Optic neuritis is the presenting symptom in a sizable proportion (15-20 percent) of patients ultimately diagnosed with clinically definite MS. Studies have shown that the presence of brain abnormalities on MRI at the time of a first attack, such as with ON, strongly predicts 15-year risk of MS and have identified certain factors that may mitigate risk (male sex, optic disk swelling, and atypical clinical features). Given this predictability, some in the specialty argue for the initiation of immunomodulatory therapies in patients with ON at highest risk for conversion to MS. Data show that initiation of immunomodulatory therapy in conjunction with corticosteroids—currently standard of care—reduces the frequency and severity of developing clinically definite MS. Still, neurologists are eager for more guidance on the proper management of ON and patients at high risk for conversion to MS.

**Diagnosis**
Optic neuritis (ON) may be considered part of a spectrum of significant optic nerve diseases, observes Thomas P. Leist, MD, PhD, Director of the Comprehensive Multiple Sclerosis Center at Thomas Jefferson University. It is important to rule out transverse myelitis or a brain stem syndrome. In patients who are over age 45, it is also important to rule out other types of optic neuropathy, such as nonarteritic anterior ischemic optic neuropathy. As such, brain MRI, imaging of the optic nerve and anterior of the eye, and cervical spine are essential for patients with symptoms of ON.

The use of corticosteroids to manage ON is standard, but, according to Peter A. Calabresi, MD, Professor of Neurology and Director, The Johns Hopkins Multiple Sclerosis Center at The Johns Hopkins University in Baltimore, “We realistically have to tell patients that there are no good data to show that you’ll be in a better place a year later if you receive corticosteroid therapy.”

However, some patients who present with ON may clearly be candidates for MS therapies.
According to Dr. Leist, “If the patient has optic neuritis and MRI that shows two or more lesions in locations appropriate for MS, then this patient becomes a candidate for treatment with MS therapies.” He notes that Betaseron (IFN-β-1b, Bayer Healthcare), Avonex (IFN-β-1a, Biogen-Idec), and Copaxone (glatiramer acetate, Teva Neurosciences) are all indicated for patients at high-risk for MS and highlights findings of the ETOMS or Early Treatment of MS trial that showed the benefits of treatment in delaying progression of or conversion to clinically definite MS.

Given the association of ON with progression to MS in certain patients, efforts are underway to improve the long-term monitoring of patients at high risk for developing MS and to identify treatments that will yield the greatest benefit for all patients with ON. The answer to both questions could possibly rely—directly or indirectly—on Optical Coherence Tomography (OCT).

OCT has been in clinical use for about a decade and a half. By providing high-resolution cross-sectional images through the retina, OCT permits diagnosis of detached retina, macular edema and macular holes, and optic nerve damage.

The imaging process has been applied to the study of MS and the effects of the disease on the retina. According to Dr. Calabresi and colleagues, the retina “is unique within the CNS in that it contains axons and glia but no myelin, and it is, therefore, an ideal structure within which to visualize the processes of neurodegeneration, neuroprotection, and potentially even neurorestoration.” Among other findings, their studies demonstrate that OCT is effective for quantifying axon thickness in the retinal nerve fiber layer (RNFL) and, importantly, that properly trained clinicians can reliably reproduce measurements over time. Furthermore, they showed that retinal nerve fiber layer thickness as measured by OCT is associated with brain parenchymal fraction and CSF volume, suggesting that OCT provides “concurrent information about MRI brain abnormality in MS.”

Other more widespread diagnostic tools are used currently to track ocular changes following ON or in suspected or definite MS. For example, Dr. Calabresi points out, clinicians can use an ophthalmoscope to identify pallor of the optic nerve head. The degree of pallor is indicative of nerve injury, but assessment of pallor is somewhat subjective, as it may be difficult to compare color variation from person to person or in an individual over time.

Changes in visual acuity as identified through the use of low-contrast charts is also emerging as a valuable monitoring tool. Low-contrast visual acuity has been used as a measure of disease progression in MS trials and has been correlated with measures of MS patients’ quality of life. “Low-contrast visual assessment is an important tool,” Dr. Leist maintains, “the question is whether it can potentially be integrated into a functional composite tool.”

The current Multiple Sclerosis Functional Composite (MSFC) includes the Paced Auditory Serial Addition Test (PASAT) for assessment of the cognitive domain, but there is evidence that “practice”—completing the test multiple times—allows the patient to improve his/her score on this test, Dr. Leist points out. Low-contrast visual acuity may emerge as an alternative to be used in conjunction with the 25-foot walk and the 9-hole peg test to provide a multidimensional functional assessment score.

“Low-contrast screening goes beyond the 20/20 acuity measure to see where patients may have subtle visual complaints,” Dr. Leist says. He notes that some patients, even after complete recovery from an attack of ON, have subtle vision changes.

Finally, visual evoked potentials (VEPs) are commonly used to identify or monitor changes in retinal nerve function. In fact, Dr. Leist points out, VEP findings suggest that many patients with MS have had an attack of ON, even if they have not had a documented clinical presentation.

OCT may have unique diagnostic or monitoring benefits. Unlike ophthalmoscopic visualization, for example, OCT offers a level of objectivity by permitting quantification of the thickness of the nerve fiber, Dr. Calabresi says. And while VEP is a phys-
In a research study currently underway and supported by the National MS Society, Dr. Calabresi and colleagues (Drs. Balcer and Frohman) are following 1,500 patients with OCT in a longitudinal manner to gather data about retinal changes over time in MS patients. These findings will hopefully allow clinicians to use information acquired from OCT to gauge MS progression and patient response to therapy. Dr. Calabresi admits that, “This information is hard to not use clinically. It sometimes makes me more aggressive in treating some patients.”

**Investigating Neuroprotection**

In terms of possible neuroprotection, there is some evidence that glatiramer acetate (GA) may...
be neuroprotective, as it has been shown to help repair laser-induced retinal damage in rats.\(^7\) A clinical trial is now enrolling (OCTAGON) to determine whether GA helps protect from progression of or even reverse nerve damage in patients with ON.

All patients enrolled in the study will receive steroids and additionally will be randomized to receive placebo or GA for six months. Thickness of the nerve fiber layers—expected to be more significant in the GA treatment group—is the primary study endpoint.

The study is intended specifically to determine the benefit of glatiramer acetate therapy for the treatment of optic neuritis and is not intended to explore the role of GA treatment for patients at risk of progressing to MS. When it comes to use of MS therapies in high-risk patients, Dr. Calabresi says, much depends on the individual presentation and the neurologist’s clinical decision-making.

“Not everyone with optic neuritis should go on chronic therapy for MS,” Dr. Calabresi observes. Certain patients are low-risk for MS with essentially normal MRIs. These individuals may have about a 20 percent risk of progressing to MS, according to available data and estimates. For these individuals, there is no strong support for initiating long-term disease modifying therapy. Yet results of the current study may indicate a role for a finite course of neuroprotective therapy.

Among patients with abnormalities evident on the MRI, however, the risk of progression to MS is about 60 percent. As described above, OCT could be useful to estimate risk and support therapy initiation or to track patients over time to monitor disease progression. In these patients, the clinician will have to weigh all the available evidence to decide whether or not to pursue therapy beyond the six month window.

**Recurrent ON and Vision Complaints**

ON is frequently considered a presenting symptom of MS, however, an attack of ON may in certain cases represent the second clinical event that confirms a diagnosis of MS. In such cases, initiation of MS therapy is clearly indicated.

For the patient already diagnosed with MS and on therapy, an attack of ON should be considered a break-through event and suggest the need to alter therapy either by offering an add-on or making a therapeutic switch, Dr. Leist asserts. For the patient on an interferon, this break-through may indicate the development of antibodies (though testing is indicated and results are potentially useful, the presence or absence of antibodies does not diminish the clinical need to alter therapy, Dr. Leist says).

Recurrent attacks of optic neuritis or chronic ON indicate a need to reconsider the diagnosis to rule out neuromyelitis optica or another diagnosis other than MS that may be present.

It is also important to keep in mind that MS patients, “Can still have any other disease that mankind is afflicted with,” Dr. Leist says. As clinicians assess ocular health and visual acuity, they should keep in mind potential diagnoses such as glaucoma, that may account for changes in the patient’s visual acuity over time. Patients should undergo full ophthalmologic evaluation at regular intervals and as indicated by clinical findings, to rule out and/or allow treatment of these conditions.

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