MS Fitness Specialist

Module 4

MS Pathophysiology and Affected Anatomy

Learning Objectives

1. Learn the pathophysiology of MS within the Brain
2. Learn the pathophysiology of MS within the Spinal Cord
3. Learn the pathophysiology of MS within the Optic Nerves

Chapter Four
Pathophysiology of Multiple Sclerosis and Affected Anatomy

Pathophysiology is a convergence of pathology with physiology. Pathology is the medical discipline that describes conditions typically observed during a disease state; whereas physiology is the biological discipline that describes processes or mechanisms operating within an organism. Referring to MS, the physiology refers to the different processes that lead to the development of the lesions and the pathology refers to the condition associated with the lesions. Nerve damage can occur anywhere in the spinal cord and/or brain, which is why MS symptoms may vary from person to person. Symptoms will occur depending on the location and severity of the white blood cell attack.

The nature of unmanaged multiple sclerosis (MS) produces recurrent attacks on the brain and spinal cord, which results in focal inflammatory lesions that can be visualized with magnetic resonance imaging (MRI). Unfortunately, 80-90% of lesions that form are silent and cannot be detected on the neurological examination, which exposes patients to a greater burden of disease and an increased risk of dysfunction. Furthermore, depending on which neurological components are affected, patients are at heightened risk for a broad suite of deficits, including weakness, spasticity, sensory loss, and cognitive issues. As the disease progresses, symptomatology may include bladder disruption, walking abnormalities, tremor, and fatigue. (See Figure 4.1)

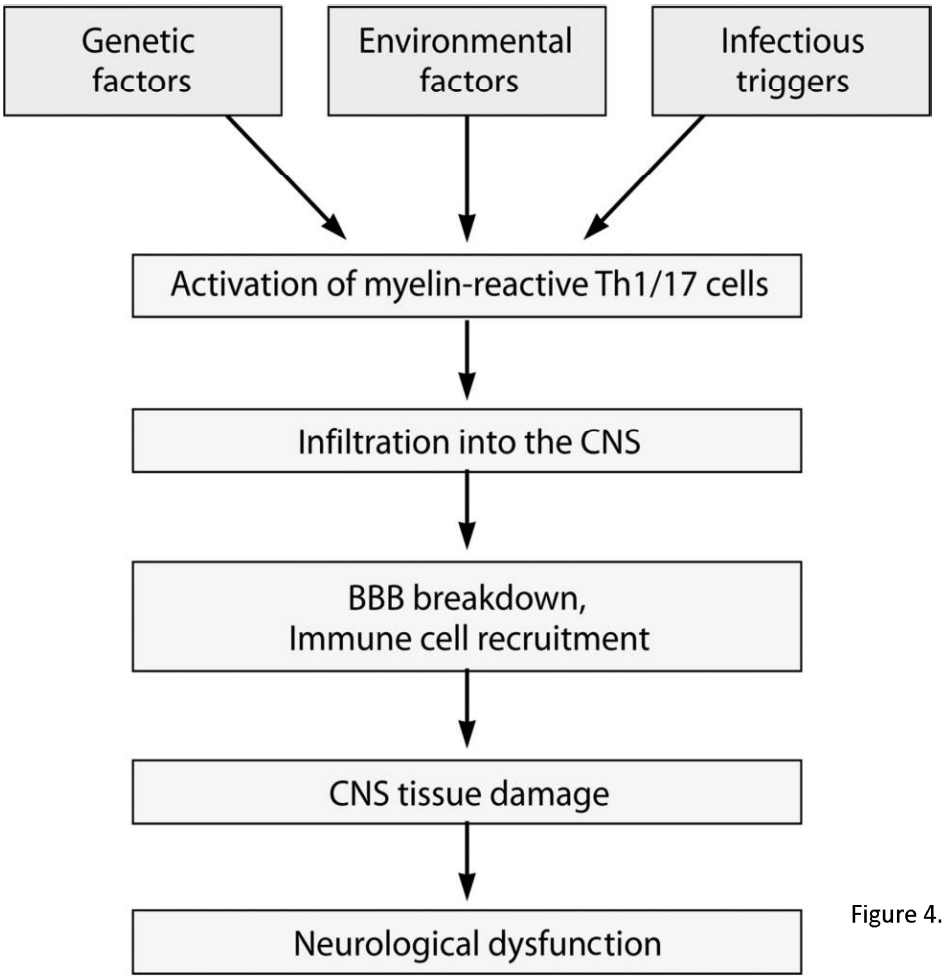
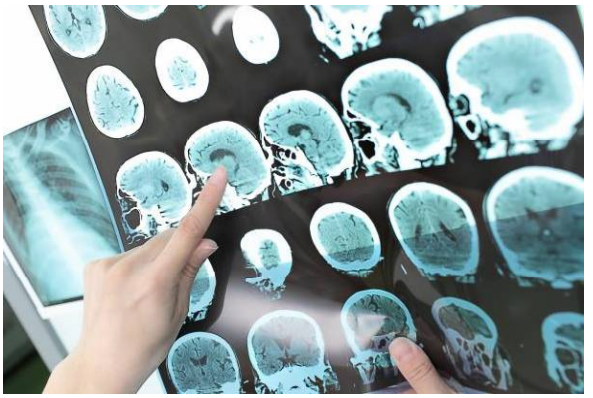


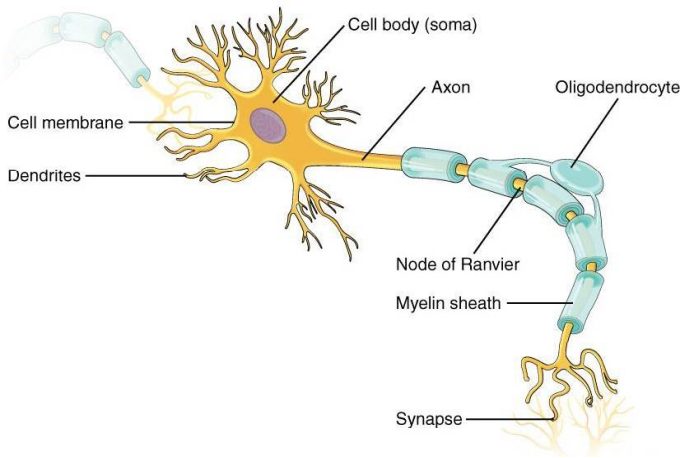
Figure 4.1

MS and the Brain



When tracking the pathology of MS, one can start at the brain. Virtually everyone with multiple sclerosis (MS) has signs of lesions in the brain, as shown by magnetic resonance imaging (MRI) scans. According to the National Multiple Sclerosis Society, about 95 percent of people with MS show brain lesions at the time of their diagnosis. The exterior portion of the brain is called the gray matter and the interior portion is called the white matter. The brain is composed of about 86 billion neurons which make up both the gray and white matter.

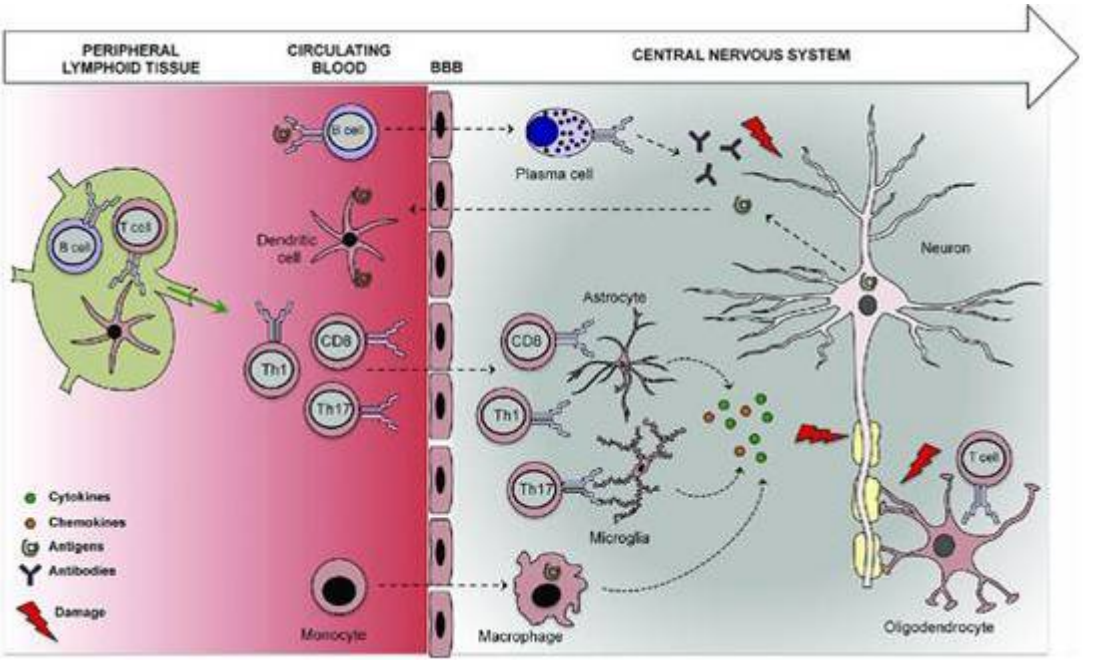
A neuron is composed of dendrites, the cell body (soma), the axon, and the axon's myelin. Also, within the neuron is the node of ranvier, oligodendrocyte, and the axon terminals. The dendrites and the cell body have a cell membrane, and that's really what gives the gray matter its color. The axon also has cell membrane, but the axon also has myelin, and it's the myelin that gives the white matter its color. Therefore, the dendrites and the cell body compose the grey matter, and the myelin that's wrapped around the axon composes the white matter. When one has MS, the lesions form throughout the white matter of the brain. This is evident because of the damage that the myelin incurs which makes up the white matter of the brain. If a person develops multiple sclerosis, one can see lesions when the immune system mistakenly recognizes the myelin as foreign and attacks it.



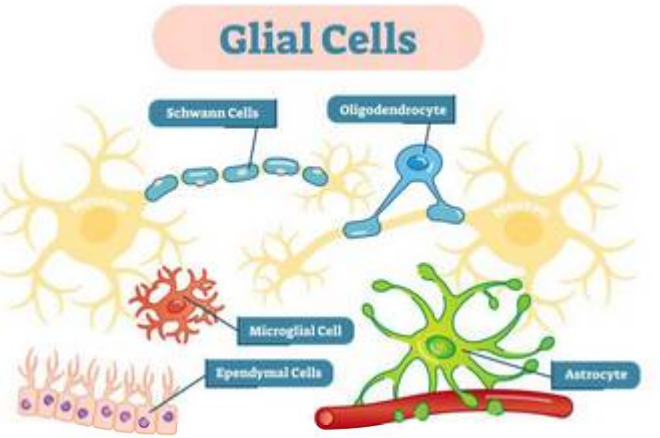
So how does the immune system actually make its way into the brain? The brain needs to receive massive nourishment from blood vessels. Ordinarily, the immune system travels through blood vessels. Coincidentally, the immune system is also traveling through the same blood vessels that the brain gets its nourishment. Outside each blood vessel are endothelial cells linked tightly together at what is called tight junctions. These linked endothelial cells outline each blood vessel by sitting on a foundation called the basement membrane. Together, the endothelial cells and the basement membrane compose what's called the blood brain barrier (BBB). The BBB is an important structure because it stops potentially harmful foreign bodies from entering the brain, i.e. viruses. The BBB also stops the immune system from entering the brain. The two main immune system cells that create damage to the myelin are the T Cells and B Cells. With a healthy BBB, these cells would not be able to enter the brain. However, if one has MS, the T Cells would be able to squeeze by the endothelial cells and break through the basement membrane. At that point, the T Cells can actually make their way into the brain which is uncharted territory or an unfamiliar environment for the T Cells.

Once the T Cell is in the brain and does not recognize a particular protein or distinct feature on the surface of the myelin, it then attacks the myelin thinking that it is a foreign object. In fact, it is the T-Cell that is the foreign entity in the brain. Once the T Cell does not recognize that part of the myelin, it'll set off an alarm and release chemicals called cytokines. Cytokines will promote the degradation of the BBB, so now the BBB becomes more permeable to more T Cells. The cytokines can also recruit

other immune cells like B Cells. Now B Cells are able to enter the BBB making antibodies for the myelin. Once B Cells make antibodies for the myelin, the myelin is targeted for further degradation. Macrophages which are a type of white blood cell of the immune system may be present as well which also physically degrade myelin. In addition, cytokines can actually be toxic to the myelin; therefore, cytokines can themselves degrade myelin leading to massive degradation of the myelin. This breaking down the BBB leads to a cluster of immune cells around a part of the brain which is called neuroinflammation.



It is thought to be inflammation that triggers the immune system to activate against the body. During a period of inflammation, attacking white blood cells can also kill glial cells. Glial cells surround nerve cells and provide support and insulation between them. They keep nerve cells healthy and produce new myelin when it's damaged. However, if glial cells are killed, they're less able to keep up with repair. Some of the new research for an MS cure is focused on transporting new glial cells to the site of myelin damage to help encourage reconstruction.



Nerve fibers also form scar tissue in areas of myelin damage. This tissue is stiff, hard, and blocks or obstructs the flow of messages between nerves and muscles. These areas of damage are typically called plaques or lesions and are a major signal of the presence of MS. In fact, the words "multiple sclerosis" mean "multiple scars."

This degradation seems pretty daunting; however, the brain actually does have a way of repairing itself. The brain also contains cells called oligodendrocytes. When myelin is degraded away, the oligodendrocyte will begin the process of remyelination. The rebuilding of the damaged myelin or the brain's natural healing process is called remyelination. However, as time goes on, that remyelination actually becomes less and less effective. The oligodendrocyte will continue to try to remyelinate the axon to the best of its abilities, but it'll ultimately just become overwhelmed by the power of the immune

system. The immune system will be persistent. The T-cells will just constantly release cytokines. The B-cells will always be around to release antibodies, and the macrophages will always be around to phagocytize or destroy the myelin. Ultimately, the remyelination process is constantly being overpowered by the immune system.

A current hypothesis states that with the progression of the disability, which marks the transition from RRMS to SPMS, occurs when ongoing irreversible tissue injury exceeds a critical threshold beyond which the nervous system can no longer compensate. It is thought that at this point that MS has primarily transitioned to a neurodegenerative condition with neurologic deterioration independent of ongoing inflammation, although superimposed inflammation can continue to cause additional injury. An important implication of this hypothesis is that the accumulation of irreversible tissue damage limits the potential for anti-inflammatory disease modifying therapies (DMTs) when used in the progressive stage of the disease. To be maximally effective, DMTs should be started early in patients with RRMS before permanent disability develops. Overall, an incomplete understanding of progressive MS pathogenesis has slowed the development of effective therapies and requires further inquiry. (Hersh and Fox, 2018)

MS and the Spinal Cord

The brain isn't the only area where lesions can develop. MS can also attack the spinal cord. Because finding these lesions involves more-elaborate imaging tests, spinal cord lesions in MS are studied less often, and many people with MS are not as aware of the role these lesions may play in the disease process.

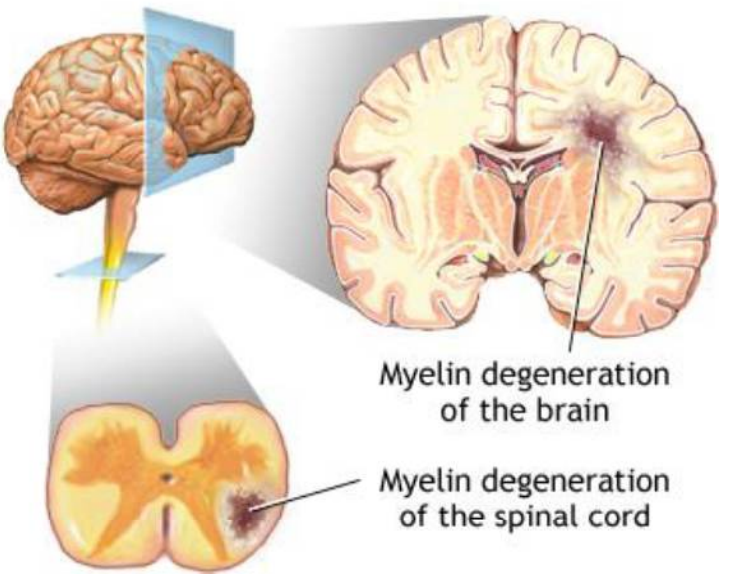
Spinal cord lesions in MS most likely form through the same mechanisms as those in the brain. White blood cells escape from the bloodstream, go through the blood–brain barrier, and get into the brain tissue. These cells cause inflammation mostly in the white matter — but also the gray matter — of the brain and spinal cord. Toxic chemicals produced by these cells strip the myelin insulation off the connections between nerves. The resulting lesions tend to be 1 to 2 centimeters in length or diameter.

Spinal MS is often associated with concomitant brain lesions; however, as many as 20% of patients with spinal lesions do not have intracranial plaques. Contrary to the white and gray matter in the brain, white and gray matter can both be affected in the spine. No strong correlation has been established between the extent of the plaques and the degree of clinical disability. Spinal cord atrophy is most relevant to progressive forms of MS (primary progressive and secondary progressive), in which it closely links to physical disability. Spinal cord lesions are more common in men, with later onset than in other forms of MS.

It's not uncommon with MS, however, to discover multiple silent brain lesions on magnetic resonance imaging (MRI) and find a person afflicted with only spinal cord problems due to the disease. Sometimes the symptomatic spinal cord lesions are more difficult to identify on scans than some clinically quiet but MRI evident brain lesions. About 90% of those with MS find that their spine is involved at some point.

As a central relay station for sensation, movement, balance and coordination for so much of the body, the spinal cord is crucial for limb function and the muscles involved in respiration.

Many with spinal cord problems and MS have numbness on one side of the body and weakness on the opposite side. They may lose standing balance or have a gait problem characterized by ataxia, such as the inability to walk a straight line. Paralysis and loss of sensation of part of the body are common. This can include total paralysis or numbness and varying degrees of movement or sensation loss.



Spinal cord lesions due to MS in the upper spine or neck (cervical region) can cause cape like sensation loss in both shoulders and in the upper arms. Quadriplegia is the great danger in cervical region MS. Anesthesia in a band like distribution around the trunk can be experienced in those with mid spinal cord inflammation and carry a chance that they could become paraplegic. All of those with MS in the spinal cord can potentially have bladder or bowel control problems. However, those with spinal cord MS of the lumbar region (the spinal cord ends at the beginning of the lumbar spine) can have symptoms dominated by retention of urine.

For those with MS, pain below the level of spinal cord involvement and sexual problems are the greatest complaints, even when there are motor difficulties in the limbs. Spinal cord induced pain is typically excruciating and often shoots down the spine (Lhermitte's Sign) or to the limb that is involved due to spinal cord damage.

Erectile dysfunction is common in men with spinal cord MS. Orgasmic and fertility problems can strike both sexes with cord lesions. Spasticity is another major problem for those with spinal cord problems of all types. The increase in muscle tone from spasticity can also be painful and movement limiting.

Medication and certain devices such as spinal cord stimulators can be valuable for many of these issues. Dyssynergia (movement incoordination) involves bladder muscle difficulties due to spinal cord MS. The incontinence and bladder emptying problems that results can be treated with medication as well.

Therapeutic research in spinal cord disorders including MS involves consideration for the transplantation of stem cells, the injection of nerve and brain derived growth factors, and medicines that can provide the energy source for spinal cord regrowth.

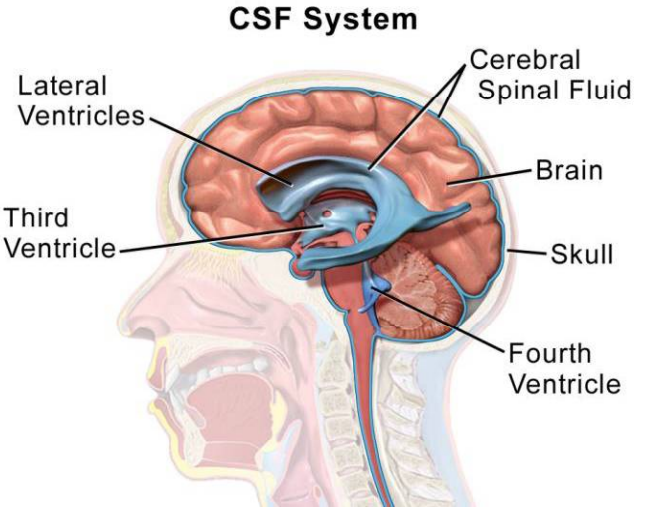
In addition, specialized conditioning and strengthening programs are critical in the rehabilitation patients with spinal cord problems.

In MS, an acute spinal cord attack is called Myelitis. Immunomodulator (medications used to help regulate or normalize the immune system) and steroid therapy is often utilized with success with a

dramatic reversal possible. If the MS patient has persistent neurological signs and symptoms from the spinal cord inflammatory attack, they are said to have a myelopathy.

Often the severity of MS is very much related to how bad the myelopathy is. Progressive MS can be characterized by spinal cord shrinkage (atrophy) over time. Reversal of this aspect of advancing MS remains a great challenge for ongoing research. Defeating the immunological process that triggers both the brain and spinal cord damage in MS is the best defense against the terrible effects of spinal cord involvement in demyelinating disease.

Cerebrospinal fluid (CSF) is a clear, colorless liquid that surrounds the brain and spinal cord. While the primary function of CSF is to cushion the brain within the skull and serve as a shock absorber for the central nervous system, CSF also circulates nutrients and chemicals filtered from the blood and removes waste products from the brain. In MS, damage to myelin causes certain types of proteins to be released into the spinal fluid. When these proteins are identified in the spinal fluid, but not in the blood, MS is thought to be one of the possible diagnoses. Spinal fluid is obtained through a lumbar puncture (also known as a spinal tap).



The CSF of people with MS usually contains:

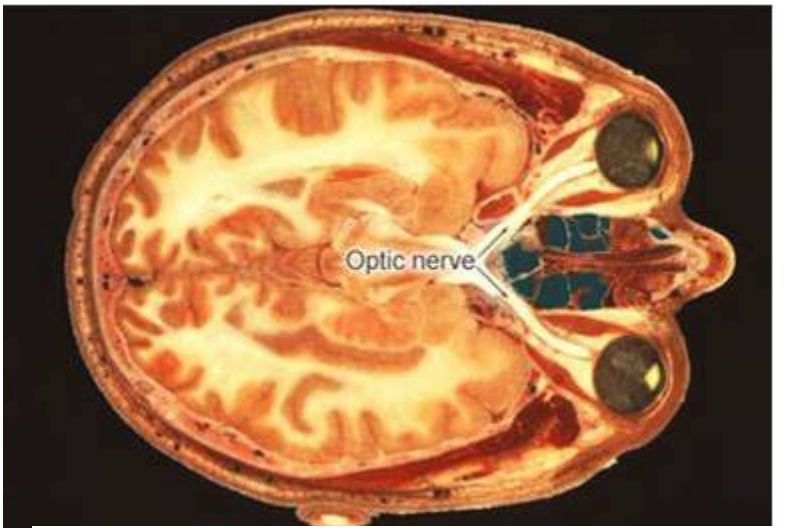
- A specific group of proteins called oligoclonal bands
- Elevation of the level of protein

These findings indicate an abnormal immune response within the central nervous system, and may be suggestive of MS. It is important to know that an abnormal immune response in the CSF is found in a number of other diseases, so the test is not specific for MS. In people with a confirmed diagnosis of MS, 5-10% do not show abnormalities in the CSF. Therefore, CSF analysis by itself cannot confirm or exclude a diagnosis of MS. The results are used in combination with the history, neurological examination, MRI and other tests to help make an accurate diagnosis.

MS and Optic Nerves

Optic neuritis (ON) is a common manifestation of multiple sclerosis (MS), and refers to an acute inflammation of the optic nerve (a bundle of nerve fibers that transmits visual information from your eye to your brain). It can be the initial demyelinating event in up to 20% of patients and occurs in almost half of patients with MS. ON associated with demyelinating disease is generally characterized by acute to subacute, painful, and monocular vision loss. Vision typically worsens over hours to days (not months), and recovery is expected to begin within 1 month of symptom onset. The pain that occurs with optic neuritis is usually ocular, retroocular, periorbital, or a frontal headache. This pain is generally exacerbated with extraocular movements and occurs in most patients with typical ON.

Furthermore, axonal damage may occur in some cases and this damage can be identified as a thinning of the retinal nerve fiber layer (RNFL) using computerized imaging technologies such as optical coherence tomography (OCT). OCT is a noninvasive imaging technique that enables high-resolution quantification of retinal structures and can detect subclinical changes in MS patients as well. RNFL and ganglion cell/inner plexiform layer (GCIP) thinning has been demonstrated in individuals with MS, not only in those with previous ON but also in those without it.



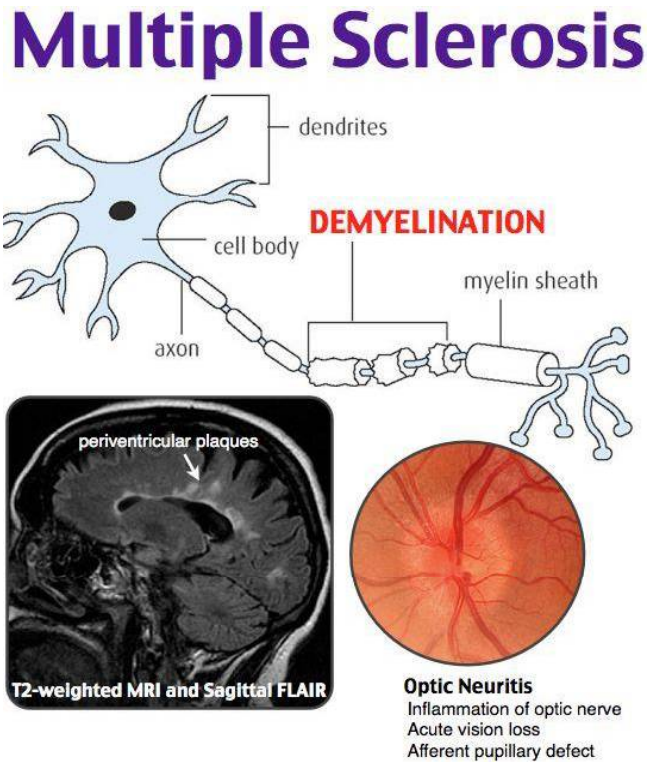
The exact cause of optic neuritis is unknown. It's believed to develop when the immune system mistakenly targets the substance covering the optic nerve (myelin), resulting in inflammation and damage to the myelin. Normally, the myelin helps electrical impulses travel quickly from the eye to the brain, where they're converted into visual information. Optic neuritis disrupts this process, affecting vision. In people with optic neuritis, the risk of developing multiple sclerosis following one episode of optic neuritis is about 50 percent over a lifetime. The risk of developing multiple sclerosis after optic neuritis increases further if an MRI scan shows lesions on the brain.

Other factors that have been linked to the development of optic neuritis include:

- Infections. Bacterial infections, including Lyme disease, cat-scratch fever and syphilis, or viruses, such as measles, mumps and herpes, can cause optic neuritis.
- Other diseases. Diseases such as sarcoidosis and lupus can cause recurrent optic neuritis.
- Drugs. Some drugs have been associated with the development of optic neuritis. They include quinine and some antibiotics.

Risk factors for developing optic neuritis include:

- Age. Optic neuritis most often affects adults ages 20 to 40.
- Sex. Women are much more likely to develop optic neuritis than men are.
- Race. In the United States, optic neuritis occurs more frequently in whites than it does in blacks.
- Genetic mutations. Certain genetic mutations might increase the risk of developing optic neuritis or multiple sclerosis.



Complications arising from optic neuritis may include:

- Optic nerve damage. Most people have some permanent optic nerve damage after an episode of optic neuritis, but the damage might not cause symptoms.
- Decreased visual acuity. Most people regain normal or near normal vision within several months, but a partial loss of color discrimination might persist. For some people, vision loss persists after the optic neuritis has improved.
- Side effects of treatment. Steroid medications used to treat optic neuritis subdue the immune system, which causes the body to become more susceptible to infections. Other side effects include mood changes and weight gain.