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Current perspectives on Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is a chronic, autoimmune disease that affects the central nervous system. It is characterized by inflammation, demyelination and axonal loss, and is typically manifested by relapses and remissions. It is the most prevalent neurological disorder worldwide, with a significant prevalence in many countries. It is the leading cause of non-traumatic neurological impairment in young adults. Although the etiology is not fully understood, genetic predisposition, environmental factors (exposure to inadequate sunlight and/or inadequate dietary intake of vitamin D, Epstein-Barr virus infection, etc.) Furthermore, an individual's lifestyle, including obesity, smoking, and other factors, plays a significant role in the development of the disease. The clinical subtypes of MS, as defined in 2013, are classified into four categories: The four main clinical subtypes of MS are: Isolated Syndrome, Relapsing-Remitting MS, Primary Progressive MS and Secondary Progressive MS. The clinical subtypes of MS are further subdivided according to the activity and progression of the disease.

MS is a heterogenous disease, with lesions affecting multiple systems. The most common clinical manifestations include fatigue, blurred vision, and ocular pain (optic neuritis), as well as weakness and sensory changes in specific body regions, such as the face, arms, and legs. Furthermore, the patient presented with symptoms including balance impairment, vertigo, memory and cognitive difficulties, and bladder control issues.

Although there is currently no cure for MS, existing treatments focus on alleviating acute attacks, improving symptoms, and reducing the impact of the disease through biological therapies. Modifying therapies for the disease (e.g., interferons, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, ocrelizumab, natalizumab, etc.) These drugs, which reduce the frequency of clinical attacks and slow the progression of the disease, also reduce the activity of MRI lesions, making them an important component of MS treatment. They are effective due to their diverse mechanisms of action, administration routes, and dosages.

Keywords: Attack, Demyelination, Inflammation, Multiple Sclerosis

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory and neurodegenerative disease caused by autoimmune reactions that cause the central nervous system (CNS) to progressively disappear.[1,2] It was first described in 1868 by the French neurologist and pathologist Jean-Martin Charcot as a new disease of the nervous system.[3] MS is a disease that usually progresses with attacks, and myelin sheath and axon degeneration due to attacks may cause physical sequelae in patients, and a progressive disability may occur in patients with the accumulation of sequelae.[4]

MS is one of the most common diseases that cause neurological disorders worldwide and is the leading cause of non-traumatic neurological impairment among young adults in many countries.[5] According to the Atlas of MS, published by the International Federation of MS (MSIF), there are 2.9 million MS patients worldwide.[6] Although the onset of symptoms typically occurs in young adults between the ages of 20 and 30, women are about three times more likely to develop MS than men.[7] MS is not just a disease that affects adults. According to data from 55 countries reporting to MSIF, there are 30,000 children under the age of 18 living with MS worldwide. [6]

The prevalence and incidence of MS varies geographically. The prevalence of the disease is higher in America (100,000 to 111 people) and in Europe (100000 to 137 people), while it is lower in Africa and the Western Pacific (100,000 people to 5 people) (Figure 1).[6] Prevalence studies conducted in the past have shown that the incidence of MS is related to latitude, with the number of MS cases decreasing closer to the equator and the incidence increasing as the latitude increases (closer to the North/South poles). The slendering-related increase in MS prevalence is explained by the assumption that people living at higher geographical altitudes may have been less exposed to sunlight and thus have lower levels of vitamin D.[8]

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Although the etiology of MS is not clear, it is known that autoimmunity, impaired immune system, genetic and environmental factors (vitamin D levels, obesity, smoking and Epstein Barr virus (EBV) infection) are influential in the onset of the disease.[9]

The pathogenesis of MS is caused by infiltration of the focal immune cell and cytokine, leading to inflammation of white and gray matter tissues.[10] Oligodendrocytes are damaged and demyellinized in the early stages of the disease due to acute inflammation. However, irreversible axonal loss is initially less pronounced and tends to increase as the disease progresses. Typical MS lesions are identified in the pons, spinal cord and periventricular region but can be seen in any region of CNS. Other common localizations include the entire cerebral cortex, cerebral, cortical and jukstakortical regions.[11] The symptomatology of MS is diverse, heterogeneous, and may vary depending on the anatomical distribution of the lesions. Symptoms of MS include fatigue, blurred vision and eye pain (optic neuritis), weakness or sensory changes in certain parts of the body, such as face, arms or legs, trouble balancing, dizziness, memory and thinking impairment, and problems with bladder control. MS patients are also at high risk of depression and anxiety.[7]

The diagnosis of MS is based on evidence of CNS lesions spreading in time and space, as well as neurological symptoms and findings.[12]

The primary goal of MS treatment is to prevent permanent disability by reducing the inflammatory response and resulting neuroaxonal damage. One of the most important factors affecting the success of treatment is the correct and early diagnosis of the right treatment at the right time.[13]

This article aims to provide information about the increasing prevalence of MS worldwide and the effects of the treatment options used.

MS

MS is a chronic, autoimmune, neurodegenerative disease characterized by inflammation, demyelination and axon loss of CNS.[14] The term "multiple sclerosis" is derived from the Greek word "sklerosis", which refers to the formation of hardened areas in the lesions present in the "multiple" sections of the CNS.[3] The definitive definition of MS was first made in 1868 by Jean-Martin Charcot.[15] MS is a disease that is often followed by attacks and remissions, which progresses over the years.[16] These seizures or progressive degenerative processes can reduce the quality of life of patients and cause permanent impairment.[17] One or more neurological deficits consistent with an acute inflammatory demyelinating process lasting at least 24 hours in the absence of fever and infection are defined as an attack. Attacks are directly related to the diagnosis, prognosis and treatment of MS, as well as the main determinant of subtypes of MS.[18]

Epidemiology

MS is one of the most common autoimmune inflammatory diseases of CNS.[19] According to MSIF's country-level MS atlas, there are 2.3 million MS patients worldwide in 2013, 2.8 million in 2020 and 2.9 million in 2023 (Figure 1).[6] According to a report by MSIF, the global median prevalence of MS has risen to 33/100,000 in 2013, from 30 per 100,000 in 2008.[20] According to 2020 data, global median prevalence is expected to reach 35.9 per 100,000.[21] According to data from 81 countries, the number of incidents worldwide is 2.1 per 100,000 per year. This is equivalent to one person in the world being diagnosed with MS every 5 minutes.[6]

Increased epidemiological studies have shown an increased prevalence of MS in many parts of the world. This rise is interpreted by two different approaches. The first is a false rise caused by easier diagnostic methods due to the spread of magnetic resonance imaging (MRI) and the frequent change of diagnostic criteria; the second approach is that it is actually a real rise and that the disease affects more and more people. The second approach involves epigenetic changes and environmental factors.[22,23] Many epidemiological studies in the past have shown that the prevalence and incidence of MS increases as they move away from the equator. This suggests that the environmental factors caused by the differences in the geographical characteristics of the places where individuals live have an effect on the disease.[24] The prevalence of the disease is high in America and Europe, while it is low in Africa and the Western Pacific. The highest prevalence rates of MS in Europe are in Germany, Italy and the Scandinavian countries.[6]

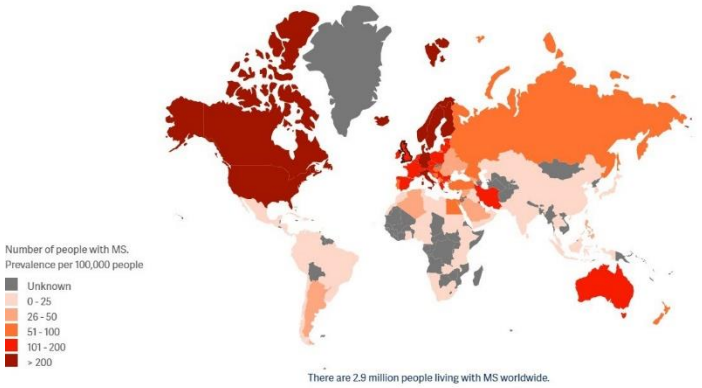

Fig. 1. Country-specific prevalence of MS on Earth. [6]

MS is a disease that usually affects young adults. Often, the symptoms begin between the ages of 20 and 30, but there are also patients diagnosed with MS in childhood or older years.[7,25] Pediatric MS (POMS) is defined as MS that begins before the age of 18. POMS accounts for 2% to 10% of total MS cases, and the highest incidence rate is between the ages of 13 and 16.[26–29] A systematic survey of the paediatric population, covering the years 1965-2018, found that the overall incidence ranged from 0.05 to 2.85 per 100,000 children, and the overall prevalence from 0.69 to 26.92 per 100.000 children.[30] In the pre-adolescent paediatric population, the incidence of MS observation is almost equal in girls and boys, while post adolescent girls are more likely to be affected.[26–29]

Etiology

The genetic predisposition, viral infections, environmental factors, and the individual's immune system are believed to be

influential in the development of MS, although the etiology is unknown.[31] Environmental factors include vitamin D deficiency, smoking, childhood obesity, non-specific infections (*Chlamydia* bacteria, etc.), fever and injuries.[9,32–35] Smokers have about twice the risk of developing MS than non-smokers.[36] Some important findings suggest that smoking causes the release of inflammatory cytokines, which are strongly linked to increased risk of neurodegenerative diseases such as MS.[37]

Risk factors

Lifestyle, genetic and environmental factors contribute significantly to the risk of developing the disease.[38] Genetic predisposition explains only part of the disease risk, but lifestyle and environmental factors are key factors that contribute to the risk of MS. High blood pressure, female sex, adolescent obesity, smoking, insufficient sun exposure and/or low vitamin D levels due to dietary intake, EBV infection, and organic solvents are some of the risk factors associated with MS. All of the risk factors described for MS can affect adaptive and/or congenital immunity modulated by MS risk alels. Unlike genetic risk factors, many environmental and lifestyle factors can be modified to provide prevention potential for those at the highest risk, especially the relatives of people with MS.[39]

Genetic Factors

The clustering of MS in families and the presence of genes predisposed to MS support the relationship between MS and genetics.[40] Many genes contribute cumulatively to disease risk and disease behavior, and these related genes and alleles vary from patient to patient.[41] Genes in the HLA region are the strongest genetic risk factors for MS.[42–45] HLA-DRB1 * 15: 01, HLA - DRB1* 13:03, HLA (DRB1) * 03:01, HLA "DRB" * 08:01 and HLA 'DQB' * 03:02 are classified as a risk factor for MS, while HLA's class I algae are preservative, HLA A * 02:01, hLA-B * 44:02, hla' - B * 38:01 and hla-b * 55:01.[45] HLA-DRB1 * 15: 01 allele has the strongest association with MS risk among the genetic risk factors, and has been associated with MS susceptibility in almost all populations studied.[46]

Exposure to Infectious Agents

Many bacteria and viruses associated with the development of MS have been identified. Bacteria that may play a role in the development of the disease include *Chlamydia pneumoniae, Porphyromonas gingivalis*, *Bacteroides fragilis* and *Staphylococcus aureus*.[47] Many persistent and chronic viral infections, primarily of the Herpesviridae family, have been considered as potential risk factors for MS. Although serological responses to these viruses have been used to assess the risk of MS, the direct mechanism of the pathogen's contribution to the development of the disease is not known. Accordingly, common theories include direct infection of the surrounding CNS tissue or oligodendrocytes, irregularity of immune tolerance mechanisms, and the possibility of molecular imitation between pathogens or autoantigens.[48] The most common viral risk factors for MS include human herpes virus 6 (HHV-6), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and human endogenous retroviruses.[47] Self antigens of HHV-6 and EBV viruses show molecular myelin similarity. This similarity suggests that they initiate autoimmune reactions with impaired immune tolerance to myelin proteins.[9]

Vitamin D

There is significant evidence that vitamin D deficiency, which has a significant impact on the development and function of CNS, may be a significant risk factor for the development of MS, especially in children.[49] Decreased levels of vitamin D are considered not only a risk factor for MS, but also a possible factor in the severity and incidence of the disease.[50] A study by Munger *et al.*[51] has shown that increased levels of vitamin D, especially before the age of 20, are associated with a decrease in MS in the later stages of life.[52,53] Historically, it has been suggested that low levels of vitamin D can support an irregular and/or hyperactive immune system that leads to CNS inflammation, making this system vulnerable to inflammations.[49] The polymorphisms in the genes DBP (vitamin D binding protein), VDR (vitamine D receptor), CYP27B1 and CYP24A1 may appear to be effective in MS sensitivity, as they play a role in both vitamin D levels and functions.[46]

Smoking

Smoking is one of the most prominent environmental risk factors associated with the onset and progression of MS in genetically sensitive individuals.[9,54] Observational studies have shown an increased risk of MS by about 50% compared to non-smokers.[55–59] These studies also show that there is a clear dose-response relationship between the cumulative dose of smoking and the risk of MS, and that both the duration and intensity of smoke are independent risk factors.[60,61] Also, passive smoking has been associated with an increased risk of MS.[62] Smoking is not only associated with an increased risk of MS, but also with the risk of developing neutralizing antibodies against biological substances such as interferon-β (IFN-β) and natalizumab used in the treatment of MS.[63,64] Several hypotheses have been proposed to explain the increased risk of MS in smokers, including effects on the immune and cardiovascular systems, increased frequency of respiratory infections, and neurotoxic effects of cigarette smoke metabolites.[65]

Cigarettes contain high amounts of free radicals. Oxidative stress caused by these free radicals has been to cause mutations in genetic material and to play a role in various neurodegenerative disorders such as MS.[66,67] Cigarette smoke has an effect on the immune system at the cellular level and causes the release of cytokines that cause inflammation.[66–68] The level of pro-inflammatory cytokines such as C-reactive protein, fibrinogen and other inflammatory markers, as well as interleukin (IL)-1B, IL-6, IL-23, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, is higher among smokers.[66,68] High levels of pro-inflammatory cytokines can contribute to permanent autoimmunity. In general, individuals with MS have higher levels of nitric oxide (NO) due to the presence of an inducible form of nitric oxide synthase (iNOS) in cells such as astrocytes and macrophages.[69] High levels of NO can lead to oligodendrosite necrosis, mitochondrial damage, axonal degeneration and ultimately impaired axonal conduction.[69,70] NO and CO (carbon monoxide) in cigarette smoke increase the inflammatory response and weaken some immune defenses, causing increased susceptibility to infections.[68,71] These changes in the immune system explain

several possible mechanisms that cause increased susceptibility to viral respiratory infections in MS patients.[66,68,71] A polyphenol-rich glycoprotein in cigarettes stimulates the proliferation of T cells and the differentiation of B cells, creating a pro-inflammatory environment.[71] In smokers, pro-inflammatory cells, such as G-protein-bound receptor 15 (GPR15) T cells are increased, and this is associated with MS.[72] Hydrogen cyanide and acrolein in cigarette smoke may also induce immunosuppression and neurodegeneration.[70,71] On the other hand, Gao and his colleagues studied the effect of nicotine and non-nicotine components in cigarette smoke on MS, using an experimental autoimmune encephalomyelitis (EAE) model in mice. Nicotine has been found to reduce the severity of EAE with reduced demyelination, increased body weight, and weakened microglial activation. This protective role of nicotine can be explained by its immunomodulatory functions.[73] Given that nicotine affects the a7 subunit of the acetylcholine receptor in immune cells by reducing the receptor activity, it stands out as an important candidate for a possible form of protection.[74]

Smoking has a significant interaction with the HLA risk genes associated with MS. Smokers who carry the HLA MS risk gene have a significantly higher risk of MS than those who do not carry this risk gene.[75] Among those carrying the genetic risk factor HLA-DRB1 15:01 but lacking protective Hla-A02, 41% of MS cases are associated with smoking.[76] Smoking has also been shown to interact with a variant of a non-HLA gene called NATI (the gene that encodes the enzyme involved in the metabolism of cigarette-related products).[36]

Obesity

There is an increasing number of evidence that supports the role of obesity in increased risk of MS.[77] Adolescence (~10 years) is the period when the effect of obesity on MS is strongest.[78] Adolescent obesity has been associated with an increased risk of developing MS due to both chronic inflammation and its correlation with low vitamin D levels.[51,79] A correlation was observed between body mass index (BMI >27) and relative risk of MS in obese or overweight girls.[78] Women with higher BMIs in childhood and adolescence tend to experience earlier menstruation, and this has been suggested to be associated with early onset of MS in women.[80–84] Studies found that women with a BMI of 30 kg/m^2 were 2.25 times more likely to develop MS when compared to women aged 18 with a normal BMI (18.5 to 21 kg/m^2).[85] Women's hormonal factors and childhood obesity, or X chromosome, can lead to an increase in the ratio of female to male MS, as shown by the fact that the risk of MS is higher in medium and highly obese girls, although it is not seen in males.[86] At least a few possible mechanisms have been identified that lead to an increased risk of MS in young obese individuals.[78] Obesity is associated with the onset of a low-level inflammatory condition in which increased levels of pro-inflammatory agents are produced in fatty tissue, and an increase in leptin levels, which is a medium linked to pro-inflammatory processes.[87–90] It also reduces the bioavailability of vitamin D and thus promotes pro-inflammatory processes.[91] Any of these potential mechanisms can increase the activation of adaptive auto-active immune cells, which can trigger attacks of neuro-inflammatory activity, a series of events supported by HLA gene interaction. The fact that the HLA genes encode the molecules that provide the antigen necessary for activation of T cells and interact with obesity supports the idea that obesities are prone to MS by promoting adaptive immunity related to MS neuron inflammation.[39] People with a high BMI, who carry DRB1*15:01 and do not have protective HLA-A02 have a 14 times higher risk of MS. This supports the causal role of obesity.[63] The largest genome-wide association study in which numerous MS cases were used revealed 70 different single nucleotide polymorphisms associated with BMI.[92] Similarly, a large-scale meta-analysis using Mendel randomization showed that the genetic risk score of 97 single nucleotide polymorphisms, known to be associated with higher BMI, contributed to a significant increase in POMS.[93,94]

Geographical Latitude

Despite the possible lack of accuracy in MS prevalence data, studies have generally confirmed that MS is more prevalent in regions with higher latitudes, and this has been associated with less sunlight intensity and lower UVB exposure in individuals.[95] Less exposure to UVB increases the risk of MS, causing less cholecalciferol production in the skin. The possible protective mechanism of UVB demonstrates its independent role in immunomodulation. UVB stimulates dentritic cells in the skin, secreting IL-10 (an anti-inflammatory cytokine thought to be protective against disease). IL-10 stimulates the local regulating T cells (Tregs) in the skin and the Tregs in the lymph nodes, and these activated Treg's perform immunomodulatory functions in CNS after entering the bloodstream.[96]

Although migration from high latitudes to low latitudes suggests a reduced risk of MS, the timing of migration has critical implications for this change.[97] Migration studies have shown that people under the age of 15 tend to embrace the risks of MS in the country where they migrate, while those older than 15 persist in their risks from the country of origin.[98] It has been discovered by Tao *et al.* that MS appears at an earlier age in populations living in areas with higher latitudes.[99]

Salt consumption

Studies and *in vitro* experiments clearly point to the relationship between excess salt consumption and MS risk.[100] A small study in the Argentine population found that people with high salt consumption with MS had significantly higher levels of depression and disease activity, as demonstrated by MRI, compared to those with low salt consumption.[101] *In vitro* experiments have shown that high salt consumption activates serum/glucocorticoid-regulated kinase 1, promotes T cell differentiation into pathogenic T_H17 cells, and mice consuming a very high salt diet develop a more severe course of EAE.[102,103] In these experiments, the amount of salt consumed by diet in humans is equivalent to >500 g of salt per day.[102]

Intestinal microbiome

In fecal microbiom analysis of MS patients, dysbiosis in the intestinal microbiome has been seen as a risk factor for the development of MS.[104,105] Changes in the abundance and diversity of the gut microbiome increase the permeability of the intestinal and blood-brain barrier, increasing the severity of

EAE.[106] Bacterial products, such as short-chain fatty acids, have also been associated with MS pathogenesis.[107] These are fermentation products of dietary fibre and are 95% composed of acetate, butyrate and propionate.[108,109] *In vitro* studies have shown that short-chain fatty acids such as propionate can support the polarisation of pure CD4+ T cells to Tregs.[110]

PROTECTIVE FACTORS

Factors such as alcohol or nicotine use, high coffee consumption and cytomegalovirus infection are associated with reduced risk of MS.[39]

Alcohol

A study found that Danish women with low alcohol consumption had a 44% lower risk of MS than non-drinkers.[111] In this regard, moderate alcohol consumption during adolescence has been associated with a lower risk of developing MS in the future.[112] Numerous studies involve consumption of red wine containing resveratrol.[113] Resveratrol, an antioxidant component found in grapes and fruits, is associated with preventing and delaying the onset of chronic diseases and reducing all-cause mortality.[111,114] Therefore, resveratrol has been tested in multiple rodent models of EAE MS and has shown increased remyelination, induction of blood-brain barrier repair and a decrease in proinflammatory cytokines.[115] Another potential mechanism of action of resveratrol is that activated T cells interact with aryl hydrocarbon and estrogen receptors, thereby inducing apoptosis or promoting phenotype change to the regulator Th17. This change reduces the overall serum levels of pro-inflammatory IFN-γ and IL12 cytokines.[116]

Coffee Consumption

The relationship between coffee consumption and MS risk has been investigated in two independent population case control studies. Those who consumption of high amounts of coffee (> 900 ml per day) had a 30% reduction in the risk of MS. Coffee contains a large number of biologically active substances, including caffeine, which stimulates CNS.[117] Caffeine, which has an antagonizing effect on the adenosine receptors found in neurons and glial cells, also binds to macrophage adenosin receptors, creating a polarizing shift from the pro-inflammatory phenotype to the anti-inflammatory phenotipe. Adenosine A1 receptors are also found in peripheral blood mononuclear cells (PBMCs), which regulate pro-inflammatory signaling for TNFα and IL-6 secretion. Blood samples from MS patients showed a decrease in serum adenosine and A1 levels, as well as fewer PBMC receptors, and also showed that TNFα was not suppressed by adenosin activation.[75]

DIAGNOSIS

In addition to a thorough history and physical examination, diagnostic tools necessary to diagnose MS and exclude other diagnoses include MRI, cerebrospinal fluid (CSF) analysis and evoked potential tests (Table 1).[13] MRI is the most important diagnostic and prognostic technique for the evaluation of MS (especially in the early stages of the disease) and the only technique that can interrogate the entire CNS *in vivo*.[118]

Anti-aquaporin-4 and anti-MOG antibody are clinically proven molecular biomarkers that allow differentiation between various inflammatory demyelinating diseases of the CNS.[119,120]

Table 1. Research on the diagnosis of MS.[13]

Primary Tests
1. Blood tests (hemogram, renal and liver function tests, electrolyte levels, sedimentation, CRP, B12, folate and vitamin D, thyroid function tests, lipid panel, viral serology (anti HIV, anti HCV, HbsAg, anti-Hbs), VDRL-RPR, ANA (1/320 titer and patterns), if ANA positive ENA profile, antiphospholipid antibodies, anti-ds DNA
2.MRI (cranial, cervical and thoracal)
3.CSF analyses (CSF protein, CSF and concurrent blood glucose, CSF albumin and IgG, CSF lactate, serum albumin and IgG, CSF IgG index, CSF OCB analysis with IEF electrophoresis)
4.In patients with optic neuritis: VEP and optic coherence tomography
Secondary Tests
1. Evoked potentials (VEP ve SEP)
2. Optic coherence tomography
3. Urodynamic testing
4. Cognitive testing
Other tests for differential diagnosis
1.Further biochemical tests (if there is suspicion of vasculitis, wider autoantibody panel, 24-hour urine analysis, GFR evaluation, for rheumatological disorders anti CCP, serum complement levels, for lymphoma serum anti beta2 microglobulins, for sarcoidosis blood and CSF ACE levels, for adrenoleukodystrophy adrenal hormone levels, long/very long chain fatty acids, for mitochondrial diseases serum piruvate, lactate levels, for neuromyelitis optica anti-aquaporin 4 and anti-MOG tests)
2.Specific tests for infectious etiologies (antibodies for Lyme disease and Brucellosis, PPD and quantiferon tests for tuberculosis)
3.Angiography (cerebral, fluorescein, MRA)
4.Biopsy (skin, lymph node, brain and/or leptomeninx, peripheral nerve, other)
5.Eye examination (retina evaluation for metabolic disorders, uvea evaluation for sarcoidosis and Behçet's disease)
6.Hearing tests (for Susac)
7.Electrophysiology (nerve conduction studies, EMG)
8.Chest X-ray (for chronic latent/sequel infectious lung disorders, and hilar adenopathy)
9.Cardiac examination (echocardiography for SLE, and mitochondriopathies)
10.Others (Schirmer test for Sjögren's disease, and salivary gland syntigraphy, for malignancies and metabolic disorders SPECT and PET)

Diagnostic Criteria

Various diagnostic criteria have been developed from the 1950s to the present to increase the sensitivity and specificity of MS diagnosis.[13] The widespread use of MRI as a diagnostic tool, the identification of clinical and imaging prognostic factors, and the increased need for early diagnosis and treatment of MS have led to various revisions in the diagnostic criteria for MS.[121]

In 2001, the International MS Diagnosis Panel, chaired by Ian McDonald, developed new MS diagnosis criteria, now known as the "McDonald criteria".[122] These diagnostic criteria have enabled MRI to be used as a central diagnostic tool in MS diagnosis.[121,122] The 2001 McDonald criteria were last revised in 2017 (Table 2).[123] Every revision of diagnosis criteria over time has enabled MS to be diagnosed earlier and more accurately.[124]

Table 2. Revised 2017 McDonald Criteria for MS Diagnosis.[123]

Number of clinical attacks	Number of lesions with objective clinical findings	Additional data needed for MS diagnosis
≥2 attack	≥2 lesion	–
≥2 attack	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	–
≥2 attack	1 lesion	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 attack	≥2 lesion	Dissemination in time demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands
1 attack	1 lesion	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI and Dissemination in time demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands

SYMPTOMS

MS symptoms vary depending on the location and size of the lesions occurring in CNS.[125] Common symptoms include spasticity, fatigue, sexual and bladder dysfunction, pain, and cognitive impairment (Table 3).[126] Cognitive impairments are especially common in advanced cases, and include memory loss, attention impairment, problem-solving abilities, slowdown in information processing, and difficulties in switching between cognitive tasks.[127]

Table 3. Symptoms monitored by retention regions in MS.[17]

Eclipse Zone	Symptoms
Cerebrum	Cognitive impairment Hemisensory and motor Aff ective (mainly depression) Epilepsy (rare) Focal cortical defi cits (rare)
Optic nerve	Unilateral painful loss of vision
Cerebellum and cerebellar pathways	Tremor Clumsiness and poor balance
Brainstem	Diplopia Vertigo Impaired swallowing
Spinal cord	Bladder dysfunction Erectile impotence Constipation
Other	Fatigue Pain Temperature sensitivity

PATHOGENESIS AND PATHOPHYSIOLOGY

The characteristic pathological feature of MS is the development of focal inflammation and themialistic lesions in the white ventricular regions of the brain, optic nerve and spinal cord. These lesions occur not only in the white vein regions, but also in the intracortical and deep gray vein areas.[128–130] Histologically, there are several basic processes that lead to the formation of these lesions: inflammation, demyelination, astrogliosis, oligodendrosite damage, neurodegeneration and axonal loss and remyelinization.[131] The generally accepted view of the immunopathogenesis of MS includes myelin-specific auto-reactive T cells activated in the peripheral immune system through interaction between environmental triggers and genetic sensitivity.[132] But more and more evidence in recent years has shown that B cells and the humoral immune cells through them and the congenital immune cell (microglia, dendritic cells, macrophages, etc.) also play an important role in the pathogenesis of MS.[133]

CLINICAL TYPES

Better understanding of MS and its pathology resulted in the 1996 MS phenotypes not reflecting the recently identified clinical aspects of the disease, which was regulated by the Committee on Clinical Research in 2013 and has been grouped into three main groups: Clinically Isolated Syndrome (CIS), Relapsing-Remitting MS (RRMS), and Progressive MS (PMS) (Secondary- SPMS and Primary-PRMS). At the same time, these main groups are also sub-categories, depending on the activity

and progression of the disease. The term "activity" is used in all forms of the disease and is defined as the onset of a clinical nuisance for a certain period of time, preferably at least one year, or the presence of new T2 or gadolinium-enhancing lesions. The term "progressive" is mainly used for the progressive forms of the disease and refers to the continuous increase in neurological dysfunction/invalidity, fluctuations and stages of stability, which are objectively documented without clinical evaluation at least once a year with no definitive recovery. PMS (whether SPMS or PRMS) has four possible sub-classifications, taking into account the level of disability.[134]

Clinical Isolated Syndrome (CIS)

CIS is defined as the first clinical presentation of a disease that shows the characteristics of inflammatory demyelination, which may be MS, but which does not yet meet the criteria for spread over time.[135] Depending on clinical and diagnostic findings, isolated symptoms have a (high/low) risk of transition to MS over time.[136]

Relapsing- Remitting MS (RRMS)

RRMS is the most common phenotype of MS, characterized by clearly defined attacks (relapse or exacerbation) and subsequent periods of partial or complete recovery (remission), where new symptoms appear or existing symptoms increase, accounting for approximately 85% of cases. During the period of remission of RRMS, all symptoms may disappear or some symptoms can persist and become permanent, while there is no noticeable progression in the disease.[137]

Secondary-Progressive MS (SPMS)

SPMS is a phenotype that follows RRMS, characterized by a decrease in seizures, with no apparent signs of remission, and a gradual worsening of symptoms over time (accumulation of weakness).[138] Studies before approved disease-changing treatments were available have shown that 50% of patients diagnosed with RRMS will transition to SPMS within 10 years and 90% within 25 years.[137,139]

Primary-Progressive MS (PPMS)

PPMS is the subtype of MS with the worst prognosis.[140] MS is a phenotype of about 10–15% of the population, characterized by worsening neurological symptoms and accumulation of disability, without attack and remission in the early stages of the disease. Walking problems are common because spinal lesions are more common than brain lesions. PPMS is usually diagnosed between the ages of 40-50 and the number of females/men is approximately equal.[137]

Radiologically Isolated Syndrome (RIS)

The term RIS, first defined in 2009,[141] describes patients with accidental MRI abnormalities who have thought of demyelination in the absence of clinical signs or symptoms.[142] Since there is no clinical evidence of the disease and the MRI findings alone are insufficient to diagnose MS, RIS is not considered a separate MS phenotype. However, RIS can raise suspicion of MS depending on the morphology and location of the MRI lesions.[141] Therefore, a RIS patient with no pronounced clinical signs or symptoms that suggest MS should be prospectively monitored.[134]

TREATMENT

MS is a disease that has no definitive cure. Although there is no definitive treatment for the disease, significant therapeutic advances have been achieved with molecular immunotherapy approaches such as peptide vaccination, administration of monoclonal antibodies, and immunogenic copolymers. The primary objectives of these therapeutic strategies are to shift the autoimmune response associated with MS to a non-inflammatory T-helper 2 (Th2) cell response, inactivate or heal cytotoxic auto-reactive T cells, induce the secretion of anti-inflammatory cytokines, and prevent the absorption of auto-active lymphocytes into CNS.[143] The goals of MS treatments are to treat specific symptoms, reduce the frequency of recurrences, and prevent the disease from progressing.[144] To achieve these goals, an individualised, dynamic, long-term treatment strategy with continuous monitoring of disease activity should be implemented. The treatment plan should be able to adapt to the changing needs of each patient based on the severity of symptoms, clinical evidence of disease progression, increased disease burden on MRI and the development of neutralizing antibodies (NAb).[145]

Although there are various treatment options available for RRMS, there are still limited treatment options for progressive MS forms (SPMS and PPMS).[146,147] Current treatments are focused on reducing biological activity through treating acute seizures, improving symptoms, and disease-modifying treatments.[148] Emerging therapies include CNS-penetrant Bruton's tyrosine kinase inhibitors and autologous haematopoietic stem cell transplantation, as well as therapies for remyelination or neuroprotection.[149]

Acute Attack Treatment

MS attacks are typically defined as a new or worsening neurological deficit that lasts for 24 hours or more in the absence of fever or infection. It is a distinctive feature of MS and is often associated with significant functional impairment and low quality of life.[150] In acute seizures, the most common symptom complexes generally relate to new or worsening inflammatory processes, including optic nerve, spinal cord, cerebellum and/or cerebrum. Therefore, the symptoms may vary, or may be a combination of visual impairment, sensory and motor impairments, balance problems, and cognitive deficiencies.[151,152] Although most MS attacks usually end with a recovery period that leads to clinical remission and sometimes results in complete recovery (especially in the early stages of the disease), symptoms that remain after the attacks can persist and contribute to the gradual progression of the disability.[150] Therefore, seizure treatment is important because it can help shorten and reduce the disability associated with the course of the disease.[153]

Different treatment methods, such as intravenous (IV) corticosteroids, plasma exchange, or adrenocorticotropic hormone (ACTH), are commonly used during periods of MS attacks.[154,155] Although these treatments are effective in reducing the duration of attacks and helping patients to recover faster, they do not have long-term neuro-protective benefits.[156–160] Synthetic forms of corticosteroids, IV and rarely oral, are the

most commonly used drugs in the treatment of seizures. [161–163] Synthetic corticosteroids used in therapy include prednisone, prednisolone, dexamethasone and methylprednisolon.[164] These agents work by preventing edema, stabilizing the blood-brain barrier, reducing pro-inflammatory cytokines, and apoptosis of T cells.[165] Plasmaferesis is a good choice for selected patients who do not respond to corticosteroid therapy and are expected to have permanent absence.[18]

Symptomatic Treatment

MS has a wide range of significant and disruptive symptoms, including fatigue, bladder dysfunction, cognitive impairment, pain and spasticity. Symptomatic treatment is aimed at eliminating or reducing symptoms that impair the functional abilities and quality of life of affected patients.[166] An untreated symptom can become worse or lead to other symptoms, causing an interlinked cycle of symptoms.[145]

Immunomodulation or immunosuppression, as well as the specific treatment of symptoms, is an important component of the overall treatment of MS. The methods available for symptomatic treatment are pharmaceutical and non-pharmaceutical. Spasticity, tonic spasms, fatigue, paresthesia, depression, sexual and bladder disorders, are some of the symptoms that require pharmacological intervention.[166]

Spasticity is the main cause of physical disability in MS patients. Non-pharmacological treatment options for spasticity include physician-recommended exercise regimens (stretching exercises to improve flexibility, aerobic exercises, and active and passive movements covering the full range of motion) and relaxation techniques (meditation, yoga).[145] When conditions such as hardness or spasm adversely affect sleep, medication is needed.[167] In pharmacological therapy, baclofen (a GABA receptor stimulant), benzodiazepines and tizanidine (a-adrenergic receptor agonist) are used.[145] The side effects of benzodiazepines, such as sedation and addiction, limit their use in MS.[168,169]

Fatigue is characterized by a lack of energy or a feeling of fatigue in 80% to 97% of MS patients.[170,171] Non-pharmacological treatment of the disease involves treating symptoms that lead to fatigue, such as sleep disorders and depression, and improving the patient's mobility through exercise.[145] In the pharmacological treatment of fatigue, drugs such as modafinil [172] and amantadine [173] are used.

Depression is a symptom that occurs in approximately 50% of MS patients.[174] Treatment of depression is aimed at preventing suicide, as well as reducing depressive emotions through appropriate psychotherapy and, if necessary, medication.[166] Selective serotonin reuptake inhibitors (fluoxetine, sertraline, escitalopram, citalopram and paroxetine), tricyclic antidepressants (nortriptyline and amitriptyline) and atypical antidepressants (venlafaxine and bupropion) are used in the pharmacological treatment of depression.[145]

Disease Modifying Treatments (DMT)

Progress in the treatment of MS has been made over the past three decades with the development of novel, highly effective disease-modifying therapies (DMTs) targeting a variety of mechanisms, including immunomodulation, immunosuppression and enhanced immune cell sequestration. (Table 4, 5, 6, 7).[149] DMTs have been significant in the treatment of MS by reducing clinical attacks, slowing the incapacity and progression of the disease, and minimizing the activity of MRI lesions. Currently 24 different DMTs are approved, including injectable, oral and infused drugs.[175] These drugs have different mechanisms of action, methods of administration and frequency, efficacy and safety, which have been shown to be effective in reducing inflammatory activity and relapse rates. DMTs approved for the treatment of RRMS include glatiramer acetate, monoclonal antibodies (alemtuzumab, natalizumab, okrelizumab), mitoxantron, dimethylfumarate, teriflunomide, fingolimod, and cladribine.[176]

Table 4. Low, Medium and High Effectiveness Treatments for MS.[177]

Low-efficacy treatments	Moderate-efficacy treatments	High-efficacy treatments
• Interferons	• Cladribine*	• Ocrelizumab
• Glatiramer acetate	• S1P modulators*	• Ofatumumab
• Teriflunomide	• Fumarates	• Natalizumab
		• Alemtuzumab

* May be considered to have moderate-to-high efficacy.

Interferon beta-1 (IFNβ-1) was the first DMT to be used in the treatment of RRMS.[178,179] The therapeutic mechanism of action in MS is to down-regulate the expression of MHC (major histocompatibility complex) molecules on antigen-presenting cells, suppress pro-inflammatory cytokines, increase anti-inflammatory cytokines, inhibit T cell proliferation and provide immunomodulation by blocking the migration of inflammatory cells to the CNS.[179] Current IFN-β therapies include both subcutaneous and intramuscular formulations with different injection frequencies.[180,181] The most common side effects in IFN-β treatment include injection site reactions and influenza-like symptoms that respond to acetaminophen, ibuprofen and glucocorticoids and tend to decrease over time.[182] Other side effects include exacerbating pre-existing spasticitis, depression, thrombocytopenia, mild anemia, and high transaminase levels. These side effects are usually not severe and rarely lead to discontinuation of treatment.[183]

Glatiramer acetate is a mixture of four amino acids (glutamic acid, alanine, lysine, and tyrosine) that are randomly combined to form an antigenically similar polymer to the basic protein of myelin.[184] Although initially used to induce experimental allergic encephalomyelitis (EAE), purified myelin has been found to prevent EAE after injection of the basic protein.[185] Glatiramer acetate, which has a variety of immunomodulatory effects,

enables this effect by strongly randomly binding to MHC molecules and thereby competing with various myelin antigens for their presentation to T cells, with a strong induction of specific Th2 suppressant cells migrating to the brain, along with the expression of anti-inflammatory cytokines such as IL-10 and TGF-B.[184] It is used in the treatment of recurring forms of MS, including CIS, RRMS, and active SPMS.[182] A phase III dose comparison study showed that both 20 mg and 40 mg doses of glatiramer acetate reduced the annual rate of attacks and the average number of Gd-enhancing lesions.[186] Glatiramer acetate, a generally well-tolerated drug, is not associated with flu-like symptoms.[187] Common adverse reactions include injection area reactions, redness, chest clogging, convulsion, shortness of breath, post-injection anxiety and, less commonly, lipoatrophy, which may rarely be distorting and require discontinuation of treatment.[187,188] Routine laboratory monitoring is not required in patients treated with glatiramer acetate and the development of binding antibodies does not impede the therapeutic effectiveness of the drug.[189]

Fumaric acid esters (FAE) is an orally available drug for the treatment of MS that has been tested in phase II/III MS trials and has proven beneficial effects on relapse rates and MR markers.[190] FAE induces the expression of endogenous antioxidative factors in brain cells by activating the transcription factor nuclear factor E2-related factor 2 (Nrf2).[191] Thus, it can protect CNS from the harmful effects of reactive oxygen intermediates released as part of the inflammatory process of the disease.[192] At the same time, the FAE also inhibits the transcription factor nuclear factor κB (NFκB) by preventing the expression of various inflammatory cytokines, chemokines and adhesion molecules.[193] Dimethyl fumarate, a methyl ester of fumaric acid, is an immunomodulator compound approved for the treatment of RRMS.[182] In two phase III trials of dimethyl fumarate for the treatment of RRMS, there was a 44-53% reduction in the annual relapse rate, a 22-32% reduction in disability progression and a reduction in MR Gd-retaining lesions of up to approximately 75-94%.[194,195] It is initially administered orally at 120 mg twice daily for 7 days, then at 240 mg two times a day. The most common side effects of dimethyl fumarate are gastrointestinal (GIS) symptoms, including diarrhea, nausea, abdominal pain, and flushing. Other side effects include leucopenia, elevated serum aminotransferase and bilirubin levels and proteinuria [182]. Dimethyl fumarate, which is generally well tolerated, has also been associated with some risk of progressive multifocal leukoencephalopathy (PML) in treatment.[196] Most of these cases are lymphopenic, so it is recommended to monitor lymphocyte values every 6-12 months during treatment.[148] Apart from dimethyl fumarate, other oral FAEs used in the treatment of MS include diroximel fumarate and monomethyl fumarate.[149] Diroximel fumarate is an oral bioequivalent compound to dimethyl fumarate, approved by the FDA for the treatment of WMS, RRMS and active SPMS, with fewer GI side effects compared to dimethyl fumarate.[182,197] Monomethyl fumarate is the main active metabolite of dimethyl fumarate and has been approved by the FDA for the treatment of CIS, RRMS and active SPMS. Monomethyl fumarate, treatment is initiated orally at 95 mg twice daily and increased to 190 mg twice daily after 1 week; tolerability profile and monitoring is similar to dimethyl fumarate with improved GIS tolerability.[198]

Teriflunomide is the active metabolite of leflunomide used in the treatment of rheumatoid arthritis.[199] It was approved by the FDA in 2012 for the treatment of recurrent forms of MS.[200] It acts by selectively inhibiting dihydroorotate dehydrogenase, an enzyme important in the synthesis of pyrimidine, and by reducing the proliferation of activated T and B lymphocytes.[199] The TEMSO study showed a relative risk reduction of 31% in the annual relapse rate of the disease, as well as a reduction in disability progression and disease activity.[201] Common side effects of teriflunomide include headache, nausea, diarrhoea, increased hepatic alanine aminotransferase (ALT) and alopecia.[148] Also, teriflunomide carries a black box warning for severe liver damage. Therefore, liver function tests should be followed every month for the first 6 months and then every 6 months. Teriflunomide should not be used in pregnancy or in male or female pregnant patients because it may affect fetal development and may remain in circulation for up to two years after discontinuation of the drug. If necessary, accelerated elimination can be achieved with activated charcoal or cholestyramine.[202]

Cladribine, a synthetic purine nucleoside analogue, is a prodrug that undergoes intracellular phosphorylation by deoxycytidine kinase. The active metabolite (cladribine triphosphate) accumulates in the cell, causing cellular metabolism disruption, DNA damage, and subsequent apoptosis.[203,204] The accumulation of cladribine triphosphate depends on the ratio of 5'-nucleotidases of deoxycitidine kinase.[205] Cladribine preferentially targets lymphocytes due to its relatively high deoxycytidine kinase/5'-nucleotidase ratio and produces rapid and sustained reductions in $CD4^+$ and $CD8^+$ T lymphocytes, with rapid, albeit more transient, effects on $CD19^+$ B lymphocytes.[203,204] Although it causes a decrease in circulating T and B lymphocytes, it also has relatively small and temporary effects on innate immune cells, such as neutrophils and monocytes.[203] An oral medicine approved by the FDA in 2019 for the treatment of relapsing forms of MS excluding CIS.[203,206] Unlike other oral DMTs, it is not taken daily but is dosed by weight (3.5 mg/kg).[206] The oral formulation of cladribine has been developed to be given in short courses over a two-year cycle.[207]

Sphingosine 1-phosphate (S1P) receptor modulators are medicines with a unique mechanism of action for recurrent forms of MS.[208] S1P is a phospholipid with five subtypes found in lymphoid tissue, endothelial cells, flat muscles, atrial myocytes, eyes, and veins. In lymph nodes, the binding of S1P to S1p receptors is important for the output of lymphocytes from the nodes. Binding of S1P receptor modulatory drugs to S1P receptors on lymphocytes leads to altered immune migration, down-regulation of S1P receptor expression and inhibition of lymphocyte egress from lymph nodes. The S1P receptor modulator, fingolimod, was the first oral treatment approved by the FDA in 2010 for the treatment of recurrent forms of MS.[209,210]

Prevents the exit of lymphocytes from secondary lymphoid organs by binding to 4 of the 5 subtypes of S1P receptors (with a higher affinity for S1P receptor type 1).[182] According to clinical studies, fingolimod was superior to both placebo and intramuscular IFNβ-1a in terms of clinical relapse and MRI activity measurements.[211,212] Although it is a generally well-tolerated drug, mild side effects such as elevation or lymphopenia can be observed in liver function tests.[211–214] Other side effects include macular edema, rarely common VZV and cryptococcal infections, PML.[148] Due to the possibility of bradycardia and heart block at the start of fingolimod treatment, a 6-hour observation period (including electrocardiogram monitoring) is recommended for all patients receiving their first dose.[215] In addition, when fingolimod therapy is abruptly discontinued without an effective switch to a new drug, rebound relapses with multiple contrasting lesions or tumefactive lesions may occur after 4-16 weeks.[216,217] Given the favourable profile of fingolimod in the treatment of MS, it has led to the development of small molecule S1P receptor modulators with shorter half-lives, greater S1P receptor selectivity and reduced side effects.[218] Siponimod is an S1P receptor modulator that selectively binds to the S1P receptor-1 and S1P receptor-5 subtypes, inhibiting lymphocyte egress with theoretically fewer off-target effects compared to fingolimod.[219] It was approved by the FDA in 2019 for the treatment of relapsing MS, including active SPMS. It is also the first oral compound approved for active SPMS treatment.[220] Side effects of siponimod include nasopharyngitis, headache, urinary tract infection and falls.[221,222]

Natalizumab, a humanised monoclonal antibody, is the first monoclonal antibody approved in 2004 for the treatment of MS.[223] It acts by inhibiting α4/β1 integrin, a component of VLA-4 (Very Late Activation Antigen-4) expressed by lymphocytes, and preventing its interaction with vascular cell adhesion molecule (VCAM) on endothelial cells. This prevents the lymphocytes from crossing the blood-brain barrier.[182] Natalizumab is highly effective in reducing relapses and slowing disease progression in relapsing forms of MS compared with placebo or IFNβ-1a.[224,225] Despite its well-known effect in reducing disease activity, there is a high risk of developing PML, an infectious and potentially fatal disease of the white matter caused by reactivation of John Cunningham virus (JCV). The risk of developing PML depends on the duration of natalizumab therapy, previous immunosuppressive therapy and exposure to JCV. Therefore, a JCV scan should be performed every 6 months during natalizumab therapy.[226] Another disadvantage of natalizumab is that discontinuation of treatment may trigger 'rebound' disease activity. This is a problem that may be encountered in patients who are non-compliant with treatment, who discontinued treatment before pregnancy or who have JCV seroconversion.[148]

Due to evidence of B-lymphocytes retention in MS pathology, anti-CD20 monoclonal antibodies have begun to be used for the treatment of MS.[19] The antigen binding of anti-CD20 antibodies activates the mechanisms that lead to a decrease in the number of B lymphocytes. Usually, these mechanisms are complement dependent cytotoxicity (CDC) or antibody dependent cell cytotoxin (ADCC). Ublituximab and ocrelizumab have a predominant ADCC effect, which contains natural-killing cells, while ofatumab and rituksimab are a dominant CDC.[227,228] Rituksimab is a chemical monoclonal anti-CD20 antibody widely used in clinical trials against RRMS and PPMS, although it has not received approval from any regulatory agency for the treatment of MS.[148]

Ocrelizumab, a humanised monoclonal antibody targeting the CD20 molecule on the surface of mature B lymphocytes[229], is the first compound approved for the treatment of PPMS.[182] Maintains pre-existing humoural immunity and the regenerative capacity of B lymphocytes by selectively depleting CD20-expressing B lymphocytes.[230,231] It was found to be highly effective in reducing the annual relapse rate compared with IFNβ-1a.[232] In addition, ocrelizumab has been to promote cell death through more ADCC activity and less CDC activity compared to rituximab, and has a more positive antigenic profile.[233–235] When administered as an IV (600 mg) every 6 months, the initial dose is usually divided into 2 infusions of 300 mg at 2 weeks intervals. Common side effects include throat pain, infusion reactions such as redness (more common in the first infusions),[236] respiratory tract and viral infections.[237] Also, although a slight increase in breast cancer risk was in clinical trials, no specific tumor risk was observed without a significant epidemiological inconsistency in the post-marketing analysis.[182]

Ofatumumab, approved for the treatment of RRMS,[238] is a fully humanised anti-CD20 monoclonal antibody that can be administered subcutaneously (a charge dose of 20 mg three times a week, followed by a 20 mg every 4 weeks) with an excellent safety profile and high effectiveness compared to okrelizumab. Common adverse events include injection-related reactions (usually a headache, redness within only 24 hours of the first 1-3 injections), nasopharyngitis, urinary tract infections, and upper respiratory infections.[182]

Alemtuzumab is a humanised monoclonal antibody against the CD52 receptor found on monocytes, lymphocytes and other immune and non-immune cells.[41,239,240]. Alemtuzumab, approved by the FDA in 2014 for use in the treatment of RRMS, is used in patients who often have an inadequate response to 2 or more MS drugs due to the widespread and severe side effects.[241] Alemtuzumab is administered as an IV infusion of 12 mg daily for 5 consecutive days, followed 12 mg daily for 3 consecutive days 12 months later. The main side effects include infections (mainly herpes infections), infusion reactions, autoimmune disorders, including thyroid autoimmunity, and immune thrombocytopenia. Full blood count, kidney, liver and thyroid function should be periodically evaluated for at least 5 years before and after treatment.[182]

Mitoxantron was approved by the FDA in 2000 for the treatment of RRMS and SPMS, but is a drug that is rarely used today due to its side effects. By binding to DNA and causing cross-linking and strand breaks, it reduces the proliferation of macrophages, T and B lymphocytes and also down-regulates the inflammatory cascade.[242] The main side effects include nausea, vomiting, hair loss, leukemia, cardiotoxicity, fatigue, infection, leukopenia and thrombocytopenia.[243]

Table 5. Injection treatments for MS.[244]

Name of the drug	Brand name	Administration Route
IFNβ-la	Avonex®	Intramuscular
IFNβ-la	Rebif®	Subcutaneous
PEG-IFNβ-la	Plegridy®	Subcutaneous or Intramuscular
IFNβ-lb	Betaseron®	Subcutaneous
Glatiramer acetate	Copaxone®	Subcutaneous
IFNβ-lb	Extavia®	Subcutaneous
Glatiramer acetate	Glatopa®	Subcutaneous
Ofatumumab	Kesimpta®	Subcutaneous

Table 6. Oral treatments for MS (National Multiple Sclerosis 2023).[244]

Name of the drug	Brand name
Teriflunomide	Aubagio®
Monomethyl fumarate	Bafiertam™
Fingolimod	Gilenya®
Cladribine	Mavenclad®
Siponimod	Mayzent®
Ponesimod	Ponvory™
Fingolimod	Tascenso ODT®
Dimethyl fumarate	Tecfidera®
Droximel fumarate	Vumerity®
Ozanimod	Zeposia®

Table 7. IV infusion treatments for MS.[244]

Name of the drug	Brand name
Ublituximab	Briumvi™
Alemtuzumab	Lemtrada®
Mitoxantrone	Novantrone®
Ocrelizumab	Ocrevus®
Natalizumab	Tysabri®
Natalizumab	Tyruko®

CONCLUSION

MS is a disease that causes lesion formation in different parts of the CNS with the effect of environmental factors and the individual's lifestyle, decreases the quality of life of individuals due to attacks and can cause permanent disabilities. It usually affects young adults, but can be seen in childhood or older age. In terms of geographical conditions, the prevalence and incidence of the disease varies depending on latitudes. People living in countries closer to the equator have been found to be at lower risk, while those living in higher-level countries are at higher risk. This proves the relationship between exposure to sunlight and/or vitamin D levels and MS. When the etiology of MS is analysed, factors such as genetic predisposition, EBV, smoking, obesity and intestinal microbiota have been found to be effective. Since the location of the lesions forms a wide range in CNS, the neurological manifestations and symptoms of MS show a heterogeneous clinical structure. MS is classified into four categories: CIS, RRMS, PPMS, and SPMS.

Since there are no clinical or laboratory findings to definitively diagnose MS, diagnostic tools such as MRI, CSF analysis and evoked potential tests are used in addition to a comprehensive history and physical examination. MRI is the most important diagnostic and prognostic technique for assessing MS (especially in the early stages of the disease).

Since MS is a progressive neurological disease, it is necessary to make an accurate and early diagnosis and start the right treatment at the right time. Otherwise, the progressive degenerative process occurring in the CNS will create permanent disabilities and negatively affect the quality of life of the person. Exercise is recommended to reduce symptoms such as fatigue and muscle weakness that adversely affect patients' daily activities. At the same time, patients should not consume harmful substances such as smoking, eat regular and healthy foods.

Although there is no definitive treatment for MS, the methods applied for the management of the disease can be categorised into three main groups: Acute relapse management, disease modifying treatment and symptomatic treatment. In acute relapse management, different treatment modalities such as IV corticosteroids, plasma exchange or ACTH are generally used; in symptomatic management, drugs such as baclofen, tizanidine, modafinil, fluoxetine, and in disease-modifying management, drugs such as glatiramer acetate, fingolimod, cladribine, alemtuzumab, ocrelizumab, dimethyl fumarate are used. Currently, CNS-penetran Bruton's tyrosine kinase inhibitors and autologous haematopoietic stem cell transplantation therapies are among the treatment options being investigated for the treatment of MS. Apart from these treatment options, research is ongoing for the definitive treatment of MS.

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