# National MS Society Information Sourcebook

www.nationalmssociety.org/sourcebook

## Clinically Isolated Syndrome (CIS)

A *clinically isolated syndrome* (CIS) is a first neurologic episode, lasting at least 24 hours, which is caused by inflammation/demyelination in one or more sites in the central nervous system (CNS). A person with CIS can have a single neurologic sign or symptom—for example, an attack of optic neuritis—that's caused by a single lesion (and referred to as *monofocal*), or more than one sign or symptom—for example, an attack of optic neuritis accompanied by weakness on one side—caused by lesions in more than one place (and referred to as *multifocal*).

Individuals who experience a clinically isolated syndrome may or may not go on to develop multiple sclerosis. The challenge for the physician is to determine the likelihood that a person experiencing this type of demyelinating event is going to experience a second demyelinating event in the future, thereby meeting the criteria for a definite diagnosis of MS. Studies have shown that when the CIS is accompanied by MRI-detected brain lesions that are consistent with those seen in MS, there is a high risk of a second neurologic event, and therefore a diagnosis of clinically definite MS, within several years. Individuals who experience CIS with no evidence of MRI-detected lesions are at relatively low risk for developing MS over the same time period.

### Criteria for the Diagnosis of Multiple Sclerosis (MS)

The diagnosis of MS requires evidence of inflammatory and demyelinating lesions (loss of nerve fiber insulation) that have occurred at different points in time, in different parts of the central nervous system (referred to as *dissemination in time and space*). In addition, there must be no other explanation for these lesions.

At the present time, there is no single test that can determine whether a person has MS. However, over the last twenty years, procedures such as magnetic resonance imaging, examination of cerebrospinal fluid, and evoked response testing have played an increasingly important role in the diagnostic process. In 2001, the International Panel on the Diagnosis of Multiple Sclerosis, chaired by the late W.I. McDonald, FRCP (Royal College of Physicians, London), issued a revised set of diagnostic criteria (*Annals of Neurology* 2001; 50:121-127*)*, commonly referred to as the "McDonald criteria*.*" While maintaining the basic requirements of dissemination in time and space, the McDonald criteria provided specific guidelines for using findings on MRI and cerebrospinal fluid analysis to provide evidence of the second attack in those individuals who have had a single demyelinating episode and thereby confirm the diagnosis more quickly. These guidelines also facilitated the diagnostic process in those patients who have had steady progression of disability without distinct attacks.

Since 2001, the McDonald Criteria for Diagnosis of MS have been used worldwide. The International Panel, chaired by Chris Polman, MD, reconvened in March 2005 to consider extensive data that had been collected since 2001 and to recommend appropriate revisions to the criteria. These revisions, referred to as the "2005 Revisions to the McDonald Diagnostic Criteria for MS," were published in 2005 (*Annals of Neurology* 2005; 58:840-846). These revisions are helping to enhance the speed and accuracy of an MS diagnosis. A detailed explanation of the revised criteria can be found at www.nationalmssociety.org/dx-tipsheet.

**Treatment for Clinically Isolated Syndromes**

Three large-scale clinical trials have been conducted to determine whether early treatment following a clinically isolated syndrome can delay the second clinical event, and therefore the diagnosis of clinically definite MS:

- The **CHAMPS** (Controlled High-Risk Subjects Avonex® MS Prevention Study) study was designed to determine 1) if using interferon beta-1a (Avonex) early in demyelinating disease could delay the second episode of demyelination (which would signal clinically definite MS) and 2) if treatment would have an impact on MRI-detected brain lesions. The subjects in the study had each experienced a single, isolated neurological event suggesting demyelination and had multiple, clinically "silent" (without symptoms) MRI lesions, making them at high risk for a second neurological event and therefore a diagnosis of clinically definite MS.

  The results indicated that interferon beta-1a significantly delayed the onset of clinically definite MS, as indicated by a delay in a second clinical attack. In addition, MRI findings showed that the patients receiving interferon beta-1a had a significantly smaller increase in the volume of brain lesions, as well as fewer new lesions.

  Based on the results of this study, the Food and Drug Administration (FDA) extended the labeling of Avonex) to include individuals who experience their first clinical episode and have MRI-detected brain lesions consistent with multiple sclerosis.

- The **ETOMS** (Early Treatment of MS) study was designed to determine whether very low dose interferon beta-1a (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.

  Results indicated that fewer people on interferon beta-1a (Rebif) developed clinically definite MS (34%) than in the placebo group (45%) during the study time. In addition, the number of new lesions and the increase in the total accumulation of areas of myelin damage were significantly lower in the treatment group. The dose of Rebif used in the study was 1/6 of that generally used in the United States to treat relapsing-remitting MS.

To date, the FDA has not reviewed the data from this study.

- The **BENEFIT** (Betaseron® in Newly Emerging MS For Initial Treatment) study was designed to determine whether interferon beta-1b can delay the onset of clinically definite MS in people with CIS who are at high risk for developing MS.

  Results indicated that treatment may significantly delay the development of clinically definite MS: At day 255 of the study, one-quarter of patients in the placebo group had developed CDMS while it took 618 days for a comparable number of patients in the treatment group to develop CDMS. At the end of the two-year study, 28 percent of patients in the treatment group had developed CDMS compared to 45 percent of the placebo group.

  Based on the results of the BENEFIT trial, the FDA has expanded the indication of Betaseron® (interferon beta-1b) to include patients with multiple sclerosis (MS) who have experienced a first clinical episode and have MRI features consistent with MS.

  The FDA's approval of expanded labeling for Avonex and Betaseron supports the earliest possible treatment for MS, which many believe may delay the development of permanent clinical disabilities.

**See also…**

**Sourcebook**

- Cerebrospinal Fluid (CSF)
- Diagnosis
- Early Intervention
- Evoked Potentials
- Exacerbation
- Magnetic Resonance Imaging (MRI)

**Society Web Resources**

- Diagnosis of MS
  www.nationalmssociety.org/Diagnosis
- For People Newly Diagnosed
  www.nationalmssociety.org/NewlyDiagnosed
- Treatments
  www.nationalmssociety.org/Treatments

## For Healthcare Professionals

- Talking with Your MS Patients about Difficult Topics: Communicating the Diagnosis of Multiple Sclerosis
  www.nationalmssociety.org/TalkingAbout

- Tip Sheet: McDonald Diagnostic Criteria for MS
  www.nationalmssociety.org/dx-tipsheet.

## Book

Kalb R. (ed.) *Multiple Sclerosis: The Questions You Have; The Answers You Need* (3rd ed.). New York: Demos Medical Publishing, 2004.
—Ch. 2 Neurology

The National Multiple Sclerosis Society is proud to be a source of information about multiple sclerosis. Our comments are based on professional advice, published experience, and expert opinion, but do not represent individual therapeutic recommendations or prescription. For specific information and advice, consult your personal physician.

To contact your chapter, call **1-800-FIGHT-MS** (1-800-344-4867) or visit the National MS Society web site: www.nationalmssociety.org.


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