

Title: Prognostication and contemporary management of clinically isolated syndrome

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## **ABSTRACT**

Clinically isolated syndrome (CIS) patients present with a single attack of inflammatory demyelination of the central nervous system. Recent advances in multiple sclerosis (MS) diagnostic criteria have expanded the number of CIS patients eligible for a diagnosis of MS at the onset of the disease, shrinking the prevalence of CIS. MS treatment options are rapidly expanding, which is driving the need to recognise MS at its earliest stages. In CIS patients, finding typical MS white matter lesions on the patient's MRI scan remains the most influential prognostic investigation for predicting subsequent diagnosis with MS. Additional imaging, cerebrospinal fluid and serum testing, information from the clinical history and genetic testing also contribute. For those subsequently diagnosed with MS, there is a wide spectrum of long-term clinical outcomes. Detailed assessment at the point of presentation with CIS provides fewer clues to calculate a personalised risk of long-term severe disability.

Clinicians should select suitable CIS cases for steroid treatment to speed neurological recovery. Unfortunately, there are still no neuroprotection or remyelination strategies available. The use of MS disease modifying therapy for CIS varies amongst clinicians and national guidelines, suggesting a lack of robust evidence to guide practice. Clinicians should focus on confirming MS speedily and accurately with appropriate investigations. Diagnosis with CIS provides an opportune moment to promote a healthy lifestyle, in particular smoking cessation. Patients also need to understand the link between CIS and MS. This review provides clinicians an update on the contemporary evidence guiding prognostication and management of CIS.

## **INTRODUCTION**

Clinically isolated syndrome (CIS) describes a solitary clinical event, of inflammatory demyelinating aetiology, affecting the central nervous system (CNS) and is frequently the first attack of multiple sclerosis (MS). CIS is a shrinking concept because of changes in the 2017 modified McDonald diagnostic criteria for MS.<sup>1</sup> The availability of MS disease modifying therapy (DMT) and the suggestion that its clinical impact may be greatest if used at the earliest stages of the illness has driven the need to identify those patients who will go on to be diagnosed with MS at an earlier time point in order to initiate DMT.

A CIS patient typically presents subacutely, with a monocular optic neuritis, focal supratentorial syndrome, brainstem or cerebellar syndrome, or partial myelitis. Symptoms of CIS must occur in the absence of fever, infection or encephalopathy and last more than 24 hours, but typically last for several weeks, before partial or complete remission. The past medical history of anyone presenting with CIS needs to be explored in detail, to ensure their presentation is a solitary clinical event and they do not already have MS. Of those who are later diagnosed with MS, up to one quarter of CIS presentations are multifocal e.g. an optic neuritis with relative afferent pupillary defect, but also a Babinski sign.<sup>2</sup> MS is the recurrence of this autoimmune demyelinating process, disseminated in both time and location within the CNS. While the cause of CIS and subsequent MS is not fully elucidated, it appears that pervasive environmental triggers in genetically susceptible individuals leads to the disease. The median age at presentation is approximately 30, and epidemiological studies show the prevalence and in some countries the incidence of MS is increasing. In 2016, the prevalence was estimated to be 165 and 127 per 100,000 in North America and Western Europe respectively.<sup>3</sup> There is an increasing female to male ratio of patients, now estimated to be between 2:1 and 3:1.<sup>2,4</sup>

### **Table 1**

How to diagnose multiple sclerosis. Adapted from the 2017 modified McDonald criteria<sup>1</sup>

Number of clinical attacks	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2	≥2	None
≥2	1 (as well as clear-cut account of a previous attack involving a lesion in a <b>distinct anatomical location</b> )	None, however, caution is needed when considering historical attacks in the absence of residual neurological deficit on examination, to avoid misdiagnosis
≥2	1	Dissemination in space demonstrated by an additional clinical attack at a different CNS site or by MRI showing typical MS lesions in multiple locations
1	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI showing simultaneous contrast enhancing and non-enhancing MS lesions or by an interval MRI with new MRI lesions or by detecting OCB
1	1	Dissemination in space demonstrated by an additional clinical attack at a different CNS site or by MRI showing typical MS lesions in multiple locations AND Dissemination in time demonstrated by an additional clinical attack or by MRI showing simultaneous contrast enhancing and non-enhancing MS lesions or by an interval MRI with new MRI lesions or by detecting OCB

*CNS – central nervous system, MS – multiple sclerosis and OCB – unpaired oligoclonal bands*

The 2017 modified McDonald criteria, summarised in Table 1, allow clinicians to substitute clinical evidence of dissemination in space with MRI evidence of typical lesions in multiple CNS locations. A typical MRI lesion is defined as ovoid or round, hyperintense on T2-weighted MRI and at least 3mm in its long axis. Lesion location is also important, with periventricular lesions, regularly involving the corpus callosum, being more specific. A second clinical event providing evidence of dissemination in time can now be substituted with simultaneous contrast enhancing and non-enhancing MRI lesions, development of new MRI lesions on serial scanning or demonstration of unpaired oligoclonal bands (OCB) in the cerebrospinal fluid (CSF) that provide supporting evidence of the immune and inflammatory nature of the disease.<sup>1</sup>

Approximately 10-15% of patients with MS have primary progressive MS, with slowly progressive neurological disability from onset, and paraclinical evidence of MS pathology.<sup>5</sup> Radiologically isolated syndrome is an incidental imaging finding consistent with MS lesions, but no history of CIS or MS relapses. It increases the risk of subsequently developing MS.<sup>6</sup> However, detailed discussion of these is beyond the scope of this review. In addition, numerous articles describe the differential diagnosis of CIS and the many mimics that clinicians should be mindful of to avoid misdiagnosis.<sup>7</sup> To this end, clinicians should only apply the 2017 modified McDonald criteria to cases of typical CIS, described above. The criteria were created to maximise their sensitivity, at the cost of reduced specificity. Thus they are only suited to application in cases which already have a high likelihood of being MS. When

the patient is from a low risk group or there are atypical clinical features the clinician should consider additional investigations for relevant MS mimics, using a higher threshold for the number of typical MRI lesions required and lumbar puncture.<sup>1</sup>

## **PROGNOSTICATION**

Prognostication in CIS patients is divided into prediction of subsequent diagnosis of MS and the longer-term prediction of severe disability in those with MS. These risks are linked to prevalence of MS in the population from which the patient is drawn and the definition of MS that is used. Most CIS prognostication studies have been conducted in young, predominantly Caucasian adults from countries with the highest global burden of MS and will not reflect the risks when applied outside of these populations. These studies applied older disease definitions, which diminishes their applicability to modern CIS cohorts. There is emerging evidence that modern MS cohorts may experience a more benign course, independent of MS DMT use.

### **Prognostic factors for developing multiple sclerosis – routine clinical use**

Approximately one third of CIS patients do not have a chronic disease and are never diagnosed with MS, even with follow up lasting up to 30 years.<sup>8,9</sup> The single most important paraclinical test in CIS patients is MRI. Detection of MS lesions on baseline brain MRI increases the long-term risk of having a second clinical event to 80%, while detecting no MRI lesions reduces the risk to 20%.<sup>10</sup> The risk of early MS (being diagnosed within five years) is higher with increasing MRI lesion load, greater than three periventricular lesions or infratentorial lesions.<sup>8,11,12</sup> Spinal lesions on MRI can assist in fulfilling the McDonald criteria of radiological dissemination in space and increase the risk of early MS.<sup>13</sup> The presence of simultaneous gadolinium enhancing and non-gadolinium enhancing lesions are sufficient to substitute for the requirement of a second clinical event as they are strongly associated with future radiological and clinical disease activity.<sup>1</sup> However, it is estimated that 10-15% of patients with CIS will only develop new radiological lesions, and not have a second clinical event consistent with a relapse, with follow up lasting up to 20 years.<sup>12</sup>

Lumbar puncture demonstrates unpaired, CSF specific, OCB in two-thirds of CIS patients. In these cases, two-thirds are subsequently diagnosed with MS, while only one-fifth of OCB negative cases are.<sup>14</sup> However, the risk of MS is substantially modified by the patient's MRI findings, and when this information is considered together in a multivariate model, OCB predictive power is modest. OCB positivity has a hazard ratio below two, while MRI lesions have a hazard ratio of 5-10 dependant on increasing lesion number.<sup>12</sup> OCB testing has its largest prognostic impact in those CIS patients who do not have MRI lesions at baseline. Some centres assess the IgG index to produce a quantitative CSF measure, when abnormal it has a similar hazard ratio for MS as OCB, but given its lower sensitivity, offers little additional information from OCB assessment using isoelectric focussing. Unpaired OCB are now an alternative way to confirm MS in patients who have already demonstrated dissemination in space.<sup>1</sup> The inclusion of this criterion in the latest iteration of the McDonald criteria has led to a substantial increase in patients with CIS being eligible for a diagnosis of MS at presentation. In one study, only half of this newly defined group had a clinical relapse within five years of follow up.<sup>15</sup> It is unclear whether this was due to short follow up, MS DMT use or misdiagnosis as MS. If significant numbers of CIS patients who never have a second clinical event are labelled as MS, then modern MS cohorts will have a milder disease course.

Clinical factors have less impact on the risk of MS, with natural history studies frequently resulting in conflicting conclusions. However, there is an increased risk with younger age, while atypical features of the CIS presentation make MS less likely.<sup>11</sup> A meta-analysis of the effect of gender showed a 20% increase in the relative risk for women compared to men, but this effect did not reach statistical significance.<sup>4</sup>

### **Prognostic factors for developing multiple sclerosis – emerging evidence**

Additional information can be gained when advanced sequences are included in the baseline CIS MRI scan. Alternative CSF markers of immune activation within the CNS have also been investigated for their prognostic value. Most recently, serum markers of neural degeneration have attracted intense interest given the relative ease of acquiring samples, even if the assay technologies are not yet standardised or widely available. Clinical information may offer prognostic clues if features have been objectively associated with disease pathogenesis. Lastly, genome-wide association studies have demonstrated the impact of immune genes on the risk of MS.

The central vein sign demonstrates the pathologically characteristic perivenular MS lesion distribution. Cross sectional and small longitudinal studies demonstrate its role as a diagnostic biomarker when greater than 40% of white matter lesions have a visualised central vein, though it is not pathognomonic.<sup>16</sup> Its prognostic role is only inferred, and large prospective longitudinal studies to assess this are now underway e.g. DECISive NCT04024969. Several MRI sequences can be used to visualise the central vein sign, with T2\* the simplest to implement clinically. Numerous MRI sequences are available to demonstrate additional elements of MS pathology in vivo. Structural MRI (T1 weighted sequences) can demonstrate grey matter atrophy, which is predictive of early diagnosis with MS.<sup>17</sup> Magnetisation transfer ratio and inversion recovery MRI sequences improve quantification of myelination status and the detection of cortical lesions respectively.<sup>18</sup> This has led to the inclusion of cortical lesions in the 2017 modified McDonald criteria as a site to demonstrate radiological dissemination in space. Magnetisation transfer sequences have yet to be implemented in routine clinical practice because acquisition and interpretation are more challenging. Magnetic resonance spectroscopy and functional MRI currently have no clinical role in managing CIS patients. The changes observed with these MR modalities in CIS or MS are subtle. There are disagreements about the temporal evolution of abnormalities, and there is a lack of reproduction in larger studies.<sup>19</sup> Optical coherence tomography (OCT) is sensitive enough to monitor the effect of optic neuritis and be considered a surrogate endpoint for optic neuritis treatment trials.<sup>20</sup> It can be used, like visual evoked potentials, as supportive evidence, when a CIS patient reports an historic episode consistent with optic neuritis, but they do not have objective signs on clinical examination.<sup>1</sup> OCT may be similar to measuring atrophy with structural MRI. A thinner retinal nerve fibre layer, when there is no history of optic neuritis, has been associated with a higher risk of conversion to MS.<sup>21</sup> However, pathological findings are not specific to MS.

The CNS should be relatively immune privileged. Hence, when performing a univariate analysis in carefully selected high-risk CIS cases, markers of both the adaptive and innate immune response in the CSF often appear to demonstrate prognostic significance. The problem with these markers, including unpaired OCB, is that they are not specific to MS. Clinicians must be mindful that these results could be associated with other long-lived neuroinflammatory or infective responses. For example, unpaired OCB are detected in half of patients with neurosarcoidosis and one fifth of patients who have had a stroke. While OCB are imperfect, they have the highest accuracy of the CSF markers so far tested. These include IgG ratio, IgM production, measles, rubella and zoster antibodies, chemokine ligand 13, kappa and lambda light chain, complement levels, chitotriosidase and chitinase 3-like 1.<sup>22-31</sup> CSF cell count is routinely available, making CSF pleocytosis an attractive potential biomarker; however, it is not consistently associated with an increased risk of MS.<sup>11</sup> A newer approach is to use proteomics or neurometabolomics in the hope that the CSF MS signature will be more specific, and recognisable at the point of presentation with CIS. The very early work to date with these techniques is promising, but the time and cost of sample processing and analysis will have to be significantly reduced prior to its consideration for clinical implementation.<sup>32</sup>

MS is a neurodegenerative condition, in addition to the principal inflammatory component. Markers of neural degeneration that have been assessed in the CSF include neurofilament heavy and light chain, tau protein and glial fibrillary acidic protein.<sup>33,34</sup> Of these, neurofilament light chain has shown the most promise as a prognostic biomarker. With an ultra-sensitive assay, serum levels can be monitored conveniently. Ongoing research aims to characterise appropriate age adjusted normal cut-off values and the range of comorbidities that influence it. After this, appropriately powered research will still need to demonstrate that it offers independent prognostic information from those factors considered above.

The presence of subtle cognitive impairment at presentation may suggest chronicity of the disease process and is associated with a small increase in the risk of MS.<sup>35</sup> There is limited evidence that non-Caucasian ethnicity is also associated with an increased risk.<sup>36</sup> Individual studies have come to conflicting conclusions about whether CIS site, including whether the clinical syndrome is monofocal or polyfocal, influences MS risk.<sup>10,36</sup> Higher Epstein Barr virus antibody titres may have a modest impact.<sup>37</sup> Tobacco smoking and low Vitamin D serum levels are modifiable risk factors that have been associated with an increased risk of MS.<sup>38,39</sup> Obesity during adolescence, particularly in women, is associated with a higher incidence of MS, rather than directly being linked to MS risk in CIS patients.<sup>40</sup>

Using genome wide association studies more than 200 genetic variants have been associated with MS disease susceptibility so far, ~90% of which are noncoding.<sup>41</sup> Genes controlling all major immune cells are implicated and microglia are, genetically, the most important CNS cell type. Many genetic variants associated with MS risk are also found in other autoimmune diseases. HLA-DRB1\*15:01 is the strongest single genetic risk factor for MS in those of European ancestry. Carriers have an odds ratio of three for developing MS and it has a small prognostic role when tested at presentation with CIS.<sup>42</sup> It is found in over 10% of the population with European ancestry. However, despite this testing is not routinely offered at present.

Although these imaging, CSF, serum, clinical and genetic factors have all been associated with increased risk of MS, the most robust predictor remains conventional MRI abnormalities. Thus, when considering all information about a patient, these additional factors only have a modest role in prognostication. Instead, their role lies in helping us to understand the heterogeneous MS disease process. They can contribute to the effort of developing DMT and possibly one day in selecting MS sub-populations for those treatments, so called personalised medicine. In addition, these factors have rarely been studied in aggregate, so there is likely co-linearity, and research has not always been performed in representative populations. Future prognostic studies need to adopt robust methodologies and recruit representative participants across multiple centres.

#### **Summary:**

- **MRI is currently the most important prognostic test for CIS patients**
- **OCB can now be substituted for clinical or radiological evidence of dissemination in time**
- **Atypical features of the CIS presentation make MS less likely, but other clinical factors have little prognostic impact**

#### **Prognostic factors for worse disability in those with multiple sclerosis – routine clinical use**

Classic natural history studies, in predominantly untreated patients, suggested that for those who do have MS after twenty years 30-40% of patients will still be fully ambulatory, 10-20% will have died due to MS and the remainder will have restricted ambulation, require an aid to walk, use a wheelchair or be immobile and almost all of these will have secondary progressive MS (SPMS).<sup>9,10</sup> However, these estimates are now outdated with MS becoming a milder disease.<sup>43</sup> This may be due to the shifting diagnostic definition, improvements in population life expectancy or the widespread

availability of over a dozen DMTs. Only the injectable therapies have long-term follow up data on disability endpoints, but the favourable comparison with historic controls may be biased for the other reasons listed.

MS is a challenging neurological condition on which to prognosticate, given it is often decades between onset with CIS and severe disability. Most research studies compare baseline factors to the number of early clinical relapses, new radiological lesions, or disability at five years from onset. This is despite only one fifth of patients rapidly acquiring permanent disability during the relapsing remitting phase of the illness.<sup>44</sup> For most patients the accumulation of disability is detected when transitioning from the initial relapsing remitting phase to SPMS. While fewer studies are available to inform us about this, baseline factors are only modest predictors of long-term outcome for individual patients. The same risk factors appear to be associated with death due to MS, significant disability and chances of developing SPMS.

While MRI abnormalities at presentation with CIS are the single most important determinant of the risk of MS, their association with long-term disability is limited. However, lesions on the baseline CIS scan affecting the brainstem and spinal cord are associated with worse prognosis.<sup>13</sup> The presence of gadolinium enhancing lesions and cortical lesions at baseline have some evidence to support an association with worse prognosis.<sup>45</sup> While not available at the point of presentation, increasing T2 lesion volume over time, particularly in the first five years, is the MRI measure best correlated with long-term disability that is routinely available clinically.<sup>10</sup>

Presence of OCB at lumbar puncture is associated with a slightly worse disease course compared to OCB negative cases in many studies.<sup>46</sup>

Male sex is sometimes associated with a slightly worse prognosis in MS, but several papers have reported no significant difference. Incomplete recovery from the CIS attack and sphincter or motor involvement at onset are more often found to be associated with poorer outcomes.<sup>9, 45</sup> The role of age at CIS is debated. Time from diagnosis to SPMS is often found to be shorter in older onset CIS patients, but is less useful than comparing age on reaching SPMS, which shows younger onset CIS patients have a worse prognosis.<sup>47</sup> The most important clinical factor is the number of early relapses, again something not possible to determine at first presentation with CIS.<sup>45</sup>

Currently none of the information available at presentation has sufficient prognostic value to provide individual patients a personalised estimate of future disability at presentation with CIS. After five years of clinical and radiological monitoring patients can be split into three groups. A low-risk group with no disease activity or adverse features and likely minimal disability for decades. This low-risk group remain vulnerable to transition to SPMS the longer they are followed, and MS may have a significant impact on their cognition or employment while they are still in the relapsing remitting phase.<sup>48</sup> The majority will be in an intermediate risk group. Up to one fifth will be in a rapidly progressive high-risk group, with significant radiological and clinical MS activity, in whom severe disability or death due to MS is a common outcome. Several prognostic tools exist to apply this information in a clinical setting. However, before using these tools to advise patients about treatment decisions, it is worth considering that their development and testing utilised relatively small datasets, consequently they are less robust than other risk scoring tools in routine clinical practice.<sup>49</sup> Instead, some clinicians rely solely on the information from the CIS baseline MRI to guide treatment decisions.

### **Prognostic factors for worse disability in those with multiple sclerosis – emerging evidence**

Given the widespread availability of DMT there will not be further natural history studies in untreated MS. Instead, contemporary observational cohorts should continue to pool data to identify

new prognostic factors that predict death due to MS, significant disability and chances of developing SPMS despite DMT use. This is important for two reasons. First, prognostic studies for MS show improving outcomes over time, and our patients need timely access to this updated information. Second, misidentification of the relative importance of prognostic factors can distort clinical decision making towards targets that do not influence the most important outcome of interest, long-term disability.

When considering information gathered in the first years of MS from MRI, brain atrophy will likely surpass the prognostic role of new focal lesions or measuring increasing T2 lesion volume.<sup>50</sup> However, measurement is currently only available in a small number of MS centres and it appears that global atrophy might be less important than grey matter atrophy. It is also necessary to distinguish MS related brain atrophy from normal ageing.<sup>51</sup> More advanced MRI techniques such as magnetisation transfer ratio and magnetic resonance spectroscopy have not been associated with worse disability in the short-term.<sup>17</sup>

In addition to the presence of OCB in the CSF, an increasing number of visualised bands, higher IgG or IgM index and higher CSF cell count may reflect disease that is more active and be relevant to prognosis.<sup>46, 52</sup> High levels of kappa light chains and chemokine ligand 13 have each been associated with worse prognosis in small studies. However, one of the strongest CSF predictors of worse medium-term disability seems to be high CSF neurofilament light chain.<sup>53</sup> While it is hoped that baseline, or serial serum neurofilament measurement will provide independent long-term prognostic information, this has not been consistently demonstrated.<sup>54</sup>

Optic neuritis or sensory-only CIS, complete recovery from CIS and a longer period to the second clinical event have all been associated with less long-term disability, but not consistently across studies. Late relapses, beyond five years of diagnosis, are not reported as associated with worse disability. However, one study found relapses between 10-15 years after MS diagnosis were still responsible for a third of disability accumulation in that period.<sup>55</sup> Smoking status and low Vitamin D levels are predictive of short-term relapsing MS activity; however, their association with worse long-term disability has not been demonstrated.<sup>56</sup> Non-Caucasian ethnicity may predispose to worse disability, if confirmed the contributors to this association require further investigation. For women, nulliparity is associated with worse disability, however this phenomenon may be due to reverse causation.

Hopefully, the widespread use of electronic healthcare records will drive further improvements in our understanding of prognostic factors linked to long-term, clinically meaningful endpoints. One difficulty with drawing inferences from observational data is how to account for the indication for why a given DMT was chosen, so datasets should consider collecting this information. Most of the long-term prognostication studies available included patients for whom higher-efficacy DMT was not available in the crucial early years of their disease or followed past treatment algorithms, making them unsuitable for prognostication of modern cohorts.

#### **Summary:**

- **Personalised prediction of long-term disability at presentation with CIS is challenging but is improved by close clinical and radiological monitoring**
- **Observational data shows outcomes are improving, even prior to widespread DMT use**
- **MRI remains the most important paraclinical test for prognostication**

## **CLINICAL MANAGEMENT**



The management of an acute inflammatory CNS insult in CIS is no different from the management of an MS relapse. Recovery can be accelerated with high dose steroids. Traditionally this has been given in the form of a short three to five-day course of 1000 milligrams intravenous methylprednisolone following the Optic Neuritis Treatment Trial. However, several recent studies have suggested non-inferiority between oral and intravenous methylprednisolone, the main benefit of which is ease of outpatient administration.<sup>57</sup> Treatment shortens the duration of neurological symptoms, but it does not improve the level of neurological recovery and is therefore not universally required. Patients should be counselled about the myriad side effects of steroids, many of which are related to the cumulative lifetime dose. Like all disabling inflammatory CNS relapses, plasma exchange can be used when steroids fail to show improvement. This treatment has a clear role in antibody-mediated diseases such as neuromyelitis optica, but there is less published evidence of benefit in CIS.<sup>58</sup> Many neurologists, and the authors of this review, instead typically use a second course of steroids and only if there is minimal improvement consider five cycles of plasma exchange, although no evidence exists to support the superiority of this approach. If there is no response to the first course of steroid, the possibility of misdiagnosis should be reconsidered. Intravenous immunoglobulin should not be used for the treatment of CIS.<sup>59</sup>

On many occasions, the clinical presentation and MRI findings are typical of MS and meet dissemination in space criteria, but dissemination in time has not been demonstrated. Clinicians frequently feel confident that this patient group will be given a diagnosis of MS, either by detecting OCB or new MRI or clinical activity over the next few months or years. A clear indication of the very likely outcome and final diagnosis needs to be given to the patient in these circumstances. This is while recognising that misdiagnosis persists despite, or partially due, to easier access to MRI. Screening for aquaporin-4 and myelin oligodendrocyte glycoprotein antibodies should occur if neuromyelitis optica spectrum disorder or myelin oligodendrocyte glycoprotein antibody associated disease are considered differential diagnoses.<sup>60</sup> Clinicians may feel that patients subconsciously exert pressure looking for definite answers, but it is inadvisable to immediately issue an unequivocal diagnosis of MS if patients do not explicitly meet diagnostic criteria. Particularly in the current treatment era in which some DMTs have rare, but more serious risks than in the past.<sup>7</sup> Misdiagnosis may also have negative psychological and material impacts such as obtaining insurance or a driving licence.

After the acute phase of CIS management, the next decision is whether to commence MS DMT. When given at presentation, injectable DMT delays clinical diagnosis with MS. However, the long-term benefit of this approach over waiting to use DMT until MS is diagnosed is uncertain.<sup>61</sup> The practice of treating CIS varies in different countries and amongst neurologists. It has consistently produced debates in MS meetings. In the latest iteration of the McDonald diagnostic criteria, the inclusion of OCB to substitute for evidence of dissemination in time facilitates faster diagnosis and has reduced the prevalence of CIS patients. Older trials showing DMT delays conversion from CIS to MS include a substantial proportion of patients who would now instead be diagnosed with MS at presentation. Therefore, those diagnosed as CIS now have greater uncertainty as to their final diagnosis, making early treatment with MS DMT more difficult to justify. If a lumbar puncture, or possibly central vein imaging, is to be arranged, most clinicians would withhold starting DMT prior to the results being known. If unpaired OCB are not present or the lumbar puncture procedure is not successful, the clinician must balance the risks of probable lifelong DMT treatment with the alternative of initiating treatment after a few months delay to allow diagnostic confirmation. Repeat MRI to look for dissemination in time before treatment is initiated is usually a safer option than starting treatment blindly. Unfortunately, despite increasing numbers of exploratory trials, no neuroprotection or remyelination therapies suitable for use in CIS have yet been developed.

When a CIS patient does develop MS, the optimum management with MS DMT is also a contentious area. Two large Phase 4 studies; DELIVER-MS NCT03535298 and TREAT-MS NCT03500328 are currently underway to help address this uncertainty.

The diagnosis of CIS offers an opportunity to discuss healthy lifestyle choices. Despite the association between MS risk and smoking status and low Vitamin D levels, randomised controlled trials have failed to show a clear benefit from intervention.<sup>56</sup> These were predominantly small studies, conducted in MS rather than CIS. Therefore, clinical practice should be to offer smoking cessation services due to the benefit to the patients' overall health, while the specific benefit for this and supplementing Vitamin D in CIS is still being investigated. Given the impact of medical co-morbidities on long-term outcomes weight management (avoiding both extremes), improving diet, exercise and sleep are steps that patients can take to improve their health, if they understand no intervention has been studied in a robust fashion to establish its impact on MS course. This is more likely to be achieved by setting specific goals for behaviour change.

**Summary:**

- **Use methylprednisolone for significantly disabling CIS symptoms**
- **Although early treatment in MS appears advantageous, initiation of DMT for CIS is still controversial**
- **Promote healthy lifestyle choices, most importantly smoking cessation**

## **WHAT PATIENTS SHOULD BE TOLD**

Understandably, a barrage of questions from the patient often immediately follows the diagnosis of CIS. Is CIS the same as MS, will I become disabled, could it be another disease and what treatment will I receive now? It is important to adjust the tone of the initial consultation depending on the certainty of diagnosis. From this dialogue, patients will have the context to interpret their test results in subsequent consultations. The first step in clinical management of CIS must be to make an accurate diagnosis, excluding common mimics of the condition, and to communicate effectively with patients. Many patients do not fully understand the link between CIS and MS.<sup>62</sup> The fluctuation of symptoms and pseudo-relapses needs to be addressed as they frequently generate a lot of anxiety. This is in addition to ensuring patients recognise clinical relapses and report them promptly to the MS team.

Online resources about CIS and MS should be offered for the patients that would like more information, in addition to their consultations with neurologists and MS specialist nurses. Not all patients will want this extra reading but signposting them to reliable resources (frequently national MS societies) reduces the risks from unreliable health websites and social media. The psychological impact of receiving a diagnosis of CIS, which on many occasions is heard by the patient as akin to a diagnosis of MS, should not be underestimated. Patients often remember the words used and support given at the first consultation for the rest of their life. The MS team can provide initial support, but some individuals will need specialist psychological input to help them adjust to the diagnosis.<sup>63</sup>

**Summary:**

- **Explain the link between CIS and MS to patients with CIS**
- **Warn patients they may experience pseudo-relapses or symptom fluctuations as well as relapses**
- **Signpost towards reliable web resources, such as those of national MS charities / organisations**

## **CONCLUSIONS**

Our ability to offer an individualised prognosis for CIS is reliable when we consider the risk of subsequent diagnosis of MS, but poor when we consider disability at twenty years after diagnosis. MRI remains the key prognostic test for these patients, while the clinical role of supplementary CSF and blood tests continues to develop. Acutely the treatment for CIS remains the same as for MS relapses. The increasing range of DMT options and the recognition that their benefit with respect to long-term outcomes appears greatest when given early in the MS disease course is driving the need for earlier recognition of MS. However, we must accept that broadening the definition of MS will create more patients with better outcomes regardless of DMT use. Our patients require information about CIS and MS at first presentation, and most will want to discuss their personalised prognosis before making treatment decisions. This gap between our patients' expectations and our current knowledge should be the focus of ongoing prognostication studies and randomised controlled trials of different DMT regimes.

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