

Multiple Sclerosis Diagnosis and Management: A simple Literature Review

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Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune demyelinating neurodegenerative disease. It targets the central nervous system (CNS) and affects approximately 2.5 million around the world. A variety of manifestations and symptoms can be seen in MS patients. Also, there are many pharmacological agents that can be used in treating MS symptoms. Disease-modifying therapies have significantly improved the management of this disease. **Objective:** In this study, we aimed to review the recent literature that discussed the presentation, diagnosis, and management of multiple sclerosis. **Method:** PubMed database was used for articles selection, and the following keywords were used in the mesh; "multiple sclerosis"[Mesh] and "management of multiple sclerosis"[Mesh]. A total of 40 papers were reviewed and included in the review. **Conclusion:** Early recognition of MS is crucial because it provides a chance for the early treatment plan before any severe or irreversible damage can occur. Diagnosing MS should depend on the history and neurological examination as well as the imaging. Head MRI should be ordered first when MS is suspected despite its lack of specificity. Disease-modifying therapies work on controlling the underlying process of the disease by limiting the immune-mediated inflammation. These medications have shown remarkable results in decreasing the attack rate. However, there is no solid proof that they can postpone the neurological deficits accumulation or the subsequent disability expected in MS cases.

Keywords: Multiple Sclerosis Management, Diagnosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic and progressive disease in the central nervous system, associated with side effects and disabling symptoms ^[1]. MS is a chronic autoimmune demyelinating neurodegenerative disease ^[2]. It targets the CNS and it is mediated by autoreactive lymphocytes that cross the blood-brain barrier (BBB). These lymphocytes enter the CNS and cause local inflammation resulting in demyelination and axonal loss ^[2, 3]. Approximately, 2.5 million individuals are affected worldwide. It mostly affects young individuals between 20 and 40 years old ^[4]. Women are affected by MS twice as often as men ^[5]. There are a considerable number of pharmacological and non-pharmacological therapies that might be used in treating MS and its symptoms. Disease-modifying therapies' availability has significantly improved the management of this disease, especially the relapsing forms ^[2, 6]. In this article, we aimed to review the manifestations, diagnosis, and management of MS.

METHODOLOGY

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PubMed database was used for article selection, and the following keywords were used in the mesh; "multiple sclerosis"[Mesh] and "management of multiple sclerosis"[Mesh]. A total of 40 papers were included in the review. The article's selection was based on the relevance to the project including multiple sclerosis. Exclusion criteria including all other articles that did not have a related aspect to multiple sclerosis as their primary endpoint or repeated studies.

DISCUSSION

MS is a chronic complex inflammatory autoimmune demyelinating disease of the CNS. There is a wide range of manifestations and symptoms that can be seen in MS patients [7]. They include vision symptoms such as unilateral visual loss, or diplopia, weakness, sensory loss or distortions, dyscoordination, or changes in bowel and bladder function. Mood disturbance and fatigue are also common burdening symptoms, but they are less diagnostic. Disease progression can eventually result in severe disability [7]. There are four clinical forms of MS: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MD (PRMS) [8]. Neurologists agree that patients may be grouped into four major categories based on the course of the disease [9, 10]:

1. Relapsing-remitting MS: It is the most common form, affecting about 85% of MS patients. It is characterized by flare-ups (relapses or exacerbations) of symptoms. After that, these relapses are preceded by the improvement or disappearance of symptoms (remission).
2. Secondary progressive MS: It can be experienced in patients with relapsing-remitting disease [9].
3. Primary progressive MS: It affects approximately 10% of MS patients. It is marked by gradual worsening of symptoms from the onset without any relapses nor remissions although some occasional plateaus are possible to occur.
4. Progressive-relapsing MS: it is a rare type, accounting for less than 5% of patients. It is progressive in nature from the onset, marked by the occurrence of flare-ups or relapses along the way without any periods of remission.

Etiology

The exact etiology of MS remains unclear [11, 12]. However, there is a suggested hypothesis regarding the pathogenesis that is most commonly accepted by the literature. MS starts as an inflammatory autoimmune disorder and involves autoreactive lymphocytes, myelin basic protein, and myelin oligodendrocyte glycoprotein [13]. It has also been suggested that MS is dominated by chronic neurodegeneration due to microglial activation [14].

Moreover, several environmental factors have shown that they increase the risk of developing MS such as vitamin D deficiency, the Epstein-Barr virus, and sunlight [15]. The MHC

on chromosome 6 is the strongest MS susceptibility region in the genome [15].

The characteristic signs of MS are the presence of multiple focal lesions of demyelination in the CNS, also known as plaques [16]. Damage in the BBB may be the reason behind the development of these plaques in MS patients. Because of this damage, lymphocytes may enter the CNS and recognize myelin antigens. This may lead to acute demyelinating inflammation, resulting in the formation of lesions in the white matter of the CNS [17]. These lesions can appear in all parts of the CNS but they affect mostly the optic nerves, cerebellum, brainstem, and periventricular white matter regions [18]. Nevertheless, recent pathologic and imaging studies have shown that demyelinated lesions are also commonly found in the cortical gray matter of MS patients [18-21].

Clinical Manifestations

Gelfand [22] reviewed the most common clinical manifestations that can be present in MS patients. The article included optic neuritis, myelitis, brainstem syndromes, and other manifestations.

In about 20% of MS patients, acute demyelinating optic neuritis is the presenting symptom. About half of MS patients will be affected with acute demyelinating optic neuritis at some point during the course of the disease [22, 23]. It can be diagnosed clinically by a history of eye pain mainly associated with subacute intermittent blurred vision or even vision loss [24]. Complaining of the blurry spots in the visual field is also common among MS patients. The swelling of the optic nerve (papillitis) appears in one-third of MS patients [24]. Magnetic resonance imaging (MRI) usually demonstrates a hyperintensity of the affected optic nerve in cases of acute optic neuritis [22]. There are differential diagnoses for acute optic neuritis that can be thought of, for example, ischemic optic neuropathy, infections such as syphilis, or herpes simplex virus, inflammatory disorders like systemic lupus erythematosus, or compressive lesions such as tumors [22].

Transverse myelitis is the impairment of motor, sensory tracts in the spinal cord because of inflammatory-mediated injury [22]. The sense of tightening around the chest or abdomen suggests transverse myelitis of the posterior columns of the spinal cord, which is also considered a typical symptom of myelitis [25, 26].

The brainstem can be involved also in patients of MS. This can be expressed by double vision, vertigo, facial weakness, or bulbar symptoms such as dysphagia [27]. This syndrome may be seen as an oscillation of vision confirmed by funduscopy if pendular movements of the optic disc are detected [22].

Most MS patients experience weakness at some point [28]. Corticospinal tract involvement in MS usually leads to the focal weakness of the lower extremities. Tonic seizures are

often seen in association with spinal cord and brainstem lesions [22, 28]. Numbness and paresthesia are also common symptoms experienced by MS patients. Sensory problems, pain, and different unpleasant feelings affect most of MS patients during the course of the disease [28, 29]. The pain that is experienced in MS patients usually present as burning or electrical sensations [22]. Cerebellar dysfunction can also appear in patients with MS causing several symptoms such as tremor, dysmetria, dysdiadochokinesia, or gait ataxia [22]. Fatigue is one of the most debilitating symptoms in MS and it affects most of MS patients [29]. It is necessary to determine whether the patient is complaining of general fatigue or from motor weakness. MS patients usually describe fatigue as a sense of low energy. Fatigue mostly persists between clinical relapses [22].

Up to 40–70% of MS patients may experience cognitive deficits [30]. Executive dysfunction slowed information processing, and impairment of memory can be observed on neuropsychologic testing [30]. In addition, major depression affects about 30–45% of MS patients [31].

Neurogenic bladder and lower urinary tract impairment is an important cause of disability in MS [32]. About two-thirds of MS patients experience detrusor hyperreflexia, which is a common manifestation of the neurogenic bladder [22].

One of the main characteristics of MS is heat sensitivity as heat aggravates the symptoms of MS. This mostly happens with vigorous exercise or in a hot shower. At higher temperatures, it is thought that the conduction of demyelinated nerves is less efficient, known as Uthoff's phenomenon. Cooling down core body temperature helps to ameliorate this physiologic process [22].

Most of the MS patients experience severe headaches and most of these headaches are attributable to migraines. Migraine was more common in women with MS. Migraine was associated with a small increased risk of MS, but having MS was not significantly associated with developing migraines [33].

Diagnosis of MS

Early recognition of MS is crucial because it provides a chance for the early treatment plan before any severe or irreversible damage can occur. Diagnosing MS should depend on the history and neurological examination as well as the imaging. The typical MS patient is a young woman with sudden onset of focal neurologic symptoms that lasts for weeks and then resolves. After that, new or recurrent symptoms will develop for months to years [34–36].

MS inflammatory lesions appear in MRI as multiple irregular hyper-dense areas in the white matter of the brain, especially in the periventricular area [35]. Almost all MS patients have an abnormal MRI. Therefore, the head MRI should be ordered first when MS is suspected. However, the low specificity is still the MRI's major disadvantage because several diseases

mimic MS features on MRI. These false positives can label patients of other diseases under the diagnosis of MS.

Cerebrospinal fluid abnormalities can accurately guide to the diagnosis of MS. Mild elevations in the protein and white blood cell counts may be seen but IgG level increase is the main finding in MS because Immunoglobulins reflect the autoimmune activation [35].

The diagnosis of MS should depend on seen sclerosis that is multiple. Two separate CNS lesions that occurred in two or more separate episodes are required to make the diagnosis. The symptoms must be white matter symptoms, not gray matter symptoms and without any other alternative diagnosis [37, 38]. Many patients experience a single symptom of demyelination like optic neuritis or transverse myelitis. These patients will eventually experience a second inflammatory attack and then, diagnosis of MS will be made. This diagnosis can be supported if, at the onset of the symptom, white matter changes appeared on the MRI scanning. Therefore, patients with a monosymptomatic episode of demyelination along with abnormal head MRI are often presumed to be diseased by MS already [37].

Management

The medications, that are used to treat MS cases, help in controlling the underlying mechanism of the disease. They mostly act on decreasing immune-mediated inflammation. This may stop the progression of the condition but does not cure MS or undo the damage that has occurred previously [7]. MS acute relapses should be managed by corticosteroids. Steroid treatments have become a traditional and accepted standard of practice for new attacks of MS. Moreover, there is a universal sense that they shorten symptoms and provide many benefits for acute relapses. A standard regimen uses intravenous methylprednisolone 1 gram daily for three to five days followed by a tapering dose of oral steroids. Steroids decrease the inflammatory process, seal the BBB, alter the immune system, and enhance nerve conduction. All these mechanisms are potentially beneficial in treating MS [37].

There are several drugs that are currently approved by the Food and Drug Administration (FDA) as disease-modifying agents. These agents alter the natural history of relapsing-remitting MS. Four self-administered medications are intramuscular beta-interferon-la (Avonex), subcutaneous beta-interferon-la (Rebif), subcutaneous beta-interferon-lb (Betaseron), and glatiramer acetate (Copaxone) [37]. These medications have shown the ability to decrease the number of attacks in relapsing-remitting MS. However, if the condition has reached a secondary progressive phase, the effect of these medications becomes weak. The mechanism of action of these drugs is poorly understood, but it is believed that interferons cause increased secretion of multiple immunomodulatory proteins. On the other hand, glatiramer probably inhibits the activation of myelin reactive T-cells [39].

Avonex is a preparation of recombinant human beta-interferon-1a and Rebif is an identical preparation. Betaseron is recombinant beta-interferon-1b, which is different from Avonex and Rebif only in one single amino acid.

Mitoxantrone (Novantrone) is preferred for secondary progressive MS as most likely to retard progression and delay disability. Novantrone is considered a chemotherapeutic drug for cancer such as lymphoma and leukemia, but it has characteristics of immunomodulation. It has the ability to postpone the damages in patients with secondary progressive MS. Nevertheless, Novantrone can lead to irreversible toxicity, particularly affecting the myocardium. Therefore, ejection fractions and echocardiograms should be followed periodically throughout treatment. Novantrone is recommended to be a short-term therapeutic choice^[37].

Copaxone is not interferon which makes it different from all the other medications. It seems to have the ability to the immune response to myelin. Glatiramer acetate mechanism of action is not well understood, but it is thought that it induces and activates T-lymphocyte suppressor cells. It is a subcutaneous preparation given daily. It was originally approved in 1996 and has been available in an extended dosage form since January 2014. It is indicated for reducing the frequency of relapses in patients with relapsing-remitting MS^[40, 41]. It has demonstrated a decrease in relapse rates and MRI lesions as well as progression on the expanded disability status scale^[42, 43]. Yet, Glatiramer acetate is considered as a safe drug in pregnancy (category B)^[41].

Pegylated interferon beta-1a was proved by the FDA in 2014. It is an interferon beta indicated for the treatment of relapsing forms of MS. For over 2 decades, Interferon beta has been the main medication in treating MS cases. However, its regimens can be challenging regarding administration frequency, which can reach to 3 injections weekly^[44]. Pegylated interferon beta-1a features an extended half-life and higher systemic exposure, ultimately leading to fewer required injections. This advantage mostly promotes greater adherence to the treatment. Pegylated interferon beta-1a peak plasma concentrations are achieved in 1 to 1.5 days after administration, and the half-life of elimination is around 78 hours. The commonest side effects experienced in patients receiving pegylated interferon beta-1a therapy are injection-site erythema, pyrexia, and headache. The greatest advantage of this medication is that it requires fewer injections compared with its predecessors, which makes it superior to older beta-1a agents^[41].

Although all of these medications have the potential to limit the rate of attacks, there is no solid proof that they can postpone the neurological deficits accumulation or the subsequent disability expected in MS cases. Their benefits in the long-term are still unclear.

CONCLUSION

Early recognition and diagnosis of MS are crucial because they provide a chance for the early treatment plans before any severe or irreversible damage can occur. Diagnosing MS should depend on the history and neurological examination as well as the imaging. Head MRI should be ordered first when MS is suspected despite its lack of specificity.

Disease-modifying therapies work on controlling the underlying process of the disease by limiting the immune-mediated inflammation. These medications have shown remarkable results in decreasing the attack rate. However, there is no solid proof that they can postpone the neurological deficits accumulation or the subsequent disability expected in MS cases.

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