

## Updates on Management of Multiple Sclerosis

Adil Alsulami<sup>1\*</sup>, Ayesha Tabassum<sup>2</sup>, Ahmed Abdullah Almarzouq<sup>3</sup>, Mashael Abdullah M Alghaidani<sup>4</sup>, Areej Abdullah Saad Abdullah<sup>5</sup>, Hammam Khaled Jafar<sup>6</sup>, Ghada Waheed AlMojadidi<sup>7</sup>, Abdullah Saeed Alghamdi<sup>8</sup>, Reem Awad farhan Alqahtani<sup>5</sup>, Hanan Bakhait Alghamdi<sup>9</sup> and Malak Abdullah Mufareh Asiri<sup>5</sup>

<sup>1</sup>Assistant Professor, Consultant Internal Medicine, Department of Medicine, University of Jeddah, Jeddah, Saudi Arabia

<sup>2</sup>King Fahd Hospital, Medina, Saudi Arabia

<sup>3</sup>Qatif Central Hospital, Qatif, Saudi Arabia

<sup>4</sup>Qassim University, Buraydah, Saudi Arabia

<sup>5</sup>King Khalid University, Abha, Saudi Arabia

<sup>6</sup>Masaryk University, Brno, Czechia

<sup>7</sup>Maastricht University, Maastricht, Netherlands

<sup>8</sup>King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

<sup>9</sup>University of Science and Technology, Sana'a, Yemen

**\*Corresponding Author:** Adil Alsulami, Assistant Professor, Consultant Internal Medicine, Department of Medicine, University of Jeddah, Jeddah, Saudi Arabia.

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### Abstract

**Background:** Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by chronic inflammation, demyelination, gliosis, and neuronal loss. The course may be relapsing-remitting or progressive in nature.

**Aim:** In this review, we will look into etiology, epidemiology, diagnosis and management of multiple sclerosis.

**Methodology:** The review is comprehensive research of PUBMED since the year 1991 to 2019.

**Conclusion:** MS is an autoimmune disorder of the CNS with an array of immune cells being either activated or suppressed leading to demyelination and disease progression. Epidemiological studies have also clarified the prognosis and reaffirmed that many patients do well. To date there is no cure for MS, and medications which decrease immunologic functions may have significant risks. The short term efficacy and safety of newer agents is being explored however the long term risks of these agents, particularly when used in combination or succession will remain uncertain.

**Keywords:** Multiple Sclerosis; Management of Multiple Sclerosis

### Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by chronic inflammation, demyelination, gliosis, and neuronal loss. The course may be relapsing-remitting or progressive in nature [1]. In the early 1900s, only a few cases of multiple sclerosis (MS) were reported, which quickly became a common occurrence for admission to neurological wards. Today, MS accounts over 2.5 million affected individuals with an estimated cost of US\$2-3 billion per annum [2]. The clinical course of the disease is quite variable ranging from a stable chronic disease to a rapidly evolving and debilitating illness. The most common form of the disease is relapsing-remitting multiple sclerosis; however, several other forms exist [3].

MS is categorized into 4 distinct types, primarily based on its clinical course, which are characterized by increasing severity: (a) Relapsing/remitting MS (RRMS), the most common form, affecting 85% of all MS patients which involves relapses followed by remission; (b) secondary progressive MS (SPMS), which develops over time following diagnosis of RRMS; (c) primary progressive MS (PPMS) affecting

8 - 10% of patients, noted as gradual continuous neurologic deterioration; and (d) progressive relapsing MS (PRMS) the least common form (< 5%), which is similar to PPMS but with overlapping relapses [4,5].

MS leads to a wide range of symptoms with various severity involving different parts of the body. MS diagnosis is mainly clinically based however, magnetic resonance imaging (MRI) assists in diagnosis. Symptoms and disease progression are varied, with some individuals experiencing little disability while most (up to 60%) require a wheelchair 20 years from diagnosis [6].

The distribution of MS varies according to geographic location. For example, the further north or south from the equator the higher the prevalence of MS; countries that lie on the equator have extremely low prevalence compared to Scotland, Norway, and Canada [7].

Unfortunately, there is no cure for MS. As a result, treatment typically focuses on slowing the progression of MS, shortening the duration and frequency of relapses, and managing symptoms [8,9].

### Etiology

The specific cause of multiple sclerosis is unknown. The most widely accepted theory is that multiple sclerosis is an autoimmune disease that preferentially destroys the CNS while the peripheral nervous system is spared [10]. Myelin can be compared to the insulation coating on electrical wires. When the protective myelin is damaged and nerve fiber is exposed, the messages that travel along that nerve may be slowed or blocked. The nerve may also become damaged itself. It isn't clear why MS develops in some people and not others. A combination of genetics and environmental factors appears to be responsible [11,12].

There are many risk factors that may increase the risk of developing multiple sclerosis like:

- **Vitamin D:** Having low levels of vitamin D and low exposure to sunlight is associated with a greater risk of MS.
- **Smoking:** Smokers who experience an initial event of symptoms that may signal MS are more likely than nonsmokers to develop a second event that confirms relapsing-remitting MS.
- **Age:** MS can occur at any age, but usually affects people somewhere between the ages of 16 and 55.
- **Sex:** Women are more than two to three times as likely as men are to have relapsing-remitting MS.
- **Family history:** If one of parents or siblings has had MS, means higher risk of developing the disease.
- **Certain infections:** A variety of viruses have been linked to MS, including Epstein-Barr, the virus that causes infectious mononucleosis.
- **Race:** White people, are at highest risk of developing MS. People of Asian, African or Native American descent have the lowest risk.
- **Climate:** MS is far more common in countries with temperate climates, including Canada, the northern United States, New Zealand, southeastern Australia and Europe.

### Pathophysiology

It has been generally accepted that chronic inflammation is the hallmark of neurodegenerative diseases, such as MS, Alzheimer's disease and Parkinson's disease. Myelin-reactive auto-T cells cross the BBB and their migration into the CNS consequently initiates an inflammatory cascade followed by demyelination of the CNS and axonal damage [13,14].

Demyelination increases the inflammatory activation processes leading to damage of BBB and stimulation of macrophage activation and oxidative stress pathways. The white matter lesions include myelin breakdown together with infiltration of monocytes, B cells, T cells and DC. Microglia and macrophages are the main innate immune cells present in MS lesions where they either act together with T and B cells, or directly cause neuro-inflammatory tissue damage [15,16].

Myelin is known to aid in the conduction of nerve impulses. Because multiple sclerosis is a demyelinating disease resulting in damage to this myelin, conduction speed is often slowed along affected nerves leading to the symptoms seen in multiple sclerosis [17].

### Epidemiology

The prevalence of MS has increased since 1955; current statistics indicate a prevalence of 3.6 per 100 000 person-years for women versus 2.0 per 100 000 person-years for men [18]. The prevalence of MS has increased progressively over time with 30/100,000 diagnosed in 2008 to 33/100,000 diagnosed in 2013 globally [19]. Approximately 350,000 individuals in the United States and 2.5 million individuals worldwide have multiple sclerosis. The disease is 3-fold more common in females than in males. While the age of onset is usually between 20 to 40 years, the disease can present at any age. Almost 10% of the cases present before the age of 18 [20].

Caucasians are especially vulnerable, particularly those of northern European extraction, and there is a geographic preference for people living in northern latitudes. Though clearly not inherited in a simple Mendelian pattern, MS tends to cluster slightly within families, as there is a 1 to 5% risk of developing MS if a parent or sibling has the disease, and at least a 25% concordance among monozygotic twins [21].

### Clinical features

Usually, MS symptoms are unpredictable and uncertain. Since this disease can affect any region of the CNS, it can generate almost any neurologic symptom. During the course of MS, some abnormalities appear to be more dominant or have a greater effect on functional ability [22].

Variability and diversity characterize the symptoms and presentation of MS. There is virtually no neurologic complaint that has not been traced to MS at one time or another, and a comprehensive account of its clinical features can become nothing more than a mere recitation of a positive neurologic review of systems. Symptoms that arise directly from damage to neurons (that is to say, gray matter symptoms) occur so rarely that their appearance casts doubt on the diagnosis of MS [23].

However, the pattern of presentation, like so many features of MS, is highly variable and symptoms may fluctuate considerably or even progress with little resolution. Attacks strike approximately every 12 to 18 months. This pattern is common when patients first develop MS and through the early years of their disease and is referred to as relapsing-remitting MS [21].

For every clinical attack, approximately 10 'asymptomatic' lesions are noted on magnetic resonance imaging (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; many more lesions can be seen at microscopic level and even more in deep and cortical grey matter [24].

### Diagnosis

The diagnosis of multiple sclerosis is a clinical diagnosis. No one test is diagnostic for the disease. Evidence of lesions which have occurred at different times in different locations must be found. This evidence can be clinical or radiographic. When evaluating clinical flares, flares are traditionally defined as symptoms that last for at least 24 hours. The McDonald Criteria is a set of criteria outlining different ways that a patient can meet the criteria for a definite diagnosis of multiple sclerosis [25,26].

Evoked potentials test that include visual, brain stem auditory, and somatosensory evoked potentials offers information about demyelination in the optic nerve and CNS. In addition, CSF analysis for myelin basic protein and immunoglobulin- gamma (IgG) determinations and blood sample analysis for detect of vitamin deficiencies may be diagnostically helpful [27,28].

The revised criteria for diagnosis of MS include the following [29]:

- At least two attacks with objective clinical evidence of at least two lesions.
- At least two attacks with objective clinical evidence of one lesion plus dissemination in space<sup>1</sup> shown on MRI or two or more MRI lesions consistent with MS plus positive CSF finding or second clinical attack.
- One attack with objective clinical evidence of at least two lesions plus dissemination in time<sup>2</sup> on MRI or second clinical attack.
- One attack with objective clinical evidence of one lesion, plus dissemination in space shown on MRI or two or more MRI lesions consistent with MS plus positive CSF findings and dissemination in time shown on MRI or second clinical attack.
- Insidious neurologic progression suggestive of MS plus one year of disease progression determined retrospectively or prospectively and two of the following: Positive brain MRI results (nine T2 lesions or at least four T2 lesions with positive visual evoked potential), positive spinal cord MRI results with two focal T2 lesions and positive CSF findings.

### Treatment and management

At least partial recovery from acute exacerbations or flares is expected. However, as discussed above, repair of damaged myelin may be incomplete. The primary goal in the treatment of multiple sclerosis is to prevent areas of damage by using maintenance therapies. Early maintenance therapies were injectable and first became available in the 1990s. Rapid growth has occurred in this area in the past several years with injection therapies, oral therapies, and infusion therapies now available [30,31].

In the last 25 years, due to the developments on the insights of MS pathogenesis, the number of disease modifying treatments in MS added up to 18. Four of these are oral agents (fingolimod, dimethyl fumarate, teriflunomide, and cladribine), approved by some health authorities over the world. A fifth oral agent, laquinimod, did not complete the approval procedures yet. Other drugs, which are parenteral, include IFN beta, glatiramer acetate, natalizumab, rituximab, daclizumab, alemtuzumab, and ocrelizumab [32].

Symptomatic treatments are aimed at maintaining function and improving quality of life. It is common practice to treat acute relapses of MS with a short course (typically 3 to 5 days) of a corticosteroid that has a rapid onset of action and that produces few adverse drug effects (AEs), such as intravenous (IV) methylprednisolone or dexamethasone. Brief courses of corticosteroids (e.g. oral prednisone 60 to 100 mg once daily, tapered over a period of 2 to 3 weeks, or IV methylprednisolone 500 to 1,000 mg once daily for 3 to 5 days) are also used to treat acute exacerbations and to shorten the duration of MS attacks [33,34].

To date, no studies have led to FDA-approved therapies for PPMS. Further, the efficacy of any of these medications varies from patient to patient. Due largely to the lack of biomarkers for disease activity and treatment response, drug efficacy continues to be measured according to the current gold standard, which is identification of gadolinium-enhancing lesions in the white matter on magnetic resonance imaging (MRI), combined with other markers of disease, including clinical relapse rate and confirmed disability progression [35].

### Conclusion

MS is an autoimmune disorder of the CNS with an array of immune cells being either activated or suppressed leading to demyelination and disease progression. Epidemiological studies have also clarified the prognosis and reaffirmed that many patients do well. To date there is no cure for MS, and medications which decrease immunologic functions may have significant risks. The short term efficacy and safety of newer agents is being explored however the long term risks of these agents, particularly when used in combination or succession will remain uncertain.

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