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Chapter

# *MS Progress Notes...*

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## **NEW DIAGNOSTICS IN MULTIPLE SCLEROSIS**

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In the past two decades major advances in technology, particularly developments in Magnetic Resonance Imaging (MRI), have allowed further understanding of the pathophysiology of multiple sclerosis (MS) and consequently better therapeutic approaches for MS patients.

Conventional MRI has become an essential component for the diagnosis and clinical management of patients with MS. Initial criteria used to diagnose clinically definite multiple sclerosis (CDMS) were mostly based on clinical features requiring two attacks and clinical evidence of two separate lesions. In cases with only one lesion, paraclinical evidence of another separate lesion by evoked potentials, spinal fluid or neuroimaging was required for the diagnosis.

With the advent of MRI, further criteria based heavily on MRI findings have been developed. These criteria, known as the McDonald Criteria, have been revised and simplified allowing the diagnosis of CDMS even after a single attack of demyelination when dissemination in space (1 or more T2 lesions in at least 2 of 4 locations: juxtacortical, periventricular, infratentorial and spinal cord) and time (new T2 lesion on a follow-up scan) are fulfilled.

Earlier diagnosis of MS has had therapeutic implications. Several clinical trials (CHAMPS, ETOMS, BENEFIT, PRECISE) have documented the benefits of disease modifying therapies in patients with clinically isolated syndrome as shown by a decrease in the number of relapses and new MRI lesions in the treated group as compared with placebo.

Hyperintense T2-weighted lesions indicate an increase in the water content and therefore are not specific for the underlying pathology. Acute hypointense T1-weighted lesions can also represent a variety of pathologies and in half of the MS patients can return to isointensity in the next several months. On the other hand, chronic T1-weighted lesions, also called "black holes", most likely represent irreversible tissue damage. Its presence, in some studies, has better correlated with disability than the T2-weighted lesions. The presence of gadolinium enhancing lesions indicates active inflammation and is more sensitive to disease activity than clinical relapses. However there has been a consistent lack of correlation, in many studies, between the clinical outcome in patients and the number of new lesions, or the T2 burden of

lesions—the so-called MRI/clinical paradox. For this reason a new generation of MRI techniques is now under active investigation, and these are reviewed below.

The development of cerebral and cord atrophy can also be evaluated by conventional MRI. In the past few years, quantification of brain atrophy using a variety of longitudinal or cross-sectional methods has shown that cerebral atrophy is a better predictor of clinical disability than the T1 or T2 lesion load. Significant correlation between spinal cord atrophy and disability in patients with MS has also been reported.

The wide availability of MRIs and its broad application in medicine have generated two very important questions: How much MS activity is too much to deserve change in treatment? What to do with patients with incidental typical MS lesions on their scan?

The first question has created debate among physicians on how to define treatment failure in patients with MS. Should we ignore worsening of MRI activity in a "clinically stable" patient? One can argue that there is no need for follow-up MRIs in those patients. Others question the validity of statements such as a "clinically stable patient", since our standard neurological evaluation often does not detect subtle cognitive impairments in MS patients. However, with the growing evidence of early development of white matter lesions as a predictor of long term outcome and the advent of new and more potent MS therapies, it becomes harder to justify a more passive approach in the face of persistent disease activity on the MRI. Data describing the risk for progression in MS patients at the earliest phases of illness is urgently needed.

Regarding the incidental finding of MRI abnormalities suggestive of MS in asymptomatic patients, also called the Radiologically Isolated Syndrome, Okuda et al recently showed further radiological progression in 59% of those patients and conversion to CIS or CDMS in approximately 33% of the cases after a median of 5.4 years. Future studies to fully define this risk are necessary before any treatment recommendations can be made.

### **New Generation MRI Techniques**

I - The development of high-field (3-4T) and ultra-high field (=or>7T) MRI scanners have the potential to revolutionize research in MS. High-field MRIs have shown to detect more T2

hyperintensities and gadolinium-enhancing lesions than 1.5 Tesla MRIs and their use might be helpful for earlier diagnosis of MS. High and ultra-field MRIs have also been of value in detecting cortical MS lesions often non-visible on standard MRI systems. However further refinement, standardization and validation of these techniques will be necessary before they can be integrated in clinical practice.

**II** - Magnetization transfer ratio (MTR) imaging measures the exchange between protons bound to macromolecules and those present in free fluids. This is done by generating a radiofrequency magnetic pulse prior to the scan. This pulse generates a gradient of magnetization between protons that are fixed, attached to myelin or cell membranes, and those that are free in water. The resulting MTR therefore reflects the state of tissue integrity. Normal values are between 40 and 50%, while the MTR of water (or CSF) is near 10%. These ratios can be compared in small areas of the brain, in plaques, in normal appearing white matter or in the whole brain. The quantitative aspect of the study is an advantage. Correlations with disability, and predictions of future disability, have been improved over standard MRI sequences in a number of studies.

**III** - Spectroscopy provides information about the biochemistry and metabolism of the brain. The N-acetyl-aspartate (NAA), choline and myoinositol metabolites represent neuronal, cell membrane and glial cell markers, respectively. Decreased N-acetyl-aspartate, increased choline and myoinositol can be seen in MS lesions but also in normal appearing white matter of MS patients. Studies of this type have been available for more than a decade. While there have been interesting studies, the clinical value of spectroscopy has lagged well behind other types of investigations.

**IV** - Diffusion-tensor imaging (DTI) provides information about the orientation, size, geometry and integrity of tissue fibers by measuring the motion of water in the tissue. Tissue damage, as seen in patients with MS, results in abnormal water motion and therefore can be identified by DTI, even in areas of normal appearing white and gray matter. Studies of lesions in different subtypes of MS have shown significant correlation between DTI findings and clinical disability. DTI can also perform fiber tracking and that can be used to investigate individual pathways in the brain or spinal cord and evaluate their response to a demyelinating lesion. A recent study showed that in a cohort of patients with MS believed to be of a benign type, a significant number had abnormalities on DTI testing that correlated with measurable changes in cognitive functioning. This study also emphasized as have many others, that assessment of MRI disability by standard EDSS testing often fails to detect disability or progression of disease.

**V** - Functional MRI. This technique uses signal changes brought about by changes in blood oxygenation level, which are then displayed as colored images, typically of regions of cortex. Adaptability and plasticity of the cortex and its connections can be seen, and may pertain to the long-term outcome after neuronal recruitment has attempted to compensate for tissue damage. The technique has only begun to be used clinically.

## **Non - MRI Techniques**

**I** - Optical coherence tomography (OCT) is a non-MRI based, noninvasive retinal imaging technology that provides a high-resolution reconstruction of the retina anatomy allowing measurement of the retinal nerve fiber layer (RNFL) thickness and macular volume. Since MS often targets the optic nerves, this technique has recently been studied in this population and interestingly enough has shown RNFL thinning not only in patients with a history of optic neuritis, but also in those without. Retinal nerve fiber layer thinning has also been reported to be more severe in patients with progressive compared to relapsing-remitting MS forms, and to correlate with the degree of brain atrophy. Therefore, it is possible that in the near future, the eyes will become our window to the ongoing mechanism of neurodegeneration present in the brain and spinal cord of our MS patients and hopefully a reliable surrogate for the neuroprotective effects of new treatments.

**II**. Investigations of less promise at this time include genetic testing derived from the human genome project, measurement of blood levels of cytokines, studies of cerebrospinal fluid, and evoked potential testing. In some instances the latter tests, of greater importance before MRI imaging became widely used, can still be useful. Genetic testing is widely believed to be the wave of the future.

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