

■ KNOWLEDGE UPDATE ON THE DIAGNOSIS OF MULTIPLE SCLEROSIS ■



MS Multiple Sclerosis Society of Canada
Quebec Division

GUIDE FOR GENERAL PRACTITIONERS



■ INTRODUCTION ■

Multiple sclerosis (MS) is a common neurological disorder but is not well known among the general public. Its severity is sometimes compared to that of cancer, although it is not fatal. People often associate MS with a major handicap, but a significant percentage of people with MS will never need to use a wheelchair on a permanent basis, and most patients will continue to contribute significantly to society through their work, family lives and/or community involvement.

Recent developments in imaging techniques and advances in knowledge about the disease now enable physicians to diagnose MS more quickly and begin treatment earlier. However, though a diagnosis can be made sooner, multiple sclerosis can also be falsely diagnosed in some people who do not have it.

General practitioners (GPs) play a key role because they are often the people who see patients in the early stages of the disease. The GP is responsible for beginning the

necessary process for diagnosis and referring the patient to the neurological specialists who will confirm the diagnosis and begin the appropriate treatment. It may be hard to distinguish between a patient who has the disease and a patient who is falsely told that he has multiple sclerosis. The purpose of this publication is to review the warning signs that indicate a patient has multiple sclerosis, as well as the traps to avoid.

■ EPIDEMIOLOGY ■

The epidemiologic context is a determining factor because it tells us about the person who is suspected of having the disorder.

In Canada, the prevalence of multiple sclerosis is one or two people in one thousand. It affects two women for every man. In most cases, it first becomes apparent between the ages of 15 and 40, but can also appear in individuals as young as 10 and as late as age 60. MS affects people of Caucasian origin far more often than other ethnic groups. It is almost unknown among American Indians.

MS is particularly widespread in temperate zones on both sides of the Equator. Canada, Europe and Oceania are among the areas where the disease is most prevalent.

Although the causes are still unknown, we know that genetics are involved in MS. In 25% of people with MS, other cases exist in the family. When one person has it, the risk that the person's children will one day be affected is 4% for a daughter and 2% for a son.

The disease is believed to have a multifactorial origin. People with MS are thought to have a genetic susceptibility to MS and exposure during their lives to some environmental factors that would trigger multiple sclerosis later. At the moment, we suspect that certain viruses play a role in triggering MS, but, so far, none have been clearly linked to the disease.

■ PROGRESSION ■

Knowledge of the progression of MS is essential for diagnosis. Since there are no neurological symptoms that are exclusive to multiple sclerosis, it is the evolution of the symptoms over time in individuals considered to be at risk (young adults, Caucasians, particularly women) that enables the clinician to make the diagnosis.

The great majority (80%) of patients begin with a relapsing-remitting form of MS. This is characterized by the onset of neurological symptoms with a duration varying from several days to several weeks, followed by remission that may last several years until a new attack occurs. This form mostly affects women whose illness begins between the ages of 15 and 40. Attacks are more frequent in the early stages, followed by an average frequency of one per year; this frequency decreases over time. Patients whose initial manifestation of the disease involves sensory or visual changes generally have a better long-term prognosis than those with motor or brain-stem related symptoms.

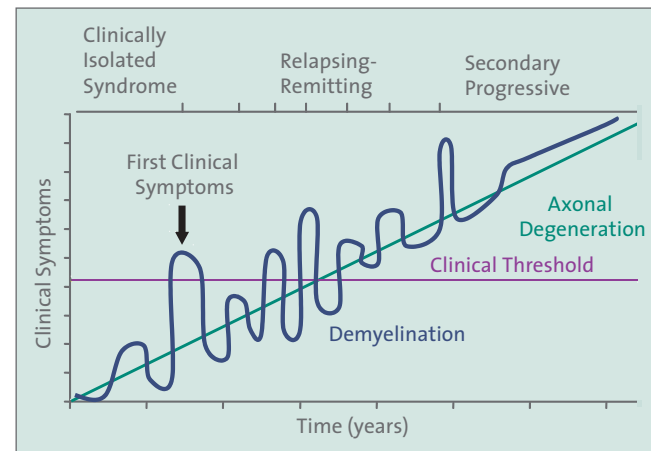
Fifteen years after initial diagnosis, about 20% to 25% of patients have a benign form of MS and are still mobile without any physical limitations, whereas about another 20% of patients need a wheelchair to get around. The main risk for people with the relapsing-remitting course of MS is the transition to the chronic secondary progressive form where they will gradually lose their capabilities, particularly walking, without any relapses. This gradual loss occurs over a long period of months or years. In most patients, this form occurs 25 years after the initial diagnosis of the disease.

Other patients, about 20%, do not have attacks in the early stages: they have the primary progressive form. This strikes as many men as women and generally begins in patients over 40 years old.

Despite all, the life expectancy of people with MS is only slightly lower than that of the general population. It has been estimated to be only 5 years less than for other people the same age.

Note that all these statistics are taken from studies that predate the arrival of the new immunomodulator treatments. These figures will probably improve in the coming years because of these drugs.

PATHOLOGICAL AND CLINICAL PROGRESSION OF MS



Source: Serono Canada Inc.

■ SIGNS AND SYMPTOMS OF MULTIPLE SCLEROSIS ■

Multiple sclerosis cannot be distinguished from other nervous system disorders on the basis of its clinical manifestations. There are many symptoms of MS that can be found in several other disorders of the central nervous system. The diagnosis is based on the presentation of different symptoms at different times in high-risk individuals for whom other neurological disorders have been eliminated. The key to diagnosis therefore is not just the symptoms that cause a patient to see a general practitioner, but first and foremost the identification in the patient's history of other events that suggest MS. This basic rule requires clear proof for the clinician of at least two attacks spread over time. We will come back to this important concept in the next section.

Even though the possible symptoms of multiple sclerosis are numerous and highly varied, they have some common points:

- the symptoms are neurological and reflect a neuroanatomic lesion in the white matter of the central nervous system
- the symptoms must last at least 24 hours to be considered significant; the one exception to this rule is paroxysmal symptoms
- symptoms evolve in most cases with attacks that last several hours to several days, followed by a plateau phase of several days, then partial or full recovery over several weeks
- patients with a progressive form see deterioration over several weeks or months, especially in motor functions, generally with no recovery.

Symptoms should therefore be compatible with one or more neuroanatomic lesions and should generally reflect an attack on the white matter of the central nervous system. Such cortical manifestations as those observed in Alzheimer's dementia are not typical signs of multiple sclerosis. Manifestations must be linked to abnormalities on the neurological examination that confirm the symptoms reported by the patient are real and not stress-related. We will define an attack as objective if the neurological examination reveals abnormalities that confirm the patient's subjective report.

The minimum duration for an attack is 24 hours: this eliminates symptoms of short duration that are not generally related to any serious neurological condition except epilepsy and cerebrovascular diseases. The only exceptions to this rule are paroxysmal symptoms (sensory, painful, motor or aphasic) that last only several seconds but generally recur frequently over several weeks.

An attack is characterized by the appearance of one or more new symptoms corresponding to one or more anatomic lesions. The symptoms generally evolve over several hours or days and are rarely sudden. Symptoms that vary in location or intensity are not to be trusted. Migratory

paresthesia is not generally a symptom of multiple sclerosis. Caution is also required with patients who present several simultaneous symptoms that have no anatomic explanation. These are often patients who suffer from anxiety.

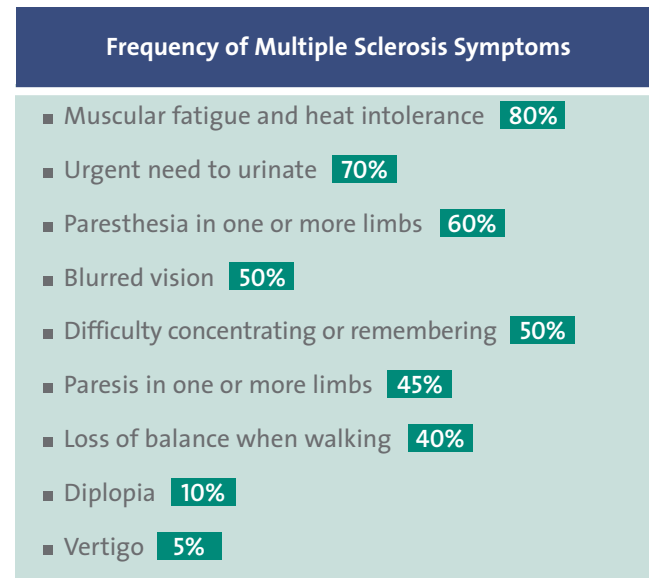


Table 1

Source: The Diagnosis of Multiple Sclerosis.

Paresthesia is frequent in multiple sclerosis. The classic presentation is related to an attack on the posterior spinal cord. The patient will feel numbness that begins distally in the toes and gradually moves upwards over several days to a level governed by the affected part of the spinal cord. In attacks on the spinal cord, the patient may complain of paresthesia only in his hands. In cervical cord attacks, the patient may describe L'Hermitte's sign when bending his neck. In cerebral lesions, the sensory attack will be contralateral whereas in brainstem lesions, the sensory attack may overlap with a sensory deficit in the ipsilateral hemiface and a deficit in the upper and lower contralateral limbs. The examination can sometimes be deceiving when the neurological signs are very subtle.

Paresis has the same characteristics as paresthesia. It may occur together with sensory attacks. Paresis presents pyramidal signs during the examination.

Visual symptoms occur frequently. Optic neuritis generally sets in within several days. It may be bilateral in 5% of the cases. The patient frequently complains of eye pain that is exacerbated by eye movement. Recovery generally takes several weeks to six months. The examination shows a

loss of visual acuity, reduced colour perception and possibly atrophy of the optic nerve in a fundoscopic examination.

Diplopia is a less frequent symptom. However, it can be linked to one of the signs in the neurological examination that is practically a pathognomic sign of multiple sclerosis: bilateral internuclear ophthalmoplegia. Diplopia is related to a brainstem attack, just like vertigo. Classically, vertigo in multiple sclerosis is intense, comparable to a labyrinthitis. Vertigo can persist for several days with the patient being bedridden during this period. The examination presents a nystagmus.

Because many patients have a neurogenic bladder, the mention of urination problems on the questionnaire helps diagnosis. Early in the disease, the patient generally has a hyperreflexic bladder with nocturia, an urgent need to urinate, and occasionally urinary incontinence. Bladder atonia problems appear later in the progression of the disease. Sexual problems like erectile dysfunction in men or anorgasmia in women may also occur.

Loss of balance when walking is often caused by paresis in the lower limbs but may also be related to ataxia resulting

from a cerebellar attack. Gait will present with a broad base and dysmetria in the heel/shin test. Cerebellar signs may also be observed in the upper limbs, and sometimes, in the most severe cases, nystagmus or cerebellar dysarthria.

Fatigue is a major problem for patients. It is the main reason for people with MS being absent from work. Fatigue is generally chronic but may intensify during attacks. Patients cannot tolerate heat because it increases fatigue. Heat may also cause a temporary re-emergence of such symptoms as loss of visual acuity in patients who have previously had optic neuritis (Uhthoff phenomenon). Heat, however, does not change the progression of the disease. Sometimes fever may bring on symptoms that disappear when the temperature returns to normal. This is a pseudo-exacerbation that is sometimes observed with urinary infections.

People with MS frequently have memory and concentration problems as the disease progresses. These difficulties are generally subtle. In the worst cases, they may be related to a frontal syndrome with emotional lability and a lack of self-criticism. Patients rarely progress to dementia.

Table 2 lists neurological symptoms rarely encountered in the disease.

Unusual Symptoms of MS

- Change in the state of consciousness
- Aphasia
- Muscular atrophy
- Cephalalgia
- Dystonia or chorea

Table 2

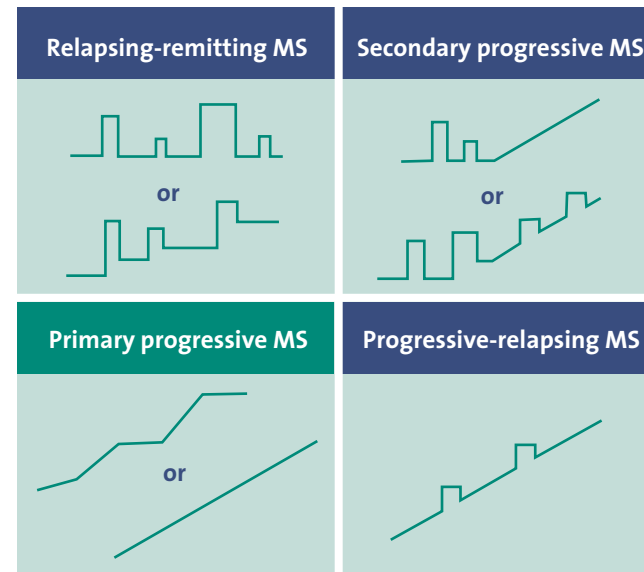
■ DIAGNOSIS OF MULTIPLE SCLEROSIS ■

Diagnosing MS is no simple task. It is first and foremost a clinical diagnosis and is facilitated by paraclinical techniques including magnetic resonance imaging (MRI), the search for oligoclonal bands in the cerebrospinal fluid (CSF) and visual evoked potentials (VEP). **Despite the recent development of MRI, clinical judgement remains fundamental to diagnosis because a patient may have multiple abnormalities on the MRI without having multiple sclerosis.** Diagnosis can be compared to a jigsaw puzzle: to obtain the final picture, sometimes two pieces of the puzzle are enough, sometimes more pieces are needed. The same goes for diagnosing multiple sclerosis: in some cases, the clinician may be convinced by clinical data only, or clinical information may need to be supplemented by MRI results and CSF analysis.

The rule physicians must follow is to confirm the occurrence of two separate attacks over time, more than 30 days apart and clinically objectified with a neurological examination, in patients whose background is compatible with multiple sclerosis and when no other neurological disease could explain the damage.

This rule is valid for the relapsing-remitting form of multiple sclerosis. For the primary and secondary progressive forms, the clinician must observe deterioration on the neurological examination over a minimum of 12 months, without evidence of an attack and in the absence of other diseases that could explain the damage.

PATTERNS OF MS



Source: Serono Canada Inc.

Two criteria underlie this rule: **dissemination in space**, i.e., proof that the disease has affected the white matter in the central nervous system at several locations, as expected in multiple sclerosis; and **dissemination in time**, or the recurrence of neurological attacks or progression of disease over time.

In this context, MRI plays an important role in diagnosis. It can show dissemination in both space and time based on new diagnostic criteria established in 2000 that we will explain later. MRI findings alone have little value if they are not linked to a clinical history that is compatible with the disease.

VEPs are useful for objectively confirming whether optic neuritis has occurred in the past. They are also used to show

asymptomatic damage to the optic nerve, especially in cases where imaging results do not meet the minimum criteria. VEPs are thus useful for showing dissemination in space.

CSF analysis is used in a very different context from MRI and VEPs. The discovery of oligoclonal bands in the CSF signals inflammation within the central nervous system. It is not used to show dissemination in time and space. But it is useful when the MRI criteria are insufficient, when the MRI results are not specific (as in elderly patients), or when the clinical history is atypical.

■ McDONALD DIAGNOSTIC CRITERIA ■

The major development of MRI as a diagnostic tool for multiple sclerosis over the past 20 years has led a committee of experts to develop new criteria for diagnosing multiple sclerosis. These are known as the McDonald criteria. They take into account the contribution of the various paraclinical assessment methods and set benchmarks for their interpretation. The availability in recent years of expensive treatments for the disease renders new, reliable criteria necessary in order to be able to treat patients who really have multiple sclerosis. Moreover, the demonstration that MRI is useful for predicting which patients have a high risk of eventually having MS based on the very first episode led the committee of experts to acknowledge a new category, the clinically isolated syndrome (CIS). The recognition of this new category came at a good time because new treatments for these patients are now available.

MRI DIAGNOSTIC CRITERIA

MRI is a very sensitive examination. It shows plaques but lacks specificity. Not all white matter lesions are necessarily caused by multiple sclerosis. Signal abnormalities observed in the white matter with MRI may be vascular lesions or even normal variations in people over 50 years of age. The McDonald criteria therefore set imaging parameters to specifically address the criteria of either dissemination in space or dissemination in time.

Dissemination in space

After reviewing several studies, the committee decided that the Barkhof imaging criteria (Table 3) represented the most sensitive and specific variables for capturing the dissemination in space criteria for the diagnosis of MS.

Dissemination in space

Barkhof Criteria

Three of the following four criteria

- 1 Gadolinium-enhancing lesion in the white matter or at least 9 lesions
- 1 infratentorial lesion
- 1 juxtacortical lesion
- 3 periventricular lesions or corpus callosum
 - 1 infratentorial lesion counts as 1 lesion
 - lesion size must be > 3mm

Table 3

Source: McDonald WI, Compston A, Edan G, et al. Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001; 50:121-127

Note that lesions must measure at least 3 mm. This eliminates many of the non-specific lesions that are related to age or are vascular in nature.

Dissemination in time

MRI can confirm the appearance of new lesions over time by comparing the results of two MRIs that are over three months apart. In this case, repetition of the test often requires an injection of gadolinium, an enhancing substance that is a sensitive marker of inflammation.

DIAGNOSTIC ALGORITHM FOR MULTIPLE SCLEROSIS

On the basis of these new recommendations, the committee developed a table for obtaining a diagnosis of multiple sclerosis. This algorithm combines clinical information, MRI results and CSF analysis. A patient who does not meet the criteria will be considered not to have multiple sclerosis or will have a diagnosis of possible multiple sclerosis if the clinician firmly believes that the patient has MS. Ongoing clinical monitoring and imaging are necessary for such cases.

Clinical Presentation	Additional Data Needed
2 or more attacks in the history; 2 or more objective clinical lesions in the neurological examination	None
2 or more attacks in the history 1 objective clinical lesion	Dissemination in space on the MRI (Barkhof) or 2 or more MRI lesions compatible with MS and positive CSF or wait for a 2 nd objective clinical attack
1 attack, 2 or more objective clinical lesions	Dissemination in space on the MRI or wait for another objective clinical attack
1 attack, 1 objective clinical lesion (first episode of demyelination)	Dissemination in space on the MRI or 2 or more MRI lesions compatible with MS and positive CSF or dissemination in time on the MRI or wait for a 2 nd objective clinical attack
Neurological progression suggestive of MS (primary progressive MS)	positive CSF and ■ dissemination in space on the MRI or abnormal visual evoked potential with 4 to 8 brain lesions and ■ dissemination in time on the MRI or continued clinical progression for 1 year

■ CONCLUSION ■

Multiple sclerosis cannot be diagnosed with MRI alone. Diagnosis is first and foremost based on clinical judgement, supported by imaging and sometimes CSF analysis or the use of evoked potentials.

The role of primary-care physicians is to identify people who are likely to develop multiple sclerosis and, if applicable, refer them to the necessary imaging and neurological resources to confirm or refute the diagnosis. Their role is extremely important because in the future, treatment will probably begin earlier.

However, caution is still required before issuing a diagnosis of MS. It would be premature to announce to a patient that he has multiple sclerosis based only on MRI results.

Such a premature announcement can cause major stress for the patient and his family and may have significant repercussions on several aspects of the patient's life, including employment and insurability.

The primary-care physician's role is also crucial for monitoring patients whose diagnosis of MS has been confirmed, especially with regard to treating the symptoms of the disease and providing psychological support that the patient may need.

■ **OTHER PUBLICATIONS OF THE MULTIPLE SCLEROSIS SOCIETY OF CANADA** ■

- The Diagnosis of Multiple Sclerosis
- Guide to MS Medications
- Coping with Fatigue
- Understanding Bladder Dysfunction in MS
- Understanding Bowel Problems in MS
- Solving Cognitive Problems
- Facts for Persons Recently Diagnosed with MS

A complete list of Multiple Sclerosis Society of Canada (Quebec Division) publications is available on the Web site at www.mssociety.ca/qc or can be obtained by calling 1 800 268-7582

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■ OUR MISSION ■

To be a leader in finding a cure for multiple sclerosis and enabling people affected by MS to enhance their quality of life.

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