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Multiple sclerosis

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Abstract

Multiple sclerosis is classified by demyelination, inflammation and neurodegeneration in the CNS. Management requires an understanding of the complex interactions between neurophysiological systems, diagnostic techniques and therapeutic methods. The pathogenesis of MS includes, complex series of processes including immunological dysregulation, inflammation and neurodegeneration. Gene predisposition, autoreactive T cells, B cells and cytokines are essential contributors in the development of the disease. Demyelination interferes with the ability of the CNS to transmit signals which can cause a variety of neurological symptoms including motor function, sensory deficiencies and cognitive decline. Neuroimaging, laboratory testing and clinical examination are all necessary for an accurate diagnosis. The aim of MS treatment options is to control symptoms, slow disease progression and enhance quality of life. Recently immunomodulatory therapies life interferon **(IFN)-B** and **Glatiramer Acetate** have proved more effective. They reduce the rate and severity of clinical relapses and in case of IFN-B delay the rate of disease progression. In addition, symptomatic therapies and rehabilitation remain mainstay of treatment for the majority of patients with MS.

Keywords: Demyelination; Diagnosis; Immunomodulatory treatment; Symptomatic therapies

1. Introduction

Multiple Sclerosis is a neuroinflammatory disease of CNS that induces demyelination and neurodegeneration. It is one of the most significant cause of disability in the young affecting quality of life, family work and social activities [1]. MS affects around 1.8 to 2.8 million people worldwide. The prevalence across UK is estimated to be over 150,000 people. This equals to 1 in every 400 people. Globally, females are twice as likely to have an MS as males. The most common age of onset is between 20 and 40 years old.

2. Risk factors & pathophysiology

Multiple Sclerosis mostly results from environmental factors including Epstein-Barr virus infection, low vitamin D, obesity and cigarette smoking [2-4]. EBV infection of autoreactive-naïve B cells may be the first step in MS pathogenesis [2]. These infected B cells remain in lymph nodes where they present as antigens that have similarities to myelin. Autoreactive B cells and T Lymphocytes (B&T cells) then enter the CNS and orchestrate immune attacks [2]. Vitamin D typically promotes development of T regularity lymphocytes and so low vitamin D may lead to an increased number of autoreactive T cells [5]. Vitamin-D-dependent promoters are also responsible for the regulation of the human leucocyte antigen HLA-DRB1*1501 genes which is a MS risk and susceptibility gene [6]. Genetic risk factors for MS also exist, the strongest being major histocompatibility complex in chromosome 6p21.3, which contains six HCA genes of which the HLA-DRB1*1501 allele has the strongest association with MS risk [7]. MS risk is tenfold higher in a first-degree relative (0.3% population risk versus 3% family risks). More severe diseases has also been associated with higher latitudes due to less sun exposure at higher latitudes and therefore less vitamin D production. Genetic factors interact with an

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environment factor to establish or maintain pathological autoreactive T-cells which after a long and variable latency period (10-20 years) are activated possibly by a systemic trigger such as a viral infection or superantigen. All these susceptibility factors lead to a decrease of regularity and anti-inflammatory activity versus a more pro-inflammatory and auto-reactive immune system setting with a reduction of T regularity -Treg lymphocytes and an increased activity of pathogenic T helper (TH) 1 and Th17 can cross the blood-brain barrier and cross-react with oligodendrocytes antigens in the CNS [8].

3. "Inside – out" hypothesis

The "Inside – out" model of MS pathogenesis begins with the release of myelin antigens from injured or destabilized myelin to the periphery (1) followed by the presentation of myelin epitopes to (2) and activation of autoreactive T cells (3). Activated autoreactive T cells then migrate into the CNS, are reactivated by CNS-resident APCs (4), and release cytokines leading to direct as well as indirect damage to myelin (5). Additional myelin epitopes released by the primary T cell response induce epitome spreading (6) leading to additional myelin destruction (7).

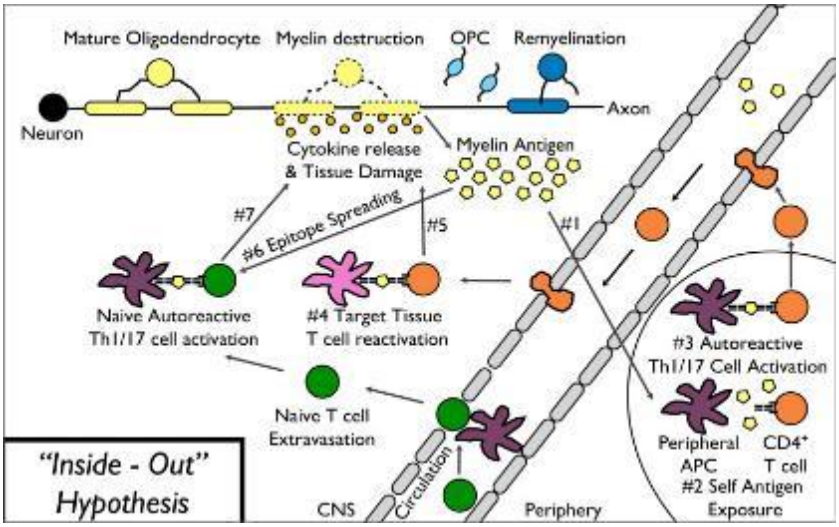


Figure 1 Frontiers in neuroscience

4. "Outside – in" hypothesis

The "Outside-in" model of MS pathogenesis begins with activation of myelin – specific T cells in response to a myelin peptide mimic epitope expressed on a pathogenic virus or other microbe exposure (1-2). Activated autoreactive T cells then migrate into the CNS, are reactivated by CNS--resident APCs (3), and release cytokines leading to direct as well as indirect damage to myelin (4). Additional myelin epitopes released by the primary T cell response induce epitope spreading (5) leading to additional myelin destruction (6)

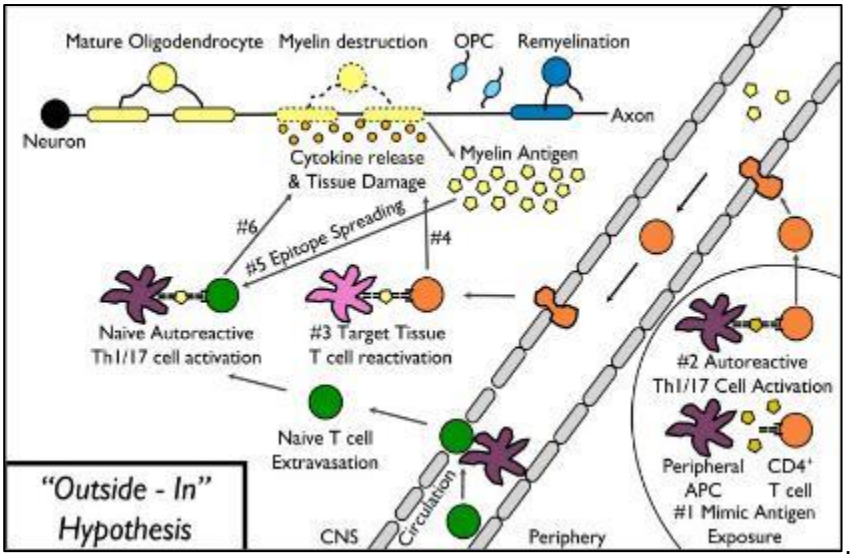


Figure 2 Frontiers in neuroscience

5. MS diagnosis

Neurologists can use a range of evidence sources including neurological examination, MRI scan, sample from a lumbar puncture or measure of nerve conductance (evoked potentials tests).

Recent changes to MS diagnostic criteria (2024 Mc Donald Criteria) include the addition of the optic nerve as the **fifth** area for showing "dissemination in space" on an MRI, the use of **Central Vein Sign** (CVS) to confirm diagnosis, and a revised approach to "dissemination in time" where it may no longer be required in certain situations.

5.1. Diagnostic criteria

Laura Balcer, NYU Grossman School of Medicine, New York, USA, introduced the optic nerve as the fifth topographic site for MS lesions in the 2024 Revised McDonald criteria (**Table 1**)

Table 1 Topographic locations for multiple sclerosis diagnosis.

CNS locations fulfilling Dissemination in Space
Optic nerve
Periventricular
Juxtacortical/cortical
Infratentorial
Spinal cord

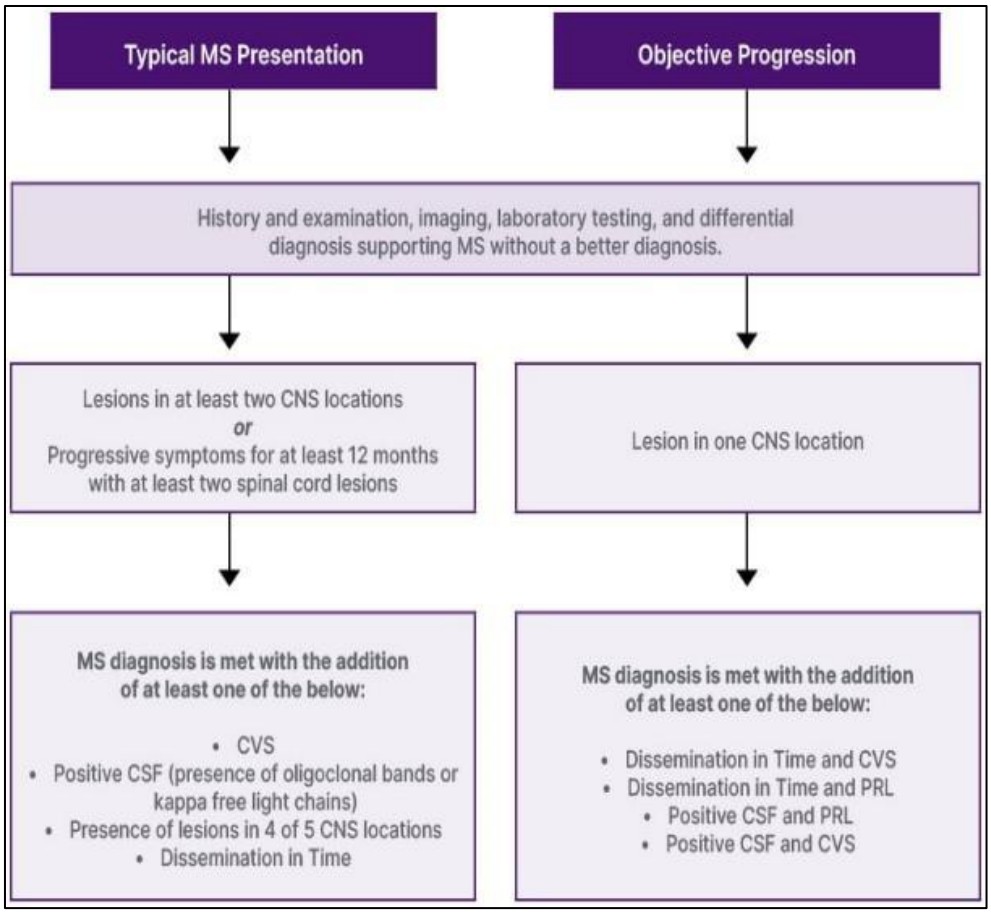
CNS: central nervous system

Table 2 Evidence of a symptomatic or asymptomatic optic nerve lesion can be determined through paraclinical testing with orbital MRI, optical coherence tomography (OCT), and/or visual evoked potentials (VEP) **(Table 2)**.[9]

Table 2 Paraclinical test criteria for optic nerve lesions.*

Significant intereye difference in OCT RNFL and/or ganglion cell layer (5 microns RNFL, 4 microns GCL)
Delayed P100 latency on visual evoked potentials
Presence of optic nerve T2 hyperintensity and/or gadolinium enhancement on MRI orbits

*Official retinal nerve fibre layer and ganglion cell layer inter eye difference measurement to be announced in the upcoming McDonald Criteria 2024 publication. The numbers provided in the Figure are based on research by Kenney et al.[10] GCL: ganglion cell layer; OCT: optical coherence tomography; RNFL: retinal nerve fibre layer.



*Diagnostic algorithm is adapted from Miller et al., 2025[9]CNS: central nervous system; CVS: central vein sign; CSF: cerebrospinal fluid; MS: multiple sclerosis; PRL: paramagnetic rim lesion

Figure 3 Diagnostic algorithm for multiple sclerosis diagnosis.*

5.2. Typical clinical syndromes and clinical features that are atypical of MS.

Typical clinical syndromes for MS include Optic Neuritis, Internuclear Ophthalmoplegia, Facial Sensory loss or Trigeminal Neuralgia, Ataxia and Partial Transverse Myelitis [11,12].

Optic Neuritis is characterized by reduced visual acuity, afferent pupillary defects and impaired colour vision and is typically unilateral in MS [13]. Visual acuity in Optic Neuritis is often better than no light perception. Pain during eye movement is common [13]. Visual deficits regularly nadir at 2 weeks and recover within 4 weeks [14].

Weakness or numbness in MS typically present over hours to days, unlike Stroke that present within minutes. MS symptoms often last for days to months, with some symptoms becoming permanent. MS relapse typically lasts for 24 hours mostly. When a fluctuation of prior MS symptoms occurs for less than 24 hours, it is considered a "pseudo-relapse", which is common after the acute inflammatory period. Risk factors for a pseudo-relapse include infection, stress and heat [15].

The initial presentation of MS often impacts the disease course. Optic Neuritis at the initial presentation is associated with a more **favourable** course [16].

In contrast, cerebellum dysfunction at onset is associated with worst **prognosis** (shorter time to a score of 6 on the Expanded Disability Status Scale) [17]. Initial spinal cord involvement is similarly associated with faster disability progression, relapse risk and poor treatment response [18-19].

Clinical feature **Atypical** for MS include bilateral or severe Optic Neuritis with poor recovery, headache, acute or subacute cognitive impairment, dizziness or vertigo without brainstem or cerebellar findings, sensory loss in the extremities without clear CNS patterns, and complete transverse myelopathy [11].

6. MRI changes

The following are the MRI changes which helps in the diagnosis of MS.

- Optic nerve as a new lesion.
- Central Vein sign means central blood vessel is visible.
- Paramagnetic rim lesion.
- Radiologically isolated syndrome – In the past, individuals with the MS-like lesions on an MRI but no symptoms were diagnosed with RIS. The 2024 criteria now allow for an MS diagnosis in some cases if there is "dissemination in space" and other evidence, such as evidence of "dissemination in time" or a positive spinal fluid test.

6.1. Lumbar puncture

Additionally, the new criteria incorporate new biomarker, such as Kappa free light chains which can be used in place of oligoclonal bands and it allows for the diagnosis of MS in some people who would previously have been classified as having Radiologically Isolated Syndrome. Kappa free light chains are produced by white blood cells, as part of immune response.

7. MS treatment

7.1. Acute MS relapse treatment

Most patients with MS flares will not require emergency care unless they present with strength, gait or vision impairment [20]. The use of intravenous corticosteroids (example 1000 mg of IV Methylprednisolone daily for 3-5 days) may shorten the flare duration, but this does not impact the overall disability outcome [20]. One exception is Optic Neuritis, for which the Optic Neuritis Treatment Trial [16] found that patients treated with high dose steroids had better visual outcomes at 6 months. Oral Prednisolone at 1250 mg daily can be a substitute for 1 gm of IV Methylprednisolone. Plasma exchange can be considered for patients with symptoms that are refractory to IV steroids [20]. IV immunoglobulin monotherapy can be considered in cases of acute MS relapse in patients with contraindications to plasmapheresis and IV steroid therapy, although there is less evidence supporting this [21].

7.2. Therapy for long term MS management

As of March 2023 - 24 different DMTs had been approved for MS treatments including injectables, oral and infused medication [22].

Resent research supported high – efficacy therapy that commences within 2 years of disease onset, since this is associated with lessened disability after 6 – 10 years compared with delaying such therapies [23].

- **Low-efficacy treatments** • Interferons
- **Moderate-efficacy treatments** • Cladribine* • Glatiramer acetate • s1p inhibitors* • Teriflunomide

- **High-efficacy treatments** • Ocrelizumab • Ofatumumab • Fumarates • Natalizumab • Alemtuzumab

7.3. Mild efficacy therapies

- **INTERFERONS**: - Interferons work by binding to cell surface receptors and initiating signalling pathways that lead to increased antiviral, antiproliferative and immunomodulatory gene products that ultimately inhibit proinflammatory cytokines and T cell activation [25]. These are given by injection.
- **GLATIRAMER ACETATE**: - GA functions via two mechanisms 1) Reducing interleukin-17 and IFN-Y production via autologous CD4+T cells, there by inhibiting proinflammatory cytokines, and 2) mimicking MBP regions, thereby functioning as a decoy receptor via molecular mimicry to be targeted by the immune system of the body [2627]. GA is the only MS drug that does not require laboratory monitoring [28]. The main side effect is skin hardening at the injection site.
- **TERIFLUNOMIDE**: - Teriflunomide [29-31] is an oral therapy that inhibits dihydroorotate dehydrogenase, which in turn reduces the levels of activated B and T lymphocytes. Teriflunomide is often administered to patients who have been treated with mild- efficacy injectables and who experience injection fatigue.

7.4. Moderate to high efficacy therapies

- **CLADRIBINE**: - Cladribine works by incorporating into DNA and inhibiting DNA polymerase and ribonucleotide reductase, thereby creating DNA strand breaks [32]. Cladribine consists of two oral treatment courses administered approximately 1 year apart, and has been found to deplete the total T & B cell counts by 40% - 50% and 80% respectively [33]. Side effects include lymphopenia and herpetic infections [34].
- **S1p inhibitors**: - s1p inhibitors such as Fingolimod, Siponimod, Ozanimod and Ponesimod [35-37] block the egress of lymphocytes from lymph nodes. They are effective at preventing MS relapse, but also have the side effect of increased infection risk, including that of progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis, as well as the risk of rebound relapse after drug discontinuation; there have been 52 documented cases of severe MS rebound after Fingolimod withdrawal [38].
- **FUMARATES**: - Fumarates are oral medications that work via various pathways to both suppress proinflammatory cytokines (example NF-kB) and activate the nuclear factor E2 pathway that leads to increased antioxidant enzyme synthesis [39]. Taking Fumarates twice daily has been found to approximately halve the frequency of MS relapse [40]. This drug class is considered to have a lower infection risk than high efficacy therapy.

7.5. High efficacy therapies

- **OCRELIZUMAB**: - Ocrelizumab was approved for both relapsing – remitting MS (RRMS) and primary progressive MS (PPMS) in 2017 [24,41,42]. It works by depleting CD20 B cells and is administered via infusion every 6 months. Although MS is historically considered a T cell disease, blockage of B cell autoreactivity inhibits neuroinflammation through several pathways, including 1) preventing B cells from acting as antigen – presenting cells that activate autoreactive T cells, 2) preventing B cells from releasing proinflammatory cytokines, 3) preventing B cells from transforming into plasma cells that may produce myelin – directed autoantibodies, and 4) preventing B cells from forming meningeal lymphoid follicles [43].
- **OFATUMUMAB**: - Another anti–CD20 B cell therapy, ofatumumab was approved for RRMS in 2020 and is administered via monthly self -injection [44]. Its side effects profile is similar to that of ocrelizumab [45,46].
- **NATALIZUMAB**: - Natalizumab is a monoclonal antibody that was approved for MS in 2004 and is administered via infusion every 4 weeks [47]. Natalizumab binds to α4β1 integrin to prevent vascular cell adhesion protein 1 mediated leukocyte transmigration across the blood brain barrier.
- **ALEMTUZUMAB**: - Alemtuzumab is an anti-CD52 monoclonal antibody with high efficacy that is administered via injection [48]. It is often utilized for RRMS and in MS cases that do not respond to multiple medications due to its side – effects profile that includes significant risks of secondary autoimmune thyroid disease, TB, HSV and infusion reactions [48].

Compliance with ethical standards

Disclosure of conflict of interest

The author declared no potential conflict of interest.

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