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REVIEW ARTICLE

Unraveling progressing neurodegeneration through multiple sclerosis: history, epidemiology, risk factors, pathophysiology, and management.

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ABSTRACT
Demyelination and axonal destruction are two hallmarks of multiple sclerosis. It is a chronic inflammatory condition triggered by the immune system that impacts the central nervous system. About 2.8 million patients worldwide suffer from the condition, which results in a wide range of neurological symptoms as well as severe disability. The prevalence of MS varies by geography and ethnicity, with higher rates found in areas further from the equator. Its development is influenced by a combination of environmental variables such as smoking, vitamin D insufficiency, viral infections, and immunological dysregulation, as well as genetic susceptibility. Myelin sheaths are the target of an abnormal immune response in MS pathophysiology, which leads to inflammation, demyelination, and eventual axonal damage. The disease's varied clinical appearance is caused by neurodegeneration, which aggravates the illness's course even more. Multiple sclerosis has several clinical signs, including sensory abnormalities, motor impairment, tiredness, cognitive dysfunction, and visual impairment. Diagnostic and illness monitoring are aided by biomarkers, such as oligoclonal bands in cerebrospinal fluid and neuroimaging results. To confirm demyelinating lesions and rule out other possible diseases, the diagnosis is based on a comprehensive approach that includes clinical evaluation, neuroimaging (e.g., MRI), cerebrospinal fluid study, and evoked potentials. Relapse prevention, delaying the course of the disease, symptom relief, and quality of life enhancement are the goals of management techniques. The cornerstone of treatment is comprised of disease-modifying treatments (DMTs), such as immunomodulators and monoclonal antibodies. DMTs are enhanced by rehabilitative therapies and symptomatic management. This review is done to understand the effect of risk factors on the progress and management of MS.
***Keywords**: Demyelination; Inflammation; Multiple Sclerosis; Biomarkers; DMT; Neurodegeneration; Abnormality; Dysregulation.*

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INTRODUCTION

Multiple Sclerosis [MS] is an autoimmune inflammatory disorder that damages the CNS by attacking myelin and nerves. In 1868, Jean-Martin Charcot, a French neurologist, was the first to officially identify MS as a unique illness[1]. MS is characterized by intricate combination of immune, viral, dietary, genetic, and epigenetic conditions that impact its development and course [2]. MS typically has a relapsing-remitting clinical history, with acute neurological symptoms followed by intervals of remission.To diagnose MS, there must be at least one clinical episode of CNS demyelination [known as CIS] along with evidence of lesions in the CNS that are disseminated in space and time [3].When a patient is diagnosed with relapsing-remitting MS, one of the most reassuring discussions involves the number of disease-modifying therapies [DMT] options available [4]. The global MS population has grown from an estimated

2.5 million in 2013 to 3 million in 2020. According to UK's International MS Federation new report in MS Atlas stating that the global incidence of MS is projected to be 38 per 100,000 persons, considered from that 3 million people worldwide are diagnosed and live with MS[5]. Till now no permanent cure is available for this condition [6] Because MS is a clinically incurable disease, it harms both individuals and communities. Thus, the safe and effective management of multiple sclerosis has emerged as a major medical concern for society[7]. This review is done to understand the progression of MS and its different aspects of history, epidemiology, risk factors, pathophysiology, and causes as well as current developing treatment strategies.

History

The word "paraplegia" applies to significant neurological condition that involves motor dysfunction. The initial documentation of MS was noted by St. Lidwina of Schiedam, Netherlands, towards the conclusion of the 14th century[7–9] . For 26 years, Augustus d'Este maintained few documents detailing how the signs leading to what we now recognize as MS developed over time. His initial symptoms, at the youthful age of 28, was a temporary vision loss caused mostly due to development of optic neuritis. He died at 54 years old from symptoms of motor dysfunction and weakness in his legs that made it challenging for him to walk [8–11]. Charcot's identifying and structuring of MS gave the foundation for defining previously incomprehensible findings and furthering MS studies into future decades. Since then, the procedure of consolidation has been continuing. The clinical signals of the disease were connected to posthumous lesions histology by Charcot's trainees. In his MS thesis from the year 1885, Joseph Babinski revealed lesions in the neurological system. In MS, Pierre Marie addressed nervous system dysfunction and mobility disabilities[8,12]. Around the mid-nineteenth century, Ernst Leyden postulated a hereditary component for MS. Curtius and others in Germany, however, did not begin systematically investigating the inherited causes of MS and the way the condition focused in specific families until the 1930s [8,10,11]. MS was distinguished and "framed" by Vulpian, Von Frerichs, Charcot, and others as a distinct, identifiable entity[8,12]. Before being diagnosed, doctors globally classified MS cases based on histology, clinical appearance, and prognosis.[10,11]. As MS awareness grew, so did etiology theories and therapy approaches; The 1935 study of research included 158 MS therapies. Following remedies including anticoagulant drugs, histamine desensitization, different dietary regimens, vaccines, and chemotherapy drugs[10,13]. In the following years after the 1960s, improvements to disease categorization and disability indices contributed to a more refined definition of randomized clinical trials. Hypotheses were offered to explain immunology alterations, genetic influences, local variations in infections, and variables related to the environment [14]. MS NGO's improved research and participate in awareness, as well as changing attitudes toward the condition[13,15]. Recent years have seen significant advances in basic investigation to clarify the root cause of the illness and mechanisms, as well as immunomodulatory medicines [8,13,15].

Epidemiology :

Some of the most frequent demyelinating diseases worldwide, The MS is primary reason of non-traumatic neurodegeneration in youth in many of these countries[16]. About 400,000 people in the US and 2.5 million active patients globally suffer from MS[17]. Females population are currently more likely than male population to get MS, but this was not always the case. There was roughly an equal sex ratio in the early 1900s. Since then, the majority of developed countries are witnessed gradual increase in the sex ratio, which is now almost 3:1 [F: M] [17,18]. Smoking increases the risk of MS by almost 50%[19]. The illness can emerge at stage of life, however the mostly occurred onset age ranges from 20 and 40 years of age old. In the age group of 0-18, around 10% of cases are diagnosed. Rarely, MS developed after 50 is called as "late-onset multiple sclerosis[LOMS]" [20]. The estimated prevalence of European ancestry in populations is one in 1000. Research indicates a least incidence among population of African origin and East Asian, and few is known regarding prevalence in non-European population. According to recent studies, the incidence rate in African-American groups is similar to that in European communities[21,22].MS is more occurred in the northern latitudes of Northen part of America and Europe, having a latitude-dependent prevalence gradient. Independent of latitude, observations revealing different genetic predisposition variables may have been noted in different human communities, suggesting the interplay of unclear understanding of genetic components and environmental factors. According to numerous research, those who move to areas with a greater frequency of MS when they are young are more likely to have the condition[23,24].

Current status of MS in India :

In India, MS was first discovered between 1954 and 1961[25]. It was believed that MS was largely a Western disease because of the regional characteristics that could alter illness prevalence. Geographically, the standard incidence is 3.2 in the southern part of India and 4.15 in the northwest

region of India [more than 15 ◦ N latitude but less than 15 ◦ N latitude][26] However, the worldwide distribution of MS indicates that the highest occurrence is seen in northern latitudes[27]. Asian and Hispanic groups, on the other hand, have notably lower prevalence. Nonetheless, African Americans are becoming more likely to get MS, which suggests alterations in the environment and genetics[28]. The most recent US study found that white people had a higher likelihood of having MS than black people[29]. About 10,000 MS patients are helped by the MS Society of India in Delhi, Kolkata, Pune, Chennai, Indore, and Hyderabad, among other cities in India. Up until the middle of the 1970s, MS was thought to be uncommon in India; but, as a result of more neurologist revisions of outdated diagnostic criteria, increased public awareness of the illness, and advancements in diagnostic technology, MS is now diagnosed more frequently[30]. Between 1975 and 1985, the West Coast regions of India saw the initial attempt to determine the prevalence rate of MS. Hospital data showed that the rate varied from 0.17 to 1.33 per 100,000[31]. More updated statistics from Bahrain,Qatar, Kuwait, and the United Arab Emirates also observed a further rise in the prevalence rates, which currently range between 55 and 85 per 100,000 individuals. The rate of occurrence and development of MS has escalated in India due to misdiagnosis, as the same diagnostic standards have been used to validate other neurodegenerative diseases[25,25,26,28–39]. The MS worldwide federations estimate that there are around 145,800 MS patients in India overall, with an incidence rate of 11 cases reports per 100,000[31]. The number of MS patients is rising, which means that there is a greater demand for accurate motor neuron dysfunction diagnosis and efficient treatments[40]. There hasn't been much research done on MS in India, and there aren't any specific medications or biological markers that can be used to identify or treat the illness. The current medical interventions solely address the symptoms and do not alter the trajectory of India's ailment[31,41].Recent years have seen significant advancements in our knowledge of and ability to treat MS[42]. Lesions dispersed over time and space in the brain’s white matter are required for a diagnosis to be made, and all other possible causes must be ruled out[43]. In India, MS was initially diagnosed using the Schumacher clinical criteria in 1950s. From 1980s, McDonald's standards have supplanted diagnostic tests globally, including in India. This includes the recently upgraded MRI, which is intended to facilitate early diagnosis [31]. Patterns of relapsing-remitting MS, primary progressive MS, and secondary progressive MS are comparable to those observed in the West[44]. Based on available data, the number of population worldwide living with multiple sclerosis like condition increasing day by day from 2.3 million [2013], 2.8 million [2020], and 2.9 million [2023] and continously new cases found everyday. It draws attention to the various obstacles and differences that persons with MS face when looking for a diagnosis, care, or therapy[45]. The Indian Map related to MS from the Multiple Sclerosis Society of India [MSSI] indicates that there are 11 cases of MS for every 100,000 persons. Maharashtra and Delhi have the highest prevalence rates in India. Women between the ages of 19 and 45 make up the bulk of MS patients. Compared to government facilities, MS patients in India have greater access to private health institutes for diagnosis and treatment[46]

Risk Factor :

a) Vitamin D deficiency

Based on its effects on immunological response, growth, and lymphocyte activation, vitamin D appears to have a significant participation in the cytology of multiple sclerosis[47–49]. Moreover, there is an increase in adaptive immune activity and innate immune system responses. Vitamin D inhibits the generation of Th1-mediated cytokines that induce inflammation[50]. The administration of vitamin D significantly changed the range of interleukin-17 and interleukin-10 in numerous experiments[48,51]. Those who belonging to further northern or southern area of the equator have high chances to dignosed with MS. Near to the equator, rate of prevalence is almost absent; still, it increases to 45-55 cases per one million individuals living 45o either northern or southern. That interesting regional pattern is most likely caused of MS development in patient by vitamin D deficiency [47,52–54].

b) Family history and genetics

MS is a genetic illness that cannot be inherited directly; nevertheless, people who have a member in family who has the HLA gene are highly get it. Over two hundred non-HLA single-nucleotide polymorphisms and at least 1 HLA allele which is protective has been reported, showing such genetic distribution in common variants so the risk of MS is relatively elevate [55,56].The SNPs are situated in close proximity to genes associated with either adaptive or innate immunity, suggesting that MS is a disorder of immunological hyperactivation. Studies on twins and familial clustering have demonstrated a genetic aspect to MS, with higher rates of clinical concordance observed in twins. Half-siblings have a lower likelihood of developing MS compared to full-siblings, and individuals adopted into families with that condition have a risk similar to that of the general population.[10,21,57,58].Some individuals may have a genetic predisposition to multiple sclerosis, although there is no specific gene solely responsible

for the condition, making this susceptibility non-inheritable [59,60]. Research on genetics has demonstrated a relationship between first, second, and third cousins[30,61].

c) Disease

Studies have shown that those with a genetic predisposition to MS could have their condition activated by viral or bacterial infections. As individuals age, the presence of foreign antigens may stimulate Th1 cells, resulting in the autoimmune reaction associated with multiple sclerosis.[52,53].

d) Gender

In many research it is suggested that women have higher risk of development of MS as compared to men, although the precise cause of this condition remains unknown**.**[62]. A study revealed that females have a higher chance of encountering environmental elements that enhance their vulnerability to multiple sclerosis[63].Based on the significant results of the Optic Neuritis Treatment Trial [ONTT], women are more at risk of developing clinically definite MS [CDMS] after experiencing their initial demyelinating symptoms like optic neuritis. Moreover, gender-specific reproductive factors following clinically isolated syndrome [CIS], such as pregnancy, may also raise the chances of developing CDMS. [64,65]. Based on this information, it can be inferred that females have a greater natural inclination towards developing MS compared to males.

e) Obesity

Globally, obesity is becoming more common and is a serious public health issue[66]. Researchers discovered that females who had a body mass index [BMI] of 30 kg/m2 during their teenage years were 2.25 times more likely to develop multiple sclerosis [MS] in comparison to females with a BMI within the 18.5 to 21 kg/m2 normal range [67]. Rise in the ratio of females to males in multiple sclerosis [MS] could be attributed to factors such as female hormonal variables, childhood obesity, X chromosome. This is supported by the higher occurrence of MS/CIS in girls who are moderately or extremely obese, while no such trend is observed in boys[66].Similar to what is observed in multiple sclerosis, obesity significantly alters the ratio of Th1 to Th2 cells, with an increase in Th1 and a decrease in Th2. Obesity has been found to elevate Th17, an immunological marker that has been extensively studied in relation to multiple sclerosis [MS][68]. Another significant increase obesity that related with insulin resistance had connected to MS which is upregulated by CD8 T cells[69].These results provide strong evidence that obesity has a major impact on how neurodegenerative diseases like MS progress.

f) Injury

Research has been conducted on the correlation between severe injuries that result in direct harm to the brain or spinal cord and their potential to trigger MS. The permeability of the blood-brain barrier [BBB] is heightened as a result of trauma, increase the infiltration of the Th1 cells inside the central nervous system. Consequently, this initiates an inflammatory response that results in the degradation of myelin and the production of lesions in individuals diagnosed with MS [70–74].

g) Cigarette smoking

There is a higher risk of MS if you smoke. Compared to non-smokers, smokers having MS have characterised by long-term prognosis and a higher chanches of brain atrophy[75,76].Additionally, in comparision with the healthy population, MS patients smoke more frequently[76]. MS patients with smoking history are linked to increased mortality rates, a higher burden of disability, and a lower quality of life[77,78].

h) Vaccine

There has been extensive reporting linking influenza vaccinations to conditions that cause demyelination of neurons in the central nervous system. In addition, anthrax, rabies, hepatitis B or A, measles, meningococcus, tetanus, rabies, yellow fever, rubella, and human papillomavirus [HPV]have all been linked to post-vaccination CNS demyelinating illnesses[79]. There have been reports of cases of demyelinating disease with COVID-19, but there haven't been many cases of newly diagnosed MS following COVID vaccination[80].

i) Epstein-Barr Virus [EBV]

Immune-induced demyelination in the spinal cord and brain could have been caused by a virus[81]. Among the likely causative agents, the EBV is the most likely culprit. After infection, the virus stays inactive in B cells for the duration of the host's life[82]. The higher rate of MS following infectious mononucleosis implies an underlying causative role for EBV[83].Determining the exact pathways via which the virus involved to the progression of MS is not proven because it is not always present in lesions associated with MS[84]. The interaction between EBV and its host body is also considered to be a contributing factor in immunological failure, despite the fact that EBV enters and alters B cells[85].A study revealed that EBV has the potential to induce inflammatory reaction in both the central and peripheral nervous systems, which initiate the development of CNS lesions in individuals with multiple

sclerosis. The activation of peripheral inflammatory pathways is supported by the immunodeficiency associated with EBV's risk factors and its ability to evade the immune system.We can state that there is a correlation among EBV and an increased risk of multiple sclerosis based on these important findings[85,86].

Types Of Ms :

Relapses or subtle progressions are two ways that multiple sclerosis clinical disease activity presents itself. In 1996, Lublin and Reingold's widely recognized taxonomy of multiple sclerosis delineated four primary categories based on the occurrence and timing of these traits.

a. Relapsing remitting MS [RRMS]

Around 85 percent of patients have relapses and remissions. An occurance of neurological impairment that lasts for at approximately one day is referred to as a relapse. A relapse frequently emerges within a short span of a few days or weeks, stabilizes at a certain level, and subsequently fluctuates in intensity, spanning from minor improvement to complete recuperation. Subsequent relapses may occur unexpectedly. In the phase of the disease characterized by relapses and remissions [without the presence of disease-modifying therapy],the average number of relapses is roughly one per year [87]

b. Secondary progressive MS [SPMS]

SPMS is a subtype of relapsing-remitting MS that progresses gradually and results in permanent neurological deficiency and disability. The percentage of individuals experiencing secondary progressive illness rises as the duration of follow-up increases. 41% of participants had relapsing remitting multiple Within 6–10 years of the disease's beginning, sclerosis reached the secondary progressive phase, rising to 58% between 11 and 15 years later. About 80% of them had secondary progressive multiple sclerosis after 20 years. Even though they originate less frequently as the illness worsens, overlapping relapses are still possible throughout the secondary progressive period[87].

c. Primary progressive MS [PPMS]

PPMS is a slowly progressing illness that does not relapse or go into remission, causing a cumulative accumulation of neurological deficiency or disability from the time of diagnosis. About 10% to 15% of cases of multiple sclerosis are caused by it. Both men and women are impacted equally often. In PPMS , the typical age of onset is around 40 years, but in RRMS, it is 30 years[87].

d. Progressive relapsing MS [PRMS]

Although PRMS is no longer often used, it describes a tiny subset of patients with progressive illness from onset with superimposed relapses. The main characteristic is the gradual advancement, with typically modest relapses. Multiple sclerosis with progressive relapses is thought to be mostly comparable to multiple sclerosis with main progression. People with primary progressive multiple sclerosis may experience relapses up to 25% of the time, and these events may occur years after the illness first develops[87].

Pathophysiology :

When we discuss about MS, we're discussing about neuron demyelination [Fig.2] plaque development, inflammation, axonal loss, and axonal damage. These plaques are seen inside gray matter, brainstem and spinal cord, optic nerves, corpus callosum and tracts, and white matter occupied by sides of the ventricles in the CNS . They have manifested in RRMS, SPMS, PPMS,PRMS. The disease's progressive phases and its relapsing-remitting course exhibit significantly different immunopathological mechanism of demyelination and oligodendrocyte apoptosis due to their variable expression throughout time[74,88–90]. MS is caused by autoimmune cells that breach into blood-brain barrier attack the CNS. Autoreactive immune cells are typically eliminated inside thymus or bone marrow through B cells[centrally tolerated] during development. Peripheral tolerance mechanisms work to stop these cells from causing harm, although some may bypass this safeguard and circulate in the bloodstream. Failure of peripheral tolerance can occur if autoreactive T cells form resistance for suppression or inadequate performance during regulation of T cells. The development of disease may be influenced by a intricate interplay between environmental and genetic risk factors, potentially affect the activity of autoreactive cells. [88,89,91–93].

Higher levels of immunoglobulin in cerebrospinal fluid point to a possible participation of B cells in MS. One characteristic of MS is intrathecal synthesis of some oligoclonal bands [OCBs] or oligoclonal immunoglobulins. Brain parenchyma and cerebrospinal fluid [CSF] contain a preponderance of CD27+ on memory B lymphocytes in MS patients. Memory B cells have class-switched immunoglobulin transcripts, somatic hypermutation, and clonally expanded brain parenchyma in the CSF. Furthermore, the existence of OCBs in the cerebrospinal fluid suggests that antibody-producing cells produced from clonally expanded B cells within the CNS play a crucial role in the overproduction of intrathecal clonal

immunoglobulins. This is supported by the similarity between the B cell immunoglobulin transcriptomes and the CSF immunoglobulin proteomes [92,94,94–96].

In patients with MS, inflammatory B cell are observed inside the meninges, and the severity of these infiltrates is associated with cortical lesion severity, neurodemyelination , and clinical motor impairment. Epstein-Barr Virus [EBV] reservoirs may reside in B cells[74,91]. B cells act as antigen-processing cells during EBV infection, enhancing the accuracy of antigen presentation. Research has shown that infected B cells by EBV can absorb and cross-present recombinant human myelin oligodendrocyte glycoprotein, leading to effective recognition from cytotoxic CD8+ T-cells. Moreover, B cells from MS patients exhibit elevated levels of CD40 on their surface, indicating their enhanced ability to deliver antigens[94,97,98].In individuals who had relapsing-remitting multiple sclerosis, a high level of volume was linked to higher production of B cell activation biomarkers. MS can proceed in part due to the absence of normal activity among the effector T-cell population, as well as conditions related with B cells[94,97–99].

EBV infection is kept under control in healthy population by CD8+ cytotoxic T lymphocytes that attenuated EBV-infected lymphoblastoid culture of cell lines. We will refer to these cytotoxic CD8+ cells as "latency-specific T cells" going forward since they are specifically designed to recognize and eliminate EBV latent protein-expressing infected cells. The EBV-specified T-cell number inclined along with rise in the latency-specified CD8+ T-cell activation during an MS exacerbation. However, when MS develops, latency-specific T cells that are CD8+ become worn out and lose their ability to avoid subconsciously infectious cells from reproducing. An increase in infected cells suppresses the autoregulatory mechanism, which further reduces the amount of T cells, creating a vicious cycle. Poor management of EBV reactivation has been associated with recurrent relapses, which can enhance viral production and naive B cell infection [97,100–102].

There are many more pathogenic mechanisms related B cell for development of MS, including antigen representation to T cells with production of substances that damaging oligodendrocytes[91]. Numerous inflammatory cytokines, including tumour necrosis factor [TNF]-α and interleukin [IL]-1β are released by CNS inflammatory cells like microglia and macrophages. These cytokines may cause neurodegeneration by inducing dysfunctional ribonucleic acid-binding proteins, inhibiting astrocytic glutamate reuptake, and causing cell death caused by the cytokines[89,91,98]. Glutamate excitotoxicity and neurodegeneration may be facilitated by the release of glutamate by macrophages and microglia. Reactive nitrogen/oxygen species, which are produced by microglia and macrophages and cause oxidative stress and damage in mitochondria, may be linked to dementia. To aid in remyelination, microglia may also exhibit anti-inflammatory behaviours [91,95]. Above mention pathophysiology by different factors and mechanism are summarised in fig.3

Clinical Manifestation :

A clinically isolated condition is commonly considered to be MS when a patient presents. The expressive lesion may present with one or more symptoms, depending on where it is located. The most frequent symptoms include brainstem, spinal cord disease and optic neuritis like conditions; however, there are other, rare symptoms as well, such as damage in cerebral area of brain like dominant parietal lobe syndromes[96,103]. MS relapses sometimes start gradually over a span of a some hours to days, stabilize for several days, and then experience a sudden improvement. In the case of early MS, relapse may seen after clinical recovery typically appears to be total, although most relapses do leave some damage behind [104]. When severe optic neuritis occurs, gross optical vision may improve, but the perception of depth, sensitivity to contrast, and colour perception remain poor. Depletion of the neural reserve causes the accumulation of neuron impairments and poor recovery from relapses, permanently limiting function[105].Magnetic resonance imaging [MRI] shows at least 10 "asymptomatic" brain lesions per clinical episode. It is possible that a little lesion in the eloquent area will cause symptoms. Lesions that are evident on an MRI or that are macroscopic in size are merely the tip of the iceberg; deep and cortical gray matter include several lesions that are observable in the microscope. About ten to fifteen years after RRMS first manifests, secondary progressive MS develops gradually, moving from isolated relapses to a steadily worsening illness. The illness categories don't clearly transition into one another; instead, relapses happen amid a slow, steady advance until passage takes centre stage[105,106]. In early MS, cognitive impairment and increased MRI atrophy suggest neurodegeneration from the moment clinical symptoms appear. In PPMS, which effect dominant neurological system, is characterized by a slow progression of disability in 6 to 16% of cases[103].The common and mostely occured PPMS clinical manifestation is progressive spastic paraparesis, while another well-known variations include cerebellar ataxia, sensory ataxia, vision loss and cognitive impairment. There is declination in the of people who have PPMS[103,104,107,108].

Currently Available Diagnosis Of MS :

In order to make a diagnosis, one must have objective proof of an inflammatory CNS damage as well as frequently extra information on how the disease is spreading "in space and time," that is, how it is impacting several CNS locations and changing over time [table]. The symptoms have to be more than twenty-four hours long and come in discrete episodes spaced at least a month apart. Magnetic resonance imaging [MRI] for lesions detection and cerebrospinal fluid [CSF] for biomarker analysis are the primary techniques widely used to support diagnosis.

The majority of patients have aberrant MRI results [109]. Intravenous administration of gadolinium is a sign of acute inflammation and is brought on by a rupturing and crossing the blood-brain barrier which happens initially during formation of an MS lesions. Even though gadolinium enhancement typically lasts less than a month, the remaining MS plaque can be clearly detected as a focal point of increased intensity [a lesion] on fluid-attenuated reversal recovery or T2-weighted MRI images. Lesions are typically situated peri ventricularly, or around the ventricles, indicating perivenular inflammation. Lesions found in the spinal cord , infratentorial white matter, and juxtacortical white matter which is near to the cerebral cortex are also indicative of multiple sclerosis, in addition to their role in "dissemination in space." White matter located beneath the cortex may be impacted by MS plaques are regarded to be non-diagnostic lesions because they are frequently associated with other conditions, yet nonetheless. In any suspected case of primary progressive multiple sclerosis, a lumbar puncture is helpful, especially in situations that are uncertain. Two instances of CSF anomalies are increased intrathecally produced IgG levels and pleocytosis of mononuclear cells. The end product of activated B cells in the CNS establishing a highly focused immune response are oligoclonal bands. Inappropriate intrathecal gamma immunoglobulin formation is observed in about 90% of MS patients, as shown via a higher IgG level or the absence of more than two distinct oligoclonal bands in a matching blood sample. When a patient presents with their first clinical manifestation of multiple sclerosis, increase in intrathecal antibody production may be utilized for the "dissemination in time" requirement. Elevated CSF antibody production is sensitive, but it is not unique to MS; it can also result from CNS infections. Since MS seldom has more than 50 cells/mm3, polymorphonuclear leukocytes, eosinophils, or a noticeably raised in the total protein level should raise doubts about the diagnosis.Other helpful test are optical coherence tomography for retinal imaging and evoked potentials for evaluating nerve conduction in CNS pathways[106,109].

a) Biomarkers:

There are various biomarkers associated with MS which can determine the progress of the condition. They are used for diagnosis as well as for validation of treatment list of biomarkers given below in tabular format [Table.1] along with type and clinical significance.

Important cellular and molecular indicators that might be used as therapeutic targets to treat and dignosis multiple sclerosis are mention in the Table. 2. From above given table the deviation from narmal range of biomarker is define progression and severity of MS.

MS patients exhibited increased levels in CSF biomarker like chitinase-3-like protein [CHI3L1]. It has been found that microglia and astrocytes produce them. Elevated expression of this biomarker inside CSF controls PPAR-γ, which causes the synthesis of cytokines like pro-fibroblast. The CNS is chronically inflamed as a result of these cytokines. Other biomarkers namely CXCL-12 and CXCL-13, have higher expression of CSF, which draws B-cells in the central nervous system, reduces anti-CD20, and results in long-term inflammation. The OGDs were degraded as a result of lower SIRT-1 in CSF. The pathway includes decreased amounts of the tumour suppressor FoxO3a and p53, which is regulator of glucose non-oxidative metabolism that function through p21 transcription, which results in greater levels of oxidative stress. And p16, two crucial G1/S cell-cycle checkpoint regulators. They then further alter cell death by blocking the CDK2-cyclin E and CDK4/6-cyclin D inhibit oligodendriocydal cell division. An increase in the transcription factor induced the generation of NF-KB signalling is another crucial inflammatory response modulator. By acting on target genes, it produces inflammatory cytokines and chemokines that increase MMP-9 levels, which have been connected to BBB degradation and, eventually, myelin sheath breakdown[Fig. 4]

The graphic [Fig.5] shows how elevated PI3k/Akt-mTOR expression elevated in pathway contributes to proliferation, neuro-inflammation, and cell damage[neuron]. These all are linked to the progression of multiple sclerosis. Increased blood biomarker synthesis, such as EBNAIgG and NF-L, results in EBV infections and neuroinflammation in the central nervous system, respectively. This activates antimyelin antibodies, which in turn cause myelin to degrade. The overexpression of the JAK/STAT signalling pathway causes direct physiological and pathological repercussions in motor neuron diseases such as multiple sclerosis. Cytokines including TNFα, IL-17, IL-12, IL-6, and IFN-γ stimulate auto-reactive CD4+ T cells and help them develop into Th1 phenotypes that overreact to inflammatory responses inside brain

through JAK/STAT signalling. Because it inhibits the activation of macrophages and cytokines, PPAR-γ has an anti-inflammatory action that makes it crucial for controlling the immune response. It also regulates the intrinsic molecular process of the T-cell, which in particular regulates Th17 differentiation. A higher level of PPAR-γ expression is associated with neuroprotective effects by lowering interleukins, inhibiting the development of Th1 cells, and lessening JAK/STAT-mediated hyperactivation of glial cells. The diagram shows how dysregulation of JAK/STAT and PPAR-γ signalling causes the inflammatory response to eliminate OPC cells, which in turn causes myelin degradation.

b) McDonald's criteria

There is widespread usage of McDonald's criteria in scientific and therapeutic contexts. Given the progress made in science over the last seven years, these guidelines might not provide doctors and researchers with the most recent knowledge available After reviewing the McDonald criteria, MS Diagnosis recommended changes. The 2017 guidelines from McDonald's place a strong emphasis on the absence of any other reasonable explanation for the presentation. These guidelines primarily apply to individuals with a specific clinically isolated condition and outline the necessary criteria to determine the extent and distribution of CNS lesions. [95,178,179].

Management And Treatment:

The goals of current therapeutic choices are to reduce biological activity, treat acute episodes, and relieve symptoms. Disease-modifying drugs such natalizumab, dimethyl fumarate interferon-beta and are the mainstay of treatment for multiple sclerosis. As soon as MS is diagnosed, therapy should begin right away. One of the short-term goals is to lower the activity of MRI lesions. 1. One of the long-term goals is to prevent the progression of secondary progressive MS. The two main concerns after starting the treatment are drug toxicity monitoring and patient compliance [117,181].

Ocrelizumab maintains the integrity of humoral immunity and the ability to regenerate B cells, while selectively eliminating B cells expressing CD20. The elimination of B cells is associated with significant disruption of B-cell movement from the peripheral to the central nervous system, diminished presentation of antigens by B cells to T cells, modified secretion of proinflammatory cytokines by B cells, and reduced differentiation and activation of plasma blasts that secrete immunoglobulins. Intravenous administration of ocrelizumab is performed every 24 weeks.

The phase 3 trial's first findings indicated a low possible risk of an increase in malignancies, including breast cancer; nevertheless, an extended follow-up revealed cancer rates that were in line with population-level estimates. Even though serious herpes virus infections are now known to occur as a side effect, post-marketing studies usually support clinical trials[182,183]. It is recommended to treat PPMS and relapsing types of multiple sclerosis [RMS]. The label states that two 300 mg starting doses are given two weeks apart, and thereafter 600 mg every six months. Patients should receive 100 mg of methylprednisolone and an antihistamine 30 to 60 minutes before to ocrelizumab infusion in order to prevent infusion reactions. Follow up with patients for sixty minutes following ocrelizumab injection[183].

Rituximab is an anti-CD20 monoclonal antibody that has never been given regulatory clearance, but early research and practical experience suggest that it works just as well against RMS and PPMS[184,185].Although rituximab was first licensed in 1997 to treat cancer, it is widely used off-label to treat a number of neurological conditions, including MS and myasthenia gravis. Different dosage schedules have been employed. Every six to twelve months, patients get 500 or 1000 mg of rituximab intravenously; this may occur after two initial administrations spaced two weeks apart[184,185]. The adhesion protein α4β1 integrin, which is generated on the surface of lymphocytes and implicated in transmigration via endothelial cells to the central nervous system, is inhibited by natalizumab. In real-world studies, natalizumab considerably slows the course of the illness and decreases relapses in patients with RMS benefits that are maintained over time when compared to placebo or interferon 1a[186].Natalizumab is given as an intravenous infusion once every month[186,187] For the treatment of RMS conditions such as secondary progressive illness, relapsing-remitting disease, and clinical syndrome, dimethyl fumarate is advised[188,189].Although there is a small risk of progressive multifocal leukoencephalopathy, dimethyl fumarate is typically well tolerated[190]. Since lymphopenia affected the majority of these people, it is important to check for it every six to twelve months[188,191].The first approved oral medication for RMS was fingolimod. It stops lymphocytes from migrating out of secondary lymphoid organs, which stops autoreactive lymphocytes from entering the central nervous system[192] . Although fingolimod is well tolerated, routine laboratory testing has shown a few modest adverse effects. Following fingolimod treatment, patients with a baseline absolute lymphocyte count [ALC] of 952/ml on the day after the first dose were more likely to experience lymphopenia. Additionally, when taking medicine, heart block and bradycardia might develop. For this reason, it is advised that all patients get

their first dosage after a six-hour observation period [192,193].In RMS, ozanimod, a recently approved selective S1P receptor modulator, showed promise and safety[194,195]. Dihydroorotate dehydrogenase is an enzyme involved in the synthesis of pyrimidines, and teriflunomide inhibits it [196].Teriflunomide inhibits the growth of activated lymphocytes that are thought to be autoreactive. In addition to treating MS, teriflunomide can stop brain shrinkage [196]. Hepatotoxicity and teratogenicity warnings are two examples of boxed warnings. Common adverse effects include headache, diarrhoea, nausea, baldness, and an increase in hepatic alanine transferase. If required, cholestyramine can be utilized to rapidly eliminate teriflunomide[196] The acetate salt of a blend of four polypeptides based on amino acids is called glutamate acetate. One possible mechanism of action might be a beneficial modulation of the proinflammatory to regulatory cytokine ratio[197].Glatiramer acetate is thought to be just as beneficial as interferon in treating recurrent myopathy syndrome [RMS], with a modest reduction in recurrence rates and some disease severity markers[197,198].Interferon-β postpones the development of disability and reduces the incidence of recurrence and MRI disease markers in a modest way[199]. Flu symptoms, mild test abnormalities, and injection site reactions to subcutaneous therapy are among the side effects of interferon-β[186,199].

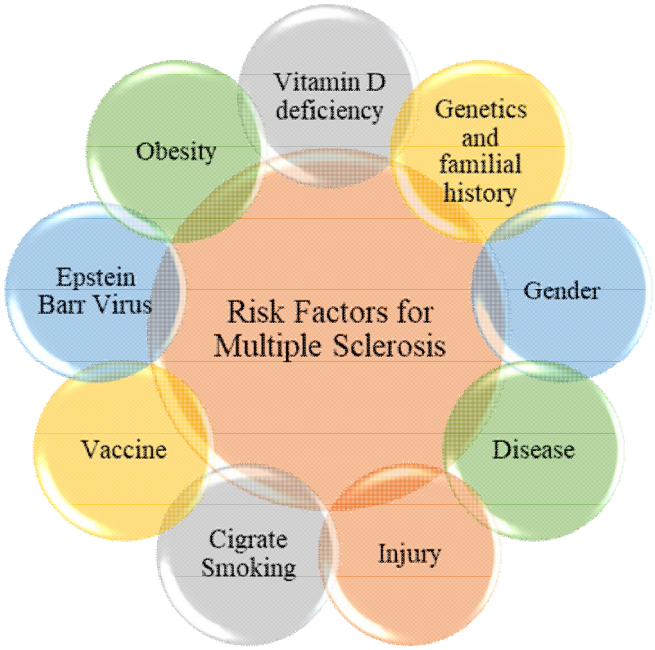

Figure. 1. Risk Factor for Multiple Sclerosis

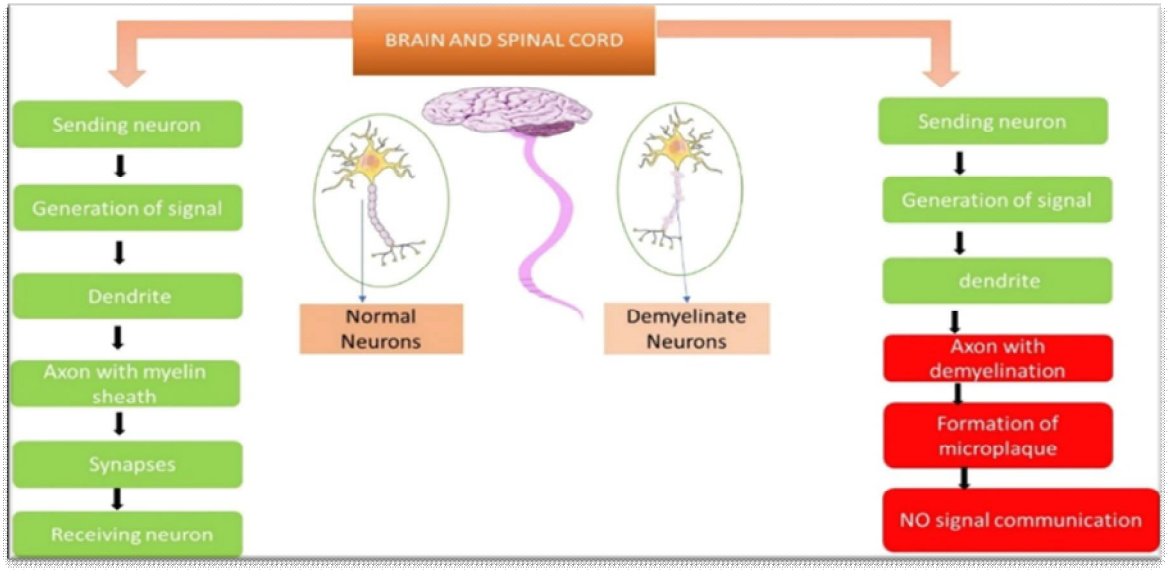

Figure. 2. Comparison between normal [healthy] neuron and demyelinated neuron

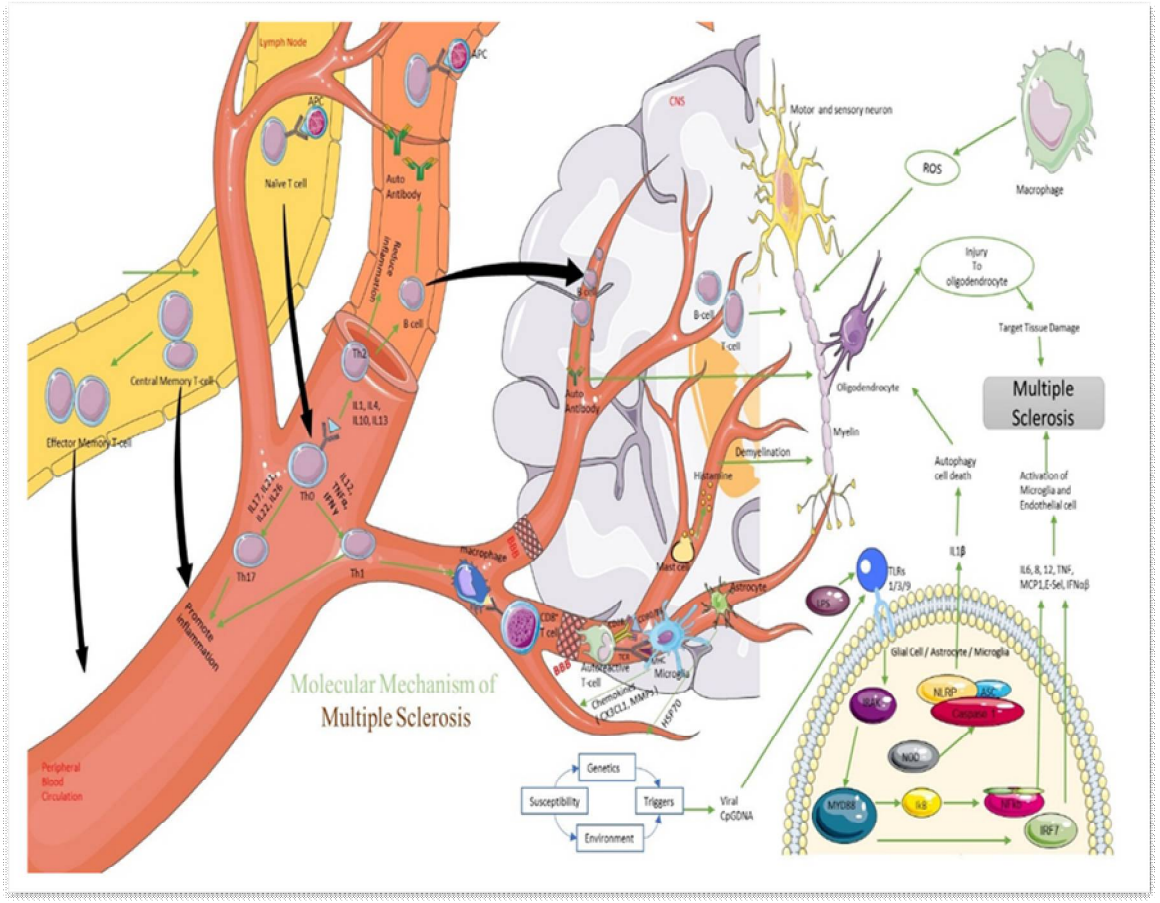

Figure. 3. Molecular mechanism of Multiple sclerosis.

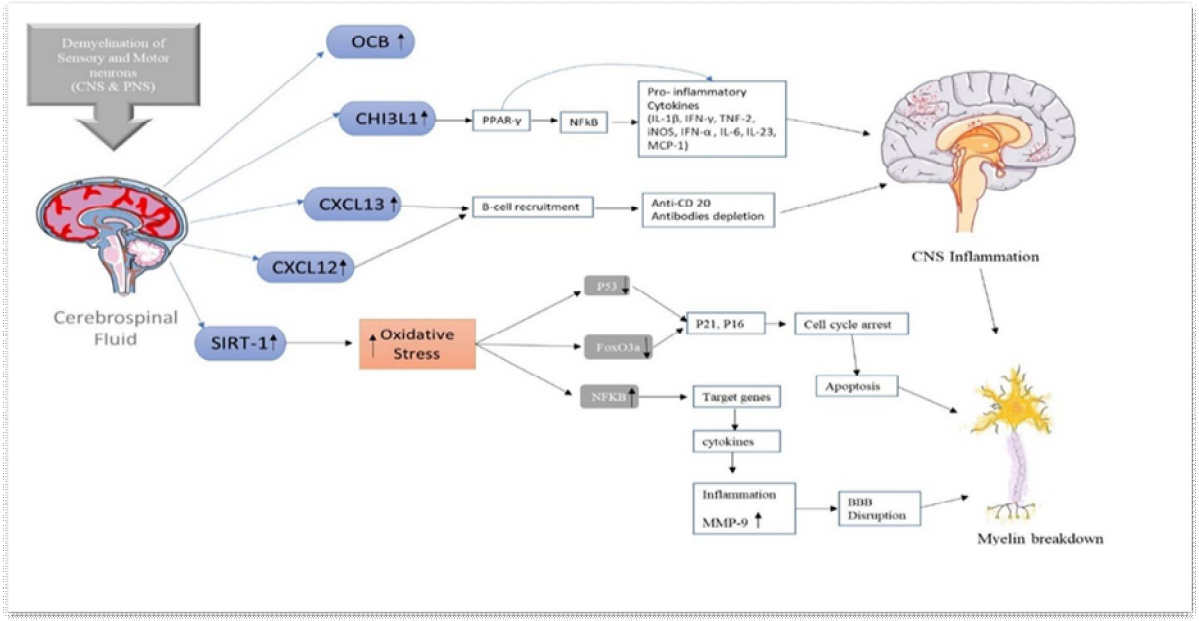

Figure. 4.Mechanism of biomarkers [CSF sample] in demyelination. MS- Multiple sclerosis. CSF- Cerebrospinal fluid. PPAR-γ- Peroxisome proliferator-activated receptor gamma, is a proteinous in nature that plays a role in regulating gene expression. Anti-CD20- monoclonal antibody that targets the CD20 protein on certain cells. SIRT-1- Sirtuin1, is an enzyme that is involved in many cellular processes. OGDs- Oligodendrocytes, are glial cell that produce myelin in the CNS. CDK- Cyclin-dependent kinase, is an enzyme that regulates the cell cycle. NF-KB- Nuclear factor kappa B, is a complex protein that controls the transcription of DNA. MMP-9- Matrix metalloproteinase 9, is an enzyme that breaks down extracellular matrix proteins. EBV-Epstein-Barr virus, is a kind of virus infects human cell and cause various diseases.

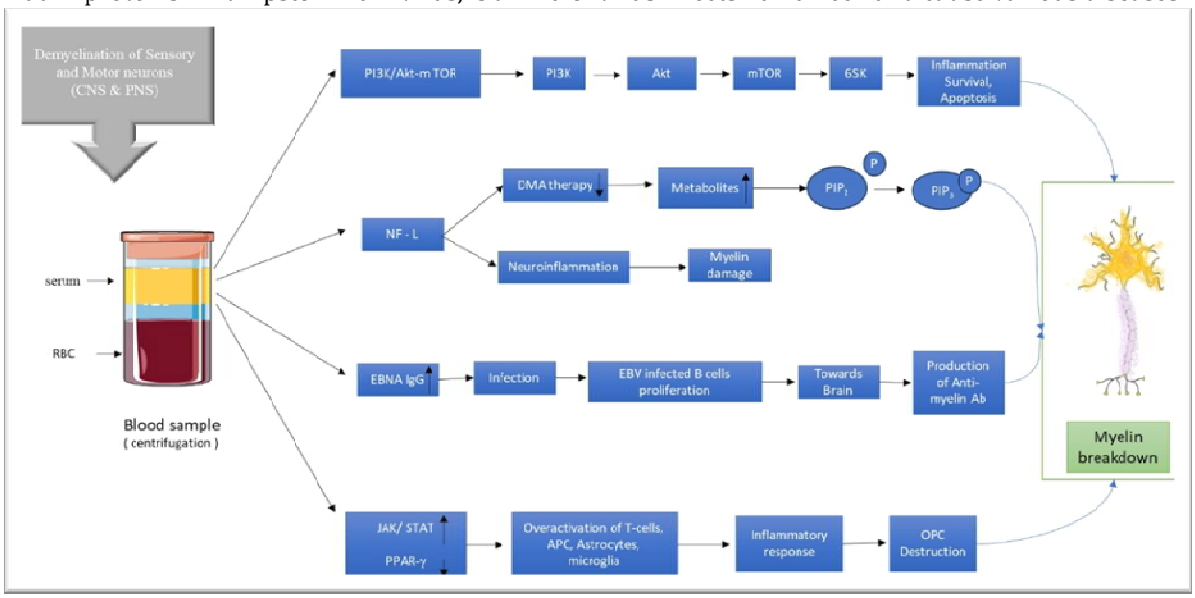

Figure. 5. Mechanism of Bimarkers [serum sample] in demyelination. NF-L- Neurofilament light chain, is a protein which is found in the nervous system. EBNAIgG- Epstein-Barr virus nuclear antigen, produce against Epstein-Barr virus as a immune response. CSF- Cerebrospinal fluid. PPAR-γ- Peroxisome proliferator-activated receptor gamma, is a proteinous in nature that plays a role in regulating gene expression. DMA- Disease-modifying agent, is a medication or treatment that aims to slow down the progression of a disease. PI3K- Phosphoinositide 3-kinase pathway, which is signaling pathway and it is involved in cell growth and survival. Th17- T-helper cell 17, is a type of immune cell that is involved in inflammation. JAK/STAT- Janus kinase signal transducers and activators of transcription, is a signaling pathway that is involved in cell communication and immune responses

Table. 1. Biomarkers associated with MS from samples from CSF, serum, saliva, urine and tear. Above mention biomarkers are predictive and prognostic biomarker.

Sr.No	Biomarker	Type	Prescence	Clinical Significance	Reference
1	Oligoclonal Bands [OCB]	IgG and IgM	CSF 95% in MS	Diagnostic indicator; Associated with CNS demyelinating disorders; Predicts development of CDMS and ON in MS; Higher inflammation response in CSF with OCGB; Not specific to MS	[110–117]
2	Nitric Oxide [NO]	NO levels	Higher in MS patients	Implicated in blood-brain barrier collapse, demyelination, axon degeneration; Potential therapeutic target; Further investigation needed	[118–121]
3	Serum Glial Fibrillary Acidic Protein [sGFAP]	sGFAP levels	Higher in PPMS	Associated with astrogliosis, severe disability and astrocyte death, in MS; Potential biomarker for MS severity	[73,122–125]
4	Myelin Basic Protein [MBP]	MBP concentration	Blood and Saliva	Lower levels in MS patients; Potential indicator for MS; Correlation between MBP levels in blood and saliva	[126–128]
5	Urea, Uric acid, Neopterin, Nitric oxide metabolites, Hippuric acid	Metabolites	Urine	Potential non-invasive diagnostic method; Altered levels in MS patients; Potential therapeutic target; Further confirmation needed	[129–136]
6	Alpha-1 Antichymotripsin	Protein	Present in Tears	Potential MS biomarker; Clinical significance and use as a biomarker require further research	[137–141]
7	OCB	IgG	Prescence in tears [55-72% in MS patients]	Unknown clinical significance; More research needed	[142,143]
8	Human Herpesvirus-6 [HHV-6]	Viral expression	Direct causative connection suggested	Predictive biomarker in association with MS disease	[111,144–146]
9	Antibodies against MOG and MBP	Autoantibodies	Present in serum of CIS patients	Potential diagnostic markers; further research needed	[41,111,113,128,147]
10	Chitinase-3-Like-1 [CHI3L1]	Protein	Elevated levels in CSF	Associated with optic neuritis, CIS, and MS; Higher levels linked to transition from CIS to MS	[148–154]
11	Neurofilaments	Protein	Elevated levels in serum	Neuronal damage biomarker; Used for disease prognosis and tracking; No diagnostic use	[113,114,155,156]
12	MicroRNAs [miRNA]	RNA molecule	Dysregulation in MS	Significant role in MS pathogenesis; Affects disease function	[157–162]
13	CXCL13	Chemokine	Higher levels in CSF	Potential biomarker for MS; Attracts B-cells into CNS; Clinical utility requires further research	[6,163–168]
14	CXCL12	Chemokine	Higher levels in actively demyelinating lesions	Implicated in axonal damage; May contribute to neuroinflammation	[165,169]
15	SIRT-1	Protein	Decreased levels in MS	Linked to neuroinflammation and demyelination; Potential therapeutic target	[41,170]
16	PI3K/AKT/mTOR	Signalling Pathway	Dysregulation in MS	Regulates cell growth, metabolism, and survival; May increase vulnerability to autoimmunity	[171–173]
17	EBNA IgG	Antibodies	Higher levels associated with Gd+ lesions	Potential biomarker for MS disease activity; More research needed	[174]
18	JAK/STAT and PPAR-γ	Signalling Pathway	Dysregulation in MS	Implicated in autoimmune responses and inflammation; Potential therapeutic targets	[175–177]

Table. 2. Summary of biomarker, biological samples, normal and MS range of biomarker and category of patient

S. N.	Biomarkers	Biological Samples	Category of MS Patients	MS range	Normal ranges	References
1.	Chitinase-3-like-1[CHI3L1]	CSF sample	RRMS	22.8 pg/mL	13-58 pg/mL	[191]
		Serum sample	CIS	20 pg/mL	10-76 pg/mL	
2.	CXCL13	CSF sample	RRMS	35.1 mg/dL	<30 mg/dL	[191]
3.	Neurofilament	Plasma sample	RRMS	11.5 pg/mL	7.5 5g/mL	[192]
4.	EBNA1 IgG	Serum sample	RRMS	310 U/mL	177 U/mL	[193]
5.	OCBs	CSF sample	SPMS RRMS	5-7 bands	1 band	[194,195]
6.	miRNA	Plasma sample	RRMS	+> 1.5 fold change	-5.30 to + 1.94Fold range	[196]
7.	Alpha-1 Anti chymotrypsin	Tears sample	RRMS = 25, SPMS = 1, PPMS = 4	1.7 ng/L	2.7 ng/L	[141]
8.	Myelin basic Protein [MBP]	Serum sample	RRMS	1055 ng/L	2750 ng/L	[129]
		Saliva sample	RRMS	476 ng/L	576 ng/L	

Table. 3. McDonald criteria

McDonald criteria			
Clinical evidence		**Additional information for diagnosis of MS**	**Reference**
Number of attacks	**Number of lesions**		
≥ 2	≥ 2	Extra information not required as clinical evidence are self sufficient	[180]
≥ 2	1	Space dissemination observed in MRI, required further clinical investigation at an alternative location in CNS.	
1	2	The timing of the dissemination displayed by MRI during of a 2nd attack, CSF sample analyzed for OCB for further diagnosis.	
1	1	Time and Space dissemination displayed by MRI. Next attack can be detected on another location in CNS.	
No attack	Initiation of lesion development	Disease progression required 1 year. 2 to 3 criteria consider for initial conformation of MS, That is evidenced by one or more T2 lesions in the brain in MS-affected areas, as well as two or more T2 spinal cord focal lesions with positive CSF.	

Table. 4. Management of MS

Patient Types	Name of Drug	Does and Route	Category of drug	Duration of Treatment	Approved in
RRMS	Fingolimod	0.5 mg p.o.daily	Peptide	6- 12 months	2010
RRMS	Interferonβ-1a	30 mcg [IM],Once a day 22 mcg [SC], TDI	Glycoprotein	24 months	2002
RRMS	Interferonβ-1a	22 mg,3 injections weekly [SC]	Glycoprotein	6-24 months	1996
RRMS	Interferon β-1b	0.25 mg [SC] q.o.d. 6 weeks	Non-glycosylated protein	24 months	1993
RRMS	Alemtuzumab	12 mg [IV] daily	Monoclonal antibody	12 months	2014
RRMS	Dimethyl Fumarate	240 mg/kg [p.o.] Twice a day	Peptide	24 months	2013
RRMS	Glatiramer acetate	20mg/kg [SC] daily	peptide	24 months	2015
RRMS	Dalfampridine	10 mg/kg twice a day	Pyrimidine analogue	4-24 weeks	
RRMS	Natalizumab	300 mg/kg [i.v.]	Monoclonal antibody	≥12 months	2004

RRMS	Ocrelizumab	300 mg/kg [i.v.]	Monoclonal antibody	6 months	2017
RRMS	Teriflunomide	14 mg/kg [p.o.]	Enamide	12 weeks	2012
RRMS	Siponimod	0.25–2 mg/kg [p.o.]	Alkoxyimino	>12 months	2019
RRMS	Rituximab	500 – 1000 mg [IV]	Chimeric murine/human monoclonal antibody	72 weeks	
RRMS and SPMS	Mitoxantrone	12 mg/kg body weight every 3 months	dihydroxyanthraquinone	2 – 3 years	2000
RRMS	Azathioprine	3 mg/kg daily [p.o.]	Purine analogue	6 months	
RRMS	Methylprednisolone	500–1000 mg/daily Oral/i.v.	Corticosteroids	3 -5 days	
RRMS	Cladribine	3.5 mg/kg [p.o.] 2 times, 4 or 5 days of treatment each year	Purine antimetabolite	2 years	2019
SPMS	Simvastatin	80 mg/kg, per day [p.o.]	Statin	24 months	
RRMS	Memantine	20 mg/day	Amine	52 weeks	
RRMS	Donepezil	10 mg/daily [p.o.]	Peptide	24 weeks	
SPMS and PPMS	Baclofen	10–100 mcg intrathecal	Peptide	4.9 years	
RRMS and SPMS	Ublituximab	150–600 mg/kg i.v. infusion	Monoclonal antibody	48 weeks	
RRMS and SPMS	Ponesimod	10,20, 40 mg/kg Daily [p.o.]	Peptide	24 weeks	
RRMS and SPMS	Ofatumumab	20 mg/kg [S.C.]	Monoclonal antibody	12 weeks	
RRMS and SPMS	Monomethyl Fumarate	95–190 mg/kg [b.i.d.], orally Delayed release capsule	Non-peptide	5 weeks	
RRMS and PPMS	Laquinimod	0.3–0.6 mg/kg [p.o.]	Amide	12–24 months	

CONCLUSION

Multiple sclerosis is an autoimmune disorder developed by various risk factor. MS is caused by smoking, vit D deficiency, vaccine etc. which damages Oligodendrocytes and affect signal transmission through demyelinating sensory and motor neurons. Which leads to the development of various life changing symptoms. In India, the rise in MS patients has been seen from the last few decades. Diagnosis of the disease is the main challenge in the case of MS. Researchers are developing new technologies to check the biomarkers for fast diagnosis along with developing new strategies to manage the condition. Fingolimod is first FDA approved drug for oral administration for MS. In upcoming years may MS will spread more due to various factors, but currently many approaches are adopted by researchers to find effective treatment and management for MS.

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