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Multiple Sclerosis – a review

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Abstract

Multiple sclerosis (MS) is the commonest non-traumatic disabling disease to affect young adults. The incidence of MS is increasing worldwide, together with the socioeconomic impact of disease. The underlying cause of MS, and mechanisms behind this increase remain opaque, although complex gene-environment interactions almost certainly play a significant role. The epidemiology of MS indicates that low vitamin D, smoking, childhood obesity and infection with the Epstein-Barr virus are likely to play a role in disease development.

Changes in diagnostic methods and criteria mean that we can diagnose people with MS increasingly earlier in their disease trajectory. Alongside this, treatments for MS have increased exponentially in number, efficacy, and risk. We now face a situation where we have the potential to diagnose “pre-symptomatic MS”, and potentially investigate preventive strategies for this disease. In this comprehensive review, we discuss MS epidemiology, potential aetiological factors and pathology, before moving on to clinical aspects of MS diagnosis and management.

Introduction

Multiple sclerosis (MS) is the commonest non-traumatic disabling disease to affect young adults[1]. There is increasing incidence and prevalence of MS in both developed and developing countries[2], the underlying cause of which remains uncertain. MS is a complex disease; many genes modestly increase disease susceptibility in addition to several well defined environmental factors, in particular vitamin D or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, obesity and smoking[3].

MS has historically been classified as an organ specific T-cell mediated autoimmune disease. However, the success of B-cell targeted therapies challenges the standard T-cell autoimmune dogma[4]. It is traditionally viewed as a two-stage disease, with early inflammation responsible for relapsing-remitting disease and delayed neurodegeneration causing non-relapsing progression, i.e. secondary and primary progressive MS[5,6].

The emergence of increasingly effective biological therapies and an active approach to treating MS, in particular treating to a target of no evident disease activity (NEDA), are changing the long-term outcome for people with MS (pwMS). More aggressive immune reconstitution therapies (IRTs), that result in a proportion of pwMS entering long-term remission, offer a small number of pwMS a potential cure[7]. Recent positive trials of DMTs in 'progressive MS' offer those with more advanced MS the hope of slowing their disease progression, with preservation of residual function[8]. The fact that treatments appear to work at multiple stages in the disease course significantly challenges the traditional 2-stage view of the natural history of MS[9].

Epidemiology and aetiology

It is often stated that the cause of MS is unknown, however this is not quite correct. EBV, sunshine (UVB), smoking and vitamin D, combined with an individual's genetic background, play important roles in the causal pathway that results in MS development[10]. Migration studies consistently support MS being secondary to an environmental exposure[11]. Adult migrants from low risk countries, such as the West Indies, to Europe are at low risk of developing MS; however, children born to migrants in Europe are at high risk. Migration studies indicate that environment trumps genetics and argue strongly for prevention studies targeting known environmental risk factors.

Being truly EBV negative protects you from developing MS[12][13]; symptomatic EBV infection (i.e. infectious mononucleosis), doubles your chances of getting MS[14]. Evidence regarding the mechanism via which EBV increases MS risk is heterogenous; molecular mimicry is historically a popular theory [15], more recently EBV-induced B-cell immortalisation and/or transformation is been thought to play an important role in disease development [16].

MS is increasingly a global disease[2] . MS prevalence increases with latitude, however this gradient is decreasing in Norway and USA, the two countries where this has been studied[17]. The latitudinal gradient in MS prevalence is strongly correlated with UVB exposure, which stimulates cutaneous vitamin D (vD) production. Low vD levels, decreased intake of vD, reduced outdoor activity and increased MS susceptibility associated with genetic polymorphisms causing low vD levels have implicated vD in the causal pathway of MS[18].

MS is more common in females, but this has not always been the case. In case series from the early 1900s the sex ratio was almost equal. Since then, the sex ratio has been steadily increasing, and is now close to 3:1 (F:M) in most developed countries[19]. Smoking, which increases MS risk by approximately 50%, can explain up to 40% of the increased incidence of MS in women[20]. Prior to the second world war few women smoked, but the number of women smoking rapidly increased post-war, mirroring the increasing incidence of MS in women[20]. The observation that organic solvents[21] and smoked tobacco[22], but not oral tobacco or snuff[23], are associated with MS has led to the hypothesis that these agents cause post-translational modifications via antigen presentation occurring in the lungs.

It is likely that MS risk modification occurs throughout life, starting in utero[10]. The month-of-birth effect and increased concordance in dizygotic twins compared to siblings, indicates that the intrauterine environment is important in establishing MS risk; it is unclear whether this is due to common environmental exposures, or epigenetic mechanisms, or both[10].

There is a genetic influence on MS susceptibility; about one in eight patients have a family history of MS[24]. Concordance in female monozygotic twins approaches 30% in the UK and Canada, but is as low as ~8.5% in southern Europe[25].

The main genetic risk associated with MS resides in HLA-DRB1*15 and/or other loci in strong linkage disequilibrium with this allele[26]. Heterozygotes for HLA-DRB1*15:01 have an OR of MS >3 and homozygotes >6[26], yet the mechanism remains unknown. It is hypothesised that HLA-DRB1*15:01's role is via antigen presentation, however this does not explain the protective effects of class 1 alleles (e.g. HLA-A*02:01)[27].

Genome-wide association studies have identified more than 150 single nucleotide polymorphisms (SNPs) associated with MS susceptibility[28]. The OR associated with the majority of these is small, around 1.1-1.2. Many of these SNPs lie close to genes associated

with immune function, typically in regulatory rather than coding regions. Functional variants identified include those within IL7R[29], IL2RA[30], TNFR1[31], BAFF[32] and CYP2R1[33]. Mendelian randomisation studies have provided evidence for a role of vitamin D[33–35] and obesity[36] as independent risk factors causing disease.

Recent work has uncovered genetic differences between RRMS and PPMS[37] not previously detected in GWAS, most likely due to the under-representation of PPMS in these cohorts. Genetic variants associated with other progressive neurological disorders are relatively over-represented in progressive MS[37]. Similar genetic risk exists when all MS-associated alleles are taken in account, indicating additional risk for progressive disease superimposed on underlying genetic susceptibility. Evidence of differential gene transcription between RRMS and PPMS[38], again hints at individual differences on a background of shared genetic risk.

Pathology & Immunology

In Charcot’s original descriptions of the pathology associated with sclerose en plaques, he described “sclerosed plaques” affecting the periventricular area, pons, and spinal cord[39].

The characteristic pathological hallmark of MS is perivenular inflammatory lesions, leading to demyelinating plaques[40]. The inflammatory infiltrates contain T-lymphocytes, dominated by MHC Class I restricted CD8+ T-cells; B-cells and plasma cells are also present, although in much lower numbers[41]. Oligodendrocyte damage and demyelination occur as a result of inflammation. Axons are relatively preserved in the early stages of the disease, however as disease progresses irreversible axonal damage develops[42]. The “classical active lesion”, with profound lymphocytic inflammation, predominates in RRMS. It is seen less commonly in progressive disease, where lesions tend to have an inactive lesion core surrounded by a narrow rim of activated microglia and macrophages[43].

Despite a clinical distinction between RRMS and progressive MS, pathologically-defined inflammatory changes are seen in both, albeit to a greater degree in relapsing-remitting disease. The composition of the inflammatory infiltrate in relapsing-remitting and progressive MS is similar, although the proportion of B-cells and plasma cells is higher in progressive MS[44]. Whether the cytokine profile or activation stage of T-cells and B-cells differs between clinical disease types remains unclear[41].

Remyelination is seen in all disease stages, most commonly in progressive disease[41].

Patients with SPMS have higher levels of demyelination, and a reduction in axonal density in the normal appearing white matter in the cervical spinal cord in PPMS[45]. There is no single characteristic histological difference between MS subtypes, instead a difference in the proportion of areas showing particular characteristics. Thus whilst three clinical forms of MS have been defined, the pathological changes form a continuum. This fits with gradual clinical disease evolution in patients, from relapsing-remitting to secondary progressive MS over a period of years.

Clinical features

MS is a journey from being at risk, through the asymptomatic, prodromal and symptomatic phases of the disease. MS is typically suspected when a person presents with a clinically isolated syndrome (CIS). This can be mono- or poly-symptomatic depending on the location of the eloquent lesion(s). The most commonly seen presentations are optic neuritis, brainstem and spinal cord syndromes, however numerous other less common presentations exist, including cortical presentations, such as dominant parietal lobe syndromes.

MS relapses usually develop subacutely over hours to days, reach a plateau lasting several weeks, then gradually recover. Gross clinical recovery from relapses often appears complete in early MS, however most relapses leave behind some damage. For example, following acute optic neuritis gross visual acuity may recover, but colour vision, contrast sensitivity and depth perception abnormalities persist. As neuronal reserve is lost, recovery from relapses becomes incomplete, and neurological deficits accrue leading to sustained disability.

For every clinical attack approximately ten “asymptomatic” lesions are noted on MRI.

Symptomatology results from a combination of location and size - a small lesion in an eloquent area is likely to cause symptoms. Macroscopic, or MRI-visible, lesions are the tip of the iceberg; with many more lesions can be seen at microscopic level and even more in deep and cortical grey matter.

Secondary progressive MS typically develops 10-15 years after RRMS onset, with a gradual evolution from discrete relapses to slowly progressive disease. There is not a distinct transition between disease types, rather relapses occur on a background of subtle progression, prior to progression being dominant. The cognitive impairment and progressive MRI atrophy seen in early MS indicate that neurodegeneration is present from clinical onset.

In 5-15% of cases there is a primary progressive onset (primary progressive MS, PPMS), typically with gradual accrual of progressive disability involving one dominant neuronal system. The commonest presentation is with a progressive spastic paraparesis, but sensory ataxia, cerebellar ataxia, cognitive and progressive visual failure are well described PPMS variants.

There has been a reduction in the proportion of people with PPMS[46]. This is likely related to the fact that there are no licensed treatments for PPMS; patients may be labelled as having relapsing MS in order to receive treatment, raising ethical questions about the division of MS into distinct subtypes. This artificial division of MS into different diseases was driven by the pharmaceutical industry to get interferon-beta licensed under the orphan drug act in the US.

Paediatric MS is considerably rarer than adult onset disease, with a highest reported incidence of 2.9/100,000 [47]. The diagnosis is based on repeated episodes of demyelination separated by time and space. Differentiating paediatric MS from ADEM can be challenging, as paediatric MS may be multifocal at onset [47]. Relapse rates may be higher, but physical recovery tends to be more complete. Few treatments are licensed for use in children, and referral to a paediatric neurologist with expertise in demyelinating disorders is recommended where the diagnosis is suspected.

Given the above, MS can be thought of as a single disease existing within a spectrum extending from relapsing (“inflammatory dominant”) to progressive (“neurodegeneration dominant”), in keeping with the 2013 revisions to the clinical course of MS [48]. At present, MS definitions place artificial distinctions between patients with progressive and patients with relapsing disease. Instead, these subtypes should be seen as points on a continuum of disease, which should be expanded to include prodromal (i.e. radiologically isolated) disease.

Preclinical disease and the at-risk population

MS has an at-risk period prior to preclinical and clinical phases[49]. Migration studies indicate that the time from exposure to environmental risk factors and the onset of disease is 10-20 years[49]. Pathological studies indicate that the preclinical phase of MS could be decades; a Danish series found that a quarter of cases with post-mortem pathological evidence of MS were never diagnosed with MS in life[50].

MS begins before the first clinical attack; most patients presenting with a CIS have older, inactive, lesions on their MRI. Radiologically isolated syndrome (RIS), or “asymptomatic MS”, is detected on an MRI done for unrelated reasons, such as headache, head injury or screening in the airline industry. Even in these earliest stages there is evidence of end-organ damage. MRI in young people with CIS shows brain volume loss compared to controls[51]. School performance in children who later develop MS, is poorer than their peers[52], and a quarter of patients with RIS have significant cognitive impairment with a profile similar to patients with established MS[53]. This appears to indicate that not only is inflammation present prior to diagnosis, but there is accompanying neurodegeneration from the start.

We predict that MS has the potential to become a model neurodegenerative disease, setting the stage for presymptomatic diagnosis for other neurodegenerative diseases, in particular Alzheimer’s and Parkinson’s disease. The big question is whether society is ready for population screening and presymptomatic diagnosis? At some point in time we are going to have accept that to have a meaningful impact on the burden associated with neurodegenerative disease we are going to have to diagnose these conditions in the presymptomatic phase.

Important differential diagnoses

Table 1 lists the most common MS differential diagnoses or mimics. Red flags include a first relapse at an older age, where vascular disease is more likely. Non-specific white matter lesions may be seen in patients with no objective persisting neurological disability and history of migraine, although migraine is more common in the MS population[54]. In those from low prevalence areas and/or ethnic minorities, differential diagnoses must be carefully considered, as neurosarcoidosis, NMOSD and infections such as TB are more likely, and MS-specific disease modifying therapy may cause a worsening of these diseases.

Another red flag is comorbid systemic symptoms and signs; this should alert clinicians to exclude multisystem diseases such as SLE, Sjogren's, Behcet's, Susac's and other vasculitides. MS can coexist with other autoimmune diseases, and so the presence of these does not necessarily exclude MS, and the overall clinical picture must be carefully considered.

We would advise a diagnostic lumbar puncture in all patients presenting with possible MS. CSF analysis is helpful in both identifying MS mimics and either supporting or arguing against a diagnosis of MS. CNS synthesis of oligoclonal IgG bands or OCBs can now be used to establish dissemination in time; this will hopefully lead to a renaissance in the use of CSF for diagnostic, prognostic and treatment response purposes.

Table 1: Differential diagnosis of multiple sclerosis

Investigations

The diagnosis of MS remains clinical. However, treatable mimics should be excluded using paraclinical investigations where indicated. All patients with suspected MS should have a lumbar puncture to help support the clinical diagnosis of MS, exclude MS mimics and to help establish a baseline prognostic profile.

(i) Serological investigations

A standard baseline profile should include anti-nuclear factor, vitamin B12, and thyroid function. Syphilis and HIV-1 serology are recommended. Depending on the clinical presentation HTLV-1&2 serology, anti-aquaporin-4 and anti-MOG antibody screening may be indicated.

(ii) MRI

All patients should undergo MRI imaging of at least the brain and if the presentation is spinal, imaging should include the spinal cord. Imaging has a dual purpose - it can help to confirm the diagnosis by demonstrating dissemination in both time and space, but it can also exclude MS mimics when interpreted by an experienced neuroradiologist. Approximately 2% of non-MS related abnormalities picked-up on MRI are incidental findings, e.g. pituitary adenomas, pineal cysts, vascular malformations, benign meningiomas and prolapsed intervertebral discs. These incidental findings may clinically complicate things, but should not distract from diagnosing MS. Visual, auditory and sensory evoked potentials and central motor conduction times can establish dissemination in space, and demonstrating slowed conduction in patients with equivocal clinical signs and MRI appearances can be useful, however they may not add much clinical value. The corollary is that normal electrophysiology can be helpful in actively excluding or undiagnosing MS; a clinical problem that is much more common than often realised.

Table 2 summarises the latest set of diagnostic criteria for RRMS[55]. As with previous renditions, they have limitations in their clinical implementation. Using baseline OCBs to provide evidence of dissemination in time means many patients previously diagnosed with CIS now meet the diagnostic criteria for MS. This could create significant problems in clinical practice, as guidelines for treatment typically mandate a clinico-radiological diagnosis of MS - reclassified patients may acquire a label of MS, but remain ineligible for treatment until a second clinical attack or MRI lesion.

Table 2: MacDonald Criteria for relapsing remitting and primary progressive Multiple Sclerosis

Some would argue that these criteria do not go far enough as they do not include a diagnosis of “asymptomatic MS”. Patients diagnosed as having RIS are not eligible for treatment. This is troubling as a proportion of these subjects already have evidence of end-organ damage with brain atrophy and cognitive impairment. Approximately 30% go onto develop MS within 5 years[56], and we may be able to prevent some, or even all, of these patients from developing clinically apparent neurological disease with early interventions. Based on the biological understanding of MS, early and effective treatment with a DMT will have benefits for individual patients.

The role of MRI in establishing prognosis and treatment response is wide ranging.

Traditionally, lesion accrual/count, together with “active” lesions (gadolinium-enhancing) has been used to estimate disease activity, however correlation with long term outcomes is imperfect. The importance of brain atrophy seen on volumetric MRI is increasingly realised, as when taken alongside lesion load there is good correlation with long-term clinical outcomes [57].

High field and double inversion MRI techniques have enabled the visualisation of cortical MS lesions, the presence and number of which appear to correlate with clinical outcomes, most notably cognitive impairment [58]. Newer MRI techniques, including magnetization transfer imaging (MTI), diffusion tensor imaging (DTI), and fMRI are providing insights into disease with widespread abnormalities outside of focal lesion development [59], however these techniques are not yet in routine clinical practice.

Treatment and management of MS

The treatment of MS can be divided up into disease modifying therapies that tend to be MS-specific, and symptomatic therapies that are often used in different disease areas to treat symptoms resulting from neurological dysfunction.

(i) Disease modifying therapies

As the number, and efficacy, of disease modifying therapies has increased, interest in early treatment of MS in order to prevent long-term disability has grown. Historically, treatments have been immunosuppressant (including fingolimod, natalizumab, ocrelizumab) or immunomodulatory (such as interferon-beta, glatiramer acetate, teriflunomide), meaning that ongoing treatment is required to maintain suppression of inflammation (and disease activity).

Immune reconstitution therapies (including alemtuzumab and cladribine), can be given as short courses with the aim of producing enduring immunological actions - this is as close as we have to a potential cure for MS. This raises the question as to whether early, or even pre-symptomatic, treatment can prevent clinically apparent disease.

Table 3: Disease modifying therapies currently licensed for the treatment of MS

Figure 1: (a) Treat-2-target algorithm of NEDA in relapsing-forms of MS; (b) Different therapeutic approaches to the “treat to target” algorithm

Figure 2: New classification of disease-modifying therapies for relapsing forms of MS

A recent concept in the treatment of MS is “No Evidence of Disease Activity”, or NEDA.

This has developed from the understanding that clinical relapses are only the tip of the iceberg in terms of MS disease activity. Ongoing inflammatory MRI activity occurs in excess of clinical relapses; in addition brain atrophy can progress in the absence of overt inflammatory disease activity. NEDA is defined by clinical parameters (NEDA-1 and 2 -

absence of relapses and clinical disease progression), inflammatory MRI activity (NEDA-3), and MRI atrophy and biomarkers (NEDA-4 and 5 - CSF neurofilament levels). In clinical practice, this has led to treatment escalation earlier in disease, or early treatment with highly active therapies as first line (figures 1b and 3).

Figure 3: NEDA rates in sentinel clinical trials of disease-modifying therapies for relapsing forms of MS

Given that MS is most commonly diagnosed in young women, pregnancy and family planning are real concerns for women with MS. Current evidence suggests that pregnancy does not increase the risk of long-term disability in MS. However, it is also important that disease modifying treatment is not unduly delayed, especially in those with active disease. European guidelines briefly discuss issues around pregnancy [60], and UK consensus guidelines are currently in press.

(ii) Symptomatic treatments

Symptomatic therapies refer to pharmaceutical and physical therapies that target symptoms arising as a result of central nervous system damage. In general terms these treatments are not MS-specific. These include anticholinergics for bladder dysfunction (which may contribute to cognitive impairment, necessitating an individualised approach), and medication for neuropathic pain (typically tricyclic antidepressants, or gabapentin and derivatives). Treating cognitive impairment in MS is complex, and centres around the avoidance of possible contributors. Several symptomatic therapies have been licensed specifically for MS. These include sativex for spasticity, and fampridine for walking difficulties. An important aspect

related to symptomatic therapies is sleep. The prevalence of difficulties with sleeping increases as MS disease duration increases, and anxiety, depression and fatigue are more common in those reporting poor sleep[61]. A detailed review of these is beyond the scope of this article.

(iii) Treatment of comorbidities contributing to long-term disability

MS reduces the brain and cognitive reserve that delays the onset of age-related neurodegenerative disorders in later life. This may explain a component of the age-related progression in older patients with multiple sclerosis.

Patients with co-morbid disease, in particular vascular disease and smoking, have a poorer outcome with more rapidly progressive disease[22]. Recurrent infections such as urinary tract infections, may not only result in transient worsening of MS-related symptoms but could upregulate mechanisms known to speed-up worsening disability.

Although the evidence supporting lifestyle and wellness modifications in MS is weak, the value of these for general health is important. Patients who exercise do better than those who don't. Patients should be encouraged to have four to five aerobic exercise sessions per week. They should avoid vigorous exercise during relapse, as this may cause excessive energy demands on an already compromised pathway, and theoretically could increase neuroaxonal loss. In patients with significant disability, a bespoke exercise programme should be designed to allow them to exercise, which is best done in conjunction with a physiotherapist with experience in neurodisability.

Despite numerous claims about dietary interventions in MS there are no randomised controlled trials to suggest that one diet is superior to the others. Patients should adopt a healthy eating pattern that is compatible with their culture; their diet should avoid processed foods, in particular sugar and other processed carbohydrates. The WHO recommends no more than 5% of dietary calories should be consumed as sugar. In general, a varied diet rich in unprocessed foods is recommended.

Future prospects

By refinement of the MS phenotype, both through expansion to include prodromal cases, and extension of disease into a single entity rather than artificially separated disease states, we can better understand and treat the illness in question. At present, disease modifying treatments are only available to people with clinically relapsing forms of the disease, and a minority of those with progressive disease - those showing high levels of inflammatory disease on MRI.

By better understanding MS as a disease continuum, it can be seen that there is potential for treatment effects in all MS subtypes. Clinical trial outcome measures for relapsing disease are relatively easy to define; in those patients with progressive disease, clinically measurable rate of change is slow, and measuring impact on this already slow rate requires more sensitive outcome measures than are in current use. Patients with progressive disease have historically been denied treatment on the basis of negative clinical trials; if the outcome measures used in these trials are insufficiently sensitive to measure treatment effects then it is our responsibility as physicians to develop outcome measures with better sensitivity, rather than artificially separate disease subtypes.

The fact that aetiological factors implicated in MS development have the potential to be modified prior to disease development opens the door to the potential for preventive trials.

However, these would need to be enriched for a high-risk population group, and will take many years to set up. In the meantime, early treatment of those at risk of long term disability is needed in order to minimise the physical morbidity associated with MS.

Figure legends

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Table legends

Table 1 Differential diagnosis of multiple sclerosis

Table 2 Diagnostic criteria for relapsing remitting and primary progressive multiple sclerosis

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Tables

Table 1 Differential diagnosis of multiple sclerosis

Clinical presentation	Differential diagnosis	Relevant aspects and investigations to consider
<i>Monosymptomatic</i>		
Acute optic neuritis (ON)	Neuromyelitis optica, NMO	Often associated with severe visual loss. May be bilateral rapidly sequential ON. AQP4 and MOG antibodies. Possible additional MRI lesions in area postrema or diencephalon.
	Leber hereditary ON	Genetic testing.
	Toxic/nutritional ON	Clinical history, alcohol and tobacco use. B12, methylmalonic acid and/or plasma homocysteine.
	Non-arteritic ischaemic ON	Age - usually in older patients. Clinical history and examination; vascular risk factors.
	Arteritic ischaemic ON	Age - usually occurs in patients aged >70. Autoimmune/ANA screen, ESR.
Transverse myelitis (TM)/spinal cord syndrome	Neuromyelitis optica, NMO	Consider if long segment transverse myelitis (>3 segments) involving much of the central spinal cord with oedema and gadolinium enhancement. Additional MRI lesions in area postrema or diencephalon. May have previous optic neuritis. AQP4 and MOG antibodies.
	T.M associated with systemic autoimmune disease	May have systemic features or clinical history of autoimmune disease (rash, renal involvement, dry eyes etc). ANA screen, ESR.
	Anterior spinal artery occlusion	Sudden, catastrophic onset with anterior spinal cord syndrome. Usually older patients and/or those with vascular risk factors. MRI may differentiate with bilateral anterior involvement in watershed mid thoracic area typical.
	Arteriovenous fistula/malformation	Stepwise onset, mixed upper and lower motor neurone. MRI and/or spinal angiography may make the diagnosis with dilated and/or tortuous dural veins seen.

	Radiation myelopathy	Clinical history, MRI may show vertebral changes
	B12/folate deficiency	Clinical history of dietary insufficiency and/or nitrous oxide inhalation. FBC/serological changes may co-exist. May have additional optic neuropathy and/or peripheral nerve involvement. Long segment changes in dorsal columns on MRI. Serum B12 and plasma homocysteine/methylmalonic acid levels.
	Copper deficiency	Clinical history of gastrectomy or excessive zinc intake. Long segment changes in dorsal columns on MRI. Serum copper levels diagnostic.
Brainstem	Ischaemic event (stroke, TIA)	Clinical history, age - usually in older patients. MRI and CSF may help differentiate.
	Space occupying lesion	More gradual onset, MRI can differentiate
	Migraine	More rapid resolution, may have severe headache. MRI can help differentiate.
	Brainstem encephalitis (Bickerstaff's)	Patients may be encephalopathic and/or obtunded. MRI and CSF can help differentiate.
	Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)	Clinical history - may have peripheral nerve involvement in brainstem.
<i>Polysymptomatic</i>		
	Migraine	More rapid resolution, may have severe headache. MRI can help differentiate.
	Ischaemic event (stroke, TIA, small vessel disease)	Clinical history, age - usually in older patients. MRI and CSF may help differentiate.
	Cerebral autosomal dominant arteriopathy with cortical infarcts and leukoencephalopathy (CADASIL)	Family and clinical history - typically migraine, stroke-like events and prominent cognitive involvement. MRI can show typical appearances. NOTCH-3 mutation testing diagnostic.
	Sarcoidosis	May have multisystem involvement - CT chest may help. OCBs often negative in CSF.

Systemic autoimmune disease	May have systemic features or clinical history of autoimmune disease (rash, renal involvement etc). ANA screen, ESR, Ro/La, SCL-70
Primary CNS vasculitis	Patients often encephalopathic. MRI shows small ischaemic (rather than inflammatory) lesions. MRI angiography can be helpful.
Susac's syndrome	Clinical history of encephalopathy, deafness and/or visual impairment may be present – most patients do not have complete triad at presentation. Branch retinal infarcts on fundoscopy. Characteristic callosal lesions on MRI. Fluroscin angiography mandatory if diagnosis suspected.
Neuro-Bechet's	Systemic and/or additional CNS features - venous sinus thrombosis and meningitis. Associated with HLA-B5.
Acute disseminated encephalomyelitis - ADEM	Acute polysymptomatic onset, often post-viral. MRI shows large demyelinating lesions all of similar age with gadolinium enhancement but without T1 black holes at presentation.
<i>Progressive disease</i>	
Spinal cord compression by disc, tumour, syrinx etc	MRI
Progressive metabolic myelopathy	Clinical history, copper/B12 levels, MRI
Genetic progressive spastic paraparesis/cerebellar ataxia (HSP, SCA)	Family and clinical history, relevant genetic test
Leukodystrophies	Very long chain fatty acids (especially in males) and white cell enzymes
Infectious causes - HTLV and HIV	Clinical (+/- family history), HTLV 1 and HIV serology

Table 2 Diagnostic criteria for relapsing remitting and primary progressive multiple sclerosis

	MacDonald 2010 (relapsing remitting MS)	MacDonald 2017 (relapsing remitting MS)
DIS	<i>Either:</i>	<i>Either:</i>
	i) Objective clinical evidence of ≥ 2 lesions, or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack involving a different CNS site <i>or</i>	i) Objective clinical evidence of ≥ 2 lesions, or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack involving a different CNS site <i>or</i>
	ii) ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, spinal cord); <i>symptomatic lesions in patients with brainstem or spinal cord syndromes are excluded</i>	ii) ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, spinal cord)
DIT	<i>Either:</i>	<i>Either:</i>
	(i) ≥ 2 attacks separated by at least 1 month, <i>or</i>	(i) ≥ 2 attacks separated by at least 1 month, <i>or</i>
	(ii) Simultaneous presence of <i>asymptomatic</i> gadolinium enhancing and non-enhancing lesions at any time, <i>or</i>	(ii) Simultaneous presence of <i>asymptomatic</i> gadolinium enhancing and non-enhancing lesions at any time, <i>or</i>
	(iii) A <i>new</i> T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of its timing with reference to a baseline scan	(iii) A <i>new</i> T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of its timing with reference to a baseline scan, <i>or</i>
		(iv) <i>Demonstration of CSF-specific OCBs (as a substitute for DIT)</i>
MacDonald 2010 criteria for primary progressive MS		
(i) 1 year of disease progression (retrospectively or prospectively determined) <i>and</i>		

(ii) 2 out of 3 of:	Evidence of DIS in the brain based on ≥ 1 T2 lesion in at least one area characteristic for MS (periventricular, juxtacortical, infratentorial), <i>and/or</i>
	Evidence of DIS in the spinal cord based on ≥ 2 T2 lesions in the cord <i>and/or</i>
	Positive CSF (OCBs on isoelectric focussing and/or elevated IgG index)

DIS: dissemination in space

DIT: dissemination in time

CNS: central nervous system

OCB: oligoclonal band

Table 3: Disease modifying therapies currently licensed for the treatment of MS

	Trade Name	Mechanism of action	Efficacy	Route of administration	Main adverse effects	Monitoring requirements
First line injectable therapies						
Interferon-beta 1a and 1b	Avonex, Rebif, Betaseron, Betaferon, Extavia	Immunomodulatory, pleiotropic immune effects	Moderate	Variable and depends on formulation	Injection site reactions, flu-like symptoms, abnormal LFTs, lymphopaenia, leukopaenia	Baseline: FBC, U&E, LFTs, TFTs, SPE, urine protein. Follow-up: 1-month, 3-month, 6-month and 6-monthly FBC, U&E and LFTs. TFTs 12 monthly. NABs 12 & 24 months
Peg-IFN-beta-1a	Pegri dy	Pegylated (long-circulating half-life). Immunomodulatory, pleiotropic immune effects	Moderate	Prefilled syringe 125ug sc 2-weekly	Injection site reactions, flu-like symptoms, abnormal LFTs, lymphopaenia, leukopaenia	Baseline: FBC, U&E, LFTs, TFTs, SPE, urine protein. Follow-up: 1-month, 3-month, 6-month and 6-monthly FBC, U&E and LFTs. TFTs 12 monthly. NABs 12 & 24 months
Glatiramer acetate	Copaxone	Immunomodulatory, pleiotropic immune effects	Moderate	Prefilled syringe 20mg sc daily or 40mg sc TIW	Injection site reactions, lipoatrophy, flushing reactions	None required
Oral immunomodulatory therapies						

Dimethyl fumarate	Tecfidera	Pleiotropic, NRF2 activation, downregulation of NFK β	Moderate/High	240mg twice daily PO	Flushing, gastrointestinal symptoms (dyspepsia, cramps and diarrhoea), lymphopaenia, abnormal LFTs, proteinuria, PML	Baseline: FBC, U&E, LFTs, urine protein. Follow-up: FBC and urine protein 3 monthly for a year, then 6-monthly.
Teriflunomide	Aubagio	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis), anti-proliferative	Moderate	7 or 14mg daily PO (7mg dose only licensed in the USA)	Hair thinning, gastrointestinal symptoms (nausea, diarrhoea), abnormal LFTs, leukopaenia,	Baseline: BP, FBC, U&E, LFTs, urine protein. Follow-up: Fortnightly LFTs for 6 months then every 8 weeks. Weekly LFT if ALT 2-3x ULN. 3-monthly FBC for 1 year then 6-monthly.
Oral immunosuppressive therapy						
Fingolimod	Gilenya	Selective S1P modulator, prevents egress of lymphocytes from lymph nodes	High	0.5mg daily PO	Bradycardia (first dose), hypertension, bronchospasm, lymphopaenia, abnormal LFTs, infections, basal cell carcinoma, macular oedema, opportunistic infections (PML, cryptococcosis, etc.)	Baseline: BP, FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV1&2, hepatitis B&C, syphilis), TB elispot, ECG. Follow-up: 3-monthly FBC, U&E and LFTs. TFTs 12 monthly. OCT at 3 months for macular oedema.

Intravenous immunosuppressive therapies

Natalizumab	Tysabri	Anti-VLA4, selective adhesion molecule inhibitor	Very high	300mg IV 4-weekly	Infusion reactions, progressive multifocal leukoencephalopathy (PML)	Baseline: FBC, U&E, LFTs, JCV-serology. Follow-up: LFTs 3 monthly for a year. NABs at 12 months. JCV serology 6-monthly.
Ocrelizumab	Ocrevus	Anti-CD20, B-cell depleter	Very high	Initially 300mg IV, followed 2-weeks later by 2nd dose of 300mg IV. Subsequent dosing 600mg IV 6 monthly	Infusion reactions, infections, possible hypogammaglobulinemia with prolonged use	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV1&2, hepatitis B&C, syphilis), TB elispot, cervical smear. Follow-up: annual serum immunoglobulin levels

Induction/immune reconstitution therapies

Alemtuzumab	Lemtrada	Anti-CD52, non-selective immune depleter	Very high	12mg IVI x 5 days yr-1, 12mg IVI x 3 days yr-2	Infusion reactions, infections, opportunistic infections, leukopaenia, secondary autoimmunity (thyroid, ITP, renal, etc.)	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV1&2, hepatitis B&C, syphilis), TB elispot, cervical smear. Follow-up (for 48 months after last course): monthly FBC, U&E and urine analysis and 3-monthly TFTs.
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Cladribine	Maveland	Deoxyadenosine (purine) analogue, adenosine deaminase inhibitor, selective T and B cell depletion	High	10mg tablets: cumulative dose of 3.5mg/kg over 2 years. Tablets given for 4-5 days in month 1 & 2 in yr 1 and the cycle is repeated in yr 2 (8-10 days of treatment per year)	Lymphopaenia, infections (in particular herpes zoster)	Baseline: FBC, U&E, LFTs, TFTs, serum immunoglobulin levels, serology (VZV, HIV1&2, hepatitis B&C, syphilis), TB elispot, pregnancy test and cervical smear. Follow-up: FBC 2 and 6 months after start of treatment in each treatment year.
Mitoxantrone	Novarone	Immune depleter (topoisomerase inhibitor)	Very high	12 mg/m ² IVI 3 monthly for 2 years; maximum dose of 140mg/m ²	Leukopaenia, hair loss, nausea, vomiting, infections, cardiomyopathy, amenorrhoea	Baseline: FBC, U&E, LFTs, TFTs, SPE, serum immunoglobulin levels, serology (VZV, HIV1&2, hepatitis B&C, syphilis), TB elispot. Follow-up: 3-monthly (predosing) FBC, U&E and LFTs. TFTs 12 monthly.
Autologous haematopoietic stem cell transplantation (AHSCT)		Autologous stem cell transplantation using standard haematology protocols	Very high	According to local protocols	Adverse events related to induction chemotherapy	Dictated by haematology protocols

PML: progressive multifocal leukoencephalopathy

PO: oral

SC: subcutaneous

IV: intravenous

SPE: Serum protein electrophoresis

TFT: thyroid function test

VZV: varicella zoster

Figure 1a. Treat-2-target algorithm of NEDA in relapsing-forms of MS

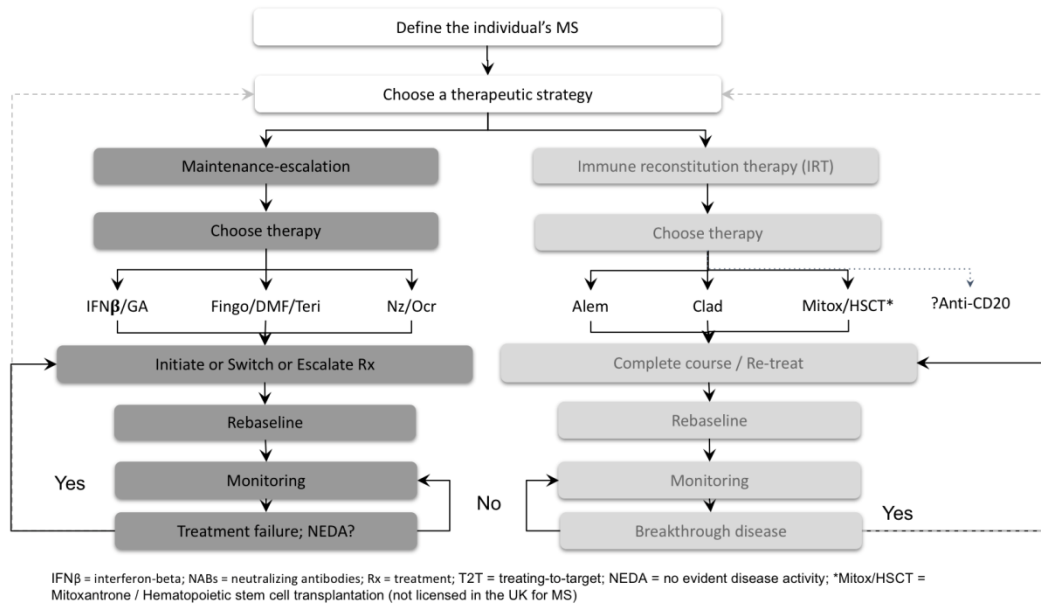
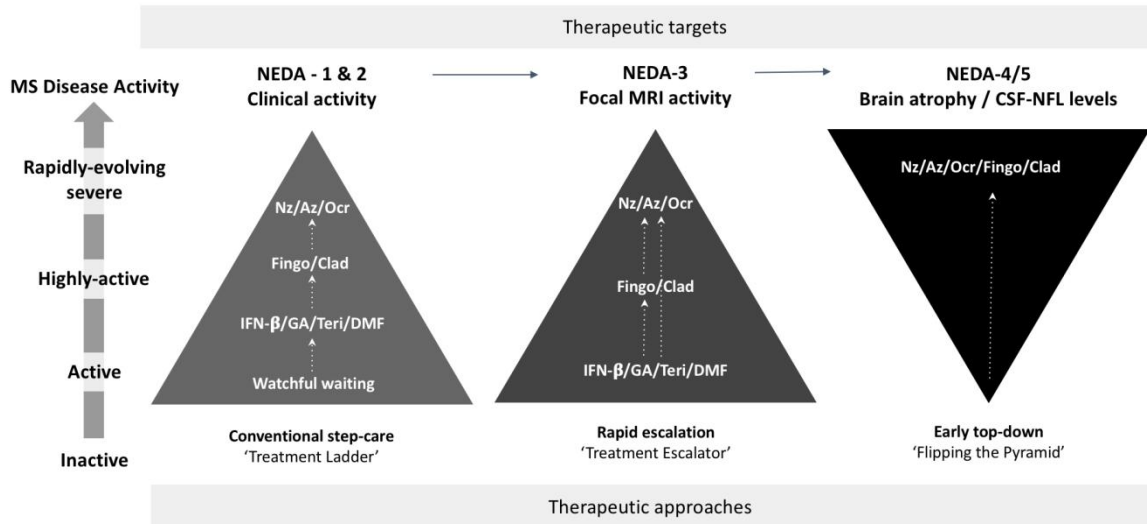


Figure 1b. Different therapeutic approaches to the “treat-to-target” algorithm



NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFN- β = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Clad = oral cladribine; Ocr = ocrelizumab

Figure 2. New classification of disease-modifying therapies for relapsing forms of MS

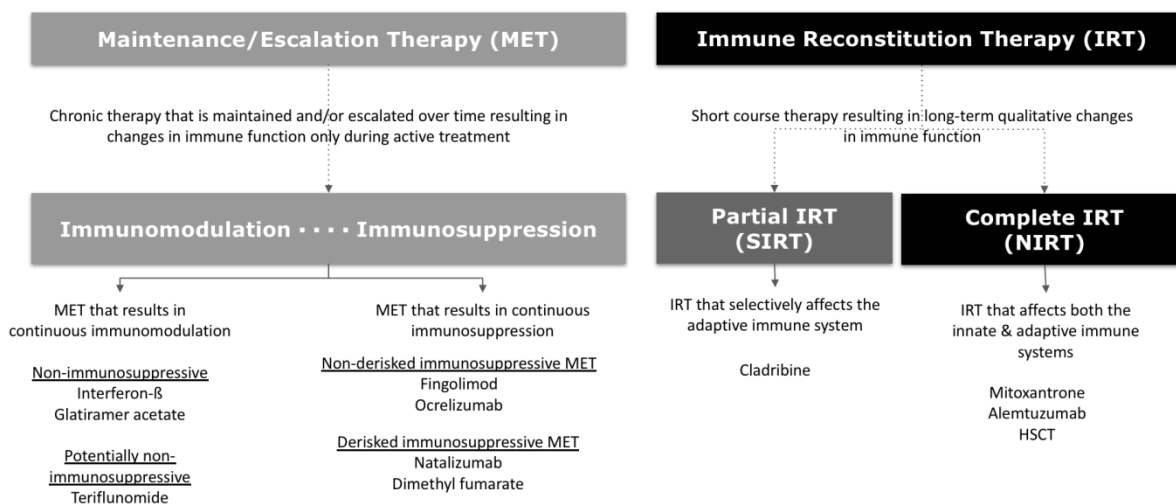


Figure 3. NEDA rates in sentinel clinical trials of disease-modifying therapies for relapsing forms of MS

