What is the Effect of Pharmacological and Physiological Treatments on Axon Demyelination of Multiple Sclerosis?

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[ABSTRACT]

In this review, several treatments for Multiple Sclerosis, both physiological and pharmacological, will be analyzed compared in terms of effectiveness. Demyelination of the axon caused by the immune system is the main factor causing Multiple Sclerosis and most physiological treatments such as cognitive behavioral therapy and physiotherapy have little to no effect on such mechanisms. Corticosteroids and plasmapheresis, however, have a more direct impact on the demyelinating mechanism and are therefore more effective in slowing the progression of Multiple Sclerosis.

[INTRODUCTION]

Multiple Sclerosis (MS) is one of the most prevalent central nervous system diseases afflicting young men and women that leads to overall body dysfunction.[1] Multiple Sclerosis has debilitating effects on various functions of the body including motor control, bowel movements, neuronal communication, and optical wellness.[1] Many of those afflicted by Multiple Sclerosis struggle with a variety of symptoms that eventually lead to overall physical disability. The most common symptoms that contribute to this eventual disability are loss of vision, limb tremors, urinary dysfunction, muscular dysfunction, and frequently, cognitive disturbances.[1] This disorder is caused by damage done to the myelin sheath protecting the axon of the affected neuron. MS is when the immune system attacks and destroys the myelinated axon of any given neuron and therefore, contributes to the breakdown of certain parts of the nervous system.[2] This loss of myelin is called demyelination. The demyelination caused by MS contributes to a decreased conductivity of the afflicted axon, which then causes problems in cognitive abilities in Multiple Sclerosis-afflicted people.[3] In addition, the decreased conductivity also lessens the chances of successful neuronal signaling along the axon.[3] Currently, there are several FDA-approved pharmacological treatments to lessen the chances of an MS-related attack but no cure for MS itself.[4]

Currently, it's estimated that approximately one million people in the United States are afflicted with Multiple Sclerosis.[1] Although the cause of MS is uncertain, experimental research suggests that it is caused by both some genetic nuances and environmental factors.[5] Current treatments focus on decreasing the chances of relapse for patients with MS. For example, many people with MS lose nerve function and in response look towards pharmacological treatments that aim to curb nerve inflammation.[6] Many of these pharmacological treatments assist with treating symptoms of MS and some specifically target the demyelination catalyzed by MS. In addition to pharmacological treatments, there are also physiological therapies that aim to curb the effects of MS on the body. The progression of MS is not linear, therefore, many of those who have achieved remission from MS may experience MS flare-ups. The frequency of these relapses depends on the intensity of MS in each case. These relapses can worsen the condition of the immune system or the central nervous system. In response to flare-ups, most

pharmacological treatments curb nerve inflammation or other internal symptoms from the root of the disorder.[6] Relapses can leave lasting effects on the musculoskeletal system and cognitive health as well which may have not been an issue before. Physiological therapies are recommended to relieve symptoms caused by MS that specifically damage motor control and cognitive wellness.

[STRUCTURE OF A NEURON]

The central nervous system is unable to function without the assistance of neurons. Neurons themselves are built from several parts that each have their own assigned role in the overall function of the cell. The cell body, or the soma, is the main part of the neuron which contains genetic information and helps to maintain cell structure. The soma also houses a cell nucleus and numerous organelles.[7] In addition to the soma, the neuron contains dendrites which are spiny, tree branch-like extensions that extend off the soma. The purpose of dendrites is to capture input from other neurons and communicate those signals to their respective neuron.[8] The neuron is surrounded by a cell membrane, which is a phospholipid bilayer with embedded proteins that protect the cell body from the external environment.[9] The part of the neuron that is impacted the most by MS is the axon. The axon is a nerve fiber that branches away from the main cell body in order to conduct nerve impulses from neuron to neuron. The axon is protected by pockets of protein and phospholipids called myelin sheaths.[10] The purpose of the myelin sheath is to help the axon maintain the conductivity of the nerve impulse along its length.[11] Each myelin sheath is equally spaced apart, and each gap between the sheaths is called the Nodes of Ranvier (Figure 1). At each node, the electrical impulse jumps from one end to the next to remain protected by the myelin sheath.[11] Finally the neuron ends with the synapses, which aids in neuronal transmission.[12] When the myelin sheath is not present, the transmission of electrical signals along axons is impaired.[18] Most axonal transections occur during the process of active demyelination.[19]

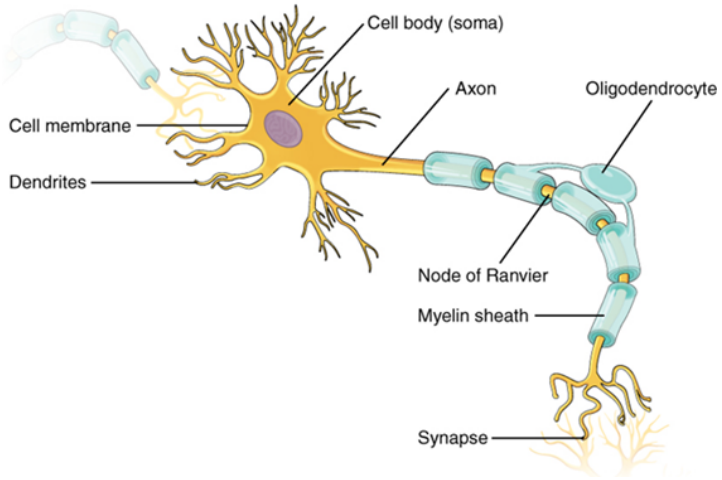

Figure 1. This image shows a neuron in a normal state. The dendrites branch off the main cell body, or the soma. The soma itself is the central part of the cell and houses a nucleus that oversees cell function. The Nodes of Ranvier and myelin sheaths that protect the action potential that travels along the axon are most affected by MS. (https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/v/anatomy-of-a-neuron)

DEMYELINATION

The destruction of the myelin sheaths that protect axons is called demyelination. This phenomenon occurs when the immune system mediates attacks on the myelin sheaths and oligodendrocytes that protect the action potential traveling along the axon.[15] This leads to the continual deterioration of myelin located on the axon, negatively impacting the conductivity of the action potential.[15] Similarly, unmyelination is just as harmful to the axon as demyelinated axons. In a fully myelinated axon, the action potential would jump along each Node of Ranvier, along the axon and be able to experience saltatory conduction, in which the signal would successfully trigger other physiological occurrences. In an unmyelinated axon, saltatory conduction does not occur due to the lack of myelin sheath[16] (Figure 2).

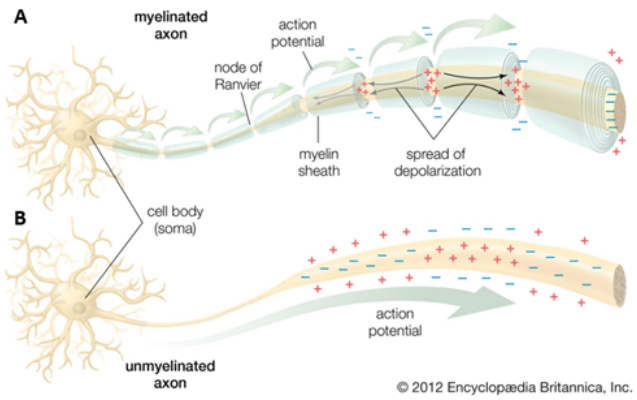

Figure 2. This image shows two diagrams of axons. A) The myelinated axon at the top of the figure has visible myelin sheaths with Nodes of Ranvier. B) The unmyelinated axon at the bottom of the figure does not have any visible myelin protection and is very similar to a demyelinated axon. This disparity between A and B leads to a difference in the conductivity of the action potential. (https://www.britannica.com/science/action-potential#/media/1/4491/66781)

[PROGRESSION OF MULTIPLE SCLEROSIS]

Those diagnosed with Multiple Sclerosis often report several neurological, physical, and cognitive disturbances that often worsen throughout the progression of the disease. One such set of symptoms experienced by those with MS is Charcot's Neurological Triad.[13] Charcot's

Neurological Triad is a set of three symptoms that cause bodily dysfunction through MS. The first is dysarthria; those who suffer from dysarthria as a result of MS experience weakness in the muscles used for speech and struggle with verbal communication.[13] Over 70% of people with MS experience cognitive disturbances, especially affecting their memory, speech, and information processing. This leads to impaired communication skills and difficulties in understanding others' words.[26] Another symptom in this set is nystagmus, which is a vision condition in which the eyes make erratic, uncontrolled movements, causing discomfort to the patient. There are several types of nystagmus that individuals with MS may experience such as gaze-evoked nystagmus, acquired pendular nystagmus, upbeat, downbeat, and torsional nystagmus, and positionally induced nystagmus.[27] In the brain stem, the immune system attacks and destroys myelin-protecting axons in a process called demyelination. The demyelination of the medial longitudinal fasciculus (MLF) in the midbrain results in internuclear ophthalmoparesis (INO), a condition very similar to nystagmus[27]. The most common type of nystagmus caused by MS is acquired pendular nystagmus, in which the immune system damages neuronal function, leading to demyelinated visual pathways. The existence of these pathways decreases the speed at which cell signals can travel from one neuron to the next, therefore, leading to nystagmus.[27] The last symptom is called intention tremor, in which victims suffer from involuntary, rhythmic muscle contractions that occur in a voluntary manner.[13] This type of tremor becomes apparent during target-directed or visually-guided movement.[17] Diagnosis of MS typically includes an analysis of a Magnetic Resonance Imaging (MRI) scan in which visible lesions on the brain signify large amounts of myelin caused by white matter plaques[14] (Figure 3).

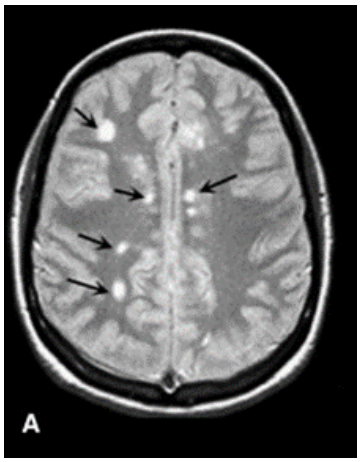

Figure 3. The figure shows an MRI scan in which lesions and white matter build-ups are visible. These white matter plaques are indicative of an abnormality. (https://pubmed.ncbi.nlm.nih.gov/17015227/)

The progression of MS varies for each type of disorder. However, MS has been categorized into four main types: Clinically isolated syndrome (CIS), Relapsing-remitting MS (RRMS), Secondary-progressive MS (SPMS), and Primary-progressive MS (PPMS)[13] (Figure 4). In CIS, the patient may experience neurological symptoms linked to MS that last for 24 hours, however, the patient is not considered to be diagnosed with MS until undergoing an MRI scan. Someone

who experiences CIS and then has an MRI which such lesions visible in the scan has a very likely chance of being diagnosed with MS and consequently progressing to RRMS[14].

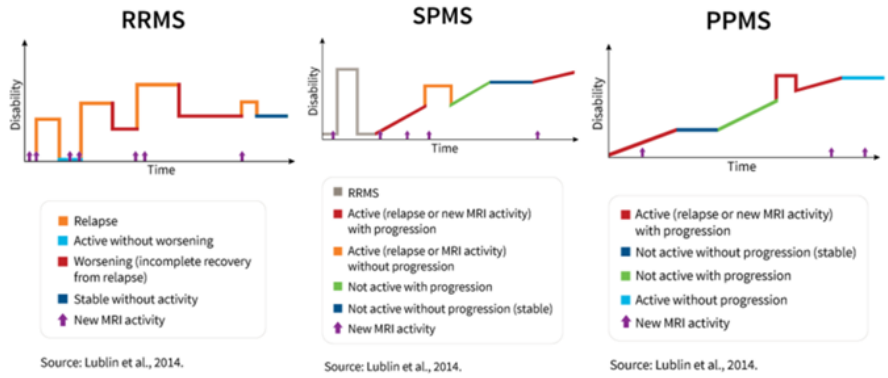

Figure 4. The figure above has three graphs depicting the progression rates of three types of Multiple Sclerosis (MS): Relapsing-remitting MS (RRMS), Secondary-progressive MS (SPMS), and Primary-progressive MS (PPMS). Based on the graphs, those with RRMS experience more frequent relapses in MS compared to those with SPMS or PPMS. In all three cases, oftentimes there is relapse and renewed activity in the brain due to MS. (https://www.nationalmssociety.org/What-is-MS/Types-of-MS)

[PHARMACOLOGY/TREATMENTS]

There are several treatments to inhibit the debilitating effects of MS on the brain and body. Corticosteroids are one of the most established treatments used to treat MS relapses and help curb nerve inflammation.[30] Although corticosteroids provide short-term relief from sudden MS attacks, there is less successful in providing a long-term solution for individuals with MS.[30] The mechanisms behind corticosteroids are immunosuppressive; the treatment slows down the destruction of myelin and the central nervous system by the immune system.[31] Corticosteroids are effective in directly impeding the demyelination caused by MS and slowing down immune system activity that causes harm to the central nervous system.[31]

Cognitive Behavioral Therapy (CBT) is a treatment for MS often used in lieu of pharmacological treatment.[28] During CBT, individuals with MS will engage in talk therapy with a psychologist or therapist, to help improve their mental condition. Mental illness is a very common symptom experienced by individuals with MS, with the majority experiencing depression or anxiety. Similarly, those with MS also experience mild to severe cognitive dysfunction, such as dysarthria. While CBT has no direct effect on demyelination or any of the internal mechanisms behind MS, it can help curb the effects of MS on the mind.[28]

Based on the data from a clinical trial done in January 2020, individuals with MS who received standard healthcare in addition to CBT showed a significant change in symptomatic depression as compared to those with MS who received standard healthcare.[29] Specifically, one group of individuals with MS received CBT plus standard care (CBT/SC) whereas the other group of individuals with MS received MS-related education plus standard care (ED/SC). Analysis of the data is based on three scores: the pain severity score (PSS), depression score (DS), and treatment credibility score TCS).[29] Before either treatment was provided, a baseline score was taken to measure the effectiveness based on the posttreatment scores. In the CBT/SC group, the difference in baseline and posttreatment PSS was 0.33 ± 0.44 (Figure 5). In the ED/SC group, the difference in baseline and posttreatment PSS was 0.71 ± 0.32. In the CBT/SC group, the difference in baseline and posttreatment DS was 2.01 ± 0.16. In the ED/SC group, the difference in baseline and posttreatment DS was 5.47 ± 2.65. In the CBT/SC group, the TCS was 42.78 ± 7.81. In the ED/SC group, the difference in baseline and posttreatment TCS score was 37.75 ± 5.47.[29] Based on the data gathered from the trial, it can be concluded that although CBT does not have a significant improvement in the bodily pain caused by the symptoms of MS, it does provide a great improvement in the mental condition of the individuals affected. In general, individuals with MS in the CBT/SC group felt that their treatment was more credible and effective compared to the results of the ED/SC group.

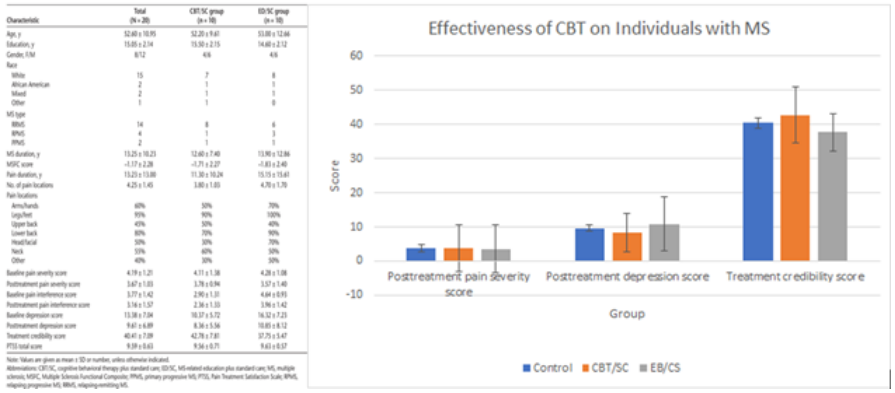

Figure 5: The figure is a chart presenting the data gathered from a clinical trial executed to test the effectiveness of CBT in individuals with MS. The figure also has a bar graph outlining the relevant data to the analysis.
(https://meridian.allenpress.com/ijmsc/article/22/1/8/12033/Cognitive-Behavioral-Therapy-for-the-Management-of)

One of the more verified forms of physiological treatments for MS is physiotherapy. Physiotherapy is a form of therapy that utilizes physical activity and exercise involving the arms, legs, and certain parts of the body. This treatment helps people who have limited motor control due to injury or disability, including those with MS. Exercise therapy, which is a subcategory of physiotherapy, can help those with MS with symptoms relating to the neuromuscular system and motor control.[22] Based on studies regarding the efficacy of exercise therapy, there is a significant improvement in motor control, cognitive reasoning, and mental illness when endurance training is executed in a clinical setting rather than a home setting.[23] [24] [25] The improvements in muscle

strength can be attributed to the guidance of medical professionals in a clinical setting. However, regardless of the setting, it is shown that physiotherapy can provide significant improvement, not only in regaining control of the muscles, but also the mental condition of the individual with MS.

It is shown that physiotherapy does not alter any physiological symptoms caused by MS such as the destruction of myelin or nerve inflammation but helps improve and maintain current body function.

[CONCLUSIONS]

There are several pharmacological and physiological treatments in place to both, directly and indirectly, fight the damage caused by MS. It is known that corticosteroids are more effective than clinical behavioral therapy and physiotherapy in directly impeding the demyelinating mechanisms caused by the immune system. However, clinical behavioral therapy is far more effective than corticosteroids in that it significantly improves the mental condition of individuals with MS. MS is a debilitating disorder that can permanently damage both the mental and physical; conditions of those who have it. Although many individuals can achieve remission, there is a high chance that they may eventually experience several relapses based on their progression of MS. Individuals who have RRMS experience constant relapse and worsening symptoms in the time between each relapse. Similarly, those with SPMS experience RRMS, and then an increase in the worsening of their symptoms. Due to the demyelinating mechanism of MS caused by the immune system, there is a distinct lack of myelin sheaths on the axons of affected neurons. This negatively impacts the speed and success of an action potential traveling along the neuron. The real issue with MS is the fact that there is no known cause or cure. This lack of information causes a distinct gap in research and treatment options for those with MS. Currently, clinical trials are being conducted testing new treatments for MS such as hematopoietic stem cell therapy, to help regain the destroyed myelin in an individual with MS. As more experimental treatments are being approved by the Food and Drug Administration, individuals with MS can get the treatment to help relieve their symptoms and avoid relapse.

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