Diagnostics in Multiple Sclerosis

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Is There Still a Role for Cerebrospinal Fluid Analysis in MS Diagnosis? To Tap or Not to Tap?

Karl Vass, MD, University of Vienna, Vienna, Austria, discussed reasons why lumbar puncture still has a role to play in the diagnosis of multiple sclerosis (MS).

According to Prof. Vass, cerebrospinal fluid (CSF) analysis adds value in several ways, including predicting the progression of clinically isolated syndrome (CIS) to MS, differential diagnosis, and research. It is extremely helpful in patients with an atypical clinical presentation, age of onset, or magnetic resonance imaging (MRI) [Awad A et al. *J Neuroimmunol* 2010].

Diagnostic CSF findings in MS patients include qualitative IgG oligoclonal banding (OCB) and the quantitative IgG index [Mayringer I et al. *Eur J Neurol* 2005]. Other biomarkers include intrathecal immunoglobulin (Ig) synthesis [Awad A et al. *J Neuroimmunol* 2010] and elevated kappa free light chains (KFLCs) [Presslauer S et al. *J Neurol* 2008].

Recent data show that the presence of OCBs has a higher accuracy than the dissemination in space on MRI in predicting the progression to clinically definite MS (CDMS) in CIS patients (70% vs 58%) [Zipoli V et al. *Mult Scler* 2009]. According to Prof. Vass, CSF analysis may help predict the development of CDMS when MRI changes are not present.

Increased IgG index or the presence of oligoclonal bands in the CSF support an MS diagnosis and aquaporin-4 antibody assays can help in the differential diagnosis process, but CSF analysis is especially important in ruling out infectious and inflammatory mimics (Table 1) [Herndon RM. *Adv Neurol* 2006].

Table 1. Differential Diagnosis of MS.

Disease sometimes disseminated in space but not in time	CNS vasculitis, ADEM, borreliosis, Behcet disease, sarcoidosis
Disease sometimes disseminated in time but not in space	Tumor, AVM, cervical spondylosis, peripheral neuropathy, adult-onset leukodystrophies
Disease often disseminated in both time and space	Cerebrovascular disease, CNS lymphoma, CNS vasculitis, SLE, Sjögren syndrome, HIV, NMO, sarcoidosis

CNS=central nervous system; ADEM=acute disseminated encephalomyelitis; AVM=arteriovenous malformations; SLE=systemic lupus erythematosus; NMO=neuromyelitis optica.

In the absence of robust clinical and paraclinical variables to predict disease course in the individual MS patient, CSF biomarkers are a promising source of information with a good potential of quantitative measure, sensitivity, and reliability [Gajofatto A et al. *Int J Mol Sci* 2011].

Currently, numerous CSF biomarkers are under investigation, including anti-myelin antibodies, sVCAM-1, 24S-hydroxycholesterol [Awad A et al. *J Immunol* 2010], glial fibrillary acidic protein [Axelsson M et al. J *Neurol* 2011], osteopontin (OPN) and interleukin-23 (IL-23) [Wen SR et al. *J Immunol* 2012], and proteomic biomarkers [Ottervald J et al. *J Proteomics* 2010] (Table 2).

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Table 2. New potential CSF markers in MS.

• Soluble vascular cell adhesion molecule-1 (sVCAM-1)	• Glial fibrillary acidic protein (GFAP)
• 24S-hydroxycholestrol	• Nitrous oxide (NO) metabolites
• Neurofilaments (NF)	• Soluble human leukocyte antigen (HLA) class I and II antigens
• Soluble intercellular adhesion molecule-1 (sICAM-1)	• Tumor necrosis factor (TNF) alpha
• Soluble (s) E-selectin	• Interleukin (IL) 6
• Soluble (s) CD30	• Interleukin (IL) 12
• Platelet/endothelial cell adhesion molecule-1(PECAM-1)	• Anti GM3 antibody
• Neural cell adhesion molecule (NCAM)	• Metalloproteinase-9 (MMP-9)
• Glial fibrillary acidic protein (GFAP)	• Antibodies against heavy chain isoform
• Nitrous oxide (NO) metabolites	• Tau
	• Actin Tubulin
	• 14-3-3 protein

The Case Against Spinal Taps

Joab Chapman, MD, PhD, Tel Aviv University, Tel Aviv, Israel, discussed reasons for not performing spinal taps. Among other subjects, he discussed zone electrophoresis and isofunctioning, differential diagnosis of white matter lesions on MRI, and the autoimmune encephalomyelitis-driven hypothesis.

The latest revision of the McDonald Criteria [Polman CH et al. *Ann Neurol* 2011] does not require CSF analyses to make a diagnosis of MS. This has led to earlier diagnosis with a high degree of specificity and sensitivity [Tintore M et al. *Neurology* 2003], enabling better counseling and earlier treatment.

Non-invasive imaging methods have become essential for assessing the effects of damage or disease processes [Stroman PW et al. *Clin Neurol Neurosurg* 2012]. MS is being studied extensively with functional MRI, in both the brain and spinal cord [Filippi M, Rocca MA. *Neuroimaging Clin N Am* 2009].

MRI may be the most widely used method for detecting pathology in the central nervous system because of its high tissue contrast and relatively high spacial resolution. It also offers several different methods for visualizing tissues and pathology. In addition to detailed anatomical imaging, it allows for angiography as well as diffusion-weighted and functional imaging [Stroman PW et al. *Clin Neurol Neurosurg* 2012].

MRI techniques may also be useful in the prediction of outcome. Structural techniques, such as diffusion tensor imaging, have been used to associate the structural integrity of white matter tracts with prediction of outcome. Diffusion tensor imaging has also been used to predict recovery following relapse in MS [Freund P et al. *Mult Scler* 2010].

Advanced MRI techniques image gray matter (GM) lesions *in vivo* and quantify structural and functional damage of the cortical and subcortical GM [Pirko I et al. *Neurology* 2007]. Evidence indicates that high and ultra-high field MRI may be useful in imaging nuclei, such as ^{31}P, and metabolites, such as glutamate [Srinivasan R et al. *Magn Reson Imaging* 2009]. This suggests the potential to elucidate the pathological mechanisms of neurodegeneration and disease progression.

High and ultra-high field strength magnets and sophisticated coil technology hold great promise for the development and implementation of techniques with greater sensitivity and specificity to the pathological mechanisms underlying disease processes [Inglese M et al. *Mt Sinai J Med* 2011].

Using MRI for Therapeutic Decisions

Ulf Baumhackl, MD, Department of Neurology, Landesklinikum, Poelten, Austria, discussed the use of MRI for early diagnosis, prognosis, and treatment monitoring of MS (the first 5 years).

According to the European Federation of Neurological Society guidelines, conventional MRI is the most important paraclinical tool available to diagnose MS and establish prognosis at the onset of the disease. Rational decision-making can be facilitated through "surveillance MRI," tracking treatment response status, and monitoring disease-modifying therapies.

Fifty to 80% of CIS patients have lesions consistent with prior disease activity. The number and extent of T2 brain lesions, and the presence of infratentorial [Minneboo A et al. *Arch Neurol* 2004] and gadolinium-enhanced (Gd+) lesions have the strongest predictive value.

Specifically, three or more T2-hyperintense lesions and two or more Gd+ lesions at baseline predict the progression to CDMS within 7 to 10 years [Frohman EM et al. *Neurology* 2003]. Near-term development of MS can be predicted based on the appearance of Gd+ (3 months) or new T2/Gd+ lesions 6 months after confirmation of CIS (baseline) [Frohman EM et al. *Neurology* 2003].

In the review and recommendations for current practice, Lövblad et al. [*Am J Neuroradiol* 2010] note that MRI in combination with characteristic symptoms provides earlier and more confident diagnosis than symptoms alone; and that the use of contrast agents can identify response to treatment in individual patients, not only predicting their disease course in the short-term, but also their disability and progression in the long-term. The technology can also detect strategic lesions that

may influence treatment decisions, and new lesions that may indicate a need for a change in treatment.

In established MS, disease activity is detected 5 to 10 times more frequently with MRI than with clinical assessment of relapses [Miller JC, Thrall JH. *J Am Coll Radiol*. 2004]. MRI provides objective and sensitive measures of activity, and is an established tool for monitoring response to treatment [Filippi M et al. *Eur J Neurol* 2008].

Prof. Baumhackl pointed out that MRI may facilitate rational therapeutic decisions in multiple ways, including reliable detection and description of older and newer lesions that represent subclinical disease activity. Sailer et al. [*Rofo* 2008] noted that such reports can be substituted for the clinical confirmation of a relapse

T2 brain lesions have a moderate correlation to disability, with the greatest predictive value early in the disease, and a higher rate of lesion growth in those who develop secondary progression MS [Fisniku LK et al. *Brain* 2008]. MRI activity outcomes can be recommended as the primary measure of treatment efficacy [Freedman MS et al. *Adv in Neurol* 2006].

Consider Other Factors

Florian Deisenhammer, MD, Innsbruck Medical University, Innsbruck, Austria, presented reasons why MRI should not be used for therapeutic decision-making. To make this point, he relied on MRIs from landmark trials (BENEFIT [Kappos L et al. *Neurology* 2006]; ETOMS [Fillipi M et al. *Lancet* 2004]; and CHAMPS [Kappos L et al. *Neurology* 2006])—all double-blind, placebo-controlled, randomized, multicenter trials.

In the BENEFIT trial, researchers examined the effect of treatment on the rate of conversion to CDMS as defined in the Poser criteria [Poser CM et al. *Ann Neurol* 1983]. They also explored therapeutic effects on the rate of conversion according to a diagnosis of MS as defined by the McDonald Criteria. [McDonald WI et al. *Ann Neurol* 2001]. These criteria systematically incorporate paraclinical findings, in particular MRI, to increase sensitivity without compromising specificity [Polman CH et al. *Ann Neurol* 2005; Dalton CM et al. *Ann Neurol* 2002; Tontore M et al. *Neurology* 2003]. In the post-hoc analyses of MRI data reading predictability of the therapeutic response according to MRI activity, no common pattern was found. In some studies, patients with high MRI activity responded better while in other studies, the opposite was true (patients with low MRI activity responded better to the treatment). To date, no prospective investigation has looked at the value of MRI for treatment decisions. There is simply not enough good quality data to rely solely on MRI to decide whether individual patients should be put on a particular treatment or should have their treatment changed.

Prof. Deisenhammer discussed further reasons why clinicians should not rely on MRIs by describing a recent neuroloy workshop. Participants, who routinely read scans were simultaneously provided with a series of cases from clinical studies, such as BENEFIT, and study-grade MRIs—highly sophisticated imaging with perfect resolution. The goal of the exercise was for neurologists to judge changes in T2 lesions and to indicate how many they thought they saw.

"This was a very humbling experience for them," he explained. "The number of lesions identified ranged from none to 30 or 40 new ones. In one instance, there was only one lesion, but the average neurologist saw six. In another case, there were at lest 20 lesions, and the average neurologist saw only two."

The technology is accurate, but our eyes may be not be, he said, noting the high volume of scans read by radiologists and the small amount of time spent on each one. Under those circumstances, the opportunity for errors in interpretations over time, especially in routine scanning, is great.

Clinicians who make judgments based on the presence of new T2 lesions, need to be very sure that they are actually seeing T2 lesions; this is especially true for small ones.

Table 3. 2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset.

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria:†
A. Evidence for DIS in the brain based on ≥T2* lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
B. Evidence for DIS in the spinal cord based on ≥T2* lesions in the cord
C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

†If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria; *Gadolinium enhancement of lesions is not required; MS=multiple sclerosis; PPMS=primary progressive MS; DIS=lesion dissemination in space; CSF=cerebrospinal fluid; IgG=immunoglobulin G.