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Recent Advances in Multiple Sclerosisi Research

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Abstract: *The chronic autoimmune disease known as multiple sclerosis (MS) is characterized by inflammation, demyelination, loss of neurons, and gliosis (scarring). Our object to review MS pathophysiology, etiology, immunopathogenesis, symptoms and treatment the most prevalent autoimmune disease affecting the central nervous system (CNS) is multiple sclerosis (MS). It is a debilitating, chronic, demyelinating illness brought on by an attack by an inflammatory disease that causes the progressive loss of the myelin sheath that envelops the axons of neurons. Epidemiology indicates that the average age at onset is between 20 and 40 years old. MS is widespread in both Europe and America and is more common among women. Pathological features include oligodendrocyte loss, axon demyelination, and areas of inflammation (plaques). The incidence of MS is rising, especially in women, and there is a global latitude gradient in its prevalence. Although the exact cause of multiple sclerosis is unknown, epidemiological evidence suggests that both genetic and environmental factors play a significant role. There are four clinical forms of MS, such as secondary progressive MS (SPMS), Primary progressive MS (PPMS), and Progressive relapsing MS (PRMS), of which relapsing remitting (RRMS) type is the most common. An essential component of treating multiple sclerosis is managing its symptoms. Identifying and treating the various symptoms accurately results in increased quality of life for multiple sclerosis sufferers. The symptoms of multiple sclerosis can be classified as primary, secondary or tertiary. The main symptoms, which include ataxia, weakness, and sensory loss are directly associated with axonal loss and demyelination. Secondary symptoms like infections of the urinary tract due to the retention of urine are caused by the principal symptoms. The social and psychological repercussions of the illness lead to tertiary symptoms as reactive depression or social isolation. Fatigue and weakness, diminished balance, stiffness, and difficulties with gait as well as depression and cognitive deficits, are typical symptoms of multiple sclerosis. Deficiencies in the bowel, bladder and sexual organs, loss of vision and sensation and neuropathic pain. The most popular treatments for multiple sclerosis include disease-modifying medications such fingolimod, dimethyl fumarate, natalizumab, and interferon- beta. Real-world studies are required to demonstrate the effectiveness and safety of these drugs*

Keywords: Multiple sclerosis, Demyelination, Inflammation, gliosis, myelin sheath

Abbreviations: MS =Multiple sclerosis, CNS =Central nervous system, SPMS=Secondary progressive MS, PPMS=Primary progressive, PRMS=Progressive relapsing MS, RRMS= Relapsing remitting MS, MMPs= matrix metalloproteinase, MHC= = Major histocompatibility complex, BBB=Blood brain barrier, MRI= Magnetic resonance imaging, LA=alpha-linoleic acid, CBT=Cognitive behavioral therapy

I. INTRODUCTION

Multiple sclerosis is a progressive, inflammatory demyelinating disease of the central nervous system (CNS) of an unknown etiology Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory disease of the central nervous system (CNS), that affects the brain and spinal cord.[1] Also known as encephalomyelitis disseminata, MS is a myelinating disease in which the immune system, which normally protects the body, attacks the protective sheath (myelin) that covers nerve fibers. The name multiple sclerosis refers to the numerous glial scars (or sclerae – essentially plaques or lesions) that develop on the white matter of the brain and spinal cord. It is an unpredictable, often disabling disease of the CNS. It is not contagious, the nerves send information from the brain and spinal cord to other nerves in the body, the myelin helping make this transmission efficient. Damage to the myelin causes communication problems

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between the brain and the rest of the body, affecting the brain and the spinal cord that make up the CNS. The condition can be thought of as a stripped electrical wire and, as with damaged electrical wires, signals sent along damaged nerves between the brain and the body can be slowed or blocked.[2] The disease results in injury to the myelin sheath, a protective covering composed of lipids that insulate nerves and transmit electrical impulses down the length of an axon.[3] Its prominent feature is the presence of disseminated foci of demyelination, mainly in the white matter, in most cases, demyelination occurs periventricularly. The complex pathomechanism of the disease and its disseminated nature make both the clinical picture and the course of MS exceptionally diverse. The symptoms include movement, visual and sensory disturbances, cerebellar symptoms and sphincter control disturbances MS is one of the most common neurological diseases in young adults and the leading cause of non-traumatic disability in young and middle-aged adults.[4] About 2 million people are living with MS worldwide, with the number of cases expected to increase as population growth continues.[4,5]

Age: Mostly, MS is identified between the ages of 20 and 50 in addition, it shows that it can take place in youth and elder people.

Gender: The study showed that a major role was played by hormones and MS was general in women more than 2 to 3 times.

Ethnicity: Amongst white people with northern European ancestry, MS is more common.

II. HISTORY

Any severe neurological condition characterized by motor disability is referred to as "paraplegia". The first record of MS dates back to Saint Lidwina of Schiedam, who lived in the Netherlands at the end of the 14th century.[6,7] For twenty-six years, Augustus d'Este chronicled in his journal how his symptoms which are now recognized as MS grew worse over time. His first symptom was a transient vision impairment, probably optic neuritis. 28-year-old with neuritis. At the age of 54, he passed away from lower extremity and motor symptoms that made it difficult for him to walk.[7,8] Charcot's nomenclature and structuring of MS offered a structure for classifying previously incomprehensible finding new information and developing MS in the future. The process of consolidation has persisted ever since. The Charcot Students made the connection between postmortem lesion histology and clinical signs of the disease. Plaques in the brain and spinal cord were described in Joseph Babinski's 1885 master's thesis. Pierre Marie emphasized autonomic impediments to gait and functioning in MS.[9] Ernst Leyden first proposed a genetic component.[10] of MS around the middle of the 1800s. That being said, Curtius and others in Germany didn't begin to evaluating the genetics of MS and the way the disease was grouped in some families in a methodical manner.[8,11] MS was distinguished and "framed" by Charcot, Von Frerichs, Vulpian, and others as a distinct, identifiable entity.[9] Before, MS cases were categorized based on their prognosis, clinical presentation, and histology. physicians all across the world are diagnosing.[11] As knowledge about MS grew, so did theories about its genesis and attempts at therapy; 158 MS therapies were included in a 1935 study. Afterwards, "cures" included anticoagulants, desensitization to histamine, different diets, vaccinations and anticancer medications.[12] With the development of illness classification and impairment indices in the decades that followed the 1960s, the definition of randomized clinical trials grew increasingly precise. To explain immunological alterations, genetic influences, regional variations, infections, and environmental factors, hypotheses were created. MS organizations improved general education and research, and changed perceptions of the circumstance[13] Significant progress has been made in basic analysis in recent years to shed light on the immunomodulatory drugs, as well as the causes and mechanisms of disease.[13]

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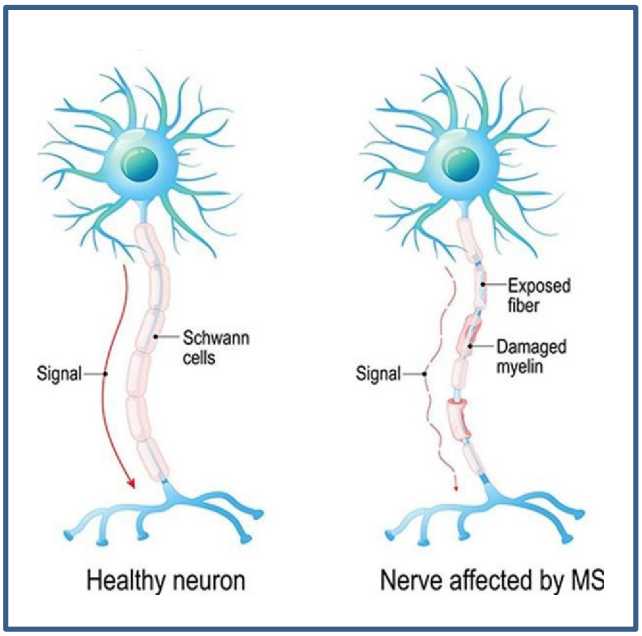

Fig 1: Difference between the healthy nerve and affected by the MS

2.1 Etiology of MS:

It is still unknown what causes MS specifically.[14] There is however, one pathogenesis-related theory that is most frequently acknowledged in the literature. MS begins as an autoimmune illness that is inflammatory and involves T cells that are reactive, myelin basic protein, and myelin glycoprotein found in oligodendrocytes. Moreover, it has been proposed that persistent neurodegeneration predominates in MS because triggering of microglia.[14] Moreover, several environmental factors have shown that they increase the risk of developing MS such as vitamin D deficiency, the Epstein-Barr virus, and sunlight.[14] Multiple localized demyelination lesions in the central nervous system or plaques are indicative of multiple sclerosis.[15]

BBB damage could be the cause of this. These plaques appearing in MS patients. Because of lymphocytes may infiltrate the central nervous system and detect this damage. Myelin antigens. Acute demyelinating could result from this. irritation, leading to the development of lesions in the cerebral white matter.[16] Although these lesions can occur anywhere in the central nervous system, they primarily impact the brainstem, optic nerves, cerebellum, and periventricular white matter areas.[17] However, current pathology and imaging according to research, demyelinated lesions are also frequently discovered in MS patients' cortical gray matter.[17,18]

2.2 Pathology:

MS plaques are concentrated areas of demyelination found in the cerebral cortex as well as the white matter of the brain and spinal cord. Deep grey matter and the cortex. Demyelination as well as White matter that appears normal might potentially show signs of inflammation. Additionally, significant axonal damage, such as transection of the axon, happens in lesions with current MS.[19] The perivascular infiltration of T cells, monocytes and occasionally B cells and plasma cells characterizes the inflammatory nature of MS lesions.[19] Three Different forms of acute MS lesions have been proposed. T lymphocytes predominate in type 1 lesions and macrophages lesions of type 2 possess extra immunoglobulins' deposition and their activation complement elements as well as type 3 lesions demonstrate apoptosis of oligodendroglia cells.[19]

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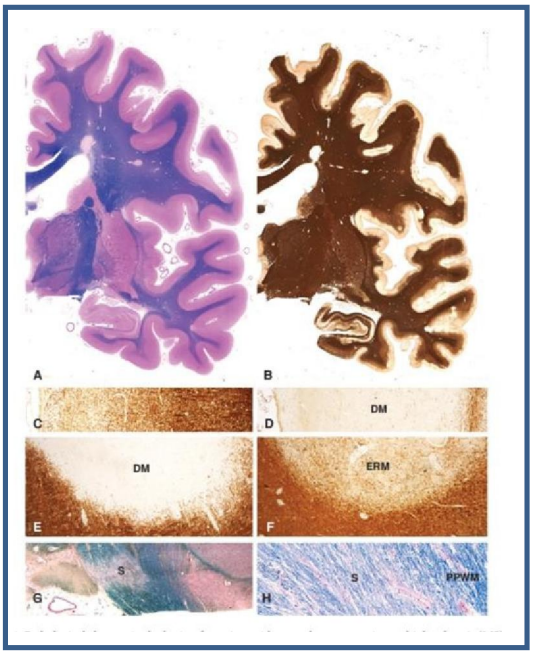

Figure 2. Pathological changes in the brain of a patient with secondary progressive multiple sclerosis (MS). Large confluent focal demyelinated lesions are present in the white matter (A). In addition, there is extensive subpial cortical demyelination, which can only be seen when sensitive immunocytochemistry for myelin proteins (e.g., proteolipid protein) is used (B). In contrast to the normal pattern of myelin in the cerebral cortex, as shown in C, there is complete loss of myelin in subpial lesions (D). Demyelinated plaques in the white matter may appear as inactive demyelinated lesions ([DMs] in E), as early remyelinated lesions with a low density of thin myelin sheaths only visible by immunocytochemistry for myelin proteins (ERM in F) or as remyelinated shadow plaques (G and H).[20]

2.3 Pathophysiology of MS:

When we talk about MS, we're talking about CNS plaque development, inflammation, demyelination, axonal damage, and axonal loss. The white matter surrounding the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts, and subpial region of the brain and spinal cord are the primary locations of these plaques the gray matter, brainstem, and spinal cord. They have shown up in every type of MS (primary, MS that is secondary and relapsing-remitting. However, as time passes, their face changes, revealing a deep Variability in the immunopathological patterns of oligodendrocyte and demyelination deterioration between the disease's progressive manifestations and its relapsing-remitting history.[21,22] Autoimmune immune cells that cross the blood-brain barrier and target the central nervous system are thought to be the cause of multiple sclerosis (MS). In the thymus or bone, autoreactive immune cells are regularly deleted during development.[23] Marrow via B lymphocytes with central tolerance. While some might avoid this procedure and be allowed to most of the time, peripheral tolerance mechanisms and circulation stop them from producing disease. Peripheral tolerance may fail through two mechanisms: the resistance of autoreactive T cells to suppression and the decreased activity of regulatory T cells. A complex interplay between genetic .Since these autoreactive cells activation and activity may be impacted by environmental risk factors, assisting in the onset of illness.[24] Th17 cells, CD4+ Th1 cells, and CD8+ T cells are the main subsets of T cells linked to multiple sclerosis. Autoreactive T cells release cytokines called interferon-gamma, IL-17 and granulocyte-macrophage colony-stimulating factors, which may be involved in the MS's pathophysiology.[24]

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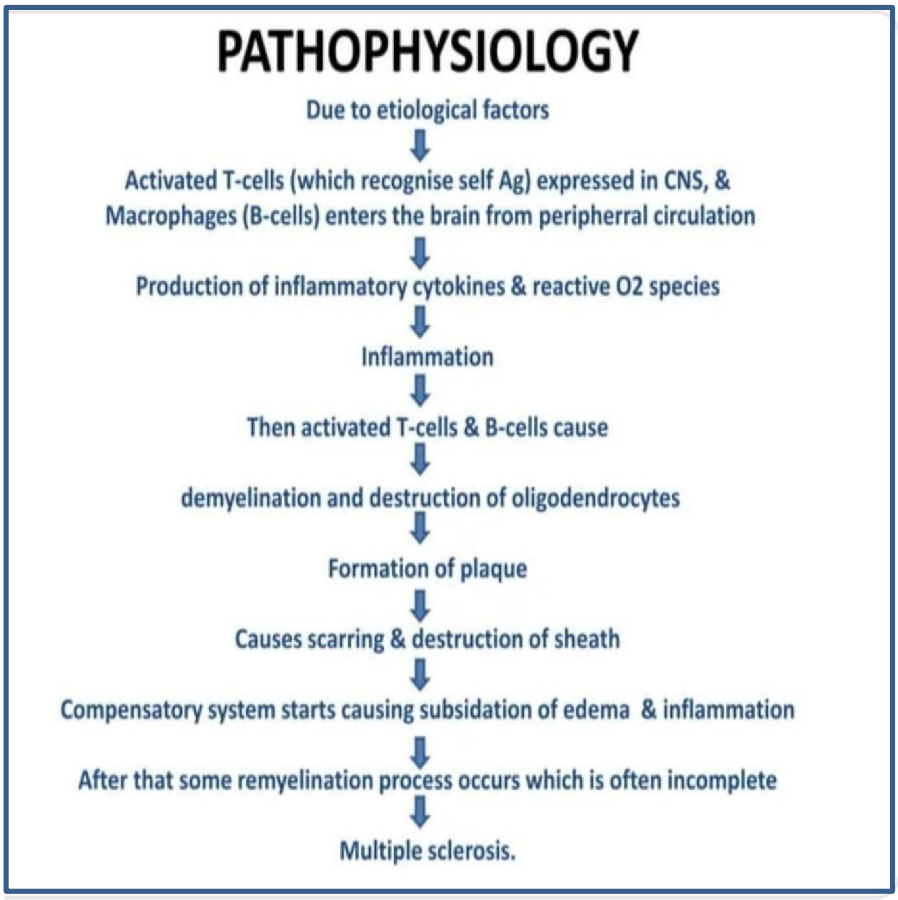

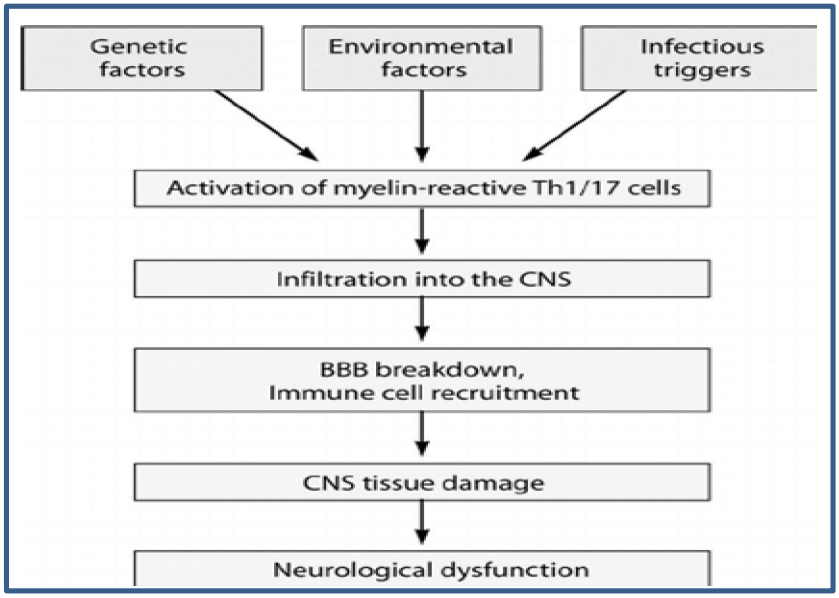

[Fig: 3] Pathophysiology of muiltiple sclerosis: potential factor that cause MS and sequential events in disease progression BBB.[25]

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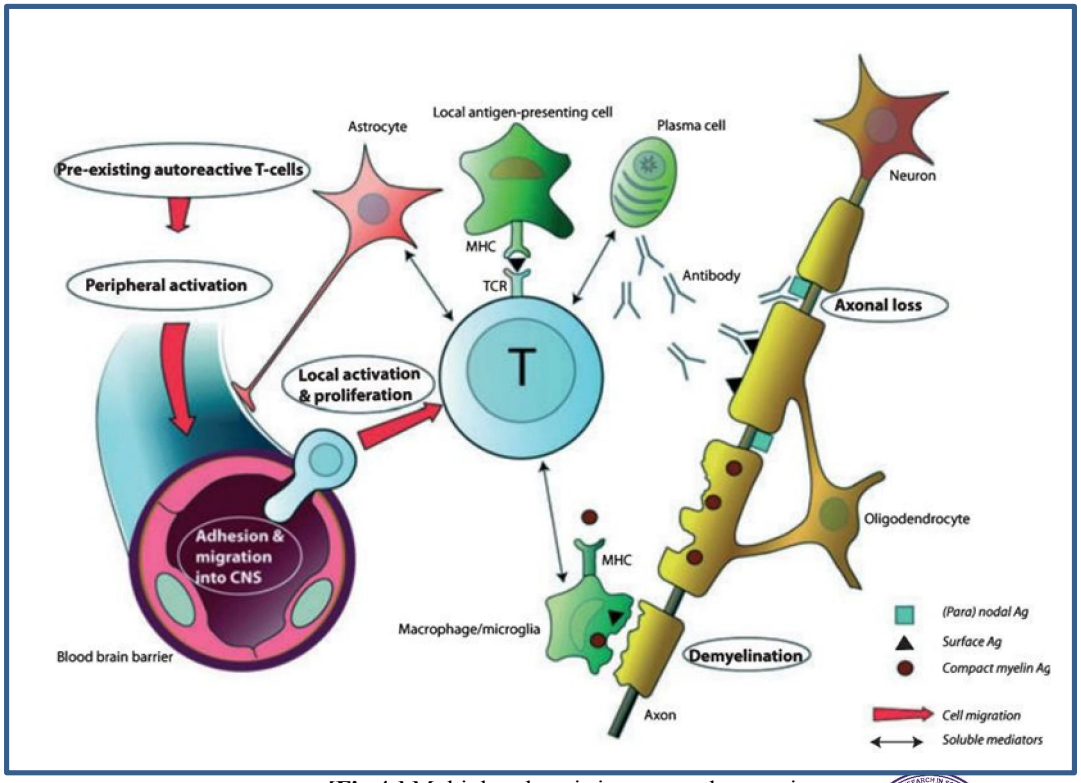
III. IMMUNOPATHOGENESIS

MS is an immune-mediated illness that affects the immune system's humoral and cellular components. The current body of knowledge regarding MS immunopathogenesis comes from the experimental animal cases of autoimmune encephalomyelitis (EAE) paradigm, where in peripheral vaccination using in the central nervous system, myelin constituents cause inflammatory demyelination, which is mediated by T lymphocytes unique to myelin. This model has made suggesting autoreactive T cell peripheral activation causes inflammatory brain disease (CNS).[26,27] According to the widely recognized theory of human MS immunopathogenesis, autoreactive T lymphocytes that are specific to myelin and not allergic are activated in the peripheral immune system by a combination of between genetic susceptibility and environmental causes.[28] It is believed that a breakdown in self-tolerance against myelin and other CNS antigens contributes to the immunopathogenesis of MS by causing autoreactive T lymphocytes.[29] Although the exact processes by which autoreactive T cells are triggered are unknown, non- specific polyclonal activation brought on by viral or bacterial antigens, or by similarities in structure between a self-protein and a harmful protein, also known as molecular mimicry.

Despite the fact that CD4 has dominated most MS models Studies on histopathology have revealed increased T cells. lately brought attention to the involvement of inflammatory CD8 T cells.[30] T lymphocytes have the ability to pass through the blood-brain barrier (BBB) once they have been activated.[31] Cell surface expression is the driving force behind this process. Integrins on inflammatory cells, such as VLA-4, that attach to the vascular cell adhesion by mediation expressed on capillary endothelial cells (VCAM-1). T cells secrete matrix metalloproteinase (MMPs) to help them pass through the extracellular matrix. MMPs have a role in the later breakdown of the components that make up myelin.[32] T lymphocytes are reactivated upon entering the central nervous system (CNS) when they come into contact with autoantigenic peptides relevant to the CNS in the presence of class 2 MHC molecules expressed by local antigen-presenting cells. as well as dendritic cells.[40] New CNS antigens are released as a result of myelin breakdown brought on by activated T cells. Pro-inflammatory cytokine cascades and the recruitment of extra inflammatory cells and particular B cells that generate myelin antibodies to the location of inflammation further more causes tissue damage.[33]



[Fig 4:] Multiple sclerosis immunopathogenesis

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Types of Multiple Sclerosis:

There are four clinical forms of MS

1. Relapsing remitting MS (RRMS)
2. Secondary progressive MS (SPMS)
3. Primary progressive MS (PPMS) [4]
4. Progressive relapsing MD (PRMS)

According to neurologists patients can be divided into four main groups according to how their disease is progressing.[35,36]

Relapsing-remitting MS:

It affects around 85% of MS patients and is the most prevalent type. Flare-ups, also known as relapses or exacerbations, are what define it. These relapses are then preceded by the symptom improvement or cessation (remission)[36] characterized by isolated attacks that progress over a few days to weeks, followed by a few weeks to months of rest.[37] There is no decline in the patient's neurological function in between bouts.[36]

Secondary progressive MS:

Patients with relapsing-remitting illnesses may experience it characterized by early relapses and a slow decline in neurological function that isn't connected to acute episodes. [38]

Primary progressive MS:

Approximately 10% of MS patients are impacted. It is characterized by symptoms that gradually get worse from the beginning without any relapses or remissions, even though there are occasionally plateaus potential to happen.[39] Marked by a progressive loss of function from the moment the illness first appeared. Never experienced a relapse.[40]

Progressive-relapsing MS:

It is an uncommon kind that affects less than 5% of patients. From the beginning, it is progressive in nature, indicated by the occurrence of flare-ups or along the journey, there are relapses but no times of remission.[40] marked by progressive functional deterioration from the time the disease first appears and thereafter superimposed acute bouts. Early on, it is impossible to distinguish between PRMS and PPMS until relapses happen.[40]

Risk Factors of MS:

A chronic inflammatory illness of the central nervous system (CNS), multiple sclerosis (MS) is brought on by a combination of genetic vulnerability and environmental factors.[41] The likelihood of having MS can be influenced by a variety of demographic, genetic, disease- related, nutritional, and environmental risk factors.[42] Age, gender, genetics, some viral infections, ethnicity, climate, vitamin D, other autoimmune illnesses, food, obesity, gut microbiome, smoking, air pollution, migraine history, and parasite infections are some of these risk factors.[43,44]

Epidemiological Risk Factors for MS:

Age

Although MS can affect persons of any age, it is most frequently diagnosed in those between the ages of 15 and 50.[45]

Sex

MS is more common in women than in men.[46,47] The relapsing-remitting form of multiple sclerosis is more likely to strike women, particularly when they are younger. While men and women are more equally likely to have the primary progressive form of MS, women are typically three times more likely to develop relapse forms of the disease.[48] Given that estrogen influences immune system and central nervous system development, the risk of MS in women declines with increasing age of menarche, indicating a role for sex hormones in MS development. A female's susceptibility to MS may be increased by an early menarche, which may indicate an estrogen imbalance.[49]

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hnicity

White people, particularly those of Northern European heritage, are more likely to have multiple sclerosis. The least at danger are those who are Asian, African, or Native American.[50] The accuracy of prevalence data however, may be impacted by variations in life expectancy, access to medical care, diagnostic criteria and magnetic resonance imaging (MRI) availability across various groups.[51]

Climate

It appears that living in a temperate climate raises the risk of MS. People who live outside of 40 degrees north or south of the equator are more likely to have the condition, especially those in North America, Southern Australia, New Zealand, Japan, and Europe.[52]

Genetic Risk Factors for MS:

People who are genetically predisposed must be the first to get multiple sclerosis. Genetic research has demonstrated the significance of genetic variables in MS susceptibility. studies on epidemiology.[53] Risk assessment through family studies to MS probands' relatives have shown a noticeable illness aggregation in families Compared to the general population, first-degree relatives typically have a 10–25 times higher risk of acquiring MS. This risk is associated with degree of kinship, with effects from the parent of origin and the magnitude of these hazards being influenced by sex.[54]

Comorbidity Risk Factors for MS:

Autoimmune Diseases

MS may co-occur with autoimmune conditions such psoriasis, type 1 diabetes, thyroid illness, rheumatoid arthritis, pernicious anemia, vitamin B12 deficiency anemia, inflammatory bowel disease, and systemic lupus erythematosus, especially in women.[55] It has been proposed that similar or shared immune pathways, environmental exposures, and genetic variables may cause autoimmune illnesses to co-occur.[56]

Migraines

An elevated chance of getting multiple sclerosis is associated with a favorable history of migraine headaches. It is yet unknown what pathophysiology underlies this association. It's possible that migraines could increase the likelihood of developing multiple sclerosis (MS), but it's also feasible that migraines could be brought on by MS.[57]

Parasites

According to an intriguing discovery, parasites called helminths, which refer to a group of worms, have the ability to suppress immune responses, which may lower the chance of developing multiple sclerosis.[58] As living conditions in some countries become more hygienic and clean, there has been a trend toward an increase in the incidence of MS.

Environmental Risk Factors for MS:

Epstein-Barr virus

It has been discovered that almost all MS patients (>99%) have an EBV infection, compared to roughly 94% of age-matched controls.[59] Compared to people with low antiEBV antibody titres, those with high titres are more likely to develop multiple sclerosis.[58,60]

The development of MS was found to be positively correlated with genetic vulnerability to high anti-EBV nuclear antigen-1 (EBNA-1) immunoglobulin G titers.[54,61] People who are EBV- seronegative have a very low probability of developing MS. The incidence of MS rose 32-fold after EBV infection and seroconversion according to a study done on young adults in the US military who were EBV-seronegative. The neurofilament light chain biomarker rose soon after EBV infection and seroconversion, indicating neuroaxonal damage, according to this study.[62,63]

Smoking

It has been discovered that smoking raises the risk of MS. Smokers are more likely to experience relapsing-remitting multiple sclerosis following an initial episode of clinically isolated illness. Smoking and the onset of MS have a definite

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dose-response association.[48] The risk of MS gradually decreases after stopping smoking, and ten years after quitting, there is no rise in the risk of MS.[64]

Latitude:

The incidence and prevalence of MS rise with latitude in temperate climate regions based on genetic and ethnic characteristics, some of the regional distribution of MS can be explained.[65] However, when adjusting for ethnic background, latitude continues to be the most significant risk factor.[66]

Dietary Risk Factors for MS:

Diet

While the exact relationship between food and MS risk is unclear, some research indicates that consuming more polyunsaturated fatty acids, particularly alpha-linolenic acid (ALA), may lower the risk of MS.[67] Plant foods including flaxseed, walnuts, pumpkin seeds, tofu, and vegetable oils are the main sources of ALA.

Vitamin D

The correlation between latitude and MS incidence may be explained by sunlight exposure and related vitamin D levels.[68] Previous exposure to sunshine has been discovered to have an inverse relationship with MS susceptibility.[69] Low vitamin D levels and little sun exposure may raise the risk of multiple sclerosis, according to research.[70,71] Given that 1 billion people globally suffer from vitamin D deficiency or insufficiency as a result of insufficient vitamin D consumption or decreased sun exposure vitamin D supplementation may be the most effective way to avoid multiple sclerosis.

Obesity

Studies have demonstrated a high correlation between childhood or adolescent obesity and the chance of acquiring multiple sclerosis, particularly in women.[72,73]

Gut Microbiota

An elevated risk of multiple sclerosis has been associated with microbial imbalance in the gut. It is believed that by influencing the immune system, changed microbiota may raise the risk of MS. Diet, obesity, antibiotic usage, and smoking are among the factors that alter gut flora.[74,75]

Symptoms of Multiple Sclerosis:

- Fatigue:
- Spasticity and muscle spasms
- Bladder problems
- Sexual dysfunction
- Deprssion
- Cognitive dysfunction
- Muscle weakness
- Numbness and tingling:
- Lhermitte's sign.
- Bowel problems
- Dizziness and vertigo
- Tremor
- Vision problems
- Gait and mobility change
- Emotional changes and depression
- Learning and memory problems
- Pain

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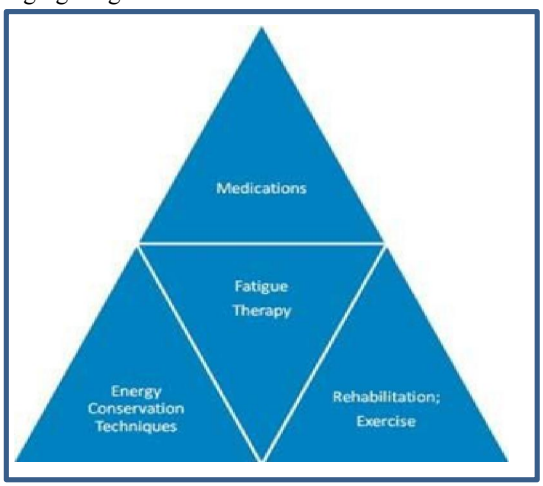
Fatigue:

At least two-thirds of MS patients experience fatigue, which is the most prevalent symptom. Moreover, fatigue is cited by about 50% of MS patients as the most incapacitating aspect of their disease. 65% or more of Fatigue is an everyday occurrence for those with MS. typically in the afternoons. The definition of fatigue is a subjective physical and/or mental energy that is felt by the individual or caregiver to interfere with routine or appealing activities.[76] Although the exact cause of weariness is unknown, it is most likely complex. A high lesion load may be linked to fatigue in damage to the brain and central nervous system that results in in response to elevated energy expenditure, dysregulation of the immunological system, sleeplessness, sadness, and a consequence to drugs (such as gabapentin, interferon, or others), other conditions (such as hypothyroidism), or lifestyle behaviors.[77] Both pharmaceutical and nonpharmacological interventions are methods for managing fatigue



Fatigue management in multiple sclerosis

Spasticity and muscle spasms:

Damage to descending motor pathways in multiple sclerosis causes spasticity, which is a velocity-dependent increase in muscle reflexes. stiffness and tone About 75% of MS patients experience spasticity.[78] Rizzo et al. examined 315 patients on oral antispasticity drugs. from the Patient Registry database of the MS Research Committee of North America The registrants' ability to carry out their daily tasks was impacted by 16% reporting no spasticity, 31% minor, 19% mild, 17% moderate, and 17% severe spasticity.[71] Patients who are having more severity were individuals who were older, male, and with a longer duration of MS. Scores for quality of life declined in direct proportion to severity.[79]

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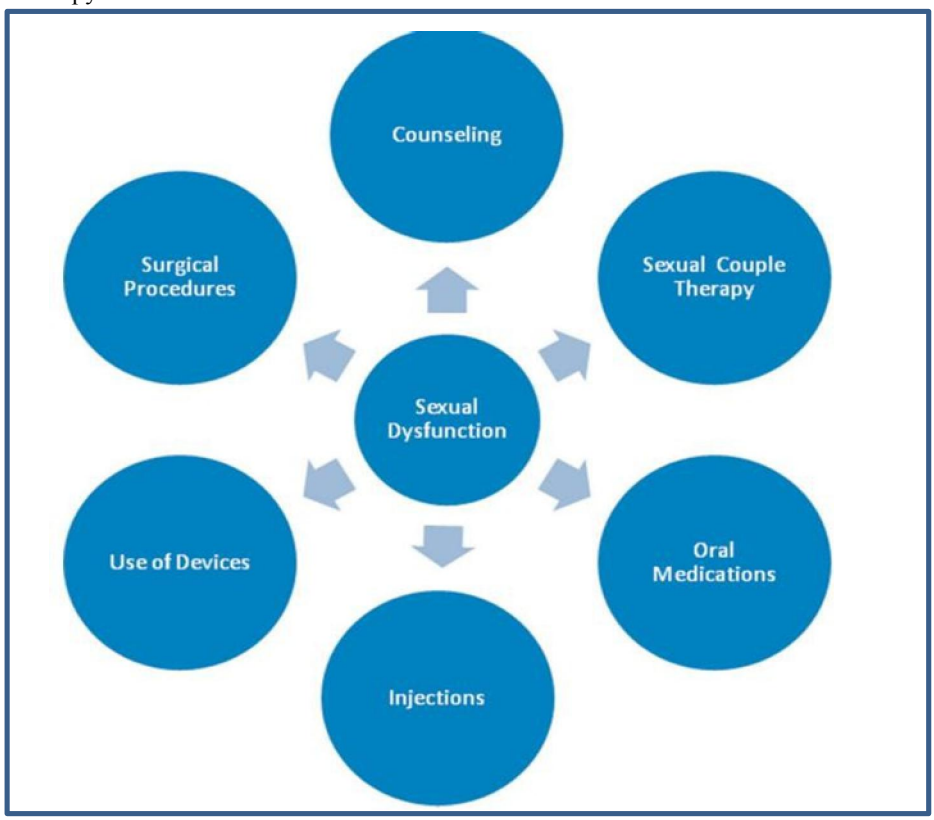
Bladder problems

Urge incontinence is the term for when a person has trouble emptying their bladder or needs to urinate frequently or unexpectedly. Bladder control loss is a precursor to multiple sclerosis .96% of individuals with MS who have had the disease for more than ten years have bladder issues, and about 80% of patients experience intermittent urine issues.[80]

Sexual dysfunction

Approximately 75 percent of MS patients experience sexual dysfunction. Erectile dysfunction, delayed ejaculation, and decreased libido are some of the symptoms that males may experience, while women may experience decreased diminished libido or anorgasmia, lubrication, and Vaginal feeling changes are rather prevalent.[81] First, Sexual dysfunction may result from secondary and tertiary symptoms.[82] malfunction in multiple sclerosis. Erectile dysfunction or diminished libido are the primary reasons, while secondary symptoms include exhaustion, cognitive impairments, sensory sensations, pain, weakness, and spasticity problems with the bowels or bladder.[83] Among the tertiary symptoms are withdrawal and reactive depression. The treatment of sexual dysfunction includes counseling, couples therapy, sexual therapy and medical care.[84]



Management of sexual dysfunction in multiple sclerosis

Deprssion

It is predicted that 50% of MS sufferers may experience clinical depression at some point in their lives. The lifetime prevalence of serious depression in MS patients varies from between 37% to 54%, indicating that significant One in two MS patients experience sadness while during their lifetime.[84] MS patients are particularly vulnerable to suicidal thoughts and attempts. The prevalence of suicidal intent throughout life is 28.6%.[85] Psychotherapy, cognitive behavioral therapy (CBT), and medication are all part of the treatment for depression.

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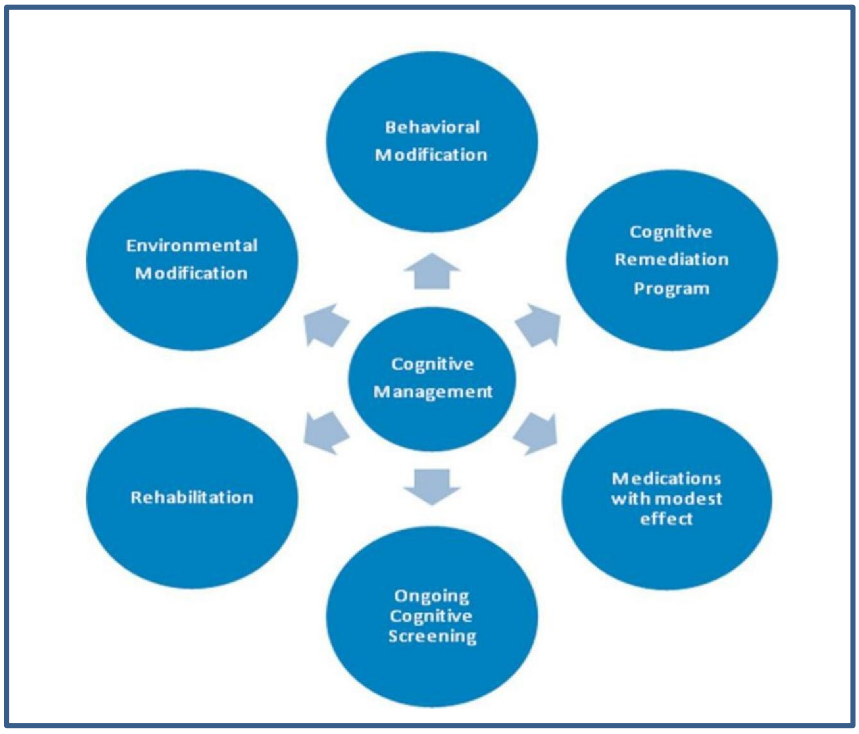
Cognitive dysfunction

Over the course of their illness, over 50% of MS patients experience cognitive problems.[86,87] MS primarily affects the following cognitive domains: visual spatial ability (20%), short-term memory (40%), concentration and attention (30%), problem-solving (20%),and speed of information processing (35%). and 10% verbal fluency.[88]



Cognitive management in multiple sclerosis

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Treatment:[89,90]

Name	Date approved	MOA	Indication	Administration	Efficacy	Side effects	Drug interaction
Ofatumumab	2020	Anti-CD20 mAb	RMS (first line)	SC injection every four weeks	Reduction in ARR compared with teriflunomide: 54%	Injection reactions, nasopharyngitis, headache, bowel obstruction, and hepatitis	Tofacitinib. Smallpox vaccine. Typhoid vaccine.
Ocrelizumab	2017	Anti-CD20 mAb	RMS and PPMS (first line)	IV infusion every six months	RMS: reduction in ARR compared to IFN βla:47% PPMS: reduction in twelve-week CDP compared to placebo: 24%	Infusion reactions, nasopharyngitis, headache, oral herpes, colitis, hypogammaglobulinemia, neutropenia, and increased cancer risk	Smallpox vaccine. Typhoid vaccine. Influenza vaccine.
Alemtuzumab	2014	Anti-CD52 mAb	RMS (first line)	IV infusion, once daily	Reduction in ARR compared to placebo: 49-69%	Headaches, rash, nausea, pyrexia, thrombocytopenia, hypo- or hyperthyroidism, and encephalitis	Tofacitinib. Siponimod. Ponesimod.
Natalizumab	2004	α4β1 integrin inhibitor	RRMS (second line)	IV infusion every four weeks	Reduction in ARR compared to placebo: 68% Reduction in sustained disease progression compared to placebo: 42%	Fatigue and allergic reaction	Infliximab Tofacitinib.
Mitoxantrone	2000	DNA intercalator	RMS, SPMS (second or third line)	IV infusion every month or three months	Reduction in relapse compared to placebo: 61%	cardiomyopathy, hepatotoxicity, promyelocytic leukemia	Valspodar. Typhoid vaccine. Influenza vaccine.

Table 1: Highly effective disease-modifying therapies for MS

ARR: annualized relapse rate, CDP: confirmed disability progression, IFN β−1a: interferon beta 1a, IV: intravenous, SC: subcutaneous, mAb: monoclonal antibody, PPMS: primary progressive multiple sclerosis, RMS: relapsing forms of multiple sclerosis, SPMS: secondary progressive multiple sclerosis. MOA: mechanism of action

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Name	Date approved	MOA	Indication	Administration	Efficacy	Side effects	Drug interaction
Ozanimod	2020	Sphingosine 1-phosphate receptor modulator	CIS, RMS, active SPMS	Oral, once daily	Reduction in ARR compared with placebo: 48%	Headache, hypotension, and herpes zoster	Abiraterone. Duloxetine. Fluconazole.
Siponimod	2019	Sphingosine 1-phosphate receptor modulator	CIS, RMS, active SPMS (first line)	Oral, once daily	Reduction in CDP compared with placebo: 21%	Headache, nasopharyngitis, urinary tract infection, and falls	Alfuzosin. Clozapine. Labetalol.
Cladribine	2019	Not fully known	RMS (second or third line)	Oral, 4-5 days over two-week treatment courses	Reduction in ARR compared with placebo: 55-58%	Headache, lymphocytopenia, nasopharyngitis, neurotoxicity, and nausea	Smallpox vaccine. Typhoid vaccine. Influenza vaccine.
Dimethyl fumarate	2013	Nuclear factor (erythroid-derived 2)- like two pathway inhibitor	RMS (first line)	Oral, twice daily	Reduction in ARR compared to placebo: 48-53%	Flushing, diarrhea, nausea, upper abdominal pain, decreased lymphocyte counts, and elevated liver aminotransferase.	Diroximel fumarate.
Fingolimod	2010	Sphingosine- 1-phosphate inhibitor	RMS (second line)	Oral, once daily	Reduction in ARR compared to placebo: 48-60%	Bradycardia, atrioventricular conduction block, macular edema, elevated liver enzyme levels, and mild hypertension	Aripiprazole. Esmolol. Sulpiride.

TABLE 2: Moderately effective disease-modifying therapies for MS

ARR: annualized relapse rate, CDP: confirmed disability progression, CIS: clinically isolated syndrome, RMS: relapsing forms of multiple sclerosis, SPMS: secondary progressive multiple sclerosis, MOA: mechanism of action.

II. CONCLUSION

Myelinated axons in the central nervous system are attacked by MS, an immune-mediated inflammatory illness that damages them to varying degrees. The review discusses the pathophysiology of MS and looks at current treatment approaches, highlighting developments in symptomatic and disease-modifying drugs. This thorough examination improves comprehension of MS and emphasizes the continuous requirement for research to create more efficient therapies. Genetics, smoking, illness, and low blood vitamin D levels have all been connected to the onset of multiple sclerosis. . Disease-modifying drugs such fingolimod, siponimod, interferon beta, rituximab, natalizumab, and dimethyl fumarate are frequently used to treat multiple sclerosis. Despite their effectiveness, these drugs have certain drawbacks.

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Despite research suggesting that More clinical and real-world assessments are needed to gather proof of these drugs' long-term efficacy and safety, even if the disease's long-term course has significantly improved with therapeutic age

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