Title

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Permalink

https://escholarship.org/uc/item/4vv9j174

Journal

The Neurohospitalist, 3(2)

ISSN

1941-8744

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Publication Date

2013-04-01

DOI

10.1177/1941874412457183

Peer reviewed

Updates on Clinically Isolated Syndrome and Diagnostic Criteria for Multiple Sclerosis

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Abstract

Clinically isolated syndrome (CIS) is a central nervous system demyelinating event isolated in time that is compatible with the possible future development of multiple sclerosis (MS). Early risk stratification for conversion to MS helps with treatment decisions. Magnetic resonance imaging (MRI) is currently the most useful tool to evaluate risk. Cerebrospinal fluid studies and evoked potentials may also be used to assess the likelihood of MS. Four clinical trials evaluating the benefits of either interferon β (IFN-β) or glatiramer acetate (GA) within the first 3 months after a high-risk CIS demonstrate decreased rates of conversion to clinically definite MS (CDMS) and a lesser degree of MRI progression with early treatment. In the 3-, 5-, and 10-year extension studies of 2 formulations of IFN-β, the decreased conversion rate to CDMS remained meaningful when comparing early treatment of CIS to treatment delayed by a median of 2 to 3 years. Diagnostic criteria have been developed based on the clinical and MRI follow-up of large cohorts with CIS and provide guidance on how to utilize clinical activity in combination with radiographic information to diagnose MS. The most recent 2010 McDonald criteria simplify requirements for dissemination in time and space and allow for diagnosis of MS from a baseline brain MRI if there are both silent gadolinium-enhancing lesions and nonenhancing lesions on the same imaging study. The diagnostic criteria for MS require special consideration in children at risk for acute disseminated encephalomyelitis (ADEM), in older adults who may have small vessel ischemic disease, and in ethnic groups that more commonly develop neuromyelitis optica (NMO).

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, degenerative disease of the central nervous system (CNS), which is disseminated in space and time.[1,2] Clinically isolated syndrome (CIS) refers to a first clinical CNS demyelinating event lasting $\geq$24 hours, which is consistent with MS but is isolated in time and may or may not be isolated in space.[3] The CIS is distinguished from radiologically isolated syndrome (RIS), in which patients have incidentally detected magnetic resonance image (MRI) T2 bright foci suggestive of demyelination in the absence of clinical symptoms.[4]

Possible presentations of CIS include optic neuritis, a brain stem and/or cerebellar syndrome, a spinal cord syndrome, or occasionally cerebral hemispheric dysfunction.[5-8] Physicians must always probe about the patient's past neurological events, such as blurring of vision, double vision, Lhermitte sign, numbness, or weakness lasting >24 hours, as these may be overlooked, especially when mild. In addition, physicians must exclude other alternative diagnoses such as infections, inflammatory disorders, metabolic disorders, genetic diseases, neoplasms, vascular disease, other autoimmune diseases, and other MS variants (see Table 1).[9-13]

There are currently no biomarkers that are pathognomonic for a diagnosis of CIS or MS. Diagnostic workup of a CIS typically begins with a brain MRI.[14] Additional MRI studies are useful in the setting of specific syndromes, such as MRI of the orbits in a patient presenting with optic neuritis or MRI of the cervical and/or thoracic spinal cord in a patient with a spinal cord syndrome or in patients for whom the clinician is trying to document dissemination in space (DIS). Cerebrospinal fluid (CSF) evaluation for oligoclonal bands (OCBs) and elevated immunoglobulin G index[15] as well as evoked potentials[16] may further assist with the diagnosis.

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Table 1. Alternative Diagnoses to MS and "Rule Out" Diagnostic Tests.[a]

Disease Category	Examples
Infectious	Syphilis, Lyme disease, HIV
Inflammatory	Sarcoidosis
Other autoimmune	Systemic lupus erythematosus (SLE), Sjogren syndrome, Behçet disease
Other MS mimics	Neuromyelitis optica, acute disseminated encephalomyelitis
Metabolic	Vitamin B12 deficiency, nitrous oxide toxicity, copper deficiency
Genetic	Leukodystrophy, mitochondrial disorder
Vascular	CNS vasculitis, small vessel ischemic disease
Anatomical or structural	Compressive lesions
Neoplastic or paraneoplastic	Lymphoma, glioma

Special considerations with the presentation of an isolated optic neuritis: glaucoma, sarcoidosis, compressive lesions, neuromyelitis optica, other autoimmune diseases (SLE, Sjogren, Behçet, antiphospholipid antibody syndrome), infection (West Nile virus, HIV, varicella zoster virus, cryptococcus, toxoplasmosis, syphilis, histoplasmosis, Lyme disease), B12 deficiency, retinal artery occlusion, retinal detachment, ischemic optic neuropathy, infiltrative optic neuropathy, hereditary optic neuropathy, recurrent idiopathic optic neuritis.

Special considerations with the presentation of an isolated myelopathy: compressive lesions, neoplasms, neuromyelitis optica, other autoimmune (SLE, Sjogren), sarcoidosis, infections (syphilis, Lyme disease, viral, TB, mycoplasma, HIV), ischemia/infarction, epidural abscess, spinal epidural hematoma, spinal arteriorvenous malformation, dural venous fistula, cervical stenosis, syrinx, toxic/metabolic (B12 deficiency, nitrous oxide toxicity, copper deficiency), hereditary spastic paraparesis, adrenomyeloneuropathy, idiopathic transverse myelitis.

Special considerations with the presentation of an isolated ataxia or brainstem syndrome: spinocerebellar ataxias, Wernicke syndrome, vitamin E deficiency, viral or postinfectious encephalitis, neoplasm, cerebrovascular disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), myasthenia gravis.

Abbreviations: MS, multiple sclerosis; TB, tuberculosis.
[a] Produced with guidance from Rinker and Cross.[17]

Radiology in the Diagnosis of CIS

Magnetic resonance imaging is a critical tool when clinical features alone yield uncertainty about the diagnosis of MS. Useful radiographic predictors of MS include the presence of multifocal homogenous or ring-enhancing white matter foci, as well as T2-hyperintense lesions affecting the corpus callosum[18,19] or the posterolateral compartment of the spinal cord.[20] Demyelinating plaques are most common in the cervical portion of the spinal cord but may affect any segment, including the conus medullaris. Ninety-five percent of patients with optic neuritis will have abnormalities of the optic nerve detected on a MRI sequence that suppresses the signal from orbital fat,[21] with enhancement of the optic nerve typically seen during the acute attack.[22] Contrary to these common features of demyelinating disease, the presence of a brain or spinal cord lesion with enhancement for >8 weeks[23,24] or spinal cord lesions greater than 3 segments in length,[23] should lead to the consideration of alternative diagnoses, although these occasionally occur in MS.

The MRI scans display clinically silent T2-bright areas more frequently than abnormalities can be detected by clinical history and examination alone. Sixty to seventy percent of brain lesions[25,26] and thirty percent of spinal cord lesions[27,28] develop without corresponding clinical attacks. New silent lesions appear 5 to 10 times more frequently than do lesions associated with clinical relapses.[29-31] Between 50% and 80% of patients with CIS have 1 or more clinically silent T2-bright abnormalities on their baseline brain MRI.[5,6,32,33] Both the presence and the number of clinically silent lesions reflect older subclinical disease activity and are predictive of development of MS in the next 5 to 14 years.[6,32,34-36]

A protocol with MRI brain 3 plane scout, sagittal fast FLAIR, axial fast spin echo proton density/T2, axial fast FLAIR, and axial gadolinium (Gd)-enhanced T1 is recommended by the Consortium of Multiple Sclerosis Centers (CMSC) to evaluate patients presenting with a possible CIS.[37] The CMSC guidelines recommend spinal cord MRI in patients presenting with symptoms at the level of the spinal cord or in patients with focal neurological signs and an equivocal brain MRI if the diagnosis of MS is still being considered.

Other Paraclinical Tests in the Diagnosis of CIS

Evoked Potentials

Visual-evoked potentials (VEPs) are abnormal in 30% of patients with CIS, regardless of clinical symptoms,[38] and >50% of patients with MS[16] who have no history or clinical evidence of optic nerve dysfunction. Somatosensory-evoked potentials (SSEPs) and brain stem auditory-evoked potentials (BAEPs) may also be used to look for evidence of demyelination that is undetectable clinically or on MRI. Pelayo et al[39] demonstrated that if all 3 evoked potentials (VEP, SSEP, and BAEP) are abnormal at the time of CIS, there is an increased risk of developing moderate disability from MS that is independent of MRI findings.

Studies of CSF

Sixty to seventy percent of patients with CIS and greater than ninety percent of those with MS have 2 or more

immunoglobulin G (IgG) oligoclonal bands (OCBs) unique to the CSF.[5,15,40-45] The OCBs from the CSF must run in parallel with those from a serum sample obtained within 72 hours of the lumbar puncture, and the preferred method of analysis for the highest sensitivity and specificity in detecting MS is isoelectric focusing on agarose gels followed by immunodetection by blotting or fixation.[46] Seventy to ninety percent of MS patients will have an elevated IgG index,[15,47] and this may be in conjunction with or independent of elevated OCBs unique to the CSF. The presence of ≥2 OCBs in the CSF have a positive predictive value of 97%, negative predictive value of 84%, sensitivity of 91%, and specificity of 94% for developing relapsing remitting MS (RRMS) after a CIS.[48] Tintore et al[49] and Masjuan et al[48] showed that having OCBs within 3 months of CIS nearly doubled the risk of having a second clinical attack over a mean of 50 months[48] or over 6 years[49] in the respective studies. On the other hand, CSF with >50 white blood cells (WBCs)/mm^3 or protein >100 mg/dL is rarely observed in MS, and this should raise the possibility of an alternative diagnosis.[11,50] It is also important to bear in mind that other disorders besides MS may cause elevated OCBs and IgG index. The differential diagnosis for the presence of OCBs unique to the CSF includes Sjogren syndrome (present in 75%-90% of patients with neurological symptoms), neurosarcoidosis (40%-70%), systemic lupus erythematosus (30%-50%), Behcet disease (20%-50%), paraneoplastic disorders (5%-25%), antiglutamic acid decarboxylase antibody syndromes (40%-70%), Vogt-Koyanagi-Harada syndrome (30%-60%), Hashimoto's steroid-responsive encephalopathy (25%-35%), subacute sclerosing panencephalitis (100%), rubella encephalitis (100%), neurosyphilis (90%-95%), neuroborreliosis (80%-90%), human immunodeficiency virus infection (60%-80%), meningitis (5%-50%), adrenoleukodystrophy (100%), ataxia telangiectasia (50%-60%), Leber hereditary optic atrophy (5%-15%), CNS vascular disorders (5%-25%), and CNS masses and structural lesions (<5%).[15]

Risk of Conversion to Clinically Definite MS

Assessing Risk by Radiographic Features

In the studies that assessed the benefit of disease-modifying therapies in CIS, clinically definite MS (CDMS) was defined by the original Poser criteria,[51] which call for 2 clinical attacks with evidence of 2 separate lesions, separated by at least a month, with each attack lasting no less than 24 hours.[51] Alternatively, Poser criteria may be met by 2 clinical attacks that lack evidence of 2 separate lesions as long as there is accompanying paraclinical evidence of a second lesion (based on radiographic studies, evoked potentials, urological studies, or neuropsychological evaluation).[51] The results of numerous studies assessing the risk of conversion from CIS to CDMS, taken in combination, suggest that patients who have asymptomatic brain MRI lesions at the time of presentation of CIS have a 60% to 80% chance of

developing CDMS by 10 years, whereas those without brain lesions have a ~20% risk of CDMS by 10 years.[32,33,52-54]

Conventional 1.5 T imaging does not capture the entire extent of MS activity. For example, cortical lesions are not identified with conventional 1.5 T scans, but it has been recently demonstrated that nearly 40% of patients with early MS have cortical involvement.[55] Cortical demyelinating lesions not seen on conventional MRI may be detected on double inversion recovery imaging[56,57] and on 7 T MRI.[58-60] The presence of at least 1 cortical lesion in patients with CIS may help identify those at high risk for conversion to CDMS.[61] Small studies respectively using magnetic resonance spectroscopy (MRS) and magnetization transfer imaging (MTI) in patients with CIS have shown that these advanced imaging techniques may also aid in the prediction of which CIS patients will convert to CDMS.[62,63]

Assessing Risk by Epidemiologic Features

In addition to the radiographic features, certain demographic and clinical factors are associated with a higher risk of conversion from CIS to CDMS. CIS patients of nonwhite race, age less than 30 years, or with involvement of fewer functional systems at first presentation are at higher risk of developing CDMS.[64,65] Others have shown that first presentation with motor or multifocal symptoms and higher Expanded Disability Status Scale (EDSS) scores at baseline may increase the risk of conversion to CDMS.[5,66,67] The CIS patients who smoke[68] or who have increased Epstein-Barr virus (EBV)-encoded nuclear antigen 1 titers have a higher risk of developing further disease activity.[69]

Acute Treatment of CIS—What Every Neurohospitalist Needs to Know

Most neurologists treat CIS (and MS) flares that result in functional impairment with high-dose corticosteroids (typically methylprednisolone 1 g/d) for 3 to 5 days, with or without a subsequent brief oral steroid taper.[1,67,70-73] High-dose corticosteroids are often administered through an intravenous (IV) route, but at least 2 studies have demonstrated that there is no advantage of high-dose IV steroids compared to high-dose oral steroids.[74,75] High-dose steroids in times of acute flare are thought to accelerate time to neurological recovery.[1,70,76,77] In addition, studies investigating the use of IV methylprednisolone or adrenocorticotropic hormone (ACTH) in the treatment of CIS or MS exacerbations have demonstrated a benefit in disability scores at 3 and 6 weeks,[78] an improvement of visual acuity in patients with optic neuritis at 30 days,[79] and a protective effect against worsening of disease activity within the first 5 weeks of treatment.[80] Steroids are also thought to reduce Gd-enhancing lesions on MRI, a marker of disruption of the blood–brain barrier, for up to 7 to 9 weeks.[81] However, the literature does not support that one pulse of steroids has a significant impact on long-term clinical

outcomes.[1,70,82] Adverse effects that are of concern with pulse high-dose corticosteroids include transient increase in bone resorption,[83] elevated glucose levels, dyspepsia, psychiatric manifestations (anxiety, depression, and psychosis), insomnia, weight gain, avascular necrosis of the shoulder or hip, and cataracts.[84] A preventive regimen including a H2 blocker or a proton pump inhibitor for gastrointestinal prophylaxis,[85] frequent glucose checks and insulin as needed,[86] and a benzodiazepine to be used pro re nata to help with anxiety or insomnia[87] can help mitigate some of these potential side effects.

For patients with substantial disability and little improvement of neurologic function a week or more after treatment with corticosteroids, plasma exchange, IV immunoglobulin (IVIg), and cyclophosphomide are additional treatment options. There is no level I evidence available to support the use of these additional therapies. There is level II evidence for the efficacy of plasma exchange in a cohort of patients with MS and other CNS demyelinating diseases, with 8 (42.1%) of 19 in the treatment group showing benefit compared to 1 (5.9%) of 17 in the placebo group,[88] and there is level III evidence that 71% of 16 steroid-resistant patients in an uncontrolled study subsequently had improvement when treated with plasma exchange.[89] A typical dosing regimen for plasma exchange would be 1.1 to 1.4 plasma volumes exchanged every other day for a total of 7 exchanges.[90] Although a non-randomized, nonplacebo controlled study showed a 68% improvement in relapses treated with IVIg within 24 hours of onset,[91] a subsequent randomized controlled trial of 76 patients followed for 26 weeks received no benefit from IVIg 1 mg/kg as add-on therapy to IV methylprednisone compared to placebo.[92] Based on the results of these studies, plasma exchange is typically favored over IVIg to manage MS relapses that are not responsive to steroid treatment. Of note, in addition to harboring all of the risks typically associated with central line placement, plasma exchange poses the additional risks of myocardial infarction, arrhythmia, hemolysis, and death in small percentages of patients.[93-95] Although specific risks of IVIg in patients with MS are not well known, extrapolating from the neuromuscular literature, IVIg may cause rash, fever, and much less commonly, aseptic meningitis, thrombosis, hemolysis, and renal dysfunction.[96]

A more recent trial demonstrated the benefit of high-dose cyclophosphamide (50 mg/kg per d for 4 consecutive days, followed by granulocyte colony-stimulating factor 6 days after completion) in 9 patients with aggressive RRMS, 8 of whom had not responded to conventional steroid therapy.[97] Although this study was conducted in patients who had clinical exacerbations between 6 and 12 months prior to enrollment, and actually excluded patients who had a flare in the 3 months prior to cyclophosphamide administration, one might extrapolate that cyclophosphamide could be utilized as a rescue treatment for acute fulminant relapses. Safety concerns with the use of short-term high-dose cyclophosphamide monotherapy in patients with MS include neutropenia and infection.[97,98]

Of note, in addition to treating demyelinating attacks with aggressive immunotherapies, rehabilitation treatments with physiatrists, physical therapists, occupational therapists, speech therapists, and cognitive rehabilitation specialists are also incorporated into the acute comprehensive care of a patient with CIS. For example, one study of 40 participants randomized to treatment with IV methylprednisolone alone versus IV methylprednisolone with planned multidisciplinary rehabilitation care showed significant improvements in motor function and balance outcomes during a 3-month follow-up period for patients receiving both steroids and rehabilitation therapy compared to those being treated with steroids alone.[99]

Disease-Modifying Therapy in CIS—Transition to Outpatient Management

One of the primary motivations for early diagnosis of MS is the potential for early treatment to delay the onset of additional clinical relapses and to possibly delay long-term disability. The first opportunity to initiate disease-modifying therapy (DMT) in patients with MS is often when they are in the CIS stage. Although it is reasonable for the neurohospitalist to broach the subject of DMT in the hospital setting, given the complexities of DMT risk and benefit profiles and the usual need for long-term monitoring of possible side effects, the usual practice is for the outpatient neurologist to discuss and prescribe DMT. Four first-line injectable therapies have been shown to reduce the risk of conversion from CIS to CDMS and to reduce new MRI lesions in patients with abnormal MRI brain scans after the first demyelinating attack.[67,71,100,101]

Clinical trials that demonstrated the benefit of DMT in delaying or preventing patients with high-risk CIS from converting to CDMS are described in detail in Table 2. The first of these studies, the Controlled High-risk subjects Avonex Multiple sclerosis Prevention Study (CHAMPS),[71] demonstrated that the cumulative probability of developing CDMS was reduced to 35% on weekly intramuscular interferon (IFN)-β1a versus the 50% probability of converting to CDMS on placebo within 3 years ($P = .002$). Based on these results, the Food and Drug Administration (FDA) extended its approval of intramuscular IFN-β1a to include patients with CIS deemed to be at high risk for MS.

The Early Treatment of Multiple Sclerosis (ETOMS) study[67] followed, demonstrating that weekly subcutaneous IFN-β1a reduced the conversion to CDMS over 2 years to 34% versus 45% on placebo ($P = .047$). A post hoc analysis of the ETOMS study found that the treatment group had a reduced rate of brain atrophy compared with those on placebo.[102] It should be noted that the 22 μg weekly dose of IFN-β1a evaluated in this trial was considerably less than the dose later approved by the FDA for treatment of MS (22 and 44 μg 3 times weekly).[103]

In the Betaferon in Newly Emerging MS for Initial Treatment trial (BENEFIT),[100] 69% of the group randomized to

Table 2. Clinical Trials Testing DMT in High-Risk CIS Patients.

Abbreviated Study Name	Study design and Duration	N	Inclusion Criteria	Treatments	Primary End Points	Percentage With CDMS At Study End	Time to CDMS (Days for 25th-30th percentile)	MRI Changes
CHAMPS[71]	Randomized, double blind 3 years (terminated early due to efficacy in preplanned interim analysis)	383	CIS onset within 4 weeks, ≥2 silent MRI brain lesions (≥3 mm diameter, with ≥1 lesion either periventricular or ovoid)	IM IFNβ-1a (Avonex) 30 μg q week versus placebo[a]	Time to CDMS	35% on IFNβ-1a 50% on placebo (P = .002)	809 on IFNβ-1a 397 on placebo	Gd-enhancing lesions, new or enlarging T2 lesions, increase in lesion volume significantly lower with IFNβ-1a
ETOMS[67]	Randomized, double blind 2 years	309	CIS onset within 3 months, ≥4 silent MRI brain lesions (≥3 lesions if there is an infratentorial or Gd-enhancing lesion)	SC IFNβ-1a (Rebif) 22 μg q week[b] versus placebo	Time to CDMS	34% on IFNβ-1a 45% on placebo (p = 0.047)	569 on IFNβ-1a 252 on placebo	New T2 lesions and increase in lesion load significantly lower with IFNβ-1a
BENEFIT[40, 76]	Randomized, double blind 2 years	468	CIS onset within 60 days, ≥2 silent MRI brain lesions (≥3 mm in diameter, with ≥1 lesion ovoid, periventricular, or infratentorial)	SC IFNβ-1b (Betaseron) 250 μg qod versus placebo	Time to CDMS	28% on IFNβ-1b 45% on placebo (P < .0001)	618 on IFNβ-1b 255 on placebo	New T2 lesions, Gd-enhancing lesions, volume of Gd-enhancing lesions significantly lower with IFNβ-1b
PreCISe[77]	Randomized, double blind 2.3 years (mean)	481	CIS onset within 90 days, ≥2 silent MRI brain lesions ≥6 mm in diameter	SC GA (Copaxone) 20 mg daily versus placebo	Time to CDMS	25% on GA 43% on placebo (P = .0005)	722 on GA 336 on placebo	New T2 lesions and volume, Gd-enhancing lesions, T1 hypointense lesions significantly lower with GA

Abbreviations: CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; FDA, Food and Drug Administration; GA, glatiramer acetate; Gd, gadolinium; IFN, interferon; IM, intramuscular; MRI, magnetic resonance imaging; q, every; SC, subcutaneous.

[a] All patients treated with high-dose methylprednisone and an 11-day prednisone taper prior to initiating study drug.
[b] Lower quantity and less frequent than the current FDA-approved dose.
Modified from Connor and Smith.[104] Reproduced with permission from Consensus Medical Communications.

IFN-β1b 250 mcg subcutaneously every other day compared to 85% in the placebo group had CDMS at 2 years.

In the intention-to-treat analysis of the Early GA Treatment in Delaying Conversion to CDMS in Participants Presenting with a Clinically Isolated Syndrome (PreCISe) trial,[101] the conversion to CDMS was reduced to 25% in patients treated with glatiramer acetate (GA) 20 mg subcutaneous daily compared to 43% on placebo (P = .0005).

More recently, open-label extension studies from the original CHAMPS and BENEFIT cohorts have suggested a possible long-term benefit of early initiation of DMT. In the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance (CHAMPIONS) trial, 203 of the original 383 patient cohort in CHAMPS were followed and outcomes were reanalyzed at 5[105] and 10 years[106] after enrollment. All patients were offered treatment with IM IFN-β1a at the end of the CHAMPS study and remained blinded to their initial treatment. Those who were treated from onset were referred to as the immediate treatment (IT) group, while those treated with a placebo for a median of 29 months after CHAMPS randomization were considered the delayed treatment (DT) group. The primary outcome was development of CDMS. At 5 years,[105] the IT group remained less likely to have CDMS compared to the DT group (36% vs 49%, respectively; P = .03). New or enlarging T2 lesions were also significantly lower in the IT group at 5 years. Disability at 5 years was similar in the 2 groups, with few patients having major disability in either group. In the 10-year analysis,[106] there continued to be a statistically significant benefit of IT over ET in terms of conversion to CDMS (58% vs 69% respectively; P = .004), but MRI outcomes between IT and DT groups were no longer statistically different. The CHAMPIONS study thus concluded that delay in treatment by up to 3 years after a first clinical demyelinating attack could lead to earlier time to CDMS but did not show a long-term effect on the development of new MRI T2-weighted lesions or long-term disability. Sampling errors and possible attrition of those with the most aggressive disease were limitations that may have biased the results of this long-term extension study.

Similar results with delayed time to CDMS in the IT versus DT groups were seen in the BENEFIT extension study at 3 and 5 years.[107,108] This study had a similar design to CHAMPIONS in that the IT and DT groups were both given the option to take IFN-β1b at the conclusion of BENEFIT, and 235 patients (80% of the original) in the IT group and 123 patients (70% of the original) in the DT group remained blinded to their initial treatment and completed the 5-year extension study. Median length of placebo exposure in the DT group was 1 year and 11 months. After 3 years,[107] 37% of the IT group and 51% of the DT group had CDMS, representing a 41% reduction in the development of CDMS in the IT group (P = .0011). Disability progression was 16% in the IT and 24% in the DT groups (P = .022). Five years after randomization,[108] the risk for CDMS was lower in the IT group (46%) compared to the DT group (57%; P = .003). However, the difference in disability progression at 5 years was no longer significantly different between the IT and DT groups, with only minimal changes in EDSS scores in both groups over the 5-year period. Limitations of the BENEFIT study were similar to those raised for the CHAMPIONS study, with a major confounding factor being that patients in the extension study could be on any form of DMT.

Keeping in mind the limitations of extension studies with dropouts and sampling errors, the data collected from the BENEFIT and CHAMPIONS extension trials suggested that delaying treatment with IFN-β by 2 to 3 years after onset of CIS resulted in a significantly higher risk of conversion to CDMS 5 to 10 years after first clinical presentation compared to those who started treatment at the onset of CIS symptoms.[105-108]

Based on the results of these initial clinical trials and extension studies, many experts recommend initiating DMT at the time of CIS.[2] This is especially relevant for patients who have the markers of poor prognosis reviewed earlier. The decision to initiate treatment has to be weighed against the notion that not all patients with CIS go on to develop additional symptoms or brain lesions consistent with MS. Also, the extension trials, in part due to their inherent design limitations, have not shown dramatic evidence that early treatment of CIS will prevent long-term disability. Based on the available data, it remains acceptable to initially hold treatment and institute close clinical and MRI follow-up for patients with CIS, especially for those with better prognostic factors or for those not ready to initiate injectable medications. The precise interval over which one should repeat an MRI brain scan after a CIS event is not well defined. One study of 60 patients with CIS followed with monthly cerebral MRI scans showed that the majority of participants who developed a new Gd-enhancing or T2 hyperintense lesion over the course of the 6-month study had developed that new lesion by 3 months after the initial scan.[109] Therapy would then be initiated only with the detection of a new or enlarged T2 or Gd-enhancing lesion on surveillance MRI brain or after the occurrence of a second clinical attack.[106]

In clinical practice, physicians will often use IFN-β or GA to treat patients with CIS. In cases of particularly fulminant first-time flares, some practitioners might opt to use second-line treatments such as natalizumab or fingolimod. New oral immunomodulatory therapies including dimethyl fumarate, teriflunomide, and alemtuzumab are pending FDA approval for the treatment of RRMS and will soon be new therapies to consider for the treatment of CIS.[110] Researchers are also trying to identify effective and safe neuroprotective agents that are anticipated to offer new avenues for prevention and repair in the future management of CIS and MS. It is likely that such agents will be used in combination with therapies that prevent MS relapses.

Diagnostic Criteria for MS

Original diagnostic criteria for MS were based on clinical features of demyelination. The Schumacher criteria required 2

clinical relapses separated in space and time in patients aged 10 to 50 years who had no better explanation for their signs and symptoms.[111] The subsequent Poser criteria added to the Schumacher definition by specifying guidelines for use of CSF inflammatory markers and evoked potentials in diagnosis.[51,112] As radiological tools have advanced,[10,11,113-118] the multiple editions of the McDonald criteria focus on the integration of clinical, laboratory, and radiographic data to establish a diagnosis of MS.[10,11,113-118]

Just as with the Poser criteria,[51] the 2001 McDonald diagnostic criteria specified that 2 clinical attacks varying in space and time were sufficient for a diagnosis of MS. Dissemination in time (DIT) could be met by either (1) a Gd-enhancing or (2) a new T2 lesion detected on repeat MRI done 3 or more months after the baseline MRI.[119,120] Dissemination in space required either meeting Barkhof/Tintore MRI criteria (3 of the 4 criteria: $\geq$1 Gd enhancing or 9 T2 lesions, $\geq$1 juxtacortical, $\geq$1 infratentorial, and $\geq$3 periventricular lesions)[114,116] or the presence of 2 silent T2-weighted brain lesions and OCBs in the CSF. The 2001 McDonald criteria were thought to be fairly sensitive, specific, and accurate for predicting conversion to MS in 1 to 3 years (74%-83%, 83%-86%, and 80%-83%, respectively).[119,120] As a result, these criteria established a diagnosis of MS after CIS earlier than did the Poser criteria,[11,51,119] more than doubling the rate of MS diagnosis within the first year of disease.[119-121] The revised 2005 criteria better defined the significance of spinal cord lesions for DIS criteria and allowed new T2-weighted lesions on brain MRI after 30 days (rather than the previous 3 months) of the baseline MRI to satisfy the criteria for DIT.[10] Again, these updated criteria led to earlier diagnosis of MS with an improvement in sensitivity compared to the 2001 criteria (60% vs 47%) while retaining good specificity (88% vs 91%).[122]

More recently, based on a large cohort study, Swanton et al[123] proposed less stringent MRI guidelines for the diagnosis of MS while improving sensitivity (72% vs 60%, respectively) and maintaining similar specificity (about 90%).[122] They demonstrated that distribution of silent lesions in space could be met by $\geq$1 lesions in at least 2 of the following locations: spinal cord, infratentorial, periventricular, or juxtacortical. There was no requirement for Gd-enhancing lesions. To meet DIT, the Swanton criteria required a new T2 lesion on any follow-up MRI scan, irrespective of timing compared to the baseline scan.

Based on the Swanton study, in May 2010, the McDonald criteria were revised with the goal of further simplification.[114] The 2010 McDonald criteria[114] have further simplified the integration of imaging criteria based on data of the MAGNIMS research group[123-125] by requiring less MRI scans to make the diagnosis of MS. To meet criteria for DIS, a patient must have 2 clinical attacks in different CNS sites or must have had 1 clinical attack and also meet Swanton's radiographic criteria.[123] Symptomatic MRI lesions in the brain stem or spinal cord are excluded from the lesion count for these MRI criteria. Gadolinium enhancement is not required

for DIS.[126] To meet DIT in the 2010 criteria, there must either be a new T2 or Gd-enhancing lesion on subsequent MRI (regardless of timing from baseline scan) or, based on the findings from the MAGNIMS group,[124,125,127,128] both asymptomatic Gd-enhancing lesions and nonenhancing lesions on the baseline MRI. Thus, the diagnosis of MS after one clinical attack may now be established on baseline MRI if there is the simultaneous presence of asymptomatic Gd-enhancing lesions and nonenhancing lesions,[118,125] bypassing a time period in-between MRI scans in which most patients typically used to be labeled as having CIS. However, if the MRI lacks a silent-enhancing lesion or alternatively, if all lesions are enhancing, the patient fails to meet DIT criteria and a follow-up MRI with a new T2 or enhancing lesion is required to secure a diagnosis of MS. Because the MAGNIMS criteria[125] are already quite simplified for requirements for DIS and because CSF findings were never tested as part of the diagnostic algorithm, unlike in McDonald 2001 and 2005 criteria,[10,11] CSF findings cannot reduce radiographic requirements for DIS in the McDonald 2010 criteria.[118] These criteria are thought to have increased diagnostic sensitivity without compromising specificity, but they still have to be validated in pediatric, Asian, and Latin American cohorts.[118]

When considering the above criteria as a tool for an earlier diagnosis of MS after CIS, it must be noted that these criteria were established in the setting of having ruled out alternative diagnoses (MS mimickers), and it is unclear how well the criteria apply for atypical CIS syndromes. In addition, these criteria have also not been studied in patients younger than 15 or older than 49[118] and were based on data generated with 1.5 T MRI magnets.[118,125] Higher field strength magnets improve the image resolution and signal-to-noise ratio, resulting in higher lesion detection, including in anatomical regions important for MS diagnosis.[129] Although there is concern that the liberal 2010 MRI criteria may lead to overdiagnosis of MS when using MRI magnet fields of strengths higher than 1.5 T, at least one small retrospective study of 40 patients with CIS showed that even though 6 participants met an additional MRI criterion for MS on the 3 T MRI, none met enough new criteria to be diagnosed with MS earlier than they did with the prior versions of the McDonald criteria.[130] It is reasonable to anticipate that these criteria will continue to require revision to achieve improved sensitivity, specificity, and accuracy as new diagnostic techniques and disease biomarkers emerge.

Special Circumstances—CIS Versus Neuromyelitis Optica

Although considered for a long time as a variant of MS, a large array of evidence now supports that neuromyelitis optica (NMO) is a separate disorder with a pathophysiology, different clinical course, prognosis, and poor response to approved MS disease-modifying therapies.[131] Both adult and pediatric NMO are defined using the modified 2006 Wingerchuk criteria,[132,133] which include required episodes of optic

neuritis and acute myelitis as major criteria and either a contiguous spinal MRI lesion extending over ≥3 vertebral segments or NMO-IgG seropositive status. Unlike the original criteria,[134] the modified criteria allow for brain lesions to also be present in NMO.[132] In NMO, optic neuropathy is often severe and bilateral, sometimes leading to fixed visual loss of 20/200 or greater, and CSF can show a pleocytosis >50 WBCs.[133] The longitudinally extensive myelopathy usually affects the central part of the cord, and intractable hiccups, nausea, or vomiting may be reported as a result of a periaqueductal medullary lesion.[135,136]

As raised in the drafting of the 2010 McDonald criteria,[118] there are special concerns for using the criteria to distinguish between MS and NMO in Asian and Latin American populations, in which there are a higher incidence of NMO.[137-141] The International Panel for the McDonald criteria[118] recommended testing for NMO-IgG antibody in these populations or in individuals of other ethnicities with features compatible with NMO. Although not all patients with NMO are NMO-IgG antibody positive, approximately 80% are, and very few MS patients are positive.[9,140,142] Early detection is important because failure to make the correct diagnosis between NMO and MS can impact treatment response.[135] In Asian and Latin American populations with a demyelinating syndrome that more closely corresponds to MS, the disease behaves like typical Western-type MS and MAGNIMS MRI criteria should apply, though the 2010 McDonald criteria have not been validated in Asian and Latin American populations.[118]

Special Circumstances—Pediatric CIS Versus Acute Disseminated Encephalomyelitis

The McDonald criteria[10,11,118] may also have limited applicability to the pediatric population, especially prior to puberty, given the atypical clinical and MRI presentations in this age range.[143] Prepubertal patients with MS tend to have an altered phenotype with a more even gender ratio, more frequent acute disseminated encephalmyelitis (ADEM)–like clinical presentation, more frequent involvement of the brain stem and cerebellum and less involvement of the spinal cord, more confluent T2-bright lesions on MRI that vanish over time, and more neutrophils and less OCBs in the CSF.[144-146] The differential diagnosis for white matter lesions in this age group includes metabolic, infectious, and genetic conditions, in addition to the alternative disease processes that are typically ruled out in adults.[147] Meanwhile, adolescents tend to have an MS phenotype similar to that of adults.[147]

ADEM is an often monophasic, often multifocal, demyelinating syndrome. ADEM is more common in pediatric patients than adults, thus introducing an additional diagnostic challenge when a child has a first demyelinating event. ADEM typically has a simultaneous polyregional and polysympomatic presentation and is usually associated with encephalopathy.[144,145,148,149] In ADEM, unlike in MS, new lesions should not develop beyond a period of several weeks after the original MRI scan, and there may be a significant pleocytosis (>50 WBC) and elevated protein in the CSF, whereas OCBs may either not be present or may disappear on follow-up.[148] Both CIS and ADEM have clinical overlap, and there is unfortunately no good biomarker or MRI criteria to definitively distinguish between the 2 diagnoses.[147]

Now that we have data from clinical trials in adults that early treatment with DMT slows time to development of CDMS,[67,71,101,105-108] the ability to distinguish between ADEM and CIS and to then treat CIS patients with DMT has gained greater importance. Even though DMT has not been tested in randomized controlled trials in children or adolescents, these treatments are now commonly used in these age groups.[147] The diagnostic algorithm for the workup of pediatric CIS is very similar to that completed in adults with CIS, using blood tests, CSF evaluation, evoked potentials, and MRI. Disorders that mimic CNS demyelination in children, and which therefore warrant further exploration depending on a patient's presentation, include vascular diseases such as migraine, coagulopathy, arteriovenous malformations, CNS vasculitis, chronic infections, perinatal or genetic diseases such as cortical dysplasia and periventricular leukomalacia, metabolic disorders including mitochondrial cytopathy, leukodystrophies, cerebral folate deficiency, CNS neoplasms, and peripheral nerve lesions.[150] Analysis of CSF is typically performed, both to rule out alternative disease processes and to look for intrathecal inflammatory markers. Studies of the prominence of OCBs unique to the CSF in a pediatric cohort demonstrate that these inflammatory markers are more common in older patients but may be missing in most cases under the age of 11.[146,151,152] Visual-evoked potentials may aid in the diagnosis of pediatric MS, and in one study, nearly 50% of children with MS that presented with a neurological disorder other than optic neuritis demonstrated increased visual latencies prior to having their second clinical attack.[153]

The panel for the 2010 McDonald criteria considered the applicability of their new MS criteria to diagnosing MS in a pediatric population.[154] They established that the MAGNIMS criteria for the use of MRI in diagnosing MS probably had utility in diagnosing pediatric MS, especially because most pediatric patients will have >2 lesions and are likely to have them in 2 of the 4 specified locations.[118] The caveat to using MAGNIMS criteria for pediatric patients is that 15% to 20% with CIS, usually aged <11 years, will present with encephalopathy and multifocal neurological deficits that can be confused with a diagnosis of ADEM.[155,156] Because MRI in patients with ADEM will often demonstrate >2 variably enhancing lesions, MAGNIMS criteria for DIS and DIT on the initial MRI is not appropriate for this population of patients, and serial clinical and MRI observations are recommended to discriminate between ADEM and CIS.[118] Although there are no standardized guidelines for the time of suggested

follow-up, it is reasonable to repeat an MRI brain scan and clinical evaluation 3 to 6 months after the first demyelinating event.[157] It should also be kept in mind that in the age group <10 years, there can be marked resolution of MRI lesions following an initial attack,[145] and it is the emergence of new lesions over time that will lead to a diagnosis of MS.

There is limited data to validate the 2010 McDonald criteria[118] in a pediatric population, but thus far a retrospective analysis of 38 pediatric CDMS cases from 3 centers in the United Kingdom[158] demonstrated that on baseline scans, the International Pediatric MS Study Group 2007 criteria was fulfilled in 68% of patients, whereas the McDonald DIS criteria were fulfilled in 84%. Eleven of the 18 children given gadolinium met both DIS and DIT criteria, meaning that with McDonald 2010 criteria, they would have been diagnosed with MS at baseline scan. The group concluded that the 2010 McDonald criteria are more sensitive than the Krupp et al 2007 criteria[154] and could allow for earlier diagnosis of pediatric MS at the time of CIS. Additional validation in a larger pediatric cohort is needed.

Special Circumstances—CIS Versus Small Vessel Ischemic Disease in Older Patients

Just as the McDonald and MAGNIM criteria have not been tested in a pediatric population, they have also not been validated in adults >50 years old.[118,125] Older adults will often have areas of T2 hyperintense signal in the white matter secondary to small vessel ischemic disease, which makes MRI interpretation challenging when there is a question of CIS. In a series of 131 healthy individuals, 4.5% of those under age 50, 30% aged 50 to 59, and 54% of participants over age 60 had multifocal white matter abnormalities on brain MRI.[159] These areas of white matter T2 hyperintense signal are often described by radiologists as nonspecific, but are thought to reflect small areas of ischemia.[160] The white matter lesions from small vessel ischemic disease to some degree are distinct in appearance from those secondary to CIS/MS, as they tend to be smaller and located in the subcortical white matter away from the ventricles, to have more frequent involvement of the basal ganglia, and if located in the periventricular region, to have a smooth contour and more symmetric distribution.[159] Conversely, the corpus callosum and spinal cord often display pathology in demyelinating disease but are rarely affected as a result of age-related vascular changes.[161,162] Unlike the McDonald and MAGNIM criteria,[118,125] the Fazekas criteria[163] have been validated to distinguish demyelinating lesions from those of small vessel ischemic disease; however, despite the criteria being quite specific for MS, some patients with small vessel ischemic disease do pose a diagnostic challenge by meeting all Fazekas criteria. Patients with more diffuse and extensive confluent changes on MRI, often termed Binswanger disease or leukoariosis, are even more challenging to distinguish from late-stage MS.[164] One discriminating feature between demyelination and leukoariosis is that the latter spares whereas the former frequently involves the subcortical U-fibers.

Special Circumstances—CIS Versus Other Rare Demyelinating Disorders

In addition to CIS/MS, ADEM, and NMO, the neurohospitalist may encounter first presentations of other more rare demyelinating disorders. These less common demyelinating entities include tumefactive MS (Marburg variant, Balo concentric sclerosis, and Schilder disease), acute hemorrhagic leukoencephalitis (AHL), Bickerstaff brain stem encephalitis, and chronic relapsing idiopathic optic neuropathy (CRION).

Tumefactive MS presents with at least one large (>2 centimeter) acute demyelinating lesion, often with accompanying edema, mass effect, and ring enhancement.[165,166] Clinical presentations vary by the size and location of the lesion, but some possible symptoms such as headache, confusion, aphasia, apraxia, and seizures are atypical from those seen with more classic CIS/MS.[166] Tumefactive lesions must be distinguished from tumors or abscesses. Marburg type and Balo concentric sclerosis are thought to be variants of tumefactive MS, distinguished by severe, rapidly evolving course, atypical neuropathological changes, and distinct radiographic changes. In Marburg disease, there are numerous large multifocal demyelinating lesions occurring in the deep white matter; whereas in Balo, concentric layers of partial demyelination alternating with bands of demyelination are visualized. Although lesions in patients with Marburg variant are sometimes biopsied, brain biopsy is often unnecessary because the diagnosis can be confirmed by MRI, including MR spectroscopy.[167] Balo concentric sclerosis can usually be diagnosed with MRI, characterized by alternating isointense and hypointense concentric rings on T1-weighted images and partial enhancement limited to the T1-hypointense areas. Untreated Marburg disease is often fulminant, leading to rapid death, and of the 60 cases of Balo concentric sclerosis reported in the literature, most patients died within a few weeks or months of diagnosis, but others had a more benign course with spontaneous remission.[168] High-dose steroids, plasma exchange, immunosuppressive therapy (cyclophosphamide, mitoxantrone, rituximab), and in some cases even autologous stem cell transplantation have been used to treat these severe forms of MS.[167] Schilder disease, also known as myelinoclastic diffuse sclerosis, was classified by Poser et al in 1986 to have 1 single or 2 symmetrically arranged lesions measuring at least 2×3 cm with involvement of the centrum semiovale in the setting of symptoms unusual for MS, absence of OCB in the CSF, exclusion of adrenoleukodystrophy by laboratory testing, and no history of fever, infection, or vaccination prior to the onset of symptoms.[169] This disease tends to affect individuals aged 5 to 41 years, with a slight female predominance. Using MRI including spectroscopy imaging, many of these cases may also be identified without requiring brain biopsy. High-dose corticosteroids are the primary method of treatment.[170]

Acute hemorrhagic leukoencephalitis (AHL), acute hemorrhagic leukoencephalomyelitis (AHEM), and Hurst acute necrotizing hemorrhagic leukoencephalitis (ANHLE) are rare, severe, rapidly progressive inflammatory and hemorrhagic demyelinating disorders of the CNS, thought to be variants of ADEM.[171] Upper respiratory infections commonly precede these episodes. White matter lesions on MRI, which tend to be large and diffuse, with edema and mass effect as well as restricted diffusion in the affected areas of the brain.[172,173] Spin-echo MRI sequences are utilized to identify the acute hemorrhage associated with these lesions. Analysis of CSF typically demonstrates elevations in WBCs, red blood cells, and protein. Without treatment, patients with these hemorrhagic variants typically die from brain edema within a week of onset of symptoms, but with early aggressive treatment using corticosteroids, IVIg, cyclophophamide, and plasma exchange, the survival rates have improved.[148,174-176]

Bickerstaff encephalitis is a post-infectious immune-mediated brain stem syndrome, with patients often presenting with external ophthalmoplegia, ataxia, disturbances of consciousness, bilateral facial palsy, hyporeflexia, and bilateral extensor plantar reflexes. It resembles ADEM in both its association with prior respiratory tract and gastrointestinal infections and its pathological findings with perivascular lymphocyte infiltration and brain stem edema. The frequent presence of GQ1b-IgG antibodies is shared with patients who have Miller-Fisher syndrome, a brain stem-predominant form of Guillain-Barré syndrome. Most patients recover, at times with the use of corticosteroids, IVIg, and plasma exchange.[177]

Chronic relapsing isolated optic neuropathy (CRION) is an immune-mediated optic neuropathy that is thought to be distinct from CIS/MS. CRION frequently manifests as unilateral or bilateral vision loss. It differs from MS-related optic neuropathy in that patients often experience a more severe degree of visual loss, persistence of pain after onset of visual loss, and a relapsing and steroid-dependent course of symptoms. In many cases, the nadir loss of visual acuity is worse than that seen with typical demyelinating optic neuritis. The MRI brain scan does not demonstrate any additional lesions aside from optic nerve inflammation, and typically there is no immunoglobulin synthesis in the CSF. CRION symptoms of pain, decreased visual acuity, and color desaturation typically respond to corticosteroid treatment, but symptoms recur when steroid therapy is tapered. Long-term immunosuppression is thus often necessary, as recovery without treatment is often poor.[178] Some CRION cases subsequently evolve to become more classic NMO, and in rare cases, MS.

Summary

When patients present with a first-time CNS demyelinating event, it is helpful to assess their risk of future MS, both to counsel about prognosis and to help with early treatment decisions. The presence of silent lesions on MRI, inflammatory markers in the CSF, and/or evidence of demyelination on evoked potentials increase the likelihood of developing future CNS demyelinating events. Clinical trials examining the benefits of DMT in high-risk CIS patients universally demonstrate that starting DMT within 3 months of a first event decreases the risk of conversion to CDMS. Extensions of these CIS trials are limited in that not all patients remain on study drug over the years, but these studies suggest a meaningful reduction on the rate of conversion to CDMS but a less clear impact on disability for those who start treatment early compared to those who delay onset of DMT by a median of 2 to 3 years after a CIS. The 2010 McDonald criteria integrate MRI and clinical data to assist with making a diagnosis of MS as early as possible after a CIS. These criteria require increased caution when applied to pediatric populations, older adults, or ethnic groups in which NMO occurs with heightened prevalence, as they have yet to be validated in these populations. In cases of atypical or fulminant first-time demyelinating events, the differential diagnosis must be expanded to include variants of tumefactive MS, AHL, Bickerstaff brain stem encephalitis, and CRION.

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