meningoencephalitis.

Treatment

Disease-modifying treatments

Several disease-modifying treatments have been discovered and approved for patients with relapsing remitting multiple sclerosis and clinically isolated syndrome (table 3, figure 3). In general, treatments target neuroinflammation and could have an indirect effect on neurodegeneration; however, their efficacy for reducing the development of brain atrophy in clinical trials has been moderate at best. Only one disease-modifying treatment (ocrelizumab) has been shown to slow progression in patients with primary progressive multiple sclerosis.[86]

Due to a paucity of head-to-head trials, comparisons between the effectiveness of disease-modifying treatments are limited to meta-analyses,[87] observational cohort studies,[88] and independent clinical trials.[89] The high efficacy of new medications has led to the concept of no evidence of disease activity (NEDA) in clinical trials, defined as an absence of relapses, disability progression, and active MRI lesions (both new or enlarged T2 lesions and gadolinium-enhanced lesions).[90] If disease-modifying treatments are prescribed at an early stage of the disease and brain MRI is repeated annually in patients with relapsing remitting multiple sclerosis as recommended,[74] NEDA could become a target in clinical practice. Guidelines for MRI protocols used to monitor patients in clinical practice have recommended the use of brain T2-weighted MRI, which reveals subclinical active (new and enlarging) lesions. If the information obtained with T2 sequences is not sufficient, contrast-enhanced T1-weighted brain MRI is recommended, but not spinal cord imaging, whose relevance for routine follow-up seems limited.[91] Brain volume measures and advanced MRI methods, although useful to understand the course of multiple sclerosis, are not recommended for routine monitoring.[91]

The increasing number of available disease-modifying treatments has made the clinical management of patients more complex. Two therapeutic approaches are available in the clinical setting: escalation strategy and induction strategy. Escalation strategy consists of starting with a first-line treatment (a moderately effective medication) and escalating to a more effective (but potentially less safe and more expensive) medication in cases of continuous relapses. Although this approach is sensible, the timing and nature of the escalation from less to more effective treatments can be challenging in terms of treatment choice. To assist in the selection of a second-line treatment, registry data have shown that the relapse rate was 50% lower after switching from injectable disease-modifying treatments to natalizumab compared with fingolimod, but none of these drugs had a substantial effect on disability worsening.[92] Escalation strategy might not be effective for patients who have a highly active or rapidly evolving disease, and so induction strategy could be more appropriate. This strategy involves starting with a highly effective therapy, such as alemtuzumab or natalizumab, with the aim of obtaining a persistent disease remission (or drug therapy-free remission), or long-term maintenance therapy with a less effective disease-modifying treatment.[93]

The more effective medications for multiple sclerosis have a higher risk of serious adverse events. Alemtuzumab has been associated with severe autoimmune related adverse events and infections (eg, listeria infection). In addition, natalizumab, as well as other disease-modifying treatments,[94,95] are associated with progressive multifocal leukoencephalopathy, caused by reactivation of the JC virus or de-novo infection. The risk of developing such disease in patients on natalizumab is estimated on the basis of the presence of anti-JC virus antibodies, prior use of immuno suppressants, and duration of natalizumab treatment.[96] Quantification of anti-JC virus antibodies has been introduced in the routine risk assessment for patients treated with natalizumab;[97] however, patients who test negative for anti-JC virus antibodies are still at risk of this leukoencephalopathy.[98] Repeated MRI scans can be used for the differential diagnosis of progressive multifocal leukoencephalopathy and multiple sclerosis related lesions, and allow the detection of asymptomatic cases of

leukoencephalopathy, which are associated with a more favourable prognosis.[99] Ocrelizumab, rituximab, dimethyl fumarate, and fingolimod have also been associated with progressive multifocal leukoencephalopathy, although the condition is primarily an issue with natalizumab treatment.[100]

Other pharmacological treatments shown to be effective against relapsing remitting multiple sclerosis and primary progressive multiple sclerosis include B-lymphocyte antigen CD20 depleting monoclonal antibodies, such as rituximab and ocrelizumab. Long-term data on safety and patient convenience of rituximab are available because it has previously been used to treat rheumatoid arthritis and haematological malignancies. Rituximab has since been shown to have an effect on inflammatory MRI lesions and clinical relapses in relapsing remitting multiple sclerosis, and in a subgroup of patients with primary progressive multiple sclerosis.[101] The efficacy of ocrelizumab, a monoclonal antibody targeting the overlapping CD20 epitope as rituximab, was demonstrated in phase 3 trials in relapsing remitting and primary progressive multiple sclerosis,[86,102] and was the first agent to be licensed for treatment of primary progressive multiple sclerosis.

Another medication approved for the treatment of highly active multiple sclerosis is cladribine. Clinical trials[103,104] have shown that cladribine can delay conversion from a first clinical demyelinating event to clinically definite multiple sclerosis and reduce relapse rates, the risk of disability progression, and MRI measures of disease activity in relapsing remitting multiple sclerosis.[105] Meta-analysis[106] did not show an increased cancer risk of cladribine when compared with other treatments; however, longer-term follow-up studies are needed for a more definite assessment of cancer risk associated with cladribine and other disease-modifying treatments. Other agents, such as minocycline, are also moving towards approval.[107]

In patients with relapsing remitting multiple sclerosis who failed to respond to disease-modifying treatments, a sustained remission of active multiple sclerosis and improvements in neurological disability were reported after treatment with high-dose immunosuppressive therapy and autologous haemopoietic stem cell transplantation (aHSCT).[108] Patients most likely to benefit from aHSCT are relatively young (≤50 years), with relatively short disease duration (≤5 years), have active relapsing remitting multiple sclerosis, are accumulating disability but are still able to walk, and have ongoing relapses and MRI activity despite disease-modifying treatments.[109] Long follow-ups and head-to-head comparisons between aHSCT and the most effective disease-modifying treatments are necessary to understand how to position aHSCT for the management of patients with aggressive multiple sclerosis.

There have also been developments in the treatment of secondary progressive multiple sclerosis; a phase 3 trial[110] showed that patients on siponimod had a 21% relative reduction of 3 month confirmed disability progression compared with patients on placebo, and a phase 2 trial[111] showed that simvastatin reduced progression of brain atrophy by 43% over 2 years (a phase 3 trial with this drug is currently ongoing [NCT03387670]). The preliminary findings of a trial[112] using biotin provide further data on treatment options for this form of multiple sclerosis. There are also encouraging results in studies of neuroprotective agents including phenytoin[113] and ibudilast,[114] and reparative agents such as clemastine.[115] In addition, the effort and commitment of the International Progressive MS Alliance[116] augur well for the future treatment of progressive multiple sclerosis.

The large range of treatments available, while welcome, also makes determining treatment plans more complex. To assist and guide decision making, a European guideline based on the Grading of Recommendations Assessment, Development and Evaluation working group[117] has been developed by the European Committee for Treatment and Research in Multiple Sclerosis and the European Academy of Neurology.[118] The guideline has 23 recommendations addressing ten specific clinical questions spanning the entire clinical spectrum of the disease from clinically isolated syndrome to primary progressive multiple sclerosis, and including issues such as treatment escalation and treatment during pregnancy. An American Academy of Neurology practice guideline on the efficacy and safety of disease-modifying treatments in multiple sclerosis and recommendations for future research is expected in 2018.

The dramatic increase in the number of approved disease-modifying treatments has also resulted in inequalities in their costs across countries.[119] Additionally, the introduction of new treatments has tended to raise the costs of older treatments, which are matching the prices of the new competitors, at an unacceptable and potentially unsustainable rate.[119] The availability of disease-modifying treatments tends to be better in high-income countries compared with middle to low-income countries,[7] and accessibility is not homogeneous even in countries where disease-modifying treatments are available through government-funded schemes.[7] The introduction of generic drugs that have equivalent efficacy, safety, and tolerability as branded treatments[120] could lead to less expensive multiple sclerosis therapies.[121]

Treatment of acute relapses

The aim of relapse treatment is to accelerate clinical recovery, as no effect on the long-term prognosis of multiple sclerosis is expected. The major focus of research has been to assess whether oral steroids have the same effect as intravenous steroids to treat acute relapses. The landmark study[122] is a multicentre, double-blind, randomised, controlled, non-inferiority trial, which demonstrated that oral methylprednisolone (500 mg a day for 5 days) was not inferior to intravenous methylprednisolone (1000 mg, once a day for 3 days). These findings could allow more patients to access steroids more rapidly, and in a more comfortable way,

and reduce the costs associated with the management of multiple sclerosis relapses.

In cases of steroid-resistant multiple sclerosis relapse, escalating treatment is indicated;[123] after a second course of high-dose intravenous methylprednisolone, the most common intervention is plasma exchange (PLEX)[124] which leads to a positive response in 72% of patients.[125] Gadolinium enhancing lesions and a relapsing disease are the best predictors of the response to PLEX.[125] PLEX is also useful for patients with methylprednisolone allergy.

Management

Active management, centring on the person with multiple sclerosis, is advocated at all stages of the condition to minimise disease impact, maximise quality of life, and espouse a philosophy of wellness.[126] Addressing the array of multiple sclerosis symptoms is a critical component of management (table 4). While drug treatments are available for some symptoms, the evidence base is poor and well designed trials with adequate numbers are the exception, though studies of fampridine provide a useful model going forward.[137] Many symptoms, such as spasticity, require a multidisciplinary approach and careful treatment selection. Distance health care could allow the assessment of spasticity from remote settings to improve patient management. The value of rehabilitation in cognitive dysfunction is now better appreciated.[138,139] This appreciation is coupled to a better understanding of underlying mechanisms relating to connectivity[140] and more innovative approaches to treatment, such as telerehabilitation.[141] Portable technology, such as wearable movement monitors, could provide objective data outside hospital visits, but appropriate testing and validation are needed before incorporation into clinical practice.

In addition, exercise has a central role in the management of multiple sclerosis following several positive studies in mobility across relapsing remitting multiple sclerosis and progressive multiple sclerosis.[142,143] The effects of exercise on cognition have also been explored[144] but the evidence base remains limited,[145] mechanisms are not well understood, and translation into clinical practice is poor.[146] Prevention of falls, associated with continence issues, previous

	Pharmacological treatment	Non-pharmacological treatment
Spasticity	For generalised spasticity: first-line: baclofen, tizanidine, gabapentin (especially for associated spasms); second-line: dantrolene, diazepam, and clonazepam (at night); third-line: add cannabidiol or tetrahydrocannabinol; and fourth-line: baclofen pump, phenol injections. For focal spasticity: botulin toxin injections, phenol injections	Exercise, physiotherapy, hydrotherapy
Fatigue	Amantadine, modafinil, and fampridine (not approved for multiple sclerosis fatigue)	Exercise, cognitive behavioural therapy, occupational therapy, energy conservation management, and aerobic training
Impaired ambulation	Fampridine (patients with poor initial drug responses might show a response after long-term treatment)[127]	Exercise, physiotherapy
Ataxia and tremor*	Propanolol, clonazepam, levetiracetam, isoniazid (limited by side-effects), botulin toxin injections if focal, limb tremor[128]	Physiotherapy, surgical interventions in selected cases[129]
Bladder dysfunction	For overactive bladder: oxybutynin, tolterodine, solifenacin, desmopressin spray (if nocturia), botulin toxin A intravesical and sphincter injection, cannabinoids,[130] mirabegron, intravesicular capsaicin	Tibial nerve stimulation and sacral neuromodulation (as an alternative to botulinum toxin A, when anti-muscarinic treatment is not effective or tolerated),[131] intermittent self-catheterisation, indwelling and suprapubic catheter (if difficulty in emptying), surgical interventions (if conservative measures fail)
Sexual dysfunction	First-line: sildenafil; second-line: intraurethral alprostadil	Cognitive and behavioural therapy (if underlying depression), pelvic floor physiotherapy (alone or combined with electrostimulation or transcutaneous tibial nerve stimulation; for female sexual dysfunction)[132]
Bowel dysfunction	For constipation: laxatives, rectal stimulants (suppositories, enemas), transanal irrigation	For constipation: assessment by continence adviser or physiotherapist, increase level of exercise, abdominal massage, biofeedback retraining. For incontinence: physiotherapy of pelvic floor, biofeedback retraining, enemas or rectal irrigation (when incontinence is caused by faecal impaction), surgery (sphincteroplasty, sacral nerve stimulation, tibial nerve stimulation, injectable bulking agents, endoscopic heat therapy, artificial sphincter, colostomy)
Depression and emotional lability	Antidepressants (SSRIs or SNRIs), amitriptyline for emotional lability, dextromethorphan and quinidine for pseudobulbar symptoms	Cognitive and behavioural therapy (for depression)
Cognitive impairment	Donepezil, memantine (although not confirmed by a randomised trial)[133]	Cognitive rehabilitation, behavioural interventions, occupational therapy
Visual problems (oscillopsia)	First-line: gabapentin; second-line: memantine	None
Pain	For neuropathic pain: first-line: amitriptyline, duloxetine, gabapentin, pregabalin; second-line: tramadol, capsaicin cream (if localised). For trigeminal neuralgia: first-line: carbamazepine, oxcarbazepine; second-line: lamotrigine, gabapentin, pregabalin, baclofen. For musculoskeletal pain: common analgesia, baclofen (if spasticity)	Physiotherapy, surgical procedures for trigeminal neuralgia

The evidence from this table comes from NICE guidelines,[134] consensus papers,[135] clinical trial data, previous reviews,[136] and our own opinion. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin-norepinephrine reuptake inhibitor. *Pharmacological treatments for ataxia and tremor are rarely successful.

Table 4: **Symptomatic management in multiple sclerosis**

falls, and medication, is another key element of good management.[147] Multidisciplinary, goal-orientated rehabilitation incorporates all these elements but methodologically sound studies are few[148] and the evidence base is poor.[149]

Future directions

The therapeutic developments seen in multiple sclerosis are unequalled in any area of neurology. The priorities now are to get the greatest benefit for individual patients from the available armamentarium and to ensure equity of access globally. The greatest outstanding challenges are to clarify mechanisms of neurodegeneration and improve trial outcomes to facilitate the development of much needed treatments for progressive multiple sclerosis. Reparative agents are likely to be used in combination with existing immunotherapies, early in the disease course, to prevent clinical progression. Further work to advance symptomatic management and rehabilitation across the entire spectrum of the disease must also be a priority.

Contributors

AJT wrote the introduction, epidemiology, diagnosis, management, and future sections. SB wrote the aetiology section. JG wrote the immune response to pathology section. BH wrote the immunology section. OC wrote all the remaining sections. All authors edited and approved the final version of this manuscript.

Declaration of interests

AJT reports personal fees from MedDay, Novartis, Eisai Ltd, Biogen Idec, and TEVA; is an Editorial Board member for *The Lancet Neurology*, receiving a free subscription; is Editor-in-Chief of *Multiple Sclerosis Journal*, receiving an honorarium from SAGE Publications; is Chair, Scientific Advisory Board, International Progressive MS Alliance (PMSA), receiving support for travel; is a member of the National MS Society (USA), Research Programs Advisory Committee, and receives support for travel; is Chair, International Medical and Scientific Board, and Board Member (2005–2015) Multiple Sclerosis International Federation (MSIF), and receives support for travel; and is a member, MSIF International Medical and Scientific Board (2015 onwards); and has received honoraria and support for travel for lecturing from EXCEMED and Remedica. OC is an Associate Editor of *Neurology* and is on the Editorial Board of *Multiple Sclerosis Journal*. She serves on scientific advisory boards for Novartis, Teva, Roche, Biogen-Idec, and Genzyme. She receives grants from the MS Society of Great Britain & Northern Ireland, EPSRC, NIHR UCLH BRC, EUH2020, Spinal Cord Research Foundation, Progressive MS Alliance, and Rosetrees Trust. SEB and JG declare no competing interests. BH has served on scientific advisory boards for F Hoffmann-La Roche Ltd, Novartis, Bayer AG, and Genentech. He has served as DMSC member for AllergyCare and TG Therapeutics. He, or his institution, have received speaker honoraria from Biogen Idec, Teva Neuroscience, Merck Serono, Medimmune, Novartis, Desitin, and F Hoffmann-La Roche Ltd. His institution has received research support from Chugai Pharmaceuticals and Hoffmann-La-Roche; holds part of two patents, one for the detection of antibodies and T cells against KIR4.1 in a subpopulation of patients with multiple sclerosis and one for genetic determinants of neutralising antibodies to interferon β. He was funded by the German MS Competence Network, the excellence Center Synergy, The Transregional Research Center TR118, and the EU project Multiple MS.

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