



MODULE 3

Diagnosing and Assessing MS

English Version





CME Module Title

Diagnosing and Assessing MS

Learning Objectives

After completing this activity, the participant should be better able to:

- Describe the neurological examination and its role in the diagnosis of MS.
- Understand the concept of dissemination in time and space outlined in the McDonald Criteria.
- Discuss critical components of the differential diagnosis in MS.
- Describe the McDonald Criteria in relation to a diagnosis of MS.
- Examine the effects of the 2010 revisions to the McDonald Criteria.
- Explain results from magnetic resonance imaging (MRI) and their relevance to a diagnosis of MS.
- Discuss the importance of the presence of oligoclonal bands in the cerebrospinal fluid (CSF).
- Describe evoked potential tests and their significance.
- Identify an MS relapse.
- Differentiate relapse from disease progression and other non MS related conditions.
- Describe the EDSS, MSFC and the MSSS assessment tools.
- Discuss how these tools assist in monitoring disease progression in MS.

Target Audience

This activity has been developed to meet the educational needs of nurses who have an interest in optimising the management of people with MS.

Accreditation

This e-learning training curriculum is accredited by the Royal College of Nursing Accreditation for the award of continuing professional development credits.

This continuing education activity has been approved by the International Council of Nurses (ICN) for the award of International Continuing Nursing Education Credits (ICNECs).

Credit Designation

The Royal College of Nursing and the International Council of Nursing designates this module of the e-learning training curriculum for a maximum of 5 credits. On completion of the course (i.e. all 5 modules) you will be able to download a Virtual College certificate.

Estimated time to complete this module: 5 hours

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Method of Participation

There are no fees for participating and receiving CME credit for this activity. During the period of TBC, 2013, through TBC, 2015, participants must; (1) read the learning objectives and faculty disclosures, (2) participate in the entire educational activity, consisting of 5 core modules, (3) complete the post-test for each module by recording the best answer to each question, and (4) complete the online evaluation form for each module. Upon successful completion of all 5 post-tests (75% or better) and online evaluation forms, you will be provided with a statement of credit which you can download, save and print.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by nurses without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Grant Statement

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MODULE 3: Diagnosing and Assessing MS



1 Module Introduction

Intro

Surveys of people with MS indicate that the majority of people feel they receive insufficient support in understanding and making sense of their diagnosis¹. Although approaches to delivering the diagnosis have improved as clinicians have become better educated, there is still room for improvement. Therefore, it is important that the MS Nurse is able to explain the diagnosis, the tests used during the diagnosis process and any likely future interventions to the individual following their consultation with the neurologist. This will empower the person and will also help to build the trust and communication needed to optimise patient care.



Surveys of people with MS indicate that the majority of people feel they receive insufficient support in understanding and making sense of their diagnosis.

Diagnostic criteria for MS have evolved considerably to align with the MRI facility – ranging from the early, clinically oriented Poser criteria introduced in 1983 to the comprehensive, revised McDonald Criteria published in 2001 and 2005 and updated in 2010²⁻⁵. Working with a person with suspected MS to arrive at an accurate diagnosis involves much more than checking off a list of criteria. There are many “real world” factors to consider, such as the inter-centre variability of MRI results, patients whose presentation does not fit neatly into the diagnostic criteria, and the emotional upheaval and socio-economic burden that this diagnosis brings for patients and their families.

This module will explain the criteria along with the associated diagnostic tools, their results and consequences in a manner that a MS Nurse can easily understand and interpret, and then relay to a person who has MS. This is important not only from the point of view of information exchange, but also for the vital development of an equal relationship built on trust between the person and the MS Nurse.

Additionally, as the person with MS moves forward from the point of diagnosis, it is important that any signs of relapse in the patient are identified and differentiated from other related, but not necessarily clinically relevant, factors such as bladder infections. Identifying a relapse, and therefore being able to treat the patient as soon as possible, may reduce the impact of that relapse (time to recovery and potentially level of effect of relapse). Knowing when a relapse has occurred and the effects and consequences of the relapse can help in building the individual’s history and indicate disease activity. Therefore, accurate history taking and note making are also an important aspect of the role of the MS Nurse.



Accurate history taking and note making are an important aspect of the role of the MS Nurse.

2 Neurological Examination

2.1 Learning Objectives

After review of this section, you should be better able to:



- Describe the neurological examination and its role in the diagnosis of MS.
- Understand the concept of dissemination in time and space outlined in the McDonald Criteria.
- Discuss critical components of the differential diagnosis in MS.

2.2 Neurological Assessments

The distribution of MS varies throughout the world and appears to be related to geographical location and genetic background. Worldwide, it is estimated that up to 2.5 million people are affected by MS and it is more common in cooler climates¹. Globally, the median estimated incidence of MS is 2.5 per 100,000 (with a range of 1.1–4)². Regionally, the median estimated incidence of MS is greatest in Europe (3.8 per 100,000), followed by the Eastern Mediterranean (2), the Americas (1.5), the Western Pacific (0.9) and Africa (0.1). Twice as many women are affected with the disease than men (lifetime risk of MS: 2.5% for women and 1.4% for men)³. The incidence appears to be highest between the ages of 35 and 64 years⁴.



Most clinicians will begin with an assessment of mental status followed by assessment of the cranial nerves, motor system, sensory system, coordination and gait.

The **cranial nerve examination** involves checking the fundi, visual fields, pupil size and reactivity of the eye. Also examined are extraocular movements, hearing and facial movements.

A **muscle examination** is carried out to investigate muscle strength, atrophy and tone of the extremities. To assess upper muscle strength, the patient may be checked for pronator drift and strength of wrists or finger extensors and flexors as well as proximal muscles. To assess pronator drift (see *Figure 1*) the individual is asked to hold both arms fully extended in front of them at shoulder level, with the palms upwards. An upper motor neuron weakness may be revealed by a tendency for one of the arms to drift on the affected side when the eyes are closed. Many other manoeuvres may be used to detect subtle strength deficits.



Figure 1 – Pronator drift examination

Patients should also be tested for lower extremity strength by, for instance, having the individual walk normally, then on heels and toes. An in-depth examination usually involves investigation of the muscle appearance, tone, strength and reflexes, including muscle stretch reflexes, skin reflexes and primitive reflexes.

The **sensory examination** is used to check if the individual can feel joint movement or position, vibration, light touch, pain and the temperature of an object in each distal extremity. In those individuals who are cooperative and have a good understanding of the assessment, the sensory examination can be extremely helpful in establishing the precise location of a lesion. In others who are less aware, it may be of little benefit. The five primary sensory modalities that should be tested in both limbs are light touch, pain, temperature, vibration and joint position. Light touch is assessed by stimulating the skin with single, very gentle touches of the examiner's finger or a cotton wool swab; pain is tested using a new pin; and temperature is assessed using a metal object that has been immersed in cold and warm water. Vibration is assessed with a tuning fork, which is made to vibrate and located on a bony prominence, such as the malleolus in the feet, or any area that can respond to vibration.



The sensory examination can be extremely helpful in establishing the precise location of a lesion.

To test coordination, examinations include rapid, alternating movement of fingers and feet, the finger-to-nose manoeuvre and the heel-to-knee manoeuvre. Finger-to-nose testing is primarily an assessment of cerebellar function: the individual is asked to touch his or her index finger to their nose and then to the examiner's outstretched finger, which moves with each repetition; this manoeuvre is performed with the patient's eyes open.

The **gait** of the patient is examined by observation of the patient walking normally, on heels and toes, and along a straight line, putting each foot immediately after the other (tandem walk).

All the tests above would be carried out on a person who had been referred to the neurologist following an episode of neurological disturbance, either sensory (e.g., numbness, paresthesias, unpleasant sensation of tightness around the thorax – the “MS hug”) or of any other kind (e.g., optic neuritis, diplopia, Bell palsy). A first-time-ever clinical presentation of MS is usually termed a ‘clinically isolated syndrome’ (CIS) and it is usually classified according to the topography of the suspected lesions: optic neuritis, myelitis, brainstem/cerebellum syndromes, hemispheric syndromes, poliregional syndromes or other. The physical tests above, together with the anamnesis of the patient, would raise the clinical suspicion of MS and would prompt the performance of magnetic resonance imaging (MRI) which will be very useful to increase the certainty of a definite MS diagnosis according to widely accepted diagnostic criteria. Briefly, MRI is used to reveal lesions in the central nervous system (CNS). These lesions may indicate areas of possible damage to the myelin sheaths on axons in the CNS which occur in people with MS. Diagnosis of MS requires MRI showing multiple lesions disseminated in both time and space. (MRI is covered in more detail later in this module).



Lesions may indicate areas of possible damage to the myelin sheaths on axons in the CNS which occur in people with MS.

Dissemination in time and space is one of the core clinical indicators of MS. What this means is that episodes of symptoms or discovery of new lesions by MRI should indicate different evolution in time (i.e., chronicity) and be located in different areas of the CNS (brain and spinal cord).



Dissemination of lesions ‘in time’ refers to evidence of increased number of lesions over time. Dissemination of lesions ‘in space’ refers to evidence of disease lesions affecting more than one part of CNS.

The diagnosis of MS requires a number of factors, as originally set out by Schumacher and colleagues⁷, with modifications by Poser and colleagues², and those detailed in the recently revised McDonald Criteria, which will be discussed in further detail later in the next section of this module⁵.

Other clinical tests which are used to help confirm the diagnosis of MS are: evaluation of cerebral spinal fluid (CSF) for oligoclonal bands (OCB), evoked potentials (delayed potentials indicating myelin damage), optical coherence tomography (OCT) and several biomarkers (mainly for exclusion/indication of another diagnosis). These tests will be detailed later in this module.

It is important to be able to explain to individuals that the neurological tests they will be required to undergo, or have already had performed, are relevant to their diagnosis and why; also that the combination of the clinical and radiological (MRI) evidence is usually required to confirm a diagnosis of MS.

2.2.1 Differential Diagnosis

Since some of the signs and symptoms of MS are not exclusive to MS and may be also indicators of other diseases, it is important to be sure of the MS diagnosis by reasonably excluding such alternative conditions.



It is important to be sure of the MS diagnosis by excluding alternative conditions.

There are a number of red flags that should raise the index of suspicion about the MS diagnosis. These include: relentlessly progressive course, particularly in younger individuals; prominent or persistent headache; prominent cortical features (seizures, aphasia, neglect syndromes); abrupt and/or transient (few minutes to hours) duration of symptoms; presence of peripheral neuropathy; and involvement of other organ systems, such as cardiac, hematologic, or rheumatologic.

The differential diagnosis of MS is extensive, so accurate and detailed clinical history taking is essential. Review of patient notes can help to reveal the correct diagnosis and one of the key points of all diagnostic criteria has been that “there must be no better explanation for the clinical picture”. Usually major categories of diseases to consider can include vasculitic, infectious, metabolic, neoplastic and neurodegenerative processes. Laboratory screening evaluations for other causes include complete blood cell counts, erythrocyte sedimentation rates, vitamin B12 levels, auto-antibody tests, thyroid-stimulating and thyroid hormone levels, and if suggested by the history, human immunodeficiency virus (HIV) and Borrelia antibody titers. In any case, the list of possible tests to undertake is very long, and should be designed according to the clinical presentation of the patient. Table 1 lists common differential diagnoses.



Accurate and detailed clinical history taking is essential.

Demyelinating diseases	Non-demyelinating diseases
Neuromyelitis optica (NMO) Acute post-infectious disseminated encephalomyelitis (ADEM) Central pontine myelinolysis Other leucodystrophies (e.g., Krabbe disease)	Systemic lupus erythematosus Systemic sclerosis Behcet's disease Sarcoidosis Subacute combined degeneration of the spinal cord Cerebrovascular disease (stroke) Meningovascular syphilis Paraneoplastic syndromes Hereditary ataxias and paraplegias Lyme disease / neuroborreliosis AIDS-related myelopathies

Table 1 – Conditions with similar symptoms to multiple sclerosis

Two specific examples are **neuromyelitis optica (NMO)** and **acute disseminated encephalomyelitis (ADEM)**. These two conditions may be considered as a part of the MS spectrum of idiopathic inflammatory demyelinating disorders. In patients who present with optic neuritis and/or transverse myelitis, the diagnosis of NMO must be considered^{8,9}. ADEM, which may sometimes be confused with an initial episode of MS, tends to occur more commonly in children after a viral illness or vaccination, is monophasic, and does not show a female predominance, as does MS.

Comorbidities may also delay diagnosis. A recent study of medical records from almost 9,000 people with MS showed that the presence of co-morbid conditions – including vascular, autoimmune, musculoskeletal, gastrointestinal, visual or mental comorbidities – may delay the diagnosis of MS anywhere from 1 to 10 years. Patients with comorbidities were also found to have a greater level of disability at the time of diagnosis than those who did not¹⁰.



The presence of co-morbid conditions may delay the diagnosis of MS anywhere from 1 to 10 years unique to them.

The **Wingerchuk diagnostic criteria for NMO** published in 2006⁸ state that in addition to optic neuritis and/or transverse myelitis, the diagnosis of NMO requires at least two of the following supportive criteria:

- brain MRI not meeting diagnostic criteria
- contiguous spinal cord MRI lesion extending over three or more vertebral segments.
- seropositivity for NMO antibodies (which are directed against the water channel aquaporin-4).

Miller and colleagues⁹ proposed a new set of diagnostic criteria for NMO in which three major criteria are required, together with at least one minor criterion.

Major criteria are:

- optic neuritis
- transverse myelitis clinically complete or incomplete but radiologically extending over three or more spinal segments
- no evidence of other conditions.

Minor criteria include:

- normal brain MRI or not fulfilling Barkhof criteria
- positive NMO antibodies.

In addition, presence of OCBs in the CSF is much less common in persons with NMO than in those with MS, occurring in only about 20% of cases.

Acute disseminated encephalomyelitis (ADEM): ADEM is clinically characterised by a subacute encephalopathy (altered level of consciousness, behaviour or cognitive function) with MRI showing diffuse brain lesions with variable gadolinium enhancement. In addition, CSF is more likely to show a pleocytosis and elevated total white cell counts and protein levels, and OCBs are less likely to be present in ADEM than in MS. Miller and colleagues⁹ proposed a set of diagnostic criteria in which the presence of encephalopathy is required for the diagnosis of ADEM and that recurrence of symptoms may occur within a three-month period but cannot occur after a period of complete remission. It is not that unusual for a patient who was initially diagnosed with ADEM to later develop a classical form of MS, emphasising the spectrum theory.

In summary, it is important to be aware of differential diagnoses for those who are undergoing investigation for a possible diagnosis of MS, and to be aware that co-morbidities can affect diagnosis as they may mimic or mask indicators of a true diagnosis of MS. Detailed note taking and an accurate patient history are also very important.

2.2.2 Clinically Isolated Syndrome (CIS)

People who present with a first neurological episode of the kind seen in MS, particularly optic neuritis, transverse myelitis or brainstem/cerebellar syndromes, are said to have a '**clinically isolated syndrome (CIS) suggestive of MS**'. These individuals may or may not fulfil criteria for the diagnosis of MS (as defined in the 2010 McDonald criteria).



People who present with a first neurological episode of the kind seen in MS, are said to have a 'clinically isolated syndrome (CIS) suggestive of MS'.

Clinically isolated syndrome (CIS) suggestive of MS

In 2008, an expert panel published a consensus statement which argued that the definition of CIS "ignores first presentations that may not be clinical but may be detected by paraclinical and laboratory findings. CIS, as currently defined, does not discriminate between patients who have a single clinical presentation with or without additional symptomatic lesions on MRI"⁹. The authors suggested that these are two entities which have different prognoses. The consensus panel recommended a more specific breakdown of CIS into subcategories (see *Table 2*) to better describe the clinical and radiological findings at the earliest stages of MS. The five types of CIS are listed in Table 2.

Subcategory	Description
Type 1	Clinically monofocal; at least one asymptomatic MRI lesion (high risk of MS*)
Type 2	Clinically multifocal; at least one asymptomatic MRI lesion (high risk of MS)
Type 3	Clinically monofocal; MRI may appear normal; no asymptomatic MRI lesions (low risk of MS)
Type 4	Clinically multifocal; MRI may appear normal; no asymptomatic MRI lesions (rare condition)
Type 5	No clinical presentation to suggest demyelinating disease, but MRI is suggestive

Table 2 – Subcategories of clinically isolated syndrome (CIS)

In the longest longitudinal study of patients presenting with CIS, Fisniku and colleagues found that the presence of one or more lesions on the baseline MRI was associated with more than 80% risk of presenting a second attack during a 20-year follow-up period¹¹. Up to 21% of patients with no cranial MRI lesions but presenting with a CIS went on to develop a second attack during the follow-up period.

2.2.3 Radiology Isolated Syndrome (RIS)

A new MRI entity that has been described is the so-called ‘radiologically isolated syndrome’ (RIS)¹². RIS is used to describe the situation in which a patient presents with characteristic MS lesions on a cranial or spinal cord MRI performed for reasons other than the suspicion of MS and in whom no previous history suggestive of a demyelinating episode can be recalled. Studies that followed cohorts of patients with RIS for several years show that approximately one-third subsequently developed clinical attacks^{13,14}. A recent study has indicated that clinically silent spinal cord lesions may be an indicator for high risk of progression to MS¹⁵. However, more studies are needed to confirm/identify factors that might help predict conversion to MS in individuals with RIS.



Clinically silent spinal cord lesions may be an indicator for high risk of progression to MS.

2.3 Summary



- There are a number of neurological tests which are carried out on people with a suspected diagnosis of MS.
 - They include assessment of cognitive status, cranial nerves, motor system, sensory system, and coordination and gait.
 - There is no single, universally accepted sequence of the assessments that make up a neurological examination.
- Paraclinical tests include assessment of oligoclonal bands (OCB) in the cerebrospinal fluid (CSF), multimodal evoked potentials (especially visual evoked potentials) and MRI.
- According to the McDonald Criteria, MRI scans can confirm the diagnosis of MS if lesions in the central nervous system (CNS) are shown to be disseminated in both time and space.
- Red flags which should raise suspicion about a diagnosis of relapsing MS include:
 - relentlessly progressive course.
 - prominent or persistent headache or cortical features (seizures, aphasia, neglect syndromes).
 - abrupt and/or transient duration of symptoms.
 - presence of peripheral neuropathy and involvement of other organ systems, such as cardiac, haematologic or rheumatologic.
- It is important to differentiate the diagnosis of MS from other diseases with similar presenting symptoms which belong to the MS spectrum (e.g., NMO and ADEM).
- First neurologic episodes of the kind seen in MS are usually described as clinically isolated syndromes (CIS).
- The presence of 1 or more lesions on initial MRI is associated with >80% probability of a second attack in the following 20 years.
- Radiologically isolated syndrome (RIS) refers to a cranial or spinal cord MRI finding incidental lesions characteristic of MS in individuals with no previous or present history of CIS.
- One-third of people with RIS subsequently develop MS attacks.
 - Clinically silent spinal cord lesions may be an indicator for high risk of developing attacks of the kind seen in MS in people with RIS.



Reflective learning point

How would you explain how the results of the various clinical and paraclinical diagnostic tests allow the neurologist to confirm or exclude the diagnosis of MS?

How would you explain the difference between MS, CIS and RIS to a patient?

How do you work with your patients to enable them to understand the nature and purpose of the diagnostic process?

3 Diagnostic Criteria

3.1 Learning Objectives

After review of this section, you should be better able to:



- Describe the McDonald Criteria in relation to a diagnosis of MS.
- Examine the effects of the 2010 revisions to the McDonald Criteria.

3.2 Introduction

Intro

As outlined previously, diagnostic criteria for MS include clinical examination as well as paraclinical assessments, with the ultimate objective of demonstrating dissemination of lesions in space (DIS) and time (DIT) once any alternative diagnoses have been reasonably excluded. Although the diagnosis can be made on clinical grounds alone, MRI can support, supplement or even replace some clinical criteria, as most recently emphasised by the “McDonald Criteria” published by the International Panel on Diagnosis of MS⁵.

3.3 The McDonald Criteria

The McDonald Criteria were first introduced in 2001³, but were revised in 2005⁴ and 2010⁵ with the aim of simplifying and speeding up the diagnosis of MS without losing specificity.

These diagnostic criteria have been previously criticised for “replacing clinical assessment”; however this was refuted by the authors who stressed in the latest revisions that the McDonald Criteria should only be applied in those people with clinical symptoms suggestive of MS or demyelinating disease⁵. Diagnostic criteria are not substitutes for clinical examination and history but can validate and confirm them.



Diagnostic criteria are not substitutes for clinical examination and history but can validate and confirm them.

The McDonald Criteria use the following evaluations to support a diagnosis:

- clinical features (evidence of clinical attacks based on symptoms which may indicate evidence of lesions).

These are supplemented where appropriate and available by:

- MRI.
- cerebrospinal fluid evaluation.

3.3.1 The 2010 McDonald Criteria

Recently, the International Panel on Diagnosis of MS published the 2010 revisions to the 2005 McDonald Criteria⁵. The 2010 revisions focussed on simplifying the criteria to improve comprehension and utility. Additionally, the panel assessed the criteria's appropriateness in populations that differ from the largely Western Caucasian adult populations from which they were derived.

Changes from the 2005 McDonald criteria that were recommended, included the following:

- Simplification of **MRI criteria for DIS** (see *Table 3*).

DIS can be demonstrated by ≥1 T2 lesion(s)^a in at least 2 of these 4 areas of the CNS:
• Periventricular
• Juxtacortical
• Infratentorial ^b
• spinal cord ^b

^a Gadolinium enhancement of lesions is not required for DIS.

^b If a subject has a brain-stem or spinal-cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.

Table 3 – 2010 McDonald MRI criteria for demonstration of DIS^{20,21}

- Simplification of **MRI criteria for DIT** (see *Table 4*).

MRI criteria for DIS

The MRI criteria previously used were based on the Barkhof/Tintoré criteria, which had been seen as difficult to interpret by non-imaging specialists¹⁶⁻¹⁹. The MAGNIMS work, reported by Swanton and colleagues^{20,21} and summarized by Montalban and colleagues²², developed a new set of criteria for the demonstration of DIS (*Table 3*) which were to be adopted by the 2010 McDonald Criteria over the Barkhof/Tintoré criteria.

MRI criteria for DIT

In the 2005 criteria, the requirement for a gap of at least 90 days after the CIS to obtain a first reference MRI scan with which to compare a second MRI scan to demonstrate a new lesion was shortened to 30 days. Tur and colleagues²³ further showed that completely removing this requirement did not compromise specificity. Therefore, the current revision of the McDonald Criteria allows a new T2 lesion to establish DIT, irrespective of the timing of the baseline MRI.

As for the presence of gadolinium-enhancing lesions to demonstrate DIT, again work by the MAGNIMS group has demonstrated that, in patients with a typical CIS, a single brain MRI study that shows both gadolinium-enhancing and non-enhancing lesions is specific for predicting early development of a second attack^{22,24}. The 2010 McDonald Criteria now indicate that the presence of both gadolinium-enhancing and non-enhancing lesions on the baseline MRI scan may substitute for a follow-up scan to confirm DIT (*Table 4*).

DIT can be demonstrated by either:

- a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
- simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.

Table 4 – 2010 McDonald MRI criteria for demonstration of DIT²²

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks ^a ; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of prior attack ^b	None ^c
≥2 attack ^a ; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacorrical, infratentorial, or a spinal cord) ^d ; or Await a further clinical attack ^a implicating a different CNS site
1 attack ^a ; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; or A new T2 and gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack ^a
1 attack ^a ; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacorrical, infratentorial, or a spinal cord) ^d ; or Await a second clinical attack ^a implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; or A new T2 and gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack ^a
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria ^d : 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacorrical, infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but the criteria are not completely met, the diagnosis is "possible MS" if another diagnosis arises the evaluation that better explains the clinical presentation, then the diagnosis is "not MS".

a. An attack (relapse/exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristics for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should however consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be correlated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

b. Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

c. No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

d. Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS=Multiple Sclerosis; CNS=central nervous system; MRI=magnetic resonance imaging; DIS=dissemination in space; DIT=dissemination in time; PPMS=primary progressive multiple sclerosis; CSF=cerebrospinal fluid; IgG=immunoglobulin G.

In the 2010 McDonald criteria, the panel points out that these criteria have not been fully validated in Asian and Latin American populations, and suggest that further studies are required to confirm sensitivity and specificity in these populations, particularly with regards to the issue of differential diagnosis of other conditions, namely neuromyelitis optica and infectious diseases that may be more prevalent in certain areas of such regions.

Using the 2010 McDonald Criteria may result in a more rapid diagnosis of MS, something that may avoid a lot of the patient anxiety when diagnosis is a prolonged affair. The sensitivity and specificity of MS diagnosis should be equivalent or better with the 2010 criteria than with the 2005 Criteria, so the level of confidence in the diagnosis should still be high – allowing the MS Nurse to be able to reassure people diagnosed with MS that their diagnosis is correct.



Using the 2010 McDonald Criteria may result in a more rapid diagnosis of MS.

Although the MS Nurse is not usually involved in making the final diagnosis, knowledge of the criteria applied may be useful in discussions with people diagnosed with MS in the days and weeks after the neurologist has confirmed the diagnosis.

Finally, it should be reiterated that diagnostic criteria should only be applied in cases where the individual has experienced a typical CIS. Patients with non-specific symptoms and/or non specific MRI findings should be referred to secondary or tertiary MS centres where available.



Diagnostic criteria should only be applied in cases where the individual has experienced a typical CIS.

3.4 Summary



- The McDonald Criteria should only be applied to individuals who have clinical symptoms typically seen in MS.
- The McDonald Criteria allow for 3 possible diagnoses:
 - MS
 - 'possible MS'
 - 'not MS'.
- The 2010 revisions to the McDonald Criteria have simplified the definition of DIS and DIT, allowing for a more rapid and simple diagnosis of MS retaining a high level of sensitivity and specificity, allowing the MS Nurse to reassure the person regarding the certainty of the diagnosis achieved.

Table 5 – 2010 McDonald criteria for the diagnosis of MS



Reflective learning point

What have been the main innovations in the revisions of the McDonald Criteria and what have they meant to neurologists and people with MS?

4 Investigations and Tests

4.1 Learning Objectives

After review of this section, you should be better able to:



- Explain results from magnetic resonance imaging (MRI) and their relevance to a diagnosis of MS.
- Discuss the importance of the presence of oligoclonal bands in the cerebrospinal fluid (CSF).
- Describe evoked potential tests and their significance.

4.2 Magnetic Resonance Imaging (MRI)

The mechanisms of MRI are extremely complex. Put simply, MRI measures the behaviour of hydrogen atoms (also called protons) in water in the body's tissues during exposure to a powerful magnetic field. MRI technology allows targeted areas, including soft tissue, to be converted into three-dimensional images and can help determine the type of tissue that is present²⁵.



MRI technology allows targeted areas to be converted into three-dimensional images.

MRI is used to reveal macroscopic tissue abnormalities in people with MS with a high sensitivity. Most research studies in the field of MS have been performed on [1.5 tesla scanners](#) (tesla is the unit for the magnetic field strength), which are also the scanners most in use for clinical purposes.



MRI is used to reveal macroscopic tissue abnormalities in people with MS.

Conventional MRI sequences, such as dual-echo (proton density and T2-weighted), fluid-attenuated inversion-recovery (FLAIR), and T1-weighted imaging (with and without administration of a gadolinium-based contrast agent) (see *Figure 2*), provide important information for diagnosing MS, understanding its natural history and assessing treatment efficacy.

[1.5 tesla scanners](#)

Currently, more powerful 3 tesla scanners are gaining ground both in research as well as in clinical facilities. However, their differential added value for the diagnosis of MS is still not completely established²⁶. Scanners with field strengths above 3 tesla are usually used only for research purposes.



Nursing tip

How would you explain the purpose of MRI in diagnosing MS, and what the results can show?

The diagnosis of MS is fundamentally about dissemination of lesions in time and place. Whilst this can be established clinically by a Neurologist, it can only be considered definite when evidence of the same is confirmed on an MRI Scan. An MRI Scan can demonstrate symptomatic or asymptomatic lesions deep in the white matter in different parts of the CNS. It will also show new and old lesions to prove dissemination in time, although serial scanning maybe necessary to further confirm this.

The presence of MRI lesions has become increasingly important over the past decade and features prominently in the latest diagnostic criteria that determine a definite MS diagnosis. There is a need for a certain number of lesions, of a particular size and in particular parts of the CNS for a definite diagnosis to be made.

An MRI can provide additional information necessary to clarify the clinical picture if the patient is injected with a contrast agent called gadolinium (Gd) which allows visualisation of damage to the Blood Brain Barrier which is a common pathological finding of MS. The gadolinium enhances most new MS lesions and is therefore a reliable measure of new, active or inflammatory lesions.



Conventional MRI sequences provide important information for diagnosing MS, understanding its natural history and assessing treatment efficacy.

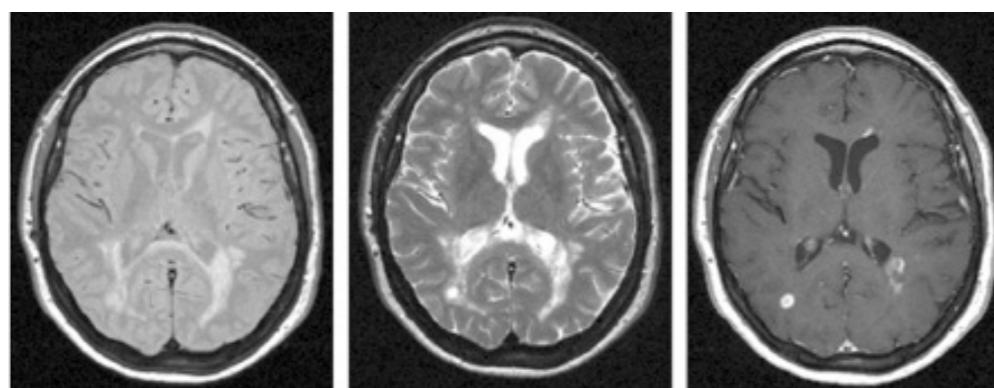


Figure 2 – Axial (a) proton density-weighted, (b) T2 weighted and (c) gadolinium-enhanced T1 weighted spin-echo MR images of the brain in a 37-year-old patient with RRMS

Multiple hyperintense lesions suggestive of a multifocal white matter disease are visible on (a). These lesions are also visible on (b), and some of them are contrast enhanced on (c) which indicates local disruption of the blood-brain barrier.

Dual-echo and FLAIR imaging have a high sensitivity for detection of MS lesions (damage to myelin and / or loss of axons in the CNS), which appear as localised areas of hyperintensity or white light patches, on these types of images (see Figure 2).

However, there is a lack of specificity due to the heterogeneous pathologic nature of individual hyperintense lesions. However lesions indicating, oedema, inflammation, demyelination, remyelination, gliosis and axonal loss all lead to a similar white light patches on dual-echo and FLAIR MRI images (See Figure 3).

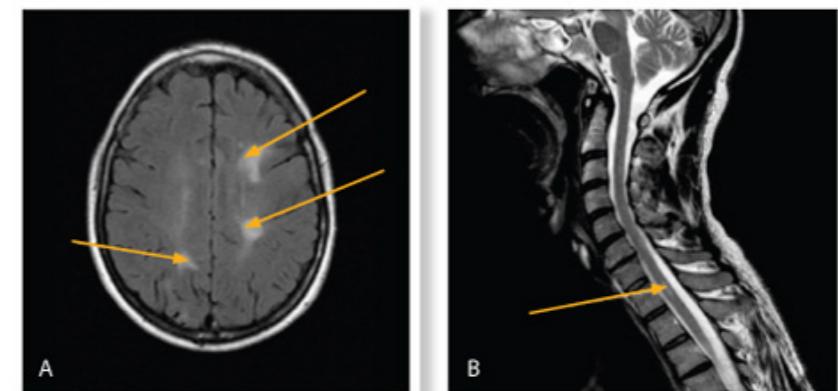


Figure 3 – MRI scans showing inflammatory lesions of MS in a newly diagnosed person with numbness in one leg.
A: Lesions in the brain; B: The spinal cord lesion responsible for the numb leg

Gadolinium-enhanced T1-weighted MRI allows active lesions to be distinguished from inactive lesions. Usually gadolinium cannot pass through the blood-brain barrier; however, increased permeability occurs in inflammatory states allowing gadolinium to pass through, resulting in enhancement of the lesions.



Gadolinium-enhanced T1-weighted MRI allows active lesions to be distinguished from inactive lesions.

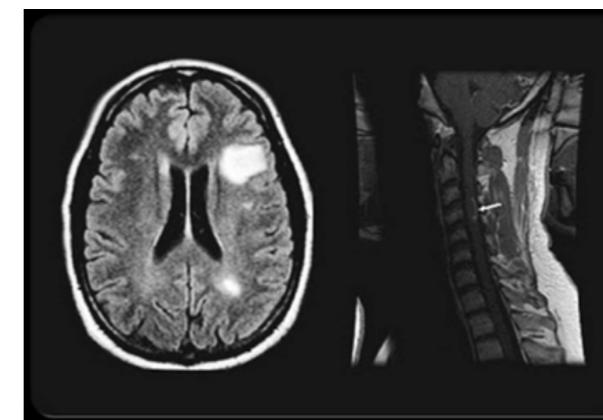


Figure 4 – MRI Images

On the left is a brain MRI of a 35 year old man with relapsing remitting multiple sclerosis that reveals multiple lesions with high T2 signal intensity and one large white matter lesion. The right image shows the cervical spinal cord of a 27 year old woman displaying a multiple sclerosis demyelinating plaque (see arrow).

Another variation of MRI (pre- and post-contrast T1-weighted images) highlights lesions that persistently appear dark rather than the white light patches previously described (lesions also known as “black holes”). These “black holes” are associated with more severe tissue damage (both demyelination and axonal loss), compared to lesions that do not appear dark on T1-weighted images²⁷.

The MRI techniques outlined above are often referred to as ‘conventional’ and newer imaging technologies are referred to as **‘non-conventional’**²⁸.

‘Non-conventional’ imaging techniques can give further insight into the pathology of MS; they have been instrumental in demonstrating damage of the so-called ‘normal-appearing’ brain tissue. Brain volume measurements (atrophy measurements) are usually listed among non-conventional techniques, but they have already been used in many clinical trials as well as in clinical settings, and are becoming “conventional”. Table 6 lists the most relevant non-conventional techniques and what they may be able to tell us about the pathology of MS, especially about the damage that is seen outside the lesions. Table 7 lists main advantages and disadvantages of the non-conventional techniques.

Technique	Short name or acronym	Description
Brain volume measurements	Atrophy techniques	Quantifies brain tissue loss
Magnetisation transfer imaging	MTI	Marker of myelin integrity
Diffusion Tensor Imaging	DTI	Marker of tissue structure disruption
Proton Magnetic Resonance Spectroscopy	¹ H-MRS	Measures concentrations of relevant brain components
Functional MRI	fMRI	Displays brain activity and may indicate brain plasticity

Table 6 – Non-conventional imaging techniques

Technique	Short name or acronym	Description
Atrophy techniques	Reproducibility	Marker of irreversible damage
MTI	Pathological specificity	Redundant information
¹ H-MRS	Pathological specificity	Technical difficulties
DTI	Evolves to tractography	Few correlations
fMRI	Marker of functional changes	Complex analysis and interpretation

Table 7 – Advantages and disadvantages of non-conventional techniques.

It is important to highlight that, in spite of the undisputed usefulness of MRI in the diagnosis and management of people with MS, clinico-radiological correlations are still far from perfect, giving rise to the term **‘clinico-radiological paradox’**²⁹.

4.3 Lumbar Puncture and Cerebral Spinal Fluid (CSF) Analysis

Cerebral spinal fluid (CSF) analysis may be performed to help establish a diagnosis of MS when there is a paucity of clinical or radiological findings. A sample of CSF is obtained by performing a lumbar puncture.



Cerebral spinal fluid (CSF) analysis may be performed to help establish a diagnosis of MS.



Figure 5 – A sample of CSF being taken through a lumbar puncture

A lumbar puncture is a procedure to obtain a sample of CSF below the spinal cord. It is performed by inserting a hollow needle into the lower part of the spinal canal to draw out a sample.

Analysis of CSF allows the detection of abnormalities in composition that may be indicative of MS; it is also useful for excluding other conditions that can mimic MS. The most common abnormalities reflect the presence of intrathecal immunoglobulin synthesis (presence of oligoclonal bands (OCB), increased IgG synthesis rate and index). However, not all people with MS have abnormal CSF, therefore, while the presence of normal spinal fluid may raise doubt about the diagnosis, it does not rule out MS.

‘Clinico-radiological paradox’

There is an assumption that a close relationship exists between extent and rate of development of MRI abnormalities and clinical status and rate of development of disability. While it may seem obvious that patients who develop new lesions are worse off than those without new lesions, the association between clinical findings and radiological extent of involvement is generally poor. Various confounders, including inappropriate clinical rating, lack of histopathological specificity (especially for axonal loss), neglect of spinal cord involvement, underestimation of damage to the normal appearing brain tissue (both white and gray matter), and masking effects of cortical adaptation can contribute to this apparent clinico-radiological paradox²⁹.



Analysis of CSF allows the detection of abnormalities in composition that may be indicative of MS; however, not all people with MS have abnormal CSF.

OCBs are made of a group of proteins that can be electrophoretically separated from CSF IgG (see Figure 6). The antigens eliciting the production of OCBs have not yet been identified. Up to 90% of people with relapsing-remitting MS show OCBs in their CSF (this figure may be somewhat lower in primary-progressive MS), and in order to indicate a diagnosis of MS, there have to be at least 2 bands present in the CSF, which are not present in the serum³⁰.



Up to 90% of people with relapsing-remitting MS show oligoclonal bands in their CSF.

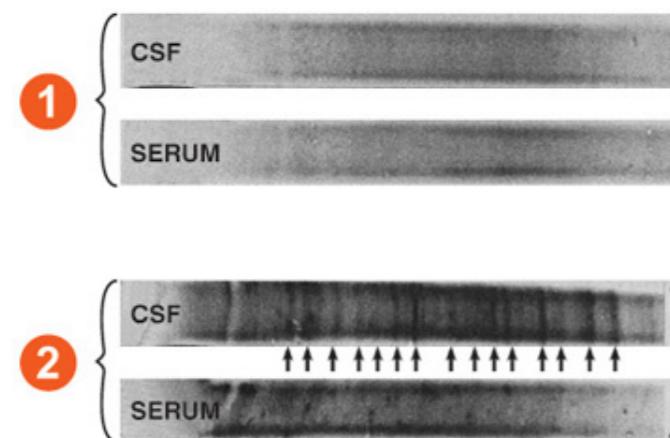


Figure 6 – Different CSF/serum patterns on isoelectric gel electrophoresis³¹

(1) Normal pattern showing an absence of clear banding; (2) typical oligoclonal banding pattern in the CSF (but not serum) of a person with clinically definite MS.

Another marker of intrathecal IgG production is the IgG index relative to serum IgG. A CSF IgG index greater than 0.7 is abnormal, and it may be elevated in about 75% of people with MS³². The level of myelin basic protein may be normal in people with MS and, even if elevated, it is a very non-specific marker and thus is not useful for diagnosis.

Routine parameters in the CSF, i.e., cell count and chemistries, are usually normal or only slightly elevated in persons with MS. If the white blood cell count is more than 50 cells/mL or the protein level is clearly elevated, alternative diagnoses should be considered³³. A notable exception is the CSF in NMO, which may often have elevated white blood cell counts and protein levels and may less commonly show the presence of OCBs³⁴.

The presence of OCBs is not required at present for a diagnosis of relapsing-remitting MS and may only be needed in the diagnosis of primary-progressive MS according to the 2010 McDonald Criteria. However, CSF analysis may still be used to provide prognostic information, to guide the differential diagnosis and to increase our diagnostic certainty³⁵.



CSF analysis may be used to provide prognostic information, to guide the differential diagnosis and to increase diagnostic certainty.

4.4 Evoked-Potential Tests

Since loss of the myelin sheath in MS slows nerve conduction, a slower-than-normal conduction speed indicates that the pathway being tested is diseased. Evoked-potential (EP) tests are simple electrical tests that measure the time it takes for nerves to respond to stimulation (e.g. how long it takes nerve impulses from the eye, ear, or skin to reach the brain). The primary utility of EP testing is to help discern clinically silent evidence of CNS lesions.



Evoked-potential tests are simple electrical tests that measure the time it takes for nerves to convey the stimulus to the brain.

The most commonly used EP modalities are [visual \(VEP\)](#), [somatosensory \(SSEP\)](#) and [brain-stem auditory \(BAEP\)](#). VEP could contribute in some specific instances to the diagnosis of MS according to previous revisions of McDonald Criteria, but it no longer features in the diagnostic algorithms of the 2010 revisions of the McDonald Criteria.

It is the VEP test that is most useful in the work-up of MS because it can provide objective evidence of an optic nerve lesion that may not be evident on an MRI scan¹. Normally, there is a 100 millisecond delay (called the P100 wave) between light entering the eye and the signal reaching the brain. In MS, the P100 wave can be absent, delayed or distorted, depending upon the severity of damage to the nerve. To record VEP, the subject has recording electrodes placed over the occipital cortex and is then asked to look at an alternating checkerboard pattern on a screen. Abnormalities in conduction are usually detected despite a normal visual acuity test or in patients who do not recall any episodes of optic neuritis in the past. This can therefore provide a useful retrospective record of a previous neurological event³⁶. In patients with a history of optic neuritis, the VEP is abnormal about 90% of the time, but on average VEP may be abnormal in more than 50% of patients who have no history of optic neuritis³⁷.

In patients with a CIS (e.g., optic neuritis, brain-stem/cerebellar syndrome or transverse myelitis), the yield of EP to predict a higher risk of developing further attacks is low³⁹.

[Visual \(VEP\)](#), [somatosensory \(SSEP\)](#) and [brain-stem auditory \(BAEP\)](#)

Hyperlink pop-up: Regardless of their non-inclusion in the current diagnostic algorithms, the American Academy of Neurology guidelines for EP state that VEP is recommended as “probably useful” to identify patients at risk for developing MS, SSEP is “possibly useful” and there is “insufficient evidence” to recommend BAEP for this purpose³⁸.

4.5 Laboratory Tests and Biomarkers

General laboratory tests such as metabolic panel and complete blood cell count, erythrocyte sedimentation rate (ESR), vitamin B12 level, double-stranded DNA test, rheumatoid factor concentration, thyroid-stimulating hormone (TSH) level and, if suggested by the history, human immunodeficiency virus ((HIV) and Borrelia titers are useful more for excluding a diagnosis of MS (by indicating other conditions), rather than a help in the positive diagnosis of MS^{40,41}.



General laboratory tests are useful for excluding a diagnosis of MS (by indicating other conditions).

Validated biomarkers of clinical disease activity would be extremely helpful in the diagnosis of MS. Reliable biomarkers would assist in choosing initial therapy, monitoring response to therapy and even helping in the a priori prediction of therapeutic failure.

As mentioned previously in this section, the presence of OCBs in the CSF is a well-validated biomarker that is useful in the initial diagnosis of MS. The discovery of antibodies to aquaporin 4 in patients with NMO identifies patients with a fundamentally different underlying pathophysiology and clinical course from MS.

The usefulness of neutralising antibodies to interferon-beta (IFN β) in identifying treatment failure and possibly guiding changes in therapy is still a matter of debate.

While numerous other candidate biomarkers in serum and CSF have been described, none have yet been validated for clinical use. The availability of multiple genetic and protein microarray technology may assist in identifying more reliable candidate biomarkers or patterns of multiple biomarkers, and offer improved specificity. The heterogeneity of MS may necessitate the identification of individualised biomarkers to assist in diagnosis and therapy⁴¹.



Nursing tip

How would you explain the investigation steps toward a diagnosis and can you think about what the term “clinical diagnosis” may mean to someone who is undergoing investigation for possible MS?

The principle consideration when diagnosing MS is whether the person fulfils the diagnosis on a clinical level. A ‘clinical diagnosis’ means that, through questioning and a neurological assessment, it is apparent the person fulfils the ‘picture’ of someone with MS, and sufficient evidence of this is seen in their history of symptoms and the results of their neurological examination. The Neurologist will accumulate evidence from the history and examination and if appropriate give a ‘clinical diagnosis’ to the person and explain there is now a need for laboratory investigations to be carried out to confirm the clinical picture.

It can take time for these investigations to be carried out and for the results to be interpreted, and this elongated waiting time represents a period of great uncertainty to the individual and their family. It could be said that the diagnosis should only be given once all the tests are completed, but because the diagnosis of MS is so significant, it is important for the Neurologist to give a ‘warning shot’ to prepare the person for what could be their outcome. There is still no one specific diagnostic test for MS so a package of laboratory investigations is valuable, although often not all of these are necessary.

For those suspected of having Primary Progressive MS, the diagnostic period can be particularly elongated because the diagnostic criteria can only be achieved once the person has demonstrated disease progression over a period of time. This can be an extremely frustrating time for the person.



Nursing tip

How would you support the family during this time?

It is not only the person who is undergoing diagnosis of MS who can feel they are on a rollercoaster of a journey, it is their family too. The time it takes to diagnose MS can be a time of fear, distress and great uncertainty for some; therefore it is important that this is acknowledged with the family and they are given the opportunity to talk and ask any questions they may have with someone who is knowledgeable about MS and its diagnosis. Whilst it is important to comfort the family at this time, remember they will never forget (or forgive) any false reassurance.

It is important that the nurse shows empathy to the family at this time; phrases such as “this must be a very difficult time for you and your family” or “it is obvious you love your ... very much and you feel a little helpless at the moment...” will give the family the permission that they need to be able to talk to you and may encourage effective two way communication.

It is important to educate the family with the process involved in diagnosing MS and that they are aware that the, sometimes prolonged, diagnostic time can represent a period of uncertainty. It is also important to explain that their loved one can fluctuate in mood and become fearful and frustrated; it maybe that they take this frustration out on their family. Family members may want to know what they can do to support their loved one and the potential of their role can be explained. They could (for example) accompany them to appointments as ‘two sets of ears are better than one’ and can also be emotionally comforting, talk to their loved one, but do not offer over (or under) optimism about the outcome of the findings. Reinforce how essential listening to their loved one can be - they should not underestimate what they can do to support loved ones at this time.

It is essential that the family is aware of where and/or who they can go to if they want to talk about their concerns and worries and they are given the details of organisations or individuals who understand what they are going through - this makes it a far less lonely experience. These resources will differ from country to country of course. It is essential to tease out the many myths and misconceptions about MS, so ask the family members what their previous exposure has been to MS so that family can be educated with accurate and up to date information. It is important that sufficient information is given to the family; providing minimalist information or using professional jargon will almost certainly cause anxiety. They may want to look for information about the diagnosis themselves, therefore ‘signpost’ them to reputable web sites or booklets that will provide them with accurate information.

Parents can feel guilty if their child is undergoing the diagnosis of MS and may feel that they must have played a direct part in their child’s diagnosis. Again, it is important to educate honestly and accurately and explain that it is not because of something that they have or haven’t done for their child.

4.6 Summary



- Dual-echo and FLAIR imaging have a high sensitivity for detection of MS lesions, which appear on the scans as focal areas of hyperintensity (white light patches).
- There is a lack of specificity to the heterogeneous pathologic nature of individual lesions.
- Gadolinium-enhanced T1-weighted MRI allows active lesions to be distinguished from inactive lesions.
- DIS and DIT are required to confirm the diagnosis of MS.
- The presence of lesions on MRI scans for the diagnosis and management of people with MS is important. The correlation between lesions and clinical aspects of relapse or disability progression is far from perfect.
- The presence of OCBs in the CSF is supportive evidence for a diagnosis of PPMS, but it no longer features in the diagnostic algorithm of RRMS.
- There have to be at least 2 bands present in the CSF, which are not present in the serum.
 - Up to 90% of people with RRMS have OCBs in their CSF.
- VEP testing might be of use in the diagnostic work-up of MS since it provides objective evidence of an optic nerve lesion that may not be evident on an MRI scan, but it does not feature in the diagnostic algorithm of MS according to the 2010 revisions to the McDonald Criteria.
- General laboratory tests are more useful in excluding a diagnosis of MS than confirming MS.
- There are as yet no clinically proven biomarkers for MS, except:
 - OCBs in the CSF are a validated biomarker for diagnosis of MS.
 - Aquaporin-4 antibody presence indicates a diagnosis of NMO.



Reflective learning point

What do an increase in the number of lesions and lesions in different locations in the CNS mean to the person with MS, and how does this relate to a diagnosis of MS?

Can a diagnosis of MS be made on the basis of OCBs in the CSF?

Are there specific biomarkers for the diagnosis of or exclusion of MS?



Reflective learning point

What is the role of the MS Nurse in the diagnostic pathway?

5 Identifying MS Relapse

5.1 Learning Objectives

After review of this section, you should be better able to:

-  • Identify an MS relapse.
- Differentiate relapse from disease progression and other non MS related conditions.

5.2 How to Identify a Relapse

Relapses, or exacerbations, in MS occur as inflammatory processes acutely damage or destroy the myelin sheath around axons or the axons themselves in the CNS (see *Module 1*), giving rise to new and transient abnormalities in the neurological examination (signs) and/or to symptoms. Attacks are usually followed by remission of signs/symptoms, and successful recovery in the earlier phase of the condition. ‘Attacks’ were defined by the 2010 Diagnostic Criteria Panel as “patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection”. Relapses must be differentiated from pseudo-attacks, most frequently occurring in the presence of fever. When signs and symptoms accumulate with no apparent remission, the situation is described as clinical progression, as it occurs from onset in people with primary-progressive MS and, in some people, after a period of relapses (secondary-progressive MS)⁴².



Relapses in MS occur as inflammatory processes acutely damage or destroy the myelin sheath around axons or the axons themselves in the CNS.



Nursing tip

How would you explain the investigation steps toward a diagnosis and can you think about what the term “clinical diagnosis” may mean to someone who is undergoing investigation for possible MS?

It is often difficult for people with MS to comprehend what really is a relapse, especially because many other environmental and emotional factors can trigger increased MS symptoms. It is essential that patients are educated at an early stage in regards to ‘what is a relapse’ so that it does not frighten them and they are able to either effectively self manage their symptoms or know when and where to ask for help. If they are not educated correctly people may seek help and advice frequently as their symptoms fluctuate over a period of time. Explain to the patient what they could do to establish whether this is a relapse, such as resting more or staying out of the heat. Explain why it is important not to panic and conjure up visions of increased disability. It is helpful to explain to patients that a useful question to consider is “Is it interfering with activity or causing significant pain?” If the answer is yes to either of these, then they should ask for help.

Patients need to be educated regarding the difference between a relapse and disease progression. It can be explained that a relapse comes on acutely, or more often sub acutely; if the symptoms have come on insidiously over a matter of months this is less likely to reflect a relapse and more likely to be disease progression. The patient could be told that a relapse involves symptoms that last at least one but, more commonly, a number of days. To be considered a new relapse, it should be explained that symptoms must occur at least 30 days after the start of a previous episode. Symptoms similar to those of a relapse can occur when there is an infection, often a urine or respiratory infection. It is therefore important to rule out infection before thinking that new symptoms are definitely due to a relapse and advice needs to be provided on who the patient should contact to do this and when. In addition to education, it is important that this is supplemented with written material and specific websites that can enable a patient to complete a checklist regarding their symptoms.

It is important to explain what is happening physiologically when a relapse occurs to decrease anxiety. The symptoms experienced will depend on the specific area of the brain or spinal cord affected. Some relapses are relatively mild while others may cause more serious problems. It is important that patients understand what triggers relapses such as fatigue, an infection and even stress, although the evidence relating to the latter remains controversial. Lifestyle issues are also important in reducing the risk of relapses. A well balanced diet and regular exercise will promote good health and can help reduce the risk of relapse triggers such as infection.

You could give a checklist to patients such as ‘you are experiencing a relapse if you answer “yes” to the following questions’:

- Am I experiencing new symptoms or worsening of existing symptoms?
- Has this worsening happened over the course of 24 hours to a couple of days?
- Have these symptoms lasted more than 24 hours?
- Has it been at least a month since my last relapse? (In other words, had these symptoms been non-existent or stable for at least 30 days before they appeared or got worse?)
- Am I free of fever or infection?

Authentic exacerbations occur at least 30 days after any previous episode began, and are typically expected to last for at least 24 hours. In an exacerbation, symptoms often involve the evolution of novel symptoms not previously experienced by the patient but also can include re-appearance of previously experienced symptoms (although in such instances, differentiation from pseudo-attacks can be very challenging). Symptoms usually appear over a few hours (possibly days) and can last from a few days to many months. This will be difficult for the patient, not only physically but also emotionally, and the MS Nurse can assist and provide support at these times⁴².



When signs and symptoms accumulate with no apparent remission, the situation is described as clinical progression.

Screening tools for assessing symptoms and disease progression will be discussed in the next section of this Module.

Clearly, continuing fatigue is not necessarily a sign of a relapse but if acute, profound in onset fatigue comes suddenly, and remains for more than a few days, then further investigation is warranted.

Since it has been well established that high-dose, short-term intravenous corticosteroid therapy provides symptomatic relief and shortens the recovery phase of acute disease-related attacks, it is important that such therapy is offered to all patients. The final decision on giving corticosteroids should only be made after a careful risk–benefit ratio assessment, as corticosteroids are not free of side effects and recovery will eventually take place regardless of treatment.

If the person with MS has a surge of symptoms in clear temporal relationship with a temporary elevation in core body temperature due to infection (e.g., UTI), fever, exercise or ambient temperature, these symptoms should not be considered a relapse rather as a pseudo-exacerbation. It is essential therefore that the MS Nurse establishes, by close questioning and referral to patient history and notes, that the person is not in any of these situations.



Nursing tip

What questions and investigations would you complete to determine if the patient is experiencing a relapse?

1. History of onset of symptoms
Ask the patient did the symptoms come on sub acutely/acute. When did they start? Have they been there continuously for more than 24 hours? Ask them to describe how their condition now is different from how they were 30 days previously. What symptoms they are experiencing? Are these symptoms new or have they had them before? Does anything make them worse?
2. How disabling are the symptoms
It is important to establish how these ‘new’ or increased symptoms affect them on a day to day basis - what can’t they do now that they could do a few days ago. Ask them to describe how these ‘new’ or increased symptoms impair them day to day such as at home or at work.
3. Eliminate a pseudo relapse
Prior to confirming a relapse, it is essential to rule out a pseudo-relapse, although this is not always straightforward. It is important to ask the patient if their symptoms seem to come on or increase when they are overheated. This does not mean that the patient is having an MS relapse, but rather it could be Uhthoff’s phenomenon, where heat can uncover older MS symptoms.

It can also be caused by physical or psychological stress, fatigue often increases MS symptoms. It is essential to ask the patient about their activity of late - they may have had a particularly strenuous or stressful life style or have been exercising more than usual which could increase their fatigue levels and so exacerbate existing neurological symptoms. Typically, once the underlying cause of the pseudo-relapse is eliminated, the neurological symptoms will resolve.

History of recent infection is essential because it is important to ensure the person does not have an infection prior to administration of steroids. Ask the patient questions about their general health. Ask them if they have had any infections recently or have been exposed to someone with an infection. Ask the patient to consider their body from their head down to their feet when considering if they have an infection. If there is a recent infection, wait for this to disappear before reassessment for steroids. Take a routine Mid Stream of Urine even if the patient is asymptomatic of any bladder symptoms.
4. Are the increased symptoms associated with menstrual cycle?
It is known that the menstrual cycle can affect MS symptoms. Some women report they experience increased fatigue and exacerbation of their other pre existing symptoms approximately 7 days before and 3 days into their period. Therefore it is important to ask women questions concerning where they are in their menstrual cycle.
5. Has the patient commenced any new medication?
Some drugs that are prescribed for people with MS have side effects which may mimic a relapse, ask the patient if they have commenced on any new medication recently.
6. It is important to carry out some form of objective measurement such as a timed 100 metre walk or a Nine Hole Peg Test. Of course it is advantageous to already have carried this out when the patient was ‘stable’ so baselines can be established and then compared to once the patient comes to see you regarding a ‘relapse’. However, it is important to do this during relapse too so any recovery can be monitored and it can be established whether steroids do help the individual patient.

5.3 Summary



- Relapses, attacks or exacerbations, are new symptoms or signs appearing in a person with MS and are typically expected to last for at least 24 hours.
 - Relapses may involve new symptoms or re-appearance of previous symptoms:
 - Symptoms can continue for a few days or over months.
 - New signs and symptoms appearing during a temporary escalation in core body temperature do not constitute a relapse but are referred to as a pseudo-relapse.
 - Temporary increases in core body temperature can be due to infection (e.g., UTI), fever, exercise or change in ambient temperature.



Reflective learning point

What are the major indicators that an individual's symptoms are indicative of a relapse?

6 Tools to Assess Disease Progression

6.1 Learning Objectives

After review of this section, you should be better able to:



- Describe the EDSS, MSFC and the MSSS assessment tools.
 - Discuss how these tools assist in monitoring disease progression in MS.

6.2 Introduction



Assessment tools are commonly used to assess MS-related disability and its evolution throughout the course of the condition. In charting the disease over time, they are used to:

- Monitor the progression of the disease in people with MS, allowing caregivers to provide the most appropriate therapy as the person's disease progresses.
 - Assess (in clinical research) the effectiveness of the therapy on trial.



Assessment tools are commonly used to assess MS-related disability and its evolution throughout the course of the condition.

To fulfil these roles, a tool needs to be concise, consistent and reproducible. The rigorous nature of clinical trials requires assessment tools that are more amenable to scientific analyses. However, the needs of caregivers and MS Nurses are such that they prefer an approach that is more personal to the needs of the individuals with MS.

There are many assessment tools. Here we will review three of the most widely used tools:

- Expanded Disability Status Scale (EDSS).
 - Multiple Sclerosis Functional Composite (MSFC).
 - Multiple Sclerosis Severity Scale (MSSS).



Nursing tip

Which assessment tools do you routinely use? How do you communicate results of these tools to your patients?

The Guys Neurological Disability Score is ideal for assessing the ability/disability of person with MS. It is a questionnaire that is very patient-orientated and much more nursing friendly compared to some of the other ‘medical’ assessment tools such as the EDSS. It assesses the patient’s disability in the previous month by patient interview and can be completed by any healthcare worker. It is practical and capable of incorporating patients’ views of their disability in a structured manner. It can be administered over the phone, completed by the patient in the waiting room, or can be posted to the patient to complete prior to their appointment.

It should be discussed with the patient that you are completing an assessment tool and why you are doing this. Any results should be explained in depth with the patient so they are not disturbed or frightened by any of the findings.

6.3 Expanded Disability Status Scale (EDSS)

The expanded disability status scale (EDSS) is the assessment tool most widely used in MS. The EDSS was created in 1983 by Dr Kurtzke⁴³ by expanding the DSS/Functional Systems (FS) tools created he had created in 1955⁴⁴. These two systems (EDSS and FS) were used in what most probably were the first two multi-centre, randomised, double-blind, placebo-controlled trials of therapy ever conducted in MS, the results of which were published in 1957 and 1965⁴⁴.



The expanded disability status scale (EDSS) is the assessment tool most widely used in MS.

The EDSS ranges from 0 – to 10 in 0.5- unit increments (except for the non-existence of a 0.5 grade) that represent sequentially higher levels of disability, with 0 relating to normal neurological examination and 10 referring to death due to MS. Scoring on this scale is based on examination by a trained examiner such as a neurologist or MS Specialist Nurse who grades a person with MS according to a set of eight Functional System Scales (see Figure 7), combined with the person’s current ambulatory function (in the middle range of the scales) and with upper limb and bulbar function in the upper range of the scale.



The EDSS ranges from 0 to 10 with 0 relating to normal neurological examination and 10 referring to death due to MS.

The 20-step ordinal scale can be summarised into the following groupings:

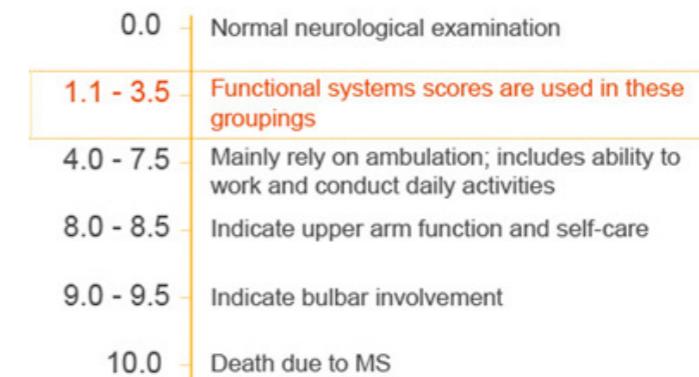


Figure 7 – Summary of the EDSS ordinal scale

The 8 Functional System Scales

- **Pyramidal** – weakness or difficulty moving limbs.
- **Cerebellar** – ataxia, loss of coordination or tremor.
- **Brainstem** – problems related to impairment of cranial nerves.
- **Sensory** – loss of sensory modalities.
- **Bowel and Bladder** function.
- **Visual** function.
- **Cerebral** (or mental) functions.
- **Other**.

Each functional system is scored on a scale of 0 (no impairment or disability) to 5 or 6 (more severe impairment or disability).

The EDSS can also be illustrated in a linear fashion, as in Figure 8.

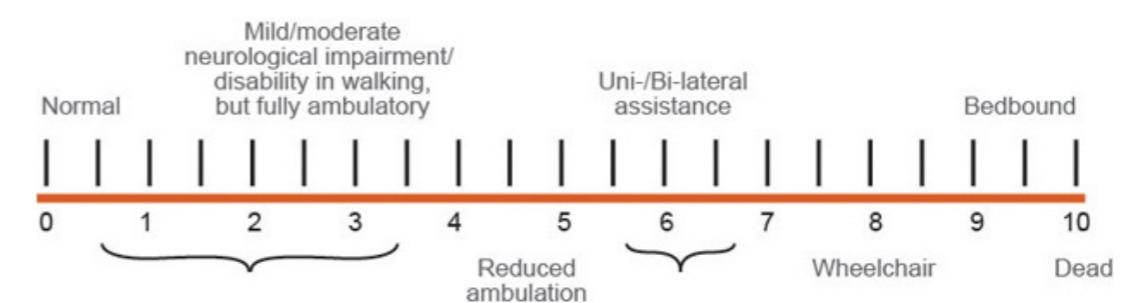


Figure 8 – Linear representation of the EDSS scale

Although the disabilities are placed in an approximate order of how they are likely to occur as the disease progresses, progression through these stages is unlikely to be linear.



The EDSS is in widespread use and its common language is familiar to neurologists. It is considered easy to use being based on neurological examination, uses a relatively straightforward scoring system and has considerable evidence to support its reliability.

Full details of the EDSS scale:

Score	Description
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc - to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair, though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel own self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of the day. Has some effective use of arms. Retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Table 8 – EDSS summarised scoring system³¹

However, the EDSS has been widely criticised, with some of the limitations being cited as⁴⁵:

- poor responsiveness in people with MS with greater disability (EDSS score ≥ 6.0).
- low reproducibility at the lower end of the scale.
- heavy reliance on ambulation in the middle range.
- limited assessment of upper limb function.
- insensitivity to cognitive impairment.

A further limitation is the non-linear nature of progression through the EDSS. Clearly, disability, as assessed by the EDSS does not naturally continue to progress at a similar rate throughout the course of a patient's MS.

In addition, the EDSS does not reflect many of the distressing symptoms of MS such as fatigue and pain, does not properly assess cognition, and most importantly, it does not include the individual's perspective on their disease.



The EDSS does not reflect many symptoms of MS such as fatigue and pain, does not properly assess cognition, and does not include the individual's perspective on their disease.

6.4 Multiple Sclerosis Functional Composite (MSFC)

This assessment tool was developed by a task force as part of an international initiative led by the National MS Society of the United States. They were asked to make recommendations for a new multi-dimensional assessment tool based on the use of quantitative measures. The resulting composite scale, the Multiple Sclerosis Functional Composite (MSFC), was recommended for future MS clinical trials⁴⁶.

The MSFC is a three-part composite that contains measures of three clinical dimensions that were identified in advance as important aspects of MS (Table 9). The MSFC requires minimal equipment and can be administered in 15 minutes by a trained healthcare professional⁴⁷.



The MSFC requires minimal equipment and can be administered in 15 minutes by a trained healthcare professional.

Clinical dimension	Measure	Units
Ambulation	Timed 25-foot walk	Seconds
Arm function	9-hole peg test	Seconds
Cognition	Paced auditory serial-addition test	Number correct

Table 9 – The Multiple Sclerosis Functional Composite (MSFC)⁴⁷

The **timed 25-foot walk (25FTW)** consists of the patient walking the specified distance in his or her usual manner quickly, but safely. The **nine-hole peg test (9HPT)** consists of moving nine pegs from an open box into each one of the nine holes excavated on a peg board, then back into an open box. The test is done twice with each hand, and the time it takes is averaged for each hand separately⁴⁸. The paced **auditory serial-addition test (PASAT)** consists in adding up sequentially, in groups of two, 60 numbers presented, producing the answer in loud voice, and the test is scored as the number of correct answers⁴⁹.

Thus, the MSFC contains tests for leg/walking function, arm function and cognitive function, but does not include tests for two further clinical dimensions that were thought important – visual function and sensory function.



The MSFC contains tests for leg/walking function, arm function and cognitive function.

Scores from the individual tests are standardised to a reference population, the direction of each resulting z score is aligned so that increasing scores represent improvement, and z scores from each clinical test are averaged to create a single score (see *Table 10*). The score consists of a single average standardized score representing relative performance on the three tasks compared with the reference population⁵⁰.

Step 1	Measure component raw scores: 25FTW (seconds) 9HPT (seconds) PASAT (number correct)
Step 2	Convert component scores to z scores based on the mean and SD of a reference population (usually the polled baseline population)
Step 3	Transform 25FTW and 9HPT z scores so that a decrease represents worsening
Step 4	MSFC z score = mean of component z scores

Table 10 – Calculating the MSFC score

Positive attributes of the MSFC include:

- It shows moderately good correlation with EDSS.
- MSFC has advantages over EDSS in that it is continuous, as opposed to ordinal (see *Figure 9*), and provides superior inter- and intra-rater reliability.
- MSFC provides good correlation with other measures that are specific for disability, including MRI and patient-reported, disease-related QOL.
- It is predictive of clinical and MRI outcome.

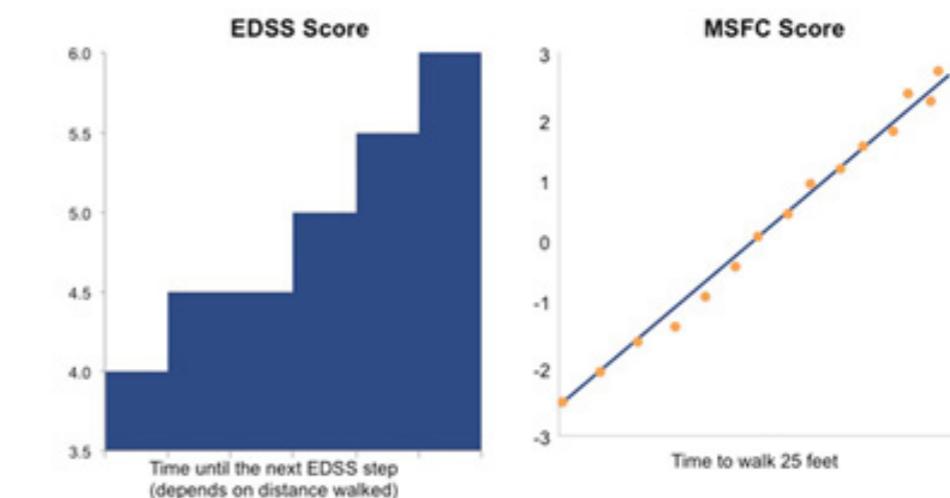


Figure 9 – A continuous scale (e.g., MSFC, shown on right) contains more information than an ordinal scale (e.g., EDSS, shown on left).

Comparisons between the EDSS and MSFC indicate that MSFC might have a better correlation with measures of disease burden, including MRI⁵¹. Correlations between MSFC and brain lesions seemed to be higher than correlations between EDSS and brain lesions in the same patients⁵². Similarly, MSFC seemed to be more strongly correlated with brain atrophy than was EDSS, in two separate studies^{52,53}. This would indicate that MSFC is more closely linked to brain pathology detected by MRI than is EDSS.

Finally, it is worth remembering that the clinical meaning of an MSFC z-score change is not obvious⁵¹, and as mentioned in the paper that first described the MSFC, “It must be kept in mind that we are searching for a composite that will work as a clinical outcome measure in a clinical trial. While the patients included spanned the entire EDSS range from low to high, this composite measure may not be suitable for individual patient care or evaluation and may not demonstrate a meaningful clinical change per se but be linked to clinical change.”⁵⁰.

6.5 Multiple Sclerosis Severity Scale (MSSS)



The multiple sclerosis severity scale is designed to provide a measure of disease severity.

The multiple sclerosis severity scale (MSSS) adds the element of disease duration to the EDSS and is designed to provide a measure of disease severity⁵⁴.

Previously no simple relation between EDSS and disease duration existed and correcting for this parameter is not straightforward. The MSSS corrects EDSS for duration by using an arithmetically simple method to compare an individual’s disability with the distribution of scores in cases having equivalent disease duration⁵⁴.

The MSSS algorithm is a simple method for adjusting disability for disease duration. Patients were stratified by the number of whole years from first symptoms to EDSS assessment. Each year was analysed with the two on either side. For example, year 5 results were generated from data for all patients with onset of symptoms attributable to MS from 3 to 7 years previously. Within each year EDSS scores were ranked and the average of the lowest and highest ranks for each possible EDSS value (0, 1, 1.5 . . . 9.5) was calculated. These averages were then normalised by dividing by the number of available assessments for that year. The normalised values were multiplied by 10 to provide a range from 0 to 10 (for easier comparison with raw EDSS). Therefore, MSSS is the decile of the EDSS within the range of patients who have had the disease for the same disease duration⁵⁴.

Roxburgh and colleagues demonstrated that the average MSSS showed stability over time, although there were considerable changes in individual MSSS scores, possibly due to the unpredictable nature of MS. This indicates that MSSS is a useful measure for studies of groups of patients but cannot be used to accurately predict later disability in an individual. In other words, one group of patients with a higher mean MSSS than another is likely to maintain a higher MSSS 5, 10, or even 15 years later, even though individual MSSS scores within the groups may fluctuate over time.

Therefore, the value of this screening tool in day-to-day care of people with MS is probably not as great as that of the EDSS or the MSFC.

At the present time it would appear that most neurologists will be using EDSS to assess disease progression, with MSFC being validated and gaining influence as time passes. It is probable that MSFC will never make to clinical practice, but might become a good surrogate for clinical trials, where, in any case, EDSS is still considered to be the primary outcome measure of choice for disability progression. It will be helpful for the MS Nurse to be able to explain to the person with MS what the EDSS and MSFC scores actually mean and what changes in these scores over time may mean to the individual.

6.6 Summary



- Assessment tools monitor the progression of the disease in people with MS.
- Three of the most widely used tools are the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC) and the Multiple Sclerosis Severity Scale (MSSS).
- At the present time it would appear that most neurologists will be using EDSS to assess disease progression.



Reflective learning point

How would you explain a change in the EDSS or MSFC scores in terms of a patient's disease progression and effects on level of disability?

How do you make a connection between outcome measures and scores with the day-to-day experience of living with MS?

Summary of Module



- The diagnosis of MS depends upon a variety of clinical and paraclinical tests and criteria.
- Clinical symptoms are essential for a confirmation of MS, but conditions which are precursors to MS (CIS and RIS) are now being identified via techniques such as MRI.
- The complexity of, and time taken for, the diagnosis of MS can be confusing and distressing to the patient.
- MS Nurses should explain tests, results and their implications to enable patients to self-manage during this very challenging time.
- This will build strong relationships and sustain and support future care throughout the duration of the MS trajectory.
- The assessment of disease status and progression will also be undertaken either following a relapse or at regular follow-up appointments.
- Once again, if the MS Nurse is able to take the patient through the tests and results, and explain the implication of changes in test scores, then the MS Nurse / patient relationship will be strengthened, through shared decision making, agreed goals and mutual trust. This will encourage patient compliance and communication.
- Knowing the patient history, comorbidities and disease status is essential for the provision of optimal patient care.
- Therapeutic options are discussed in Module 4.

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