Clinically isolated syndromes

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Clinically isolated syndrome (CIS) is a term that describes a first clinical episode with features suggestive of multiple sclerosis (MS). It usually occurs in young adults and affects optic nerves, the brainstem, or the spinal cord. Although patients usually recover from their presenting episode, CIS is often the first manifestation of MS. The most notable risk factors for MS are clinically silent MRI lesions and CSF oligoclonal bands; weak or uncertain risk factors include vitamin D deficiency, Epstein-Barr virus infection, smoking, HLA genes, and miscellaneous immunological abnormalities. Diagnostic investigations including MRI aim to exclude alternative causes and to define the risk for MS. MRI findings incorporated into diagnostic criteria in the past decade enable MS to be diagnosed at or soon after CIS presentation. The course of MS after CIS is variable: after 15–20 years, a third of patients have a benign course with minimal or no disability and a half will have developed secondary progressive MS with increasing disability. Prediction of the long-term course at disease onset is unreliable. Disease-modifying treatments delay the development from CIS to MS. Their use in CIS is limited by uncertain long-term clinical prognosis and treatment benefits and adverse effects, although they have the potential to prevent or delay future tissue damage, including demyelination and axonal loss. Targets for future therapeutic progress are to achieve safe and effective long-term immunomodulation with neuroprotection and repair.

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Introduction

About 85% of people with multiple sclerosis (MS) have onset of MS with a relapse.[1,2] This relapse consists of an episode of neurological disturbance known as a clinically isolated syndrome (CIS). With improvement in diagnosis and the advent of disease-modifying treatment for MS, there has been much interest and research in patients with CIS. Studies have aimed to better understand disease cause and pathogenesis, to improve the accuracy of MS diagnostic criteria and differential diagnosis, and to assess disease-modifying treatments, both for the acute CIS and for modification of the subsequent course in individuals thought to be at high risk of developing MS and disability.

Since our previous reviews of CIS in 2005,[3,4] many studies have been done. This updated Review will consider the definition of CIS and its relation to MS (including diagnostic criteria), risk factors for MS and long-term disability, non-conventional MRI abnormalities, radiologically isolated syndromes, differential diagnosis, and treatment. We conclude with outstanding questions that warrant further research.

CIS and its relation to MS

CIS is a term widely used in contemporary neurological practice to describe a first clinical episode in which a patient has symptoms and signs suggestive of an inflammatory demyelinating disorder of the CNS.[5] The term CIS is typically applied in a young adult (aged 20–45 years) with an episode of acute or sub-acute onset, which reaches a peak quite rapidly (within 2–3 weeks). To be termed CIS, the episode should last for at least 24 h and occur in the absence of fever or infection, with no clinical features of encephalopathy.[5,6]

A CIS is, by definition, always isolated in time (ie, monophasic). Clinically, it is usually also isolated in space (ie, monofocal) with signs indicating a lesion in the optic nerve (a common presentation in many reported CIS studies), spinal cord, brainstem or cerebellum, or (rarely) a cerebral hemisphere. However, some patients with a CIS have clinical evidence for dissemination in space (ie, multifocal); clinically multifocal CIS presentations (eg, optic neuritis with an extensor plantar response [symptoms indicate a single lesion but signs identify dissemination], or simultaneous optic neuritis and internuclear ophthalmoplegia [symptoms and signs indicate dissemination]) are less common than monofocal presentations. An undetermined topographical presentation is seen in other patients with CIS. MS can present with a first episode that is not suggestive of an acute demyelinating, inflammatory event in the CNS, as defined above, and include symptoms such as cognitive changes, seizures, and encephalopathy. Paroxysmal symptoms occurring in MS for longer than 24 h can also provide evidence of a demyelinating event[7] and can be the presenting episode. Panel 1 summarises clinical aspects that are typical for demyelination as seen in MS and atypical features that should trigger a consideration of other diagnoses.

The sex ratio of both CIS and MS is about 2·5 (women and girls) to 1 (men and boys).[8] The usual age group of CIS presentation is that of MS: 70% of patients present between 20 and 40 years (mean 30 years), but patients can present at older and younger ages.[8] Childhood onset of MS is almost invariably with a CIS: the primary progressive onset, seen in 15% of adult patients, is rare in children. Clinical features of CIS in children are similar to those seen in adults, although a multifocal presentation is not uncommon. If a first clinical event in children includes encephalopathic features, it is not classified as CIS and the differential diagnosis includes acute disseminated encephalomyelitis,[6] although encephalopathy can be a feature of the first episode of MS.

The term CIS suggests the possibility of MS, a CNS disease disseminated in time and space. The best

Panel 1: Clinically isolated syndrome features that are typical and atypical for multiple sclerosis

Optic nerve

Typical features

- Optic neuritis in one eye
- Mild pain on eye movement
- Reduced visual acuity and reduced colour vision
- Normal disc or mild disc swelling
- Improvement begins within 3 weeks from onset
- Afferent pupil defect

Atypical features

- Optic neuritis in both eyes at the same time
- Painless or very severe pain
- No perception of light
- Severe haemorrhages and exudates
- Extended loss of vision
- Vitritis and neuroretinitis
- Photophobia

Brainstem or cerebellum

Typical features

- Bilateral internuclear ophthalmoplegia
- Ataxia and gaze-evoked nystagmus
- Sixth nerve palsy (in patients aged 20–40 years)
- Paroxysmal phenomena (occurring for at least 24 h)
- Multifocal signs (eg, facial sensory loss and vertigo)

Atypical features

- Complete external ophthalmoplegia
- Vascular territory signs
- Isolated trigeminal neuralgia
- Progressive trigeminal sensory neuropathy
- Movement disorders
- Fluctuating ocular or bulbar weakness, or both

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(Continued from previous column)

Spinal cord

Typical features

- Incomplete transverse myelitis
- Lhermitte's syndrome
- Sphincter symptoms
- Asymmetric limb weakness
- Deafferented hand
- Progression to nadir between 4 h and 21 days[12]

Atypical features

- Complete transverse myelitis
- Complete Brown-Séquard syndrome
- Cauda equina syndrome
- Anterior spinal artery territory lesion
- Localised or radicular spinal pain
- Progressive and symmetrical spastic paraparesis or progressive sensory ataxia (from involvement of posterior columns)
- Sharp level to all sensory modalities
- Areflexia

Cerebral hemispheres

Typical features

- Hemiparesis
- Hemisensory disturbance

Atypical features

- Encephalopathy
- Epilepsy
- Cortical blindness

Absence of recovery is an atypical feature for all clinically isolated syndromes. Adapted from Miller and colleagues.[5]

studied CIS in relation to MS is optic neuritis, in which follow-up studies have reported conversion to clinically definite MS in between 10% and 85% of patients.[8–10] In patients with spinal cord CIS, conversion to MS has been reported to vary between 41% and 61%.[10–12] The proportion of patients with brainstem syndromes who develop MS varies between 53% and 60%.[10,11] These different conversion rates reported by previous studies might be because of different population prevalence of MS—eg, in regions where MS has a high prevalence (northern Europe and North America) the risk for optic neuritis converting to MS is generally high.[13] In addition to the geographical variations in the course of the disease, the different lengths of follow-ups and the proportion of patients who do not develop MS, but might have been lost to follow-up, could also contribute to the variation in recorded conversion rates. Overall, the risk of developing MS seems to be much the same across all types of CIS.[11]

Risk factors for MS

Many risk factors for the development of CIS to MS have been investigated: MRI, CSF, clinical, genetic, environmental, and immunological. Of these, only MRI and CSF findings are routinely used in clinical practice to inform patients with CIS about the risk of conversion to MS.

MRI

50–70% of adults with CIS have multiple asymptomatic white matter brain lesions, suggestive of demyelination, on T2-weighted MRI. Early follow-up studies in the 1990s showed that the presence of lesions was associated with a higher risk of future clinical events indicating dissemination in space and time leading to the diagnosis of clinically definite MS. The presence of MRI lesions in patients with CIS was needed for inclusion in subsequent trials of disease-modifying treatments that aimed to delay conversion to clinically definite MS.

Three long-term studies with follow-ups of 7 years, 15 years, and 20 years have reported rates of conversion to clinically definite MS in 65%, 72%, and 80% of patients with an abnormal scan and in 8%, 25%, and 20% with a

Panel 2: 2010 McDonald MRI criteria[7] for multiple sclerosis (dissemination in space and time) in patients with a clinically isolated syndrome

Dissemination in space

- At least one lesion* visible on T2-weighted scan in at least two of the following four locations: juxtacortical, periventricular, infratentorial, and spinal cord

Dissemination in time

- A new T2 lesion or gadolinium-enhancing lesion visible on a follow-up scan when this is compared with a previous scan (which is thought to be the baseline scan) obtained at any time after the onset of clinically isolated syndrome
- A scan showing both gadolinium-enhancing and non-enhancing lesions that do not cause clinical signs (ie, asymptomatic lesions)

*If the clinically isolated syndrome affects a patient's brainstem or spinal cord, all lesions within the symptomatic regions are excluded from the criteria.

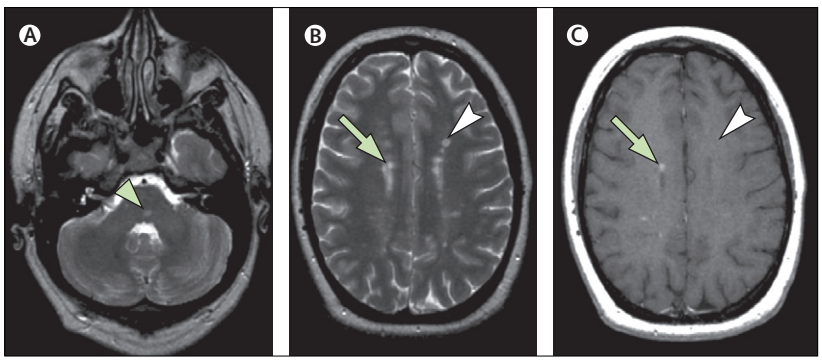

Figure 1: **MRI scan of a patient with clinically isolated syndrome**
The patient presented with a clinically isolated syndrome 5 weeks before the scan. T2-weighted scan, infratentorial lesion (arrowhead; A); T2-weighted scan showing multiple periventricular lesions (B) and corresponding gadolinium-enhanced T1-weighted image showing one of the periventricular lesions enhancing (green arrow) and one non-enhancing (white arrowhead; C).

normal baseline scan, respectively.[9,10,14] It is, therefore, safe to conclude that the long-term risk for clinically definite MS is 60–80% when lesions are present and about 20% when scanning is normal apart from the symptomatic lesion. Although studies of conversion of CIS to MS have included populations in which most patients had optic neuritis, evidence exists that abnormal brain MRI is also a predictor for development of MS in the other types of CIS (acute myelitis[15] and brainstem syndromes[10,11]), except for patients with multifocal presentations, in whom MRI findings did not seem to stratify the risk for clinically definite disease.[16]

When examining the features of the lesions that are associated with the risk of conversion, two factors are important: the number of lesions (0, 1–9, 10, or more) and the number of Barkhof criteria (0, 1–2, 3–4),[3,17] which take into account both location and number of lesions. Both these factors identify patients with low, medium, and high risk of presenting a second attack.[14] Patients who have at least one lesion in the infratentorial regions at onset of CIS have increased risk of conversion, the risk being slightly higher in those with a lesion in the brainstem than it is in those with a lesion in the cerebellum.[11]

The importance of MRI in the prediction of conversion to MS is shown by the inclusion of MRI findings in the diagnostic criteria for MS. The MS diagnostic criteria take into consideration clinical symptoms and (conventional) MRI findings to provide evidence for dissemination in space and time. These criteria have been revised several times. With each revision, the requirements from imaging have been simplified. The revised McDonald criteria, published in 2005,[17] increased the role of spinal cord lesions in fulfilling dissemination in space and a new T2 lesion any time more than 30 days from CIS onset confirmed dissemination in time. These criteria have been difficult to implement in CIS because of complex criteria for dissemination in space and the need for a second scan after a specific interval. Therefore, simplified criteria have since been developed that are specific and sensitive for clinically definite MS when applied in typical cohorts of adults with CIS.[18–20] These simplifications are incorporated in the 2010 revisions to the McDonald criteria (panel 2).[7] The dissemination in space included in these latest criteria requires a clinically silent lesion in two of four locations characteristic of demyelination: juxtacortical, periventricular, infratentorial, and spinal cord (figure 1). However, in patients with brainstem and spinal cord syndromes, all the lesions within the symptomatic region, including those that are not directly responsible for clinical signs, are excluded from the criteria. Dissemination in time is satisfied by the presence of gadolinium-enhancing and non-enhancing lesions on a scan, or a new lesion on any follow-up scan irrespective of timing of the baseline scan (figure 2). Thus, the diagnosis of MS at the time of CIS presentation is now possible in some patients. However, these criteria should only be applied in CIS when clinical features are characteristic of MS, because the MRI criteria taken on their own can be fulfilled in other disorders (including acute disseminated encephalomyelitis, neuromyelitis optica, neurosarcoidosis, CNS vasculitis, systemic lupus erythematosus, CNS lymphoma, and even small vessel disease).

Although atrophy of grey and white brain matter is not included in MS diagnostic criteria, it has been seen in early relapsing-remitting MS,[21] and the occurrence at presentation or subsequent development of global or regional grey matter atrophy in patients with CIS has been associated with conversion to MS.[22–24] For example, in a 4 year follow-up study of 105 patients with CIS, multivariate analysis identified atrophy of superior frontal gyrus, thalamus, and cerebellar grey matter as independent predictors of conversion to MS.[22] The specificity and practical utility of such tissue-specific

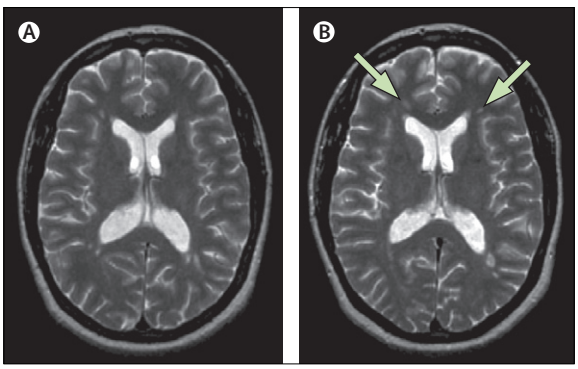

Figure 2: **A T2 lesion on a follow-up scan in a patient with clinically isolated syndrome**
A baseline scan (A) can be undertaken at any time (in this case obtained 4 weeks after symptom onset) and compared with a subsequent scan (B) also undertaken at any time (in this case 3 months later), with the appearance of any new lesion (arrows) sufficient to fulfil the dissemination in time criteria (McDonald 2010 criteria).[17]

atrophy measures needs to be established before they can be considered suitable to include in diagnostic criteria.

CSF

Although CSF oligoclonal bands (OCBs) increase the risk of CIS developing to MS, they add little to MRI-assigned risk: Tintoré and colleagues[25] recorded conversion to MS in 59% of all patients with CIS with more than 10 brain lesions and in 64% who had more than 10 brain lesions and CSF OCBs. For MS diagnosis or prediction, many neurologists think that MRI alone is sufficient. However, CSF examination helps to predict conversion to MS in patients with negative MRI or with an MRI showing few lesions (ie, MRI that does not meet the McDonald criteria for dissemination in space). In patients with negative MRI, the presence of OCBs increased the risk for developing MS from 4% to 23%.[25] Therefore, the development of MS is unlikely in patients with a CIS showing few or no MRI lesions and no CSF OCBs.

Apart from OCBs, several markers in the CSF are specific for disease process, such as inflammation and immune dysfunction, or cell type, such as B cells.[26] Some of these markers have been shown to predict conversion to MS in patients with CIS. A higher conversion to MS in patients with CIS has been reported with the presence of IgG antibodies against the neurotropic viruses measles, rubella, and varicella zoster, which indicates a polyspecific intrathecal B-cell response.[27] In agreement with the idea of a proinflammatory, B-cell-promoting environment in MS, increased CSF concentrations of chemokine CXCL13, which is a key regulator of B-cell recruitment, were shown to be the best predictor of conversion to MS in patients with CIS over 2 years' follow-up.[28] CSF IgG heavy-chain bias was detected in patients with CIS who converted to MS within 6 months of CIS presentation,[29] but the group of patients studied was small (n=10). CSF markers of axonal damage, including tau and neurofilaments, might be more specific than MRI for predicting conversion of CIS to MS.[30] A proteomic analysis of CSF samples reported that high concentrations of CSF chitinase 3-like 1, which is up-regulated during inflammation, were associated with shorter time to clinically definite MS in patients with CIS.[31] Despite these encouraging results, none of these CSF markers can be recommended for routine implementation in clinical practice, mainly because of methodological limitations, including small studies, short follow-ups, different study designs, lack of standardised (or combined) assay, and scarcity of confirmation of findings in different independent laboratories. Large and multicentre studies are needed to translate CSF biomarkers to the clinical setting.

Clinical features

Several clinical features in CIS are associated with a higher risk of further relapses in the subsequent 1–2 years: younger age,[32,33] ethnic origin (non-white),[32] sex (female),[34] and greater number of functional systems affected at onset.[35] However, the predictive value of multifocality for risk of clinically definite MS is controversial and two other clinical trials showed that multifocal clinical presentation was not associated with increased risk of conversion to MS.[33,36] In patients with monofocal disease, but not in those with multifocal disease, the risk for MS was shown to be dependent on MRI findings, because the presence of disease dissemination (at least nine T2 lesions) and activity (at least one gadolinium-enhancing lesion) predicted a shorter time to conversion to MS.[16] This finding suggests that subclinical MRI dissemination is indicative of more active disease in patients with monofocal disease, although in patients with multifocal disease it might indicate an extended subclinical disease evolution, which is not relevant for a second clinical event. These different results are also likely to depend on the method used to classify patients (ie, local investigators *vs* central assessment, only neurological signs *vs* a combination of signs and symptoms). Alternatively, an observational study showed that a lower number of functional systems affected in a patient's CIS[32] was associated with higher risk of a second relapse within 1 year, which might suggest that patients with multifocal onset are more predisposed to suppress disease activity in the short term compared with patients with onset limited to fewer systems, or that the presence of symptoms due to the involvement of multiple functional systems at onset masks a second (subtle) relapse affecting one of these functional systems. Considering the potential effect of identification of predictors of a second event on the management of patients, further studies in large cohorts to investigate clinical and radiological predictors are needed.

In one study of patients with optic neuritis,[37] a history suggesting a previous demyelinating event, which had not been confirmed clinically at the time of the

symptoms, was shown in 24% of patients. This past event, when combined with an MRI scan showing dissemination in space, had a high sensitivity and specificity for conversion to MS.[37] This finding leads to an important observation: in clinical practice, a previous event suggestive of demyelination can be an acceptable indicator of a diagnosis of MS in a patient presenting with a CIS and MRI dissemination in space only. Cognitive impairment in CIS has also been associated with higher conversion to MS.[38]

Genetic and environmental features

Several genetic and environmental factors have slight association with conversion to MS; gene–environment interactions are hypothesised to have a stronger effect[39] and the interplay between these factors might be due to common pathogenic mechanisms.[40] Despite the fact that clinically useful genetic and environmental markers of prognosis in CIS are not available, we will briefly mention relevant findings from the past 5 years, because a strong link probably exists between genetic and immunological factors, exposure to the sun, vitamin D status, infections in early childhood or during adolescence, other environmental factors (including smoking), and risk of MS in patients with CIS. However, all these factors might not be necessary to trigger MS, and a combination of specific factors might be relevant for different individuals.[41]

A genome-wide association study of a very large (n=9772) MS cohort identified more than 50 susceptibility loci, many of which are closely mapped to immunologically relevant genes.[42] The strongest association, known for more than 30 years, is with HLA DRB1 risk alleles. In patients with CIS with MRI lesions, positive *HLA-DRB1*1501* status has been associated with a higher lesion load[43] and conversion to MS.[44] However, a genome-wide association study[42] done in 2011 did not show an association between susceptibility genes and disease course in MS, and in another study[45] a weighted genetic risk score, based on assessment of 16 MS susceptibility loci, did not correlate with conversion of CIS to MS.

An Australian case-control study of CIS investigated possible environmental associations, and found that differences in leisure-time sun exposure, serum vitamin D concentration, and skin type additively contribute to the increase in CIS incidence from low-latitude to high-latitude regions.[46,47] Findings from another study showed that higher vitamin D levels during adolescence were associated with a significantly lower risk for MS.[48] In an attempt to link genetic and environment risk factors, Ramagopalan and colleagues[49] identified a vitamin D-responsive element in the *HLA-DRB1* promoter region, suggesting the potential for vitamin D to modify the expression of an MS susceptibility gene. Taking into consideration both the finding of an insufficiency of serum concentrations of vitamin D in MS, even at the earliest stages of the disease, and the immunological role of vitamin D,[41] it is likely that vitamin D deficiency is one of the risk factors for MS. Future studies should clarify the role of vitamin D deficiency as a risk factor for MS and assess whether vitamin D treatment affects the conversion of CIS to MS.

Whereas Epstein-Barr virus (EBV) infection is evident in 90% of the adult population, it is seen in 99% of individuals with MS.[50] In a 7 year follow-up of patients with CIS, increased EBV-encoded nuclear antigen 1 (EBNA1)-specific IgG responses were associated with a two times higher risk of developing MS, as well as greater disability and more new MRI lesions.[51] In another study,[52] higher anti-EBV-specific IgG titres and a history of infectious mononucleosis were associated with increased CIS risk and an additive interaction with *HLA-DRB1*1501* status was recorded.[52] The investigators concluded that past infection with EBV is associated with increased CIS risk and that the association can be modified by immune-related gene variants.

In a 3 year follow-up study of 129 patients with CIS and abnormal brain MRI, 75% of smokers but only 51% of non-smokers developed clinically definite MS, and smokers had a shorter time to their first relapse.[53] Although the effect of cigarette smoking on MS susceptibility has been shown,[53] its effect on disease progression is less certain.[54]

Blood and immunological features

The contribution of B cells to the mechanisms of conversion to MS is shown not only by CSF B-cell-associated biomarkers, but also by blood (and immunological) markers. For example, an increase in B lymphocytes expressing the molecule CD5 in peripheral blood predicted earlier conversion to MS in patients with CIS and OCBs, who are therefore at high risk of conversion.[55] Additionally, immunological mechanisms involving T cells have been implicated in the pathogenesis of MS. Gene expression analysis of CD4+ T cells in patients with CIS has shown that down-regulation of *TOB1*, with consequent activation and proliferation of naive T cells, identifies patients with CIS at higher risk of conversion to clinically definite MS.[56] Future studies will confirm whether this is a robust gene-expression signature for risk of MS and whether early molecular changes can be used to predict conversion to MS in individual patients. In agreement with an involvement of T cells in the disease, the expression of phosphorylated STAT3, which is a transcription factor necessary for the differentiation of T-helper-17 cells, in circulating CD4+ T cells was higher in patients with CIS who converted to clinically definite MS than in those who did not.[57] This result suggests that the persistency of CD4+ T cells expressing high titres of phosphorylated STAT3 in peripheral blood might promote conversion to MS. Therefore, the investigation of transcription factors (and cytokines) in peripheral blood subpopulations

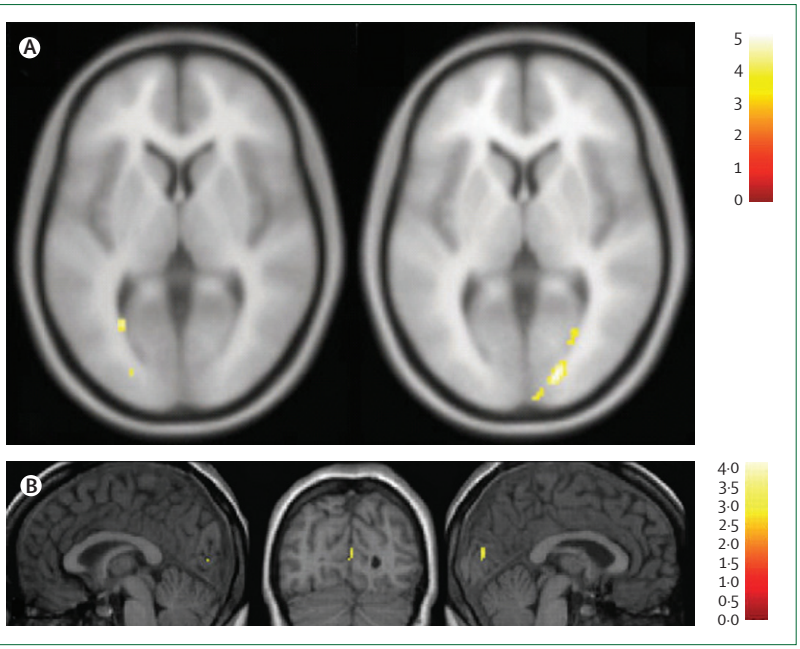

Figure 3: **Postsynaptic morphological changes after optic neuritis in clinically isolated synrome**
(A) Abnormal voxel-based diffusion connectivity in the left and right optic radiation of patients with optic neuritis.[79] (B) Magnetisation transfer ratio (MTR) decrease in patients with optic neuritis is seen bilaterally in the visual cortex (Brodmann's area 17) when compared with healthy individuals.[80] The voxels in yellow indicate the regions where there is a reduced MTR value in patients when compared with controls, using a voxel-by-voxel analysis and two-sample *t* test, corrected for multiple comparisons at p<0·05 with a small volume correction for the occipital cortex; results are displayed on a normalised (sagittal and coronal) T1 scan. The colour scale indicates T score.

might be useful in the identification of patients with CIS who will develop MS.

An imbalance in serum chemical elements and oxidative status has been shown to be associated with conversion to MS,[58] although the exact neurobiological mechanisms are unclear. Absence of confirmation of many of these findings in many independent laboratories and in larger, multicentre studies limits the interpretation of their importance. An initial high-profile study reported an association of serum antimyelin antibodies in patients with CIS with conversion to MS[59] but this was not confirmed in subsequent studies,[60] emphasising the need for more independent studies to confirm robust predictors of disease evolution.

Risk factors for MS in children with CIS

A large nationwide study in Canada followed up a group of children presenting with a clinical event suggestive of demyelination for 3 years.[61] The findings showed that the risk of MS was increased (by about two times) by the presence of *HLA-DRB1*15* alleles, remote EBV infection, and low serum vitamin D concentrations. Similar to previous studies in adults, brain lesions detected on MRI (relative risk=9), and CSF OCBs (relative risk=6) carried the highest risk for MS. The same Canadian study group has since done a prospective natural cohort study and shown that the presence of at least one T1 hypointense lesion and at least one periventricular lesion was associated with increased likelihood of a diagnosis of MS.[62]

A retrospective, nationwide study in the Netherlands[63] identified a higher conversion to MS in children with a CIS with the following: a monofocal (24 of 54; 44%) versus polyfocal (13 of 63; 21%) presentation, an increased IgG index and presence of CSF OCBs, and positive MRI criteria that are thought to be characteristic of MS in adults[17] and children.[64] Many children presenting with polyfocal onset and no encephalopathy remained monophasic.

Risk factors for long-term disability

Whereas robust risk factors are available to predict the evolution from a CIS to MS, prediction of the long-term course is weak. Clinical aspects of CIS that have been associated with future disability are pyramidal and cerebellar motor deficits and incomplete recovery. A short interval to the second relapse and a high relapse rate in the first 2 years[1] and involvement of multiple systems at onset[65] also indicate a poorer prognosis. Features that are associated with a better outlook are a purely afferent CIS, with sensory symptoms or optic neuritis. None of these clinical prognostic features is robust.

A relation between lesion load measured by MRI at CIS presentation with disability has been reported in some[10,14] but not all[9] studies with follow-ups ranging from 7 years to 20 years. Brainstem lesions are associated with higher disability after 7 years.[11] Increasing total lesion load after CIS has been associated with clinical outcome at 20 years follow-up:[10] those who had developed secondary progressive MS had a greater increase in lesion volume especially during the first 5 years. Furthermore, when the rate of lesion growth over 20 years was analysed, patients with secondary progressive MS showed, on average, a three times higher rate of lesion accumulation than did those with relapsing-remitting MS,[10] although there was much variation between individuals in both groups.

Non-conventional MRI abnormalities in CIS

Much evidence exists from non-conventional imaging studies that suggests a more disseminated CNS disorder in patients with CIS than is shown by MRI-visible lesions. Other non-conventional MRI abnormalities in CIS include regional atrophy in both cortical and deep grey matter,[22,66,67] decreased magnetisation transfer ratio in white and grey matter,[68,69] decreased N-acetyl aspartate in whole brain[70] and normal-appearing white matter,[71,72] increased myoinositol in normal-appearing white matter,[73] abnormal diffusion parameters in white matter,[74,75] and abnormal active and resting state functional MRI responses.[76–79] Quantitative magnetic resonance abnormalities in the occipital radiation[80] and visual cortex[81] after CIS optic neuritis are consistent with trans-synaptic degeneration (figure 3). However, a robust

non-lesion predictor of long-term prognosis has not emerged. In a multivariate analysis that included lesion and non-lesion MRI measures, the main predictors of disability 6 years after presentation with clinically isolated optic neuritis were spinal cord and brainstem lesions at presentation and new lesions after 3 months.[82]

Radiologically isolated syndromes

Brain MRI features typical of demyelination and fulfilling MRI criteria for MS are sometimes seen in healthy individuals or patients with non-specific symptoms (eg, headache, dizziness), and have been termed radiologically isolated syndromes. Follow-up studies done over 2–5 years have independently reported that about 30–40% of such people have one or more clinical events leading to a diagnosis of CIS or MS.[83–85] This group can thus be thought to be at high risk for MS. The MRI criteria for radiologically isolated syndrome have required several characteristic features for demyelination—eg, lesion number (>9 T2 lesions), location (periventricular, juxtacortical, infratentorial), and activity (gadolinium enhancing). Non-specific, mainly small and subcortical lesions that are likely to be caused by small vessel diseases, are often encountered in otherwise healthy people—in such circumstances it is inappropriate and potentially harmful to suggest a diagnosis of radiologically isolated syndrome or MS.

A retrospective review identified asymptomatic cervical spinal cord MRI lesions in 25 of 71 patients with radiologically isolated syndrome, in whom 21 (84%) developed a CIS or primary progressive MS within 1·6 years.[86] The authors suggested that cord lesions in radiologically isolated syndrome imply a high risk for future clinical events independent of brain MRI. However, the finding differs strikingly from non-spinal CIS, in which prospective MRI studies from onset showed that almost all individuals with asymptomatic cord lesions also have silent brain lesions[87] and that cord lesions do not independently predict conversion to MS.[88] Further studies of cord imaging in radiologically isolated syndromes are recommended before concluding that it has an independent prognostic role.

Differential diagnosis

The differential diagnosis of CIS can be divided into three broad categories: idiopathic inflammatory demyelinating CNS diseases (IIDD; MS, acute disseminated encephalomyelitis, neuromyelitis optica, idiopathic transverse myelitis), inflammatory non-IIDD CNS diseases (eg, sarcoidosis, vasculitis, Behcet's disease, systemic lupus erythematosus), and non-inflammatory CNS diseases (eg, ischaemia or infarction, compression, haemorrhage, metabolic disorder). Panel 3 summarises the diagnostic criteria for the diagnosis of acute disseminated encephalomyelitis and neuromyelitis optica in children and adults.[5,6] The key factors that need to be considered for diagnosis of acute disseminated encephalomyelitis are the presence of an event of encephalopathy (eg, altered consciousness, behavioural and cognitive abnormalities, seizures), with clinical evidence for multifocal disease and subsequent clinical improvement (panel 3). Acute disseminated encephalomyelitis is more common in children (when MS is less common); a similar presentation with encephalopathy can occur in MS, and such a presentation of MS should always be borne in mind, especially in young adults, when MS is common and acute disseminated encephalomyelitis is uncommon.

Although it usually becomes a multiphasic relapsing disorder, the first episode of neuromyelitis optica[89] (panel 3) presents with optic neuritis or transverse myelitis, sometimes both simultaneously. The episode tends to be more severe in neuromyelitis optica than it is in CIS due to MS, with poorer visual and motor recovery. A characteristic feature is a longitudinally extensive spinal cord lesion (three or more vertebral segments); in CIS due to MS, cord lesions are usually less than 1–2 segments long and occupy only part of the cord cross-sectionally. Spinal lesions can be T1 hypointense in

***Panel 3:* Diagnostic criteria for acute disseminated encephalomyelitis and neuromyelitis optica**

Acute disseminated encephalomyelitis

- An event of acute (or subacute) encephalopathy, which can vary in severity, from irritability, behavioural, and cognitive changes to coma
- New symptoms can emerge over the course of 3 months from onset, without remission of initial symptoms
- The episode is characterised by clinical recovery (partial or complete)
- Brain MRI shows multiple lesions that are predominantly in the white matter, are large, and have the radiological features of acute lesions; grey matter and spinal cord lesions and single, large, white matter lesions are also possible
- No history of a previous demyelinating event and exclusion of other possible causes

Neuromyelitis optica

Major criteria

- Optic neuritis (in one eye or both eyes)
- Acute myelitis
- Optic neuritis and acute myelitis can occur simultaneously, or weeks or years apart

At least two of the following three supportive criteria

- Spinal cord lesion extending for at least three vertebral segments on T2-weighted MRI scans (ie, longitudinally extensive spinal cord lesion)
- Brain MRI scans do not fulfil criteria for multiple sclerosis
- Seropositivity for neuromyelitis optica IgG (or anti-acquaporin-4 antibodies)

Adapted from Miller et al,[5] Krupp et al,[6] and Wingerchuk et al.[89]

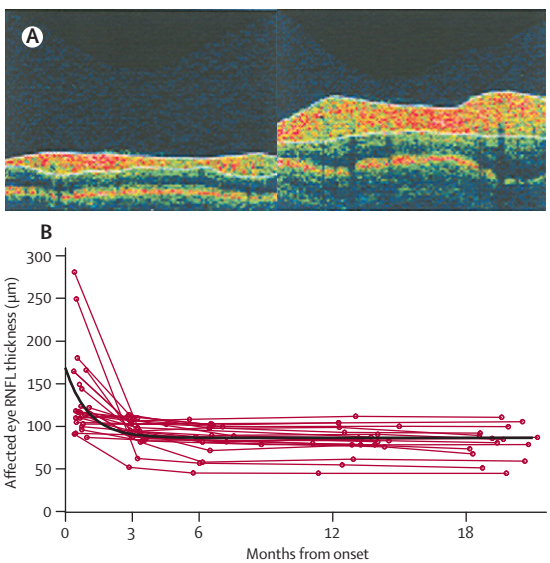

Figure 4: **Optical coherence tomography and temporal behaviour of the retinal nerve fibre layer thickness**
Optical coherence tomography images showing retinal nerve fibre layer (RNFL) swelling at onset of optic neuritis in a patient's right eye (on the right), and normal RNFL thickness in their left eye (on the left; A). (B) Serial RNFL thickness of a patient's affected eye after optic neuritis, fitted with the exponential model; this graph shows RNFL thickness evolution from swelling to atrophy, with a significant thinning of the affected eye occurring within 1–2 months.[96]

neuromyelitis optica but almost never in CIS and MS. Brain MRI is often normal or can have abnormalities in distinctive locations, including the medulla, corpus callosum, and hypothalamus. About two-thirds of patients with neuromyelitis optica have antibodies to aquaporin 4 (panel 3).

MRI is crucial in all patients with a brainstem or spinal cord CIS to identify alternative structural disorders—eg, spinal cord compression due to tumour or intervertebral disc protrusion, or brainstem syndrome due to an arteriovenous malformation. In optic neuritis, brain MRI is undertaken mainly to detect clinically silent demyelination. CSF examination might be necessary for differential diagnosis (eg, exclusion of Lyme disease in regions where it is prevalent).

It is beyond the scope of this Review to consider the many disorders that enter the CIS differential diagnosis. Reviews identify clinical and MRI warning signals that suggest a diagnosis other than inflammatory demyelination.[5,90]

Treatment

Many CIS episodes are mild and resolve without therapeutic intervention. Clinical features that favour treatment include severe visual loss, pain in optic neuritis, or both, and pronounced motor dysfunction, ataxia, or vertigo in spinal cord and brainstem syndromes.

High-dose intravenous methylprednisolone in acute optic neuritis shortens the duration of visual deficit but not visual outcome after 1 year.[91] It does not prevent optic nerve atrophy[92] or visual evoked potential delay after optic neuritis, suggesting little effect on axonal loss and demyelination.[93] Oral high-dose methylprednisolone (1 g per day for 3–5 days) is probably an acceptable alternative to intravenous methylprednisolone (1 g per day for 3–5 days).[94]

In CIS optic neuritis, optical coherence tomography provides a measure of retinal nerve fibre layer (RNFL) thickness, and thus a direct non-invasive in-vivo measure of axonal loss. Reduction in thickness of this layer is associated with persistent visual dysfunction after optic neuritis,[95] suggesting that axonal loss underlies the failure to recover after a CIS. With regard to thinning with time, analysis of preliminary data showed no further loss of thickness 6 months after an episode of optic neuritis.[96] Our longitudinal analysis of patients after optic neuritis showed that after initial swelling during the acute phase, thinning of the retinal nerve fibre layer in a patient's affected eye relative to their other eye typically appears within 1–2 months, and at least half the final loss is evident after 3 months (figure 4); a continuous but slower loss is predicted to occur for up to 12 months (but almost all has occurred by 6 months).[97] The median loss of RNFL thickness after an episode of optic neuritis is 15–20%.[97] The decrease in thickness after acute optic neuritis is thought to be indicative of both resolution of inflammation and oedema (the cause of initial swelling) and axonal degeneration. Furthermore, it is clinically relevant—faster RNFL thinning in the first 3 months is associated with a poorer clinical recovery.[97] Prevention of RNFL loss is an appealing outcome measure for future trials of experimental neuroprotection in CIS optic neuritis.

β-interferon and glatiramer acetate extend the time to next relapse—ie, clinically definite MS. Patients treated with intramuscular β-interferon-1a (30 µg) once a week had a 37% conversion to clinically definite MS after 2 years compared with 50% of patients who received placebo.[36] Weekly subcutaneous β-interferon-1a (22 µg) was associated with a 35% conversion to MS after 2 years compared with 50% in those given placebo.[35] Subcutaneous β-interferon-1b (250 mg) on alternate days reduced conversion to clinically definite MS from 55% (in placebo) to 35% after 2 years.[98] Daily subcutaneous glatiramer acetate (30 mg) was associated with a 35% conversion to clinically definite MS compared with 50% in the placebo group.[99] These treatments also reduce new MRI lesion formation and might slow down brain atrophy.[100]

The CIS trials did not persist with placebo treatment beyond the point of the development of clinically definite MS, at which point patients were offered active treatment. In the study of β-interferon-1b, the cohort was followed up for 3–5 years. A reduction in disability was evident after 3 years in the early versus delayed β-interferon group,[101] but this difference was not apparent after 5 years.[102] This

would suggest that, despite the short follow-up, the effect of disease-modifying treatments initiated in CIS on long-term disability is, overall, minimal. However, our natural history longitudinal data for 20 years of follow-up suggest that slowing accumulation of new T2 lesions, especially in the first 5 years, would delay or prevent secondary progressive MS.[10] Therefore, a need exists for longer-term and methodologically sound follow-up before concluding whether a delay in the occurrence of the second relapse (and concurrent reduction in MRI activity until that time) has a definite and substantial effect on the long-term course of MS.

Future challenges

Grey matter lesions are often seen at post mortem in MS but rarely seen on conventional MRI. However, their detection is improved with the double inversion recovery sequences[103,104] and their detection at CIS onset was associated with increased conversion to clinically definite MS in one study.[105] Further work is needed to confirm this observation. The utility of detection of more white matter[106] and grey matter[107] lesions with a 3 T scanner in comparison with a 1·5 T scanner for MS diagnosis is subject to debate.[108] It is expected that improved detection of lesions in anatomical regions that are important for the MS diagnostic criteria, such as the infratentorial areas, will have an effect on MS diagnosis. However, this might not lead to an earlier diagnosis of MS.[109] Ultra-high field (7 T) scanners are expected to allow a higher detection rate of lesions compared with the use of lower magnetic fields,[110] and improved visualisation of special pathological features of lesions that are specific to MS pathology.[111] The utility of non-conventional MRI techniques for diagnosis of MS also deserves further research.

A pressing need exists for better predictors of long-term disability, which would allow treatments to be targeted early on to individuals most likely to benefit in the long term. It is especially important to optimise benefit over risk when embarking on a potential lifelong treatment in a young adult with a CIS, when the spectrum of outcomes is highly variable.

The absence of robust long-term predictors is accompanied by a restricted understanding of the mechanisms that underpin the variable long-term course of MS—why do some patients have benign non-disabling disease and others develop disabling secondary progressive MS?

MRI measures, which represent in vivo underlying pathological mechanisms, are similarly affected in CIS and relapsing-remitting MS, but they show an overall lower extent of pathology, and more extensive cortical reorganisation in CIS than in relapsing-remitting MS.[79] Relapses are caused by new inflammatory demyelinating lesions in CNS white matter. Clinically silent new lesions are often seen on MRI and initially display gadolinium enhancement, indicating leakage of the blood–brain barrier with inflammation. Relapses and new MRI lesions are reduced by immunomodulating and immunosuppressive treatments, which provide the rationale for such treatment in CIS and relapsing-remitting MS when objective clinical and MRI disease activity is seen.

In secondary progressive MS, white matter lesions are less inflammatory but can exhibit much axonal loss. There are also extensive demyelinating cortical grey matter lesions and diffuse low-grade inflammation with axonal loss in normal-appearing white matter.[112] Extensive pathological changes are seen in a patient's spinal cord, with demyelinating lesions in grey and white matter and axonal loss in lesions and non-lesion white matter tracts.[113]

The relation between white matter inflammatory lesions and the more extensive neurodegenerative changes is unclear. One hypothesis is that MS starts with primary focal white matter inflammation and demyelination that is mediated by an adaptive immune system response to an unknown antigen or antigens. The process triggers complex events in the CNS affecting the innate immune system with microglial activation, astrocyte proliferation, persistent demyelination, increasing axonal vulnerability, and, ultimately, axonal loss. According to this hypothesis, aggressive immunomodulation early on will be the most effective way of ameliorating all the pathology and hence the long-term course of MS. An alternative view is that the focal and diffuse processes are fundamentally unrelated and evolve independently from an early stage, and therefore that immunomodulation will have no effect on long-term risk for secondary progressive MS and increasing neurodegeneration. These two hypotheses imply a different approach to the treatment of patients with CIS and early relapsing-remitting MS, but no conclusive evidence exists to favour either approach.

Because substantial axonal loss occurs after CIS optic neuritis, a clear need exists for acute neuroprotection in CIS (and MS relapses in general). Corticosteroids seem inadequate for this purpose because they do not reduce persistent deficit or optic nerve atrophy after optic neuritis. Other acute relapse trials have been negative—eg, natalizumab[114] and intravenous immunoglobulin.[115] A serial study of optic neuritis with visual evoked potentials and optical coherence tomography showed that extended latency in visual evoked potentials at presentation and after 3 months was associated with greater axonal loss (RNFL thinning), suggesting that the extent of early demyelination affects axonal survival.[116] Such a finding encourages strategies to enhance early remyelination after a CIS.

The approach to treating CIS is variable. Some clinicians recommend β-interferon or glatiramer acetate when there are features suggesting a poorer prognosis—eg, disabling CIS, incomplete recovery, large lesion load, gadolinium-enhancing lesions, or new lesions on follow-up. Although these agents have well recognised

Search strategy and selection criteria

We searched PubMed from Jan 1, 1997, through to Oct 31, 2011, with the search terms "clinically isolated syndrome" and "multiple sclerosis". Only papers published in English were reviewed. The final list of publications was selected by the authors on the basis of relevance to the topic.

side-effects (eg, injection site reactions, influenza-like symptoms, hepatic dysfunction [β-interferon], transient dyspnoea, lipoatrophy [glatiramer acetate]), long-term experience[117] (10 or more years) has not identified more serious treatment-associated risks, an important plus when treating young adults with a lifelong disease and variable prognosis. Although controlled trial evidence for long-term benefit is not available, some clinicians recommend treating CIS to prevent new clinically silent pathology and to modify the immunopathogenic process when it is thought to be less complex.

Although more potent disease-modifying treatments could, in theory, enhance long-term benefit if given early, no evidence shows that they do so, and they might have serious, although uncommon, adverse effects. Natalizumab is associated with progressive multifocal leukoencephalopathy; fingolimod with severe herpetic infections, macula oedema, and bradyarrhythmias; and alemtuzumab with thyroid dysfunction, Goodpasture's syndrome, and idiopathic thrombocytopenic purpura.[118] Furthermore, the prognosis for CIS is better than that for established relapsing-remitting MS. About 20% of patients with CIS with an abnormal MRI scan will not convert to clinically definite MS even after two decades[10] and about 10% develop MS only on radiological grounds after extended follow-up.[119] In those who develop clinically definite disease, a third have minimal disability after 15–20 years. The median time to develop secondary progressive MS, the major cause of long-term disability, is up to 15–20 years.[120] It is vital that future therapeutic trials in CIS and early relapsing-remitting MS focus on achieving a good long-term safety and effectiveness profile.[118]

In addition to the suppression of inflammation, a compelling case exists for treatments to prevent neurodegeneration as CIS evolves to MS and beyond. Ultimately, a combination of anti-inflammatory and neuroprotective treatments might be needed to prevent long-term disability. Strategies for neuroprotection have included sodium-channel blockers, statins, glutamate antagonists, cannabinoids, and remyelination with stem cells and other molecular targets that promote repair. No effective neuroprotective agent has been identified for MS. Their identification might be aided by the use of sensitive imaging markers for neuroaxonal loss in trials, because years can pass before the consequences of neurodegeneration become clinically apparent. Measures include whole-brain and grey matter atrophy and evolution to persistent T1 hypointense lesions.[121] Imaging measures for remyelination include lesion magnetisation transfer ratio and myelin water imaging.[121]

Much has been learnt in the past 5–10 years about CIS and its relation to MS. Robust and practical new diagnostic criteria aid an earlier MS diagnosis in patients with a typical CIS, and immunomodulatory treatments favourably modify the early clinical course (over 2–5 years) in those at high risk for MS. There is, however, only a restricted capacity to predict long-term disability, and whether such disability can be prevented by early use of existing disease-modifying treatments is unclear. Future research should focus on obtaining a better understanding of the evolving pathogenesis of CIS to MS and long-term disability; the development of novel therapeutic strategies based on the emerging understanding of pathogenesis; and studies—with both clinical and biologically plausible paraclinical outcome measures—to elucidate the long-term effectiveness and safety of disease-modifying treatment interventions.

Contributors

DHM wrote the review; DTC and OC made changes and edited the paper. All authors approved the final version.

Conflicts of interest

DHM has received honoraria from Biogen Idec, Novartis, GlaxoSmithKline, and Bayer Schering, and research grant support for doing MRI analysis in multiple sclerosis trials sponsored by GlaxoSmithKline, Biogen Idec, and Novartis. OC has received honoraria from Bayer and General Electric for lectures; she is on the editorial board of *Neurology* and is a clinical editor for *CML Multiple Sclerosis*. DTC receives research support from the Multiple Sclerosis Society of Great Britain and Northern Ireland, and holds stocks in GlaxoSmithKline.

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