**Clinically Isolated Syndrome**

**What is Clinically Isolated Syndrome (CIS)?**

Multiple sclerosis (MS) is a disease that has attacks affecting different locations in the nervous system. In addition to the requirement for multiple locations, to make a diagnosis of MS there must be multiple attacks at different times. This presents a problem for how to classify people who have had only a single attack. These patients are at high risk of having MS, but technically cannot be diagnosed with the disease until they have a second attack. This situation is called CIS.

**What are the symptoms of CIS?**

The symptoms of CIS are the same as those of MS. Each patient has different symptoms depending on which area of the nervous system is involved. Some people have more than one location during their CIS attack, leading to several different symptoms.

**Does CIS improve?**

After a CIS attack, symptoms generally improve. There is an initial rapid recovery over several days or a few weeks. This is followed by a slow improvement over many months. Some patients have symptoms that remain long term, though these are usually not as severe as the initial attack. It is difficult to predict the degree of improvement.

**What is the risk of CIS becoming MS?**

For many patients, CIS is the first attack of what turns out to be MS. Patients can be divided into those at high risk of having MS and at low risk of having MS based on the MRI of the brain. This is true even if the CIS attack did not involve the brain. For example, if the CIS attack involved the spinal cord, the risk of developing MS is determined by the brain MRI, not the spinal cord MRI. There are two research studies that are particularly useful in this regard.

The group from Queen’s Square Hospital in London followed 140 patients with CIS for an average of 20 years after their CIS event (Fisniku LK. Brain. 2008;131:808). After 20 years, 63% of the people with CIS had gone on to develop MS. There were an additional 5% that probably had MS since they had experienced additional symptoms, but they had no new findings on physical examination so they were not classified as MS. The total conversion to definite or probable MS was 68%. The rates of conversion to MS were similar for those with optic neuritis, spinal cord or brainstem presentations. If the MRI of the brain was normal at the time of their CIS, only 21% went on to develop MS. If the MRI of the brain was abnormal at the time of their CIS, 82% went on to develop MS.
The optic neuritis treatment trial studied 389 patients with optic neuritis (Optic Neuritis Study Group. Arch Neurol 2008;65:727). Other forms of CIS were not included. After 15 years, the risk of developing MS was 50%. If the MRI at the time of the CIS was normal the risk of developing MS was 25%. If the MRI at the time of the CIS was abnormal the risk of developing MS was 78%.

**When does MS develop after CIS?**

If the MRI obtained at the time of CIS was abnormal, 30% had developed MS by 1 year, 65% by 5 years, and 83% by 10 years. It is rare for patients to develop MS beyond 10 years after CIS. In the optic neuritis treatment trial patients with baseline MRIs that were abnormal, 42% developed MS by 5 years. Of the remaining patients, 30% developed MS between 5 and 10 years and another 32% of the remaining patients developed MS between 10 and 15 years.

If the MRI obtained at the time of CIS was normal, 3% developed MS by 5 years, 11% by 10 years and 19% by 14 years. In the optic neuritis treatment trial patients with baseline MRIs that were normal, 16% developed MS by 5 years. Of the remaining patients, 9% developed MS between 5 and 10 years and another 2% of the remaining patients developed MS between 10 and 15 years.

**Does spinal fluid analysis help predict the risk of developing MS?**

Evaluation of cerebrospinal fluid may be used to exclude other diseases that might mimic CIS. In addition, tests for oligoclonal bands, IgG index and IgG synthesis rates may be seen in people with MS. In patients with CIS, these cerebrospinal fluid tests are often abnormal in patients who go on to develop MS. However, the MRI is much better at predicting who goes on to develop MS. Once an MRI has been performed, cerebrospinal fluid analysis does not contribute additional information to change the risk of CIS becoming MS (Butzkueven H. Multiple Sclerosis 2010;16: S14).

**How is CIS monitored?**

Clinical examinations and MRI are the most common methods of following people with CIS. Because the risk of developing MS is greatest in the first 10 years, particularly the first 5 years, we commonly get MRI scans annually for 5 years and then every other year up to 10 years. We see patients in clinic for neurological examinations about every 6 months.

**How is CIS treated?**

If the initial MRI is normal, then long term treatment is not indicated. Treatments to help with remaining symptoms may be needed however.
If the initial MRI is abnormal, then long term treatment for MS is recommended. Studies have shown benefit for Avonex, Betaseron, Copaxone and Rebif in CIS. In general, these studies indicate that the medications are likely to be more effective the earlier they are started. Also, patients who were on the placebo arms of these studies developed more disability than those on treatment. After 2 years, all patients in these studies were offered treatment with the real medication. In those patients on the placebo arms of the studies for 2 years, their rate of disease progression slowed after starting the medication, but they never caught up with those who started treatment early even several years later.