JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CASE STUDY Open Access

Multiple Sclerosis: II. Diagnosis and Symptoms Management

Dr. Alain L. Fymat*

Professor, International Institute of Medicine & Science, California, USA.

Received date: May 23, 2023, **Accepted date:** May 29, 2023, **Published date:** June 04, 2023.

***Corresponding Author:** Dr. Alain L. Professor, International Institute of Medicine & Science, California, USA.

Abstract

Multiple sclerosis (MS) is typically diagnosed based on the presenting signs and symptoms in combination with supporting medical imaging and laboratory testing. It is a differential diagnosis. It may be important to distinguish between a clinically-isolated syndrome and MS. In this article, I review the diagnosis process in its several components and discuss the McDonald's diagnostic criteria and their several revisions. I also present newer diagnostic tools including the McArdle's sign and an antibody test that measures immunoglobulin kappa free light chains. I systematically discuss the management of eighteen specific MS symptoms as well as the management of the disease per se. Lastly, I elaborate on the self-management of the disease including the management of co-morbidities.

Abbreviations

BON: Bilateral ON; CBT: Cognitive behavioral therapy; CDMS: Clinically-definite MS; CRT: Cognitive rehabilitation therapy; CDMS: Clinically-definite MS: CIS: Clinically-isolated syndrome; CNS: Central nervous system; CSF: Cerebrospinal fluid; CVS: Central vein signs; DID: Dissemination in space; DIT: Dissemination in time; DMD/T: Disease-modifying drug/therapy; EDSS: Expanded Disability Status Scale; Igκ: Immunoglobulin κ; JCV: John Cunningham virus; LCFA: Long-chain fatty acids; LETM: Longitudinally extensive transverse myelitis; MOG: Myelin oligodendrocyte glycoprotein; MOGAD: MOG antibody-associated disease; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; NMO: Neuromyelitis optica; NMOSD: NMO spectrum disorder; ON: Optic neuritis; PML: Progressive multifoal leukoencephalopathy; PMS: Progressive MS; PPMS: Primary progressive MS; RRMS: Relapsing-remitting MS; SPMS: Secondary progressive MS. TMJ: Temporo-mandibular joint.

Keywords

Multiple sclerosis; diagnosis process; Mc Donald's diagnostic criteria; symptoms management; disease

management; self-management; McArdle's sign; immunoglobulin antibody test.

Introduction

Multiple sclerosis (MS) is typically diagnosed based on the presenting signs and symptoms in combination with supporting medical imaging and laboratory testing. It can be difficult to confirm MS, especially early on, since the signs and symptoms may be similar to those of other medical problems. It is not uncommon for a diagnosis to take several months and, frustratingly, it can take even longer. A range of other possible causes need to be explored and many different tests need to be carried out.

Neurologists base the diagnosis on repeated neurologic symptoms and signs disseminated in both space and time. They use recently developed diagnostic criteria taking advantage of significant advances in radiological imaging. These criteria, named for the senior member of an international panel, Dr. W. Ian McDonald, are the most commonly used method of diagnosis with the Poser and the older Schumacher criteria being of mostly historical significance. They rely on the number and location of MRI lesions as well as the number of attacks. Neurologists also use certain cerebrospinal fluid (CSF) findings and evoked potentials (see later) to support a diagnosis. Nonetheless, despite the above exhaustive approach, MS is commonly misdiagnosed due to the lack of clinical signs and MRI findings specific to the disease.

The diagnosis of MS requires evidence of at least two areas of damage in the CNS, which have occurred at different times. Still maintaining a high sensitivity and specificity, neurologists now diagnose MS during its first episode. They can institute therapy and blunt, although not halt, the illness early in its course. Using current criteria also allows neurologists to follow patients' subclinical as well as clinical progression and monitor their response to treatment. Before proceeding with the issues surrounding the diagnosis-making, it may be important to distinguish between a clinically-isolated syndrome (CIS) and MS.

The Clinically-Isolated Syndrome

CIS refers to a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS. It can be either monofocal or multifocal. In the former episode, the person experiences a single neurologic sign or symptom (for example, an attack of optic neuritis, ON) that is caused by a single lesion. In the latter episode, the person experiences more than one sign or symptom (for example, an ON attack accompanied by numbness or tingling in the legs) caused by lesions in more than one place. It usually has no associated fever or infection and is followed by a complete or partial recovery.

How is CIS different from MS?

Based upon clinical symptoms alone, CIS and MS may appear to be the same. In both, demyelination (damage to the myelin sheath) interferes with the way nerve impulses are carried from the brain, resulting in neurologic symptoms. By definition, a person with CIS is experiencing the first episode of symptoms caused by inflammation and demyelination in the CNS. On the other hand, a person with MS has experienced more than one episode. With CIS, an MRI may demonstrate damage only in the area responsible for the current symptoms. By contrast, with MS, there may be multiple lesions on MRI in different areas of the brain. According to the 2017 revisions to the diagnostic criteria for MS (see below), the diagnosis of MS can be made when CIS is accompanied by MRI findings (old lesions or scars) that confirm that an earlier episode of damage occurred in a different location in the CNS. The new criteria also allow for the presence of oligoclonal bands in a person's CSF to help make the diagnosis. As MRI technology becomes more advanced, it is likely that the diagnosis of MS will be made more quickly and there will be fewer people diagnosed with

CIS.

Progression from CIS to MS

Individuals who experience a CIS may or may not go on to develop MS. In diagnosing CIS, two challenges present themselves, namely (1) whether the person is experiencing a neurologic episode caused by damage in the CNS and (2) determining the likelihood that this demyelinating event will develop MS.

Risk of developing MS

There is a risk spectrum of developing MS, including:

• **High risk of developing MS:** When CIS is accompanied by MRI-detected brain lesions that are similar to those seen in MS, the person has a 60%-80% chance of a second neurologic event and diagnosis of MS within several years.

• **Low risk of developing MS:** When CIS is not accompanied by MRI-detected brain lesions, the person has about a 20% chance of developing MS over the same period of time.

An accurate diagnosis at this time is important because people with a high risk of developing MS are encouraged to begin treatment with a disease-modifying drug/therapy (DMD/T) in order to delay or prevent a second neurologic episode and, therefore, the onset of MS. In addition, early treatment may minimize future disability caused by further inflammation and damage to nerve cells, which are sometimes silent (occurring without any noticeable symptoms). Several medications have an FDA indication for CIS (Avonex®, Betaseron®, Extavia® and Mayzent®).

Who gets a CIS and when?

Like MS, CIS is not directly inherited, and it is not contagious. CIS is two- to three- times more common in women than men. Seventy percent of people diagnosed with CIS are between the ages of 20 and 40 years (average 30 years), but people can develop CIS at older or younger ages.

The Diagnostic Process

MS is complex and difficult to arrive at because it can cause many different symptoms. It is hard to pinpoint exactly when it begins, but the early signs and symptoms are different for everyone. It is not uncommon for a diagnosis to take several months and may even take longer. A range of other possible causes need to be explored and many different tests need to be carried out.

As of 2017, there is no single test (including biopsy) that can provide a definitive diagnosis of MS. Brain and spine MRI may show areas of demyelination (lesions or plaques). Gadolinium can be administered intravenously as a contrast agent to highlight active plaques and, by elimination, demonstrate the existence of historical lesions not associated with symptoms at the moment of the evaluation.

In addition to brain atrophy seen in MRI, central vein signs (CVS) have also been proposed as a good indicator of MS in comparison with other conditions causing white lesions. One small study found fewer CVS in older and hypertensive people. Further research on CVS as a biomarker for MS is ongoing.

Testing obtained from a lumbar puncture can provide evidence of chronic inflammation in the CNS. The fluid is tested for oligoclonal bands of IgG on electrophoresis, which are inflammation markers found in 75%–85% of people with MS.

Lacking specific tests, the diagnosis often relies on ruling-out other conditions that might produce similar signs and symptoms – this is known as a 'differential diagnosis'. There are several diseases that present similarly to MS such as: intractable vomiting; severe

ON, bilateral ON (BON), suspicion for neuromyelitis optica spectrum disorder (NMOSD). Involvement of multiple cranial nerves raises suspicion for neurosarcoidosis. Longitudinally extensive transverse myelitis (LETM), in which spinal cord damage spans three or more vertebral segments, raises suspicion for NMOSD, neurosarcoidosis, anti-MOG–associated myelitis, systemic rheumatologic disease, or a paraneoplastic disorder.

In most people with relapsing-remitting MS (RRMS), the diagnosis is fairly straightforward; it is based on a pattern of symptoms consistent with the disease and confirmed by brain MRI imaging scans. Diagnosing can be more difficult in people with unusual symptoms or progressive disease. In the latter cases, further testing with spinal fluid analysis, evoked potentials, and additional imaging may be needed. The process follows the following steps:

• **Medical history:** It may be the most important of the examination. It includes the story of the symptoms and complaints, and the general life time health including operations and accidents, illnesses in the family, occupational information, and other details.

• **General and neurological examination:** Here, the neurologist may carry out a general physical examination (lungs, heart, blood pressure, muscles and skin) and a neurological examination (simple tests for balance, movement, coordination, reflexes, vision, attention span, speech, swallowing, sense of touch, memory and thinking, and bowel and bladder function). Thereafter, some or all of the following tests may be recommended.

• **Laboratory blood tests:** They help rule out other diseases with symptoms similar to MS. Tests to check for specific biomarkers associated with MS are currently under development and may also aid in diagnosing the disease.

• **Lumbar puncture (spinal tap):** Under local anesthetic, a needle is inserted in the lower back into the space around the spinal cord. It collects a small sample of fluid, which is then tested in the laboratory to examine certain proteins for the presence of oligoclonal bands, abnormalities, and the presence of antibodies associated with MS. It can help rule-out infections and other conditions with symptoms similar to MS. It can also show abnormalities in antibodies that are associated with MS. The lumbar puncture can leave the patient with a headache for a few days.

• **MRI:** A machine called an MRI scanner uses magnetic fields and radio waves to build up an inside picture of the brain and spinal cord. These pictures (scans) create images of cross-sections of the brain and spinal cord. Any lesions (areas of damage and scarring) that show up on the scan can reveal inflammation, damage to the myelin surrounding the nerves, and scars (or lesions) that may be caused by MS. The test may require an intravenous injection of a contrast material to highlight those lesions that indicate if the disease is in an active phase. Brain atrophy, also revealed by the MRI scan, is seen as an indicator of MS. MRI has become the most accurate and helpful test for MS. Nonetheless, it is important to remember that MRI does not show MS, only changes that could be due to MS. Further, MRI does not indicate the state of the disease (mild, advanced, getting worse, less inflammatory changes such as those in the grey matter or in areas that appear normal). For those patients who might experience anxiety, mild sedation can be administered such as Lorazepam (Ativan) or Diazepam (Valium).

• **Evoked potential tests:** These tests measure how fast messages go from the brain to the eyes, ears, and skin. They record the electrical signals produced by the nervous system in response to stimuli. The tests may use visual or electrical stimuli. They measure the rate and form of the impulses as they pass through specific nerves. One watches a moving visual pattern, or short

electrical impulses are applied to nerves in the legs or arms. Electrodes measure how quickly the information travels down the nerve pathways. Thus, to measure vision, patterns are shown on a screen. Small pads are placed on the head to measure how the brain reacts to what one sees. To test hearing, the patient listens to clicks through headphones. Another test measures how fast muscles react following tiny shocks on the skin that feel like 'pins and needles. Reactions are usually slower if MS has damaged the myelin around nerves that control the body parts being tested.

• **"Hot bath" test:** Many years ago, to diagnose MS, a person suspected of having the disease was immersed in a hot tub of water. The appearance of or worsening neurologic symptoms was taken as evidence the person had MS.

Diagnosing primary progressive MS (PPMS)

To diagnose PPMS, the patient should not have had any relapses and the disability must have worsened over at least a year.

• **MRI scan:** The scan must show two or more lesions in different parts of the brain or spinal cord. These must have happened at different times.

• **Lumbar puncture:** It must also show signs of MS (antibodies) in the cerebrospinal fluid.

Diagnosing secondary progressive MS (SPMS)

To diagnose SPMS, the patient must have had relapses in the past, with a steady increase in disability for at least six months that is not linked to any relapse. The Expanded Disability Status Scale (EDSS), discussed in article I in this series, can be used to measure disability and track if it is getting worse.

The McDonald's diagnosis criteria

Proposed in 2001, these criteria have been revised in 2005, 2010, and 2017. For a diagnosis, they propose either of the following alternatives: "MS", "possible MS", or "not MS". They maintained a scheme for diagnosing MS based solely on clinical grounds but also proposed for the first time that, when clinical evidence is lacking, MRI findings can serve as surrogates for dissemination in space (DIS) and/or time (DIT) to diagnose MS. To prove the existence of demyelinating lesions, by image or by their effects, MRI should show lesions in different areas of the nervous system (DIS) and that they accumulate over time (DIT). They facilitate the diagnosis of MS in patients who present with their first demyelinating attack and significantly increase the sensitivity for diagnosing MS without compromising the specificity (Table 1).

Clinical presentation	Additional data needed
• 2 or more attacks (relapses) • 2 or more objective clinical lesions	• None. Clinical evidence will suffice (additional evidence is desirable but must be consistent with MS)
• 2 or more attacks • 1 objective clinical lesion	• Dissemination in space demonstrated by: • MRI, or • o Further clinical attack involving a different site
• 1 attack • 2 or more objective clinical lesions	• Dissemination in time demonstrated by: • MRI, or • A positive CSF (specific oligoclonal bands) and 2 or more MRI lesions consistent with MS; or • o Second clinical attack
• 1 attack • 1 objective clinical lesion (mono-symptomatic presentation)	• Dissemination in space demonstrated by: • MRI, or a • Second clinical attack implicating a different CNS site • and

	• Dissemination in time demonstrated by: • MRI, or • Second clinical attack, or • o CSF-specific oligoclonal bands
• Insidious neurological progression suggestive of MS (primary progressive MS)	• 1-year of disease progression (retrospectively or prospectively determined) • and 2 of the following: • Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive visual evoked potential (VEP) • Positive spinal cord MRI (two focal T2 lesions) • o Positive CSF

Table 1: The McDonald's diagnosis criteria for multiple sclerosis

While very useful, the above criteria have been criticized by some in the following regards: None or low specificity, low sensitivity, false positives, and unclear definition of "lesions typical of MS". However, the criteria have good predictive quality with respect to the conversion of clinically-isolated syndrome (CIS) to clinically definite multiple sclerosis (CDMS) when evaluated in non-selected populations.

Common examples of patients who are initially classified as having possible MS are those who present with their first symptom (since they have had only one episode, they are identified with a CIS) or those who have had repeated episodes but always in one site (thus, not multiple episodes in the areas involved).

Newer Diagnostic Tools

A new clinical sign for the reliable detection of MS

The Mayo Clinic has described a new clinical sign that is highly specific for the diagnosis of MS – the McArdle's sign, which is a clinical phenomenon in which neck flexion induces rapid, reversible weakness. The pathophysiology of the sign is uncertain but it is speculated that it might be due to a nerve conduction block induced by the mechanical stretching of the spinal cord with neck flexion. If that possibility is borne out, McArdle's sign might potentially help identify patients who would benefit from treatment with conduction-enhancing medications such as Dalfampridine. The phenomenon might indicate that despite demyelination, patients might have sufficient viable axons to overcome conduction block with medication. The sign can be quantitated using a torque measurement device developed at the Mayo Clinic for the study. It allows for both isometric and isoinertial testing.

The McArdle's sign is moderately sensitive for a diagnosis of MS when compared with other myelopathy conditions that mimic MS. The sign can be immediately translated into practice. Finger extensor muscles, which are among the first muscles to weaken in people with MS provide a convenient means of testing. Patients with symptoms of MS might have a completely normal clinical exam, with normal reflexes and strength, but lost strength with neck flexion.

A new antibody test for MS

Instead of the current CSF gold standard testing (oligoclonal bands), the new antibody test measures immunoglobulin kappa (Igκ) free light chains. The test's results are available in about 20 minutes.

The test was developed by researchers at the Mayo Clinic. They analyzed paired CSF and serum samples from 702 patients who had immunoglobulin kappa (Igκ) CSF testing and oligoclonal band testing. The test results' specificity and sensitivity for diagnosis were evaluated to determine a value comparable to the detection of oligoclonal bands. The value was then

validated in 657 prospective paired samples. The key points of this test are: A measure of 0.1 mg/dL provides similar sensitivity and specificity for the diagnosis of MS compared to oligoclonal band testing; testing is less labor-intensive, less time-consuming, and less costly than oligoclonal band testing; testing is more automated than oligoclonal band testing, substantially limiting subjective visual interpretation; and the test meets class I criteria for the diagnostic accuracy of MS as a biomarker.

Test	Remarks
Symptom patterns + Differential diagnosis (ruling-out other conditions)	Plus MRI scans • Myelitis (longitudinal extensive transverse, LETM) • Myelitis (MOG-associated) • Neuritis (bilateral; severe optic) • Neuromyelitis (NMOSD) • Neurosarcoidosis • Paraneoplastic disorder • Systemic rheumatologic disease • o Vomiting (intractable)
Spinal tap (oligoclonal bands)	"Gold standard"
Biopsy	Not definitive
JCV (Stratify JCV antibody ELISA)	Screen for risk factors for PML development (an opportunistic viral brain infection caused by JCV)
Laboratory blood tests	Specific biomarkers
Immunoglobulin kappa	New antibody
Central vein signs	Fewer in older and hypertensive people
PMS (or unusual symptoms)	Evoked potentials
PPMS	MRI + lumbar puncture
SPMS	Past relapses + disability increases
Other: Hoth bath test	Worsening neurologic symptoms
Other: McArdle's sign	Neck flexion induces rapid reversible weakness

Source: A. L. Fymat (2023)

Key: JCV: John Cunningham virus; LETM: Longitudinal extensive transverse myelitis; MOG: Myelin oligodendrocyte glycoprotein; NMOSD: Neuromyelitis optica spectrum disorder; PML: Progressive multifoal leukoencephalopathy; PMS: Progressive MS; PPMS: Primary progressive MS; SPMS: Secondary progressive MS.

Table 2: Possible MS diagnostic tests

Management of MS Symptoms

Managing MS is an ongoing process, beginning with the very first symptoms and continuing throughout the disease course. It is never too soon or too late to think about how to access high quality, comprehensive, interdisciplinary care. Knowing what to look for, where to find it, and how to work effectively with the attending doctor and other health professionals is essential to health, wellness, and quality of life. Prior to managing one's MS symptoms, one must first come to terms with a diagnosis of the disease.

It is important to recognize at the outset that although a wide range of symptoms may occur with MS, a given individual may experience only some of them and never have others. Some symptoms may occur and resolve, and perhaps never return. Because it is such an

individual disease, it is not helpful and even misleading and frightening to compare oneself with anyone else, who often will have different symptoms, a different pattern of disease, and a different disease course.

There are many treatments that can help with symptoms or disability, including drugs (a total of 98 drugs and counting), therapies, and equipment. These will be summarized in Table 3 below. Here, only tried-and-tested techniques are used to help deal with MS challenges.

I have identified 18 different categories of symptoms and, for convenience, have treated them below in alphabetical order (# 1 through #18). These could also be rearranged into 4 broad classes: Physical (including # 1, 4, 6, 8, 9, 10, 11, 12, 14, 15, 17, and 18); sensory (# 14); emotional (including # 2, 5, 7, 11, 13, and 16); and cognitive (# 3). [Note: Here # 11 (muscle weakness and spasticity) and # 14 (sexual dysfunction) have been classed as both physical and sensory.] For all these drugs, by trial and error, a customized dosage should be progressively attained and prescribed for each patient.

1. Bladder control and bowel symptoms

A number of problems with the bladder can occur in MS, each of which needs a specific approach to management. Nonetheless, bladder problems are common in MS and can be managed with simple measures in most cases, but they can also lead to serious complications if left untreated. Bladder control and constipation may include urinary frequency, urgency, or the loss of bladder control. A small number of individuals retain large amounts of urine. Medical treatments (26 of them) are available for bladder-related problems. On the other hand, bowel control problems (primarily constipation) are less common than bladder problems and can be simply managed:

• For dysfunction (14)

- Botox (Onabotulinumtoxin A®).
- DDAVP Nasal Spray (Desmopressin®).
- Detrol (Tolterodine®).
- Enablex (Darifenacin®).
- Flavoxate hydrochloride (Urispass®).
- Flomax (Tamsulosin®).
- Myrbetriq (Mirabegron®).
- Oxybutin chloride (Ditropan®; Ditropan XL®).
- Oxytrol (Oxybutynin®).
- Propantheline bromide (Pro-Banthine®).
- Prazosin.
- Tofranil (Imipramine®).
- Tolterodine tartrate (Detrol®).
- Vesicare (Solifenacin succinate®).

• For infection (7)

- Bactrim.
- Cipro (Ciprofloxacin®).
- Hiprex (Methenamine®).
- Levaquin (Levofloxacin®).
- Macrodantim (Nitrofurantoin®).
- Pyridium (Phenazopyridine®).
- Septra (Sulfamethoxazole®).

• For bowel dysfunction (8)

- *Colace (Docusate®).*
- *Dulcolax (Hisacodyl®).*
- *Enemeez (Docusate ® stool softener laxative).*
- *Fleet Enema (Sodium phosphate®).*
- *Metamucil (Psyllium hydrophilic musilloid®).*
- *Mineral Oil.*
- *Phillips milk of magnesia (Magnesium hydroxide®).*
- *Sani-supp suppository (Gylcerin ®).*

2. Clinical depression (1)

Clinical depression is frequent among people with MS. MS may cause depression as part of the disease process and chemical imbalance in the brain. Depression can intensify symptoms of fatigue, pain, and sexual

dysfunction. It is most often treated with cognitive behavioral therapy (CBT) and:

- Selective serotonin reuptake inhibitors: Antidepressant medications, which are less likely than other antidepressant medications to cause fatigue.

3. Cognitive impairment (1)

Cognitive impairment (a decline in the ability to think quickly and clearly and to remember easily), affects up to three-quarters of people with MS. These cognitive changes may appear at the same time as the physical symptoms or they may develop gradually over time. Drug used is:

- Donepezil: May be helpful in some cases. (Note: Repetitive use of steroids can have long-term effects that include cataracts, osteoporosis, and weight gain or, rarely, avascular necrosis of the hip that requires a hip replacement).

4. Constipation (3)

Constipation is also common and can be treated with:

- High-fiber diet.
- Laxatives.
- Stool softeners.

5. Depression (7)

- Celexa (Citalopram®).
- Cymbalta (Duloxetine hydrochloride®).
- Effexor (Velafaxine®).
- Paxil (Paroxetine®).
- Prozac (Fluoxetine®).
- Wellbutrin (Bupropion®).
- Zoloft (Sertraline®).

6. Dizziness and Vertigo (3)

In MS, the problem is often in the nerve connection within the brainstem and brain. It usually is transient, lasting hours or occasionally weeks. Drugs are:

- Antivert (Meclizine®).
- Diazepam (Valium®): A sedative.
- Intravenous steroids

7. Emotional changes (1)

- Nuedexta (Dextromethorphan® + Quinidine®).

8. Eye and vision problems (1)

Eye and vision problems are common in people with MS, but rarely result in permanent blindness. Inflammation of the optic nerve (optic neuritis) or damage to the myelin that covers the nerve fibers in the visual system can cause blurred or grayed vision, temporary blindness in one eye, loss of normal color vision, loss of depth perception, or loss of vision in parts of the visual field. Uncontrolled horizontal or vertical eye movements (nystagmus), “jumping vision" (opsoclonus), and double vision (diplopia) are common in people with MS and RRMS. Uhthoff's phenomenon is probably related to an increase in body heat that affects nerve conduction. Vision returns when the person stops exercising and cools down. Intravenous steroid medications, special eyeglasses, and periodically resting the eyes may be helpful:

- Methylprednisolone: An intravenous steroid. High dose.is the standard treatment.

9. Fatigue (7)

Fatigue is a common symptom of MS; it is reported in up to 90% of people with MS. It may be both physical (for example, tiredness in the arms or legs) and cognitive (slowed processing speed or mental exhaustion). Its cause is not well understood. However, some types of fatigue may happen due to nighttime waking from bladder dysfunction, pain, depression or

the effort it takes to perform daily duties.

- Adderall (Dextroamphetamine® and amphetamine).
- Amantadine.
- Methylphenidate
- Modafinil
- Provigil (Modafinil®).
- Prozac (Fluoxetine®).
- Ritalin (Methylphenidate®).

Daily physical activity programs of mild to moderate intensity can significantly reduce fatigue, although people should avoid excessive physical activity and minimize exposure to hot weather conditions or ambient temperature. Occupational therapy can help people learn how to walk using an assistive device or in a way that saves physical energy.

Note: Can the dietary supplement Acetyl-L-carnitine relieve MS fatigue? (1)

Acetyl-L-carnitine is a form of L-carnitine, an amino acid that is found in nearly all cells of the body. L-carnitine plays a critical role in the production of energy from long-chain fatty acids (LCFA). In addition, it increases the activity of certain nerve cells in the CNS. Some studies have suggested that supplements could ease MS-related fatigue in people with low blood levels of L-carnitine. A small study found that Acetyl-L-carnitine works better than certain medications, such as Amantadine, used to treat fatigue. But, additional studies have had inconclusive results, showing a possible, but not statistically significant, benefit of this supplement. Currently, there is not enough evidence to support the claim and more studies are needed. Although Acetyl-L-carnitine generally has few or mild side effects, it can interfere with blood-thinning medications and other drugs.

10. Itching (1)

- Vistaril (Hydroxyzine®).

11. Muscle weakness and spasticity (2)

Muscle weakness and spasticity is common in MS. It may affect one or both legs, may be transient (lasting days or weeks), or progressive over many years as a major symptom. For those MSers age forty or over, leg weakness and spasticity may be the only symptoms, progressing slowly without any acute attacks. The weakness pattern can be asymmetrical, involving one limb or one side more than the other, or it can seem to be only in the legs.

Mild spasticity can be managed by stretching and exercising muscles using water therapy, yoga, or physical therapy. It is very important that people with MS stay physically active because physical inactivity can contribute to worsening stiffness, weakness, pain, fatigue, and other symptoms. Various aids ankle brace for foot drop, cane) may also be necessary. During an acute attack, weakness can be treated with intravenous steroids. If the pain persists, physical therapy may be prescribed.

Medications employed that can reduce muscle spasticity are:

- Gabapentin®.
- Baclofen®.

12. Pain (16)

Pain from MS can be felt in different parts of the body. Trigeminal neuralgia (facial pain) is treated with anticonvulsant or antispasmodic drugs, or less commonly pain killers. Central pain, a syndrome caused by damage to the brain and/or spinal cord, can be treated with Gabapentin and Nortriptyline. Treatments for chronic back or other musculoskeletal pain may include heat, massage, ultrasound, and physical therapy.

Several types of pain may occur in the face, including

temporo-mandibular joint (TMJ) pain, tension headache, and migraine. If trigeminal neuralgia is the cause, it is treated with a group of medications that decrease the nerve firing:

- Baclofen.
- Carbamazepine (Tegretol®).
- Cymbalta (Duloxetine®).
- Diphenylhydantoin (Dilantin®).
- Duloxetine hydrochloride (Cymbalta®).
- Effexor (Venlafaxine®).
- Elavil (Amitriptyline®).
- Gabapentin (Neurontin®).
- Lamictal (Lamotrigine®).
- Lyrica (Pregabalin®).
- Neurontin (Gabapentin®).
- Nortriptyline.
- Pamelor.
- Tegetrol (Carbamazepine®).
- Trileptal (Oxcarbazepine®).

13. Pseudobulbar effect (4)

Inappropriate and involuntary expressions of laughter, crying, or anger—symptoms of a condition called pseudobulbar effect—sometimes are associated with MS. These expressions are often incongruent with mood, e.g., people with MS may cry when they are actually happy or laugh when they are not especially happy. The combination treatment of the following drugs can treat pseudobulbar effect:

- Amitriptyline.
- Citalopram®.
- Dextromethorphan®).
- Quinidine®.

14. Seizures

Seizures are not common in MS, but occur in about 6% of patients. They are effectively treated with anticonvulsants:

- Phenytoin (Dilantin®).
- Carbamazepine (Tegretol®).

15. Sensory (9)

• Hearing changes: On occasion, MS can cause a decrease in hearing. Significant changes are rare.

• Numbness: Disruption of the sensory nerves can be caused by damage to the spinal cord, the brainstem, or the brain itself. Facial numbness (one side of the face) similarly to dental anesthesia is a common, upsetting, but minor symptom that usually clears without treatment.

◦ Methylprednisolone or other intravenous steroids: For dyesthesias.
◦ Amitriptyline (Elavil®): An antidepressant.

• Pain (see # 12). L'Hermitte's phenomenon is the feeling of an electric shock-like in the back of the limbs on flexing the neck:

◦ Methylprednisolone.

• Sexual dysfunction: Sexual dysfunction can result from damage to nerves running through the spinal cord. Sexual problems may also stem from MS symptoms such as fatigue, cramped or spastic muscles, and psychological factors. Some of these problems can be corrected with medications. Psychological counseling also may be helpful.

- Cialis (Tadalafil®).
- Levitra (Vardenafil®).
- MUSE (Alprostadil®).
- Prostin VR (Alprostadil®).
- Stendra (Avanafil®).
- Viagra (Sildenafil®).
- **Vision loss (see # 8)**

15. Spasticity (8)

This is the simultaneous contraction of muscles that help (agonists) and those that oppose (antagonists) movement, causing tone to increase in all muscles, limbs to feel tight, and limb movements to be slower and less smooth. Spasticity can be reduced by exercise and normal muscle use to prevent contractures. Symptoms produced include: spasms, cramps, pain, aching. Helpful drugs are:

- Baclofen (Liorisol®): Not tolerated by everyone. Helpful in reducing spasms and pain sometimes associated with spasticity and improving function.
- Botox (Onabotulinumtoxin ®).
- Dalfampridine (Ampyra®): A potassium channel blocker to improve walking speed. (See also category # 18)
- Dantrium (Dantrolene®).
- Klonopin (Clonazepam®).
- Tizanidine (Zanaflex®): Especially effective for night spasms. Its combined use with Baclofen may be an optimal anti-spasticity drug.
- Valium (Diazepam®).
- Zanaflex (Tizanidine®).

16. Stress

Stress management programs, relaxation training, membership in an MS support group, or individual psychotherapy may help some people.

17. Tremors (4)

Tremors (or uncontrollable shaking) develop in some people with MS. Assistive devices and weights attached to utensils or even limbs are sometimes helpful for people with tremors. Deep brain stimulation and drugs, such as Clonazepam, also may be useful.

- Klonopin (Clonazepam®).
- Laniazid - Nydrazid (Isoniazid®).
- Onabotulinum toxin-A.
- Propanolol (Inderal®): A beta-blocker.

18. Walking, balance, gait, and ataxia (1)

Problems with walking and balance occur in many people with MS because they can be caused by changes in different parts of the nervous system. The most common walking problem is ataxia—unsteady, uncoordinated movements—due to damage to the areas of the brain that coordinate muscle balance. People with severe ataxia generally benefit from the use of a cane, walker, or other assistive device. Physical therapy also can reduce walking problems. In 2010, the (U.S.) FDA has approved the following drug to improve walking speed in people with MS (see also category # 15):

- Ampyra (Dalfampridine®).

MS Management Key Points

The following key points should be noted:

• One lesser known effect of some commonly prescribed antidepressants is that they can exacerbate muscle spasticity and further impede walking.

• Even though managing MS symptoms may overshadow a person's medical concerns, regular preventive health care remains important. Women with MS should still get regular Pap tests and mammograms, and women and men should have colonoscopies.

• Any new aches and pains should be addressed as they would be for anyone.

• A physical medicine and rehabilitation specialist can help a patient address and correct musculoskeletal issues, which may alleviate pain.

- As flu season approaches, people with MS should check with their neurologist about receiving a flu vaccine.

For selected applications, some of the more frequently used approaches (pharmacological, non-pharmacological, other) have been summarized in Table 3:

Symptom(s)	Pharmacological	Non-pharmacological	Other
Bladder control & constipation	o Botulinum toxin (aka '*Botox*'®)	o High-fiber diet o Laxatives o Stool softeners	
Clinical depression	o Anti-depressants o *Selective Serotonin Reuptake Inhibitors* (SSRI)	`	Cognitive behavioral therapy
Cognitive impairment	o *Donepezil*®		
Eye & vision problems	Intravenous steroids	Special eyeglasses	Periodic rest of the eyes
Fatigue	o *Amantadine*® o *Methylphenidate*® o *Modafinil*®	o *Acetyl-L-carnitine (?)* o Assistive device	Occupational therapy
Muscle weakness & spasticity	o *Baclofen*® o *Gabapenti* ® o *Sativex (Nabiximols®)* derived from cannabis		o Stretching o Muscles exercise using water therapy, yoga, or physical therapy.
Pain	o *Gabapentin*® o *Nortriptyline*® o Anticonvulsant or antispasmodic drugs o Pain killers		o Massage o Ultrasound o Physical therapy
Pseudobulbar effect	o *Dextromethorphan*® o *Quinidine*® o *Amitriptyline*® o *Citalopram*®		
Sexual dysfunction	*Cialis (Tadalafil®)* *Levitra (Vardenafil®)* *MUSE (Alprostadil®)* *Prostin VR (Alprostadil®)* *Stendra (Avanafil®)* *Viagra (Sildenafil®)*		Psychological counseling
Stress			Psychotherapy
Tremor	o *Clonazepam*®	o Deep brain stimulation o Assistive devices and weights	
Walking, balance & Ataxia	o *Dalfampridine*® o *Fampyra (Fampridine®)*	Cane, walker, or other assistive device	o Physical therapy o Improves walking speed and ability by up to 25% in four out of 10 people.
Acute attacks	o *Methylprednisolone*® o Other IV corticosteroids	Plasmapheresis treatment	
Relapses	o Disease-modifying drugs/therapies (DMD/Ts) o *Steroids*		o Rehabilitation o Physiotherapy o Occupational therapy o Dietary advice o Support at work o Help in the home

Source: A. L. Fymat (2023)

Table 3: Management of multiple sclerosis symptoms

Managing The Disease

Managing MS aims to modify the disease course, treat relapses, and seek rehabilitation to promote functional mobility, safely and independence, and participation at home, at work and in the community. It involves:

Comprehensive care

A complex disease such as MS requires a comprehensive approach. Not being currently a curable disease, effective strategies can help modify or slow the disease course, treat relapses, manage symptoms, improve function and safety, and address emotional health.

The model of comprehensive MS care involves the expertise of many different healthcare professionals, each contributing in a unique way to the management of the disease and the symptoms it can cause. Sometimes, this team works within a single center but, more often, a referral by the MS physician is made to other specialists in the community. In either case, the goal is comprehensive and coordinated care to manage the disease and promote comfort, function, independence, health and wellness.

For most people with MS, being a specialist in diseases of the nervous system, a neurologist functions as the leader of the team, makes diagnosis, identifies treatment strategies, and coordinates these treatment efforts with other members of the team.

MS is only part of overall health

Comprehensive MS care is part — but not all — of the overall health management strategies. Like the general population, any individual is subject to medical problems that have nothing to do with one's MS. Regular visits with a primary care physician, age-appropriate screening tests, routine dental care, and taking care of dental issues are important and can help prevent complications from infections. The parts that make up the whole include:

• **Modifying the disease course**: Several FDA-approved disease modifying drugs/therapies (DMD/Ts) to treat symptoms, CIS, relapsing, secondary progressive MS, and other forms of the disease have been discussed at length in this series of articles. These medications reduce the frequency and severity of relapses, reduce the accumulation of lesions in the brain and spinal cord, and may slow the accumulation of disability for many.

• **Treating exacerbations:** An exacerbation of MS is caused by inflammation in the central nervous system (CNS) that causes damage to the myelin and slows or blocks the transmission of nerve impulses. To be a true exacerbation, the attack must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. However, most exacerbations last from a few days to several weeks or even months. Exacerbations can be mild or severe enough to interfere with a person's ability to function at home and at work. Severe exacerbations are most commonly treated with high-dose corticosteroids to reduce the inflammation.

• **Promoting function through rehabilitation:** Rehabilitation programs focus on function. They are designed to help improve or maintain the ability to perform effectively and safely at home and at work. Rehabilitation professionals focus on overall fitness and energy management while addressing problems with accessibility and mobility, speech and swallowing, and memory and other cognitive functions. Rehabilitation is an important component of comprehensive quality healthcare for people with MS at all stages of the disease.

• **Providing emotional support:** Comprehensive care includes attention to emotional health as well as physical health. Mental health professionals provide support and education, in addition to diagnosing and treating the depression, anxiety, and other mood

changes that are common in MS. Neuropsychologists assess and treat cognitive problems.

Self-management programs

When diagnosed with MS, a patient should receive information about symptom management, but symptoms and needs change over time so a management care plan should also be offered. This should include a single point of contact (usually, an MS specialist nurse or a general practitioner) to coordinate care and help the patient and the patient's family access the right health and social care services. A range of health professionals including physiotherapists, occupational therapists, speech and language therapists, psychologists, dietitians, social care, and incontinence specialists can help with symptom management. Such programs include lifestyle changes, which can protect the health of the brain, slow down how fast the disability gets worse, and protect from other problems like diabetes (see Table 4):

Program	Purpose
Cognitive behavioral therapy (CBT)	o Manage fatigue o Deal with anxiety and depression.
Cognitive rehabilitation therapy (CRT)	Combat problems with memory, attention span or concentration
Exercise and activities	Slowing down the pace of disability
Nutrition and diet	o Slowing down MS o Reducing relapses
Rehabilitation	o Help maintain function, activity, and independence o Keep different parts of the body to work well o Deal better with fatigue o Move more easily o Alleviate bowel and bladder problems o Sleep better o Manage side effects from medication
Relaxation	o Reduce fatigue, anxiety, and stress o Improve working memory, attention, and planning abilities.

Source: A. L. Fymat (2023)

Table 4: Self-management programs for multiple sclerosis

Cognitive behavioral therapy (CBT)

CBT focuses on specific, practical problem-solving techniques. It can help manage fatigue, as well as dealing with anxiety and depression.

Cognitive rehabilitation therapy (CRT)

CRT is designed to help combat problems with memory, attention span or concentration that occur in between 50% to 60% of people with MS.

Exercise and activities

No matter what the level of disability, keeping active can slow down how fast the disability gets worse. There are special exercises for certain symptoms. Short bursts of moderate aerobic exercise, like walking or steady cycling, can help with fatigue and quality of life. Resistance exercise and activities include stretching, yoga, Pilates, and weights. Pilates exercises are designed to build up core stability so they are ideal for MSers, as they can help improve balance and walking. Many people find resistance exercise (stretching, yoga, and weights) less challenging. A physiotherapist can advise on the best exercises.

Nutrition and diet

A healthy, balanced diet helps stay as well as possible.

Currently, there is no evidence or clinical research supporting the claim that so-called 'MS diets' slow down MS or reduce relapses.

Relaxation

Relaxation techniques, including meditation and mindfulness, can help reduce fatigue, anxiety and stress, and improve working memory, attention, and planning abilities.

Rehabilitation

The aim of rehabilitation is to help maintain function, activity, and independence as much as possible. It helps keep different parts of the body work well, deal better with fatigue, move more easily, alleviate bowel and bladder problems, sleep better, and manage side effects from medication.

Managing acute attacks

An acute attack (or relapse) means that new patches of inflammation and demyelination are occurring in either new or old spots in the CNS (brain, spinal cord, optic nerves). During severe symptomatic attacks, administration of high doses of intravenous corticosteroids, such as Methylprednisolone, is the usual therapy. Oral corticosteroids seem to have a similar efficacy and safety profile. Although effective in the short term for relieving symptoms, corticosteroid treatments do not appear to have a significant impact on long-term recovery. The long-term benefit is unclear in optic neuritis. The consequences of severe attacks that do not respond to corticosteroids might be treatable by plasmapheresis.

Managing relapses and pseudo-relapses

Treatments include disease modifying drugs/therapies (DMD/Ts) for fewer and less serious relapses. DMD/Ts can reduce the number of relapses and slow down the rate at which disability happens. They work better the earlier one starts taking them.

Damage caused by MS builds up over time, so the sooner one begins treatment, the less damage will have built up before treatment starts to take effect. Some milder relapses will not need any special treatment beyond DMD/Ts. For more serious relapses, a short course of steroids may be helpful. Like any drug, though, steroids can have side effects. Also, whether a relapse is treated or not does not make any difference to how much permanent disability it could cause. Rehabilitation after a relapse can help, including physiotherapy, occupational therapy, dietary advice, support at work, and help in the home.

Managing co-morbidities

Many people living with MS also live with conditions (co-morbidities) like diabetes, hypertension (high blood pressure), heart disease, lung disease, and certain mood disorders. Some people also live with other autoimmune conditions. These co-morbid conditions can negatively impact MS by delaying diagnosis, delaying treatment, increasing the number of hospitalizations, speeding-up disease progression, and reducing quality of life. Treating these additional medical or psychiatric conditions is essential not only to overall health and well-being but also to the effective management of MS as well. One should not assume that everything is related to MS, should ensure that health care providers are communicating, and should keep an updated list of all medications and supplements taken.

Summary And Conclusions

Multiple sclerosis (MS) is typically diagnosed based on the presenting signs and symptoms in combination with supporting medical imaging and laboratory testing. The diagnosis is complex and difficult to arrive at because it can cause many different symptoms. Further, it is hard to pinpoint exactly when the disease begins,

but the early signs and symptoms are different for everyone. It is not uncommon for a diagnosis to take several months and may even take longer. A range of other possible causes need to be explored and many different tests need to be carried out. There is no single test (including biopsy) that can provide a definitive diagnosis.

Brain and spine MRI may show areas of demyelination (lesions or plaques). Gadolinium can be administered intravenously as a contrast agent to highlight active plaques and, by elimination, demonstrate the existence of historical lesions not associated with symptoms at the moment of the evaluation. Lacking specific tests, the diagnosis often relies on ruling-out other conditions that might produce similar signs and symptoms.

There are several diseases that present similarly to MS such as: intractable vomiting, severe optic neuritis, bilateral optic neuritis, suspicion for neuromyelitis optica spectrum disorder, neurosarcoidosis, extensive transverse myelitis, anti-myelin oligodendrocyte glycoprotein –associated myelitis, systemic rheumatologic disease, or a paraneoplastic disorder. Two new clinical tools have been propounded (the McArdle's sign and new antibody test that measures immunoglobulin kappa free light chains. Managing MS is an ongoing process, beginning with the very first symptoms and continuing throughout the disease course. 18 different categories of symptoms have been identified along with their individual pharmacotherapies.

A complex disease such as MS requires a comprehensive approach. Not being currently a curable disease, effective strategies are employed to help modify or slow the disease course, treat relapses, manage symptoms, improve function and safety, and address emotional health.

References

1. Awad A, Hemmer B, Hartung H-P, Kieseier B, Bennett JL, and Stuve O (2010). "Analyses of cerebrospinal fluid in the diagnosis and monitoring of multiple sclerosis". Jof Neuroimmunology 219(1–2):1–7. doi:10.1016/j.jneuroim.2009.09.002.
2. Brettschneider J, Jaskowski TD, Tumani H, Abdul S, Husebye D, Seraj H, Hill HR, Fire E, Spector L. Yarden J, Dotan N, and Rose JW (2009). "Serum anti-GAGA4 IgM antibodies differentiate relapsing remitting and secondary progressive multiple sclerosis from primary progressive multiple sclerosis and other neurological diseases". J of Neuroimmunology 217(1–2):95–101. doi:10.1016/j.jneuroim.2009.07.017.
3. Brex P and Williams V (2019). “Updated criteria for diagnosing multiple sclerosis”, ACNR 18(2).
4. Castellaro M, Tamanti A, Pisani AI, Pizzini FB, Crescenzo F, and Calabrese M (2020). "The use of the central vein sign in the diagnosis of multiple sclerosis: A systematic review and meta-analysis”.Diagnostics 10(12):1025. doi:10.3390/diagnostics10121025.
5. Chong HT et al. (2006). “Proposed modifications to McDonald diagnostic criteria for Asians with multiple sclerosis”, Neurology Asia 1187–90.
6. Chong HT, Kira J, Tsai C, Ong B, Li P, Kermode A, and Tan C (2009). "Proposed modifications to the McDonald criteria for use in Asia".

Multiple Sclerosis 15(7): 887-8. doi:10.1177/1352458509104587.

7. Engell T (1989). "A clinical patho-anatomical study of clinically silent multiple sclerosis". Acta Neurol Scand.79(5):428–30. doi:10.1111/j.1600-0404.1989.tb03811.x.
8. Ferré JC, Shiroishi MS, and Law M (2012). "Advanced techniques using contrast media in neuroimaging". Magnetic Resonance Imaging Clinics of North America 20(4):699-713. doi:10.1016/j.mric.2012.07.007.
9. Filippi M, Rocca MA, De Stefano N, Enzinger C, Fisher E, Horsfield MA, Inglese M, Pelletier D, and Comi G (2011). "Magnetic resonance techniques in multiple sclerosis: The present and the future". Archives of Neurology 68(12):1514–20. doi:10.1001/archneurol.2011.914.
10. Filippi M, Rocca MA, Ciccarelli), De Stefano N, Evangelou N, Kappos L, Rovira A, Sastre-Garriga J, Tintorè M, Frederiksen JL, Gasperini C, Palace J, Reich DS, Banwell B, Montalban X, and Barkhof F (2016). "MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines". The Lancet Neurology 15(3):292–303. doi:10.1016/S1474-4422(15)00393-2.
11. Fortini AS, Sanders EL, Weinshenker BG, and Katzmann JA, (2003). "Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis isoelectric focusing with IgG immunoblotting compared with high-resolution Agarose gel electrophoresis and cerebrospinal fluid IgG index". American J of Clinical Pathology 120(5):672-5. doi:10.1309/Y5VFF2UAW0RK5W63.
12. Fymat AL (2023). "Multiple Sclerosis: The progressive demyelinating autoimmune disease", Tellwell Talent Publishers pp 504, 30 March 2023. ISBN:978-0-2288-9292-2 Hardcover); 978-0-2288-3 (Paperback). https://portal.tellwell.ca/Tellwell/Design/212669.
13. Fymat AL (2023). "Multiple sclerosis: I. Symptomatology and etiology", Neurology and Psychology Research J 4(1):1-46 (May 20, 2023).
14. Gaetani L, Prosperini L, Mancini A, Eusebi P, Cerri MC, Pozzilli C, Calabresi P, Sarchielli P, and Di Filippo M (2017). "Revisions of McDonald criteria shorten the time to diagnosis of multiple sclerosis in clinically isolated syndromes". J Neurol.265(11):2684–7. doi:10.1007/s00415-018-9048-8.
15. Habek ME et al. (2018). "2010 versus 2017 McDonald criteria". Mult Scler Relat Disord. 25:99-103. doi:10.1016/j.msard.2018.07.035.
16. Keller A, Leidinger P, Lange J, et al. (2009). "Multiple sclerosis: microRNA expression profiles accurately differentiate patients with relapsing-remitting disease from healthy controls". PLOS ONE 4(10): e7440. doi:10.1371/journal.pone.0007440.
17. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, et al. (2018). "Neurofilaments as biomarkers in neurological disorders". Nature Reviews Neurology 14(10):577-89. doi:10.1038/s41582-018-0058-z.
18. Lassmann H (2010). "Acute

disseminated encephalomyelitis and multiple sclerosis". Brain 133(Pt 2): 317–9. doi:10.1093/brain/awp342.

19. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, and Wolinsky JS (2001). "Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis". Annals of Neurology 50(1):121–7. doi:10.1002/ana.1032.
20. McGinley MP, Goldschmidt CH, and Rae-Grant AD (2021). "Diagnosis and treatment of multiple sclerosis: A review". JAMA 325(8):765-79. –779. doi:10.1001/jama.2020.26858.
21. Medaer R (1979). "Does the history of multiple sclerosis go back as far as the 14th century?". Acta Neurologica Scandinavica 60(3):189–92. doi:10.1111/j.1600-0447.1979.tb08970.x.
22. Mehta V, Pei W, Yang G, Li S, Swamy E, Boster A, Schmalbrock P, and Pitt D (2013). "Iron is a sensitive biomarker for inflammation in multiple sclerosis lesions". PLOS ONE 8(3): e57573. Bibcode:2013PLoSO...857573M. doi:10.1371/journal.pone.0057573.
23. Miller DH, Weinshenker BG, Filippi M, Banwell BL, Cohen JA, Freedman MS, Galetta SL, Hutchinson M, Johnson RT, Kappos L, Kira J, Lublin FD, McFarland HF, Montalban X, Panitch H, Richert JR, Reingold SC, and Polman CH (2008). "Differential diagnosis of suspected multiple sclerosis: A consensus approach". Mult Scler. 14(9):1157-74. –1174. doi:10.1177/1352458508096878.
24. Milo Miller A (2014). "Revised diagnostic criteria of multiple sclerosis". Autoimmunity Reviews 13(4–5):518–24. doi:10.1016/j.autrev.2014.01.012.
25. Nickles D et al., (2013). “Blood RNA profiling in a large cohort of multiple sclerosis patients and healthy controls”, Hum Mol Genet. 22(20):4194-205. doi:10.1093/hmg/ddt267.
26. Ntranos A and Lublin F (2016). "Diagnostic criteria, classification and treatment goals in multiple sclerosis: The chronicles of time and space". Current Neurology and Neuroscience Reports 16(10): 90. doi:10.1007/s11910-016-0688-8.
27. Oh J, Vidal-Jordana A, and Montalban X (2018). "Multiple sclerosis: Clinical aspects". Curr Opin Neurol. 31(6):752–9. doi:10.1097/WCO.0000000000000622.
28. O'Neill JH et al. (1987). “McArdle's sign in multiple sclerosis”. J of Neurology, Neurosurgery, and Psychiatry 50:1691.
29. Pearce JM (2005). "Historical descriptions of multiplesclerosis". European Neurology 54(1):49–53. doi:10.1159/000087387.
30. Petzold A (2005). "Neurofilament phosphoforms: Surrogate markers for axonal injury, degeneration, and loss". J of the Neurological Sciences 233(1–2):183-98.

doi:10.1016/j.jns.2005.03.015.

31. Polman CH, Reingold SC, Edan G, Filippi M, Hartung H-P, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, and Wolinsky JS (2005). "Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'". Annals of Neurology 58(6):840–6. doi:10.1002/ana.20703.
32. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, and Wolinsky JS (2011). "Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria". Annals of Neurology 69(2):292–302. doi:10.1002/ana.22366.
33. Popescu BFG, Pirko I, and Lucchinetti CF (2013). "Pathology of multiple sclerosis". Continuum: Lifelong Learning in Neurology 19(4 Multiple Sclerosis):901-21. doi:10.1212/01.CON.0000433291.23091.65.
34. Poser CM and Brinar VV (2004). "Diagnostic criteria for multiple sclerosis: An historical review". Clinical Neurology and Neurosurgery 106(3):147–58. doi:10.1016/j.clineuro.2004.02.004.
35. Quintana FJ, Farez MF, Viglietta V, et al. (2008). "Antigen microarrays identify unique serum autoantibody signatures in clinical and pathologic subtypes of multiple sclerosis". Proc Natl Acad Sci U.S.A. 105(48):18889–94. doi:10.1073/pnas.0806310105.
36. Rovira À (2017). "Diagnosis of multiple sclerosis". J of the Belgian Society of Radiology 101 (S1):12. doi:10.5334/jbr-btr.1426.
37. Runia TF, Jafari N, and Hintzen RQ (2013). "Application of the 2010 revised criteria for the diagnosis of multiple sclerosis to patients with clinically isolated syndromes". European Journal of Neurology 20(12):1510–6. doi:10.1111/ene.12243.
38. Saadeh RS, et al. (2022). "CSF kappa free light chains: Cutoff validation for diagnosing multiple sclerosis". Mayo Clinic Proceedings 97:738.
39. Savoldi F et al. (2019). "McArdle sign: A specific sign of multiple sclerosis". Mayo Clinic Proceedings 94:1427.
40. Sinnecker T, Clarke MA, Meier D, Enzinger C, Calabrese M, De Stefano N, et al. (MAGNIMS D - Solomon AJ (2019). "Diagnosis, differential diagnosis, and misdiagnosis of multiple sclerosis". Sclerosis Continuum 25(3):611–35. doi:10.1212/CON.0000000000000728.
41. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara, K, Galetta SL, Hartung HP, Kappos L, Lublin F, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, and Cohen, JA (2018). "Diagnosis of multiple sclerosis: 2017

revisions of the Mc Donald criteria". The Lancet Neurology 17(2):162-73. doi:10.1016/S1474-4422(17)30470-2.

42. Trojano M and Paolicelli D (2001). "The differential diagnosis of multiple sclerosis: classification and clinical features of relapsing and progressive neurological syndromes". Neurological Sciences 22(Suppl 2): S98-102. doi:10.1007/s100720100044.
43. Tsang BK, Macdonell R (2011). "Multiple sclerosis: Diagnosis, management and prognosis". Australian Family Physician 40(12):948–55.