

# Diagnostic Imaging Pathways - Multiple Sclerosis

## Summary

This pathway provides guidance on imaging patients with multiple sclerosis.

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## Quick User Guide

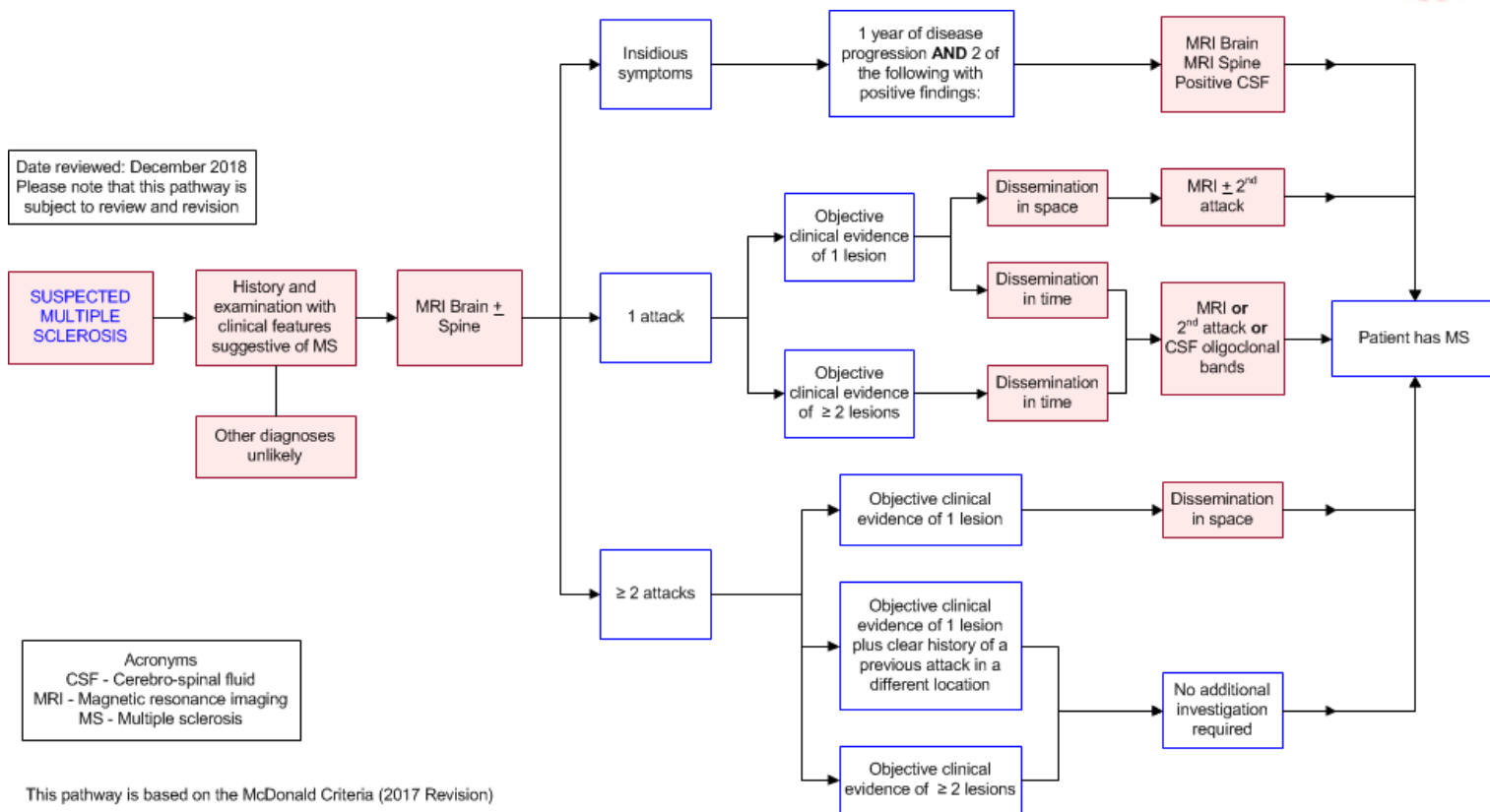
Move the mouse cursor over the **PINK** text boxes inside the flow chart to bring up a pop up box with salient points.

Clicking on the **PINK** text box will bring up the full text.

The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

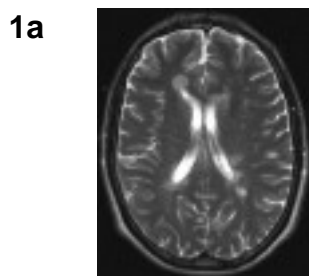
SYMBOL	RRL	EFFECTIVE DOSE RANGE
	None	0
	Minimal	< 1 millisieverts
	Low	1-5 mSv
	Medium	5-10 mSv
	High	>10 mSv

## Pathway Diagram



## Image Gallery

*Note: These images open in a new page*

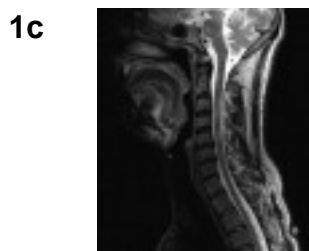
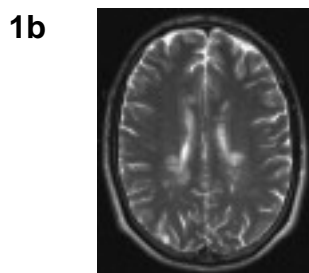


### Multiple Sclerosis

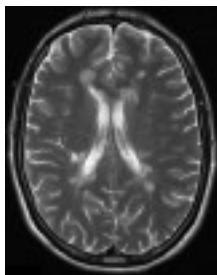
32yo M presented with several days of worsening numbness and weakness of his R leg.

1a, 1b: Initial MRI sequence demonstrates multiple periventricular and pericallosal hyperintense lesions. Images shown are T2 weighted turbo spin echo MRI images.

1c: There are also multiple hyperintense lesions in his spinal cord. These satisfy the criteria for dissemination in space.



2a

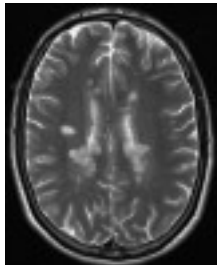


### Follow-up scan

2a, 2b, 2c: Follow-up MRI scan of same patient performed 3 months after initial MRI. There are multiple new white matter supratentorial lesions demonstrated, predominantly within the right posterior and left temporal lobes, as well as a new spinal cord lesion at the level of C7. These satisfy the criteria for dissemination in time.

Additionally, the patient also had oligoclonal bands in his CSF.

2b



2c



## Teaching Points

- Multiple sclerosis (MS) is an idiopathic inflammatory disease of the central nervous system, characterised pathologically by demyelinating foci termed 'plaques'
- Diagnosis of MS requires demonstration of dissemination in space and dissemination in time as well as exclusion of alternate diagnoses
- The 2017 revision to the McDonald Criteria make several consensus and/or evidence-based recommendations concerning the diagnosis of multiple sclerosis
- MRI can support or replace clinical information for the demonstration of DIS and DIT

## Suspected Multiple Sclerosis

- Multiple sclerosis (MS) is an idiopathic inflammatory disease of the central nervous system, characterised pathologically by demyelinating foci termed 'plaques' [1](#)
- In 2009, there were an estimated 23,700 people with MS in Australia [2](#)
- MS affects more women than men, with a female to male ratio reported to be approximately 2-3:1 [3](#)
- The prevalence of MS varies geographically, with a reported positive association between MS prevalence and latitude [4](#)
- Other risk factors include: [5](#)
  - Infectious mononucleosis (EBV)
  - Smoking
  - Low serum 25-hydroxyvitamin D levels
  - Obesity in childhood or adolescence
  - Genetic susceptibility: >100 polymorphisms associated with MS, amongst the strongest are alleles of the major histocompatibility complex (MHC), particularly the HLA-DRB1 locus

- Clinically, MS is a heterogeneous disorder with several recognised MS subtypes, including;
  - Clinically Isolated Syndrome (CIS)
    - Defined as the first clinical episode with features suggestive of MS
    - A CIS should last for at least 24 hours and occur in the absence of fever or infection, with no clinical features of encephalopathy [6.7](#)
    - In a cohort of patients with acute unilateral optic neuritis as a CIS, after 15 years, the probability of developing MS was 50% and was strongly related to presence of lesions on the baseline brain MRI (25% for no lesions and 75% for one or more lesions) [8](#)
  - Relapsing-Remitting MS (RRMS)
    - Affects the majority of MS patients (85%)
    - Characterised by acute episodic periods of worsening neurological symptoms (“attacks”) followed by (partial or full) recovery
  - Primary-Progressive MS (PPMS)
    - Affects approximately 10-15% of MS patients
    - Characterised by gradual progressive deterioration
    - Occasional plateaus, temporary minor improvements, or acute relapses are still consistent with the definition
  - Secondary-Progressive MS (SPMS)
    - Follows the initial relapsing-remitting course, which then follows onto a progressive course with or without occasional relapses
    - Approximately half of patients with RRMS will convert to SPMS at the ten year mark and 90% at the twenty five year mark [9](#)
  - Radiologically Isolated Syndrome (RIS)
    - Brain MRI features typical of demyelination and fulfilling MRI criteria for MS seen as incidental findings in healthy individuals or patients with non-specific symptoms (e.g. headache, dizziness) [6](#)
    - High risk for developing clinically definite MS (CDMS), with clinical events identified in 34% of individuals within a 5-year period from the first brain MRI study [10](#)

## History and Examination Suggestive of MS

- Diagnosis of MS requires demonstration of dissemination in space and dissemination in time as well as exclusion of alternate diagnoses
- Clinical assessment is an essential part of the diagnostic work up of MS [11](#)
- Symptoms and signs can be classified as either monofocal (indicative of a single lesion) or multifocal (indicative of more than one lesion)
- Clinical findings can be used to indicate dissemination in space and/or time and a purely clinical diagnosis remains appropriate when MRI and other investigations are not possible
- Clinical features suggestive of an MS attack may include: [12](#)
  - Sensory disturbances
  - Unilateral optic neuritis
  - Diplopia
  - Limb weakness
  - Clumsiness
  - Gait ataxia
  - Lhermitte's sign
  - Bowel or bladder disturbance

## Exclusion of Alternative Diagnoses

- A diagnosis of MS requires exclusion of other conditions that can mimic MS by their clinical and laboratory profile [11,13](#)
  - As MS is a progressive neurodegenerative disorder, clear differentiation of MS from MS-mimics is essential to provide early appropriate therapy
  - In patients presenting with symptoms and signs of MS, the differential is broad and work up includes a range of clinical, biochemical and imaging tests
  - An approach to the exclusion of alternative diagnoses in patients with presentations suggestive of MS has been proposed, and involves: [14](#)
1. Exclusion of diseases not likely to be MS or non-MS idiopathic inflammatory demyelinating disease, including but not limited to:
    - Vascular: embolic disease, vasculitis, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts), primary angiitis of the CNS
    - Infectious diseases: meningitis, encephalitis, progressive multifocal leukoencephalopathy (PML)
    - Metabolic: vitamin B12 deficiency, hyperhomocysteinaemia
    - Neoplasm: glioblastoma, lymphoma
    - Congenital: Chiari I malformation
  2. Differentiation of prototypic MS from non-MS idiopathic inflammatory demyelinating disease:
    - Neuromyelitis Optica Spectrum Disorder (NMOSD): differentiating features from MS include [15](#)
      - Simultaneous bilateral optic neuritis
      - ≥3 vertebral segments of longitudinally extensive transverse myelitis lesions
      - Detectable serum antibodies that target the water channel aquaporin-4 (AQP4-immunoglobulin G [IgG]) are highly specific and may be involved in the pathogenesis of NMOSD
    - Acute Disseminated Encephalomyelitis (ADEM)
      - An immune-mediated demyelinating disease that predominantly affects children in response to a preceding infection or vaccination
      - Most cases are monophasic
      - Lesions are typically located in the basal ganglia and thalamus [16](#)
- Timely recognition of imaging 'red flags' in the work up of patients suspected of having MS should alert clinicians to reconsider the differential diagnosis more extensively and perform additional analyses [13,14,16](#)

## Magnetic Resonance Imaging (MRI)

- Since the addition of MRI to the 2001 McDonald criteria to support or replace clinical information, MRI has become a vital component in the diagnosis of MS [17](#)
- The 2010 McDonald criteria have been validated in Caucasian [18,19](#) and non-Caucasian [20-22](#) populations and are widely accepted for the MRI diagnosis of MS
- The 2017 McDonald criteria presents recommendations for the diagnosis of MS including several revisions to the 2010 McDonald criteria
- These recommendations include:
  - Defining the role of CSF-specific oligoclonal bands in the diagnosis of MS

- Oligoclonal bands represent IgG unique to the cerebrospinal fluid without corresponding IgG in the serum [23](#)
- Several techniques have been developed to test for CSF oligoclonal bands. The current gold standard, with a sensitivity over 95%, is isoelectric focusing on agarose gel followed by immunoblotting or immunofixation for IgG with paired CSF and serum
- Many studies looking at the utility of CSF oligoclonal bands in the diagnosis of MS have shown that it is an independent predictor of conversion of CIS to MS when controlling for clinical and imaging variables [7,23-25](#)
- The 2017 McDonald criteria have recommended that for patients with a typical CIS meeting the criteria for DIS, CSF-specific oligoclonal bands can be used for the diagnosis of MS in the absence of CSF findings atypical for MS [7](#)
- The importance of using appropriate and standardised technology is emphasised
- The DIS category 'juxtacortical' expanded to 'cortical/juxtacortical'
  - Pathology studies have shown involvement of the grey matter in MS and different cortical locations have been identified (intracortical, leukocortical and juxtacortical) [26](#)
  - Imaging cortical lesions with conventional clinical MRI protocols is challenging [13](#)
  - Currently, intracortical, leukocortical and juxtacortical lesions cannot be reliably and consistently distinguished on conventional MRI scans using most available MRI scanners in the clinical setting [13](#)
  - Advanced imaging sequences such as double inversion recovery (DIR) and phase-sensitive inversion recovery (PSIR) are currently being investigated for detection of cortical lesions [13](#)
  - However, availability, limited inter-observer agreement and lack of standardised terminology have limited the use of these sequences in clinical practice
  - Hence, new guidelines recommend the use of 'cortical/juxtacortical' to expand the concept of juxtacortical lesion in the DIS criteria, by including all MS cortical lesion types and the involvement of the white matter next to the cortex [13](#)
  - When available, the use of advanced imaging sequences are recommended to visualize cortical lesions
- Identical DIS criteria used for primary-progressive (PPMS) and relapse-onset MS
  - The diagnostic criteria for PPMS have undergone a number of revisions in the last 20 years and have remained distinct from the criteria for RRMS
  - Previously, in the 2010 McDonald criteria [11](#), a diagnosis of PPMS required at least one year of disease progression plus two of the following three criteria
    - Evidence for DIS in the brain based on ? 1 T2 lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)\*
    - Evidence for DIS in the spinal cord based on ?2 T2 lesions in the cord\* or
    - The presence of CSF oligoclonal bands
    - \*Only asymptomatic MRI lesions counted
  - One retrospective study found that if the requirement of ? 2 spinal cord lesions was changed to ?1 (asymptomatic or symptomatic), the sensitivity increased from 77% to 84% [27](#)
  - Hence, the 2017 McDonald criteria recommends the use of identical DIS criteria for PPMS and RRMS [7](#)
- Distinction does not need to be made between symptomatic and asymptomatic MRI lesions for both DIS and DIT [13](#)
  - For DIS criteria in the 2010 McDonald criteria, when the patient's symptoms are referable to the brainstem/cerebellum or spinal cord, then lesions in the symptomatic region are



- excluded [11](#)
- The exclusion of lesions in the symptomatic region was based on a desire to maximize the specificity of MRI criteria by requiring lesions in 2 sites outside the symptomatic region to establish DIS and to simplify previous MRI criteria [28](#)
  - However, the criteria are ambiguous as to whether all lesions in the symptomatic region should be excluded or only the symptomatic lesion
  - Recently, studies have shown that inclusion of symptomatic lesions for DIS increases sensitivity and accuracy without sacrificing specificity [28-30](#)
  - Inclusion of symptomatic lesions in the DIT criteria has been shown to increase the proportion of patients satisfying the MRI diagnostic criteria for MS to 33%, compared to 30% of those diagnosed without including such lesions [29](#)
  - Indeed, deciding what is symptomatic or not is often challenging

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