

Updated criteria for diagnosing Multiple Sclerosis



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Key take home messages

- The diagnostic criteria for MS have been recently updated
- These criteria should only be applied to populations in whom MS is common and patients who present with typical symptoms for which no better explanation can be found
- All patients with suspected MS should have an MRI brain scan; spinal cord imaging is not mandatory
- Unmatched oligoclonal bands in the CSF can be used as a substitute for demonstrating dissemination in time, allowing an earlier diagnosis than was previously possible

Abstract

The fourth update of the McDonald criteria enables an earlier diagnosis of MS in people presenting with typical symptoms. It broadens MRI evidence for dissemination in space to include symptomatic and cortical lesions and allows dissemination in time to be demonstrated by unmatched oligoclonal bands in the CSF as well as by new or enhancing MRI lesions. To avoid misdiagnosis, it should be used with caution in patients with atypical symptoms or in populations in which MS is uncommon.

The history of diagnostic criteria for multiple sclerosis (MS)

Multiple Sclerosis (MS) became widely recognised after Jean-Martin Charcot (1825 – 1893) (Figure 1a) described it in his lectures in the late 18th century. Prior to this patients with MS would typically have been described as having a palsy, paralysis or paraplegia, without much understanding as to the cause.

In May 1960, a symposium on the 'Evaluation of Drug Therapy in Neurologic and Sensory Diseases' held at the University of Wisconsin concluded that criteria for MS were required to provide a common ground of terminology amongst investigators to facilitate therapeutic trials.

A committee of experts chaired by George Schumacher (1912 – 2008) was formed and published the Schumacher criteria in 1965.¹ This enabled a diagnosis of definite MS in

- a typically aged individual (defined as between 10 and 50 years)
- with a compatible history – attacks lasting at least 24 hours, separated by at least a month;

or in the case of progressive MS, a slow or step-wise progression of disability over a period of at least six months

- and objective clinical evidence of lesions in two or more distinct sites in the white matter of the central nervous system
- with no more satisfactory explanation.

The Schumacher criteria were purely clinical, although investigations were encouraged (blood, urine, chest X-ray, CSF analysis) to exclude alternative conditions.

Over the next few years modifications to the Schumacher criteria were published^{2,3} but in 1983 the Schumacher criteria were replaced by criteria developed by a committee chaired by Charles Poser (1923 – 2010).⁴ The Poser criteria incorporated laboratory and clinical tests developed in the previous decade to support the diagnosis with 'paraclinical evidence' of lesions. This included evoked potentials, computed tomography (CT) or NMR scans (as MRI was known in its early days), as well as induced hyperthermia (the hot bath test) and expert urological assessment. The acceptable age of onset was extended to 10 to 59 years of age. The criteria emphasised that symptoms should be consistent with MS and the diagnosis made by a 'competent neurologist'.

The criteria divided patients into two groups – 'Definite' and 'Probable' MS – each with two sub-groups – 'Clinical' and 'Laboratory-supported'; the latter referring to the presence of oligoclonal bands or raised IgG in the CSF. Clinically Definite MS became the requirement for entry into therapeutic trials of the time and required two attacks and objective clinical evidence of two lesions; or two attacks with objective evidence of one lesion and paraclinical evidence of another separate lesion. Certain historical symptoms could be substituted for clinical evidence in some instances, e.g. Lhermitte's phenomenon in the absence of cervical spondylitis; painful optic neuritis in an under 50-year-old, trigeminal neuralgia in an under 40-year-old.

In 2001, Poser's criteria were replaced by McDonald's criteria,⁵ developed by the International Panel on MS Diagnostics, chaired at their first meeting by Ian McDonald (1933 – 2006) (Figure 1b). These criteria placed a much greater emphasis on the use of MRI lesions (areas of T2 hyperintensity at least 3mm in cross-section) to demonstrate dissemination of disease in space and time. These criteria enabled a diagnosis of MS after a single clinical attack which allowed clinical trials to include patients at a much earlier stage than had previously been possible. Progressive MS, which had not been



Figure 1a: Jean-Martin Charcot (1825 – 1893).

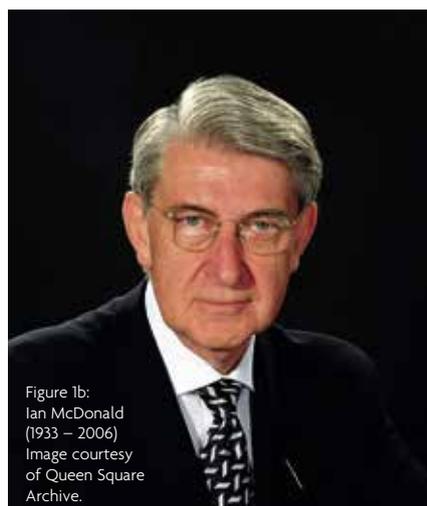


Figure 1b: Ian McDonald (1933 – 2006). Image courtesy of Queen Square Archive.

regions. Changes to the diagnostic criteria were evidence-based and not just based on expert opinion.

The most significant change is the revitalisation of the role of CSF analysis. The finding of two or more oligoclonal bands was found to be more reliable than a raised IgG index and their presence has been shown to have high predictive value for conversion from clinically isolated syndromes to MS. The panel agreed the presence of unmatched oligoclonal bands in the CSF could confirm dissemination in time in place of clinical or MRI evidence. The panel also stressed the importance of CSF in excluding MS mimics.

The MRI criteria for dissemination in space have also been changed. Cortical lesions can now be counted in place of juxtacortical ones when assessing for lesions in one of the four typical sites (the other sites are periventricular, brainstem or spinal cord lesion). However, cortical lesions are not well appreciated on currently available clinical MRI scans conducted outside of research and so this will not have a great impact on most clinicians. The panel did not increase the number of periventricular lesions required, as was recommended in a 2016 MAGNIMS MRI criteria paper,⁹ but suggested this may be advisable in older patients and those at high risk of having white matter lesions, e.g. vascular risk factors, migraine. They did allow for the inclusion of symptomatic lesions when assessing for radiological evidence of dissemination in space – an exception being high signal in the optic nerves in people with optic neuritis.

As with the criteria that have predated it, the McDonald criteria do enable MS to be diagnosed without the need for any supporting investigations, but the panel recommended all patients in whom a diagnosis of MS was being considered should have an MRI brain. An MRI of the cord is not mandatory but advisable when signs localise to the cord, in progressive MS and in populations in whom MS is more unusual.

Whilst the sensitivity and specificity of the McDonald MRI criteria have been shown to be high when applied to patients with typically clinically isolated syndromes suggestive of MS,¹⁰ there have been a number of papers published demonstrating that they over-diagnose MS in a 'real world' setting.¹¹⁻¹³ The McDonald criteria were not developed to diagnose MS in patients with atypical symptoms or to distinguish it from other conditions which can cause high signal in the white matter lesions on MRI, e.g. acute disseminated encephalitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD), vascular disease, migraine and even normal ageing. Caution should be exercised in people outside the typical presenting age for MS (although MS can present in childhood and in individuals over 60 years) and in ethnic groups in whom MS is uncommon. The benefits of expert neuro-radiological input cannot be over-emphasised.

A diagnosis of multiple sclerosis should never be made based on MRI appearances

Table 1. New diagnostic criteria for RR MS ⁸		
Number of clinical attacks*	Number of lesions with objective clinical evidence	Additional evidence required
≥ 2	≥ 2	None
≥ 2	1 plus good historical evidence	None
≥ 2	1	Dissemination in space by a further clinical episode at another site or by MRI
1	≥ 2	Dissemination in time by a further clinical episode, by MRI or the presence of CSF oligoclonal bands
1	1	Dissemination in space by a further clinical episode at another site or by MRI AND Dissemination in time by a further clinical episode, by MRI or the presence of CSF oligoclonal bands

*attacks should be separated by at least 30 days between onset

Table 2. New diagnostic criteria for PP MS ⁸
1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse.
Plus two of the following criteria:
<ul style="list-style-type: none"> One or more T2-hyperintense lesions characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial Two or more T2-hyperintense lesions in the spinal cord Presence of CSF-specific oligoclonal bands

addressed by the Poser criteria, was defined in McDonald's criteria and required the presence of oligoclonal bands or raised IgG index in the CSF supported by typical MRI findings +/- delayed visual evoked potentials (VEPs) and dissemination in time demonstrated either by progression of disability over a year or new MRI lesions.

The McDonald panel have subsequently met approximately every 5-years to refine and

simplify the criteria.^{6,7} The number of lesions required to provide evidence of dissemination in space have been reduced and evidence of dissemination of disease in time may be obtained from a single MRI with both enhancing and non-enhancing lesions. The criteria for progressive MS were changed so that insidious neurological progression became the main requirement and oligoclonal bands or elevated IgG index in the CSF were no longer mandatory if there were typical MRI findings in the brain and spinal cord. The term 'possible MS' was added for people with a typical clinically isolated syndrome who did not meet the criteria.

The 2017 revisions to the McDonald criteria

Following meetings in November 2016 and May 2017 the fourth version of the McDonald criteria was published in *Lancet Neurology* in January 2018.⁸ This panel was expanded to include additional expertise in clinical, imaging and laboratory aspects of MS diagnosis, and to address criticisms that they were only applicable to European and North American populations, included a broader representation from different geographical

alone, although some patients with these so-called Radiologically Isolated Syndromes will develop typical symptoms of MS in time¹⁴ and may require counselling and follow-up.

Application of the 2017 revised McDonald criteria in patients with typical clinically isolated syndromes followed up for five years has been demonstrated to have greater sensitivity but less specificity for a second attack than the 2010 criteria with similar accuracy.¹⁵ This means it will diagnose more patients with less active MS.

In conclusion, the McDonald Criteria are helpful in providing an accurate and earlier diagnosis of MS in patients following a single attack with typical symptoms, however when the presentation is atypical, or in populations in which MS is uncommon, investigation should be extended beyond MRI, with a low threshold for further investigation, particularly examination of the CSF.

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A Lab of One's Own: Science and Suffrage in the First World War

A Lab of One's Own is a fascinating and compelling look not just at the stories of several unsung female pioneers in science, medicine and engineering during World War One, but at the struggles of the Suffragette movement amidst a backdrop of entrenched and pervading gender stereotypes, such as those held by the renowned scientist Charles Darwin.

Fara states that from the turn of the twentieth century "To demonstrate their modernity, suffrage supporters allied themselves with scientific and technological progress." Indeed, Sylvia Pankhurst aligned technology with universal emancipation and although seemingly simple inventions, such as the bicycle, gave some women a little freedom of independent travel, and though the typewriter provided an acceptable way for a single woman to earn a living away from the drudgery of domestic servitude, it was not until World War One that women's traditional roles in society were first challenged.

Drawing on Virginia Woolf's 1929 essay, "A Room of One's Own", in which Woolf discusses how women might redefine themselves outside their traditionally subservient and economically dependent roles, the author explores the immense hurdles women had to overcome to enter the hitherto impenetrable realm of men, not just to gain the right to a university degree, but by rallying against widely held attitudes that 'education can do little to modify her nature' and that studying was bad for a woman's health.

It is common knowledge that women worked in nursing, munitions, or kept the home fire burning while their husbands fought in the trenches, but Fara expands this view by describing their work in laboratories, aeroplane production and chemical research, with Suffragettes temporarily holding a truce to invest their energies into supporting the war effort. During the War, female scientists were able to thrive in many previously inaccessible posts. Women such as Ruth King, who studied picric acid (explosives), Marie Stopes (increasing coal production and making mines safer), Frances Micklethwait (chemical weapons) and Beatrice Mabel Cave-Brown (aeroplane design) are but a few mentioned who had fascinating war careers. New medical fields of radiography and physiotherapy also flourished during the war, thanks to pioneering efforts by women to treat soldiers in the field and at home. The War also allowed women to study on scientific, technology, engineering and medicine university courses in much greater numbers than had previously been possible.

On the whole, men and women resumed their traditional gender roles after Armistice Day. However, as Fara rightly asserts, what changed forever was the traditional understanding of gender roles. With the Representation of the People Act of 1918 finally giving women over the age of 30 (who owned property) the right to vote, they were rewarded, in part, for their huge contribution to the war effort. It is worth noting that it also finally entitled all men over the age of 21 to vote, thus helping to contract the class divide somewhat. And, in large part due to the tireless efforts of Ida Smedley and Martha Whitely, women began to be admitted to professional societies (the Chemical Society) soon after the War, in 1920.

This thought-provoking book should be of interest to the scientist and non-scientist alike as women continue to fight for equality in the workplace and across society today. With regard to the medical profession, Fara states that "women were paid less than men for doing the same work, passed over for promotion and excluded from medical societies". Even today, despite a predominantly female workforce, including at senior levels, nine out of ten NHS Trusts have a gender pay gap.¹ Moreover, a recent survey of 1700 neurologists in the United States found that men outnumber women at all faculty ranks in top-ranked academic Neurology programmes, and that this discrepancy increases with advancing rank.² As the author writes "What happened a century ago is important for understanding the present."

A very slight irritation is that, although the author includes a brief mention of Anna Airy, one of the first women to be commissioned as a war artist, a lithograph by the renowned Christopher R.W. Nevinson has been used as the front cover. Female artists, as well as female scientists, continue to suffer lack of recognition!

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