

Brief Note on Multiple Sclerosis

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Received 13 Apr 2020; Accepted 23 May 2020; Published 30 May 2020

Abstract

Multiple sclerosis (MS) is the most common potentially disabling disease affecting people. The incidence of MS is increasing day by day around the world, and it also has many social and economic impacts. The underlying causes of MS and the mechanisms behind the development of the disease are so widespread. Genetic and environmental interactions are almost certainly contributing to the formation of this disease. MS epidemiology illustrated that low levels of vitamin D, childhood obesity, smoking and infection with Epstein-Barr virus have a very important role in disease progression. Developments in diagnostic criteria and methods aim to increase the early recognition and diagnosis of MS. Hence, given the increasing advances in the medical field, it is now possible to detect MS before symptoms. As a result, potential preventive strategies can be studied. In this review, the MS epidemiology, potential pathogens, pathophysiology, MS types, symptoms, their diagnosis and treatment, and disease management are discussed.

Keywords: Multiple sclerosis • Central nervous system • Clinically Isolated Syndrome • Relapsing-remitting multiple sclerosis • Primary progressive multiple sclerosis • Secondary-Progressive multiple sclerosis • Progressive-relapsing multiple sclerosis • RRMS • PPMS • SPMS • PRMS

Introduction

Multiple Sclerosis is briefly called MS. It's an inflammatory disease in which the myelin sheaths of the nerve cells are damaged in the brain and spinal cord. The body mistakenly attacks the protective material around the neurons (axons) of the brain and the spinal cord. This means that the immune system which typically works against infections, confuses and attack to internal tissues with foreign objects such as bacteria. In the MS, the immune system attacks to myelin sheets over nerve fibers. This condition can damage the myelin and eliminate it from the nerve field partly or completely and makes wounds that are called lesion, plaque or sclerosis. Damage to myelin results in disruption of the messages transfer in the direction of the nervous system. The message may be slow or inaccurate and it also may be transmitted from one strand to another or rejected altogether. This damage can interfere with the parts of the nervous system ability that are responsible for communication, resulting in high levels of physical symptoms.

Permanent neurological problems, especially with the advancement of the disease, occur continuously in the next stages. Usually, MS is diagnosed based on signs and symptoms of medical tests. Multiple sclerosis is a progressive autoimmune disorder in which nerve cell protective coatings are damaged and reduce brain and spinal cord function. Although MS has been detected in 1868, the cause of MS remains largely uncertain. So far, nearly 400,000 people in the United States and 2.5 million people worldwide have MS.

Research shows the damage to the nerves caused by inflammation, but the cause of inflammation is still unknown. Symptoms of MS are variable and unpredictable. None of the people with MS disease have exactly the same symptoms and the symptoms of each person can change over time or fluctuate. One person may experience only one or two symptoms of MS, while in the other person, more of these symptoms may appear. A person with MS has all the signs or symptoms of neurology; the most common symptoms of these are problems with the autonomic, visual, motor, and sensory nerves. Certain symptoms are identified through the wound sites in the nervous system, including low odds or tightness, such as molestation, spasticity, muscle weakness, involuntary reactions, muscle cramps or disabilities, inability to coordinate and balance muscle imbalance, difficulty in speaking or Dysphagia, visual problems (the eyeball movement, vision loss, or dystonia), fatigue, severe pain, or chronic pain, and difficulty in urination and stool. Difficulty in thinking and emotional problems such as depression or emotional unconsciousness is common among MS patients.

Epidemiology

It is often stated that the cause of MS is unknown; However, this is not quite true. EBV, sun (UVB), smoking and vitamin D with the individual's genetic background plays an important role in MS development [1,2]. Also, Other potential environmental risk factors in MS include infection, stress, vaccinations, climate and diet.

With a prevalence of 50 to 300 per 100,000 people, it is estimated that around 2.3 million people live with MS around the world. Although it is likely to be underestimated due to the relative shortage of large populations such as India and China. In general, the global distribution of multiple sclerosis increases with increasing distance from the equator, although there are exceptions (Figure1) [3].

In addition, while the disease is common in the densely populated areas of the Nordic countries, this effect has been modified, given where these people were in primary life.

Immigration studies from the 1970 show that migration from areas with low-risk to high-risk areas in childhood is completely associated with a low risk of developing multiple sclerosis and vice versa. For example, Mature migrants from low risk countries such as West India to Europe are at risk for MS and the children born to immigrants in Europe are at risk as well. On the other hand, Minorities in the United States, such as the Hispanic Americans and the black Americans, experience disease progress faster than white Americans.

These studies indicate that the environment is a combination of genetics and is strongly opposed to preventive studies that target environmental factors. Multiple sclerosis is more common in women. In the early 1900s, the sex ratio was almost equal. Since then, the sex ratio has steadily increased, it is now close to 3: 1 (F: M) in most developed countries and one of the most important reason of it is incidence of multiple sclerosis in women [4]. However, most patients are in early adulthood, but presentation awareness has increased since childhood. Most of the patients in later life (more than 60 years) are progressive from onset [5,6].

Disappointment in patients with multiple sclerosis and has a negative effect on the outcome and adherence to therapy and therefore should be properly recognized and managed. In summary, the epidemiological evidence implicates environmental factors, including psychosocial stressors, operating against a background of genetic susceptibility or resistance during childhood manifesting as altered immune responsiveness [7,8].

Cause

The cause of MS has not yet been proven, but evidence indicates that there is a complex interaction between environmental and genetic factors. This stimulates the immune system to provide an autoimmune inflammatory response targeting myelin forming cells. Over time, loss of axon and neurodegeneration leads to an increase in disability [9]. However, MS is not directly inherited and unlike some of the complications, only one gene does not result in it. It's possible that a combination of genes will make some individuals more susceptible to MS. But these genes are among the population as well. Therefore, genes are only part of the story, and other factors are involved in MS. Although MS can occur in more than one person in the family, it is unlikely to be controlled. As stated above, a genetic component is probably not inherited in the common sense of MS. Hence, Families who have a member with MS have a higher risk of developing a disease than families

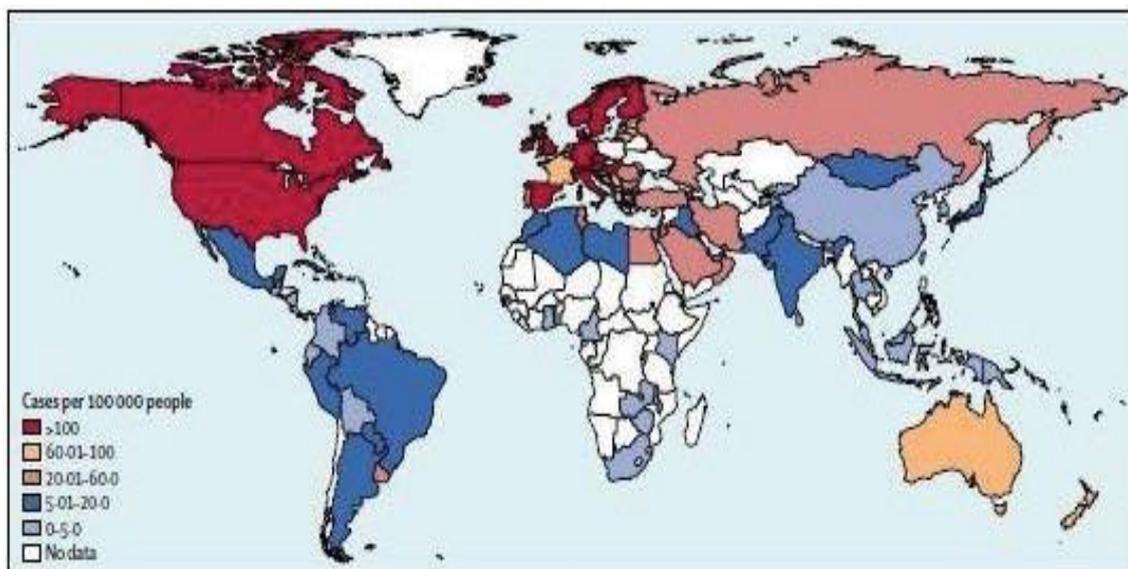


Figure 1. Global prevalence of multiple sclerosis.

that no one has MS. If the parents have MS, the risk for their children is 15-20 times higher than the general population, although this risk is still relatively low. So far, there is no definitive conclusion to explain that a hereditary process can exist [10,11].

for example, a person who is genetically susceptible to MS is in danger when exposed to the environment and develops the disease. Of course, just because one thing is associated with another, we can not necessarily say that it causes the others. Despite all these issues, we know what the relevant factors are or what the situation can increase the risk of the MS.

on the other hand, this degeneration is in the early stages of therapy and other risk factors have evidence to influence them. Month and place of birth, family risk, sex, diet and circulation levels of vitamin D3, exposure to UVB, along with smoking, may be part of them. Migration affects risk and positive Epstein Barr serology, particularly accompanied by early infectious mononucleosis, is also likely to increase risk [12-14].

also, some environmental factors (possibly infections) gain access to a person with pre-puberty genetics [15]. Evidence of this theory is that a person living in tropical areas is unlikely to develop MS, but if a person moves into a moderate environment before puberty, they are at risk. although here is ongoing work in this area [16,17].

Risk Factor

These factors increase the risk of multiple sclerosis:

Age: MS may occur at any age, but usually occurs in people between the ages of 16 and 55.

Sex: Women have more than two to three times the risk of developing MS.

Family History: If one of your parents or siblings has MS, you are at risk of developing a disease.

Some Infections: Types of viruses are related to MS, including Epstein-Barr, a virus that causes infectious mononucleosis [18].

Race: White people, especially the northern generation, have the highest risk of developing MS. Asian, African or native Americans are at the lowest risk.

Weather: MS is very common in temperate countries, including Canada, northern United States, New Zealand, Southeast Australia and Europe [19].

Vitamin D: Having low levels of vitamin D and low sunlight increases the risk of MS.

Some autoimmune diseases: If you have thyroid disease, type 1 diabetes or inflammatory bowel disease, the risk for MS is higher.

Smoking: Smokers who have a primary symptom that may report MS signals are more likely to develop MS than non-smokers.

Pathophysiology

Demyelination is a division of the myelin sheath caused by an inflammatory and malignant process, an axon that has been partially or completely denuded. The Destruction of the myelin sheath disrupts the natural transfer of the nerve resulting in neurological symptoms and neurological symptoms. At first, the

majority of axons are retained, although some axons may be lost, especially in large chronic plaques [20].

Certain features of MS lesions include perivascular inflammation, followed by myelin scarring, loss of oligodendrocyte and proliferation of astroglial, and these processes are limited to Remyelinas and the formation of plaque. The traditional view shows that there are four stages of focal inflammation. The initial stage is characterized by the accumulation of inflammatory cells, lymphocytes and monocytes around the venules within the CNS [21]. Inflammation is sufficient to produce a functional block through the myelinated axons. Further, there is active degradation of oligodendrocyte and myelin sheath as a result of contact with macrophage and microglia. This is followed by depletion of oligodendrocytes in which denuded axons are seen within the lesion. Ultimately, the lesion is improved by the formation of an oscillation due to astrocytic response, hardened patches or plaques called the disease [22,23].

This view of the mechanism of the foundation of the new plaques has recently been challenged. A group of scientists, based on recent pathological studies of early changes in acute lesion, suggested that the death of the oligodendrocytoplasty before the inflammation and demyelination occurs in MS lesions [24]. This means that a MS lesion begins with the death of oligodendrocytes and related changes in the myelin sheath, which activates the local malignant macrophage, along with the strengthening of the inflammatory response. Within a few months, the pathology of multiple sclerosis is transformed, and the changes associated with the end stage of the disease indicate that the inflammatory response is increasingly "divided" and therefore largely separated from systemic effects with time. However, the cause of the death of oligodendrocyte is still unknown. In short, the relative contribution of "immune" proteins to the "mouthpiece nerve" in the pathophysiology of the disease is still being answered [25].

The most common sites of lesions in the MS are in the brown border, the perioentricular region, the white matter of the cerebellum, the vision nerve, and the cervical and spinal cord, but this disease can include any part of the CNS. Until recently, MS was widely recognized as a "white matter" of the CNS. Recent advances in imaging techniques and post-mortem studies have shown that MS lesions also occur in gray-brown matter with a very high prevalence in progressive forms of the disease. In demyelinated areas, the rate of conduction is reduced, while conduction along the non-affected parts of the axon on both sides of the lesion is normal [26]. The conduction block along with semi-deep axons is the main cause of negative symptoms such as weakness and numbness. It may also explain fatigue that has been criticized by many patients. These nearly demyelinated axons may be spontaneously discharged and accounting for unpleasant distortions of sensation reported by a high percentage of patients. Increasing the temperature sensitivity in many patients after exercise or immersion in hot water may be explained by semi-demyelinated axons [27].

Remyelination, which includes the reconsideration of demyelinated axons with new myelin shells, occurs in MS, and is an important process of "repairing lesions." Unexpectedly, this process occurs at an early stage of the development of lesions in both white and gray lesions. Conversely, remyelination often does not occur in old lesions, where inflammatory activity is minimal. In these old lesions, there is oligodendrocyte, but they are not active in the active remilinin and they are not likely to produce new myelin [28]. However, the amount of remilinin in MS varies greatly between patients. Generally, the amount of repair of lesions related to age, the number of

oligodendrocytes and macrophages in the lesions. Animal studies indicate that a critical event due to failure of remyelination is a disruption of the function of phagocytic macrophages to purify myelin residues [29]. These debris contain powerful agents that prevent the differentiation of oligodendrocyte precursor cells widely distributed throughout the CNS to oligodendrocytes. Therefore, inflammatory response in MS has both destructive effects (causing demyelination) and beneficial (facilitating remyelination). Understanding remyelination and its failure will open up new challenges for future research and can provide new therapeutic strategies [30].

Symptoms

MS symptoms in people are variable. The two people do not have the same symptoms, and the symptoms of each person can change over time or fluctuate. A person may experience only one or two of the possible symptoms, while another person experiences more than others [31]. More information about your symptoms or the person who has been considered is listed below. Many of these symptoms can be effectively managed with medication, rehabilitation, and other management strategies. Managing effective factors by an interdisciplinary team of healthcare professionals is one of the most important part of MS's comprehensive care [32].

Some of more common symptoms are: Fatigue, Walking Difficulties, Numbness or Tingling, Spasticity, Weakness, Vision Problems, Dizziness and Vertigo, Bladder Problems, Sexual Problems, Bowel Problems, Pain & Itching, Cognitive Changes, Emotional Changes, Depression, Speech Problems, Swallowing Problems, Tremor, Seizures, Breathing Problems and Hearing Loss [33].

Types of MS

While there is no way to predict with any certainty of the individual disease period, the four basic MS disease courses (also called type or phenotypes) are defined by the International Advisory Committee on MS Clinical Trials in 2013: Clinically isolated syndrome, relapsing remitting, secondary progressive and primary progressive [34].

Although a MS course is not considered, radiological syndrome (RIS) is used to classify people with MRI disorders in the brain and / or spinal cord in accordance with MS lesions, which is not explained by another diagnosis as well and There is no past or present neural signs or abnormalities in the nerve test [35]. Most people with MRI have been diagnosed with other symptoms, such as headache, and lesions similar to MS [36].

While these people may begin to develop symptoms and then be diagnosed with MS, not everyone is developing MS. There are no specific treatment guidelines for RIS. MRI and neurological monitoring and neurological examination are generally recommended to quickly detect changes. If diagnosis is MS, treatment can begin sooner. There is a lot of interest in RIS research and there are several studies that can provide more guidance for monitoring and treatment [37].

1. Clinically Isolated Syndrome (CIS)

Clinically isolated syndrome (CIS) is one of the MS disease courses. This type refers to the first part of the neurological symptoms that lasts for at least 24 hours and is caused by central nervous system (CNS) due to inflammation or demyelination (loss of myelin that covers the neural cells). It can also be either monofocal or multifocal:

Mono-focal area: A person experiences a single neurologic sign or symptom - for example, an optic neuritis attack caused by a single lesion.

Polygon area: The person experiences more than one sign or symptom - for example, an attack of optic neuritis that is accompanied by numbness or burning in the legs - results from lesions in more than one location [38].

This section usually does not have fever or infection and is followed by complete or partial recovery.

CIS progression to MS

People who experience CIS may or may not continue to develop MS. In identifying CIS, a health care provider faces two challenges: first, determining whether a person is exposed to neurological damage due to CNS; and, secondly, to determine whether a person experiencing this type of demyelinating event, continue to develop MS [39].

High risk of MS: When CIS is diagnosed with magnetic resonance imaging (MRI) that is similar to MS, the person has a 60 to 80 percent chance of developing second neurological disease and diagnosis of MS for several years.

Low risk of MS: When the CIS is not associated with brain lesions detected by MRI, this person has a 20% chance of developing MS in a similar period of time. Due to the revision of 2017 to MS diagnostic criteria, MS diagnosis can be done.

Regarding the reconsideration of MS diagnostic criteria, MS diagnosis may occur when the CIS is associated with MRI findings (old lesions or wounds) that confirms that one part of the previous damage occurred at another location in the CNS. New criteria also allow the presence of oligoclonal bands in the cerebrospinal fluid to help diagnose. As MRI technology becomes more advanced, MS detection is likely to be faster and there will be fewer people diagnosed with CIS [40].

The exact diagnosis is important at this time because people who are at risk for MS are encouraged to begin treatment for a change in the disease in order to delay or prevent a second neuronal stage and, thus, start MS [41]. In addition, the initial treatment may reduce the future disability caused by further inflammation and damage nerve cells, which are sometimes silent (occurring without significant symptoms). Several medications have a Food and Drug Administration (FDA) indication for CIS: Avonex®, Betaseron®, Extavia® and Mayzent®. Like MS, CIS is not directly inherited and is not contagious. CIS is two to three times more common than women. Seventy percent of people with cis are diagnosed between the ages of 20 and 40 (on average 30 years), but people can develop cis at an older or younger age [42].

How is CIS different from MS?

Based on clinical symptoms alone, CIS and MS may be the same. In both cases, damage to the myelin sheath (demyelination) with the way nerve impulses are carried from the brain, causes neurological symptoms.

A person with CIS, in the first instance, experiences symptoms of inflammation and anemia in the CNS; a person with MS has experienced more than one episode.

With CIS, MRI may show damage only in the area responsible for current symptoms; with MS, there may be multiple lesions in the MRI in different regions of the brain.

Due to the past revision of the diagnostic criteria, when the CIS is accompanied by evidence of an MRI that occurred at another stage, MS diagnosis can be done. The presence of oligoclonal groups in the cerebrospinal fluid can also help diagnose.

2. Relapsing-remitting MS (RRMS)

RRMS- The most common course of disease is characterized by clearly marked attacks of new or increasing neurologic symptoms. These attacks also show rebound or exacerbation - followed by partial or complete recovery (remission). During the remissions, all signs may disappear, or some signs may continue and become permanent. However, during recovery, there is no significant improvement in the disease. Increased disability is confirmed when the person in the next planned neurological assessment, as usually 6 to 12 months later, shows the same disability. Approximately 85% of people with MS are initially diagnosed with RRMS (Figure 2) [43].

This graphic shows the types of disease activity that can occur in the RRMS. However, each person's experience with RRMS will be unique. After relapse, new symptoms may disappear without increasing the level of inability, or new symptoms may only disappear and lead to increased inability. New lesions in the MRI, shown by arrows, often become part of a recurrence. However, new MRI lesions indicating MS activity may also occur without symptoms that the person is aware of it.

Relapsing-remitting MS characterized by inflammatory attacks on myelin (membrane layers insulated around neural fibers in the central nervous system (CNS)) as well as the nerve fibers themselves. During these inflammatory attacks, active immune cells cause small areas of local injury that cause MS symptoms. Since the site of the damage is very variable, none of the two people have exactly the same symptoms [44].

Why are modifiers used to describe RRMS?

Physical activity and progression should be evaluated at regular intervals with neurological examination and MRI. It is now able to describe your disease at different times, helping you and your care provider provide you with the treatment options and the results you expect. For example:

If RRMS is active and worsened, you and your MS Care Provider may want to discuss different treatments, including if there is no evidence of an activity or worsening. Together, you can consider the potential risks and benefits of other treatment options.

If your symptoms do not worsen about the treatment you are currently taking, but you are witnessing a new illness in the MRI, you and your health care provider may be worried about another change in treatment with another mechanism and Have more effective activity to control the disease and prevent it from getting worse [45].

If your RRMS remains stable without evidences of MRI activity or deterioration, you and your healthcare provider can be sure that the current treatment works effectively.

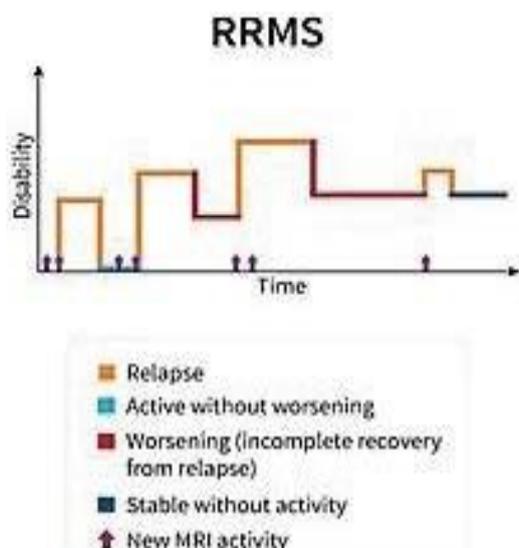


Figure 2. Relapsing-remitting MS (RRMS).

How does RRMS differ from progressive types of MS?

While RRMS is defined by attacks or relapses of new MS symptoms, progressive MS forms include fewer attacks.

- People with RRMS tend to create new brain lesions that are called plaques or wounds on magnetic resonance imaging (MRI).
- People with RRMS, tend to have more inflammatory lesions on MRI (seen when gadolinium dye is used during the MRI).
- People with primary progressive MS (PPMS) tend to have more spinal cord lesions.
- In the RRMS, women are two to three times more likely to be injured than men; in PPMS, the number of women and men is almost equal.
- RRMS is generally diagnosed before progressive disease courses.
- Most people with RRMS are diagnosed at their 20s and 30s (although they may occur in childhood or later adulthood), while PPMS is diagnosed at 40 or 50 years of age.
- The transfer of RRMS to SPMS generally occurs in people who live with RRMS for at least 10 years.

The most commonly reported symptoms in RRMS include fatigue, numbness, visual problems, spasticity or stiffness, bowel and bladder problems, and cognitive problems (learning and memory, and information processing). People with MS who progress gradually are more likely to be exposed to behavioral and mobility problems, along with symptoms that they may have.

3. Secondary progressive MS (SPMS)

SPMS- follows an initial relapsing remitting course. Most people who are diagnosed with RRMS ultimately lead to a progressive secondary course, which during the course of time is exacerbated by the progression of neurologic function (disability accumulation). SPMS can be active at different points in time (with relapse and / or evidence of new MRI activity) or inactive, as well as with progression (evidence of worsening of the disease in measuring target changes over time, with or without relapse or without progress (Figure 3) [46].

This is the type of disease activity that can occur in SPMS. However, each person's experience with SPMS will be unique. After a period of reversible illness, the disability gradually increases over time, with or without evidence of disease activity (relapse or change in MRI). In SPMS, occasional relapses and periods of stability may occur [47].

Why are modifiers used to characterize SPMS?

Physical activity and progression should be performed at least annually with neurological examination and MRI.

- If SPMS is active, you and the MS Care Provider will want to talk about modifying the disease to reduce the risk of recurrence.
- If your SPMS is active and progresses, despite the medications you are taking, talking to a MS Specialist Care Provider may be about the potential benefits and risks associated with changing an aggressive strategy.
- If your SPMS is not active, but there is evidence of progression and disability accumulation, you and the MS Healthcare Provider want to

focus on rehabilitation strategies to help improve performance and mobility and promote safety and independence.

- If your SPMS is sustained without activity or progress, a conversation with your MS Care Provider can focus on rehabilitation and other symptom management strategies to help you maintain performance.

How does SPMS differ from the other disease courses?

SPMS occurs in people who initially had a relapsing-remitting disease course. In other words, SPMS is the second stage of the disease for many people. In SPMS, people may or may not experience recurrence of disease due to inflammation. The disease gradually changes from the inflammatory process seen in the RRMS to a stage that progresses steadily and is characterized by damage or neurological damage [48].

Prior to the availability of improved treatment modalities, studies showed that 50% of those with RRMS were transferred to Advanced Secondary MS (SPMS) within 10 years and 90% would transition over a 25-year period.

While MS experts believe that medications affect the progression of the disease, it is too soon to tell the extent to which the disease-modifying treatments alter or delay the transition to SPMS.

4. Primary progressive MS (PPMS)

PPMS is an intensification of nerve function (accumulation of disability) from the onset of symptoms, without early relapses or remissions. PPMS can be active at different points in time as active (with occasional relapse and / or evidence of new MRI activity) or inactive, as well as with progression (Evidence of deterioration in the measurement of the goal of change in length Time, with or without relapses or new MRI activity) or without progress. Approximately 15% of MS patients with PPMS are diagnosed (Figure 4).

This graphic shows the types of disease activity that can occur in PPMS. Nevertheless, each person's experience with PPMS will be unique. PPMS can occur in short periods of sustained disease, with or without relapse or new MRI activity, as well as when the disability is increased with or without relapse or new lesions in the MRI [49].

Why are modifiers used to characterize PPMS?

Activity and progression of the disease can be assessed by neurological examination and MRI. Monitor your course of illness at different points of time and your health care provider has important talk about your treatment options and prognosis. For example:

- If your PPMS is activated, with a new MRI or relapse, your conversation with your MS care provider can be about starting treatment with disease-modifying therapy to reduce the risk of relapses, as well as rehabilitation can help to improve performance and Mobility.
- If you have PPMS and is stable without any activity or progress, discussions with your MS Care Provider can include the role of rehabilitation to help you maintain your performance as well as other symptoms management strategies that you may need.
- If your PPMS is not active (no new MRI or recurrence activity), but with increasing disability, conversation with your MS service provider can focus on rehabilitation strategies that can help you maintain function and keep you safe and independently mobile.

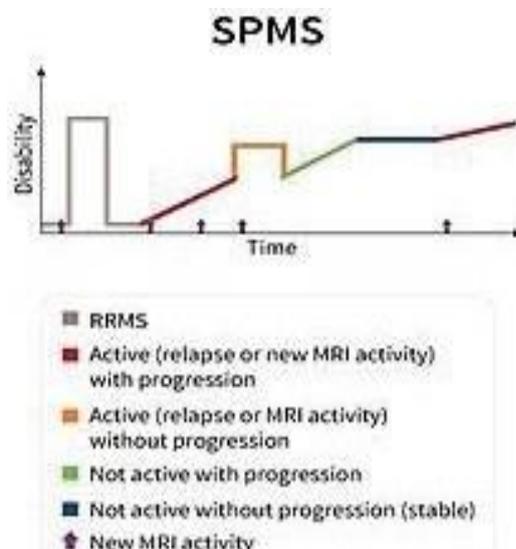


Figure 3. Secondary progressive MS (SPMS).

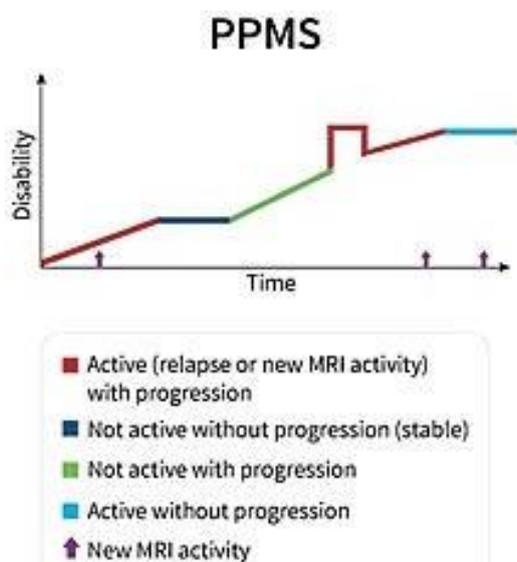


Figure 4. Primary progressive MS (PPMS).

How does PPMS differ from the other disease courses?

Although there are many variables among PPMS people, we know that as a group, they differ in different ways from people with MS relapsing forms:

MS relapsing forms (including relapsing-remitting MS, and secondary progressive in those individuals who continue to experience relapses) are defined as inflammatory attacks of myelin. PPMS contains less inflammation than the type observed in recurrent MS. As a result, people with PPMS tend to have less brain damage (also called plaque) than those with relapsing MS, and the lesions tend to contain fewer inflammatory cells. People with PPMS also have more lesions in the spinal cord than the brain. Together, these differences make PPMS more difficult to diagnose and treat than MS forms.

- In relapsing forms, women are two or three times more likely to be infected than men; in PPMS, the number of women and men is roughly equal.
- The average age of onset is approximately 10 years later in PPMS than in relapsing MS.
- People with PPMS tend to have more problems walking and remaining in the workforce.
- In general, people with PPMS may also need more help with their daily activities.

Diagnosis

The diagnosis of multiple sclerosis is based on the integration of clinical, imaging and laboratory findings. Clinical expertise is essential to demonstrate evidence of dissemination at a time and place, and most importantly, to eliminate other neurological conditions. MRI can provide this evidence and, apart from other conditions, provide early detection with increased confidence with successive versions of diagnostic metrics [50]. The diagnostic criteria known as McDonald's criteria have improved since technology has improved to make definitions better, easier, and more accessible to parts of the population, while preserving the specificity and sensitivity. However, several strategies to determine if you have met the old criteria for diagnosis of MS or for other possible causes of symptoms that are experiencing. Some of these strategies include: Accurate medical history, neurological exam and various tests, including spinal fluid analysis, and blood tests to eliminate other conditions [51].

There are many possible causes of neurological symptoms. When MS is considered as a potential diagnosis, before the MS diagnosis is discontinued, other causes should be identified through the following tools and tests [52]. While this deprivation process may be fast for some, it can also be much longer, by repetitive testing, which is sometimes necessary. MS detection is possible quickly and accurately and is important for several reasons:

In timely and accurate diagnosis, you live with frightening and distressed signs and you should know your discomfort. Detection allows you to start the adjustment process and eliminate worries about other illnesses, such as cancer [53]. Also, we now know that permanent nerve damage may occur even in the early stages of MS, that's why it is important to confirm the diagnosis so that you can begin the appropriate treatment in the early process of the disease [54].

Criteria for a diagnosis of MS

At this time, there are no signs, physical findings, or laboratory tests that can determine whether you have MS. The doctor uses several strategies to

determine if you meet MS diagnostic criteria. In order to diagnose MS, the physician should:

- Finding evidence of injury in at least two distinct parts of the central nervous system (CNS), which includes the brain, the spinal cord and the optic nerve
- Finding evidence that the damage occurred at different points in time
- Reject all other diagnoses

The McDonald Revised criteria, published in 2017 by the International Panel on Multiple Sclerosis, include specific guidelines for the use of MRI and cerebrospinal fluid analysis to accelerate the diagnostic process.

MRI can be used to search for a second area of injury in a person who has experienced only one attack (also as a relapse or exacerbation) of symptoms of MS, such as clinical isolated syndrome (CIS).

MRI can also be used to confirm that damage has occurred at two different points in time. In some cases, the presence of oligoclonal bands in cerebrospinal fluid analysis can be used instead of dissemination in time to confirm the diagnosis of MS [55].

Tools for making a diagnosis

Your health care provider:

- Takes a careful history for the identification of past or present signs that may be created by the MS.
- Gathering geographic information, family history, environmental effects, history of other diseases and places of travel that may provide clues.
- Perform a comprehensive neurological exam that includes bone marrow tests (vision, hearing, face sensation, strength, swallowing), feeling, reflex, coordination, walking and balance.

In many cases, medical history and neurological examination provide enough evidence to meet diagnostic criteria. Other tests are used to confirm the diagnosis or identification of possible causes of other symptoms or neurological findings [56].

Clinically Isolated Syndrome (CIS)

In the CIS, it is important to reject other possible causes, as some may need immediate intervention. The diagnostic process includes the following:

- A complete medical history, including information on specific symptoms and the current time.
- Neurological examinations.
- Magnetic resonance imaging (MRI) to find signs of inflammation and demyelination in the CNS.
- Blood tests are used to identify or reject possible causes of other symptoms.

A lumbar puncture (spinal cord) may be performed for the examination of the cerebrospinal fluid (CSF) for the oligoclonal bands. McDonald's 2017 criteria for diagnosing MS allows the presence of oligoclonal tapes in a cerebrospinal fluid to help speed up detection.

Relapsing-remitting MS (RRMS)

The criteria for diagnosis of MS that resurface require evidence of at least two areas of damage ("diffusion in space") in the central nervous system (CNS) that occurred at different points in time (propagation at time). Diagnostic criteria using MRI results in combination with the history of symptoms as well as findings in the neurological examination to help diagnose. In addition, the physician should be able to reject any illness or other conditions that may be responsible for the symptoms. Recent changes to these criteria allow the presence of oligoclonal bands in the spinal cord fluid to be a substitute for "playback in time," thus accelerating the speed of diagnosis for many [57].

Secondary progressive MS (SPMS)

An inflammation that occurs early in the MS disease process and a sign of returning (RRMS) slowly decreases over time. Lower inflammatory changes occur in the central nervous system and the person experiences relapses[58]. Although there are several complications at this stage in the disease, symptoms worsen over time; this worsening is known as progression of the disease. The term "advanced secondary" is recognized by the fact that advanced secondary MS (SPMS) is only detected in an individual who has previously experienced RRMS.

Since the transition from relapsing-remitting course to more progressive one is a gradual process, the healthcare provider is not able to tell exactly what is happening [59]. If the symptoms get worse, the challenge for the provider is to determine if:

- The worsening of the last relapse (in other words, the permanent, but stable, damage that has come to an end after the inflammatory attack), which means that the person is exposed to RRMS.
- The disease is still increasing, even if the person does not experience relapses of inflammation, this means that the person has been transferred to the SPMS disease period.

Types of strategies, including the exact history of changes in person's symptoms, neurological examination, and repetitive magnetic resonance imaging (MRI) scans, helps determine whether the transition to SPMS has occurred [60].

Primary progressive MS (PPMS)

Unlike MS relapsing forms, the progression of the primary MS (PPMS) is characterized by a relatively stable and gradual change in functional ability over time, which is often related to walking - without any relapses[61]. Due to this fundamental difference in the course of the disease, various criteria for the accurate diagnosis of PPMS are used. The PPMS diagnostic criteria are:

- One year of progression of the disease (deterioration of the functioning of the brain without a recovery).

Two of the following:

- A type of lesion in the brain that is known by experts as an example of MS.
- Two or more similar spinal cord lesions.
- Evidence in the spinal cord of the oligoclonal group or a high IgG index, both indicating the activity of the immune system in the central nervous system.

Meeting these criteria can sometimes take a relatively long time, especially if the person has recently begun to experience neurological symptoms. Several studies have suggested that PPMS diagnosis may take two to three years longer than relapsing MS [62].

Treatment

More than a dozen of the disease-modifying therapies approved by the US Food and Drug Administration (FDA) are available for the treatment of MS. Each drug has an indication of the FDA for the type of MS that can be used for treatment [63]. There are currently more treatments available for relapsing forms of MS than progressive forms. Scientists around the world are actively working to find more effective therapies for MS progressive forms and address advanced MS challenges as a primary goal of research strategy [64].

Clinically Isolated Syndrome (CIS)

An MS disease-modifying therapy (DMT) is often recommended for those with a syndrome who are advancing in the clinical diagnosis of MS (CDMS) and aiming for a delay in a second attack. DMTs approved by the United States Food and Drug Administration (FDA) for renewal of copper relapses forms. Initial and ongoing treatment of MS is supported by the MS Alliance, which includes the National Association of Multiple Sclerosis. This evidence-based agreement is in the context of disease-modifying treatments that are useful when discussing treatment options with healthcare providers and supporting insurers for access and coverage [65].

Relapsing-remitting MS (RRMS)

The US Food and Drug Administration (FDA) has approved more than 10 medicines for the treatment of MS recurrent diseases, including common clinical syndrome, recurrent cancer (RRMS) and secondary advanced disease (recurrent SPMS). Research has shown that all MS medications can:

- Reduce the number of relapses (also attacks or escalation)
- Limiting the new MS activity (new damages in the name of plaque or ulcers) in the central nervous system (CNS) and observation in magnetic resonance imaging (MRI)
- Getting worse (progress)

Years of research show that the onset of one or more of these drugs is the most effective way to manage MS disease shortly after MS diagnosis. These MS drugs alter MS and are also known as disease-modifying treatments (DMT).

Each of the disease-modifying treatments have side effects and the risks associated with them. The onset of a DMT or change in DMT are decisions by a person with MS and a MS healthcare provider, after discussing how the drug is taken, the side effects, risks and costs.

Secondary progressive MS (SPMS)

More than 12 disease-modifying treatments have been approved by the US Food and Drug Administration (FDA) for use in MS recursive forms, including: Common Clinical Syndrome, Repetitive Cancer (RRMS) and Secondary Secondary Disease (SPMS) With flush). People who have been reintroduced or revised at one stage of the disease are likely to continue, unless they have enough control over their illness [66].

A drug - Ocrevus® (Ocrelizumab) - is developed by the US Food and Drug Administration (FDA) for the treatment of primary-progressive MS (PPMS), as well as for clinically isolated syndrome, relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses). Disease modifying treatments primarily reduce inflammation in the central nervous system (CNS), they also work in a course of disease that is characterized by nerve degeneration rather than inflammation. For this reason, they have not been shown to be effective in progressive disease types unless the person indicates a relapse or MRI activity due to inflammation [67].

A number of these factors, including Copaxone® and an experimental drug called Rituxan, have been studied in PPMS, but unfortunately without having a positive effect on progression. There are several clinical trials recently conducted for Advanced MS Forms or some other PPMS.

In addition to treatment with a disease-modifying therapy, there are other symptom management and rehabilitation strategies that people with PPMS and health care teams can use to manage the illness [68-70].

Conclusion

Today, our understanding of MS has progressed greatly, and this understanding has partly led to MS treatment, especially in the stages of relapse and inflammation. According to research in this area, major advances in MS depend on the identification of abnormal responses to the immune system and how they are measured and corrected. It is now clear that MS is primarily an autoimmune disease, not an ongoing infection, even if an infectious agent causes the disease or is associated with the disease. All genetic studies refer to the immune system, which is recognized as the main cause of pathology, resulting in a complex interaction between genes and the environment. Imaging through MRI provides an important opportunity to monitor the disease. In this pathway, the absence of a positive effect of anti-TNFa therapy and a dramatic effect of the anti-CD20 treatment was amazing. Precision research has evolved as a major issue in medicine and has become a major goal in MS. The main question is the key to the response in MS to how to treat and better understand the disease. This will require new approaches to the CNS processes. If MS is triggered through the environment to suspected and at-risk people, MS may be prevented. Of course, some people believe that vaccination against EBV or treating children with high risk of developing MS with vitamin D can be an effective approach. Prevention can be the ultimate treatment for MS and depends on treatments that modulate the immune system in childhood or adolescence. Such a vaccine may initially be given to high-risk person, such as children whose parents have MS, and who have a strong family history. The most important factor in identifying an infectious agent is really related to the disease. Over the past century, MS has resulted from an unknown and untreatable disease to one with many treatment options and many unknown paths.

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