Patients with radiologically isolated demyelinating syndrome should be considered for MS disease modifying therapy: No

Brian Weinshenker, MD
Mayo Clinic
Rochester MN

MS is mainly a silent disease in its early phases. Furthermore, most inflammatory disease MS activity detected by MRI scans is subclinical. Hence, it is not surprising that a clinically silent phase precedes overt manifestations of MS in most patients. What was needed to prove this hypothesis was: 1) unfettered access to MRI technology in large numbers of individuals with symptoms irrelevant to MS (e.g. migraine headaches and other non-MS related symptoms) and 2) an interest in the MS community to follow patients with silent MS-suggestive lesions. In recent years, both these requirements have been satisfied, and there is now a robust interest in the early subclinical phase of MS within the MS community. The term most widely applied to this condition is radiologically isolated syndrome (RIS), and it is clear that it can be the precursor of relapsing remitting MS, and in some prospectively documented cases of primary progressive MS[1]. Wisely, experts have cautioned against making the diagnosis in a confident way in individuals without symptoms of neurological disease and to avoid disease modifying treatment. They have recognized the lack of specificity of MRI markers of MS. While no doubt some will "convert" to MS, it is unclear whether this is the majority. Even if the majority eventually convert, it is not justifiable to expose all patients with subclinical white matter lesions who might eventually manifest symptoms to extremely expensive, indefinitely prescribed and potentially hazardous treatments. In this debate, I will argue against institution of treatment or conducting clinical trials with outcome measures that are predictable (e.g. reduced risk of "conversion to MS") but should not, in their own right, lead to inappropriate practice recommendations if the trials were to yield positive results.

While strong arguments can be made against instituting long term MS disease modifying treatment (DMT) in every patient with early demyelinating disease until it is clear that relapses occur, the strongest argument against use of DMT in patients with RIS is that the diagnosis is uncertain. Nonspecific white matter lesions are extremely common. While current criteria for RIS proposed by Okuda use the more rigorous criteria of Barkhof rather than the more liberal Swanton criteria that have replaced the Barkhof criteria in the latest (2010) version of the McDonald criteria[2], even the Barkhof criteria have not been rigorously assessed in a general practice setting. The criteria were based on predicting whether dissemination in time and space will be satisfied in patients presenting with typical clinical characteristics of MS such as optic neuritis. A far more common problem occurs in patients who have anything less than an unequivocal presentation of demyelinating disease (e.g. major visual loss and afferent pupillary defect in a patient with optic neuritis). Many patients experience symptoms (e.g. visual migraine, paresthesias in the context of fibromyalgia) that are mistaken for symptoms of demyelinating disease. It is very common to detect nonspecific white matter lesions in the brain that are touted as evidence that patients have radiological evidence for "dissemination in space" and hence MS. Often, the diagnosis is not removed even when the patient sees an expert who is strongly convinced that the diagnosis was made in error and even when the patient is on long term immunomodulators[3, 4]. While many neurologists may argue that the correct diagnosis will eventually declare itself and modifications in therapy will be made, some conditions such as fibromyalgia lead to continuing but unchanging symptoms; definitive evidence of an alternative neurological diagnosis will never emerge. Such patients are at risk of being left on disease modifying therapies (DMT's) for lengthy periods of time until the diagnostic error is identified, if it ever is.

As is the case for MS, but even more convincingly for RIS, the prognosis is indeterminate. Many patients with MS have lengthy periods of remission with no or punctuated by only small numbers of attacks with few sequelae. Benign MS, while only diagnosed confidently retrospectively, is nonetheless common[5, 6] While it is difficult, if not impossible, to reliably assign a prognosis early, continued observation clinically and monitoring with MRI's generally permits early detection of recurrent disease activity and institution of DMT's at a point when the diagnosis is convincing and the prognosis is clearer. The point at which therapy should be introduced is still not well-defined, although there is a trend for treatment to be instituted as soon as a diagnosis of MS is satisfied using McDonald criteria. While perhaps more aggressive than can be justified, even such this approach is preferable to routine institution of treatment before a confident diagnosis of MS is established.

Patients are understandably concerned when they are told that they have RIS that they might suffer a devastating demyelinating attack from which they may not recover. It is possible to monitor patients with RIS and identify informative lesions. The benefits of being sure that a long term DMT is necessary outweigh any realistic concerns about a patient experiencing a devastating clinical attack that will not respond to rescue treatment.

It is difficult to know after initiating treatment whether a patient's course deviates from what might be expected for that patient give the variability in the natural course of MS and the incompleteness and variability of outcomes of patients on virtually all DMT's for MS. It is easy to attribute success to a drug that is unwarranted especially without a period of prior observation to gauge the natural course of disease in a given patient. Furthermore, there are no guidelines for stopping of DMTs, so at the present time, commitment of a patient to a course of therapy is for an indefinite period, a further argument in favor of being certain about the indications for treatment.

References

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