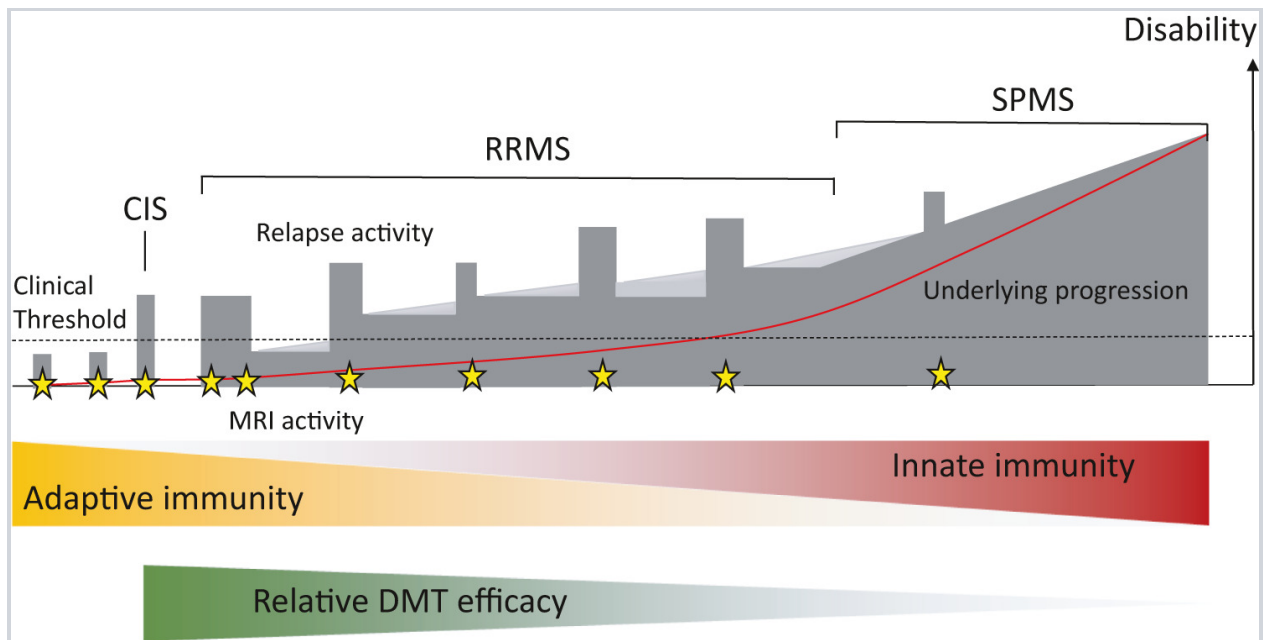


Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease defined by inflammation leading to demyelination and periventricular (spinal cord and pons) and plaques in the brain, resulting in physical and cognitive dysfunction. The demographics of this disease is most common in young children or older adults, while in referring to gender statistics MS is most common in women compared to men at a 3:1 ratio. MS is separated in 3 subdiagnoses defined as Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), and Primary Progressive Multiple Sclerosis (PPMS). RRMS is more inflammatory based and looked at as occasional flare ups and formation of plaques. SPMS is one step above RRMS as this sub diagnosis is defined as multiple occasions of RRMS and onset PPMS. PPMS is more aggressive and highly irreversible, this sub diagnosis shows cognitive and physical dysfunction and is yet to have any real cure. In all occurrences of MS there is inflammation and formation of periventricular plaques in the demyelination in the brain. Although there isn't a cure there are some disease modifying therapies (DMTs) licensed and available in the United States. In this comprehensive review of Multiple Sclerosis we will look into the background, some causes and risk factors, the symptoms and diagnosis process, some treatment options, and upcoming treatments for this disease.



“In most patients, MS starts as a relapsing–remitting disease (RRMS), which is termed Clinically Isolated Syndrome (CIS) after a first bout of clinical symptoms. This is often preceded by a phase of subclinical disease activity that can be detected with magnetic resonance imaging (MRI; yellow stars denote MRI signs of active inflammation). In later stages of RRMS, patients accumulate persistent disabilities, where recent evidence suggests that a progressive component may start already soon after diagnosis (light grey). This underlying progressive disease component becomes more pronounced at later stages, when the disease converts to secondary progressive MS (SPMS). The fact that inflammatory disease activity, as reflected by frequency of bouts or MRI activity, diminishes over time suggests a shift from adaptive to innate or local disease mechanisms, which may explain the relative loss of efficacy of disease-modulatory treatments (DMT).” © 2020 The Authors. Journal of Internal Medicine published by John Wiley & Sons Ltd on behalf of Association for Publication of The Journal of Internal Medicine

There are some key physiological factors that should be understood when considering MS. First is the periventricular apparatus. This includes the pons which control all of your unconscious involuntary movements such as breathing, muscle movement, and even sleeping. It also connects your spinal cord to your brain allowing electrochemical signals to propagate routinely. Oligodendrocytes are the myelinating cells (produce myelin) of the Central Nervous System (CNS) which allow neuronal signals from the body to the brain through the myelination of axons, which are the part of the brain cell that signals propagate through. Myelin is a compound made of phospholipids and proteins that create a sheath around nerve fibers that help with the efficiency of neuronal signal propagation. The lymph system is a network of cells that runs throughout the body containing your memory immune cells. The lymphocytes (B and T cells) help with binding to MHC complexes in antigen presenting cells (APCs) and producing antibodies.

MS begins with lymphocytic inflammation of the periventricular area in the brain. This inflammation causes damage to the oligodendrocytes leaving lesions on the neural axons which ultimately damages the myelin sheaths. This means that electrochemical signals cannot be propagated efficiently, at this point you will begin seeing dysfunction. There are occurrences of remyelination in all stages of MS, but at more progressive stages this damage can be irreversible.

There is a high correlation with those who have been infected by Epstein-Barr Virus (EBV) and those who develop MS. It was found in a study published in 2022 that a protein in EBV called EBNA1 mimics a protein called GlialCAM in your myelin sheath according to William Robinson, MD, PhD, professor of immunology and rheumatology at Stanford. The correlation means that your immune system when attacking EBV is also attacking the protein in the insulated region of the axon which is the region that is being damaged in MS. There is a slight genetic factor in MS, although it isn't directly inherited, there are some genes that can affect the chances of developing the disease. Smoking is another factor that is highly associated with developing MS. Smoking increases the chances of developing Multiple Sclerosis by 50%. The toxic compounds in cigarette smoke directly cause damage to the myelin producing Oligodendrocyte cells which can trigger an immune reaction in that area of the brain. Deficiency in Vitamin D is also a factor in developing MS. Without Vitamin D, the immune system may not perform properly leading to a lack of immune response or an over activation of immune response. Overactivation can lead to unnecessary inflammation. Connecting back to the correlation with EBV, a vitamin deficient patient with overactive immune response as well as autoimmune attacks on myelin sheath calls for a high risk of developing MS.

MS is suspected when a patient presents a Clinically Isolated Syndrome (CIS) which is the first clinical onset of the disease. Some symptoms can include; optic neuritis, which is the inflammation of the optic nerve that can lead to color vision loss, severe insomnia, brainstem and spinal cord syndromes, parietal lobe dominant syndromes such as lesions, chronic migraines, bladder and bowel problems, and loss of independence in activities in daily living (ADLs) such as getting dressed, toileting, hygiene, cooking etc. These initial symptoms help to pinpoint what the next steps in investigation for diagnosis. In the later stages of RRMS symptoms of onset PPMS include muscle tightness and weakness, cerebellar and sensory ataxia, neurodegeneration, as well as cognitive and visual failure. All symptoms and their severity are based on the size, number and location of demyelinated lesions in the brain. There are challenges in getting to a confident diagnosis of MS due to the complexity of the disease. There are multiple differential diagnoses, which are other diseases who share symptoms that include TB, neurosarcoidosis (organ inflammation), and neuromyelitis optica spectrum disorder (brain and spinal inflammation of the optic nerve). Doctors try to exclude other autoimmune diseases with multiple symptoms

when looking into an MS case. It is important to be thorough in testing and administration of treatment because a misdiagnosis can lead to treatment that can worsen the symptoms of MS. Using modern technology such as Magnetic Resonance Imaging (MRI) allows doctors to see established plaques (demyelinated lesions) in the brain. This machinery can even see into deeper gray matter and even lesions on a microscopic level. Recently, using a soluble protein marker that illuminates on the infected region makes plaques easier to see, and may bring up lesions that could not have otherwise been detected. Extraction of the cerebrospinal fluid (CSF) can also help with diagnosis as doctors are able to analyze the fluid for Immunoglobulin G bands (IgG bands).

There are available treatments for MS called disease modulating therapies (DMTs) that can help prevent, but not eliminate, worsening symptoms. Some of these include Sativex which is an oral spray that contains THC and CBD for muscle spasticity and fampridine with an active ingredient FAMPYRA that blocks potassium from leaving the nerve cells. Aerobic exercise is also very important for MS patients as it encourages usage of muscles, coordination, and balance. It is recommended to do aerobic exercise 4-5 times weekly, while this is important this should not be vigorous as it can potentially worsen symptoms. For patients with complex dysfunction, seeing a physiotherapist can also help prevent worsening symptoms. Immune reconstitution is the closest to a cure for MS in 2019 including alemtuzumab which targets the protein CD52 on B cells stops them from getting to the brain before inflammation can occur, and cladribine which also prevents lymphatic inflammation. There is ongoing research on hematopoietic stem cell (HSC) stem cell therapies that are only in the beginning stages of development which is something to look forward to in the future.

MS can have a significant impact on daily life, especially those with aggressive PPMS. One can expect severe memory deficiency and confusion making it difficult to navigate through a typical lifestyle. Muscle ataxia can also make it difficult to use basic motor movement such as walking, sit to stand, bedding, basic hygiene, and toileting, harsh mood responses. Insomnia can also make it difficult to preserve the natural circadian rhythm which has a lot of influence on sleeping and eating schedules. It is extremely important for those with MS to have a reliable support system with a deep understanding of the disease because it is a difficult diagnosis to care

for. Without proper support, a patient will not be able to thrive on their own, and can potentially be a danger to themselves depending on the severity of their condition.

MS is a serious autoimmune disease with harsh impacts on the body and daily life. It is important to keep the complexity of the disease in mind when in treatment and care of affected patients. Developing treatments will lead us closer to a potential cure to this prestigious disease. So far, B cell targeted therapies are the closest we have to a cure, but keeping up with DMTs are important in lessening symptoms and allowing a patient to continue a semi typical quality of life. The future in MS research is promising, as there are multiple high level studies happening today.

Works Cited

Multiple Sclerosis – a Review - Dobson - Wiley Online Library,

onlinelibrary.wiley.com/doi/full/10.1111/ene.13819. Accessed 4 Dec. 2023.

News Center. “Study Identifies How Epstein-Barr Virus Triggers Multiple Sclerosis.” *News Center*, 24 Jan. 2022,

med.stanford.edu/news/all-news/2022/01/epstein-barr-virus-multiple-sclerosis.html.

“Smoking and MS: Unraveling the Links, Impact on Disease Progression, and Cessation Strategies.” *Cleveland Clinic*,

my.clevelandclinic.org/departments/neurological/depts/multiple-sclerosis/ms-approaches/ms-and-smoking#:~:text=Cigarette%20smoke%20contains%20thousands%20of,those%20that%20have%20never%20smoked. Accessed 4 Dec. 2023.

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Authors. *Journal of Internal Medicine* published by John Wiley & Sons Ltd on behalf of Association for Publication of The Journal of Internal Medicine,

onlinelibrary.wiley.com/doi/full/10.1111/joim.13215. Accessed 4 Dec. 2023.