Pathophysiology, Subtypes, Diagnostic Support, and Treatment Strategies for Multiple Sclerosis: A Literature Review

Ridwan Hardiansyah[1], Suryadi Islami[1*][a], Fahmi Ilham Hatimi[1], Nisa Karima[1], and Khairun Nisa[1][b]
[1]*Faculty of Medicine, University of Lampung, Prof. Dr. Ir. Sumantri Brojonegoro No.1, Bandar Lampung, Indonesia*
suryadi.islami@fk.unila.ac.id

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Abstract: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by chronic inflammation in the central nervous system (CNS), leading to demyelination and disability. This review discusses the pathophysiology, subtypes, diagnostic tests, and management strategies of MS. By exploring the pathophysiological mechanisms and recent advancements in treatment, this article aims to provide valuable insights for medical practitioners treating patients with MS. The pathology of MS involves demyelination plaques, neuronal and axonal degradation, and astrocyte scarring. Genetic predisposition to MS is associated with a cross-reaction between environmental antigens and myelin components, oligodendrocytes, or myelin proteins. This reaction leads to T lymphocyte sensitization and autoreactivity against myelin and oligodendrocytes. MS is classified into three main subtypes: Relapsing Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), and Primary Progressive Multiple Sclerosis (PPMS). Diagnosis involves Magnetic Resonance Imaging (MRI) and clinical evaluation, with additional supportive tests including evoked potentials and cerebrospinal fluid (CSF) examination. Management consists of relapse therapy and long-term therapy, with relapse therapy administered during relapses and long-term therapy tailored to the MS subtype, involving early administration of disease-modifying drugs (DMDs) to slow disease progression.

1 INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease that causes chronic inflammation in the central nervous system (CNS). The demyelination process in the CNS in MS can lead to disability. The primary cause of non-traumatic neurological disability in young adults is multiple sclerosis (MS) (Browne et al., 2014). This disease is more common in young women, with a higher incidence ratio compared to men, ranging from 2:1 to 4:1 (Al Johani et al., 2023; Krysko et al., 2020).

The etiology of MS remains unclear. Various studies have shown that there is an interaction between genetic and environmental factors in triggering an immunological response that leads to demyelination. Environmental factors that have been extensively studied include geography, solar radiation, and vitamin D levels, a history of Epstein-Barr virus (EBV) infection, immune response to EBV, Cytomegalovirus (CMV) infection, smoking habits, childhood obesity, consumption of salt and hygiene levels (Ascherio & Munger, 2016; Walton et al., 2020). Although the number of MS cases in Indonesia is still relatively rare, its prevalence continues to increase. The challenges in diagnosing MS and the high cost of treatment become a significant economic burden.

According to data from the Multiple Sclerosis International Federation, the number of MS patients worldwide increased from approximately 2.1 million in 2008 to 2.3 million in 2013 and 2.8 million in 2020 (Walton et al., 2020). Multiple sclerosis (MS) is a prevalent inflammatory neurological disorder affecting about 33 individuals per 100,000 globally.

The disease manifests with varying clinical patterns and susceptibility factors across different populations. Since 1990, there has been a notable increase in the prevalence of MS, especially in low and middle-income countries, leading to significant healthcare and economic challenges (McGinley et al., 2021). The first documented case of MS dates back to 1933, as reported by Curtius. The prevalence of MS varies significantly between regions, with Europe and North America experiencing rates over

[a] https://orcid.org/0000-0002-7345-6960
[b] https://orcid.org/0000-0001-5707-464X

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100 cases per 100,000 people while Sub-Saharan Africa and Eastern Asia report much lower rates, around 2 cases per 100,000 people (Vidal-Jordana & Montalban, 2017).

If left untreated, multiple sclerosis (MS) can lead to a significant increase in the risk of physical disability and neurological functional impairment in patients. Uncontrolled disease progression can result in various complications, including mobility impairment, sensory impairment, cognitive dysfunction, visual impairment, coordination impairment, and urinary and bowel dysfunction (Ontaneda et al., 2017; Thompson et al., 2018).

In addition to the physical manifestation2s5, multiple sclerosis (MS) can also significantly increase the risk of developing mental health disorders, such as depression and anxiety, which can have a profound impact on overall quality of life (Feinstein et al., 2014). Furthermore, MS-related complications can lead to an elevated risk of other medical conditions, including urinary tract infections, pressure sores, osteoporosis, and the risk of injuries from falls (Ontaneda et al., 2017). Consequently, proper and integrated management is essential in managing MS to mitigate the risk of potentially detrimental complications for patients.

This article provides a review of the pathophysiology, subtypes, diagnostic support, and treatment strategies for MS. By examining the underlying mechanisms of pathophysiology and recent advancements in treatment, this article aims to serve as a valuable resource for medical practitioners in the care of patients with MS. The article aims to provide a detailed and up-to-date overview of this complex disease, as well as offer practical insights for medical practitioners in their role in managing patients with MS.

2 METHODS

This literature review article was conducted by searching for relevant keywords on Google Scholar, PubMed, and ResearchGate. The inclusion criteria required articles to be published in relevant journals and books, using keywords and titles for the search. Exclusion criteria included articles older than ten years, those unrelated to the title, and articles published in predatory or non-citable journals.

3 RESULT AND DISCUSSION

The pathological characteristics of MS include the presence of plaques resulting from inflammation, demyelination, neuronal and axonal degeneration, axonal damage and astrocytic scarring (Dighriri et al., 2023; Sospedra & Martin, 2016). These plaques are found in the brain and spinal cord, predominantly in the white matter near the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts, and the subpial regions of the spinal cord and brainstem, as well as in the gray matter (Dighriri et al., 2023). In individuals with genetic susceptibility to MS, a cross-reactive response occurs between environmental antigens and components of myelin, oligodendrocytes, or myelin proteins such as S-100 and phosphodiesterase (Sospedra & Martin, 2016). This reaction triggers T-cell sensitization, leading to autoreactivity against myelin and oligodendrocytes that have undergone cross-reactive responses (Hemmer et al., 2015). Several types of T cells are believed to be involved in MS such as CD8+ T cells, CD4+ Th1 cells, and Th17 cells. Interferon-gamma, IL-17, and granulocyte-macrophage colony-stimulating factors are cytokines produced by autoreactive T cells that contribute to the pathophysiology of MS (Dighriri et al., 2023)

When the cross-reactive antigen interacts with the body, macrophages phagocytose the antigen (Frischer et al., 2015). Antigen-presenting cells (APCs) like dendritic cells present this antigen by forming a complex between the antigen and major histocompatibility complex (MHC) on the cell surface (Dobson & Giovannoni, 2019; Frischer et al., 2015).2 This antigen-MHC complex is recognized by receptors on the surface of CD4+ T cells, causing activation and differentiation into T helper 1 (Th1) cells. Th1 cells subsequently release proinflammatory cytokines that activate endothelial adhesion molecule receptors on the blood-brain barrier (BBB), leading to increased blood-brain barrier permeability to T cells (Dobson & Giovannoni, 2019; Thompson et al., 2018). Mast cells also release histamine and tryptase, which contribute to the opening of the BBB and the recruitment of inflammatory cells into the CNS (Rodríguez Murúa et al., 2022).

Following transmigration across the blood-brain barrier, Th1 cells are reactivated by antigen-presenting cells (APCs) that present myelin proteins as antigens (Dobson & Giovannoni, 2019; Sospedra & Martin, 2016). This reactivation triggers the production of proinflammatory cytokines, nitric oxide, antibodies, complement, and molecules that mediate apoptosis. Proinflammatory cytokines also stimulate microglia and astrocytes, further increasing blood-brain barrier permeability (Dobson

& Giovannoni, 2019; Sospedra & Martin, 2016). Chemotactic molecules that facilitate the entry of T cells, antibodies, and macrophages are also stimulated (Li et al., 2018). This immunological cascade ultimately leads to edema, demyelination, and axonal death, thereby disrupting neural impulse transmission (Figure 1).

Multiple sclerosis is classified into three subtypes: Relapsing Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), and Primary Progressive Multiple Sclerosis (PPMS). Relapsing-Remitting Multiple Sclerosis (RRMS) is the most common, approximately 85% of cases (Xie et al., 2020). Characterized by a relapsing-remitting pattern, RRMS is marked by periods of remission that can last several months to years without new symptoms (Mackenzie et al., 2014). Approximately 65% of patients with RRMS will eventually develop secondary progressive MS (SPMS) (Leray et al., 2016).

Secondary Progressive Multiple Sclerosis (SPMS) is a continuation of RRMS. The median time between diagnosis of RRMS and the onset of progressive disease is 20 years in untreated patients (Cree et al., 2021; Dobson & Giovannoni, 2019). Men are more likely to experience progressive disease more quickly, and older age at diagnosis is associated with a faster progression (Cree et al., 2021; Scalfari et al., 2014). In SPMS, the relapsing-remitting pattern becomes less frequent, replaced by progressive neurological symptoms (Leray et al., 2016; Scalfari et al., 2014).

Primary Progressive Multiple Sclerosis (PPMS) is found in 10-15% of cases. PPMS does not have a relapsing-remitting phase like SPMS; the disease is progressive from the onset of symptoms, with accumulating disability (Braune et al., 2023; Miller & Leary, 2007). The condition can experience a plateau phase for a period of time. Patients with PPMS are generally older than those with other subtypes and are more often found in men (Cree et al., 2021; Dobson & Giovannoni, 2019; Thompson et al., 2018).

The symptoms of multiple sclerosis (MS) reflect damage to the myelin sheath in the central nervous system (CNS) (Dobson & Giovannoni, 2019). Patients often do not recognize or ignore early symptoms as neurological symptoms. Early symptoms can appear as single or combined symptoms, with a subacute onset over several days to weeks (Thompson et al., 2018). However, in some cases, symptoms can appear with an acute onset. If early symptoms are mild, patients often do not seek treatment, and the condition can persist for several months to years (Leray et al., 2016). Early symptoms usually improve within 6-12 weeks (Hosseinnataj et al., 2023; Thompson et al., 2018). The manifestations of MS are highly variable, with characteristic symptoms including fatigue, depression, cognitive dysfunction, spasticity, pain, urinary and bowel dysfunction, erectile dysfunction, and visual impairment. Other symptoms can include tremors, ataxia, vertigo, weakness, extrapyramidal symptoms, sensory impairment, and movement disorders (Ontaneda et al., 2017).

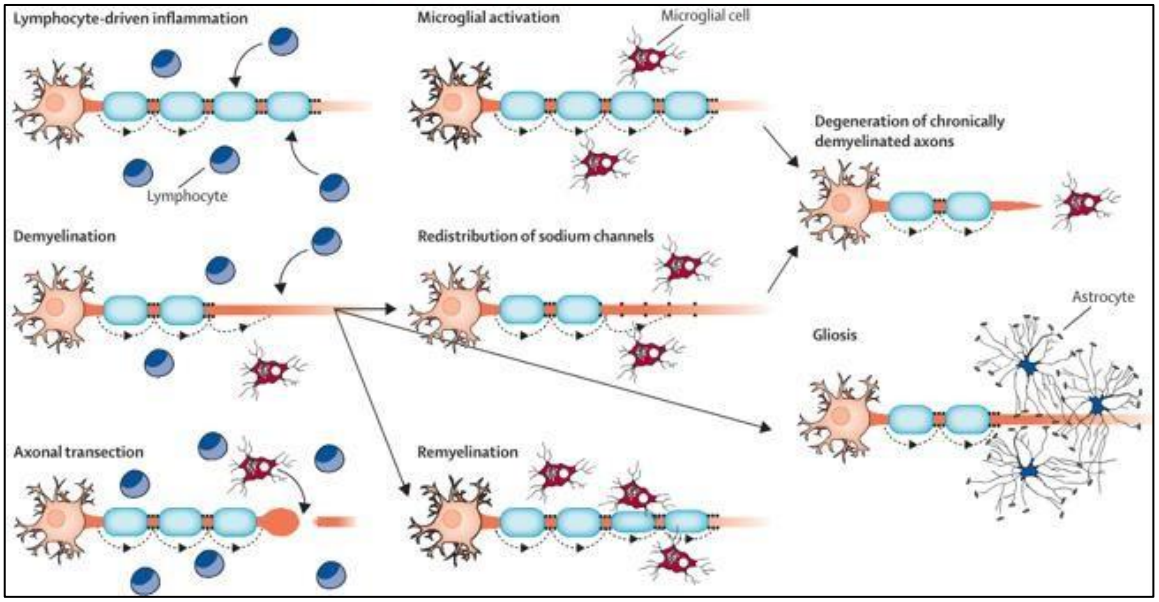

Figure 1: Pathogenesis of multiplesclerosis (Ciccarelli et al., 2014).

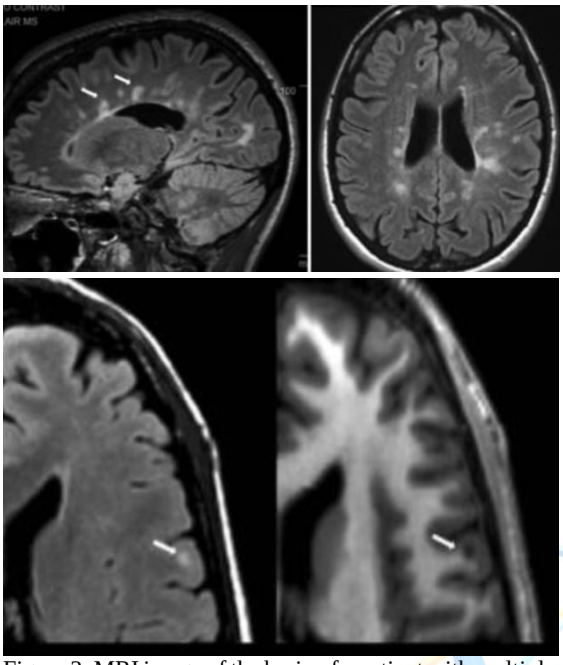

Figure 2: MRI image of the brain of a patient with multiple sclerosis. There are perivenular lesions, known as 'Dawson's fingers' (arrow), and several periventricular lesions with a dominant ovoid/oval configuration (Hemond & Bakshi, 2018).

Magnetic Resonance Imaging (MRI) is a crucial component in the diagnosis of MS after clinical evaluation (Filippi et al., 2016). The T2 sequence is able to detect lesions in the infratentorial region more effectively, while the fluid-attenuated inversion recovery (FLAIR) sequence has high sensitivity for lesions in the cortical or juxtacortical and periventricular white matter (Filippi et al., 2016; Sati et al., 2016). Contrast enhancement is typically seen in active lesions (Absinta et al., 2016; Filippi et al., 2016). The shape and location of lesions can help identify MS lesions on MRI. Characteristic lesions include those with an ovoid shape within the white matter or extending to the corpus callosum (Dawson's finger) (Figure 2) (Filippi et al., 2016).

Additional diagnostic tests that can aid in the diagnosis of multiple sclerosis (MS) include evoked potentials and cerebrospinal fluid (CSF) analysis, although both tests are not specific to MS. Evoked potentials, such as visual evoked potentials (VEPs), are commonly used and have a relatively high sensitivity (Thompson et al., 2018). VEPs are utilized to verify the existence of visual disorders or to identify subclinical, symptomless issues within the visual pathway (Leocani et al., 2018). Results showing demyelination lesions can serve as an objective clinical evidence (Balcer et al., 2015; Thompson et al., 2018).

CSF analysis helps rule out differential diagnoses, particularly infections. The analysis of IgG and oligoclonal bands has high sensitivity but is not specific to MS. Oligoclonal bands can also be found in other diseases such as systemic lupus erythematosus, neurosarcoidosis, intracranial hemorrhage, and others (Thompson et al., 2018)2. According to the 2017 McDonald criteria, the role of oligoclonal bands in establishing the diagnosis of MS becomes more significant, as they can replace the criterion of dissemination in space (DIS) and time (DIT) (Thompson et al., 2018).

The management of MS is divided into relapse therapy and long-term therapy. Relapse therapy is only given during relapses and not for long-term treatment. The first choice for relapse therapy is intravenous or oral methylprednisolone with a dose of 500-1000 mg for 3-5 days (Talanki Manjunatha et al., 2022). The controversy surrounding the reduction of methylprednisolone doses after administration remains (Talanki Manjunatha et al., 2022). A study comparing groups with and without dose reduction of methylprednisolone showed no significant difference in recovery between the two groups (Spelman et al., 2021).

Long-term therapy is tailored to the subtype of multiple sclerosis (MS). It is recommended to administer disease-modifying drugs (DMDs) to patients diagnosed with MS as soon as possible to slow disease progression (Thompson et al., 2018). Currently available DMDs in Indonesia include interferon-1a, interferon-1b, and fingolimod. Interferon-1a and interferon-1b are the preferred treatments for clinically isolated syndrome (CIS) and relapsing-remitting multiple sclerosis (RRMS) (Marziniak & Meuth, 2014; McGinley et al., 2021). Interferon-β works by binding to specific receptors on the surface of immune cells, altering the expression of several genes, which ultimately leads to a decrease in adhesion molecules, inhibition of MHC-II expression, reduced migration of inflammatory cells into the central nervous system, inhibition of pro-inflammatory cytokine synthesis, and increased synthesis of anti-inflammatory cytokines. Interferon-β1a is administered at a dose of 22-44 µg, 2-3 times a week, subcutaneously (Dargahi et al., 2017). Fingolimod is an oral disease-

modifying drug with a dose of 0.5 mg per day (Calabresi et al., 2014). Disease-modifying drug therapy in multiple sclerosis can be seen in Table 2. Fingolimod is used in highly active MS or in RRMS that does not respond to interferon therapy. Fingolimod works by activating sphingosine-1- phosphate receptors, thereby inhibiting the release of lymphocytes into circulation from lymph nodes (Dargahi et al., 2017; Kleiter et al., 2016; McGinley et al., 2021).

Table 2: Disease-modifying drug (DMD) therapy in multiple sclerosis (McGinley et al., 2021)

Drug	**Mechanism of action**	**Indication**	**Dose**
Highly effective			
Ocrelizumab	Anti-CD20 mAb	RMS and PPMS (first line)	300 mg IV×2 doses 2 weeks apart, then 600 mg every 24 weeks
Ofatumumab	Anti-CD20 mAb	RMS (first line)	20 mg SQ weekly on weeks 0, 1, 2, then 20 mg every 4 weeks starting in week 4
Natalizumab	α4β1 integrin inhibitor	RMS (second line)	300 mg IV once a month. Option for every 6 weeks after 24 weeks on therapy
Alemtuzumab	Anti-CD52 mAb	RMS (first line)	Year 1:5 days of 12 mg IV daily with steroids Year 2:3 days of 12 mg IV daily with steroids
Moderately effective			
Fingolimod	Sphingosine -1- phosphate inhibitor	RMS (second line)	0.5 mg PO daily
Siponimod	Sphingosine -1- phosphate inhibitor	CIS, RMS, active SPMS (first Line)	Initial: 0.25 mg PO once daily on days 1 and 2; 0.5 mg on day 3; 0.75 mg on day 4; 1.25 mg on day 5 Maintenance: 2 mg once daily, beginning on day 6
Ozanimod	Sphingosine -1- phosphate inhibitor	CIS, RMS, active SPMS	Initial: 0.23 mg once daily on days 1–4, 0.46 mg on days 5–7, then 0.92 mg daily
Dimethyl fumarate and diroximel fumarate	Nuclear factor (erythroidderived 2) − like 2 pathway inhibitor	RMS (first line)	Initial: 120 mg PO BID then after 7 days increase to maintenance dose of 240 mg BID Take with food
Cladribine	Not fully known	RMS (second or third line)	2 oral treatment courses, each approxim-ately 5 days each and 1 year apart Total dose of 3.5 mg/kg (1.75 mg/kg per treatment course)
Modestly effective			
Teriflunomide	Dihydrooro-tate dihydrogen-	RMS (first line)	14 mg PO daily

	ase inhibitor		
Glatiramer acetate	Not fully known	RMS (first line)	20 mg SQ daily or 40 mg TID

IFN-β1a	Not fully known	CIS and RMS (first line)	Rebif 44 mcg SQ TIW, Avonex 30 mcg IM once a week, Plegridy 125 mcg IM once every 2 weeks. Betaseron 0.3 mg SQ every other day
IFN-β1b	Not fully known	CIS and RMS (first line)	

4 CONCLUSION

Multiple sclerosis is a complex autoimmune disease characterized by demyelination, neuronal and axonal degradation, and astrocytic scarring. The disease is triggered by a cross-reactive response between environmental antigens and components of myelin, leading to T-cell sensitization and autoreactivity against myelin and oligodendrocytes. The symptoms of MS are highly variable and reflect damage to the myelin sheath in the central nervous system. MRI is crucial in diagnosing MS, and characteristic lesions include those with an ovoid shape or Dawson's finger. Additional supportive tests include evoked potentials and cerebrospinal fluid (CSF) analysis. Relapse therapy for MS uses intravenous or oral methylprednisolone, while long-term therapy is tailored to the subtype of MS, using disease-modifying drugs (DMDs) such as interferon-1a, interferon-1b, and fingolimod to slow disease progression. If DMDs cannot be used, immunosuppressants like azathioprine are an alternative.

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