Clinically isolated syndromes suggestive of multiple sclerosis, part 2: non-conventional MRI, recovery processes, and management

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The onset of multiple sclerosis (MS) in 85% of young adults is with a subacute clinically isolated syndrome (CIS) of the optic nerves, brainstem, or spinal cord. Whereas multifocal brain lesions are present on MRI in many patients with a CIS, some patients have additional abnormalities on quantitative MRI in otherwise normal-appearing white and grey matter that suggest an extensive pathological process. Functional outcome for patients with symptomatic CIS lesions is determined by the interplay of inflammation, demyelination, axonal damage, remyelination, and cortical adaptation. Recovery of function may be accelerated by high dose corticosteroids, and although interferon beta delays the development of a second relapse, its long-term effect is unknown. A better understanding of pathological and pathogenetic processes in patients with a CIS will facilitate the development of disease-modifying treatments for patients with MS before they become disabled. Continued clinical and laboratory investigation of patients with a CIS should be encouraged.

Introduction
In 85% of young adults who develop multiple sclerosis (MS), onset is with an acute, clinically isolated syndrome (CIS) of the optic nerves, brainstem, or spinal cord. In part 1 of this review, published in the May 2005 issue, the clinical presentation, pathogenesis, diagnosis, and prognosis of CISs were covered. In part 2 we review non-conventional MRI findings, recovery processes, and management of patients.

Abnormalities on non-conventional MRI
Progressive brain atrophy is a well-known feature of MS and is thought to be a marker of irreversible tissue damage. However, the exact causes and timing of atrophy in MS are unknown. The assessment of brain and spinal-cord atrophy in patients with a CIS should help to define how early irreversible tissue loss occurs in MS. Dalton and co-workers prospectively followed up 55 patients with CISs for 3 years. After 1 year, patients with MS (according to the McDonald criteria) had substantially more ventricular enlargement than those without such disease progression. After 3 years, 29 (53%) of the patients had progressed to MS and ventricular volume and grey-matter atrophy were greater in those with MS than in those who did not have MS. White-matter volume did not change over time in either subgroup. Measures of lesion load and atrophy measures were moderately related, suggesting that T2-visible lesions account only partially for the observed changes in brain volume. Similar results were also found when brain atrophy was measured in the Early Treatment of MS (ETOMS) trial. In 43 patients with a CIS, atrophy of the spinal cord was also assessed; although the area of the spinal cord in patients with a CIS and an abnormal brain MRI at presentation was slightly smaller than that of healthy controls, there was no measurable change in patients or controls over 1 year.

Conventional MRI shows T2-visible lesions but does not show other abnormalities. However, several quantitative MRI techniques can show abnormalities in otherwise normal-appearing brain tissue; these techniques have the potential to increase knowledge of the pathobiology of MS. Conventional MRI lesion measures are of limited value for prognosis in the early stages of the disease, and quantitative MRI techniques have potential to give a clearer prognosis. Magnetisation-transfer MRI has been one of the most widely used methods for the assessment of patients with MS and can detect “occult” tissue damage in the brain and cervical cord. Low magnetisation-transfer ratios have been detected in normal-appearing brain tissue of patients with CIS at presentation, and in one study, the extent of these abnormalities was reported to be an independent predictor of subsequent disease progression. However, other studies with region-of-interest or whole-brain-histogram analysis of magnetisation-transfer MRI data did not find that low magnetisation-transfer ratios predict disease progression. Another study showed magnetisation-transfer-ratio abnormalities in a group of patients with a recent onset of CIS and in a group with a remote onset of CIS; the similar findings in both groups, and in those with normal and abnormal conventional scans, prompted the researchers to propose that magnetisation-transfer MRI abnormalities in CIS suggest susceptibility to demyelination. Recent studies of patients with CISs have found no abnormality in cervical-cord magnetisation-transfer-ratios but abnormal measures of diffusion in normal-appearing white matter; however these findings were not predictive of subsequent lesion dissemination (as defined by the McDonald criteria) at 3 months and 12 months. Overall, the published findings on magnetisation-transfer ratio and diffusion suggest that subtle white-matter damage might occur at a very early stage of the disease.
stage in patients with a CIS but do not predict short-term lesion development.

In patients with established MS, proton-magnetic-resonance spectroscopy studies have found low N-acetylaspartate and high myoinositol concentrations. By contrast, small and preliminary studies on patients with CIS found no abnormalities in brain metabolites. More recently, one of us with other researchers used a new unlocalised proton-magnetic-resonance spectroscopy technique to show a decrease in the concentration of N-acetylaspartate in the whole brain in a group of 31 patients with a CIS. Fernando and co-workers studied 96 patients with CIS within 6 months of the clinical episode and found high myoinositol and creatine in white matter, suggesting that glial proliferation is an early event in MS (figure 1).

As found in patients with established MS, in patients with a CIS non-conventional MRI measures might be better than lesion load in reflecting clinical status. Notably, patients with a CIS and cognitive impairment had a lower ratio of N-acetylaspartate to creatine and a lower brain parenchymal fraction than patients with a CIS and normal cognition, whereas there was no difference in T2-lesion and T1-lesion volumes between the two groups. Patients with CIS in this study also had white-matter volume loss but not grey-matter volume loss.

In about 20% of patients with MS, optic neuritis is the initial symptom of the disease. Although the assessment of optic-nerve pathology has been hampered by several methodological factors (the small size of the nerve, motion artifacts, and the effect of surrounding CSF, lipids, and bony structures) it is possible to obtain high quality T1-weighted and T2-weighted images, as well as reliable quantitative data. In patients with MS, the magnetisation-transfer ratio is substantially lower in affected optic nerves than in unaffected ones. Furthermore, low magnetisation-transfer ratio is associated with delay in the latency of visual evoked potentials. Inglese and co-workers found that magnetisation-transfer ratio was lower in the optic nerves of patients with MS without recovery than in those with clinical recovery, and that magnetisation-transfer ratio was similarly low in patients with Leber's hereditary optic neuropathy, suggesting that axonal loss is likely to be an important contributor to low magnetisation-transfer ratio in MS. Further support for the idea that axonal loss is one of the pathological substrates of optic-nerve damage comes from findings of nerve atrophy after an episode of optic neuritis.

Recovery processes

Structural repair mechanisms and insights from MRI in optic neuritis

The optic nerve, when studied both experimentally and clinically, serves as a window revealing general mechanisms of symptom onset and recovery equally applicable to isolated and recurrent demyelination elsewhere in the CNS. Altered structure and function in the complex oligodendrocyte–axon unit should be part of any explanation of symptom onset and recovery. In addition, given the capacity for CNS plasticity and functional adaptation, clinical recovery might not result from structural repair within the primary lesion alone.

Acute cytokine release induces transient conduction block, probably caused by damage from nitric oxide. With intact myelination and preserved axons, the recovery mechanism involves removal of inflammatory mediators and reversal of the functional deficit. More prolonged exposure impairs both structure and function, leading to persistent demyelination and axonal damage. Recovery can occur through three mechanisms: remyelination, development of continuous conduction through sodium channels that develop along the demyelinated segment, and cortical plasticity. Substantial axonal loss could occur and result in permanent loss of structure and function. Axon loss might be acute, caused by the effects of inflammation, or

Figure 1: T2-weighted MRI of a patient with a CIS
The square shows short echo-time proton spectra from a voxel of white matter (left). Spectrum from the white-matter of a patient with a CIS (middle) and a healthy person (right). The peak in myoinositol is larger in the patient than in the control. Reproduced with permission from Oxford University Press.

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chronic, caused by persistent inflammation or lack of trophic support from myelin.

In patients with optic neuritis, recovery is related to MRI findings for both the location and extent of abnormality. Long lesions located in the optic canal have been associated with poor visual recovery. In 101 of 107 patients with acute optic neuritis, assessment with gadolinium enhanced fat-suppression MRI found that the affected optic nerve was enhanced but none of the unaffected nerves were enhanced. MRI with gadolinium therefore seems to be sensitive in the detection of acute optic neuritis. Although lesions in the canal or over longer segments of the optic nerve were predictive of poor vision at onset, they were not predictive of recovery. Pain was common when optic neuritis involved the orbital segment of the optic nerve.

Changes in magnetisation-transfer ratio over 1 year were assessed with magnetisation-transfer MRI in 29 patients with acute optic neuritis and in healthy people. Whereas magnetisation-transfer ratios of the unaffected optic nerve and of the optic nerves of healthy controls were stable during follow-up, the diseased optic nerve magnetisation-transfer ratio decreased over time and was lowest at about 240 days. The magnetisation-transfer ratio of the diseased optic nerve seems to increase after reaching the lowest point, although not significantly. Time-averaged magnetisation-transfer ratios and mean visual-evoked-potential latency were related, suggesting that magnetisation-transfer ratio is a measure of the structural integrity of the optic nerve and, possibly, the extent of myelination. A decrease in optic-nerve magnetisation-transfer ratio early in the disease process is consistent with demyelination and Wallerian degeneration, whereas occurrence of the lowest magnetisation-transfer ratio late in the disease process might be caused by slow clearance of myelin debris; a subsequent rise in magnetisation-transfer ratio could be due to remyelination.

Tissue volume of optic nerves changes for up to 1 year after the onset of optic neuritis. At first, nerves swell; the cross-sectional area of the nerve increases by a median of 20%. Consistent with acute inflammation, swelling resolves over several months. Atrophy then starts, with a mean decrease of 12% in nerve area after 1 year. The mean loss of nerve tissue after a single attack of optic neuritis is small, which suggests that only a few optic nerve axons are lost. Thus, patients’ generally good visual outcome is not surprising.

Cortical adaptation and insights from functional MRI

One of the factors that might contribute to visual recovery after acute optic neuritis is cortical adaptation. Study of 12 patients with acute monosymptomatic optic neuritis found a low functional MRI (fMRI) response, reflecting low input during acute visual loss. However, 5 weeks after onset of optic neuritis, there was a significant increase in the volume of activation and in blood-oxygenation level dependent signal in response to binocular stimulation. Monocular stimulation of the affected eye resulted in cortical activated volumes and BOLD signal increases that were consistent with the results of visual testing. These findings suggest that transient adaptive changes happen in the visual cortex during recovery.

Comparison of 20 patients who had acute unilateral optic neuritis with 46 healthy people over 1 year by use of fMRI found differences over time in the patients’ visual cortex and extraoccipital regions—including the lateral temporal cortex, insula, corpus striatum, orbitofrontal cortex, and inferior parietal region—when either the affected or unaffected eyes were used. These differences were most prominent soon after clinical onset and subsided after a few months. Markers of optic-nerve structure (cross-sectional area and gadolinium enhancement), clinical function, and the fMRI response for both the affected and the unaffected eyes were associated, particularly at baseline. Visual function at baseline was inversely related to optic-nerve damage and directly related to the extent of response on fMRI. At baseline and 1 month later, low fMRI responses (for both affected and unaffected eyes) were associated with substantial optic-nerve damage, whereas at 3 months, baseline optic-nerve damage was associated with the amount of fMRI activity outside the visual cortex. Two studies suggest there are prominent dynamic spatiotemporal functional cortical changes after acute optic neuritis, which might have an adaptive function during early recovery.

fMRI has also been used to assess functional cortical changes associated with motor tasks in patients with a CIS. When patients do a simple motor task with the dominant hand, cortical activations in the “classic” motor areas differ, suggesting that cortical reorganisation might occur early in MS. The extent of these cortical activations is strongly associated with the concentration of N-acetylaspartate in brain tissue. In patients with a CIS, there is pronounced use of the contralateral primary sensorimotor cortex when the same motor task was done with the non-dominant hand. The findings are similar when these patients do the task with the dominant foot and there is an anterior shift of the centre of activation. During a complex motor task involving the dominant hand and foot, patients with a CIS have an increased recruitment of a widespread network (including the frontal lobe, the insula, and the thalamus), thought to commonly function in motor, sensory, and multimodal integration processing. The effect of isolated spinal-cord disease on cortical activation has been assessed through study of a group of patients with a previous episode of acute myelitis. Increased activation of several cortical regions of the “classic” motor network was found, and the activity of some of these areas was related to the severity of spinal-cord damage.
In a 1 year follow-up study of patients with a CIS, those who developed clinically definite MS had a different fMRI response on motor tasks at first presentation than those who did not (figure 2). By comparison with those who did not develop MS, those who did had substantial bilateral activations of the superior frontal sulcus, the superior frontal gyrus, the infraparietal sulcus, and the putamen; in addition, they had high activation of the ipsilateral middle frontal gyrus, superior temporal gyrus, cuneus, and contralateral fusiform gyrus. Those who did not develop MS had more substantial activations than those who did develop MS in the contralateral primary somatomotor cortex and supplementary motor area, the ipsilateral paracentral lobule, and the cerebellar hemisphere. These results suggest that activation of the regions normally involved in a task seems to be a favourable prognostic factor, whereas a widespread recruitment of additional areas seems to be associated with short-term disease activity.

Overall, fMRI studies of patients with a CIS suggest that cortical reorganisation occurs and has the potential to improve long-term patient outcomes, even at this early stage of the disease process.

Management

Acceleration of recovery from the CIS

Many patients with a mild CIS will recover spontaneously without the need for specific treatment. Corticosteroids are used when the symptoms are functionally disabling or when the patient is not improving spontaneously. The CIS that has been most carefully studied in randomised-controlled trials is optic neuritis. The Optic Neuritis Treatment Trial (ONTT) showed that treatment with a 3 day course of intravenous methylprednisolone and then 11 days of oral prednisone was associated with a more rapid recovery of vision compared with placebo. After 1 year, vision was not different between the group given an active treatment and that given a placebo. A 2 week course of oral prednisolone alone did not accelerate recovery compared with placebo, but was associated with an increased probability of having recurrent episodes of optic neuritis.

The Quality Standards Subcommittee of the American Academy of Neurology concluded: “Higher dose oral or parenteral methylprednisolone or ACTH [adrenocorticotrophic hormone] may hasten the speed and degree of recovery of visual function in persons with acute monosymptomatic optic neuritis. There is, however, no evidence of long-term benefit for visual function. The decision to use these medications to speed recovery but not to improve ultimate visual outcome should therefore be based on other non-evidence-based factors such as quality of life, risk to the patient, visual function in the unaffected eye, or other factors that the clinician deems appropriate.”

Plasma exchange has been assessed in a small trial that included a “sham-exchange” control in patients with a severe neurological deficit due to an episode of CNS inflammation that did not improve after conventional treatment with intravenous methylprednisolone. Eight (42%) of 19 patients in the treatment arm improved compared with one (6%) of 17 patients in the control arm. Improvement was most likely if plasma exchange was given within 2 weeks of presentation with a severe neurological deficit. This finding was supported by the results of subsequent use of plasma exchange in a non-trial setting; about half of the patients substantially improved in the days and weeks after treatment. Plasma exchange is likely to be beneficial only when the patient acquires a severe neurological deficit from a single acute inflammatory CNS lesion, not if many lesions cause the deficit to accumulate in small steps. Response to plasma exchange might reflect an antibody-mediated pathogenesis of the underlying disease, and this is supported by IgG and complement deposition in the lesions of responsive patients.

A recent double-blind, placebo-controlled trial of intravenous immunoglobulin in 68 patients with acute optic neuritis showed no effect of treatment on vision during 6 months of follow-up.

Treatments to delay the development of MS

Although the ONTT did not aim to assess whether treatment delayed conversion to MS, patients treated with intravenous methylprednisolone and oral

![Figure 2: Pattern of cortical activations during a simple motor task](http://neurology.thelancet.com)
prednisone had a lower risk of developing clinically definite MS over the next 2 years than patients given a placebo (9% vs 17%). However, after the third year of follow-up the treatment and placebo groups’ risks of conversion to clinically definite MS did not differ.7

Two randomised, double-blind, placebo-controlled trials of interferon beta-1a in patients with a CIS and an abnormal MRI brain scan found an association between treatment with interferon beta-1a and a delay in the development of clinically definite MS.46,47

Subgroup analysis in the ETOMS trial found that conversion to clinically definite MS was more common as the number of Barkhof MRI criteria met increased, and treatment was more likely to delay conversion to MS in those who fulfilled many of the MRI criteria. Thus, in patients who met one or two Barkhof criteria at presentation, clinically definite MS developed in five (23%) of 22 who took placebo and in four (21%) of 19 who took interferon beta-1a; in those who met three or four criteria, these figures were 64 (49%) of 132 for placebo and 48 (35%) of 135 for interferon beta-1a.48 In the Controlled High Risk Subjects Avonex MS Prevention Study (CHAMPS), development of clinically definite MS was more common in patients with gadolinium enhancing lesions at presentation; the treatment effect was also larger in this patient subgroup. Follow-up in the ETOMS trial and CHAMPS was not long enough to assess whether treatment delayed the development of irreversible disability. Nevertheless, in the ETOMS study, a low, weekly dose of interferon beta-1a reduced the brain tissue lost in 2 years by about 30%.7

Findings from longer follow-up (over 5 years) of some of the patients in the CHAMPS study suggest that the disease course was improved in those who received immediate treatment with interferon beta-1a.50 However, about 30% of patients were lost to follow-up.

More frequent treatment with interferon beta-1b (8 mU on alternate days) is now being trialled in patients with a CIS; the primary endpoint of this study, like that of earlier CIS trials, is clinically definite MS. In addition, patients are being recruited for an extension study designed to compare immediate and delayed interferon-beta treatment and also to investigate the development of disability.

A trial of glatiramer acetate is also in progress in patients with CISs. Intravenous immunoglobulin has been studied in a placebo-controlled trial in 91 patients presenting with a first episode of suspected demyelination; after 1 year of active treatment patients were less likely to develop clinically definite MS; however, the short follow-up and small size of this study limit the interpretation.51

Diagnosis and treatment of individual patients
The questions coming from group studies of diagnosis, natural history, and treatment trials are how, and when, these studies’ findings should affect the management of the individual patient. Three issues are generally relevant: the existing chance of conversion to clinically definite MS or development of disability, the usefulness of the diagnostic test, and the effectiveness of treatment. Evidence is accumulating that treatment may delay the onset of clinically definite MS, although data about the effect on disability are lacking. One study suggests early treatment might decrease cerebral atrophy,5 which is notable because cerebral atrophy could signify disability.54 Most clinicians who see patients with a CIS or suspected early MS would now agree that it is important to diagnose early, and having done so, to weigh-up the potential benefits, risks, and uncertainties of disease modifying treatment, while ensuring the patient is fully informed and participates in the decision-making process.

When to diagnose MS
A single contrast-enhanced scan from a patient who presents with a CIS could be sufficient to diagnose MS, some have argued, because the presence of both enhancing and non-enhancing lesions strongly suggests simultaneous dissemination in space and time.55 However, MRI criteria from the scan at presentation have been only modestly reliable in the prediction of clinically definite MS,56,57 and monophasic acute disseminated encephalomyelitis—an important, although less common, clinical and radiological differential diagnosis in this setting—can not be excluded. An alternative strategy is to require follow-up MRI scans to show dissemination in time by the development of new, subclinical lesions at least 3 months after the CIS presents, as recommended by the McDonald criteria,1 especially if a new T2 lesion is included at any time after 3 months of follow-up.58 This approach is not likely to delay diagnosis for long—with these criteria about 50% of patients with a CIS are diagnosed as having MS within 1 year. Use of MRI to assess dissemination in space and time—which we favour (panel 1)—will also reduce diagnostic and treatment errors from undue hastiness, and this approach is supported by prospective group studies that show a high specificity for clinically definite MS.56,57

A more conservative approach to diagnosis would be to require the traditional criteria for clinical dissemination in space and time. Delaying the diagnosis might further reduce the risk of false-positive diagnosis—eg, in patients with recurrent cerebrovascular insults mistaken for demyelination. However, there are disadvantages to a conservative approach: patients who clearly have MS are denied the diagnosis; and delayed diagnosis increases the risk of cerebral atrophy and disability, particularly in high-risk patients (eg, with a CIS that is severe clinically and has many cerebral lesions on MRI) in whom the treatment benefit may be greater in the short term.59

An early MRI-assisted diagnosis might confront patients with the implications of a serious, chronic disease, and although these patients might not have been
When to start disease-modifying treatments

Although there is strong evidence that patients with a CIS and an abnormal MRI are likely to develop clinically definite MS, and that interferon beta delays the development of clinically definite disease, the long-term effect of the treatment is unknown. Many patients with a CIS and MRI lesions develop MS but have a benign course, with little or no disability for the next 10–14 years.62,63 Moreover, not all of these patients will relapse further. In the ONTT, 44% had not developed clinically definite MS after 10 years.56 Interferon-beta treatment of all patients with a CIS who have an abnormal scan would include many patients who would have had a good prognosis without treatment. Old10–13 and more recent17 natural history studies have shown that many patients experience a benign, long-term course of MS, especially if they are free of disability 5 years after onset of CIS. Together these findings suggest that an initial approach of wait-and-see for the use of disease-modifying treatment will serve the best interests of patients with CIS in whom the clinical episode was mild and reversible, even if accompanied by an abnormal scan. However, the best follow-up of such patients is unknown. For example, should these patients have repeat MRI studies, and if these show new lesions, should disease-modifying treatment be offered? Prospective follow-up studies are needed to address these issues.

Whether treatment after a first attack has any greater effect than delaying treatment until a second episode has occurred is unknown. The traditional criterion for treatment in many countries is a second episode. MRI lesion load at presentation52–54 and the increase in lesion load over the next 5 years55 is associated with future disability. Because interferon beta reduces the accumulation of new MRI lesions, the potential for benefit may be greater if the drug is given earlier.

A balance between treating all patients with a CIS and an abnormal MRI or none of these patients seems sensible. Treatment could be offered to those patients who have had a clinical episode of moderate or substantial severity—particularly if multifocal or associated with poor recovery—and are diagnosed with MS on the basis of early MRI dissemination in space and time, noting that such patients have a high risk of relapse.56–58 We find this approach to be satisfactory (panel 2); it seems acceptable to begin treatment after MS is diagnosed.

Summary and future research

Important progress has been made in the study of CISs. The relation between CIS and MS has been elucidated and diagnostic advances now provide a reliable prediction, soon after presentation, of the risk of MS. The mechanisms of acute dysfunction, subsequent recovery, and persistent deficit from the CIS are better understood. In addition to multifocal white-matter lesions, abnormalities are present in the normal-appearing white and grey matter, and progressive brain atrophy—suggesting neuroaxonal loss—develops early in those who develop MS. Tools for treatment monitoring—both clinical and paraclinical—provide a more efficient and comprehensive assessment of therapies that target inflammation, axonal protection, and remyelination than was possible 10 years ago.

The potential for a better understanding of pathogenetic mechanisms and effective disease-modifying treatments

Panel 1: Merits of MRI assessment of dissemination in space and time for diagnosis of MS in patients with a CIS

| Facilitates open discussion of potential for MS and appropriate assessment with MRI to clarify prognosis (abnormal MRI=high risk; normal MRI=low risk) or to make the diagnosis | Early MRI-assisted diagnosis with existing criteria is highly specific for clinically definite MS | Making the diagnosis of MS can reduce the patient’s anxiety about the unknown diagnosis and facilitate support from MS nurses | Opportunity to introduce an education programme at an early stage so that patients can think about the implications of diagnosis and participate in establishing a management plan that incorporates decisions on lifestyle, work, and family | Opportunity for patient and physician to discuss use of MS disease-modifying treatment before more CNS tissue damage occurs |

Panel 2: Reasons for and against the use of disease-modifying treatments in patients with a CIS

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<tr>
<td>Clinically severe CIS with persistent disability</td>
<td>Clinically mild CIS with recovery</td>
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<td>MRI criteria for MS fulfilled (dissemination in space and time)</td>
<td>Normal MRI or few lesions</td>
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<td>Delay time to next relapse</td>
<td>Not known if disability is prevented in the long term</td>
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<td>Early treatment offers better chance of long-term benefit</td>
<td>Early treatment will include patients who would otherwise have had a benign long-term course</td>
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are compelling reasons for continuing to assess patients with a CIS. Diagnostic criteria will likely evolve as new data emerges from imaging and CSF research studies; other plausible biomarkers should also be assessed for their diagnostic use. Prediction of disability and the long-term course of MS are limited: combinations of conventional and non-conventional imaging and other biomarker measures may be informative and long-term prospective studies will be needed to establish convincing association between laboratory and clinical findings. A better understanding of early pathogenetic mechanisms would come with access to pathological tissue from patients with a CIS, but because this is rarely available, greater reliance will inevitably be placed on in vivo surrogate measures. New measures should be sought and verified as a high priority for their cellular, pathological, and immunological specificity.

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References


