Methods of Diagnosis and Treatment of MS Disease Based on a Clinical Trial: The Original Article

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Abstract
Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system and causes disabilities in various organs, including eyes and muscles. Magnetic resonance imaging (MRI) is often used to diagnose and determine MS disease lesions in the brain and spinal cord. Diagnosing MS lesions in MRI images is very difficult due to the variation in lesion location, size, shape and anatomy between different individuals. There are methods to evaluate, diagnose and treat MS lesions. These methods detect and segment from MRI scans taken from the brain. Since the manual diagnosis and analysis of these lesions from brain images is expensive and time-consuming and also has human errors, this article reviews the methods proposed in recent years. Although these articles have good accuracy in recent years, there is a need for significant accuracy in the field of health. According to the recent advances, a completely robust approach for the classification of MS lesions has not yet been presented as a standard for clinical practice.
Keywords: *MS, MRI, Inflammatory Disease, Imaging.*

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Introduction

MS or Multiple Sclerosis is a chronic and progressive autoimmune disease that affects the central nervous system. MS occurs when the immune system attacks myelin [1-3]. Myelin protects nerve fibers in the brain and spinal cord. This event is known as demyelination and causes communication problems between the nerves and the brain. It means that the myelin covering the nerve is destroyed. Finally, it can cause nerve damage [4]. This disease can cause different symptoms for the patient. In most cases, at the beginning, the complications of MS occur and go away. Over time, some of these symptoms persist and can cause a person's disability [5-7]. Although there is no specific cure for this disease, medications and treatment of MS in various ways can reduce the number of relapses and associated symptoms and disabilities [8].

Diagnosis of MS by imaging by MRI is the best method to help diagnose this disease. This method can be used repeatedly to track the progress of MS disease, determine disease status and drug performance, although the doctor may not use this method widely [9-11]. In MRI, a powerful magnetic field and computer-generated radio waves are used to measure the amount of water in areas of the body such as tissues, nerves, organs, and bones, and it is the most non-invasive and sensitive imaging method available (Figure 1). It is from the brain, spinal cord and other parts of the body. MRI scanning equipment creates a magnetic field around the body that is strong enough to redraw a small but significant percentage of water molecules in tissues [12].

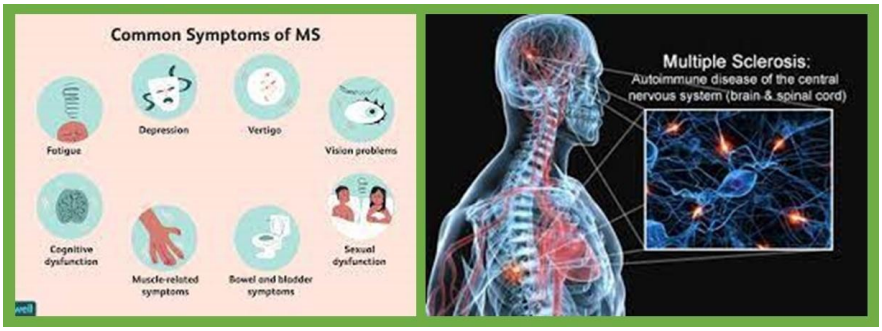

Figure 1. Multiple sclerosis

After aligning in the direction of this field, radio waves are then passed through to break this new alignment and allow the water molecules to relax as the waves stop. When the water molecules relax and resume their original alignment, their protons release resonance signals, then the computer processes D-3 images or D-2 slices of the tissue. Discrimination in water molecule response between healthy and deliquescent nerve fibers is effective in MS diagnosis and tracing. Depending on the type of scan used, the disturbances are in the form of bright or darker white spots in the images obtained from the scan [13].

Causes of MS

This disease is an autoimmune disorder in the human body. This condition means that the cells of the body's immune system, which normally attack bacteria, viruses and other such things, attack the body itself in this disease [14-16]. When the disease is activated, parts of the immune system, mostly called T cells, attack the myelin sheath of the nerve, which covers the nerve fibers in the brain and spinal cord (Figure 2). These conditions cause small inflammation spots and injuries on this sheath. Certain factors probably cause the immune system to activate and function incorrectly. A theory proposed in this regard pointed to the presence of a viral agent or other environmental factors. These factors can affect the condition of some people whose immune system has special genetic conditions and cause this disease [17].

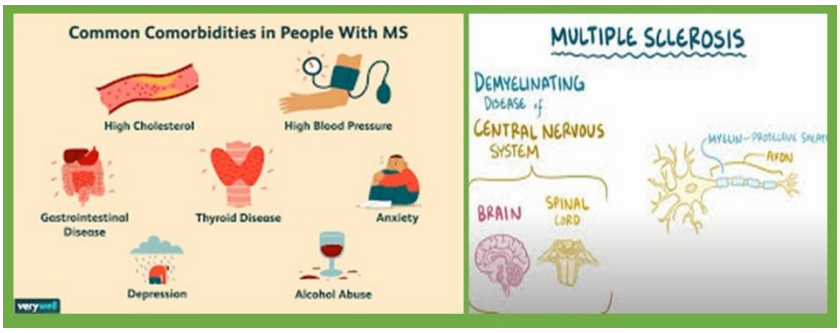

Figure 2. How MS Can Affect Life Expectancy

With the disease, the inflammation created around the shell or membrane of the nerve makes the damaged nerve fibers unable to perform their proper function, and thus the symptoms of the disease progress. When the inflammation caused by this sheath is recognized by the body, the damaged myelin sheath may be repaired and healed by the body [18-20]. In this way, nerve fibers start their activity again. However, inflammation or re-injury can cause small injuries (sclerosis) in the myelin membrane and permanently damage the nerve fibers. In some people with this disease, several small areas of injury are created in the brain and spine. These injuries are sometimes called plaques [21].

Symptoms of MS

This disease can bring a wide and diverse set of MS symptoms to a person. Many people in this condition only face a limited number of these symptoms, and the probability of seeing all of these symptoms in one person is small and insignificant. The symptoms of this disease are usually unpredictable [22]. MS disease can relapse at any time and its symptoms are different each time it relapses. Symptoms during relapse depend on the part or parts of the brain or spine that are affected by the disease [23]. In this condition (Table 1 & 2), the patient may have only one symptom in one part of his body, or he may see multiple symptoms in different parts of his body. These symptoms are caused because the damaged nerve fibers stop working properly [24].

Table 1. Distribution of MS variables in people

Test result	Type MS	treatment plan	
X=35.325 P=0.901	79	NO.	Test 1
	46	NO.	Test 2
	75	NO.	Test 3

Table 2. Average, median and standard deviation of duration variable

The result of the Mann-Whitney test	NO.		Group	Variable
Z=0.687 P-Value=0.442	50.36	Average	Test 1	Time
	17.20	Standard Deviation		
	20.96	Average	Test 2	
	10.34	Standard Deviation		
	28.68	Average	Test 3	
	22.46	Standard Deviation		

The most common symptoms of this disease are as follows:

1. Vision problems: The first symptom of this disease for about one out of four patients is visual impairment. In this case, pain is felt behind the eyes and sometimes the sick person loses a part of his vision. This condition usually affects only one eye. Other eye symptoms in this condition can include blurred vision or double vision [25].

2. Muscle spasms and convulsions: In this situation, some muscles may experience spasms. Spasms are usually caused by damage to the nerves that carry brain messages to these muscles. Some muscles may be shortened (contracted) and tightened in this state, making it difficult to move them. In terminology, this condition is called a seizure [26].

3. Pain: People with MS experience two main types of pain. Neuropathic pain is the first type of pain that the patient experiences due to damage to the nerve fibers. This condition can cause shooting pain or burning sensation on different parts of the skin. In addition, this damage may cause hypersensitivity (Figure 3) of the skin in some parts of it. Another type of pain is usually musculoskeletal pain, which can be seen in damaged muscles due to spasms or seizures [27].

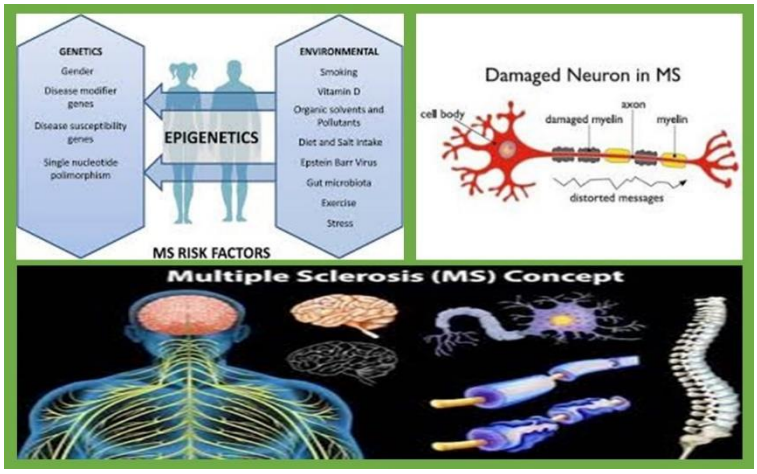

Figure 3. Disease Modifying Therapy for Multiple sclerosis

4. Fatigue: Fatigue is another symptom of this disease, such that the amount of fatigue is more than what is expected after doing sports or physical activities. This fatigue can even affect the patient's balance and concentration [28].

5. Emotional problems and depression: In this condition, the patient may simply laugh or cry without any reason. In addition, people with these disease face symptoms of depression or anxiety in some stages of the disease [29].

Other symptoms of this disease can include the following:

- Numbness or burning in different parts of the skin, which is the most common symptom of the first recurrence of the disease.
- Weakness or paralysis in some muscles that can have a negative effect on a person's movement ability.
- Creating problems related to maintaining balance and coordination of body parts.
- Difficulty in focusing and paying attention.
- Trembling or spasm of some muscles.
- Confusion and distraction.
- Difficulty urinating.
- Inability to have sexual intercourse in men.
- Difficulty with speaking.

The purpose of MRI for MS

When a doctor suspects MS and orders an MRI, he looks for two things:

1. Any other type of disorder that could rule out MS and point to a different diagnosis, such as a brain tumor, should be investigated [30].

2. It also looks for evidence of demyelination.

Advantages of doing MRI

- Studies have shown that brain MRI is the best type of brain imaging in people with symptoms of MS.
- The diagnostic power of MRI in MS is very high and the imaging method is very sensitive and suitable.
- MRI can show more lesions in the brain and spinal cord than CT-Scan and MS plaques can be seen well with it.
- MRI makes the diagnosis of MS easier and monitors the disease process more.

Types of MRI

An MRI provides different information, depending on how it is performed. A variety of MRI and radiology tests are performed to diagnose the disease, including:

- **T1-weighted brain MRI:** Contrast material is used to detect active inflammation, while new lesions or growing lesions are also examined. At the same time, dark areas are also shown, which indicate possible permanent damage.
- **T2-weighted brain MRI:** This scan detects all new and old lesions and helps to measure the overall disease process [31].
- **Fluid attenuated inversion recovery (FLAIR):** Since it is a sensitive scan, this test can detect brain lesions.
- **Spinal cord MRI:** This test detects spinal cord lesions (Figure 4).
- **Computed tomography (CT) scan:** This scan includes radiation that detects demyelination areas, but its details are less than MRI.

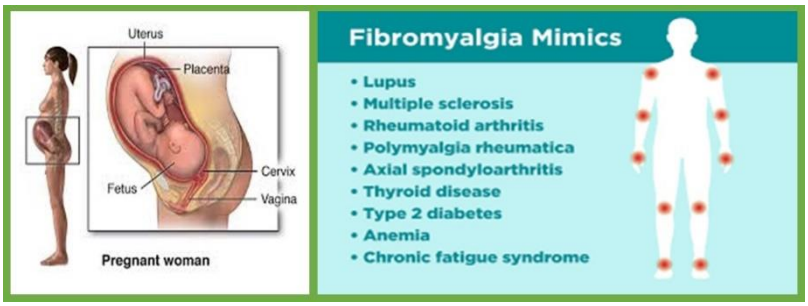

Figure 4. Fibromyalgia Misdiagnosis

How to do MRI

To perform an MRI to diagnose MS, the patient is placed on the examination bed and a headphone is used to reduce the noise caused by the machine during imaging. If there is a need to inject a contrast material that helps identify abnormalities in certain parts of the body in the images, the nurse or technician injects this material into the patient's vein. During this procedure, the patient goes inside the machine and imaging of certain areas is done [32].

Preparing for the MRI test

You must remove all jewelry before entering the MRI department. If you have any metal clothing (including zippers or metal buttons), you will be asked to remove them or change into hospital clothing. You will need to lie in the MRI machine (which is open on both sides) for about 30-45 minutes during the test. Some devices may be used depending on the patient's condition [33].

Be sure to tell your doctor if you have the following:

- Metal implants;
- Heart rate regulator;
- Tattoos or tattoos;
- Injected drugs;
- Artificial heart valves;
- A history of diabetes;

- And any other conditions you think may be relevant.

Complications of MRI

A specific complication of the magnetic field resulting from MRI has not yet been discovered in the body; But in people who have a metal device in their body (such as platinum or an artificial heart valve, etc.), it is better to inform the doctor [34-36]. MS is an autoimmune disease that is part of brain and nerve diseases, which has grown a lot in recent decades, especially among women. If this disease is diagnosed in the early stages, it will play a significant role in preventing its progress. Due to the quality of magnetic resonance images, neurologists face a serious challenge in making decisions about disease diagnosis [37].

How does a blood test help diagnose MS?

Approximately 2.3 million people worldwide have MS. Blood tests are often an effective way to rule out or confirm other problems. Blood tests help the doctor rule out other diseases, such as Lyme disease, which has some symptoms similar to MS. Thus, the doctor is one step closer to the correct diagnosis. Because symptoms come and go, a single test is not enough to make a definitive diagnosis.

Eliminate the possibility of other similar diseases

The symptoms of several diseases are similar to those of MS. All these things can be checked. Some diseases such as progressive multifocal leukoencephalopathy virus (PML) and brain tumors can be diagnosed with the help of MRI. Symptoms of several diseases such as Lyme are similar to MS. Blood tests give clues about other diseases similar to MS. like the:

Lyme disease

Numbness or numbness of arms, hands and legs is one of the common symptoms of MS and Lyme disease. Lyme disease is an infection that is transmitted from ticks to humans and spreads to the central nervous system. In Lyme disease, you also experience skin discomfort. Although it is still not 100% certain, enzyme immunoassays and western blot blood tests can show the occurrence of Lyme disease in the blood (Figure 5). Although some symptoms of these two diseases are similar, the treatment method for MS is different from Lyme disease. In most cases, Lyme disease can be cured in the early stages by taking antibiotics [38].

Figure 5. Lyme disease

Systemic lupus erythematosus

Lupus is an inflammatory autoimmune disease that affects the central nervous system. Just like MS, there is no specific blood test to diagnose lupus. Common symptoms of lupus and MS include the following:

- Numb;
- Tingling;
- Fatigue;
- Visual impairment.

Just like MS, there is no specific test to diagnose lupus. If the antinuclear antibody and other antibodies are positive in the blood test, it indicates lupus or other autoimmune diseases, but it is not related to MS [39].

Duke's disease

Neuromyelitis optica, more commonly known as Duke's disease, is an immunological disorder that bears an uncanny resemblance to MS. There are many common symptoms between these two diseases. **Including:**

- Blurred or loss of vision;
- Weakness;
- Numb;
- Bladder problem;
- Spasticity (seizure state).

NMO-IgG blood test is negative in people with MS but positive in 70% of people with Duke's disease. Duke's disease does not respond to MS drugs and can be treated with steroids and other immunosuppressive drugs.

Vitamin deficiency

Deficiency of certain vitamins, such as vitamin B-12, causes symptoms similar to MS. In general, several different tests should be performed to reach a definitive diagnosis of MS. Damage to the protective covering around nerve fibers in the central nervous system is called demyelination, which is seen in both B-12 deficiency and MS. Symptoms of vitamin B-12 deficiency include numbness and tingling in hands and feet, weakness and extreme fatigue. Deficiency of copper, zinc and vitamin E also causes neurological symptoms. A simple blood test can show the amount of essential vitamins in the blood. The doctor will help you choose the best treatment method by taking supplements and changing your lifestyle [40].

Other diagnostic tests

To diagnose MS, the doctor must find the following:

- The occurrence of damage in two separate parts of the central nervous system.
- Damage occurred during two different periods of time.
- The possibility of other diseases has been eliminated.

In general, several different tests should be performed to reach a definitive diagnosis of MS. In addition to the history of symptoms and blood tests, the doctor prescribes the following tests.

MRI

MRI is painless and non-invasive and provides an accurate picture to determine MS disease. An MRI, done both with and without contrast dye, shows injuries to the brain and spinal cord. Photos show whether the scars are old, new (Figure 6), or currently active. In addition to diagnosis, MRI helps to control the progression of the disease [41].

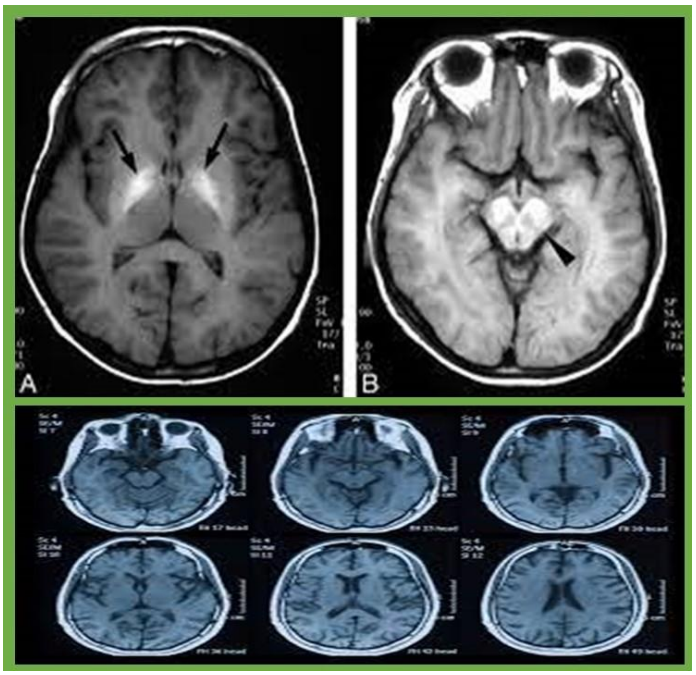

Figure 6. MRI

Extraction of spinal fluid

Although a lumbar puncture does not rule out or confirm the possibility of MS, it does help diagnose it. In this method, spinal fluid is obtained by injecting a needle between the bones below the spinal cord. Sometimes the spinal fluid in people with MS contains high amounts of IgG antibody or a protein called oligoclonal band, which also occurs as a result of other diseases. About 5 to 10% of people with MS do not have any problems in the spinal fluid.

Visual evoked potential

In this test, the person is asked to stare at a screen whose images are constantly changing. With the help of this method, any defect in the path of the optic nerve is determined. The first step after the diagnosis is to determine the treatment plan with the help of the doctor. The list of drugs designed to reduce relapses and slow the progression of MS is growing. These strong drugs need to be used continuously to be effective and may have serious side effects [42].

Be sure to consult your doctor about the advantages and disadvantages of each of these drugs. Other symptoms, such as extreme fatigue, can also be treated. If blood tests and other tests confirm MS, know that MS does not have a definitive cure, so its control continues throughout life, but

the quality of life of many people with MS is good. Your doctor may refer you to local resources for information about MS. You can join MS support groups in person or online. Although each person's experience with MS is different, it can be helpful to share your experiences with others. In addition to a general practitioner, you need a neurologist to assess symptoms and monitor disease progression. Sometimes MS can lead to severe disability, but many people with MS have a good quality of life and a normal lifespan [43].

Multiple sclerosis (MS) is a debilitating disease of the brain and spinal cord (central nervous system).

In MS, the immune system attacks the protective sheath (myelin) that covers nerve fibers, causing communication problems between the brain and the rest of the body. Finally, this disease can cause permanent damage or destruction of nerves. The signs and symptoms of MS are very different and depend on the extent of nerve damage and which nerves are affected. Some people with severe MS may lose the ability to walk independently or completely, while others may experience long periods of remission without any new symptoms. Multiple MS signs and symptoms may vary from person to person and over the course of the disease depending on the location of the affected nerve fibers. Symptoms often affect movement, such as:

- Numbness or weakness in one or more limbs that usually occurs on one side of the body at a time, or the legs along with the trunk
- A feeling of electric shock caused by certain movements in the neck, especially bending the neck forward (Lermitt's sign)
- Tremors, lack of coordination or unsteady gait.

Vision problems are also common, including:

- Partial or complete loss of vision, usually in one eye at a time, often accompanied by pain when moving the eye.
- Prolonged diplopia.
- Blurred vision.

Symptoms of multiple sclerosis may also include:

- Tongue tie;
- Fatigue;
- Dizziness;
- Numbness or pain in parts of the body;
- Problems with sexual function, intestines and bladder.

Courses of MS

Most people with MS have a relapsing-remitting disease course. They experience episodes of new symptoms or relapses that occur over days or weeks and usually resolve partially or completely. Following these relapses, there are periods of recovery that can last for months or even years. Mild elevations in body temperature can temporarily worsen MS signs and symptoms, but are not considered relapses [44]. In about 60 to 70 percent of people with relapsing-remitting MS, symptoms eventually progress steadily with or without periods of remission, known as secondary

progressive MS. Worsening symptoms usually include problems with movement and walking. The rate of disease progression varies among people with secondary progressive MS. Some people with MS experience a gradual onset and steady progression of symptoms without any relapses. These patients are known as primary progressive MS.

Discuss

Genetic and environmental factors play a role in determining the chances of contracting this disease. The onset of the disease mostly occurs in early to mid-adulthood, and its prevalence is three times higher in women than in men. About 5.2 million people worldwide are affected by MS, and the clinical course of this disease can be highly variable, ranging from a benign disease to a rapidly progressive and debilitating disease. The onset of this disease may be loud or quiet and gradual. In some patients, the symptoms are so minor that the patient does not see a doctor for months to years. The most common form of this disease is in the form of recurrent attacks of focal nervous dysfunction, which usually lasts for weeks to months, followed by different degrees of recovery [45].

In some people, the disease manifests itself with a decrease in neurological function, which progresses slowly. Symptoms are often transiently worsened by fatigue, stress, exercise, or heat. Manifestations of MS are different, but they generally include weakness or sensory symptoms involving organs, vision disorders, impaired walking and muscle coordination, frequent urination, and abnormal fatigue. Movement involvement can appear as heavy, stiff, weak or slow limbs. Localized tingling and numbness are common. Optic neuritis can cause blurring of vision, especially in the center of the visual field, which is often associated with pain behind the eyeball and is aggravated by eye movement. Brain stem involvement may cause diplopia, nystagmus, vertigo and symptoms of facial pain, numbness, hemi-spasm weakness, or myokymia (rippled muscle contractions). The history of MS dates back to 1868, when Jean-Martin Charcot, a French neurologist, was the first to recognize multiple sclerosis as a distinct disease. Charcot named this disease "sclerosis en plaques" with the help of previous reports and by adding his pathological and clinical observations. The three symptoms of this disease include involuntary movement of the eyeball, purposeful tremor, and telegraphic speech (intersection speech), although it is important to mention that these symptoms are not specific to MS. Charcot also noticed cognitive changes in his patients, which caused "significant memory weakness" and "decreased perceptual power" in them [46].

Before Charcot, Robert Carswell (1793–1857), an English professor of pathology, and Jean Crovilleher (1791–1873), described and illustrated many of the clinical details of this disease, but failed to establish it as a distinct disease. recognize in particular, Carswell called the injuries he had identified "specific damage to the spine with tissue analysis." In 1863, the Swiss pathologist George Eduard Reinfleisch noticed, using a microscope, that inflammatory lesions spread around blood vessels. In the 20th century, theories about the cause and pathogenesis of this disease were presented, and effective treatments for this disease were discovered in the 1990s [47].

The incidence of MS disease is increasing in Iran, so that according to the statistics of the Iranian MS Disease Association, there are about 70,000 registered MS patients. The most common age of occurrence is 20 to 40 years old and the city with the highest MS disease rate is Isfahan. It seems that its prevalence is more than the above statistics because not all patients are registered in the association. Unfortunately, it is not known why this disease is increasing in Iran. Before examining the different dimensions of MS disease, it is better to first examine the physiological dimensions of this disease. Nerve conduction in myelinated axons has a jumping pattern. In this way, the transmission of the nerve impulse from one node to another takes place without depolarization of the axonal membrane under the myelin sheath between the two nodes. This situation causes a significant increase in the speed of current conduction in myelinated nerves compared to non-myelinated nerves. A temporary nerve impulse conduction block occurs when a demyelinated lesion has developed, but sodium channels (which are normally concentrated at the site of the node) have not yet had time to distribute and extend along the demyelinated axon. The redistribution of sodium channels at the site of the lesion allows the continuous propagation of the action potential along the demyelinated part of the nerve [48].

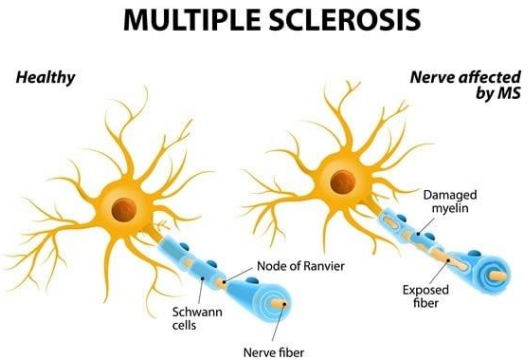

Figure 7. Multiple Sclerosis

This conduction block may be incomplete and involve only high-frequency impulses. Some conditions such as increased body temperature or metabolic changes may cause some degree of nerve conduction block. This phenomenon can justify the fluctuation of clinical symptoms that change from hour to hour and are caused by exercise or fever.

Pathology of MS disease

The main finding in the pathology of MS is demyelination, and the evidence of myelin destruction is seen in the first stages of tissue destruction. One of the special features of MS plaques is that oligodendrocyte progenitor cells remain alive. Even in many lesions, their number is higher than normal, but these cells do not differentiate into mature myelin-producing cells. In some lesions, oligodendrocytes that have remained intact or those that have differentiated from progenitor cells may myelinated living demyelinated axons. partially regenerate and cause the creation of shadow plaques. As the lesions progress, the proliferation of astrocytes becomes evident (gliosis). Although axons are not typically involved in MS, partial or complete destruction of axons may be seen,

particularly in lesions that are highly inflammatory [49]. Therefore, MS is not only a disease related to myelin, and neuronal pathology is more and more important as an important cause of irreversible disability of neurological function in MS. Also, inflammation, demyelination, and plaque formation are evident in the cerebral cortex, and the dramatic reduction of axons, which indicates neuron death, is especially abundant in advanced cases of MS.

Genetic factors in MS

MS disease is more common in some families, and the study of adopted children, half-brothers and sisters, twins, and spouses indicates that family prevalence is caused by genetic causes and not by environmental factors. Susceptibility to MS disease is multigene in such a way that each gene slightly increases the risk of contracting it. The most important gene is HLA-DRB1, which alone is responsible for approximately 10% of the risk of developing MS. Also, whites are at a higher risk for MS than Asians and Africans [50].

Autoreactive lymphocytes

The autoimmune response in MS is likely mediated by two different populations of pro-inflammatory (autoreactive) T lymphocytes:

- **T-helper type one:** These cells, which produce interferon gamma (IFN-g), form a key and influential population.
- **T-helper type 17:** In recent years, the major role of highly inflammatory Th17 cells has been identified. Th17 is induced by transforming growth factor beta (TGF-b) and IL-6 and enhanced by IL-21 and IL-23. The number of Th17 cells and the levels of their dependent cytokines (IL-17) are increased in MS lesions and in the blood of patients with active MS. High levels of IL-17 in the blood may also be a marker for more severe MS. Th1 cytokines including IL-2, TNF- a and IFN-g play a key role in establishing and maintaining the immune response. Also, TNF- a and IFN-g can directly damage oligodendrocytes or myelin membrane.

Humoral immune response

It seems that B-cell activation and antibody-dependent response (referred to as humoral immune response) are also necessary for the development of complete demyelinating lesions in MS, in experimental and human models. In CSF, increased levels of locally produced immunoglobulins and oligoclonal antibodies derived from B cells and plasma cells enclosed in colonies located in the CNS are diagnostic features of MS. Oligoclonal band pattern is unique in each person and efforts to determine the target of these antibodies have been fruitless so far.

Neurodegeneration

Axonal damage (neurodegeneration) occurs in all new lesions of MS, and the cumulative effects of axonal damage are one of the major causes of irreversible disability in MS. In patients with advanced paraphrases caused by MS disease, approximately 70% of the axons of the lateral corticospinal pathway have been lost. MRI studies show that progressive axonal degeneration occurs over time in inactive MS lesions. Demyelination can lead to reduced axon nutrient supply, redistribution of ion channels, and membrane potential instability. Axons initially adapt to these changes, but over time, degeneration occurs in the terminal regions and backwards.

Therefore, strengthening myelin regeneration is one of the most important therapeutic goals. Another feature of progressive MS is that inflammation is often not associated with blood-brain barrier or BBB disruption. Probably, this finding can explain the failure of immunomodulatory treatments in the treatment of patients with progressive MS due to the inability to cross the BBB. Available evidence suggests the role of one or more of the following mechanisms in progressive MS: Axonal and neuronal death as a result of glutamate toxicity, oxidative damage, iron accumulation, or mitochondrial damage [51].

Epidemiology of MS

According to the most comprehensive epidemiological studies that have been conducted for MS, the prevalence of this disease in women is almost three times higher than in men. The age of onset of this disease is usually between 20 and 40 years, while the symptoms in men begin a little later than in women. But MS disease may occur at any age. The change in the prevalence of MS disease based on geographical regions has been observed many times. So that the highest prevalence of MS disease has been seen in the Orkney Islands in the north of Scotland. In other areas with similar temperature, such as North America, Northern Europe, Southern Australia and Southern New Zealand, the prevalence of MS is 0.1 to 0.2%. On the other hand, in tropical regions such as Asia, Equatorial Africa and the Middle East, the prevalence of the disease is 10 to 20 times lower. The prevalence of MS has increased significantly in some regions of the world during the last half century, which is probably due to the effects of some environmental factors. Also, since this increase in prevalence happened more in women, it seems that women are more sensitive to these environmental factors (Figure 8).

Figure 8. Epidemiology of MS

Proven risk factors for MS include vitamin D deficiency, exposure to EBV after early childhood, and smoking. Recent findings suggest that high levels of sodium in the diet activate autoreactive pathogen T lymphocytes. This indicates that the consumption of a high-salt diet, which has become common in recent years in Western countries, may be part of the explanation for the increase in the prevalence of MS in recent years.

Clinical symptoms of MS

The onset of MS symptoms may be gradual or sudden. These symptoms may be severe or so mild that the patient does not see a doctor for months or years. The symptoms of MS are extremely diverse and depend on the location of the lesions in the CNS and their severity. The symptoms can be different in each person compared to another person, and its intensity can change from year to year, month to day, and even day to day (Figure 9). Fatigue and difficulty in walking are the most common symptoms [52].

Figure 9. Clinical symptoms of MS

Examination usually shows evidence of neurological impairment in asymptomatic areas. For example, a patient may have symptoms in one leg, but during the examination, evidence of involvement of both legs is obtained. Weakness of the limbs may appear as a decrease in strength, speed, skill of movements, fatigue or impaired walking. Weakness due to physical activity and exercise is a diagnostic symptom in MS. Weakness is the type of upper motor neuron involvement and is usually associated with other pyramidal symptoms such as spasticity, tendon reflexes and Babinski sign. Rarely, a tendon reflex may be lost, and this occurs if the lesion of the MS disease has cut off the afferent fibers of the reflex in the spinal cord.

Spasticity: This disease is usually associated with spontaneous and movement-dependent muscle spasms. This phenomenon is associated with painful spasms that can disrupt the patient's work and daily activities. In rare cases, spasticity causes body maintenance and involuntary support of body weight while walking.

Optic neuritis (ON) and sensory disorders usually manifest as reduced visual acuity, blurred vision, and reduced color perception in the central parts of the visual field. These symptoms may be mild or lead to severe vision loss. In rare cases, complete loss of light perception occurs. Ocular symptoms usually occur in one eye but may be bilateral. Pain around the eye, which is aggravated by eye movement, often occurs before or at the same time as vision loss. Optic disc pallor (optic atrophy) commonly occurs after optic neuritis. Blurred vision may be caused by optic neuritis or diplopia. If the blurred vision improves by closing one eye, the cause is double vision.

Other visual disturbances in MS include: Horizontal visual paralysis, "one-one" syndrome (horizontal visual paralysis with INO) and acquired pendular nystagmus. Sensory symptoms are

varied and include paresthesia (tingling sensation), tingling, sensation of insects crawling on the skin and hypoesthesia (decreased sensation). Unpleasant sensations (feeling of swelling of a part of the body, wetness and a feeling of being swaddled in a part of the body) are also common. Pain is a common symptom in MS that is reported in more than 50% of patients. This pain can occur in any part of the body and its location can change over time. Ataxia usually manifests as cerebellar tremors. Ataxia may involve the head, trunk and voice and cause a speech disorder with characteristics of cerebellar involvement.

Bladder disorder is present in more than 90% of MS patients, and in one third of patients, this disorder can cause weekly or even more frequent urinary incontinence.

Constipation occurs in more than 30% of patients. However, fecal incontinence is less common but can be socially debilitating [53].

Cognitive impairment may include memory loss, attention deficit disorder, impaired executive function and problem solving, and decreased information processing speed.

At first, it was thought that euphoria is one of the characteristics of MS, but today it is known that this is not very common and is observed only in less than 20% of patients. It is rare for cognitive impairment to interfere with daily activities. Depression develops in about half of patients, which may be endogenous, reactive, or as part of the disease itself, and can lead to fatigue.

Fatigue is present in about 80% of people with MS, which can lead to an inability to perform daily tasks. Other symptoms include sexual dysfunction, facial weakness, dizziness, sensitivity to heat (a type of neurological disorder), trigeminal neuralgia, and glossopharyngeal neuralgia.

Clinical course of MS

In terms of clinical course, MS is divided into four different types. The diagnosis and differentiation of the clinical forms of this disease seem very necessary to choose the treatment method and determine the prognosis of the disease.

These four types are:

- **Relapsing-remitting MS or RRMS:** Eighty-five percent of MS cases are initially this form. It is characterized by attacks that occur over days to weeks, and complete recovery is often achieved within several weeks to several months. However, in cases where movement is severely impaired during an attack, about 50% of patients do not recover.
- **Secondary progressive MS (SPMS):** Its onset is similar to RRMS. Of course, in some stages, the clinical course of RRMS changes in such a way that the patient's performance deteriorates continuously and without connection to acute attacks. The rate of permanent disability caused by SPMS is higher than that of RRMS. The risk of developing SPMS in each patient with RRMS is about 2% per year. This means that a significant number of RRMS cases eventually turn into SPMS.
- **Primary Progressive MS (PPMS):** It accounts for about 15% of MS cases. These patients have not experienced any attacks and have experienced a continuous course of loss of function since the beginning of the disease. The disease occurs at an older age (average age is about 40 years) and leads to disability more quickly.

- **Progressive-relapsing MS (RRMS):** Accounts for about 5% of MS cases. In these patients, like patients with PPMS, the course of the disease is progressive from the beginning, while occasionally, like SPMS patients, they experience attacks in addition to the progressive course of the disease.

MS diagnostic tests

MS is usually diagnosed based on presenting signs and symptoms, along with medical imaging (MRI) and necessary laboratory tests. Clinical data alone may be sufficient to diagnose MS if a person has isolated episodes of neurological symptoms. People who seek medical care after just one attack should have other tests done to diagnose the disease. The most common diagnostic tools are imaging of the nervous system, analysis of cerebrospinal fluid and evoked potentials. Magnetic resonance imaging of the brain and spine may show areas of demyelination (lesions or plaques). Gadolinium can be administered intravenously as a contrast agent to delineate active plaques and, through removal, reveal the presence of histological lesions unrelated to the symptoms present at the time of evaluation.

Cerebrospinal fluid testing obtained from a lumbar puncture can provide evidence of chronic inflammation in the central nervous system. Cerebrospinal fluid is tested for immunoglobulin oligoglobulin (IgG) groups on electrophoresis, which are markers of inflammation and are seen in 75-85% of people with MS. It is possible that the nervous system in people with MS is less responsive to the stimulation of the optic nerve and sensory nerves due to the demyelination of these pathways. These brain responses can be tested using vision and sensory evoked potentials. Optical coherence tomography (OCT) is a non-invasive imaging test in which light waves are used to produce a cross-sectional image of the retina, which can be used to assess thinning of the optic nerve. For a doctor to make a diagnosis, evidence of MS must be seen in at least two separate areas of the central nervous system. These injuries must have occurred in different parts. McDonald's criteria are also used to diagnose MS [54].

According to the 2017 update, MS can be diagnosed based on these findings:

- Two attacks or the appearance of symptoms (so that the symptoms last at least 24 hours and there is a gap of 30 days between the attacks) and the creation of two lesions.
- Two attacks, one lesion and evidence of diffusion in the same place (or a different attack in different parts of the nervous system).
- One attack, two lesions and evidence of dissemination at the same time (or finding a new lesion – in the same location – compared to the previous scan, or the presence of immunoglobulins, called oligoclonal bands, in the cerebrospinal fluid).
- An attack, a lesion and evidence of diffusion in one place and time.

Worsening of symptoms or lesions and spread in the place can occur in the following two cases:

- Brain MRI;
- MRI of the spine and cerebrospinal fluid.

Differential diagnoses of MS

There is no single specific clinical symptom or test to diagnose MS. It occurs in young patients with recurrent and improving symptoms along with the involvement of different areas of the white matter of the CNS, and the possibility of other diagnoses other than MS should always be considered.

Conditions that suggest other diagnoses other than MS include the following:

- When symptoms are exclusively located in the posterior cranial fossa, craniocervical joint, or spinal cord.
- The age of the patient is less than 15 or more than 60 years.
- The clinical course of the disease is progressive from the beginning.
- The patient has never experienced visual, sensory, bladder disorder symptoms.
- Laboratory findings (such as MRI, CSF or EP) are atypical for MS.

Prognosis of MS

Although the long-term prognosis of MS has improved in recent years, in part due to advances in the treatment of primary relapsing forms (PRMS), most patients with clinical evidence of MS eventually develop progressive neurological disability. PRMS is more common in women. In older studies that were conducted before the widespread use of immunomodulation treatments for MS, after 15 years from the onset of the disease, only 20% of patients had no functional limitations, and between one-third and one-half of cases progressed to SPMS. Furthermore, approximately 80% of patients reach this level of disability 25 years after the onset of symptoms. Death as a direct consequence of MS is not common. However, it is estimated that survival for 25 years is expected in only 85% of cases. Death may occur during an acute attack of MS. More commonly, death occurs as a complication of MS (e.g., pneumonia in debilitated individuals). Death can also occur by suicide. It seems that the application of disease-modifying treatments in its early stages will reduce this excess mortality [55].

Methods of improving MS disease

Although there is no known cure for MS, several treatments have been shown to be helpful in improving it.

The available treatments for MS can be divided into several categories:

1. Treatment of acute attacks.

2. Treatment with disease-modifying agents that reduce the risk of biological activity of MS disease.

3. Symptomatic treatment.

As with any other medical treatment, drug therapy used in the management of MS has several side effects. Some people use alternative therapies even though there is no reliable evidence in this field. Regular exercise is important for the physical and mental health of every person, even if they have disabilities; Swimming or exercising in pool water can help people with movement disorders. Yoga classes are also provided for people with MS. On the other hand, a balanced diet with a lot of nutrients and fiber helps to maintain the general health of the body. It is better to avoid eating a

lot of red meat, salty and fatty foods and replace them with fish, edible nuts, fruits, vegetables and low-fat foods.

Improving acute attacks of MS

During acute symptomatic attacks, high-dose intravenous corticosteroids, such as methylprednisolone, are the usual treatment for these attacks, and seem to be similar in efficacy and safety to oral corticosteroids. Corticosteroids are usually effective in reducing symptoms in the short term, but this type of treatment will not have much effect on long-term improvement. Severe attacks unresponsive to corticosteroids may be treated with plasmaphereses. Side effects of short-term treatment with glucocorticoids include fluid retention, potassium loss, weight gain, stomach upset, acne, and emotional instability. It is recommended to use a low-salt and high-potassium diet at the same time and not to use diuretics that cause potassium excretion. Oral lithium carbonate is prescribed to control emotional conditions and insomnia, as well as cimetidine or ranitidine along with the main drugs for patients with a history of peptic ulcer [56].

Modulating therapies for RRMS and SPMS forms

Several types of drugs have been approved by the medical institutions for the treatment of modulating forms of RRMS and SPMS.

These drugs include:

Interferon-β, glatiramerstat, natalizumab, fingolimod, dimethyl fumarate, triflunomide and mitoxantrone.

Interferon-β is a class I interferon known primarily for its antiviral properties. The effectiveness of this drug for MS is probably due to its properties in regulating the immune system. Interferon-β should be considered in patients with RRMS or SPMS with attacks. Common side effects of this drug include flu-like symptoms (such as fever, chills, and body aches) and mild abnormalities in routine laboratory evaluation (such as elevated liver enzymes, lymphopenia). Rarely, more severe hepatotoxicity may occur.

Glatiramer acetate reduces the rate of attacks in RRMS. This drug also improves disease severity indices, although its effect on clinical disability is less well-proven than interferon-β. However, two very large trials showed that the effect of glatiramer acetate on attack rate and ability reduction was equivalent to high-dose and high-frequency interferon-β.

Figure 10. Interferon-β

Therefore, in patients with RRMS, glatirameracetate should be considered as an alternative treatment with the same efficacy as interferon-β. About 15% of patients may experience one or

more attacks of hot flashes, pressure in the chest, shortness of breath, palpitations and anxiety after prescribing this medicine. Of course, these systemic reactions are unpredictable, have a short duration, and usually do not recur. Natalizumab is a human monoclonal antibody against the α4 subunit of integrin α4β1, which is a type of cell adhesion molecule on the surface of lymphocytes. This antibody prevents the attachment of lymphocytes to endothelial cells. Therefore, it prevents lymphocytes from penetrating the BBB and entering the CNS (Figure 11).

Figure 11. Tysabai

Natalizumab is very effective in reducing the rate of attacks and significantly reduces all disease severity indicators (clinical indicators and MRI-based indicators). In addition, this drug is well tolerated and its intravenous dose is once a month. However, progressive multifocal leukoencephalopathy (PML), a life-threatening infection, occurs in 0.3% of patients treated with natalizumab. Also, the findings indicate that in patients with RRMS, natalizumab is preferable to IFN-β-1α with a low dose (weekly).

Fingolimod is a sphingosine-1-phosphate inhibitor that prevents the egress of lymphocytes from secondary lymphatic organs such as lymph nodes and spleen. This drug reduces the rate of attacks and significantly reduces all measures of disease severity in MS (Figure 12).

Figure 12. Gilenyya

Mild abnormalities in routine laboratory evaluation (elevations in liver function tests or lymphocyte counts) are more common than in controls and sometimes require discontinuation of therapy. 1st and 2nd degree heart block as well as bradycardia (decreased heart rate) may also occur when starting treatment with fingolimod. All patients should be observed for a period of 6 hours

after taking the first dose of the drug. Patients with a history of heart failure should probably not receive this drug. Among other complications, macular edema and rarely disseminated varicella zoster virus infection can be mentioned. Although dimethyl fumarate does not have a well-known mechanism of action, it seems to have anti-inflammatory effects and cause a modulation between pro-inflammatory and anti-inflammatory cytokines [57].

This drug reduces the rate of attacks and significantly improves all disease criteria in MS patients. Gastrointestinal side effects (abdominal discomfort, nausea, vomiting, flushing and diarrhea) are common at the beginning of the treatment, but they decrease with the continuation of the treatment. Other side effects include mild decreases in lymphocyte and neutrophil counts and mild increases in liver enzymes. Triflunomide inhibits the mitochondrial enzyme dihydrourtate dehydrogenase. This drug exerts its effects by limiting the infiltration of rapidly proliferating B and T cells. Triflunomide is well tolerated and is better accepted by the patient with a once-daily oral dose (Figure 13).

Figure 13. Aubagio

In clinical trials, mild hair loss and gastrointestinal symptoms (nausea and diarrhea) were more common than in the control group. An important limitation of this drug, especially in women of reproductive age, is due to its teratogenic effects. This drug remains in the blood for up to two years and it is recommended that cholestyramine or activated charcoal be prescribed for women and men who have taken the drug and are planning to have children, in order to reduce the remaining level of the drug. Mitoxantrone hydrochloride is indicated for use in SPMS, PRMS, and patients with worsening RRMS. This drug may have cardiotoxicity (cardiomyopathy, reduced left ventricular output, and irreversible CHF). Also, more than 40% of women experience amenorrhea, which may be permanent. Finally, the risk of mitoxantrone-induced acute leukemia with a probability of 1% may occur during treatment. Due to these risks and the increasing availability of alternative treatments, mitoxantrone is rarely used in the treatment of MS today. Alemtuzumab is a humanized monoclonal antibody against the CD52 antigen expressed on the surfaces of monocytes and lymphocytes. This drug causes a decrease in all types of lymphocytes

and changes in the ratio of lymphocyte subtypes [58]. In preliminary studies, alemtuzumab significantly reduced attacks and significantly improved all measures of disease severity. However, in two phase three studies, its effect on clinical disability was not convincing.

The worrisome toxicities of this drug include:

1. The development of autoimmune diseases including thyroiditis, Graves' disease, thrombocytopenia, hemolytic anemia, pancytopenia, basement membrane anti-glomerular disease and membranous glomerulonephritis.
2. Malignancies include thyroid cancer, melanoma, breast cancer, and HPV-related cancers.
3. Severe infections.
4. Reactions caused by drug injection.

Symptomatic treatments

Before mentioning the types of treatments for the symptoms of this disease, it is important to mention that in all patients, encouraging attention to a healthy lifestyle including a proper diet, regular exercise as tolerated (swimming is usually better tolerated due to the cooling effects of cold water), the importance has it. Correcting vitamin D deficiency and consuming a diet containing unsaturated fatty acids, which are present in fish oil such as salmon, are recommended due to its possible biological role in the pathogenesis of MS, safety and positive effects on health.

Ataxia/tremors are often resistant. Medications such as clonazepam, primidone, propranolol or ondansetron may help. Spasticity may improve with physical therapy, regular exercise, and stretching. Effective treatments include baclofen, diazepam, tizanidine, dantrolene, and cyclobenzaprine hydrochloride.

Weakness is sometimes improved with potassium channel blockers such as 4-aminopyridine and 3,4-diaminopyridine, especially when lower-extremity weakness interferes with the patient's mobility [59]. Pain is controlled with anticonvulsants (carbamazepine, phenytoin, gabapentin), antidepressants (amitriptyline, nortriptyline, desipramine, venlafaxine), or antiarrhythmic drugs (mexiltine). Bladder disorder is better controlled by conducting urodynamic examinations. Limiting fluid intake in the evening or frequent voluntary voiding are helpful in detrusor hyperreflexia. If these methods fail, propantheline bromide, oxybutynin, hyoscyamine sulfate, tolterodine tartrate, or solifenacin may be helpful. Treatment for constipation includes a high-fiber diet and fluids. Natural laxatives or other laxatives may be helpful. Reducing dietary fiber may be effective in controlling fecal incontinence. Depression must be treated. Effective medications include selective serotonin reuptake inhibitors (fluoxetine or sertraline), tricyclic antidepressants (amitriptyline, nortriptyline, or despyramine), and non-tricyclic antidepressants (venlafaxine). And finally, cognitive impairment may respond to donepezil hydrochloride.

The positive perspective of MS disease treatment

Several clinical trials are currently underway in the field of MS treatment. **Among them, the following can be mentioned:**

- Monoclonal antibodies against CD20 to reduce B cells and against interleukin 2 receptor.

- Oral form of selective sphingosine 1-phosphate receptor antagonists to isolate lymphocytes in secondary lymphoid organs.
- Estriol to induce a pseudo-pregnancy state.
- Molecules that enhance myelin regeneration.
- Bone marrow transplant.

Summarizing the article MS

Multiple sclerosis is a neurological disease with an unknown cause that affects the central nervous system, i.e. the brain and spinal cord. Unfortunately, scientists have not yet been able to find out the real cause of this disease, and on the other hand, there is no definitive treatment for this disease. Therefore, to achieve successful control of symptoms, multiple control is needed to prevent or stop the cycle of symptoms. Effective communication, education, exercise training and pharmacological interventions are vital for effective control of multiple sclerosis symptoms. Increasing the awareness of multiple sclerosis patients and using the right treatment methods can significantly reduce the problems they face and bring about relative improvement for these patients [60].

Causes of MS

The cause of multiple sclerosis is unknown. This disease is considered an autoimmune disease in which the body's immune system attacks its own tissues. In the case of MS, this immune system defect destroys the fatty substance that protects nerve fibers in the brain and spinal cord (myelin). Myelin can be compared to the insulating coating on electrical wires. When myelin is damaged and a nerve fiber is exposed, messages traveling along that nerve may slow or stop. The nerve itself may also be damaged. It is not clear why MS occurs in some people. A combination of genetic and environmental factors seems to be responsible.

Treatment of MS attacks

Corticosteroids: Such as injectable prednisone and methylprednisolone, are prescribed to reduce neuro inflammation. Side effects of these drugs include insomnia, increased blood pressure, mood changes, and fluid retention.

Plasma exchange (plasma milling): The liquid part of your blood (plasma) is removed and separated from the blood cells. Then the blood cells are mixed with a protein solution (albumin) and returned to the blood. If the symptoms of the disease have recently appeared in your body, their intensity is high, or your body does not respond properly to steroids, plasma exchange is used.

Treatment methods to correct the progression of the disease

So far, no treatment has been shown to slow the progression of early progressive MS. There are many treatment options for relapsing remitting MS.

Treatment methods for relapsing remitting MS include:

Interferon beta: These drugs are among the most commonly prescribed drugs for the treatment of MS. These drugs are injected under the skin or into the muscles and can reduce the number and severity of disease attacks.

Glatiramer Acetate (Copaxone): This drug can prevent the immune system from attacking the myelin sheath and must be injected under the skin (Figure 14).

Dimethyl fumarate (Tacfedra): This twice-daily oral medication can reduce attacks.

Fingolimod (Gilnia): This once-daily oral medication reduces the number of attacks.

Triflunomide (Abagio): This once-daily oral medication can reduce the number of attacks.

Figure 14. Glatiramer Acetate (Copaxone)

Natalizumab (Tysabri): This drug is designed to prevent the movement of harmful immune cells from the bloodstream to the brain and spinal cord. This drug can be used as a first-line treatment for people with severe MS, and as a second-line treatment for others.

Alemtuzumab (Lametrada): This drug targets a protein on the surface of immune cells, killing them and reducing MS relapses.

Mitozantrone: This drug weakens the immune system, can be harmful to the heart and also contributes to the development of blood cancer. As a result, its use for the treatment of MS is very limited. Mitosantrone is usually only used to treat severe and advanced cases of MS.

Treating the signs and symptoms of MS

Physical therapy: A physical therapist or occupational therapist can teach you stretching and strengthening exercises and show you how to make daily activities easier with the help of special equipment. Physical therapy, along with the use of mobility aids when needed, can help a person manage leg weakness and other walking problems that are common in MS.

Muscle relaxants: You may experience painful and uncontrollable cramps in your muscles, especially in the muscles of your legs. Muscle relaxants such as baclofen (Liversal) and tizanidine (Xanaflex) can help.

Medicines used to reduce fatigue

Other medications: Medications may also be prescribed to treat depression, pain, sexual dysfunction, and bladder and bowel problems associated with MS [61].

Alternative medicine: Many people with MS use alternative and complementary therapies, or both, to manage their symptoms. Alternative methods such as exercise, meditation, yoga, massage, proper diet, acupuncture, and relaxation techniques can improve general mental and physical health, but little research has confirmed their effectiveness in managing MS symptoms.

Brain MRI imaging

Studies have shown that brain MRI is the best type of brain imaging in people with symptoms of MS. The diagnostic power of MRI in MS is very high and the imaging method is very sensitive and appropriate. MRI can show more lesions in the brain and spinal cord than CT-Scan and MS plaques can be seen well with it.

Features of the MS license plate

MS plaques can be seen in areas around the cerebral ventricles, near the cerebral cortex, around the cerebellum, and in the spinal cord (especially the cervical spine). These plaques are whiter (Hyper-intense) than the surrounding areas in the T2 MRI sequence and darker (Hypo-intense) than the surrounding areas or the same color (Isointense) of the surrounding areas in the T1 MRI sequence.

MRI of the spinal cord

The prevalence of MS plaques in the spinal cord is almost as high as in the brain. In these patients, the cervical spinal cord is usually involved.

Features of spinal plaques associated with MS include:

- Absence of spinal cord inflammation.
- They are at least 3 mm in size, but their length is less than 2 spinal cords.
- They are usually seen in the posterior-lateral area (dorsolateral) of the spinal cord.
- They are local.

The difference between an active MS license plate and an inactive license plate

Acute and active MS plaques are usually larger than inactive plaques. Acute plaques may have an indistinct border due to surrounding edema. When these plaques become chronic or inactive, they gradually become smaller and have a more defined border. In MRI with gadolinium injection (MRI with Gadolinium), active lesions become darker in the T2 sequence of MRI and less colored in the T1 sequence. Because active plaques absorb more gadolinium due to the edema around them and the inflammation in that area.

Black holes in MRI

Most MS plaques are seen in the MRI image in the T1 sequence in the same color (Isointense) with the white matter of the surrounding areas, but sometimes they may be seen darker (Hypo-pointense) and these plaques are called black holes. These black holes usually return to their normal state after a few months and the same color as the surrounding white matter. The disappearance of black holes is due to the regeneration of myelin and the disappearance of edema around the

lesions. The long-term presence of black holes can be a sign of severe loss of myelin and axons. Loss of axons can be irreversible and cause long-term complications.

Lumbar cerebrospinal fluid (CSF) test

Among the auxiliary tests that are very useful in the diagnosis of MS is the examination of the cerebrospinal fluid (CSF) through the back. In this test, which is popularly known as taking lumbar fluid, the doctor inserts a needle from the lumbar region into the spinal cord and takes out some of the cerebrospinal fluid and sends it to the laboratory [62].

When is a cerebrospinal fluid test needed?

Sending a cerebrospinal fluid test is not necessary to diagnose MS, but it can help diagnose MS in the following cases:

- When the patient's symptoms do not accurately indicate MS and the doctor has clinical doubts.
- When the patient has the outward symptoms of MS, but in the MRI imaging, the findings are not completely in favor of the diagnosis of MS.
- When the patient's symptoms and imaging findings are not helpful.
- In populations where MS would not be expected (e.g., the very elderly or children).

Features and findings of cerebrospinal fluid test in MS

In the laboratory examination of the cerebrospinal fluid in people with MS, the following can be found:

- Oligoclonal bands are found in 95% of people with MS.
- Increased IgG in cerebrospinal fluid (CSF) compared to other proteins.
- Cerebrospinal fluid pressure is usually normal in MS patients.
- The number of white blood cells (WBC) in the cerebrospinal fluid reaches 15 numbers per microliter in two thirds of normal patients and 15 numbers per microliter in a third of patients, and more than 50 numbers per microliter in a small number.
- Lymphocytes are the predominant cells in the cerebrospinal fluid.

Of course, the above should be interpreted with the imaging findings and the patient's symptoms and alone cannot help because about 8% of people who do not have MS may have oligoclonal bands in the cerebrospinal fluid, and on the other hand, infectious agents such as meningitis or viral encephalitis. Also, neuropathies can increase white blood cells and proteins in the cerebrospinal fluid.

The role of blood tests in the diagnosis of MS

Sending a blood test is useful in terms of checking the presence of antibodies to aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein IgG in patients in whom there is a diagnostic doubt and the symptoms and imaging findings do not contribute to a definitive diagnosis of MS.

Diagnosis of MS based on patient symptoms, laboratory findings and imaging

MS diagnosis is based on clinical findings and history and physical examination play an important role in this field. After taking a history and performing a physical examination, brain MRI imaging can be very helpful in diagnosing MS. In addition to all this, if there is still a diagnostic doubt, a cerebrospinal fluid test and a blood test should be performed.

McDonald Diagnostic Criteria

MacDonald's diagnostic criteria, by combining physical, imaging, and laboratory findings, can help the physician diagnose MS. These criteria have been reviewed and revised in 2017.

Diagnosis of relapsing MS

Relapsing-remitting (or remitting) MS is the most common type of MS. To know about the types of MS disease, we suggest you read the article on the types of MS disease and their course and characteristics.

To be diagnosed with relapsing-remitting MS according to McDonald's criteria, the following must be present:

- For patients with a history of 2 or more attacks who now have 2 or more specific lesions, there is no need for further investigation and the diagnosis of MS is confirmed [63].
- For patients with a history of 2 or more attacks who now have only 1 definite lesion, additional findings are needed to diagnose MS. Regarding these patients, one should look for multiple plaques in multiple places by performing brain MRI again [64].
- For patients who had only one attack, there is a need for further investigation in terms of the distribution of attacks in time by examining brain MRI for the presence of multiple active and inactive plaques or examining the cerebrospinal fluid for the presence of oligoclonal bands (Figure 15).

Diagnosis of primary progressive MS

For patients suspected of having primary progressive MS, there must be a history of progressive neurological disease for at least one year along with 2 of the following 3 conditions to confirm the diagnosis of primary progressive MS:

- One or more plaques on a T2 brain MRI sequence around the cerebral ventricles or near the cortex or in the back of the brain near the cerebellum [65].
- 2 or more plaques in the spinal cord [66].
- Presence of oligoclonal bands in cerebrospinal fluid [67-69].

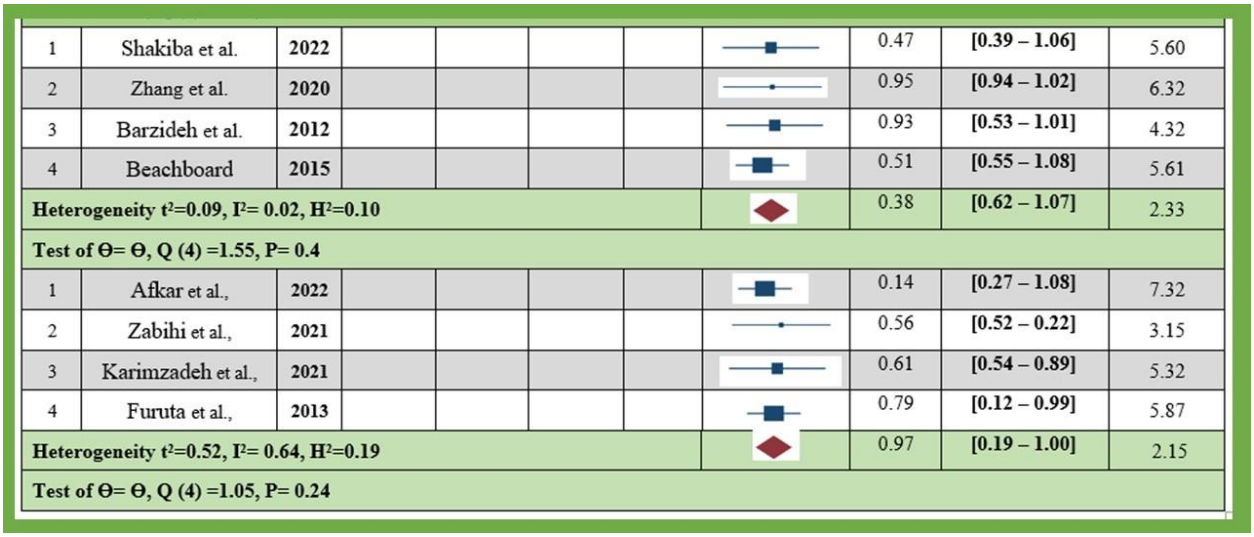

Figure 15. Forest plot showed Diagnosis and Treatment of MS in Patients Suffering

Conclusion

As mentioned here, the diagnosis of MS requires clinical and imaging findings and sometimes laboratory findings. Now, if the patient fulfills McDonald's criteria and the patient's symptoms are not justified by any other disease; It can be said that the diagnosis of MS is definite and the treatment should be started. To diagnose MS, there must be a set of clinical symptoms and imaging and laboratory findings. Patients must have a history of attacks in the past or there must be a gradual and progressive course in the last year. MS plaques should be seen in brain MRI images, and if there is still doubt about the diagnosis, cerebrospinal fluid and blood tests should be sent. To evaluate a patient who is suspected of having MS, a detailed history and a complete physical examination should be performed. In the history, the existence of attacks and relapses of the disease in the past should be investigated. The patient should be asked if he has had similar symptoms in the past. For any patient suspected of having MS, brain MRI should be performed, and then based on the McDonald Diagnostic Criteria, and if necessary, the cerebrospinal fluid from the lumbar region (CSF) should be diagnosed. MS should be placed. If there is no specific history of attacks in the past and we have diagnostic doubts, it is better to check MRI and cerebrospinal fluid (CSF), aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies also be checked. Sending a blood test for the presence of these antibodies can help distinguish MS from other diseases.

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