Case Study:

A Classical Presentation of Optic Neuritis Leading to a Non-classical Case of Multiple Sclerosis

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ABSTRACT

Acute optic neuritis (ON) is an inflammation of the optic nerve that is commonly associated with multiple sclerosis (MS). However, the differential diagnosis of MS is extensive, and variants and mimickers of MS can easily confound the diagnosis. This case study reviews the current diagnostic work up strategies for MS and teaches a practical lesson: diagnosis depends on both clinical findings and an exclusion of alternate explanations.
INTRODUCTION

Optic neuritis (ON) is an acute inflammation of the optic nerve that classically presents with sudden monocular vision loss and pain on eye movement. This inflammation can occur along any segment of the optic nerve. One-third of cases will present with swollen optic nerves, termed as optic papillitis, where as in two-thirds of cases, the optic nerve will appear normal and is termed retrobulbar neuritis. The differential diagnosis for the etiology of optic neuritis is lengthy and includes infections, autoimmune disorders, ischemia, and diabetes; however the most common etiology is multiple sclerosis (MS). In 20-30% of cases, optic neuritis is the initial manifestation of MS and up to 50% of patients with MS will develop an episode of optic neuritis \(^1\),\(^2\). Multiple sclerosis is an autoimmune disease that causes the destruction of the myelin insulation that covers the nerve fibers in the brain and spinal cord of the central nervous system (CNS). Approximately 300,000 individuals in the United States are affected by MS as it represents the most common debilitating illness among young female adults\(^2\).

In my case study, the patient presented with a very classical presentation of retrobulbar neuritis and MRI lesions pathognomonic for MS. However, further testing started to reveal atypical findings that warranted further investigation into the case. Surprisingly, researchers have suspected that 5-10% of patients diagnosed with MS in fact had a different disease masquerading as MS\(^3\). The differential diagnosis of MS ranges from inflammatory diseases, neoplasm, and infections, to metabolic and genetic disorders. This case report reviews the management of patients with MS, discussing current diagnostic work-up strategies and ruling out common mimickers of MS as they relate to the case presented. It is important for clinicians to decipher and challenge all clinical findings and be conscious of other multi-systemic diseases that may confound diagnosis. The case report will also review the most current treatment options
for MS, and finally the management of MS from an ophthalmic stand-point utilizing imaging technology.

CASE STUDY

JC, a 23 year old Caucasian female, presented to the eye clinic on November 23 2010, complaining of constant, moderate pain around her left eye for the past four days. She also reported that her left eye was blurry centrally and attributed these symptoms to her outdated glasses. She reported that she had experienced a few episodes of similar eye pain in the past, but not to this degree. She was currently taking naproxen to help alleviate her symptoms.

JC’s ocular history was unremarkable. Her medical history was only significant for recurrent urinary tract infections. She did not have a history of neurological problems and denied symptoms of dizziness, tingling, tremors, sensory changes, speech changes, and focal weaknesses. Besides her current use of naproxen, she denied taking any other medications including oral contraceptives. Her family ocular history was significant for glaucoma in her father and paternal grandfather. Her family medical history was positive for multiple sclerosis by her maternal grandfather, who was diagnosed at age 29 and passed away at the age of 58 from MS.

Ocular examination findings:

The patient’s entering visual acuities with correction were OD: 20/20 and OS: 20/80 pinhole no improvement. Her pupils exhibited a 3+ APD OS. The extraocular motilities were full but the patient reported pain in her left eye in all gazes. The intraocular pressures were 20mmHg OD and OS measured by GAT.

Slit lamp biomicroscopy revealed that the anterior segment was healthy OU. The corneas were clear, conjunctivae were white and quiet, anterior chamber angles were open 1:1 using Van
Herrick technique with no cells or flare, irises were flat and avascular, and lenses were clear OU. The patient was dilated and ophthalmoscopy also revealed that her posterior segment was healthy. The cup-to-disc ratios were 0.4 round, neuroretinal rims were healthy and intact, retinal vessels appeared normal with an arterial-venous ratio of 2/3, maculae were flat, avascular with (+)FR, vitreous was clear with no cells, and no retinal breaks or defects were noted in the periphery OU.

A red-cap saturation test was used as a diagnostic assessment for contrast sensitivity. The patient reported that the cap appeared dullest centrally and in superior view with her left eye as compared to her right eye. A color vision test using Ishihara pseudoisochromatic plates was then performed. The patient correctly answered 6/6 plates on the right eye and 6/6 plates with difficulty on the left eye. A Humphrey 24-2 threshold visual field was also performed. The visual field on the right eye showed diffuse VF loss with two superior paracentral defects (see image #1). The visual field on the left eye exhibited a dense central scotoma and superior altitudinal defect (see image #2). The visual fields showed good fixation (fixation losses 0/14 OD, 1/10 OS) and good reliability (2% false positive errors, 0% false negative errors OD and 0% false positive errors, 6% false negative errors OS). Her blood pressure was 118/84 right arm sitting. Her tentative diagnosis was retrobulbar optic neuritis in the left eye.

A same day consult with an ophthalmologist was obtained for the management of the retrobulbar optic neuritis, and a same day magnetic resonance imaging (MRI) of brain and orbits with gadolinium and fat suppression was ordered. The ophthalmologist began immediate treatment of intravenous (IV) Solu-Medrol (methylprednisolone sodium succinate) 1g/day X 3 days, followed by oral prednisolone 60mg qd X 11 days taper.

**Diagnostic workup and clinical findings:**
JC returned for a follow up appointment with the ophthalmologist after two days of IV methylprednisolone and reported no improvement to her vision or decreased eye pain. In the mean time, she was also referred to a neurologist. The MRI of the orbits demonstrated that the optic nerves and optic chiasm were normal in size, globes were intact, and the extra-ocular muscles and retrobulbar fat were normal. The MRI of the brain revealed numerous demyelinating plaques located in the right and left cerebral hemispheres and the right medulla. The lesions involved the periventricular and subcortical white fibers with six enhancing lesions indicative of active demyelination and highly suspicious of MS. One week later, JC then underwent a second MRI of the cervical and thoracic spine to rule out transverse myelitis. JC’s MRI demonstrated a 1.7 cm lesion on the left ventral cord at the C2 and C3 vertebrae; no lesions were seen in the thoracic spine (MRI images provided below).

JC had reported numbness and sensitivity of bilateral hands for two days during her IV methylprednisolone; however, the numbness resolved after about a week. Her neurological evaluation was significant for left-sided hyperreflexia, slowed and dysrhythmic rapid alternating movement in left hand and left leg, and mild dysmetria left leg. She was negative for Lhermitte sign, a sign indicative of neck or spinal abnormalities. Her visual acuity had improved and was 20/40 OS but she reported that the ocular pain in her left eye still persisted. There were no new signs of visual disturbances like diplopia, nystagmus, and ophthalmoplegia.

Several laboratory tests were also obtained to rule out mimickers of multiple sclerosis. The lab tests were significant for elevated antinuclear antibody (ANA), positive anti-Ro/SSA and anti-La/SSB, and positive Epstein Barr Virus (EBV). Her urinalysis was also significant for increased leukocyte esterase. With positive ANA and antibody titers, JC was then referred to a rheumatologist for further evaluation. The rheumatologist concluded in her assessment that there
was no clear clinical evidence of systemic lupus erythematosus (SLE) or Sjögren’s syndrome (SS). Although the neurologist was confident that the diagnosis was MS, she was still concerned with the laboratory results and decided to perform a lumbar puncture and CSF analysis. The pathologist reported that the patient's CSF contained greater than five well defined gamma restriction bands (oligoclonal bands) that were not present in the patient's corresponding serum sample, supportive evidence of MS.

After a month of extensive examination and testing, JC was diagnosed with multiple sclerosis in January 2011. The neurologist discussed the treatment options and the mechanisms of action, risks and benefits for current MS therapies with the patient. After much research and contemplation with her family, JC decided that she would initiate Avonex, an interferon beta-1a drug that is administered through intramuscular injections weekly. To date, JC’s visual acuity has returned to 20/20 OU with no complaints of ocular pain or signs of ocular disturbances. She is scheduled to return for a repeat visual field and eye follow-up appointment in early February. She is also scheduled for a repeat MRI of the brain and spinal cord in early March.

**DISCUSSION**

Visual function in optic neuritis can spontaneously return within eight to ten weeks, but can also lead to permanent vision loss. The Optic Neuritis Treatment Trial (ONTT) indicated that systemic intravenous treatment with corticosteroids may accelerate recovery time and reduce the risk of developing MS, but did not improve the eventual visual outcome. At the one year follow-up in the ONTT study, at least 95% of patients had visual acuity better than 20/40, and of these 50% had visual acuity of 20/20. The visual field defects that are commonly found are diffuse central or centrocecal scotomas, however any VF defect may be present. Interestingly, patients can also have a diffuse or central VF abnormality in the uninvolved eye at the time of
the optic neuritis attack. These central VF losses generally progress to paracentral and arcuate defects due to localized loss in the nerve fiber axons. At one year, studies have shown that localized abnormalities existed in 35.7% of affected eyes and 34.4% in the fellow eye, indicating that both eyes show similar patterns of nerve fiber bundle loss over time. Additionally, these localized defects tend to remain for the next 15 years. Temporal pallor of the optic disc may also develop after 4-6 weeks; however, despite the significant axonal loss, the long-term visual prognosis still remains good. Other common MS-related visual disturbances include permanent visual impairment in contrast sensitivity, color vision, and motion perception, as well as diplopia, bilateral internuclear ophthalmoplogia (INO), and pendular nystagmus.

When optic neuritis occurs, patients are referred for a brain MRI, and selectively for cervical and thoracic spine MRI. The MRI may demonstrate white-matter T2 signal abnormalities consistent with demyelination or enhancing lesions in the brain and spinal cord indicative of multiple sclerosis. The most common lesions occur in the periventricular white matter, subcortical white matter, and pons. The final ONTT indicated that the presence of brain MRI abnormalities at the time of an optic neuritis attack is the strongest predictor of the 15-year risk of MS. Cervical and thoracic MRI is typically ordered in cases of spinal cord dysfunction. A rare variant of MS know as neuromyelitis optica (NMO) or Devic’s disease for example, is characterized by optic neuritis and transverse myelitis with lesions that extend over three or more vertebral segments.

The presence of white matter abnormalities alone however is not sufficient to definitively diagnosis multiple sclerosis. Due to the variable sign, symptoms, and pathogenesis of MS, researchers have formulated specific diagnosis criteria over the decades to simplify and aid in the diagnosis of MS. Currently, the revised “McDonald criteria”, an extensive list that incorporates
both clinical assessments and MRI findings, is used to diagnosis clinically definite MS\textsuperscript{11}. However, despite these specific diagnostic criteria, several diseases that masquerade as MS and even variants of MS can produce similar clinical signs and neuro-radiological lesion patterns.

Other diagnostic workup procedures like visual evoked potential (VEP), lumbar puncture with cerebral spinal fluid (CSF) analysis, and laboratory blood tests are thus also performed in atypical cases of optic neuritis and to exclude other systemic diseases, supporting the diagnosis of MS. Atypical cases of ON include: marked optic disc swelling, progressive vision loss after two weeks, persistent pain, lack of partial recovery within four weeks after onset of ON, vitritis, and orbital inflammation\textsuperscript{12}. Abnormal VEPs provide data to support the diagnosis of acute demyelinating disease, ON, or MS\textsuperscript{2}. The presences of oligoclonal bands in the CSF (and lack of these bands in the blood serum) indicate abnormal synthesis of immunoglobulins produced within the CNS and are suggestive of CNS disease. These oligoclonal bands are important indicators in the diagnosis of MS, as approximately 79\%-90\% of all MS patients will have permanent observable oligoclonal bands of high frequency (likely 10 or more bands)\textsuperscript{13,14}. Panels of laboratory blood tests typically for serum antibodies are also used to differentially diagnosis autoimmune inflammatory diseases, neoplasms, and infections that are known to mimic MS\textsuperscript{15}.

Two of the most notable inflammatory autoimmune diseases that mimic MS are systemic lupus erythematousus (SLE) and Sjögren’s syndrome (SS). Both diseases often present with symptoms and clinical signs similar to MS such as optic neuritis, neuro-radiological lesions, and surprisingly, antibodies which are commonly used to detect the presence of SLE and SS\textsuperscript{15-18}. Antinuclear antibodies (ANA) for example, are known to be present in high frequency in cases of SLE. MS patients however can have positive ANA titers with a frequency range between 3-27\%. Anti-Ro (SS-A) antibodies that are detected in 40-70\% of SLE and up to 90\% of SS cases,
can also be found in an alarming rate of 2-15% in MS\textsuperscript{16}. With the lack of determinant tests, distinguishing between MS and autoimmune diseases can lead to misdiagnosis. Evidently, one study found that 10 of 60 patients with confirmed primary progressive MS actually had Sjögren’s syndrome\textsuperscript{17}. To further complicate the matter, controversy remains as to whether or not these two diseases may actually co-exist together. A particular study described a patient who had definite MS and anti-SSA/Ro antibodies, but concluded that the association between the two was weak and that the clinical findings may have been due to chance\textsuperscript{18}. Other studies have confidently concluded that Sjögren’s and MS can coexist in the same individual\textsuperscript{16,19}. Whether or not an autoimmune disease can co-exist with MS remains for future study, but creates yet another challenge in the diagnosis and management of MS patients.

Acute treatment options for optic neuritis include intravenous treatment with corticosteroids or observation alone; oral prednisolone alone is not standard of practice. The ONTT study also indicated that patients treated with IV corticosteroids were found to have a significantly decreased risk for the development of MS for two years; however there was no beneficial effect after three years\textsuperscript{1}. Subsequently, long term treatment using immunomodulation agents are often initiated in patients who are considered high-risk candidates for MS (those with abnormal brain MRI at baseline) to prevent the development, progression, and relapse of the disease. Currently there are seven disease-modifying drugs that are FDA approved, as there is no known cure for MS. The current drugs that are administered parenterally (intramuscularly or subcutaneously) include: Avonex and Rebif (interferon beta-1a), Betaseron (interferon beta-1b), Copaxone (glatiramer acetate), Mitoxantrone, and Tysabari (natalizumab). Two new breakthrough drugs that have been recently approved by the FDA and are the first to be
administered orally are Gilenya (fingolimod) and Ampyra (dalfampridine). Until 2010, efficacious oral therapies have been an unmet need in MS treatment.

Several studies have shown that immunomodulation therapy during an initial attack can greatly decrease the chance that a patient will develop MS. The Controlled High Risk Avonex Multiple Sclerosis Study (CHAMPS) demonstrated a 44% reduction in the three year cumulative probability of developing MS. There was also significant reduction of new MRI brain lesions in the Avonex group. The five year follow-up study, Controlled High Risk Avonex Multiple Sclerosis Study in Ongoing Neurological Surveillance (CHAMPIONS), demonstrated that immediate treatment resulted in significant reduction in the rate of development of MS as compared with delayed treatment. The Early Treatment of Multiple Sclerosis (ETOMS) study also highlighted that the risk of MS was reduced at the two year follow up by 34% as compared to the 45% in the placebo-treated group. The Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study also showed comparable results in decreased risk of MS by 50%. Current studies suggest that the newest immunomodulation drug, natalizumab is also effective in reducing disease activity in patients with relapsing multiple sclerosis and those who have inadequate response to other therapies.

Recent clinical trials have demonstrated efficacy of Gilenya in reducing the relapse rate of MS as well, and attaining higher levels of treatment adherence due to the oral administration of the drug. Ampyra has been indicated as an oral treatment to improve walking, as walking or mobility impairment is one of the most physically disruptive consequences of MS. Although preliminary results show decrease probability in the development of MS, each drug differ in efficacy rate, adverse side effects, and variation in patient responses. The long-term effects and
benefits of all drugs still remain for future study, making the prognosis of MS difficult to predict\textsuperscript{20-24}.

Traditionally, MS is believed to be an inflammatory disease that destroys the myelin sheath, sparing the axons until advanced stages. However, recent studies suggest that axonal damage may actually occur in early stages of MS leading to permanent disability\textsuperscript{12}. Studies have thus aimed to use optical coherence tomography (OCT) to evaluate the integrity of optic nerve axons in patients with MS, using the retina as a marker for neurodegeneration\textsuperscript{25}. Studies have shown significant RNFL reduction in all MS patients with and without prior episodes of ON. Axonal loss in the RNFL were also found to be correlated to visual impairment as measured by low-contrast letter acuity (even if visual acuities were 20/20 or better) and disability scores in CNS dysfunctions and disease activity (such as white matter lesions on MRI)\textsuperscript{26}. The results of these studies have thus substantiated the use of OCT as a structural biomarker of axonal loss in MS, becoming a promising tool in treatment trials. Additionally, the use of OCT may play a crucial role in the management and evaluation of patients in ophthalmic practices in the future\textsuperscript{25,26}.

**CONCLUSION:**

Optic neuritis and MRI lesions are heralding manifestations of multiple sclerosis, and in most cases, the diagnosis of MS can be confidently made without further testing. However, with atypical findings and the lack of unequivocal tests, differentiating between MS and the mimickers and variants of MS can easily lead to misdiagnosis. This poses a serious problem as the prognosis and treatment of these diseases differ greatly. This case demonstrates the current diagnostic strategies of MS and the importance of weighing all clinical evidence before a definitive diagnosis is made. Overall, it is important for clinicians to realize that although
patients may present with classical signs and symptoms of a disease, clinical cases are seldom textbook-like. Clinicians should meticulously evaluate patient history and demographics, and interpret all pertinent clinical signs and symptoms in conjunction with laboratory results and imaging. A clinician should diagnose with confidence based on clinical evidence and exclusion of all alternate explanations before initiating treatment. Once a diagnosis is confidently made, studies have shown that immunomodulation therapy may decrease the risk of MS and prevent progression of the disease. Finally, OCT is a promising tool in measuring neuronal degeneration and may play a crucial role in drug trials and the future ophthalmic management of MS in practice.
HVF 24-2: Right Eye (image #1)
MRI IMAGES

Axial T2 FRFSE (Fast Relaxation Fast Spin Echo) - numerous periventricular lesions also known as “Dawson’s Fingers”

Same section as above using FLAIR (Fluid Attenuation Inversion Recovery) technique

Axial T1 + Contrast- enhancing lesion indicative of active demyelination
Sagittal FLAIR- numerous lesions in cerebrum, also note lesion in medulla

Sagittal T2 FSE (Fast Spin Echo)- lesion at C2 and C3, on left ventral spinal cord
BIBLIOGRAPHY


