Cleveland Clinic

Mellen Center Approaches: Use of paraclinical testing in MS

What paraclinical tests are most commonly used in MS care?

- Blood tests
- Lumbar puncture/Spinal fluid analysis
- Evoked potentials (visual, brainstem/auditory, somatosensory)
- Biomarker blood tests
- Optical Coherence Tomography (OCT)

What is the role of paraclinical testing in establishing or excluding the diagnosis of MS?

Importantly, the diagnosis of MS is made clinically based on a synthesis of the history, examination, imaging, plus paraclinical testing where necessary. No single paraclinical test can rule in or rule out MS with certainty.

Paraclinical testing can be used to fulfill the criteria for dissemination in space (usually evoked potentials or OCT) and verify an inflammatory etiology to the neurological disorder (spinal fluid analysis). We routinely use blood and spinal fluid tests to exclude "mimics" of MS at the time of diagnosis. Paraclinical testing such as evoked potentials and spinal fluid analysis can also be used to show a lack of pathology, in order to exclude the diagnosis of MS.

Is a lumbar puncture/spinal fluid analysis required to accurately establish the diagnosis of MS?

In most cases, if the clinical history, examination, and imaging are typical for MS, there is no need for spinal fluid analysis. Though evidence of intrathecal antibody synthesis (oligoclonal bands or elevation of IgG index) is supportive of the diagnosis, these tests are neither the most sensitive nor the most specific tests for MS. Oligoclonal bands and elevated IgG index can be found in many neurological disorders. Note that if cerebrospinal fluid protein is high then IGG synthesis rate may be falsely elevated.

The performance characteristics of CSF laboratory measures can vary substantially based on the methodology used. Isoelectric focusing is increasingly becoming the standard method used to evaluate for oligoclonal bands, because of its sensitivity. We find free kappa light chains to have low utility due to methodologic variability. Detection of myelin basic protein in the CSF occurs in many neurologic and nonneurologic disorders and should not be used in isolation to support a diagnosis of MS.

In which specific situations is a lumbar puncture/spinal fluid analysis utilized to help in the diagnosis of MS?

1. Exclusion of other alternative etiologies (infectious, inflammatory, granulomatous disorders) if atypical features are present
2. Diagnosis of primary progressive MS (especially to distinguish PPMS from neurodegenerative disorders)
3. Diagnosis of MS in older individuals or those with vascular risk factors, where white matter lesions on MRI may have a vascular or other non-MS etiology
4. In patients with pacemakers or other reason precluding MRI, if the diagnosis of MS is suspected
5. In situations where disease modifying therapy is being considered (such as after a severe clinically isolated syndrome) but imaging and evoked potentials alone provide insufficient evidence to support a diagnosis of MS

continued on next page

13-NEU-535

Mellen Center Approaches: Use of paraclinical testing in MS, continued

Does spinal fluid analysis help to predict the risk of future attacks in a clinically isolated syndrome/ first attack?

A brain MRI is the most predictive test for determining the risk of future attacks after a clinically isolated syndrome. However, CSF studies do add additional predictive value, with the presence of oligoclonal bands in the CSF conferring almost double the risk of a second attack, independent of brain MRI. We tend to utilize CSF analysis most often in this situation to exclude other non-MS etiologies for the neurological symptom. If used for risk estimation, it is generally only if the brain MRI is equivocal and the patient or physician would change their decision to start disease modifying therapy based on the result. At the Mellen Center we tend to follow MRI rather than check CSF to guide the decision to start therapy.

When are evoked potentials useful in making the diagnosis of MS?

Evoked potentials are useful for demonstration of dissemination in space. Most commonly utilized are visual evoked potentials and somatosensory evoked potentials, which are sensitive tests for demyelination in the visual and somatic sensory pathways, respectively. Brainstem (auditory) evoked potentials are also sometimes utilized. In the setting of neurological symptoms of uncertain etiology, evoked potentials can be useful to demonstrate presence or lack of CNS pathology, though a positive result is not specific for a primary demyelinating etiology.

At the Mellen Center evoked potentials now play a limited role as they have been superseded by more disease specific studies including MRI of the brain and spinal cord and CSF studies. Evoked potentials may be useful in the situation of a patient with a single lesion who has an asymptomatic slowing of evoked potentials in a different part of the neuraxis consistent with a second lesion.

Does paraclinical testing help in predicting the future severity of MS?

The number of oligoclonal bands and the IgG index in CSF do not correlate with severity of disease. Having multiple abnormalities on evoked potentials appears to correlate with a worse prognosis in MS (Invernizzi 2011), however early in MS evoked potentials are often normal. At the Mellen center we do not use evoked potentials to provide prognostic information as we have not found this useful in patient care.

Does paraclinical testing help to follow response to therapy?

No paraclinical test (except MRI) is currently used to follow response to therapy. Patients will often ask if their spinal fluid will normalize while on treatment with disease modifying therapy, and the answer to that is no. Even after immunoablation and hematopoetic stem cell transplantation in patients with MS, CSF findings of oligoclonal bands and elevated IgG index remain abnormal.

Are there any biomarker blood tests that aid in the diagnosis or management of MS?

There is currently no blood test available that can specifically be used to diagnose MS with certainty, though some such tests do exist.

The aquaporin-4 IgG antibody (NMO-IgG) is a blood test that has approximately a 76% sensitivity and 94% specificity for neuromyelitis optica (NMO), and we do routinely check for that antibody in the blood if there are clinical or imaging features suggestive of NMO. On rare occasions this test will be positive in the CSF when it is negative in the blood and this may be diagnostically useful.

We do routinely utilize the JC Virus antibody (JCV IgG) assay in the blood to screen for JC virus exposure status, useful in estimating risk for progressive multifocal leukoencephalopathy associated with natalizumab therapy for MS (but not useful in monitoring for PML on natalizumab)(See Mellen Center Approach to natalizumab).

What is Optical Coherence Tomography (OCT)?

OCT is an office-based imaging method that uses near-infrared light to generate cross sectional images (in this case of the retina), analogous to B-mode ultrasound. Though OCT has been used for a number of years by ophthalmologists to monitor nerve fiber layer thinning in glaucoma, applications for neurological diseases, especially MS which commonly affects the optic nerves, are being explored.

continued on next page

Mellen Center Approaches: Use of paraclinical testing in MS, continued

Is OCT clinically helpful in managing patients with MS?

OCT has been proposed to have a role in the following situations:

1. Evaluating for macular edema prior to starting and while on fingolimod therapy for MS
2. During recovery from acute optic neuritis, to quantify axon loss relative to visual deficits.
3. On a yearly or biyearly basis, for monitoring longitudinal neurodegeneration in MS
4. To identify RNFL thinning to demonstrate a history of remote optic neuritis

We routinely use spectral domain (high definition) OCT as the test of choice to screen for macular edema prior to and after starting fingolimod therapy for MS.

In certain circumstances, if a patient with optic neuritis has a persistent severe deficit despite a standard course of intravenous methylprednisolone, an OCT showing preserved axonal integrity may prompt additional immunotherapy, whether a second course of IVMP, plasma exchange, or IVIG.

Though OCT has potential to become useful as a tool to monitor longitudinal neurodegeneration or axon loss, neuroprotective therapies do not yet exist to intervene on that process. Some physicians will still request OCT for longitudinal monitoring, to establish a patient's baseline in anticipation of an effective neuroprotective therapy in the future.

REFERENCES:

Gronseth G, Ashman EJ. Neurology 2000;54:1720-1725

Invernizzi P et al. J Neurol 2011;258:1933-1939

Polman CH et al. Ann Neurol 2011; 69: 292-302.

Tintore M et al. Neurology 2008 70:1079–1083.

Weinstock-Guttman B et al. Mult Scler 2003; 9:529-534