Multiple Sclerosis: The Most Common Neurological Disorder of Young Adults

Thomas Campbell*

CLINICAL POINTS

Multiple sclerosis (MS) is more common in women and usually occurs between the ages of 15 – 45, peaking at around 30, though the disease is not limited to this age group.

It can present with a wide variety of symptoms including motor weakness, paraesthesia, urinary symptoms and optic neuropathy. However, it may present with any neurological abnormality.

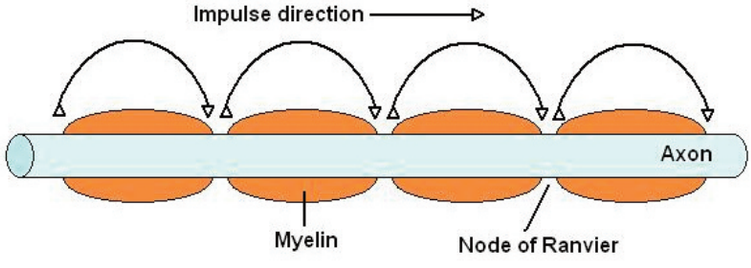
The gold standard for diagnosing MS is an MRI scan of the brain and spinal cord with a compatible clinical picture. This is supported with CSF analysis and electrophysiological testing.

Current treatments do not cure MS, but can significantly improve quality of life.

*3rd Year Medicine, TCD

Abstract

Multiple sclerosis is a chronic progressive inflammatory condition of the central nervous system which leads to neuronal demyelination and loss of neurological function. It can present with a wide variety of symptoms. The cause of MS is unknown; however studies show that there are both genetic and environmental components. Genetic components include variations in the human leukocyte antigen system. Environmental components include infectious agents such as viruses (Epstein-Barr virus, canine distemper virus and HHV-6). The gold standard investigation is an MRI of the brain/spinal cord. Lesions on MRI and a compatible clinical picture are sufficient to diagnosis MS. This can be supported with CSF analysis and electrophysiological testing. Disease progression determines which subtype of MS patients' experience (relapsing remitting; secondary progressive; primary progressive; progressive relapsing.). The principles of management are to attenuate autoimmune activity, manage symptoms and provide rehabilitation.



▲ ***Fig. 1. Saltatory conduction.***
In myelinated fibres, the impulse jumps from node to node, skipping over the myelinated sections of the axon. This increases the velocity of impulses along axons. Unmyelinated fibres have no myelinated sections for impulses to skip over; hence transmission velocity ranges from 0.5 to 2.0 m/s (15). Myelinated fibres can conduct impulses approximately 50 times faster than unmyelinated fibres of similar diameter (14).

Introduction

Multiple sclerosis (MS) is the most common neurological disorder of young adults, with a prevalence of between 121 and 185/100,000 in Ireland[1]. This progressive autoimmune disorder is characterized by chronic inflammation of central nervous system (CNS) myelin, the fatty substance that insulates each neuron, resulting in a loss of myelin and a loss of neurological function[2]. Four main types of MS exist: relapsing remitting; secondary progressive; primary progressive; and progressive relapsing[3].

MS prevalence has been demonstrated to be latitude-associated, with countries at latitudes of 50-65°N demonstrating a prevalence of 60-100/100,000, while in countries at 30°N, prevalence falls below 10/100,000[4]. Immigrants younger than 10 years old who travel from low to high prevalence zones tend to acquire the prevalence of their destination[4], implying that genetics alone cannot account for the distribution of MS. However, relatives of MS patients are at a 10-50 fold greater risk of developing MS[5], and the high concordance rates between monozygotic twins (30%) compared to dizygotic twins (2.4-14.3%) indicate that genetics do play a significant role in MS development[6,7].

With the advent of the field of Molecular Medicine, our understanding of both the pathogenesis and the aetiology of MS has developed greatly in recent years. This has provided inspiration for new approaches to the treatment of this severely disabling disorder.

This review aims to provide a broad overview of MS pathogenesis and aetiology, and of how this translates into presentation, diagnosis and treatment.

Pathogenesis

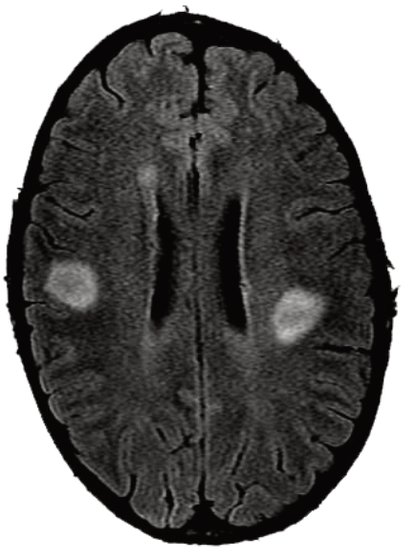
The disease is characterised by progressive chronic inflammation of CNS myelin[8], the substance that insulates neurons and increases the velocity of impulses (see Fig. 1). Chronic inflammation leads to a loss of myelin.

The blood brain barrier (BBB) is a specialised system of brain microvascular endothelial cells (BMVEC) which regulates the passage of substances between the brain and systemic circulation. BMVEC are connected via junction complexes, which prevent immune cells entering the brain from the circulation. In MS the BBB is dysfunctional[9]. BBB disruption in MS is incompletely understood, however it is believed that this results from disruption of junction complexes between BMVEC[9]. This leads to the formation of a paracellular route (i.e. between the BMVEC)[9] through which immune cells can then enter the brain parenchyma[9].

Lymphocytes and monocytes express the glycoprotein α4β1 integrin on their cell membrane[4] allowing for stable interactions between cells and their environment. Normally glycoprotein α4β1 binds to VCAM-1 (vascular cell adhesion molecule 1), located on vascular endothelial cells plasma membrane. This is a physiological process allowing immune cells to move between blood and other tissues.

In MS this interaction allows immune cells to adhere to the BMVEC, utilise the paracellular route, infiltrate the brain parenchyma and cause inflammation. Evidence suggests that this inflammation is initiated by helper T lymphocytes[10]. In MS, CD4+ TH1 lymphocytes cells react against the body's own myelin antigens and secrete cytokines that activate macrophages in the brain[10]. These activated immune cells release harmful substances (proteolytic enzymes; cytokines; oxidative products; and free radicals) that can damage axons[11].

Reactive T lymphocytes also present antigens to microglia[9], the natural phagocytic immune cells of the CNS. Upon activation, microglia produce several reactive oxygen species and proinflammatory cytokines that are detrimental to neuronal function and integrity, possibly leading to neuronal death[12]. ➔



▲ ***Fig. 2. Magnetic resonance image.***
MRI displaying two large plaques, characteristic of MS.

In addition, cytotoxic CD8+ T lymphocytes directly attack myelin-producing cells (oligodendrocytes)[12]. This leads to demyelination of neurones. The presence of demyelinated areas of neural tissue, called plaques[8], is the cardinal feature of MS[4]. Plaques are usually 6-15mm in diameter[13] and are surrounded by an infiltrate consisting mainly of macrophages and T lymphocytes (mostly CD4+, some CD8+). Plaques are most commonly located in the periventricular region, followed by subcortical, pontine, corpus callosum, cerebellar and other locations (medulla oblongata, spinal marrow)[13].

The loss of myelin slows transmission of impulses in the affected neurons and causes failure of saltatory conduction, as there are no ion channels on the denuded axon (see Fig. 1)[14,8]. In addition, impulse conduction in neighbouring myelinated fibres is compromised by oedema and inflammatory exudate[15], though inflammation subsides during remission periods.

It is thought that remission periods occur due to temporary remyelination or insertion of new voltage-dependant Na+ channels along the plaque[8]. However, plaques recur and the accumulation of damage causes irreversible deficits in nerve function[8]. Eventually, plaques are replaced by glial scar tissue[15].

Aetiology

The aetiology of MS is multifactorial; there is evidence for both genetic and environmental factors contributing to the development of the disease[8].

Environmental

Many studies linking infectious agents and MS have been carried out. It is thought that viruses may act as a molecular mimic of myelin and hence antibodies produced against the virus may erroneously attack and cause inflammation of myelin.

Epstein-Barr virus (EBV) is a leading candidate agent for triggering of MS[16]. Following infectious mononucleosis (caused by EBV) there is a 2.8 times increased risk of developing MS[17].

Similarly, a high titre of canine distemper virus (CDV) antibodies is significantly associated with MS[18]. 29% of MS patients have elevated CDV antibody titres, compared with 6% in healthy individuals[18].

Also of note, over 70% of MS patients show evidence of active human herpes virus 6 (HHV-6) infection[14]. HHV-6 may remain dormant in nerve fibres following childhood infection[14].

Genetic

The association between human leukocyte antigen (HLA) and MS is well established[19]. The HLA system is a group of genes located on chromosome 6 that codes the major histocompatibility complex (MHC), which is displayed on the human cell surface. The MHC allows the immune system to differentiate between the body's own cells and foreign antigens. Inherited variations in the human leukocyte antigen (HLA) system increase the risk of developing MS[19]. Alone, the HLA-DRB1*1501 variant may explain about 50% of MS cases[19].

Clinical presentation

MS patients can present with almost any neurological abnormality. The most common presenting symptoms are:

Unilateral optic neuritis (ON) is an inflammation of the optic nerve. Swelling of the optic disc may be seen on fundoscopy. ON causes blurred vision in one or both eyes, developing over hours-days[4]. Mild ocular pain is common also[4].

Limb paraesthesia (numbness and tingling in the limbs) occurs due to lesions in the posterior column white matter[15] of the spinal cord which transmits fine touch, fine pressure, vibration and proprioception.

Lhermittes's sign is a tingling shock like sensation which passes down the arms or trunk when the neck is flexed, a nonspecific indication of disease in the cervical cord. 41% of MS patients experience Lhermitte's sign at some stage during their illness[20].

Leg weakness occurs due to lesions in the corticospinal tract (tract containing motor axons) and occurs in one or both legs[15].

Brainstem / cerebellar signs associated with brainstem lesions cause combinations of diplopia (double vision), vertigo, facial numbness/weakness, dysarthria (difficulty speaking) and dysphagia (difficulty swallowing)[4].

Urinary symptoms are seen in 68% of MS patients[21]. These include: increased frequency of micturition; nocturia (waking from sleep to pass urine); urgency; hesitancy (difficulty initiating a stream); intermittency (stream starts and stops repeatedly); incontinence; and sensation of incomplete micturition. It is thought that interruption of central autonomic fibres between the brainstem and lower spinal cord causes urinary retention[15].

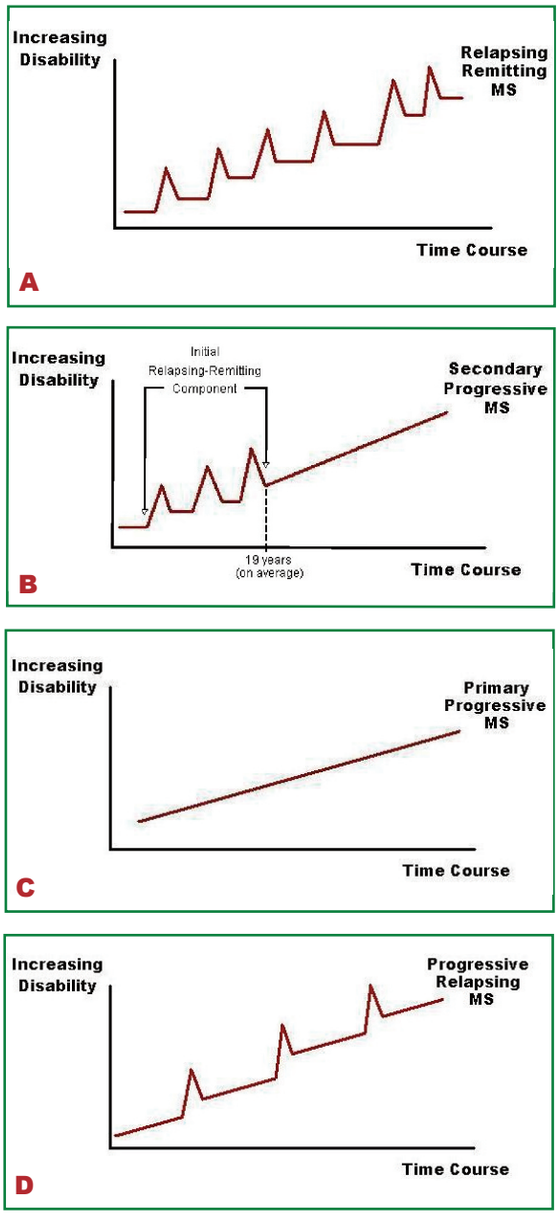
Investigations/Diagnosis

Routine investigations into those suspected of having MS include magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis and electrophysiological assessment.

An MRI scan of the brain and spinal cord is the gold standard investigation for diagnosis of MS[4]. Multiple plaques are usually visible in the periventricular region, brainstem and cervical cord (see Fig. 2). MRI assisted diagnosis is up to 92% sensitive for MS[22].

CSF analysis helps to support the diagnosis through the use of gel electrophoresis (a technique whereby an electric field is used to separate proteins suspended in a gel matrix). Uniquely in MS, a small number of clonal B lymphocytes in the CSF produce the protein IgG. This IgG gives rise to well-defined oligoclonal bands (OBs) upon gel electrophoresis of MS patients' CSF[23]. Over 95% of MS patients have CSF IgG OBs[24]. OBs may be seen in other less common demyelinating disorders[23].

The IgG : albumin ratio is generally increased from <10% to 50%[23]. Greater sensitivity is obtained if the IgG:albumin ratio of the CSF is compared with that of serum. This ratio is elevated in approximately 70% of cases[24]. However it can also be abnormal with CNS tumours, ➔



▲ ***Fig. 3. Progression of multiple sclerosis.***
(A) *Relapsing-remitting.*
(B) *Secondary progressive.*
(C) *Primary progressive.*
(D) *Progressing relapsing.*

neurosyphilis and following a stroke[23]. Delays in visual-evoked responses seen in optic neuropathy and also support a diagnosis of MS[4].

Disease progression

The pattern of disease progression seen with MS is dependent on subtype.

Relapsing-remitting (RR) MS accounts for 85% of initial presentations[25]. These patients experience unpredictable attacks followed by periods of months to years of remission (see Fig. 3(a)). During remission periods there are no new signs of disease activity while neurological deficits suffered during attacks may either resolve or become permanent. RR MS may progress to secondary progressive MS (see Fig. 3(b))[3].

Secondary progressive (SP) MS involves progressive neurological decline between acute attacks without periods of remission[3]. The mean conversion rate from RR MS to SP MS is 2.5% per year[25] and studies show that 30-40% of RR MS patients develop SP MS within 10 years of disease onset[25]. On average this transition occurs 19 years after the initial event[25].

Primary progressive (PP) MS patients do not experience remission periods (see Fig. 3(c)). Their disease progresses steadily from initial onset. This subtype accounts for 10 -15% of MS patients[26].

Progressive relapsing (PR) MS is the least common subtype and describes patients who experience a persistent neurological decline (see Fig. 3(d)) with clear superimposed attacks[3]. Approximately 5% of patients MS have PR MS at initial diagnosis[27].

Cases of MS with irregular characteristics have also been described (e.g. Balo, Marburg and Schilder forms)[28]. These are referred to as "borderline forms" and debate remains as to whether these are actually forms of MS.

Studies show mean survival ranges from 20 years to nearly 45 years from onset[29] with MS patients tending to live 5-10 years less than healthy individuals[29]. End-stage MS involves severe disability, with patients experiencing[4] spastic tetraparesis (weakness in the limbs due to hypertonicity), ataxia (loss of the ability to coordinate muscular movement), nystagmus (rapid rhythmic repetitious involuntary eye movements), pseudobulbar palsy (bilateral functional impairment in cranial nerves 9-12) and dementia. Death most commonly occurs due to respiratory disease[30], whereby respiratory muscles become weak and the ability to cough is lost[31] and life threatening pneumonia may occur[4].

Treatment

Management of MS can be divided into rehabilitation (exercise, physiotherapy and occupational therapy) for physical symptoms and therapeutic[32]. Rehabilitation programmes do not alter the level of impairment but can improve patients' quality of life[33,34].

Though therapy cannot cure MS, it may reduce relapse rate and the severity of attacks. It involves immunomodulation, immunosuppression and symptomatic control. For acute relapses, short courses of IV or high dose oral steroids are used and reduce the attack severity[34].

A number of different drugs can be used for long term management. First line agents include interferon-β, azathioprine, and glatiramer acetate[35].
Interferon-β is used in relapsing-remitting and secondary progressive MS[36]. The mechanism of action of IFN-β is not well understood[37] but both IFN-β 1a and 1b reduce the frequency of relapses and severity of inflammatory lesions seen on imaging[36,38].

Azathioprine, a guanine analogue, inhibits DNA synthesis and decreases turnover of inflammatory cells, thus reducing inflammation. Oral azathioprine has been shown to reduce inflammatory lesions, relapse rate and provide benefit regarding disability[39].

Glatiramer acetate (GA) is a random polymer consisting of four amino acids that resembles myelin basic protein (MBP)[40]. It is used to treat RR MS[41]. The mechanism of action of GA remains unknown however there are two proposed theories. Firstly, given its resemblance to the myelin component MBP, GA acts as a molecular mimic of myelin and may divert the immune system away from myelin[41]. Secondly, GA alters cytokine secretion[40], leading to a shift of T lymphocytes from pro-inflammatory TH1 cells to regulatory TH2 cells that suppress the inflammatory response[40]. GA reduces relapse rate by almost 33% and reduces the number of lesions seen on MRI[42].

2nd line agents include monoclonal antibodies and mitoxantrone[35].

Natalizumab is a monoclonal antibody and an α4-integrin antagonist. It prevents the migration of immune cells into the brain parenchyma[43]. Natalizumab can reduce the number of lesions by 94% in RR MS[44]. In a 6 month trial amongst patients with RR or SP MS, natalizumab reduced the number of patients who had relapses by 50%[43].

Mitoxantrone, a type II topoisomerase inhibitor, disrupts DNA synthesis/repair. In a 1 year study, average relapse rate decreased by 95% and 80% of patients were relapse-free one year after starting mitoxantrone treatment[45]. However, its use is associated with cardiotoxicity and an increased risk of leukaemia[46,47].

Looking to the future

Cannabis derivatives are used for relief of painful spasms. A cannabis derivative containing equal proportions of tetrahydrocannabinol (THC) and cannabidiol (CBD)[48], Sativex®, is used in the treatment of central neuropathic pain in MS[48]. THC is a partial CB-1 receptor agonist and CBD is a non-euphoriant, anti-inflammatory analgesic[48]. Sativex® is currently licensed in Canada and may become licensed in Ireland in the coming years.

Similarly, ajulemic acid (AjA) is a cannabis derivative →

that selectively increases specific eicosanoids[49], facilitating the resolution of inflammation. Studies suggest that AjA may have value as a therapeutic agent for the treatment of diseases characterized by inflammation, such as MS[49].

A recent case report found that an MS patient was producing a unique antibody to her own T lymphocytes. Research has shown that these antibodies recognise S1P1 receptors[50], located on the surface of TH1 lymphocytes. When this receptor is disabled by anti-S1P1 antibodies, T lymphocytes fail to leave the lymph nodes, reducing their numbers in the bloodstream[50]. Purified human anti-S1P1 antibodies reduced mouse blood lymphocyte levels by an average of 72% and also reduced the severity of induced colitis in mice[50]. This could be applied to treat MS, other inflammatory conditions and help prevent transplant rejection.

Fingolimod (FTY-720), currently undergoing clinical trials, is an S1P partial agonist which over time acts as a functional antagonist at S1P receptors[51]. In a two year study, 79-91% of MS patients were lesion-free on MRI following 24 months of oral fingolimod therapy[52]. Furthermore, 77% of patients remained relapse free[52].

Summary

From review of the current literature, it is impossible to predict the likelihood of a cure for MS. However, with a rapidly growing understanding of the molecular mechanisms involved in MS, the potential for new and more effective therapy is promising. The use of human purified anti-S1P1 antibodies is exciting given the broad variety of applications that they may have. Fingolimod shows promising results although its long term effects are not yet understood. Apart from new drug development, research into optimal drug regimens will also play a role in providing patients with a greater quality of life so that those suffering with MS can look to the future with hope. ■

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