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Terrorism in Your Brain: The Battles of Multiple Sclerosis (MS)

Paul W. Asper
Gettysburg College

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Abstract

This paper is a review of Multiple Sclerosis (MS) looking at the phenotypes, epidemiology, etiology, pathology, and immunology. Additionally, this paper examines the clinical presentations and criteria for diagnosis along with the treatment and management of symptoms.

Keywords

Multiple Sclerosis, MS, demyelination

Disciplines

Medicine and Health Sciences | Nervous System Diseases | Neurology

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Paul Asper

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Professor Drury

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Introduction

Multiple sclerosis (MS) is a complex condition that targets and affects the nervous system. More specifically, MS is a frequent autoimmune demyelinating disease of the central nervous system (CNS) (Ruiz, Vigne, & Pot, 2019; Torres-Pareja, Sánchez-Lastra, Iglesias, Suárez-Iglesias, Mendoza, & Ayán, 2019). MS often affects individuals in their early adult life. It is seen more commonly among women (Lopez-Leon, Geissbühler, Sabidó, Turkson, Wahlich, & Morris, 2020). This disease is one of the leading causes of disability in young adults in the United States (Garg & Smith, 2015). This disease is most prevalent in the United States and Europe with 2.3 million cases worldwide (Doshi & Chataway, 2017; Klineova & Lublin, 2018). These individuals are often drastically impacted regarding their quality of life (Persson, Lee, Yood, Wagner, Minton, Niemcryk, Lindholm, Evans, & Jick, 2019; Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018). MS often has relapse phases where focal areas of demyelination occur over the course of twenty-four hours and persist for days or weeks. Generally, but not always, these symptoms will improve (Doshi & Chataway, 2017). While the exact cause of MS has yet to be pinpointed, it is understood that it is a multifactorial disease. Some of these factors include genetic and environmental factors interacting with other factors. The interaction of these factors causes an aberrant autoimmune attack resulting in damage to myelin and axons (Garg & Smith, 2015). To diagnose this condition accurately an MRI must be used to look at markers of the disease (Garg & Smith, 2015). This can be further enforced by paraclinical data (Doshi & Chataway, 2017). The purpose of this paper is to provide a condensed overview of multiple sclerosis using information gained from academic journals.

MS Phenotypes

There are several phenotypes of MS known as the subtypes. The five most common subtypes of MS are; Clinically Isolated Syndrome (CIS), Radiologically Isolated Syndrome (RIS), Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), and Primary Progressive MS (PPMS) (Disanto, Barro, Benkert, Naegelin, Schädelin, Giardiello, Zecca, Blennow, Zetterberg, Leppert, Kappos, Gobbi, & Kuhle, 2017; Doshi & Chataway, 2017; Kamińska, Koper, Piechal, & Kemona, 2017; Klineova & Lublin, 2018). The CIS subtype is the most common phenotype of MS during the initial phases in eighty percent of cases. CIS is described as an acute clinical attack that affects one or more of the CNS sites (Doshi & Chataway, 2017). These CNS sites include the optic nerve, the brainstem, and the spinal cord. This type of the disease usually resolves over time given there are no relapses that occur causing the disease to worsen and convert to a different type (Thompson et al., 2018). RIS is similar to CIS with the difference being in how they are found. The RIS type is found incidentally during an MRI scan rather than having clinical presentations of the disease (Thompson et al., 2018).

The CIS and RIS forms of MS can, over time, end up converting into the RRMS phenotype (Thompson et al., 2018). This conversion occurs in approximately twenty-one percent of patients at twenty years of age if that patient's MRI scan is normal. If the MRI scan is abnormal then the chance of conversion changes drastically for the patient. An abnormal reading would be considered having one or more clinically silent white matter lesions on the MRI. If this were the case, then the chances of conversion from CIS to RRMS jump to eighty-two percent rather than the twenty-one percent chance that accompanies a normal MRI scan. Despite the

conversion of CIS to RRMS being a progression in the disease, the recovery from RRMS clinical episodes or relapses often have positive outcomes (Doshi & Chataway, 2017).

During these two early stages of MS, there is often an increase in inflammation along with a decrease in energy. The inflammation is often accompanied by T- and B-cell clonal expansion. The inflammation, as well as T- and B-cell, changes are triggered by an inflammatory pathological substrate with the migration of autoreactive lymphocytes across the blood-brain barrier. The lack of energy comes as an effect directly correlated to the mitochondrial injury that is sustained during these stages of the disease process. Each relapse that occurs over time causes more and more damage. Although the individual can recover from the relapse, they are never back to one hundred percent. The patient may get back close to where they were before but over time their maximum overall well-being will slowly decrease never allowing them to get back to what they had prior to each continuous relapse. After enough relapse events, this could lead to a drastic difference in the individual's overall maximum health potential. The age of relapse-onset is about thirty years old, and it occurs in females at a ratio of 2:1 compared to males (Doshi & Chataway, 2017; Kamińska et al., 2017).

After approximately ten to fifteen years after being diagnosed with RRMS most patients go through another transition. This time from RRMS to Secondary Progressive MS (SPMS). This takes place in about eighty percent of RRMS patients after the ten-to-fifteen-year time frame. In this stage of the disease progression, patients will have further axonal injury as well as atrophy of both the white and grey matter (Doshi & Chataway, 2017). This is most likely going to be accompanied by underlying neurodegenerative pathogenesis. Additionally, during this phase, the patient will often notice less inflammation. These previous subtypes of MS should

additionally be classified as active versus non-active. When active there would be evidence of clinical relapse or new T2 lesions on the MRI scan over at least one year. Active is different from disease progression. When active the patient is experiencing clinical relapse or new lesions which is what causes their worsening (Doshi & Chataway, 2017). Disease progression makes an individual feel worse due to worsening disability over time. The fourth main subtype is known as primary progressive MS (PPMS). This type is found in ten to fifteen percent of patients. These patients will have progressive disability from the onset of the disease. This is often caused by spinal cord disease. The age of onset for this type is a bit older at forty years old, which is a decade later than the age for relapse onset MS. This type also affects both males and females equally at a 1:1 ratio in most studies (Doshi & Chataway, 2017). Along with this type patients will often notice progressive spastic paraparesis. The progressive spastic paraparesis is due to the spinal cord dysfunction that is taking place (Doshi & Chataway, 2017)

Epidemiology & Etiology of MS

MS is widespread disease that mainly affects people between twenty to forty years old. The estimate of 2.3 million people having MS worldwide is thought to be an understatement. Some of the larger populated places in the world such as China and India have a lack of relative data which is leading to the estimate likely being low. In the United States, MS is one of the leading causes of disability with four hundred thousand cases (Garg & Smith, 2015). North America and Europe have the highest prevalence of MS with 140 and 108 cases per 100,000 people respectively (Doshi & Chataway, 2017; Persson et al., 2019). The lowest prevalence is in sub-Saharan Africa and East Asia with 2.1 and 2.2 cases per 100,000 people respectively (Doshi & Chataway, 2017). Additionally, it is approximated that there are 120,000 people with MS in

the UK (Doshi & Chataway, 2017). MS is more common in females than males and most likely to occur during early adulthood, although there has been an increase in awareness in recent years of presentation during childhood (Spanier, Nashold, Mayne, Nelson, & Hayes, 2015; Thompson et al., 2018).

While the exact cause of MS is still yet to be figured out, some things are likely to put an individual at a higher risk of developing MS. These factors are either external in one's environment or could be within an individual's genetics (Song, Westerlind, McKay, Almqvist, Stridh, Kockum, Hillert, & Manouchehrinia, 2018). The factors from the environment that increase a person's risk for MS are called environmental risk factors. Some of these types of factors include sunlight, Vitamin D, diet, obesity in early life, and cigarette smoking (Thompson et al., 2018). The two main factors among these are low Vitamin D levels and cigarette smoking. If an individual has a Vitamin D deficiency, they could correct that and lower their risk of developing MS. However, Vitamin D deficiency has not been shown to increase an individual's risk for MS when the deficiency occurs as a neonatal (Thompson et al., 2018). Cigarette smoking has an increased risk associated with an increase in duration and intensity. The risk that comes with smoking cigarettes has been shown to affect men more so than it does women. Regarding obesity early in life, there is a strong correlation at a twofold increase in risk for both men and women alike. This factor may be in part due to a low level of Vitamin D in obese individuals. Additionally, it is hypothesized that with increased infections comes the increase in the risk of MS as seen with the hygiene hypothesis (Thompson et al., 2018). The hygiene hypothesis is supported by many epidemiological observations (Garg & Smith, 2015). The hypothesis suggests that improved sanitation and reduced childhood infections in developed countries may account for the increased rates of autoimmune diseases (Garg & Smith, 2015). This comes from the idea

that in more developed countries the infections that are observed to lead to MS happen later (early adulthood) than compared to those individuals living in less developed countries (Thompson et al., 2018).

In addition to the environmental factors, an individual's genetics also play an important role in assessing one's risk of MS. Hundreds of human diseases, including most autoimmune diseases, have been associated with the human leukocyte antigen (HLA) region. Multiple studies have been able to replicate evidence that serotype D2 (also known as DRB1*15:01) is associated with MS. It has been estimated from studies since two thousand and eighteen that individuals who carry the HLA DRB1*15:01 allele are three times more likely to develop MS than compared to those individuals who are not carrying the HLA DRB1*15:01 allele. There have been additional studies that have focused on the HLA region that has identified additional risk and protective alleles (Thompson et al., 2018). With the values of HLA allele sharing by descent in sibships, it has been estimated that the HLA locus accounts for twenty to thirty percent of the genetic susceptibility in MS. There have also been findings that associate two non-HLA genes, IL2RA and IL7RA, along with other genetic variants that have minor effects with their impact on MS risk in individuals. Overall, genetic studies have been largely successful in providing a large roster of common variants associated with susceptibility to MS (Thompson et al., 2018).

Pathology of MS

Multiple sclerosis is the presence of inflammatory demyelinating lesions within the central nervous system (Lassmann, 2013; Lassmann, 2018). The inflammatory infiltrates are mostly made up of T-cells. The activated $CD4^+$ T cells that are specific for myelin peptides presented by HLA class II molecules migrate into the Central Nervous System (CNS) and

accumulate in nascent lesions (Spanier et al., 2015). A main feature of MS is the selective and primary nature of demyelination. MS focuses on destroying oligodendrocytes. While the myelin is destroyed, the axons are preserved for the most part with the amount of axonal damage differing between patients and even between the lesions of one patient (Lassmann, 2018).

There are additionally B-cells and Plasma cells, however, they are in a much lower quantity in comparison to the T-cells. This lymphatic inflammation is partnered with significant expression of Major Histocompatibility (MHC) molecules. An expression of adhesion molecules, as well as chemokines and cytokines as part of the inflammatory infiltrates, are also associated with the inflammation process as well as in part in astrocytes. This leads to the suggestion of a T-cell mediated inflammatory process that drives the disease and tissue injury (Lassmann, 2013). The formation of large confluent demyelinated plaques in the white and grey matter of the brain is the most characteristic change pathologically for the brain of someone with MS (Lassmann, 2013).

Evidence shows an inverse correlation between ambient UV light and MS prevalence (Spanier, Nashold, Olson, & Hayes, 2012). The relationship between UVB photons synthesizing vitamin D_3 and the presence of vitamin D receptors found in active T lymphocytes raised a hypothesis. This hypothesis is that active vitamin D_3 hormone could selectively regulate the $CD4^+$ T lymphocytes that cause autoimmune-mediated pathology in MS (Spanier et al., 2012; Spanier et al., 2015). There is evidence to support the theory that the hormonal form of D_3, calcitriol, might be selectively regulating autoimmune T cells (Spanier et al., 2015). This theory is supported by the evidence that the risk of MS is significantly higher in those individuals who

carry rare *CYP27B1* gene lesions. These gene lesions decrease calcitriol synthesis (Spanier et al., 2015).

Additionally, studies have shown a correlation between a decrease in D_3 status and an increase in the risk of MS. This relationship is found more in women than it is in men. Therefore, it is hypothesized that peripheral T cell self-tolerance induction in women depends on an interaction between estradiol and D_3 that is not required for tolerance induction in men. (Spanier et al., 2015). It was also scientists discovered that about a seventy percent decrease in the mean annual MS relapse rate during the third trimester of pregnancy. This decrease and timing correlated with a two hundred- and eighteen-fold increase in circulating E2 as well as a little over two-fold increase in calcitriol (Spanier et al., 2015). Studies also found support through both animal and human models that E2 serves an anti-inflammatory and neuroprotective role for E2 in MS (Spanier et al., 2015).

Immunology of MS

Both genetic and pathological studies point towards the adaptive immune system as a main player in the pathogenesis of MS. The adaptive immune system mainly consists of T- and B-cells. The inflammation that is seen with MS only targets the CNS. This suggests that T- and B-cells are selectively attracted by specific target antigens that are only expressed within the CNS (Thompson et al., 2018). In addition to the adaptive immune system, the innate immune system also seems to play an important role in the initiation and progression of MS (Thompson et al., 2018). The innate immune system mainly consists of phagocytic cells. The macrophages are pro-inflammatory cells that respond to the T and B cells and execute tissue damage. Microglial cells may also play a major role in MS. They may contribute the MS

pathology through several mechanisms. These mechanisms include secretion of pro-inflammatory cytokines, chemokines, free radicals, and increased release of glutamate (Thompson et al., 2018).

Regulatory T (Treg) cells that are also referred to as $CD4^+$ and $CD25^+$ T cells can modulate the immune system response to provide a critical level of protection against self-antigens and autoimmunity in several autoimmune models such as experimental autoimmune encephalomyelitis (EAE) (Noori-Zadeh, Mesbah-Namin, & Saboor-Yaraghi, 2017). EAE is a mouse model of MS. Treg cells have been shown to be the main cellular constituent of the tolerance system to suppress autoimmunity (Noori-Zadeh et al., 2017).

The main transcription factor that is expressed in the Treg cells is forkhead box P (FOXP3). This acts as the main regulator and polarizes naïve T cells into the Treg lineage. Therefore, *FOXP3* expression was discovered to be integral for Treg cell development and thus its suppressive function (Noori-Zadeh et al., 2017). Treg cells have shown through studies done on scurfy mice that they can prevent immune-pathological conditions as well as other autoimmune disorders. The main autoimmune disorder focused on with mice is Experimental Autoimmune Encephalomyelitis (EAE). The Treg cells demonstrated their ability to control motility and proliferation of the effector T-cells in the CNS thus mediating the recovery from EAE. Treg cells influence EAE by affecting the priming, polarization, and proliferation of effector T-cells in the periphery and within the CNS (Ruiz et al., 2019). The transfer of Treg cells in the periphery is enough to protect mice from the onset as well as the progression of both active and spontaneous EAE (Ruiz et al., 2019). However, if the Treg cells are depleted the disease is exacerbated.

It has been shown that induction of genes involved in the transcriptional signature of Treg cells can be optimized by a synergic action of *FOXP3* with other main transcription factors such as GATA1 (GATA-binding factor) (Noori-Zadeh et al., 2017). One of these transcription factors that has yet to be studied through the EAE mouse model is the BTB domain and CNC homolog 2 (BACH2). By analyzing the genome-wise function of *BACH2,* it was revealed that *BACH2* represses genes that are associated with effector T-cell proliferation. Therefore, it appears that *BACH2* is necessary for the efficient development of Treg cells and consequently for Treg cell-dependent suppression of inflammation in EAE (Noori-Zadeh et al., 2017). In healthy CNS, Tregs are vital to promoting neuroprotection as interactions occur between the resident cells of the CNS and the infiltrating Tregs to modulate the local immune responses (Ruiz et al., 2019).

Clinical Presentations and Diagnosis

Multiple sclerosis is characterized by heterogeneity in the symptoms, disease course, and outcomes (Klineova & Lublin, 2018). One of the most common symptoms of MS is fatigue with a prevalence of up to eighty-three percent. Fatigue exerts the greatest impact on the quality of life of patients with MS (Manjaly, Harrison, Critchley, Do, Stefanics, Wenderoth, Lutterotti, Müller, & Stephan, 2019). The concept of fatigue can vary drastically in meaning. Through an attempt to standardize taxonomy distinguishes two major dimensions of fatigue: perception of fatigue and performance fatigability (Manjaly et al., 2019). Performance fatigability refers to objectively measurable aspects of fatigue such as the observable decrease in performance during a cognitive or motor task (Manjaly et al., 2019). On the other hand, the perceptual dimension is not objective, but rather subjective and therefore cannot be assessed directly by an external

observer. Understanding the subjective perception of fatigue requires a cognitive perspective, in particular, concepts of interoception and metacognition (Manjaly et al., 2019).

Outside of the distinct MS phenotypes previously mentioned there is an additional phenotype that has drawn attention, Radiologically Isolated Syndrome (RIS). The term RIS was first introduced in 2009 (Klineova & Lublin, 2018). RIS refers to patients who have accidentally found MRI abnormalities that are increasingly suggestive of demyelination in the absence of clinical signs or symptoms. These abnormalities include dissemination in space and lesion-specific morphologic features to enhance diagnostic certainty and rule out patients with nonspecific white matter changes caused by other causative etiologies (Klineova & Lublin, 2018). Various studies have concluded that spinal cord lesions are the strongest predictor for future clinical events (Klineova & Lublin, 2018).

In addition to RIS, there is a similar phenotype, Clinically Isolated Syndrome (CIS) that occurs in patients. Patients with CIS typically show symptoms such as monofocal, which evolve acutely or subacutely over days to weeks, and involve the optic nerve, spinal cord, brain stem, or cerebellum (Klineova & Lublin, 2018). Similar to other MS attacks, CIS episodes are expected to last for at least twenty-four hours and occur without fever or infection. About fifty to seventy percent of patients with CIS have asymptomatic T2 white matter abnormalities on the baseline brain MRI, consistent with demyelinating lesions (Klineova & Lublin, 2018).

The most common MS phenotype is Relapsing Remitting MS (RRMS). This phenotype is found in about eighty-five percent of patients with MS. RRMS is characterized by alternating periods of relative clinical stability free of new neurological symptoms (Klineova & Lublin, 2018). RRMS also hold several neurological symptoms such as weakness, altered sensation,

balance impairment, impairment of visual acuity, and color vision or double vision. These symptoms may be present during a relapse and last at least twenty-four hours without infection or metabolic derangement (Klineova & Lublin, 2018).

Relapse does not generally exceed 1.5 per year and decreases as the disease advances as well as with age. The most relevant relapse factors to everyday clinical practice include infections, stress, and pregnancy. Studies show that there is a correlation between infections and increased relapse rate, prolonged relapse duration, and increased accumulation of disability (Klineova & Lublin, 2018). Stress appeared to have more of an additive effect on relapse rather than causative of relapse (Klineova & Lublin, 2018).

The majority of patients with RRMS will progress into Secondary Progressive MS (SPMS) after nineteen years, on average, if left untreated. The diagnosis for SPMS is most often established retrospectively, years after the actual progression started (Klineova & Lublin, 2018). The most common reason for the uncertainty and therefore late diagnosis comes from subtle and often fluctuating initial symptoms. Only a few of the predictors of the conversion from RRMS to SPMS have been identified. These predictors are higher age at RRMS onset and male gender. However, these were not consistent in all studies. Additionally, spinal cord symptoms and incomplete relapse recovery have also been shown to shorten the time to progression (Klineova & Lublin, 2018).

One of the rarer phenotypes, only occurring in ten to twenty percent of patients, is Primary Progressive MS (PPMS). Similar to SPMS, PPMS has a complex pathology and includes neurodegeneration along with mild-to-moderate inflammation. Patients with PPMS have shown the absence of the initial Relapsing Remitting (RR) phase. The progression of the

disease is not uniform throughout the course. In addition, patients experience superimposed relapses as well as periods of relative disease stability (Klineova & Lublin, 2018).

One of the main tools used in diagnosing and tracking the progression of MS is Magnetic Resonance Imaging (MRI). The dominant marker of change in areas of T2 signal change, which may also enhance with gadolinium (Doshi & Chataway, 2017). The revisions made in 2010 to the McDonald diagnostic criteria advise that additional evidence of dissemination of MS lesions in time and space are possible as shown by MRI evidence. There are also many other MRI indices, both already existing and in the process of being developed. Although they have yet to be fully incorporated into standard clinical practice. To further reinforce the diagnosis of MS, paraclinical data can be used in the form of increased latency of evoked potentials that are seen in up to ninety percent of patients with MS (Doshi & Chataway, 2017).

Treatment/Management of MS

While there is no known cure for MS there are several ways in which it can be treated and managed. One of the more common treatments is the use of vitamin D. Vitamin D plays a role in lymphocyte activation and proliferation, T-helper cell differentiation, and its regulatory effects on immune response (Feige, Moser, Bieler, Schwenker, Hauer & Sellner, 2020). When using vitamin D supplementation, high doses were able to reduce the proportion of IL-17-producing $CD4^+$ T-cells and increase central memory $CD4^+$ T-cells and naïve $CD4^+$ T-cells (Feige, et al., 2020). Additionally, it was reported that patients with definite MS, who were supplemented with vitamin D, had a significant reduction in anti-EBNA-1 IgG levels. The importance of this is linked to the association between higher levels of anti-EBNA-1 IgG levels and an increase in the number of active MRI lesions (Feige, et al., 2020).

Patients with MS often experience symptoms that impact their emotional and mental health in addition to their physical health. One treatment that has been studied and found to help MS patients to manage their symptoms is cryotherapy. Study results show that cryogenic temperatures have a large impact on mental and physical health, especially in improving the patient's mood (Pawik, Kowalska, & Rymaszewska, 2019). Cryo-stimulation led to an immediate improvement in the somatic and mental well-being. Additionally, cryo-stimulation caused psycho-motor relaxation in patients (Pawik, et al., 2019). These results are partially attributed to a significant increase in the concentration of beta-endorphins and testosterone in the hypothalamus-pituitary-adrenal axis according to Pawik et al. The study also states that "whole-body cryotherapy significantly reduced the perceived symptoms of depression and improved the patients' functional status" (Pawki, et al., 2019). Short-term exposure to extremely low temperatures causes several neurotransmitter changes within the central nervous system.

The associated decrease in depressive symptoms might be explained by the increase in catecholamine levels in areas of noradrenergic neuron clusters. This occurs when hypothalamic structures are activated which then leads to the release of endogenous catecholamines, ACTH, cortisol, and beta-endorphins (Pawki, et al., 2019). In addition to the mental health benefits, whole body cryotherapy also provides the added benefit of alleviating pain by reducing nerve conduction velocity, inhibiting nociceptors, blocking C fibers, and reducing the release of pain mediators (Pawki, et al., 2019). This is also most likely associated with the reduction of peripheral sensory-motor endings including a partial blockade of the motor endplate and gamma-motor neurons (Pawki, et al., 2019).

Along with adverse mental, emotional, and physical health effects, MS patients often have cognitive problems as well. It is reported that up to seventy percent of MS patients experience cognitive problems (Lincoln, Bradshaw, Constantinescu, Day, Drummond, Fitzsimmons, Harris, Montgomery, & das Nair, 2019). To address these symptoms, cognitive rehabilitation has been created. It is structured as a set of therapeutic activities aimed at retraining the cognitive skills or improving a person's ability to cope with cognitive deficits throughout daily life. The study conducted by Lincoln et al. found that there were some positive effects associated with cognitive rehabilitation in the short term. These benefits were found to include a more positive effect with coping in daily life (Lincoln, et al., 2019).

Conclusion

While MS is a serious and debilitating disease, there is still much that scientists have yet to figure out. Due to the complexity of this disease, on a cellular level, it is more difficult to attain a comprehensive grasp of the pathophysiology of the disease. However, with the information that is known advancements are being made to find ways to help those patients who suffer from MS. While there is not yet a cure, scientists are continuing to search for ways to treat and manage the symptoms associated with MS. Treatments focus on the mind as well as the body of the patient. Symptoms have been targeted at both a cellular level with treatments such as vitamin D as well as a whole-body level with the recent whole-body cryotherapy developments.

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