CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Management of Possible Multiple Sclerosis

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A 24-Year-Old Woman with Blurred Vision

Clement D. Lee, M.D.

A 24-year-old woman presents to the emergency department with blurred vision that has developed in the past few days. Symptoms are worse with her left eye closed, and her vision normalizes when her right eye is closed. She has pain, mainly in the right globe, with movement of her eyes. She has no history of medical problems and takes no medications; no myopia, hyperopia, or astigmatism was noted at her last optometric assessment a year ago. She reports no history of or current double vision, difficulty in speaking, weakness, tremor, urinary incontinence, or abnormal spinal sensations. There is no family history of neurologic or ophthalmologic disease.

Examination shows visual acuity of 20/60 in the right eye and 20/20 in the left eye and normal extraocular movements, without nystagmus. A relative afferent pupillary defect (in which a light shone in one eye results in less pupillary constriction than light shone in the other eye) is present on the right side, and the patient is unable to identify 9 of the 10 numbers on Ishihara plates (a test of red–green color discrimination) with the right eye. Dilated funduscopy shows normal optic disks in both eyes. T2-weighted magnetic resonance imaging (MRI) of the optic nerves, brain, and entire spinal cord, performed with the administration of gadolinium, shows enhancement of the right optic nerve with optic-nerve swelling, a finding consistent with retrobulbar optic neuritis. A single, small, nonenhancing ovoid lesion is also noted in the periventricular white matter without surrounding edema. The patient undergoes lumbar puncture, and intravenous glucocorticoids are administered.

Routine laboratory studies are normal. There are no oligoclonal bands in the cerebrospinal fluid (CSF), and testing for anti–aquaporin-4 (anti-AQP4) and anti–myelin oligodendrocyte glycoprotein (anti-MOG) antibodies in serum is negative.

As the admitting physician, in addition to treating her optic neuritis, you consider whether the patient's symptoms and test results suggest the possible onset of multiple sclerosis. You must decide whether this patient should receive disease-modifying therapy for multiple sclerosis or whether monitoring alone is appropriate at this time.

MANAGEMENT OPTIONS

Which one of the following approaches would you take? Base your choice on the literature, your own experience, published guidelines, and other information.

1. **Recommend initiation of disease-modifying therapies for multiple sclerosis.**
2. **Recommend monitoring only at this time.**

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

OPTION 1

Recommend Initiation of Disease-Modifying Therapies for Multiple Sclerosis

Steven L. Galetta, M.D.

Clinically isolated syndromes are defined as first episodes of central nervous system inflammatory demyelination that are harbingers of multiple sclerosis. Patients with clinically isolated syndromes commonly have symptoms and findings that involve the optic nerve, brain stem, or spinal cord.[1] The patient in the vignette presents with features consistent with demyelinating optic neuritis, an initial manifestation of multiple sclerosis in approximately 20 to 25% of patients. The patient also has one lesion on MRI of the brain, which places her at high risk for the development of multiple sclerosis over ensuing years.[1,2] The likelihood of multiple sclerosis, as opposed to another demyelinating disease, is further supported by the negative serum tests for anti-MOG and anti-AQP4 antibodies.

The widely cited 2017 McDonald criteria[3] for the diagnosis of multiple sclerosis allowed for symptomatic brain stem or spinal cord lesions to potentially count toward dissemination in both space (damage occurring to diverse parts of the CNS) and time (damage occurring on separate dates) — both of which are hallmarks of multiple sclerosis. Therefore, patients with such lesions require a brain lesion in only one other qualifying location to meet the diagnostic criteria for multiple sclerosis, and establishing such a diagnosis would support initiation of disease-modifying immunomodulatory therapy. According to current diagnostic criteria for multiple sclerosis, there are not enough data to warrant treating patients who present with optic neuritis alone, such as the patient in the vignette, in a fashion similar to the treatment of those presenting with a brain stem or spinal cord lesion. This distinction has been confusing to both patients and physicians, especially since there are many patients who present with optic neuritis.[4]

Over the past 5 years, data have emerged showing that inclusion of the optic nerve as a site of demyelination to indicate dissemination in space (in addition to lesions in the brain stem or cerebellum, periventricular region, juxtacortical or cortical areas, and spinal cord) would increase the accuracy of a diagnosis of multiple sclerosis.[4] Specifically, studies involving patients with a clinically isolated syndrome have suggested that incorporation of optic-nerve dysfunction as noted on visual-evoked potential testing, optic-nerve abnormalities on MRI, or abnormal results on optical coherence tomography that are consistent with optic neuropathy would improve the diagnostic accuracy for multiple sclerosis.[5]

The potential long-term benefits of early immunomodulatory treatment for persons at high risk for multiple sclerosis, including those whose first presentation is acute optic neuritis, include a lower risk of relapse, less-severe long-term disability, fewer lesions, and less loss of brain volume on serial brain MRI.[1] A recent large registry study of patients with optic neuritis also showed that early immunomodulatory therapy was associated with less-severe subsequent visual and physical disability.[6] Since the detrimental effects of delaying treatment may be recognized only decades later in the form of increased disability, I would initiate therapy as soon as the diagnosis of multiple sclerosis can be established.

Therefore, I would treat this patient with long-term immunomodulatory therapy in addition to short-term intravenous glucocorticoid therapy, which may accelerate recovery of vision. Although starting with high-efficacy therapies such as B-cell depleting agents is linked to better long-term outcomes than starting with weaker agents, this patient has favorable prognostic indicators (low lesion burden and absence of spinal cord or infratentorial involvement), and a drug with moderate efficacy such as a sphingosine-1-phosphate receptor modulator or a fumarate derivative would be a reasonable option. It is important to note that selection of medication for multiple sclerosis should be a shared decision with the patient.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Neurology, NYU Grossman School of Medicine, New York.

OPTION 2

Recommend Monitoring Only at This Time

Ruth Dobson, Ph.D., F.R.C.P.

The importance of prompt initiation of disease-modifying therapy in patients with multiple sclerosis is increasingly recognized. The 2017

revisions to the diagnostic criteria for multiple sclerosis facilitate earlier diagnosis by incorporating lesions on MRI and oligoclonal bands in CSF as surrogates for clinical events.[3] However, most disease-modifying therapies have long-term implications for immune function, family planning, and adverse events, including infection. Rapid initiation of treatment after a first demyelinating event, in the absence of a confirmed diagnosis of multiple sclerosis, is not always the best option.

This patient has a symptomatic, gadolinium-enhancing optic-nerve lesion and a single periventricular lesion; she does not meet current diagnostic criteria for multiple sclerosis.[3] Although both symptomatic and asymptomatic demyelinating lesions can contribute to the diagnostic requirement of lesions disseminated in time and space, symptomatic optic-nerve lesions are specifically excluded because their inclusion decreases specificity.[3] Single periventricular lesions can be detected in healthy persons and do not satisfy MRI criteria for multiple sclerosis proposed by consensus groups.[7]

Of all clinically isolated syndromes, optic neuritis carries the lowest risk of subsequent conversion to multiple sclerosis.[8] Only 38% of patients in the Optic Neuritis Treatment Trial had definite multiple sclerosis after 10 years.[9] Furthermore, populations enrolled in longitudinal studies of optic neuritis often include patients with other risk factors for the development of multiple sclerosis. Patients completing the 10-year follow-up in the Optic Neuritis Treatment Trial had a higher prevalence of baseline MRI lesions than those lost to follow-up (144 of 302 patients [48%] vs. 16 of 49 patients [33%]).[9] Such studies may therefore overestimate the population risk of multiple sclerosis after a single episode of optic neuritis.

The absence of oligoclonal bands in the CSF further reduces the risk of subsequent multiple sclerosis. Oligoclonal bands are associated with an increased risk of multiple sclerosis in patients with clinically isolated syndromes,[8] an effect that persists even when considering MRI lesions and factors including age and sex.[8] The relative paucity of MRI abnormalities and negative oligoclonal bands in the CSF mean that this patient's risk of multiple sclerosis is approximately 26% at 3 years.[10]

This patient's final diagnosis may not be multiple sclerosis. Several autoimmune conditions can manifest with optic neuritis, no oligoclonal bands, and white-matter lesions on MRI, including sarcoidosis, systemic lupus erythematosus, and Sjögren's syndrome. Aside from neuromyelitis optica spectrum disorder, a frequent reason for misdiagnosis is misinterpretation of nonspecific MRI findings, such as those seen in this case, in patients not meeting 2010 McDonald criteria. The 2017 revisions to the McDonald criteria broadened the spectrum of MRI lesions that can be used to show dissemination in time and space, including both cortical lesions and a symptomatic lesion if it is in the brain stem or spinal cord. However, these guidelines explicitly recognize the potential trade-off between sensitivity and specificity and the need to consider incidental findings and alternative diagnoses, particularly in patients presenting with a single attack. The 2017 guidelines recommend considering interval clinical and radiologic review when diagnostic criteria are not met[3] — a recommendation that is pertinent to this case.

Treatment decisions must be collaborative rather than directive. Up to 20% of people with multiple sclerosis miss more than 20% of their doses of disease-modifying drugs, and this proportion increases with time since the initiation of treatment.[11] Family planning may result in difficult decisions regarding treatment continuation, with many disease-modifying drugs relatively contraindicated immediately before and during pregnancy and breast-feeding. Even when safety data exist, regulatory advice with respect to pregnancy can be slow to change, which means that patients need to consider stopping, switching, or using treatments off-label while trying to conceive and during pregnancy. Immunosuppressive therapies have been associated with reduced vaccine responses, infections, and progressive multifocal leukoencephalopathy.[12] Disease-modifying therapy may not reduce the risk of the development of clinically definite multiple sclerosis in low-risk patients[8]; studies examining rapid initiation of disease-modifying therapy after a first demyelinating event are ongoing.

Therefore, for patients such as the woman in the vignette, it is feasible to offer monitoring without immediate initiation of disease-modifying therapy. Active follow-up with imaging can enable the diagnosis of multiple sclerosis in the absence of additional overt clinical events, allowing prompt treatment initiation in patients who

are most likely to benefit, while avoiding unnecessary treatment in those with no ongoing central nervous system inflammation. Therefore, I would use an active watchful waiting approach for this patient — as long as this decision is made in partnership with her.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London.

1. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008;131:808-17.
2. Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. Arch Neurol 2008;65:727-32.
3. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
4. Brownlee WJ, Miszkiel KA, Tur C, Barkhof F, Miller DH, Ciccarelli O. Inclusion of optic nerve involvement in dissemination in space criteria for multiple sclerosis. Neurology 2018;91(12):e1130-e1134.
5. Vidal-Jordana A, Rovira A, Arrambide G, et al. Optic nerve topography in multiple sclerosis diagnosis: the utility of visual evoked potentials. Neurology 2021;96(4):e482-e490.
6. Kenney R, Liu M, Patil S, et al. Long-term outcomes in patients presenting with optic neuritis: analyses of the MSBase registry. J Neurol Sci 2021;430:118067.
7. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016;15:292-303.
8. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015;138:1863-74.
9. Beck RW, Trobe JD, Moke PS, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. Arch Ophthalmol 2003;121:944-9.
10. Arrambide G, Tintore M, Espejo C, et al. The value of oligoclonal bands in the multiple sclerosis diagnostic criteria. Brain 2018;141:1075-84.
11. McKay KA, Tremlett H, Patten SB, et al. Determinants of non-adherence to disease-modifying therapies in multiple sclerosis: a cross-Canada prospective study. Mult Scler 2017;23:588-96.
12. Cauchi M, Willis M, Andrews A, et al. Multiple sclerosis and the risk of infection: Association of British Neurologists consensus guideline. Pract Neurol 2022 July 21 (Epub ahead of print).

DOI: 10.1056/NEJMclde2300812