Multiple Sclerosis
Counseling Points™
Enhancing Patient Communication for the MS Nurse

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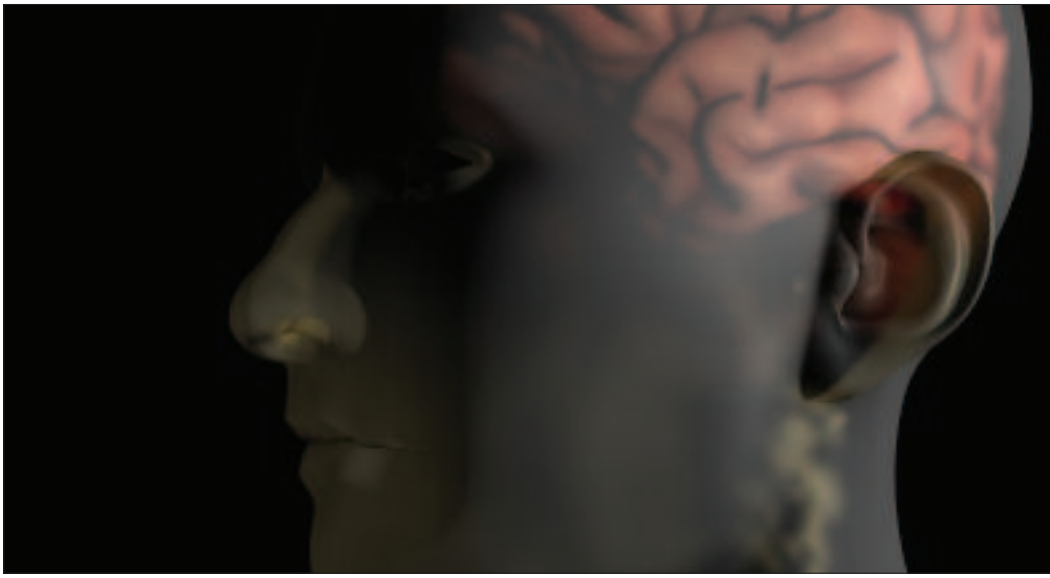
Clinically Isolated Syndrome—Precursor to Multiple Sclerosis

A Roundtable Discussion

The term clinically isolated syndrome (CIS) is often used to describe a central nervous system (CNS) event that may or may not be a precursor to multiple sclerosis (MS). A CIS encompasses a constellation of signs and symptoms that is potentially the result of demyelination in the CNS. Clinicians and patients alike sometimes have trouble understanding the concept of a CIS. And, of course, once a CIS is identified, the question remains: Will this CIS be the precursor to MS in this individual? Hopefully, this issue of *MS Counseling Points™* will clarify some of the questions and concerns surrounding CIS.



Defining a CIS

Experts have struggled for years to come up with a satisfactory definition of a CIS. Fortunately, in 2007, the National Multiple Sclerosis Society (NMSS) organized a group of adult and pediatric neurologists and other specialists to develop consensus definitions of various inflammatory demyelinating disorders of the CNS.[1] This group defined a CIS as a "first acute clinical episode of CNS symptoms with a presumed inflammatory demyelinating cause for which there is no prior history of a

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Welcome to MS Counseling Points™

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Dear Colleague,

You have probably heard the term "clinically isolated syndrome" or CIS used in reference to multiple sclerosis (MS). CIS is the first neurologic episode that is caused by inflammation and/or demyelination within the central nervous system. Much attention is now paid to CIS for two reasons. First, CIS can be a precursor to MS. Second, there is evidence that disease-modifying treatments used in MS can be effective in the treatment of CIS due to their ability to delay the next neurological event that may herald the onset of MS.

What is the presentation of a CIS? Can we predict whether or not individual patients with a CIS will go on to develop MS? Should we treat all patients who have an isolated event? These are some of the questions we'll be looking at in this issue of *MS Counseling Points™.* In addition, we'll address the best way in which to raise the possibility with patients that the event they are experiencing might foreshadow the development of MS. As always, our role as nurses is to foster open communication with our patients and nurture hope, even in the face of a potential diagnosis of MS.

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Continued from cover

demyelinating event. This clinical event may be either monofocal or multifocal, but usually does not include encephalopathy (except in cases of brainstem syndromes)."[1]

A CIS is defined as a "first acute clinical episode of CNS symptoms with a presumed inflammatory demyelinating cause for which there is no prior history of a demyelinating event."

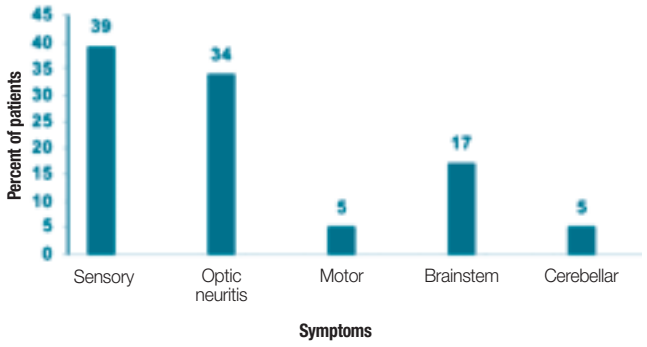

Figure 1. Presenting features of 103 patients with CIS suggestive of MS.[3]

Monofocal events refer to episodes in which the symptoms can be attributed to a single CNS site, whereas multifocal events are attributable to more than one site in the CNS.[1] Some investigators restrict use of the term CIS only to describe patients who have a single clinical phenotype, referable to a single CNS lesion—i.e., they do not consider multifocal events to be a CIS. Generally, it is also felt that an event should last at least 24 hours to be categorized as a CIS.

CIS Presentation

In general, patients can present with a single symptom or a combination of symptoms, including sensory and/or motor symptoms, ocular dysfunction, and autonomic dysfunction. Some neurological exam findings that may be associated with a CIS are:

- spasticity, which is usually more marked in the legs than in the arms;
- exaggerated deep tendon reflexes, as well as extensor plantar responses;
- dysmetria, decomposition of complex movements, hypotonia, or an intention tremor;
- ocular findings of visual loss, nystagmus, ocular dysmetria, and failure of fixation suppression (square wave jerks), which suggest cerebellar or cerebello-vestibular connection dysfunction;
- speech that is scanning or explosive in character;
- sensory loss or change; and
- motor weakness.[2]

Examples of a discrete CIS include, but are not limited to, optic neuritis, transverse myelitis, and brainstem syndrome.[1] A study by Berger and colleagues sheds light on the percentage of patients with a CIS suggestive of MS who present with various features **(Figure 1)**.[3]

Patients can present with a single symptom or a combination of symptoms, including sensory and/or motor symptoms, ocular dysfunction, and autonomic dysfunction.

Optic Neuritis

Optic neuritis refers to inflammation of the optic nerve.[4] It is not clear if demyelination is the primary cause of this inflammation or if the inflammatory response itself causes destruction of myelin.

Patients generally present with the classic triad of loss of vision, ocular pain, and dyschromatopsia (impaired color vision).[4] In adults, 70% of cases are unilateral. Optic neuritis is characterized by retrobulbar pain on movement of the eye or light palpation of the eye through a closed eyelid and worsening visual acuity. The pain often resolves over a period of days, while the visual dysfunction can evolve over days to weeks. Visual recovery typically begins within 2 to 3 weeks of onset and stabilizes over months.[4]

Optic neuritis has a strong association with MS, with 15% to 20% of clinically definite MS cases manifesting in this way. Between 38% and 50% of patients with clinically definite MS develop optic neuritis at some time during the course of their disease.[4] In addition, as we will see shortly, optic neuritis is a common precursor to MS.

Transverse Myelitis

Transverse myelitis is a focal inflammatory disorder of the spinal cord that results in motor, sensory, and autonomic dysfunction due to inflammation of a segment of the spinal cord.[5] Autonomic dysfunction may consist of increased urinary urgency, bowel or bladder incontinence, difficulty or inability to void, incomplete evacuation, or constipation.[5]

Symptoms of transverse myelitis vary, and approximately 50% of patients will have lower-extremity plegia while nearly all experience bladder dysfunction. Eighty percent to 94% experience numbness, paresthesia, or band-like dysthesias.[5] Around 33% of patients recover with little to no long-term deficits; another 33% are left with a moderate degree of permanent disability, while the remainder have severe disabilities.[5]

Transverse myelitis is a focal inflammatory event of the spinal cord that results in motor, sensory, and/or autonomic dysfunction.

Some patients with MS may initially present with transverse myelitis. Those who are eventually diagnosed with clinically definite MS are more likely to have asymmetric clinical findings and predominant sensory symptoms with relative sparing of motor systems.[5]

Brainstem Syndrome

The classical brainstem syndrome is the lateral medullary syndrome. It is typically characterized by ipsilateral impairment of facial pain and temperature sensation, Horner syndrome (a combination of ocular ptosis, miosis, and anhidrosis), dysarthria, and dysphagia. Vertigo is a major complaint.[6]

A study performed in the 1980s suggests that over 50% of patients who present with a brainstem syndrome go on to develop MS.[7]

CIS Diagnosis

Diagnosis of a CIS can be challenging and confusing. However, presentation with symptoms and signs referable to the CNS, without previous history of symptoms and without another cause for the symptoms, makes it reasonable to conclude that the individual is experiencing a CIS. Based upon clinical symptoms alone, it is not possible to definitively predict if the individual with CIS will develop MS. However, a magnetic resonance imaging (MRI) scan obtained at the time of the CIS that is highly suggestive of MS with multiple lesions increases the risk that the individual will develop MS. On the other hand, an individual with CIS and a negative MRI is at low risk of developing MS.

Brainstem syndrome is typically characterized by ipsilateral impairment of facial pain and temperature sensation, Horner syndrome, dysarthria, and dysphagia.

Diagnosis of a CIS is primarily based on clinical findings. It is important to exclude other conditions that may mimic a CIS. These are generally the same disorders that form the differential diagnosis of MS **(Table 1)**.[8-10] Tests often used to diagnose MS, such as visual evoked potentials, MRI, and cerebrospinal fluid (CSF) analysis, can be useful in confirming that the patient is experiencing a demyelinating event.

The major feature that separates a CIS from clinically definite MS is the fact that to confirm a diagnosis of MS, patients must experience demyelinating events disseminated in space and time.[11] The most widely adhered to guidelines for the diagnosis of MS are the McDonald criteria, which we've discussed in detail in previous issues. In brief, these criteria attempt to formalize a way to incorporate clinical symptoms,

Table 1. Differential Diagnosis of CIS[8-10]

- Inflammatory/immune diseases (e.g., systemic lupus erythematosus, Sjögren's syndrome, vasculitis, sarcoidosis)
- Infections (e.g., Lyme disease, progressive multifocal leukoencephalopathy, herpes zoster)
- Genetic disorders (e.g., metachromatic leukodystrophy, inborn errors of metabolism)
- Metabolic disorders (e.g., vitamin B12 deficiency)
- Neoplasms (e.g., lymphoma, glioma, meningioma)
- Structural disease (e.g., degenerative or vascular malformations)
- Other (e.g., age-related white matter changes, ischemic optic neuropathy)

imaging, and tests into the diagnosis of MS. Adjunctive tests and imaging, namely CSF analysis, evoked potentials, and MRI, fulfil the requirement for dissemination in space and time.[11]

The major feature that separates a CIS from clinically definite MS is the fact that to confirm a diagnosis of MS, patients must experience demyelinating events disseminated in space and time.

Thus, for a diagnosis of MS to be made, clinicians must find evidence of damage in at least two separate areas of the CNS and evidence that the damage occurred at least a month apart, as well as rule out other possible causes.[12] A patient with a CIS may fulfil the space criteria if they have a multifocal event. However, by definition, they cannot fulfil the time criteria.

CIS Prognosis

The most crucial question preying on the mind of any patient who has experienced a CIS is "Will I end up getting MS?" Over the last 20 years, a number of trials have addressed this question. One of the most important of these is the Optic Neuritis Treatment Trial, which between 1988 and 1991 enrolled patients with acute optic neuritis and followed them prospectively for 15 years.[13] Investigators in this study found that by 15 years after onset of optic neuritis, the cumulative probability of developing MS was 50%. The development of MS was strongly related to the presence of lesions on baseline non-contrast-enhanced brain MRI. Seventy-two percent of patients with 1 or more lesions at baseline developed MS during follow-up, compared with only 25% of patients with no lesions at baseline.[13] At 10 years, the risk for the latter group was very low, but was substantial for those with lesions. Baseline factors associated with a lower risk of developing MS in the absence of MRI-detected lesions included being male, optic disc swelling, and atypical features of optic neuritis.[13]

A longitudinal MRI study confirms the findings from the Optic Neuritis Treatment Trial. Brex and co-authors investigated the relationship between early lesion volume, changes in volume, and long-term disability among 71 patients with a CIS.[14] Follow-up was performed an average of 14 years after the CIS. Of the 50 patients with abnormal MRIs at initial presentation, 88% developed clinically definite MS compared with 19% of patients with initially normal MRIs. The mean Expanded Disability Status Scale (EDSS) score among those with MS was 3.25, while 31% had an EDSS score of 6.0 or greater. The authors concluded that there is a moderate correlation between increases in MRI lesion volume in the first 5 years after a CIS and the degree of long-term MS disability.

In a 10-year follow-up study of 81 patients with a CIS, O'Riordan and colleagues reported that 83% of patients with an abnormal MRI at baseline progressed to clinically definite MS.[15] Of these, 20% had relapsing-remitting MS (RRMS), 24% had secondary-progressive disease, and 39% had what, in those days, was termed benign RRMS (EDSS <3). These authors found a significant relationship between the number of lesions at presentation and EDSS score ($P<0.001$), and the type of disease course at follow-up ($P<0.0001$).

Given these data, according to the NMSS, when a patient with a CIS has MRI-detected brain lesions similar to those seen in MS, that patient has a high risk of a second neurological event and therefore a diagnosis of clinically definite MS within several years.[12]

[Evidence from the Optic Neuritis Treatment Trial indicated that] by 15 years after onset of optic neuritis, the cumulative probability of developing MS was 50%.

CIS Treatment

Immediate treatment of a CIS is similar to that of treatment for a MS exacerbation. Patients are often given intravenous glucocorticoids, which may or may not be followed by a regimen of oral steroids tapered over several days or weeks to reduce inflammation and speed recovery.

It is critical to attempt to identify patients who are at high risk of developing MS because, with the advent of disease-modifying therapies (DMTs), we can offer them treatment. Four major clinical trials have studied whether treating patients with a CIS delays the progression to MS. On the whole, the results of these trials were very positive.

The first major trial to look at this issue was CHAMPS (Controlled High-Risk Subjects Avonex® MS Prevention Study).[16] This study looked at whether interferon β (IFNβ)-1a via intramus-

cular injection (Avonex®) early after an initial demyelinating event could delay a second episode (which would signal clinically definite MS). It also examined if treatment would have an impact on MRI-detected brain lesions. Patients who had a CIS and multiple clinically silent MRI lesions, which put them at high risk of going on to develop MS, were eligible to participate in the trial. Compared with placebo, IFNβ-1a significantly delayed the onset of clinically definite MS (P=0.002). After 3 years, 35% of patients in the interferon group and 50% of patients in the placebo group had had a second attack. Patients on IFNβ-1a also had a significantly smaller increase in the volume of brain lesions, as well as fewer new lesions. Based on the results of CHAMPS, in addition to being approved for slowing the accumulation of physical disability and decreasing the frequency of clinical exacerbations, labeling of IFNβ-1a via intramuscular injection now includes patients who experience a first clinical episode and have MRI-detected brain lesions consistent with MS. Five-year results from CHAMPIONS, an extension of the original CHAMPS trial, show the development of clinically definite MS remains significantly reduced 5 years after a first CIS in patients treated within 1 month of symptom onset.[17]

The ETOMS (Early Treatment of MS) study was designed to determine whether low-dose IFNβ-1a via subcutaneous injection (Rebif®) would delay the onset of clinically definite MS in people who had experienced one clinical event and had multiple MRI-detected lesions consistent with MS.[18] After 2 years, 34% of IFNβ-1a patients and 45% of placebo patients had converted to clinically definite MS (P=0.047). The time to first relapse was significantly shorter in interferon-treated patients (569 days versus 262 days in the placebo group; P=0.023). Compared with placebo, significantly fewer patients in the IFNβ-1a group had MRI activity (16% versus 8%, respectively; P=0.005). It should be noted that the dose of IFNβ-1a via subcutaneous injection used in this trial was one-sixth of the dose that the Food and Drug Administration (FDA) has approved for the treatment of RRMS.

The BENEFIT (Betaseron® in Newly Emerging MS For Initial Treatment) study examined whether or not IFNβ-1b (Betaseron®) delays the onset of clinically definite MS in patients with a CIS who are at high risk for developing MS.[19] During the 2 years of the trial, the probability of progressing to clinically definite MS among interferon-treated patients was 28% compared with 45% in the placebo group (P<0.00001). IFNβ-1b also significantly delayed the time to onset of MS (618 days versus 255 days for placebo; P<0.0001). The cumulative number of newly active MRI lesions, new T2, gadolinium-enhanced lesions, and volume of gadolinium-enhanced lesions were significantly lower in the active treatment group (P<0.0001). IFNβ-1b is now approved to treat patients who have had a first clinical event and have MRI features consistent with MS.

The results of DMT studies are extremely encouraging.

The PreCISe (Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis in Subjects PREsenting with a Clinically Isolated SyndromE) study evaluated whether early treatment with glatiramer acetate (Copaxone®) delays the progression to clinically definite MS in patients with a CIS. An interim analysis of data based on approximately 80% of the 3-year study exposure was presented at the 60th Annual American Academy of Neurology Meeting in Chicago in April 2008.[20] Treatment with glatiramer acetate significantly reduced the risk of developing clinically definite MS by 45% compared with placebo. The proportion of patients who converted to clinically definite MS decreased from 43% in the placebo group to 25% in the active treatment group (P<.0001). In addition, the time to progression to MS was 722 days among glatiramer acetate-treated patients versus 336 days in the placebo group (P=0.0005). MRI activity, including the number of enhancing lesions and the number of new T2 lesions, was significantly lower in the glatiramer acetate group. When the results of this interim analysis were reviewed by the study's data safety monitoring board, the group recommended stopping the double-blind phase of the trial and enrolling all patients in the active treatment group.

The results of these studies are extremely encouraging and underline the importance of recognizing patients with a CIS who are at high risk for developing MS, and treating them early with a DMT.

Counseling Your Patients

Although many MS pundits would recommend treatment for patients with a CIS at high risk to develop MS, this is not a universal recommendation. It is important for clinicians to present the known facts about CIS to the patient and family

members. The discussion should include the risk, whether high or low, for future development of MS. In addition, the results of the clinical trials with DMTs in CIS should be thoroughly discussed so the patient can make an informed decision regarding the initiation of treatment.

Obviously, when we raise the issue that MS may follow a CIS, we need to do so carefully and frame the discussion with hope. Although there is a certain degree of risk for developing MS when someone presents with a CIS, there are effective treatments that have been shown in well-designed clinical trials to delay the onset of a second neurological event, and thus delay MS and modify disability.

The NMSS recommends that CIS patients at high risk for MS as suggested by MRI findings should be offered a DMT. Many MS clinicians recommend close follow-up for CIS patients that includes regular neurological exams as well as MRI follow-up. In fact, it is often recommended that all patients who have had a CIS should be evaluated at least every 6 months, if not more often, and the MRI repeated yearly or, if new symptoms occur, at that time, irrespective of whether they are being treated or not. Unfortunately, many patients who have experienced a single episode deny the potential for developing MS and believe they'll never have another attack. These people are frequently lost to follow-up and only reappear if other symptoms occur.

Conclusion

A CIS is defined as an inflammatory demyelinating event of the CNS that lasts at least 24 hours and can be accompanied by a constellation of neurological signs and symptoms. The most important thing to remember is that these episodes can be a precursor to the development of MS, particularly if MRI findings are consistent with MS. The good news is that there is now a wealth of evidence that early recognition and treatment of a CIS can significantly delay the onset of MS.

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MS Counseling Points™

Clinically Isolated Syndrome—Precursor to Multiple Sclerosis

- A clinically isolated syndrome (CIS) is a first acute clinical episode of central nervous system (CNS) symptoms lasting at least 24 hours with a presumed inflammatory demyelinating cause for which there is no prior history of a demyelinating event.
- Monofocal events refer to those where the symptoms can be attributed to a single CNS site, while multifocal events are attributable to more than one site in the CNS.
- In general, patients can present with a single symptom or a combination of symptoms, including sensory and/or motor symptoms, ocular dysfunction, and autonomic dysfunction.
- Examples of discrete clinically isolated events include, but are not limited to, optic neuritis, transverse myelitis, and brainstem, cerebellar, and/or hemispheric dysfunction.
- Diagnosis is based on clinical findings.
- Other possible causes such as infections or other autoimmune diseases should be excluded.
- The major feature that separates a CIS from multiple sclerosis (MS) is the fact that to confirm a diagnosis of MS, patients must experience demyelinating events disseminated in space and time.
- When a patient with a CIS has magnetic resonance imaging (MRI)-detected brain lesions similar to those seen in MS, that patient has a high risk of experiencing a second neurological event, and therefore receiving a diagnosis of clinically definite MS within several years.
- Acute treatment of a CIS involves intravenous glucocorticoids, which may or may not be followed by an oral taper.
- It is critical to identify patients with a CIS at high risk of developing MS because they can be treated with disease-modifying therapies (DMTs) to delay the onset of MS.
- Patients at risk should be informed of their chances of developing MS and offered DMTs.

In the Literature

The real-life impact of early versus delayed treatment

At the 60th annual Academy of Neurology meeting held in Chicago in April 2008, Italian researchers presented findings on the effect of early versus delayed treatment with interferonβ (IFNβ) on disability in patients with relapsing-remitting multiple sclerosis (RRMS). A group of 625 patients who had commenced treatment within 2 years of disease onset was compared with a group of 1,655 who had not started treatment until later. The researchers found that, compared with delayed treatment, early treatment significantly reduced the risk of patients reaching an Expanded Disability Status Scale (EDSS) score of 4.0 (P=0.017) and tended to reduce the risk of reaching a score of 6.0 (P=0.08). The authors concluded that patients with mild disability and high disease activity benefited the most from early intervention.

Patients with mild disability and high disease activity benefited the most from early intervention.

Trojano M, Amato MP, Avolio C, et al. The real life impact of early versus delayed treatment of interferon beta on long-term disability progression in relapsing-remitting multiple sclerosis. Presented at 60th Annual Meeting of the American Academy of Neurology, Chicago, IL, April 12-19, 2008. P02.152.

A classic study from 2003: Revised McDonald diagnostic criteria identify more patients who convert to MS

Tintoré and colleagues examined the utility of the revised McDonald diagnostic criteria in patients with a clinically isolated syndrome (CIS) suggestive of MS. They followed 139 patients with a CIS for a median of 3 years. These patients had brain magnetic resonance imaging (MRI) scans within 3 months of their first event and another 12 months later. After 12 months, the researchers compared the number of patients who had clinically definite MS according to the McDonald criteria with the number according to the older Poser criteria. Poser criteria suggested that only 11% of patients had developed MS by 1 year compared with 37% using the McDonald criteria. These revised criteria had a sensitivity of 74%, a specificity of 86%, and accuracy of 80% in predicting conversion to MS. The major difference between the two sets of criteria is that the McDonald criteria incorporate MRI results.

Tintoré M, Rovira A, Río J, et al. New diagnostic criteria for multiple sclerosis: Application in first demyelinating episode. *Neurology*. 2003;60:27-30.

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MS Counseling Points™

Clinically Isolated Syndrome—Precursor to Multiple Sclerosis

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Value of the *Counseling Points™* summary (page 8)? ⑤ ④ ③ ② ①

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❑ Yes ❑ No

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