Seminar: Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) has experienced an explosion in therapeutic interventions over a relatively short period of time. Early diagnosis is therefore critical and diagnostic criteria continue to evolve. Patients without typical symptoms but with imaging abnormalities identical to those with MS (radiologically isolated syndrome) are now recognised. Clinical phenotypes now focus on the underlying clinical and imaging disease activity. Investigations into the genetic and environmental factors have disclosed part of the complex genetic architecture of the disease, and an increased risk of developing MS associated with low vitamin D levels, smoking and Epstein Barr virus infection. The adaptive and innate immune responses play a crucial role in the pathogenesis of MS. Magnetic resonance imaging is useful for monitoring treatment effect and safety, and has provided endpoints for clinical trials. The dozen or so treatments available for relapsing-remitting MS almost exclusively target the immune system and require a personalised medicine approach to maximise benefit. Treatment guidelines are now emerging. Treatment for the disabling, progressive phase remains limited, and a neuroprotective strategy, in combination with an immunotherapy, has the greatest potential to prevent progression.

Introduction

Multiple sclerosis (MS) is a complex and poorly understood condition, where many of the fundamental questions relating to causation and susceptibility remain unanswered. It affects individuals in their early adult life, and has a huge impact functionally, financially and in terms of quality of life. Costs are considerable and rise steadily with increasing disability.[1]

The last two decades have seen developments in our understanding and management of MS, but there are two facts that stand out above all others. The first is the explosion in the number of disease-modifying treatments (DMTs) available for relapsing-remitting MS (RRMS), in contrast to the paucity of effective treatments for the progressive forms of the condition, coupled with the lack of a major effect of DMTs on relapse-unrelated disability.[2]

The second development is the greater focus on active management, with the patient at the centre. The emergence of effective treatments has created an impetus to diagnose as early as possible and encourage interventions at the earliest point in time.[3] This is particularly apposite given the emerging evidence for activity prior to any overt clinical manifestations.[4] These developments may have contributed to the improved longevity in MS,[5] and improved rates of worsening and evolution to secondary-progressive MS (SPMS) when compared to earlier natural history cohorts.[6] The plethora of new agents also poses challenges in selecting the right drug for the right person at the right time and the era of personalised medicine for MS has certainly come of age.[7] Other key issues are the impact of age on the pathophysiology and clinical manifestations of the condition,[8] and the adverse influence of co-morbidities on outcomes.[9]

Epidemiology

With a prevalence ranging from 50 to 300 per 100,000, it is estimated that there are approximately 2.3 million people with MS in the world today, though this is likely to be an underestimate given the relative lack of data in large populations notably in India and China (**Figure 1**).[10] MS is more commonly seen in women than in men, and there is accumulating evidence of increased incidence of MS, notwithstanding improved diagnostic techniques, particularly in women with relapsing-remitting onset.[11] Most patients present in early adult life but in recent years there has been increased awareness of presentation in childhood.[12] The majority of patients presenting in later life are progressive from onset, but this is not uniformly the case.[13]

Although the global distribution of MS increases as one moves away from the equator,[10] there are exceptions to this generalisation and, while MS is common in regions populated by people from northern Europe, this effect is modified by where these individuals live in early life. Migration studies going back 50 years[14] indicate that migration from low risk to high risk regions in childhood is associated with a low risk and vice-versa. However the precise cut-off is less clear and it is likely that the risk of exposure spans a wider range than was initially thought.[15]

Aetiology

Environmental, genetic and epigenetic factors play a causal role in MS and potentially interact with modifiable risk factors.[16] Current discussions concern the identity of risk factors and the extent to which they contribute to MS aetiology.

Environmental risk factors

More recently, the role of risk factors such as sunlight, Vitamin D, diet, obesity in early life and cigarette smoking has received considerable attention.[17] Chief amongst these are low Vitamin D levels and cigarette smoking, both of which are associated with and increased risk of developing MS.[18–21] Therefore, correction of Vitamin D insufficiency could be important towards preventing MS, though there is no evidence of an association between neonatal Vitamin D levels and MS risk.[22] The risk 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 across men and women and may be due in part to lower Vitamin D levels in obese individuals. The long history of a potential association of MS with infection has moved to Epstein Barr virus, with evidence that infection as a young adult increases the risk of subsequently developing MS (relative risk 3.0).[23] This is in keeping with the hygiene hypothesis postulates that multiple infectious exposures in early childhood, as is often the case in tropical and subtropical areas, whereas in temperate zones, these infections tend to be delayed until early adult life.[24]

Genetics

The increased heritability within families and the directly proportional decrease in risk with degree of relatedness argue that genetic factors play a prominent role.

The human leukocyte antigen (HLA) region has been associated with hundreds of human diseases, including most autoimmune diseases.[25] In MS, an association with the serotype DR2 (later known to be the gene DRB1*15:01) has been known since the 70's[26] and consistently replicated in multiple studies (**Figure 2**). The most recent estimates indicate that carriers of the HLA DRB1*15:01 allele are three times more likely to develop MS than non-carriers.[27] More recent studies focused on the HLA region identified additional risk and protective alleles.[27] Using the values of HLA allele sharing by descent in sibships, it has been estimated that the HLA locus accounts for 20–30% of the genetic susceptibility in MS.[28]

With the introduction of high throughput genotyping technology and supported by world-wide collaborative efforts, genome-wide association studies (GWAS) allowed to identify genetic variants with minor effects including genes in IL2RA and IL7RA, the first two non-HLA associations.[29] Subsequent GWAS and a meta-analysis identified another dozen associations including the regions of CD58, TYK2, STAT3, and TNFRSF1A.[30] Altogether, the GWAS data seems to support the long-held view that MS susceptibility is conferred by the action of common

(i.e. those with a risk allele frequency of >5%) sequence allelic variants in multiple genes.[31] These studies were extended over the last decade, and a new meta-analysis of all previous GWAS in MS, and its corresponding replication in a large cohort (>15,000 cases) has been recently conducted by the IMSGC; this work has now brought the total number of associations to more than 200[32]. These data provide the genetic architecture of MS, which suggest a key role of the immune system in MS.

Genetics studies in MS have been largely successful in providing a large roster of common variants associated with susceptibility to this disease. The next generation of genetic studies will likely focus on the identification of determinants of disease progression and on how individual information can be used to personalize treatment and follow-up, in order to provide a more comprehensive and integrative care for MS patients.

Immunology of MS

Genetic and pathological studies point towards the adaptive immune system, which consists of T- and B-cells, as a key player in the pathogenesis of disease[33,34]. Inflammation in MS only affects the CNS strongly suggesting that T- and B-cell are selectively attracted by specific target antigens (probably autoantigens) that are only expressed in the CNS. Although several candidate antigens have been proposed, none has been confirmed[35,36].

Why immune responses are initiated against CNS antigens and maintained in MS 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. It is well established that 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[37] in two ways: (i) The CNS intrinsic model hypothesizes 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, which eventually targets the CNS (**Figure 3**). (ii) By contrast, the CNS extrinsic model hypothesizes that the initial event takes place outside of the CNS (e.g. in the context of a systemic infection) and leads to an aberrant immune response against the CNS (**Figure 3**). Several mechanisms (e.g., reactivity between microbial antigens and autoantigens or priming autoimmune responses by a strong inflammatory stimulus) may 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 (**Figure 3).** The sequence is quite compatible with the relapsing-remitting nature of diseases.

The innate immune system, mainly consisting of phagocytic cells, also seems to play an important role in the initiation and progression of MS. Macrophages promote the pro-inflammatory response of the T and B cells and execute tissue damage. Early microglial activation may be one of the initial events in the development of MS lesions, and may be essential for intrinsic ignition mechanisms. When activated, microglial cells may contribute to MS pathology through a number of possible mechanisms, including secretion of pro-inflammatory cytokines, chemokines, free radicals and increased release of glutamate.

During the progressive phase of disease the contribution of the peripheral immune system decreases and immune responses seem to be confined to the CNS compartment. CNS pathology changes from focal to diffuse white matter injury associated with microglia activation and diffuse lympho- and monocytic infiltrates[38] and increasing cortical involvement, which has been reported by some to be associated with lymphoid like follicles in the meninges.[39] This implies that the immune response is sequestered to the CNS compartment with little contribution from the periphery. It is, however, unclear whether diffuse tissue injury observed in progressive MS is caused by the compartmentalized immune response, involving both innate and adaptive immune cells, or a consequence of diffuse tissue injury caused by other mechanisms, including degeneration of chronically demyelinated axons,[40] and damage or dysfunction of other glia cells,[41,42] including microglia activation,[43] even in the absence of additional inflammatory damage, or the combination of both mechanisms.

From the immune response to pathology

Although it is unknown whether the mechanisms mediating the occurrence of MS lesions are qualitatively and/or quantitatively different between the white matter and grey matter, there may be processes that are “common” to the two compartments and link the different components of the innate and adaptive immune responses to MS pathology. The hallmarks of MS pathology are axonal or neuronal loss, demyelination, and astrocytic gliosis. Among these neuropathological characteristics, axonal (or neuronal) loss is particularly relevant because it is considered to be the main underlying mechanism of permanent clinical disability. Axonal loss may occur acutely in new inflammatory lesions, but also more slowly over time in the chronic demyelinated lesions. The exact mechanisms that lead to axonal loss are becoming to be understood, and some of them, such as the neuronal energy deficit, may 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, may be unique to the chronic phase.

At the top of the cascade of events that lead to axonal loss (**Figure 4**) and link the activity of the inflammatory cells to the MS lesions, there may be the production of reactive-oxygen species (ROS) and nitric oxide (NO) from activated microglia and infiltrated macrophages.[44] ROS and NO may induce neuronal mitochondrial dysfunction through several mechanisms; impaired mitochondrial activity, in turn, leads to further oxidative stress through increased ROS generation. Mitochondrial injury may contribute to all the pathological features that are typical of MS lesions, including demyelination, apoptosis of oligodendrocytes, and degeneration of axons (mainly of those with thin calibre)[45]. Specifically within axons, the reduced production of adenosine triphosphate (ATP) due to mitochondrial dysfunction may lead to increased calcium levels,

with consequent neuronal death (**Figure 4**).[46] Recent evidence points towards mitochondrial DNA deletions in cortical neurons[47], and iron accumulation within oligodendrocytes, as possible mechanisms that further enhance the neuronal oxidative stress induced by inflammation and mitochondrial dysfunction[45].

Pathogenic events, including inflammation, demyelination, axonal loss, and gliosis can be studied in vivo by using both conventional and advanced imaging techniques (**Figure 4**). As mentioned above, the consequences of the cascade of pathogenic events is neurodegeneration, which is captured in-vivo by reduced brain volume (or brain atrophy), measured by volumetric MRI; whole brain atrophy in MS occurs at rates of 0.5-1.5%, and faster rates may 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 resolution of the images, technical advances have led to the identification of structural, metabolic, and molecular imaging biomarkers[49,50] that reflect underlying pathological changes, correlate with clinical changes and can be used in clinical trials to monitor the efficacy of treatments.

From pathology to clinical features

Early MS is usually characterised by acute episodes of neurological deficits (or relapses), which 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. Optic neuritis will be therefore used in this section as a model to illustrate the mechanisms that link pathological abnormalities to clinical symptoms.

Pro-inflammatory cytokines and NO 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 the visual loss, which is 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 carried out in patients following an episode of optic neuritis, have found that acute (and persistent) optic nerve demyelination is associated with increased vulnerability of axons and predicts the development of axonal loss after 6 months;[52] these findings support the hypothesis that the lack of myelin-derived trophic support[53] and mitochondrial dysfunction[46] contribute to the degeneration of chronically demyelinated axons, responsible for irreversible disability in the progressive phase of the disease.[45] Additionally, in progressive MS, pathology may shift from a “focal” pattern to a more extensive and diffuse pattern, affecting both the white and grey matter, and changes (either de- or increases) of functional connectivity have been observed.[54,55]

Tissue repair, plasticity and clinical recovery

Clinical deficits caused by acute inflammatory demyelination may be reversible because of restoration of nerve conduction. The restored nerve conduction is more continuous (rather than saltatory) and is achieved because the demyelinated axonal membrane shows several changes following demyelination, including increase in sodium channels. In addition, remyelination leads to new myelinated internodes, which are, however, shorter and thinner than normal[56]. All these changes leads to increased energy demand (or increased ATP production), which, consequently, may induce changes in the size and number of mitochondria.[46]

Particular attention has been paid to the spontaneous phenomenon of remyelination, which is overall sparse in chronically demyelinated MS lesions, despite the presence of axons and oligodendrocyte precursors in some of them.[56] The main role of remyelination is to ensure axonal survival, rather than the restoration of nerve conduction.[53]

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

Diagnosis

The increasing acceptance that early intervention is important in the treatment of MS together with the growing awareness of the need to personalise treatment so that it aptly addresses the level and extent of disease activity have together emphasised the importance of early and accurate diagnosis and meaningful description of the disease course.

The diagnosis of MS remains fundamentally clinical and requires the necessary clinical expertise to demonstrate evidence of dissemination in time (DIT) and space (DIS) and, importantly, the exclusion of other neurological conditions. The incorporation of MRI can provide this evidence and assists in excluding other conditions. MRI has added accuracy and allowed earlier diagnosis with greater certainty. The criteria have evolved as technology has improved, to refine definitions, become simpler, more accessible and applicable to a larger proportion of the population while maintaining specificity and sensitivity.[60,61] The latest revision continues this trend while re-instating the role of abnormalities of the CSF.[61] All changes were evidence-based and arrived at by consensus (**Table 1**). Inevitably these criteria will continue to evolve, particularly as MRI becomes increasingly more sophisticated. Standardized protocols for the evaluation of patients with suspected or clinically definite MS have been suggested for baseline and follow-up scans and for brain and spinal cord imaging[62].

The diagnostic criteria should be applied to diagnose patients who present with symptoms typical of MS and in whom MS is suspected, and not to differentiate MS from other neurological disorders. Inappropriate application of diagnostic criteria to patients with symptoms atypical for demyelination was the main contributor to MS misdiagnosis.[63] A combination of MRI, serological and genetic testing, in association with clinical features and history, should be taken into account to navigate through the differential diagnosis of idiopathic inflammatory disorders, including neuromyelitis optica spectrum disorder (NMOSD),[64] and other relapsing disorders that can mimic MS (**Table 2**).

Phenotype

The overwhelming majority of those developing MS begin with a single episode, clinically isolated syndromes (CIS) (**Figure 5 (A)**), involving the optic nerve, brainstem and spinal cord, which resolves over time. The concept of CIS is now well established[65] and is being incorporated into the WHO-ICD 11. CIS patients subsequently have a further episode (relapse) and are described as having RRMS. About one third of this population will develop progressive disability with or without superimposed relapses and are then described as having secondary-progressive MS (SPMS)[66]. This proportion, though, will likely continue to evolve as we gain more insights to the impact of DMTs on the natural history of the disease. In contrast about 15% of patients have a slowly progressive onset (PPMS)[67]. More recently, there has been a focus on the earliest stages of the condition. Patients with incidental MRI findings consistent with MS, the so-called 'radiologically isolated syndrome' (RIS) (**Figure 5 (A)**),[68] has been described and indicators for those more likely to demonstrate clinical symptoms of MS and further MR abnormalities over time are emerging.[69] Evolution of patients with RIS into RRMS and PPMS has recently been demonstrated[70]. Finally, there has been further exploration of the two forms of progressive multiple sclerosis and an appreciation that they are more similar than different, i.e. the differences between them are relative rather than absolute.[71]

While we have become accustomed to this terminology, as advocated by Lublin and Reingold over 20 years ago[72] it is clear that they are purely descriptive and don't provide information about the underlying pathophysiology. The recent phenotype paper, has begun to address this by advocating a focus on the presence or absence of activity, whether clinical or imaging, and addressing the two key components: relapses and progression and, on MRI, new lesions indicating inflammatory activity and atrophy indicating progression[73] (**Figure 5 (B)**).

Predicting clinical course

Efforts have been made to identify clinical and radiological features that predict the clinical course of the disease. Thirty-four percent of patients with RIS develop a first acute clinical event consistent with CIS/MS within 5 years follow-up;[74] risk factors for developing a first symptomatic event include male sex, younger age at the time of RIS diagnosis (<37 years), and presence of spinal cord lesions.[74] Spinal cord lesions and male sex predicted evolution of RIS to PPMS, which has a prevalence of 12% in a large, multicentre cohort.[70] In patients with CIS, 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 10 or more brain lesions on brain MRI is a high-impact prognostic factor for conversion to clinically definite MS and disability.[75] In addition to baseline lesion number, the increase in lesion volume during the first 5 years is associated with higher disability after 20 years.[76] In patients with CIS and non-spinal presentation, the presence of spinal cord lesions predicts a second clinical event.[77] Receiving DMT prior to the second attack is associated with a lower risk of reaching moderate disability.[75] DMT exposure is the most protective factor against disability-worsening events in paediatric CIS.[78] Clinical outcomes, including disease activity and neuropsychological tests, suggest a persistent, long-term benefit of an early treatment at onset of CIS.[79] In patients with CIS on DMT vitamin D levels predict disease activity and prognosis.[19] Once MS 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.[48,80] Because of several, technical issues relating to MRI techniques and methodology, brain atrophy cannot yet be recommended in clinical practice for prognosis (or diagnosis)[62]. Females have a higher relapse rate than males throughout the course of MS.[81] Overall, an active management of MS with DMTs is associated with a favourable clinical outcome, reflected by 11.3% of MS patients transitioning to SPMS during 10-year follow-up[6]. In patients with MS on DMT, the presence of on-therapy relapses is associated with poor-prognosis.[82]

Treatment

Disease modifying-treatments (DMTs)

Over the last ten years several DMTs have been discovered and approved for patients with RRMS (**Figure 6**). In general, these DMTs target neuroinflammation, and are considered to have a marginal, if any, effect on neurodegeneration, which is the main underlying mechanism of progression of disability in MS. The efficacy of DMTs on reducing the development of brain atrophy in clinical trials has been moderate at best (**Table 3**). At present, only one DMT (ocrelizumab) is approved by regulatory authorities in the United States, Australia and Switzerland (but not by the European Medical Agency) to slow down or stop progression in patients with progressive MS.

Although the comparison between the effectiveness of DMTs relies on meta-analysis,[83] and observational cohorts studies[84] because of the lack of head-to-head trials, the recently licensed DMTs are more effective in reducing the relapse rate than older DMTs (**Table 3**). The higher efficacy of newer medications has introduced the concept of “no evidence of disease activity” (NEDA) into clinical trials; this is defined by the absence of relapses, disability progression, and active MRI lesions (both new or enlarged T2 lesions and gadolinium-enhanced lesions)[85] If DMTs are prescribed at an early stage of the disease, and brain MRI is repeated annually in patients with RRMS, as recommended,[73] NEDA could become a target in the clinical practice. Guidelines on the MRI protocols for monitoring of patients in clinical practice have recommended the use of T2-weighted and contrast-enhanced T1-weighted brain MRI, which reveal (subclinical) acute and active inflammation; spinal cord imaging, brain volume measures, and advanced MRI methods, although useful to understand the course of MS, are not recommended for routine monitoring[86].

The high number of DMTs available has made the management of patients more complex. Two therapeutic approaches are available in the clinical setting. The first is termed “escalation” strategy. It consists of starting with a first line DMT, and then escalating to a more effective medication, if the patient’s relapse rate has not changed when compared with the pre-treatment period. Although this is a sensible approach, the timing and nature of the escalation from less effective medications to more effective treatments can be challenging in terms of treatment choice. In an attempt to help choosing the next drug, recent registry data have demonstrated that the relapse rate was 50% lower after switching from injectable DMTs to natalizumab than fingolimod, but none of these drugs had a significant impact on disability progression.[87] Additionally, the escalation strategy may not work for patients who have a highly active or rapidly evolving disease. For these cases, the “induction” strategy may be more appropriate. It consists of starting with a very effective medication, such as alemtuzumab or ocrelizumab, which is followed by a permanent disease remission or a long-term maintenance treatment with a less effective DMT, if needed.[88] The choice between these two strategies should be ideally made on the basis of prognostic biomarkers that identify patients who are more likely to benefit from a specific treatment plan.

The most effective medications for MS have the highest risk of serious adverse events. Alemtuzumab has been associated with severe autoimmunity related adverse events and infections (e.g., Listeria); natalizumab and, more recently, other DMTs,[89,90] have been associated with progressive multifocal leukoencephalopaty (PML), caused by the reactivation of the JC virus. An estimation of the risk of PML in patients on natalizumab is obtained on the basis of the anti-JC virus antibodies status, prior use of immunosuppressants, and duration of natalizumab treatment.[91] The quantification of anti-JCV antibodies levels has been introduced in the risk assessment routinely performed in the clinical practice.[92] However, patients with negative anti-JCV antibody are still at risk of PML either because of a de-novo infection, or because of false negative test results, or because of a too low peripheral viral activity that does not reach the threshold.[93] This urges clinicians to remain alert and consider the possibility of PML even when treating JCV-seronegative patients. Repeated MRI scans help the differential diagnosis between PML and MS-related lesions, and allow detection of asymptomatic cases of PML, who are associated with a more favourable prognosis.[94]

New data on the safety and efficacy of CD20 depleting monoclonal antibodies, such as rituximab, ocrelizumab, and ofatumumab[95], are encouraging. The last agent and ocrelizumab are anti-CD20 monoclonal antibodies. Long-term experience of safety and patient convenience of the anti-CD20 therapy is provided by rituximab, which has been used to treat rheumatoid arthritis and hematologic malignancies; rituximab has been demonstrated to have an effect on inflammatory MRI lesions and clinical relapses in RRMS and in a subgroup of patients with PPMS.[96] The efficacy of ocrelizumab, an mAb targeting the same CD20 epitope than rituximab, was recently demonstrated in phase III trials in RRMS and PPMS[97,98]. However, treatment with monoclonal antibodies may be a unique, predisposing factor for the development of PML (for example, PML has been observed with rituximab). The effects of these antibodies on the immune system that may predispose to PML has to be fully understood in order to develop strategies for prevention and treatment of PML. Additionally, novel DMTs have an unknown long-term safety profile.

The last medication approved by the European regulatory agency for the treatment of highly active MS is cladribine. Clinical trials with cladribine have provided evidence of its efficacy in delaying conversion from a first clinical demyelinating event to clinically definite MS[99,100] and in reducing relapse rates, the risk of disability progression, and MRI measures of disease activity in RRMS[101]. A recent meta-analysis has supported an increased cancer risk of cladribine when compared with other treatments[102] .

The first steps towards the treatment of progressive MS have been made over the last decade. A phase II trial in secondary progressive MS has shown that simvastatin reduces progression of annualised brain atrophy by 43% over 2 years,[103] and a phase III trial with this medication is currently ongoing. The effect of simvastatin on brain atrophy, the preliminary findings of recent trials with biotin[104] and ocrelizumab,[98] the current treatment trial with laquinimod in primary progressive MS to define its optimal dose and indication, and the impressive effort and commitment of the international Progressive MS Alliance,[105] represent a good auspice for the approval of the first treatment for progressive MS in the near future.

After the halt of disease activity and progression, there is the aspiration to obtain an improvement in clinical disability. A sustained remission of active MS and improvements in neurological disability were reported in RRMS patients who failed to respond to DMTs and received a high-dose immunosuppressive therapy and autologous hemapoietic cell stem transplantation (aHSCT).[106] Patients most likely to benefit from aHSCT are relatively young (50 years of age or less), with relatively short disease duration (5 years or less), have active RRMS, are accumulating disability but still are able to walk, and have ongoing relapses and MRI activity despite DMT.[107] Longer follow-ups and head-to-head comparisons between aHSCT and the most effective DMTs are necessary to understand how to position aHSCT for the management of MS patients with the most aggressive disease.

While the dramatic increase in the number of approved DMTs is welcome, inequalities across countries in the DMTs costs has become apparent;[108] additionally, the introduction of newer DMTs has tended to raise the costs of older DMTs, which are matching the prices of the new competitors, at an unacceptable and potentially unsustainable rate.[108] The availability of DMTs tends to be higher in high-income countries than medium-low income countries,[10] and the accessibility to medications is not homogeneous even in countries where DMTs are available through government-funded schemes.[10] The introduction of generic drugs that have equivalent efficacy, safety, and tolerability as the brand DMTs[109] may lead to less-expensive MS therapies.[110]

Treatment of acute relapses

The major focus of research over the last decade has been to assess whether oral steroids have the same effect as intra-venous (IV) steroids to treat acute relapses. The 2012 Cochrane review that performed a meta-analysis of the previous five randomised trials that compared oral and intravenous steroids for the treatment of relapses concluded that there were no significant differences in clinical and MRI outcomes

between oral and intravenous administration, but larger trials, with greater statistical power, were needed.[111] The landmark study is a multicentre, double-blind, randomised, controlled, non-inferiority trial which has been recently published[112]; it compared oral vs. intravenous methylprednisolone, 1000 mg, once a day for 3 days and found that the oral treatment was not inferior to the IV one. The patient characteristics were a mix of visual, pyramidal, sensory, cerebellar and brainstem relapses and both treatment groups had similar relapse rate over the subsequent six months. These findings may allow more patients to have access to steroids more rapidly, and in a more comfortable way, and reduce the cost of the management of MS relapses.

Management

Active management, centring on the person with MS, is advocated at all stages of the condition to minimise disease impact, maximise quality of life and espouse a philosophy of wellness.[113] Exercise is now playing a central role following a number of positive studies in mobility across relapsing/remitting and progressive MS.[114,115] Effects on cognition are now being explored[116]. However the evidence base remains limited,[117] mechanisms are not well understood and translation into clinical practice is poor.[118] Prevention of falls, a frequent occurrence in MS, associated with continence issues, previous falls and medication is another key element of good management.[119] Multidisciplinary, goal-orientated rehabilitation incorporates all these elements but again methodologically sound studies are few[120] and, as a consequence, the evidence base is relatively poor with few level 1 recommendations.[121] More studies on modifiable risk factors, including lifestyle and Vitamin D, known to worsen the condition are also required[117].

Addressing the array of symptoms that are seen in MS 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.[122] Many symptoms, such as spasticity, require a multi -disciplinary approach and the careful selection of treatments appropriate to the severity of the symptom. Overall it requires a sound knowledge base and a continuing treatment plan. The value of rehabilitation in cognitive dysfunction is now better appreciated.[123,124] This is coupled with a better understanding of underlying mechanisms relating to connectivity[125] and more innovative approaches to treatment.[126]

Future

The therapeutic developments seen in MS are unequalled in any area of neurology and the challenge now is to get the greatest benefit from the available armamentarium and ensure equity of access globally. The greatest outstanding challenges are to clarify mechanisms and improve trial outcomes, which will facilitate the development of much needed treatments for progressive MS. It is expected that reparative agents will be used in combination with existing immunotherapies to prevent clinical progression. Advances in symptomatic management and rehabilitation across the entire spectrum of MS are needed.

Acknowledgments
AJT and OC acknowledge the support of the National Institute for Health Research University College London Hospitals Biomedical Research Centre. We thank Dr Arman Eshaghi, Dr Carmen Tur, Dr Marcello Moccia, and Professor Gavin Giovannoni for providing the Figures and help with the Tables and References.

Disclosures
AJT reports personal fees and other from MedDay, Novartis, Eisai Ltd, Biogen Idec, and TEVA, outside the submitted work; and Editorial Board member, The Lancet Neurology, received free subscription; Editor-in-Chief, Multiple Sclerosis Journal, honorarium from SAGE Publications; Chair, Scientific Advisory Board, International Progressive MS Alliance (PMSA), support for travel member; National MS Society (USA), Research Programs Advisory Committee, support for travel; Chair, International Medical and Scientific Board, and Board Member (2005-2015) Multiple Sclerosis International Federation (MSIF), support for travel; member, MSIF International Medical and Scientific Board (2015-); Received honoraria and support for travel for lecturing from EXCEMED and Remedica. OC reports other from Neurology, other from Multiple Sclerosis Journal, grants and personal fees from Novartis, grants from Biogen-Idec, grants from General Electric, personal fees from Genzyme, grants from MS Society of Great Britain & Northern Ireland, grants from EPSRC, grants from UCL/UCLH NIHR BRC, grants from Wellcome Trust, grants from EUH2020, grants from Spinal Cord Research Foundation, grants from Rosetrees Trust, outside the submitted work. .SEB, BH, JJGG have nothing to disclose.

Funding statement
BH was funded by the German MS Competence Network, the excellence Center Synergy, The Transregional Research Center TR118, and the EU project Multiple MS. OC and AJT acknowledge support from the Department of Health's NIHR Biomedical Research Centre; JJGG and SB did not declare any particular funding source. Funders had no influence on the content of the manuscript.

Search strategy and selection criteria
Resource publications for this seminar were identified through searches of PubMed and MEDLINE, and references from selected articles, using search terms relevant to each section of the Seminar, and a filter for publication date (up to September 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.

Table 1: The 2017 McDonald Criteria for diagnosis of multiple sclerosis in patients with an attack[a] at onset

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS
≥2 clinical attacks and objective clinical evidence of ≥2 lesions; or ≥2 clinical attacks and objective clinical evidence of 1 lesion and clear-cut historical evidence of a prior attack involving a lesion in a distinct anatomic location[b]	None[c]
≥2 clinical attacks; and objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: A second clinical attack implicating a different CNS site **OR** Demonstration of DIS by MRI[d]
1 clinical attack; and objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by: A second clinical attack **OR** Demonstration of DIT by MRI[e] **OR** Demonstration of CSF-specific OCBs[f]
1 clinical attack; and objective clinical evidence of 1 lesion	Dissemination in space and time, demonstrated by:

	For DIS: A second clinical attack implicating a different CNS site **OR** Demonstration of DIS by MRI[d] **AND** For DIT: A second clinical attack **OR** Demonstration of DIT by MRI[e] **OR** Demonstration of CSF-specific OCBs[f]

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS. If MS is suspected by virtue of a CIS but the 2017 McDonald Criteria are not completely met, the diagnosis is "possible MS." If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is "not MS." (From Thompson et al, Lancet Neurol 2017[61], Permission to reproduce obtained).

Table 2. Differential diagnosis of MS: clinical, MRI and serological findings of the main disorders that can resemble RRMS

	Typical neurological features	**Typical MRI features**	**Typical blood tests and CSF findings**
Neuromyelitis optica spectrum disorder	Concomitant or concurrent (severe) optic neuritis and transverse myelitis; nausea and vomit; paroxysmal tonic spasms	Longitudinally extensive spinal cord lesion (>3 vertebral segments); optic chiasmal involvement; pencil-thin ependymal enhancement and cloud-like enhancement	Serum autoantibody to aquaporin-4 (AQP4-Ab) and to myelin oligodendrocyte glycoprotein (MOG-Ab)
Neurosarcoidosis	Cranial nerves involvement (in particular facial and optic nerve involvement); headache; raised intracranial pressure; meningitis; seizures; myelopathy	Meningeal enhancement with pituitary, hypothalamic and cranial nerves involvement; brain white matter lesions; simultaneous enhancement of all lesions	Raised serum and CSF ACE
Neuro-Behçet's disease	Brainstem syndrome; myelopathy; meningoencephalitis	Large brainstem lesions; basal ganglia, subcortical white matter and spinal cord lesions; gadolinium enhancement; cebral venous sinus thrombosis	HLA-B5; CSF pleocytosis
Connective tissue disorders (systemic lupus erythematosus (SLE), Sjögren syndrome, antiphospholipid antibodies syndrome)	Optic nerve, brain and spinal cord involvement; neuropsychiatric symptoms; seizures; ischaemic episodes	Brain infarcts and hemorrhage; basal ganglia lesions; punctuate (subcortical) lesions; spinal cord lesions; cebreal venous sinus thrombosis; parotid gland involvement in Sjögren	Serum antinuclear antibody (ANA); ENA (in particular, anti SS-A(Ro) and SS-B(La) antibodies for Sjögren, and anti-Sm for SLE)
Central nervous system vasculitis	Confusion, headache, personality change; seizures; stroke-like	Ischemic, multiple lesions; predominance of lesions at the cortico-subcortical junction; intracranial haemorrhage;	Serum anti-neutrophil cytoplasmic antibodies

	symptoms;	meningeal enhancement; simultaneous enhancement of all lesions; microbleeds	(ANCA)
Hypoxic-ischaemic vasculopathies (in particular: small vessel disorder (SVD), cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)	Stroke events; cognitive decline; focal neurological signs; gait disturbance	SVD: Punctuate and peripheral white matter lesions, sparing U-fibers; symmetrical and confluent, periventricular lesions; lacunar infarcts; involvement of central transverse fibres in the pons; microbleeds. CADASIL: Temporal pole lesions; external capsule and U-fibers lesions; microbleeds.	Serum testing for vascular risk factors (diabetes, hypercholesterolemia)
Susac's syndrome	Visual loss; sensorineural hearing loss; encephalopathy; headache; memory loss; behavioural disturbances	Focal and small lesions in supra and infratentorial regions (both white matter and grey matter); involvement of corpus callosum (snow ball lesions); leptomeningeal enhancement;	
Fabry disease	Stroke events; vertigo	Posterior infarcts; multiple white matter lesions with pulvinar involvement (T1 hypointense lesions)	Reduced activity of the alpha-galactosidase enzyme; analysis of GLA gene

Table 3. A summary of the approximate efficacy of the approved DMTs on relapse rate, new MRI lesions, disability progression and brain atrophy when compared with placebo.

DMTs	Reduction in relapses	Reduction in new MRI lesions	Reduction in disability progression	Reduction in whole brain atrophy
Alemtuzumab[127–129]	75%	95%	42%	42%
Interferons beta	30%	50-70%	n.s.	n.s.
Cladribine[101,130]	55-58%	73-77%	33%	16%
Daclizumab[131]	45%*	54%*	n.s.	n.s.
Dimethyl fumarate[132,133]	51%	60%	38%	30%
Fingolimod[134,135]	52%	75%	18%	35%
Glatiramer Acetate	30%	30%	n.s.	n.s.
Natalizumab[136,137]	68%	83%	42%	44%
Ocrelizumab[97]	46%*	77-83%*	40%*	23%
Teriflunomide[138,139]	30%	50%	30%	25%

* compared to interferon-beta

Table 4. Symptomatic management in MS

Symptoms	Pharmacological treatment	Non-pharmacological treatment
Spasticity	***For generalised spasticity:*** 1st line: Baclofen; Tizanidine; Gabapentin (especially for associated spasms); 2nd line: Dantrolene; Diazepam and Clonazepam (at night); 3rd line: add THC:CBD 4th line: Baclofen pump; phenol injections ***If focal spasticity:*** Botulin toxin injections; phenol injections	Exercise; physiotherapy; hydrotherapy
Fatigue	Amantadine; modafinil and fampridine (not approved for MS fatigue)	Exercise; cognitive behavioural therapy; occupational therapy; energy conservation management and aerobic training
Impaired ambulation	Fampridine (patients with poor initial drug responses may show a response after long-term treatment[140]	Exercise; physiotherapy
Ataxia and tremor	Propanolol; clonazepam; levetiracetam; isoniazid (limited by side effects); botulin toxin injections if focal, limb tremor[141]	Physiotherapy; surgical interventions in

		selected cases[142]
Bladder dysfunction	***For overactive bladder*:** Oxybutynin; tolterodine; solifenacin; desmopressin spray (if nocturia); botulin toxin A intra-vesical injection; cannabinoids[143]	Tibial nerve stimulation and sacral neuromodulation (as an alternative to botulinum toxin A, when anti-muscarinic treatment is not effective or tolerated);[144] intermittent self-catheterisations; indwelling and suprapubic catheter (if difficulty in emptying); surgical interventions (if conservative measures fail)
Sexual dysfunction	1st line: Sildenafil 2nd line: Intraurethral alprostadil	Cognitive and behavioural therapy (if underlying depression); pelvic floor physiotherapy (alone or combined with electro-stimulation or transcutaneous tibial nerve stimulation) (for female sexual dysfunction) [145]
Bowel dysfunction	***For constipation:*** Laxatives; rectal stimulants (suppositories, enemas); transanal irrigation	***For constipation:*** Assessment by continence advisor/physiotherapist;

		Increase level of exercise, abdominal massage; biofeedback retraining ***For incontinence*:** Physiotherapy of pelvic floor; biofeedback retraining; enemas/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	Amitriptyline; antidepressants; dextromethorphan and quinidine for bulbar symptoms	Cognitive and behavioural therapy (for depression)
Cognitive impairment	Memantine (although not confirmed by recent randomised trial)[146]	Cognitive rehabilitation; behavioural interventions; occupational therapy;
Visual problems (oscillopsia)	1st line: Gabapentin 2nd line: Memantine	
Pain	***For neuropathic pain:***	Physiotherapy; surgical

	1st line: Amitriptyline; Duloxetine; Gabapentin; Pregabalin 2nd line: Tramadol; Capsaicin cream (if localised) ***For trigeminal neuralgia:*** 1st line: Carbamazepine 2nd line: Oxcarbazepine, Lamotrigine, Gabapentin, Pregabalin, Baclofen ***For Musculoskeletal pain:*** Common analgesia; Baclofen (if spasticity)	procedures for trigeminal neuralgia

Note: The evidence from this Table comes from the AAN guidelines[147], NICE guidelines[148], consensus papers[149], clinical trial data, previous reviews[150], and our own opinion.

Figures Legend

Figure 1. Atlas of MS.

Figure 2. Genetics. The history of genetic discoveries in MS is depicted as a series of images. In each panel, MS is at the center and the associated loci are shown as triangles with direct edges or connections. The concentric circles denote the strength of associations in terms of odds of the ratios (OR; a measure of genetic effect size).

Figure 3. Immunology. Model for the Interaction between immune system and CNS in MS. Activated T and B cells infiltrate the CNS most likely attracted by autoantigens expressed in the myelin sheets or the oligodendrocyte. These cells recruit macrophages and activate microglia which mediate tissue damage. As a result antigens are released and drained to the periphery (e.g. cervical or paraspinal lymph nodes) where they are taken up by antigen presenting cells. This will further activate autoreactive T and B cells which will egress from the lymph node and invade the CNS.

Figure 4. Pathogenic mechanisms of MS and their imaging targets. Inflammation is generally studied by counting gadolinium-enhancing areas on T1-images. Neuroaxonal degeneration is measured by determining whole brain atrophy and compartment-specific atrophy (e.g. white, grey and deep grey matter). Demyelination is quantified with MTR. Microstructural changes within neurons and axons are measured with DWI, ODI and NDI. Specific molecular and metabolic targets for astrocyte activation, neuro-axonal degeneration, microglia activation, energy failure, glutamate excitotoxicity and demyelination have been developed on MRS and PET. Sodium imaging quantifies intra- and extra-cellular sodium content, and the subsequent ionic imbalance. (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: Gamma-Aminobutyric acid; Chol: choline-containing compounds; TSPO: translocator protein; NAA: *N*-Acetyl-aspartate; Cr: creatine; Pcr: phosphocreatine; Glu: glutamate; Gln: glutamine; Gd: Gadolinium; MTR: magnetization transfer imaging; RD: radial diffusivity).

Figure 5. Phenotypes. This scheme illustrates the relationship between lesions on MRI with clinical signs, and clinical phenotypes. **(A)** Radiologically Isolated Syndrome (RIS) and Clinically Isolated Syndrome (CIS) are characterised by the presence of inflammatory demyelinating lesions, without or with associated clinical symptoms/signs. CIS and RRMS can be further defined on the basis of the presence/absence of clinical (relapses) and MRI (new/enlarging T2 and gadolinium-enhanced lesions) activity. **(B)** Progressive MS can be defined on the basis of the presence/absence of clinical and MRI (brain atrophy) progression.

Figure 6. Disease-modifying treatments in MS with their year of discovery/licensing.

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Figure 1.

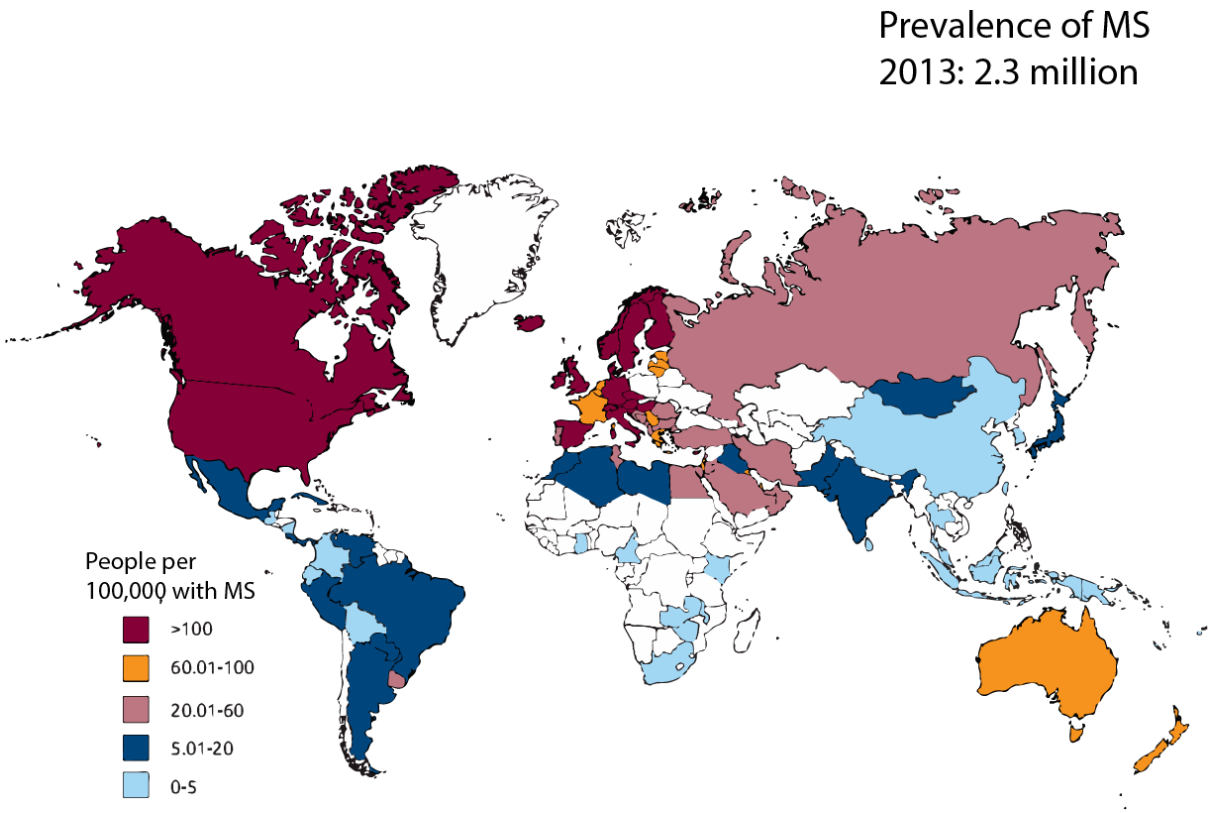

Prevalence of MS
2013: 2.3 million
People per
100,000 with MS
>100
60.01-100
20.01-60
5.01-20
0-5

Figure 2.

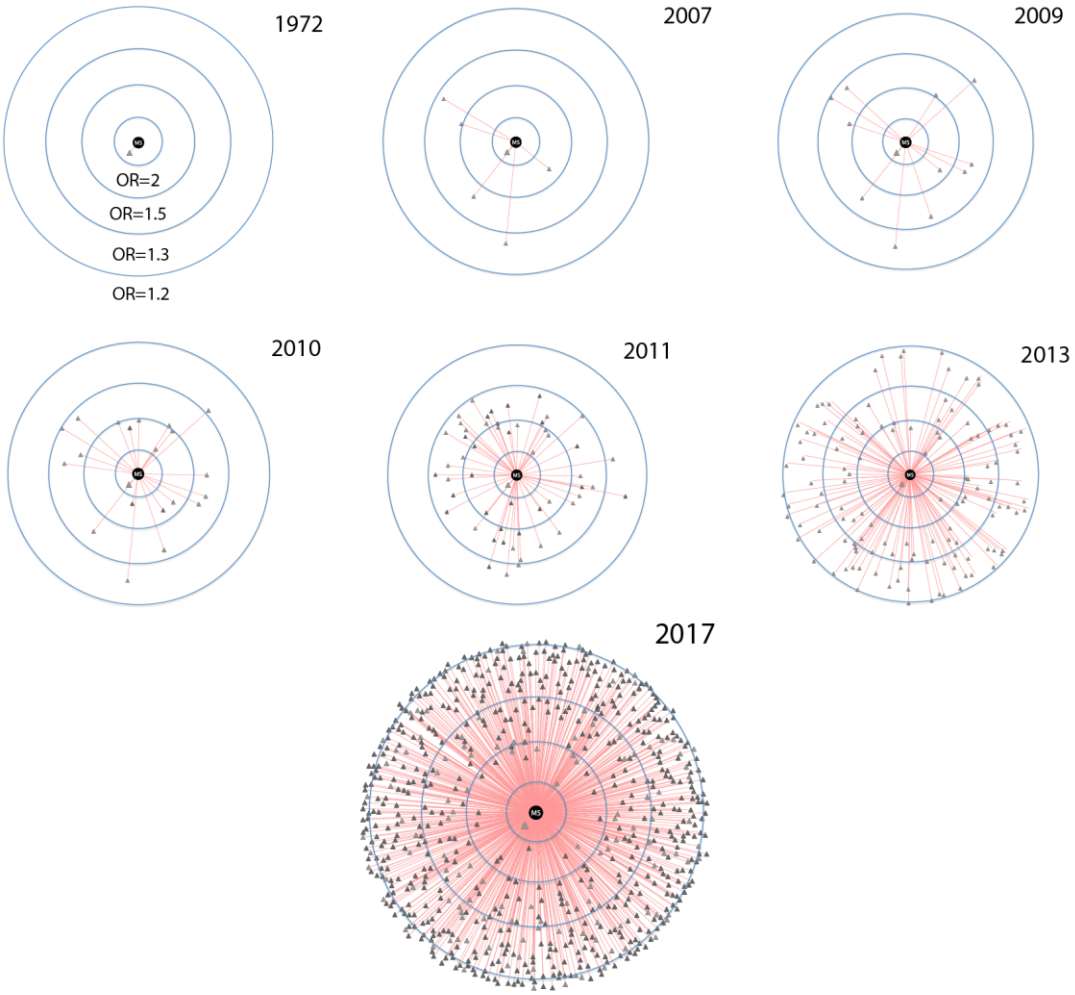


Figure 3.

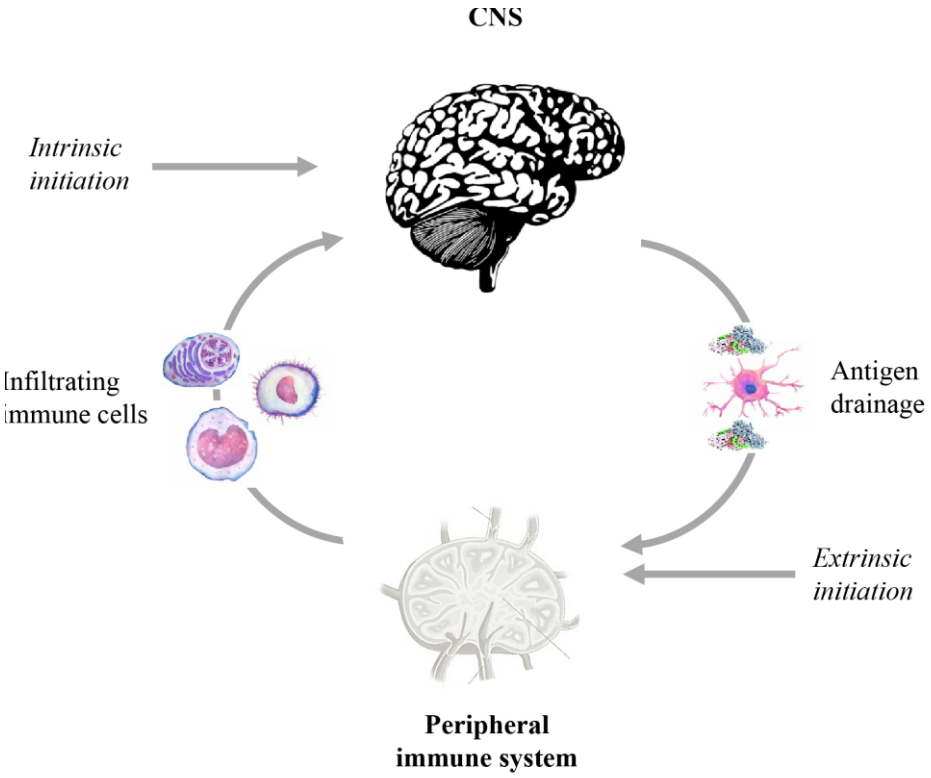

CNS
Intrinsic initiation
Infiltrating immune cells
Antigen drainage
Extrinsic initiation
Peripheral immune system

Figure 4.

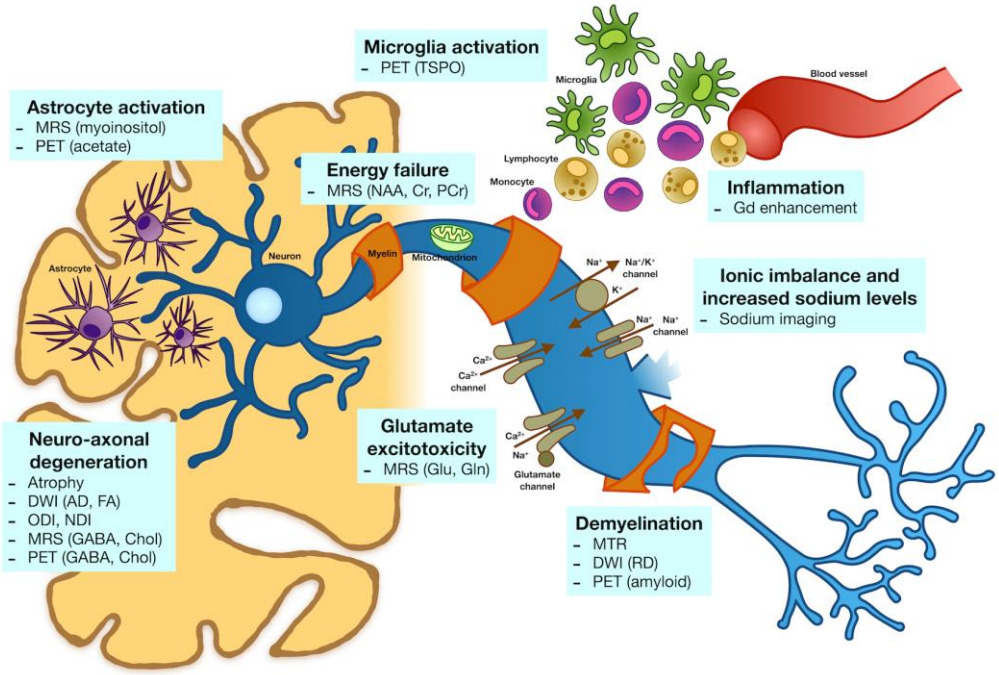
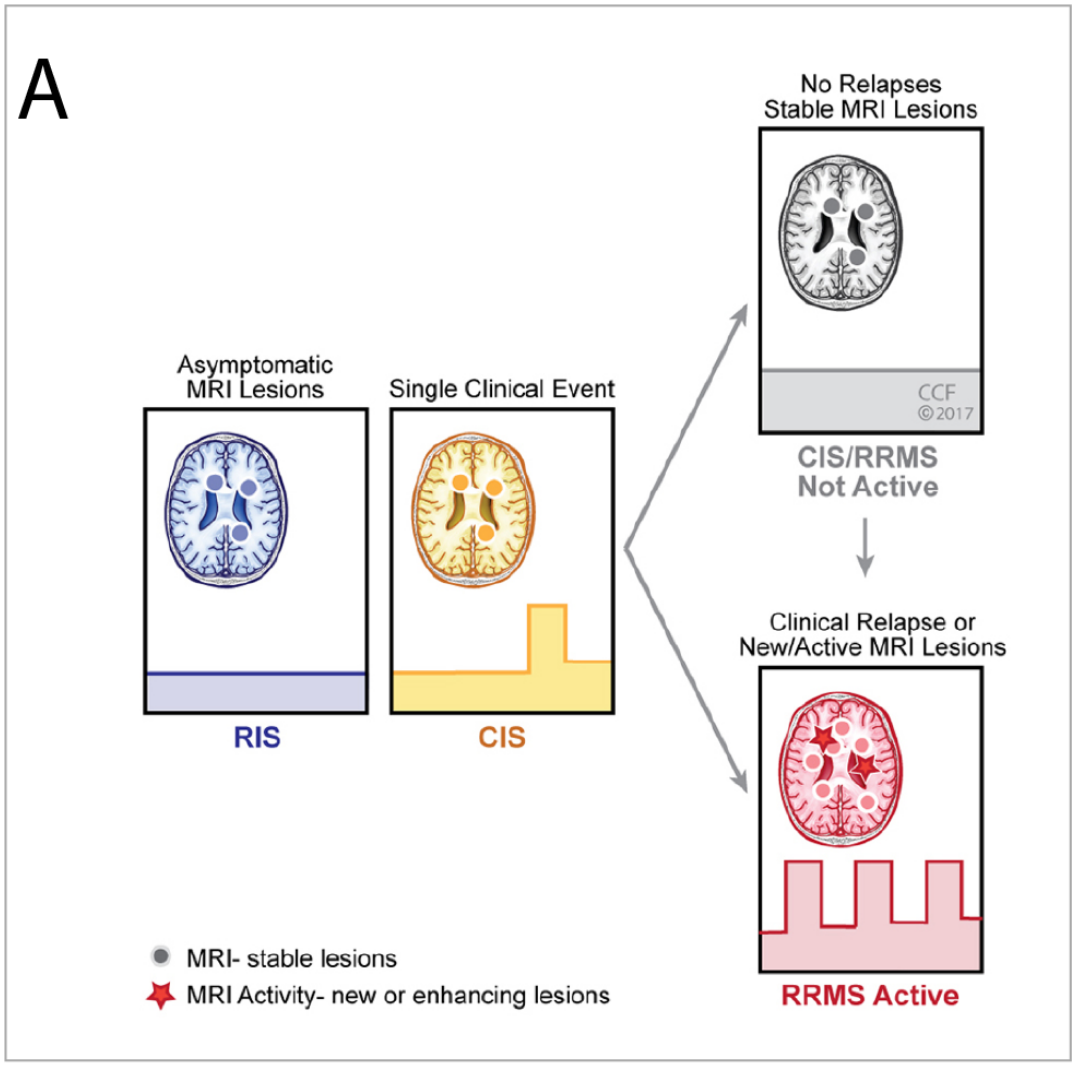

Microglia activation
- PET (TSPO)
Astrocyte activation
- MRS (myoinositol)
- PET (acetate)
Energy failure
- MRS (NAA, Cr, PCr)
Inflammation
- Gd enhancement
Ionic imbalance and increased sodium levels
- Sodium imaging
Glutamate excitotoxicity
- MRS (Glu, Gln)
Neuro-axonal degeneration
- Atrophy
- DWI (AD, FA)
- ODI, NDI
- MRS (GABA, Chol)
- PET (GABA, Chol)
Demyelination
- MTR
- DWI (RD)
- PET (amyloid)
Microglia
Blood vessel
Lymphocyte
Monocyte
Astrocyte
Neuron
Myelin
Mitochondrion
Na+
Na+/K+ channel
K+
Na+
Na+ channel
Ca2+
Ca2+ channel
Ca2+
Na+
Glutamate channel

Figure 5.


A
No Relapses
Stable MRI Lesions
CCF
©2017
CIS/RRMS
Not Active
Asymptomatic
MRI Lesions
Single Clinical Event
Clinical Relapse or
New/Active MRI Lesions
RIS
CIS
RRMS Active
MRI- stable lesions
MRI Activity- new or enhancing lesions

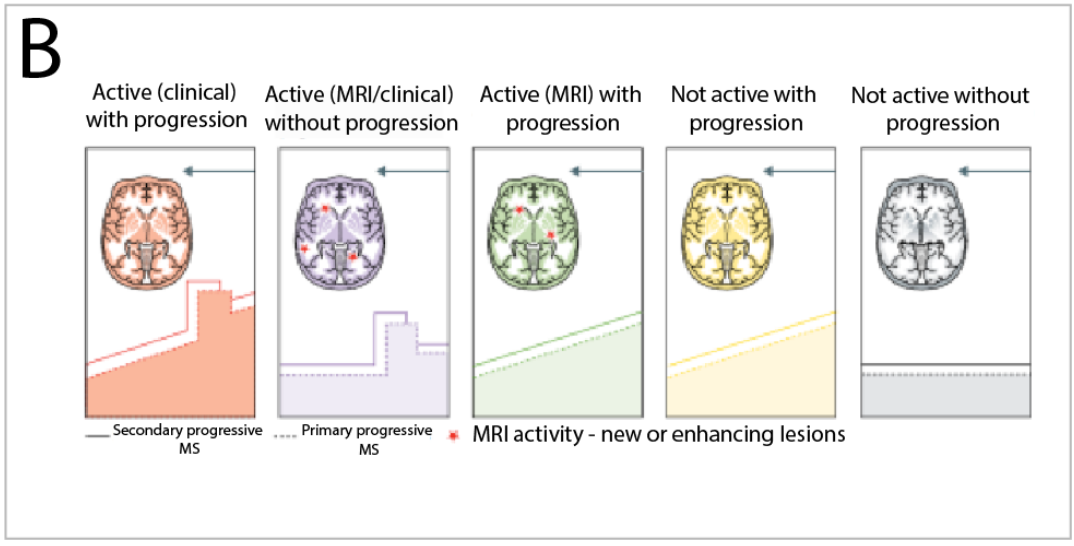
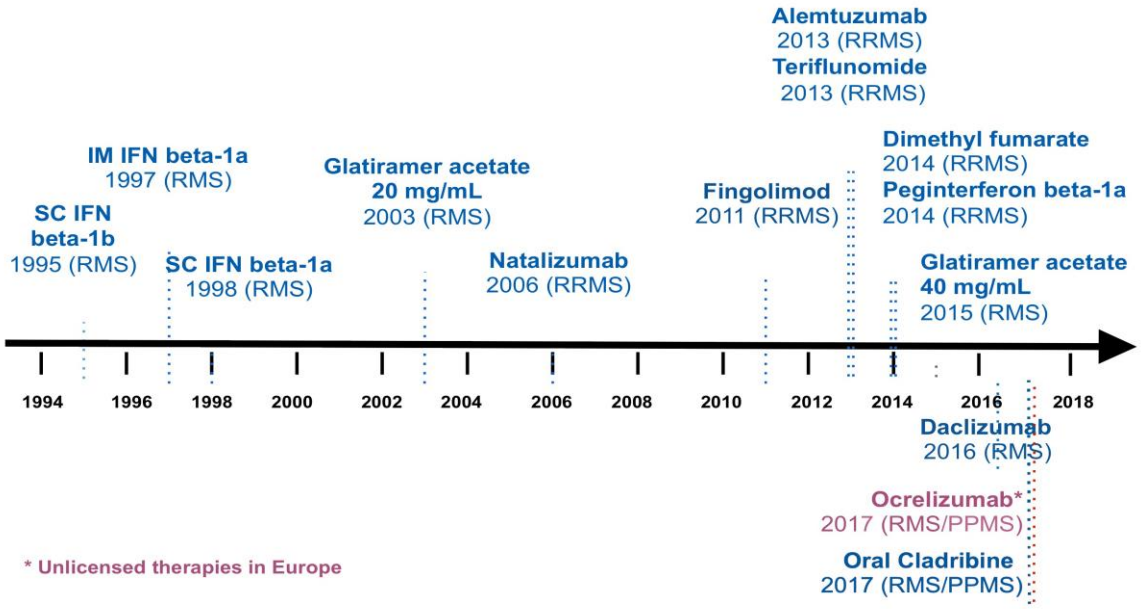

B
Active (clinical)
with progression
Active (MRI/clinical)
without progression
Active (MRI) with
progression
Not active with
progression
Not active without
progression
Secondary progressive
MS
Primary progressive
MS
MRI activity - new or enhancing lesions

Figure 6.


Alemtuzumab
2013 (RRMS)
Teriflunomide
2013 (RRMS)
IM IFN beta-1a
1997 (RMS)
Glatiramer acetate
20 mg/mL
2003 (RMS)
Dimethyl fumarate
2014 (RRMS)
Fingolimod
2011 (RRMS)
Peginterferon beta-1a
2014 (RRMS)
SC IFN
beta-1b
1995 (RMS)
SC IFN beta-1a
1998 (RMS)
Natalizumab
2006 (RRMS)
Glatiramer acetate
40 mg/mL
2015 (RMS)
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
Daclizumab
2016 (RMS)
Ocrelizumab*
2017 (RMS/PPMS)
* Unlicensed therapies in Europe
Oral Cladribine
2017 (RMS/PPMS)