Multiple Sclerosis: Diagnosis and Treatment Management in Allopathy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

This article summarizes the literature related to the pathogenic mechanisms and treatment options for multiple sclerosis, an autoimmune, demyelinating disorder of the central nervous system. The etiology of MS is not known, both genetic and environmental factors are known to play a role. The risk factor that is strongly associated with MS Epstein-Barr infection. Other factors subjected to modification are childhood obesity, smoking and vitamin deficient individuals. Vitamin D deficiency as a risk factor has been proposed to explain the increase in prevalence of MS with increase in the latitude. The pathogenesis involves a response which is mediated by T-cell directed against myelin and other similar proteins. The function of B-cells in the disease process is not known. Recent advancements in the understanding of multiple sclerosis has led to development of disease modifying therapies, which in turn has led to a decrease in severity of the disease and relapse rates. Disease modifying therapies act by modulating or suppressing the immune system. Moreover, several drugs have shown effectiveness in certain studies. A number of treatment

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options have now become available making treatment of MS possible. The management of MS is divided into 3 categories:

i)   Treatment of Exacerbations
ii)   Slowing disease progression with Disease modifying therapies
iii)   Symptomatic treatment

1. INTRODUCTION

Multiple Sclerosis (MS) is an idiopathic, putatively autoimmune, chronic inflammatory disease of the central nervous system (CNS) that is characterised by multifocal demyelination and axonal loss and results in a wide range of the clinical features due to the participation of the sensory, visual, motor, and autonomic systems [1,2]. It is a disorder which involves neurodegeneration and chronic inflammation of the CNS that usually affects young individuals (particularly women) [2]. It is one of the leading causes of neurological disability in young adults around the world [3]. Although the exact cause of the disease is unknown, environmental and genetic variables are now known to play a role and are involved in disease pathogenesis [4].

Inflammation, demyelination of the nerves, and axonal loss are all symptoms of MS, which cause lesions of the white matter in the CNS. For more than 60 years, the focus of the neurological studies has been the treatment of the disease. MS is now manageable thanks to the development of an increasing number of disease-modifying treatments (DMTs). These drugs work to reduce the inflammatory reaction in MS patients. They function by lowering the risk of recurrence, reducing the likelihood of newer CNS lesion formation, and slowing the progression of impairment. Interferon- and glatiramer acetate were the first MS medicines to hit the market. These act by moderating the inflammatory response through a variety of ways, which are briefly described here. Since then, newer medicines have been available, drastically altering the advancement of MS treatment. Oral medications like fingolimod, dimethyl fumarate, and teriflunomide are among them. Natalizumab and alemtuzumab are two more FDA-approved second- and third-line medicines. Natalizumab is one of the most effective medicines for preventing recurrence. Ocrelizumab is a monoclonal antibody which targets CD20 on the B cells and is expected to be approved by the FDA soon, is a very successful MS treatment [5].

2. MATERIALS AND METHODOLOGY

In this article we have gained the literature on Multiple Sclerosis from PubMed, Lancet, StatPearls [Internet], Elsevier, Google Scholar, Sage journals. While searching various databases. The given keywords and phrases were used in different platforms and amalgamation: multiple sclerosis, demyelination, neurodegenerative, disease-modifying treatment. A potential source of information was also the reference list of pertinent articles. There were no attempts to find unpublished data. MS involves neurodegenerative as well as inflammatory mechanisms that affect both the white and grey matter.

3. RESULTS AND DISCUSSION

Aetiology: Origin of MS is frequently characterised as not very well known; however, this is not entirely accurate. In the causative route that leads to MS development, EBV, smoking tobacco, sunlight (UVB) and vitamin D in combination with the person's genetic background, play vital roles. MS is regularly linked to an exposure to environmental factors in migration studies. Adult migrants to Europe from nations with decreased risk of MS, such as the West Indies, have decreased chances of acquiring MS; nevertheless, children of migrants in Europe have a significant risk of developing MS. Migration studies show that the genetics plays a lesser role than environment, emphasising the importance of prevention research focusing on recognised environmental risk factors [6].

The strongest evidence of relationship, according to meta-analysis, is associated with the positivity of Epstein-Barr virus biomarker, smoking and infectious mononucleosis. With regards to genetic susceptibility, the strongest risk of susceptibility is linked to HLA-DRB1 in the class II region of the Major histocompatibility complex and accounts for around 10% of the underlying risk [1].

Subtypes: There are four major classifications for the clinical course of MS: relapsing–remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS) (SPMS). In around 80% of instances of multiple sclerosis, Clinically Isolated Syndrome (CIS) is the first symptom. Acute infirmary attack affecting more than one CNS locations is referred to as CIS, and it can progress to relapsing remitting MS (RRMS) [1].

With RRMS, each clinical episode or relapse usually results in a good recovery. The autoreactive lymphocytes migrate to the CNS crossing the blood-brain barrier, this is hypothesised to have an inflammatory pathogenic substrate in the early stages of MS with underlying demyelination. This sets off a chain reaction of inflammation that includes clonal proliferation of T-cells and B-cells , activation of the microglia, oxidative stress, injury to the mitochondria, and energy failure, all of which contribute to the formation of the distinctive plaque [1]. Disability accumulates over time, and each relapse results in an incomplete recovery. Up to 80% of persons with RRMS develop secondary progressive MS 10–15 years after diagnosis. The white and grey matter involve less inflammation, and there is comparatively more damage and atrophy of the axons, with a likely neurodegenerative aetiology.

These MS subtypes should be further classified as active or non-active. A clinical relapse which is seen as a new gadolinium-enhancing or T2 lesions on MRI should occur at the minimum of once annually if the disease is active. When the patients' disabilities worsen with time, as compared to those who got worse due of a diasease relapse, the phrase "disease progression" is employed. Because of spinal cord degeneration, 10–15 percent of individuals experience progressive disability from the start. Primary progressive MS is the term used to describe this type of MS (PPMS) [1].

Pathophysiology: CNS inflammation, demyelination, axonal damage, and axonal loss are all symptoms of MS. It's thought to be an autoimmune illness, although the immune response's antigen specificity is unknown.

The disease pathophysiology in the initial phase of RRMS is dominated by focal white matter lesions which are inflamed known as 'plaques' characterized by primary demyelination, axonal loss, along reactive gliosis.

T cells that have been activated in the body outside of the CNS and penetrate the BBB get rejuvenated by the antigen-presenting cells in the local area. Pro-inflammatory cytokines excite microglial cells and astrocytes, recruit more inflammatory cells, and lead to plasma cells, producing antibodies. This inflammatory mechanism eventually results in plaque tissue damage. Remyelination, on the other hand, is conceivable and can heal damaged tissue to some extent. Based on the dominant pathophysiological causes, several 'patterns of demyelination' have been recognized.

The early stages of the disease also affect the cortex. Inflammation and demyelination of the cortex, its neurodegeneration, including the destruction of the neurons, nerves, and oligodendrocytes, glial cells, and cortical atrophy are all symptoms of this condition. Myelin degradation is assumed to cause axonal injury, which causes the lesion to move from the outside to the inside (myelin to the axon) and is known as the 'outside-in' model. Primary axonal injury, on the other hand, could lead to demyelination and inflammation later on (the 'inside-out' paradigm). It's unclear whether it is one pathway that is primarily responsible for the development of MS pathology or if both the mechanisms operate at the same time.

In progressive illness, activated white matter lesions are uncommon, and diffuse grey and white matter atrophy dominates the pathophysiology. Pre-existing plaques gradually enlarge, with inflammation of low grades and activation of microglia at the margins if the plaque. Furthermore, it involves widespread damage to the normal-looking white matter outside of that plaque, which includes inflammatory reaction in the microglia and its activation, as well as injury to the axons and myelin, and secondary demyelination. The broad degenerative process of grey and white matter that is ongoing defines the progressive nature of progressive disease processes [7].

Signs and Symptoms: MS is an immune-mediated inflammatory illness of the CNS that generates a wide range of symptoms and indicators due to the distinct inclusion of the visual, sensory, motor and autonomic nervous systems.

(i)Optic neuritis (optic nerve inflammation)

(ii)Uhthoff phenomena are two characteristics of MS (the symptoms of MS worsen and fluctuate

transiently with an increase in the temperature of the body)

(iii)The Lhermitte phenomenon (a sensation which is electric-shock like which is abnormal and runs down the spine and limbs of the individual on flexion of the neck) [1].

Relapses and/or disease progression are common in MS patients' clinical courses. Relapses are defined as new neurological symptoms that arise without fever or an infection that lasts more than 24 hours. Relapses can last for days or weeks, or they can leave you with long-term deficits. A consistent aggravation of clinical features over a period of at least six months is considered disease progression. [7].

Diagnosis and Investigations: MRI of the brain and the spinal cord is the investigation of choice. The McDonald 2017 and 2010 criteria, as well as the enhanced use of MRI, have been demonstrated to revolutionize the diagnosis of clinically definite MS in the CIS group [1].

Management: The development of increasingly strong biological therapies, as well as an active treatment strategy for MS, known as managing a target of no evident disease activity (NEDA), is improving abiding outcomes for people with MS. A small number of pwMS may be cured with more intensive immune reorganization therapy that leads to a proportion of pwMS entering into long-term remission. Recent promising trials of disease-modifying therapies (DMTs) which includes four forms of interferon (IFN) beta, glatiramer acetate, natalizumab, fingolimod, alemtuzumab, teriflunomide, and dimethyl fumarate (BG-12) in progressive Multiple Sclerosis provide hope to patients with advanced MS of decreasing disease progression while maintaining surplus function. The actuality that treatments appear to be effective at many phases of the disease course casts doubt on the classic two-stage concept of MS's characteristic history [6].

Treatments for MS have been divided into 3 classes:

(1). Management of Acute Relapse
(2). Disease Modifying Treatments which slow the progression of the disease
(3). Symptomatic Treatment

1) Management of Acute Relapse

The first problem in managing a relapse is establishing if the episode is a true relapse or a pre-existing demyelinating lesion-induced exacerbation or fluctuation. In any situation, identification and treatment of concomitant illnesses (such as urinary tract infections) that could be causing the symptoms should be the first priority .If you're still unsure, a gadolinium-enhanced MRI can identify new intensifying lesions up to 6 weeks after a recurrence begins. Methylprednisolone therapy in high doses of 500–1,000 mg/day for 3 to 5 days, should be considered on the condition that the recurrence is of moderate or greater functional severity, according to local norms. Disease-modifying corticosteroids, on the other hand, have been shown to shorten relapse times. Plasma exchange may be used as a supplement to other therapies or as a stand-alone treatment if the relapse is severe or advancing quickly. To help with healing, early treatment therapies like physiotherapy should be used.

2) Disease-modifying treatment

In MS, DMTs suppress the inflammatory response. They lower the likelihood of relapses, the growth of new lesions on CNS MRI, and the progression of disability in the individual. The concluding goal of DMT is to combine clinical (no MS relapses or disability progression) and MRI features (no new T2 lesions or atrophy) characteristics into a single phrase: "no evidence of disease activity" (NEDA). Neurologists monitor DMT in MS patients, according to the National Institute for Health and Care Excellence's (NICE) guidelines. Interferon-beta and glatiramer acetate were the first MS treatments available in the early 1990s. The processes by which these drugs function are as follows:

i) IFN suppresses inflammatory responses in MS patients through a variety of processes, which include controlling the secretion of pro inflammatory and anti-inflammatory cytokines, suppressing the activation of T cells , and instigating neural stem cell differentiation to oligodendrocytes, which results in nerve cell repair and prevention of further damage.

ii) Glatiramer Acetate (GA): GA works in a unique way. Glatiramer acetate (GA) or Copolymer 1 is a four-amino-acid synthetic molecule that resembles the T-cell autoantigen myelin basic protein (MBP). GA stimulates the production of GA-specific regulatory T cells while inhibiting the myelin reactive T cell formation and because of its structural closeness to MBP, it promotes production of Th2 anti-inflammatory cytokines.

GA has a high promiscuous binding to major histocompatibility complex components at first, but then competes for T cell presentation with a variety of (myelin) antigens.

Since then, newer medications have been available, significantly altering the outcomes and progression of the treatment of MS. Oral medications include teriflunomide, fingolimod, and dimethyl fumarate. Natalizumab and alemtuzumab are two more FDA-approved second- and third-line medicines.

i) Natalizumab is one of the most potent anti-recurrence medications currently on the market. Antibody testing for the JC virus has helped to stratify the risk of progressive multifocal leukoencephalopathy (PML), a brain infection caused by the virus.

ii) Alemtuzumab, which has a high risk of side effects, is also quite successful.A monoclonal antibody, Ocrelizumab that targets B cells particularly the CD20 on them and is likely to receive FDA approval soon, is a highly effective MS treatment. MS accounts for a large portion of healthcare costs, and providers must be aware if the DMTs' are obtainable and its benefits. It's crucial to get started on treatment as soon as possible after receiving a diagnosis. A change in therapy options should be considered when there is evidence of disease activity, including the build-up of impairment or safety or endurability issues.

3.1 RRMS Treatment

DMTs are typically used in accordance with NICE guidelines, which are based on factors such as the no. of relapses of clinical symptoms, MRI radiologic activity and the amount of disability. Nevertheless, given the condition's heterogeneity, the decision must be made on an individual basis, including physician advice on weighing benefit against risk, monitoring requirement, and administration method. DMT may help to reduce disability accumulation, according to early evidence from the UK risk-sharing scheme, and it is hoped and expected that as DMTs become more effective, they may help to reduce the burden even more. When it comes to how DMTs should be utilised, there are two primary schools of thought:

(1)Induction – it includes the usage of highly efficacious drugs early in disease course to perhaps prevent disability augmentation, inspite of their significant side effect profile.

(2)Escalation – this involves beginning the treatment with less efficacious but potentially safer drugs and if there is treatment failure, moving up the treatment ladder.

Despite the importance of clinical and MRI monitoring in assessing response,currently there is a lack of long term evidence on induction versus escalation regimens. Furthermore, keep in mind that we have only a few direct head-on comparative studies on DMTs, thus data from different research should be interpreted with caution.

Glatiramer acetate, Interferons, dimethyl fumarate, teriflunamide, and fingolimod are categorised as moderately effective DMTs (category 1) with an ARR of about 40%, and higher effective DMTs (type 2) with an Annual relapse rate greater than 50%. After activation of the John Cunningham virus (JCV), the most serious adverse effect was natalizumab, an improved monoclonal antibody directed against the cell adhesion protein alpha 4-integrin, which produced progressive multifocal leukoencephalopathy (PML).

Around half of the population has John Cunningham Virus infection. The risks for developing PML have been thoroughly defined, and they constitute treatment with natalizumab over more than two years along with initial chemotherapy or suppression of the immune system(immunosuppression), both of which increase the risk of developing PML. You should have the status of your MRI and JCV monitored often when using Natalizumab. Fingolimod and dimethylfumarate, two oral medications, have also been associated to PML, but in a much rarer form. The drugs employed are determined by clinical and radiological variables. For example, the Modified Rio Criteria for interferon usage are in the process being developed depending on relapse rates and new T2 or new gadolinium enhancing lesions [5].

3.2 CIS Treatment

DMT has been demonstrated to hold up clinically definite MS in clinical trials of people having CIS by around a year. In the United Kingdom, the only approved treatments for CIS interferons and glatiramer acetate. If MRI data validates the presence of MS according to the McDonald's

criteria (2010) or envisages an increased risk of recurring episodes in people with CIS within 12 months of the incident, these may be administered. Additionally, according to the BENEFIT research, starting the injectable medications before clinically confirming MS, have led to an improvement in the cognitive outcome measures. It is estimated that around half of the people with CIS suffer with cognitive impairment.

3.3 Progressive MS Treatment

Sadly, no licenced DMTs are available for progressive MS. With reference to prescribing interferon-1 beta or glatiramer acetate, there is an admonition for patients with SPMS who have more than two relapses within two years and realtively slow advancement of fewer than two Expanded Disability Status Score (EDSS) points. Intravenous mitoxantrone can be used in patients with quickly advancing SPMS, but it must be closely monitored for adverse effects of the heart and acute myelogenous leukaemia. In SPMS, pulse therapy IV methylprednisolone may be investigated, but there is no long term data.

DISEASE-MODIFYING TREATMENT for PPMS: For the clinically isolated syndrome, RRMS, and rarely SPMS, several medications to potentially build on the natural history of illness are available. The clinical course, illness stage, and disease activity all have a role in determining the indication. Therapy should be started as soon as possible in most cases. There is yet to be a medication authorised for the treatment of PPMS.

The distinction between first-line basic therapy and second-line escalation therapies is important. Typically, treatment begins with basic medicines, and the patient is then clinically evaluated with an MRI. Therapy is continued if the disease is stable and the treatment is well tolerated. If there is continuous clinical and/or radiological disease activity, as well as relevant adverse effects, escalation therapy can be commenced. Patients who have one relapse/year, no complete recovery from relapses, a prolonged EDSS progression of one, and MRI progression with or without clinical symptoms are characterised as "treatment non-responders" requiring a transfer from basic to escalation therapy [7].

3.4 Basic Therapeutics

Glatiramer acetate (Copaxone) IFN- beta (Avonex and Rebif) and are immunomodulating

drugs with more than 20 years of experience as first-line therapies. They decrease the annualised relapse rate (ARR) by around 29% while causing no serious adverse consequence [7].

3.5 Escalation Therapy

In general, escalation therapies (IFN-/ glatiramer acetate) are more potent than basic treatments; nonetheless, these drugs have potentially substantial adverse effects.

First-Generation Self-Injectable Therapies : For relapse MS, four interferon beta and glatiramer acetate (GA) preparations have been licenced. Despite competition from novel oral medications, interferon beta lowers BBB disruption and regulates T-cell, B-cell, and cytokine activities, while monitoring requirements are not well understood. There is a lack of biological markers or pharmacogenomic profiles which can indicate whether a patient would have a better outcome with a given medicine.

Concurrent medical ailments, preferences of patients for the type of injection and frequency, and the desire to avoid particular side effects (such as the flu-like symptoms associated with interferon beta) are also variables. GA is thought to boost regulatory T cells. For both clinically isolated condition and relapsing MS, these immunomodulating medications have similar efficacy, lowering clinical relapse to around two-third and slowing the evolution of new brain MRI lesions over periods of one to three years. Interferon beta medications also reduce EDSS deterioration in relapsing MS, but they have no effect in the established disease.

The formation of chronic high-titre interferon beta neutralising antibodies, particularly in sc preparations, has been linked to decreased efficacy of all medicines in the class [7-10].

3.6 Symptomatic Treatment

Patients with MS may have ataxia, spasticity, pain, tremor, tiredness, depression, seizures, nystagmus, difficulty in sleeping, sexual dysfunction, and urogenital and bowel disorders, all of which could be treated with medications or physical and/or occupational therapy. This is crucial in MS patient care for the sake of improvement in the life quality and ability to work. To increase the quality of life for the treatment of spasticity, medical practices like baclofen pump and botulinum toxin injections are recommended [11-14].

4. CONCLUSION

There has been a huge amount of change in the management of relapse of MS, including huge variety of accessible DMTs that must be adequately customized with the needs of the individual with MS in terms of efficiency and safety. It's almost victory though, because the next battleground is MS progression, which is where the global effort is currently focused. Addressing symptoms, treating acute exacerbations, and lowering long-term disability through disease modification are all important aspects of effective MS care. Self-injectable, oral, and intravenous DMTs are currently available for MS, and they all reduce the frequency and severity of relapse and MRI lesion accumulation in RRMS to varying degrees, but with varying safety profiles. Treatment for MS should begin as soon as feasible after diagnosis and continue indefinitely until the patient no longer responds to the treatment adequately, has unbearable side effects, or fails to follow the treatment schedule. Not following proper treatment modalities are associated with comparatively poor outcomes including an increase in rates of relapse and disease progression.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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