Optic Neuritis

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Chief complaint: 40 year-old female with cloudy vision of the right eye

History of Present Illness: The patient is a 40 year-old female who was well until two weeks prior to her clinic visit when she noticed visual loss in her right eye. It was accompanied by pain with eye movements and a dull retro-orbital ache. She also noted decreased perception of color and contrast. She denied weakness, numbness, tingling, double vision or headache. She recalled one episode of similarly blurred vision in the left eye one year ago, which resolved spontaneously.

Past Ocular History:

- Recurrent corneal abrasion in the right eye
- Prism in glasses since age 8

Past Medical History:

- Migraine headaches
- No history of hypertension, hyperlipidemia, or diabetes

Medications:

- Fexofenadine-pseudoephedrine (Allegra-D®)
- Multivitamin

Allergies:

- Azithromycin – stomach pain
- Betamethasone – hives
- Sulfadoxine – headaches

Family History:

- Sister with multiple sclerosis, diagnosed 10 years ago, with a history of optic neuritis.
- Mother with amblyopia in right eye (OD), migraine
- Maternal and paternal grandfathers with glaucoma

Social History:

- 1-2 alcoholic beverages per week
- No history of smoking

Review of Systems: As above, otherwise negative.

Ocular Exam:

Best-Corrected Visual Acuity:

- Right eye (OD): 20/20
- Left eye (OS): 20/20

Pupils:

- OD: 3 mm (dark) to 2 mm (light), slow, 0.3-0.6 log unit relative afferent pupillary defect
- OS: 3 mm (dark) to 2 mm (light), brisk, no relative afferent pupillary defect

Intraocular pressure (applanation): OD: 15 mmHg, OS: 15 mmHg

Extraocular motility: Full OD and OS, pain with adduction and abduction OD, 4 prism diopters of comitant esophoria

Confrontation visual fields:

- Full to finger confrontation OD and OS
- Red target testing revealed red desaturation OD temporally and centrally, normal OS

External: Normal both eyes (OU)

Slit Lamp Exam:

- Lids/lashes: Normal OU
- Conjunctiva/sclera: Normal OU
- Cornea: Clear OU
- Anterior chamber: Deep and quiet OU
- Iris: Normal architecture OU
- Lens: Clear OU
- Vitreous: Normal OU

Dilated Fundus Exam (shown in Figure 1):

- Optic nerves: No pallor or edema OU, small cup:disc OD>OS
- Macula: Normal OU
- Vessels: Normal course and caliber OU
- Periphery: Normal OU

Goldmann perimetry (Figure 2):

- OD: Inconsistent answers and mild constriction of I2e and I1e isopters
- OS: Full

Spectral-domain optical coherence tomography (SD-OCT) of the optic nerve heads (Figure 3):

- No thinning of retinal nerve fiber layer OU. Smaller cup-to-disc ratio OD than OS

Optical coherence tomography of ganglion cell + inner plexiform layer (Figure 4):

- OD: Normal ganglion cell layer thickness
- OS: Reduced ganglion cell layer thickness inferiorly

Critical flicker fusion:

- OD: 17.9 (standard deviation 0.8) (depressed)
- OS: 24.2 (standard deviation 1.6)
- Magnetic resonance imaging (MRI) of the orbits and brain with and without contrast show contrast enhancement of the right optic nerve, and multiple ovoid periventricular white matter lesions, seen in Figures 5 and 6.

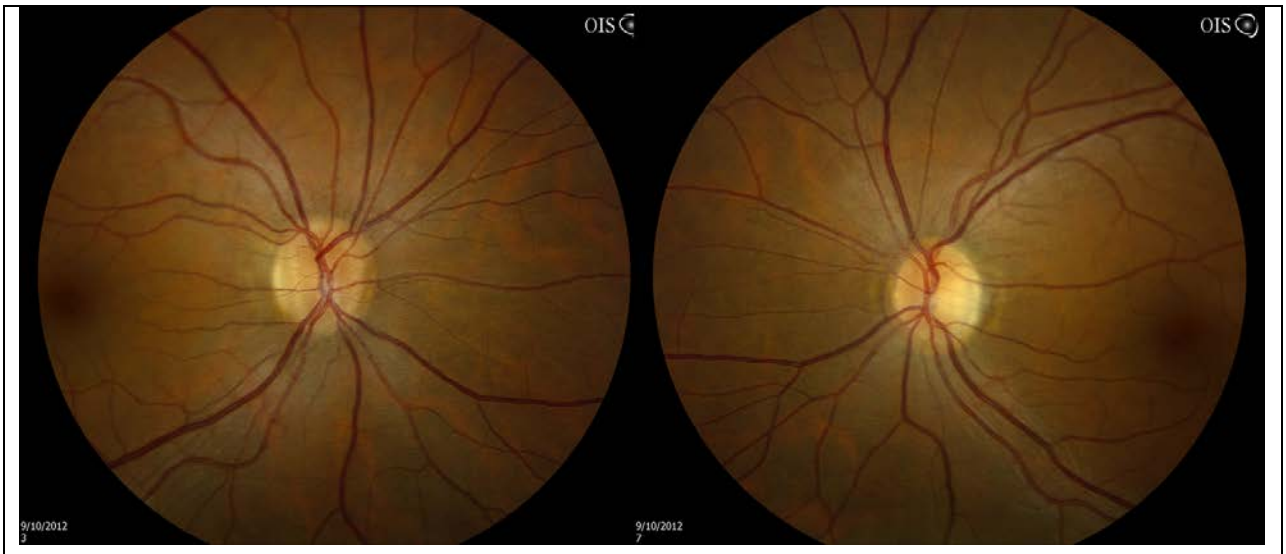

Figure 1: Color fundus photographs of the right and left eye show no optic disc edema. There is temporal pallor of the optic disc in the left eye.

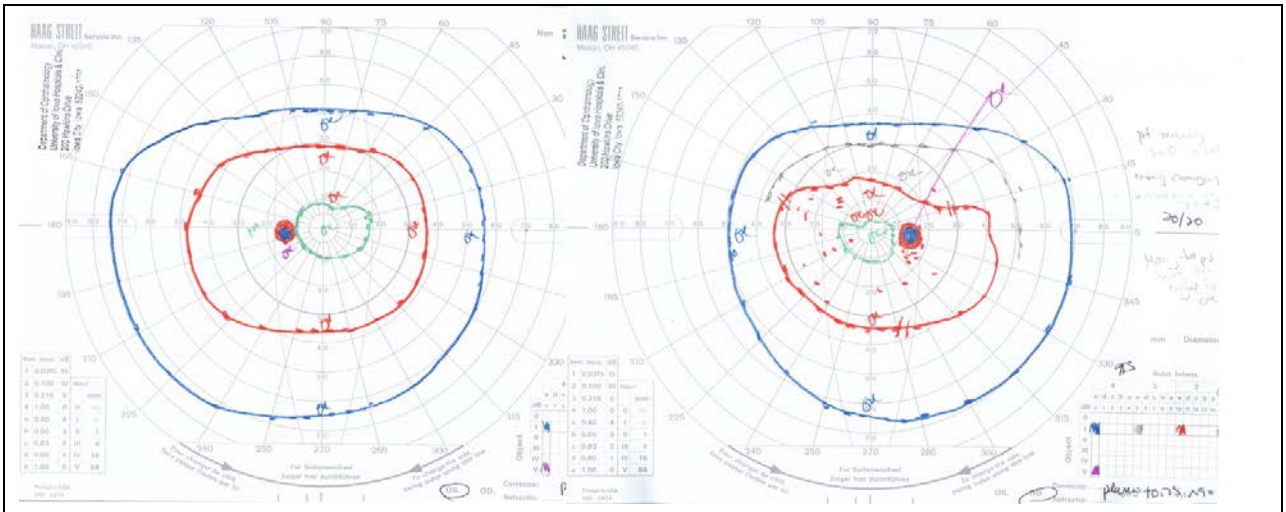

Figure 2: Goldmann perimetry OS (left) and OD (right)

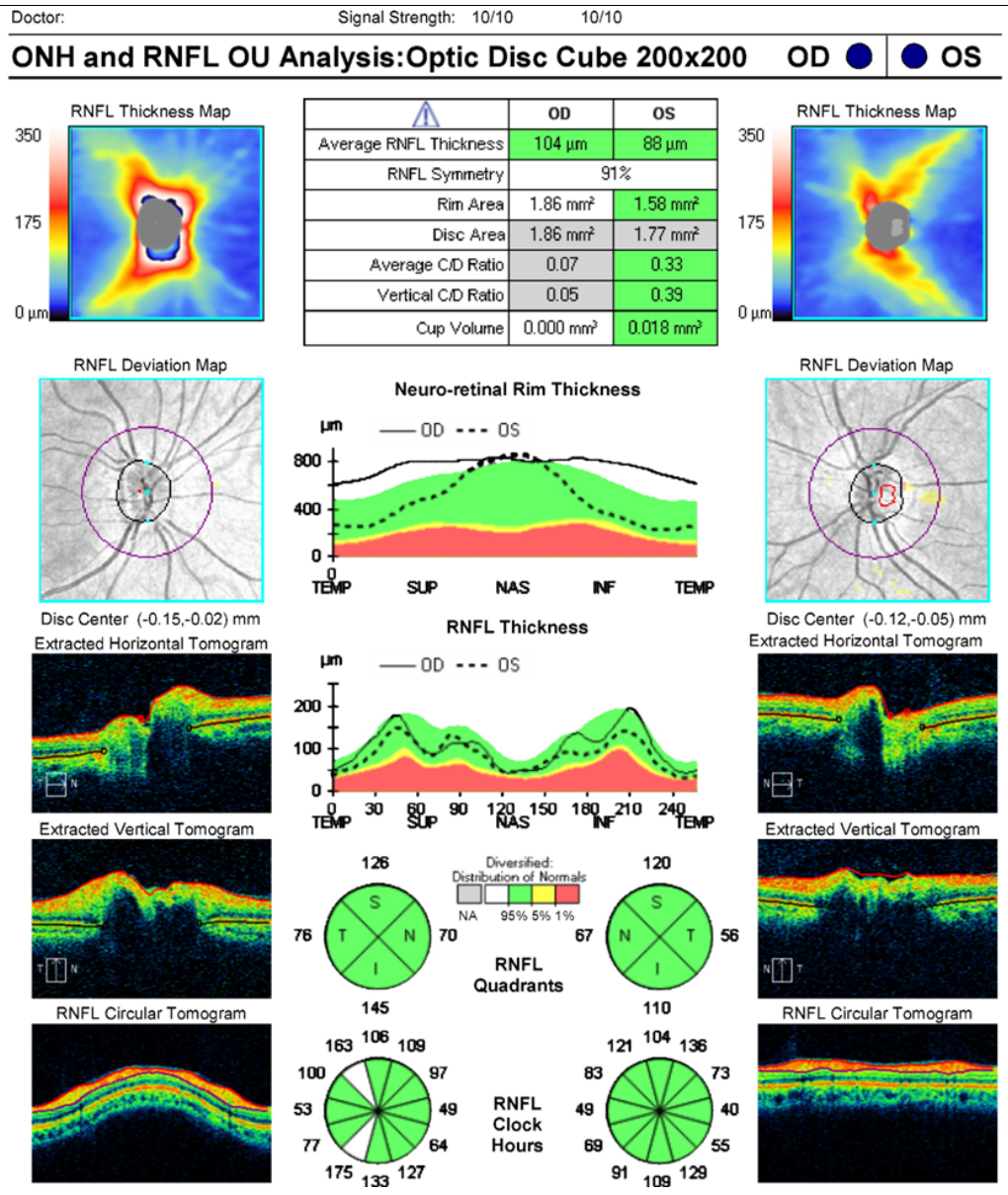

Figure 3: SD-OCT of optic nerve heads

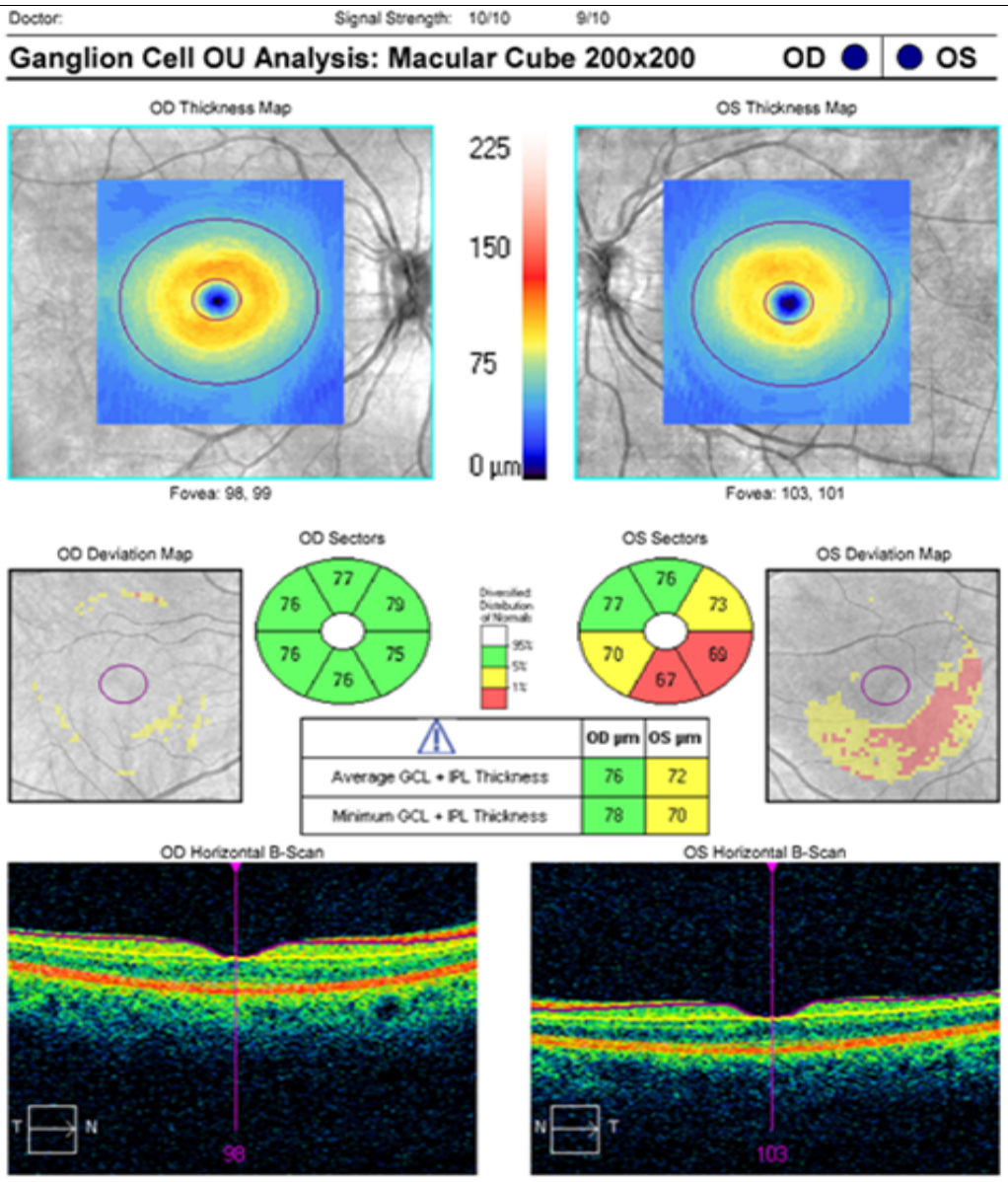

Figure 4: SD-OCT of ganglion cell + inner plexiform layer

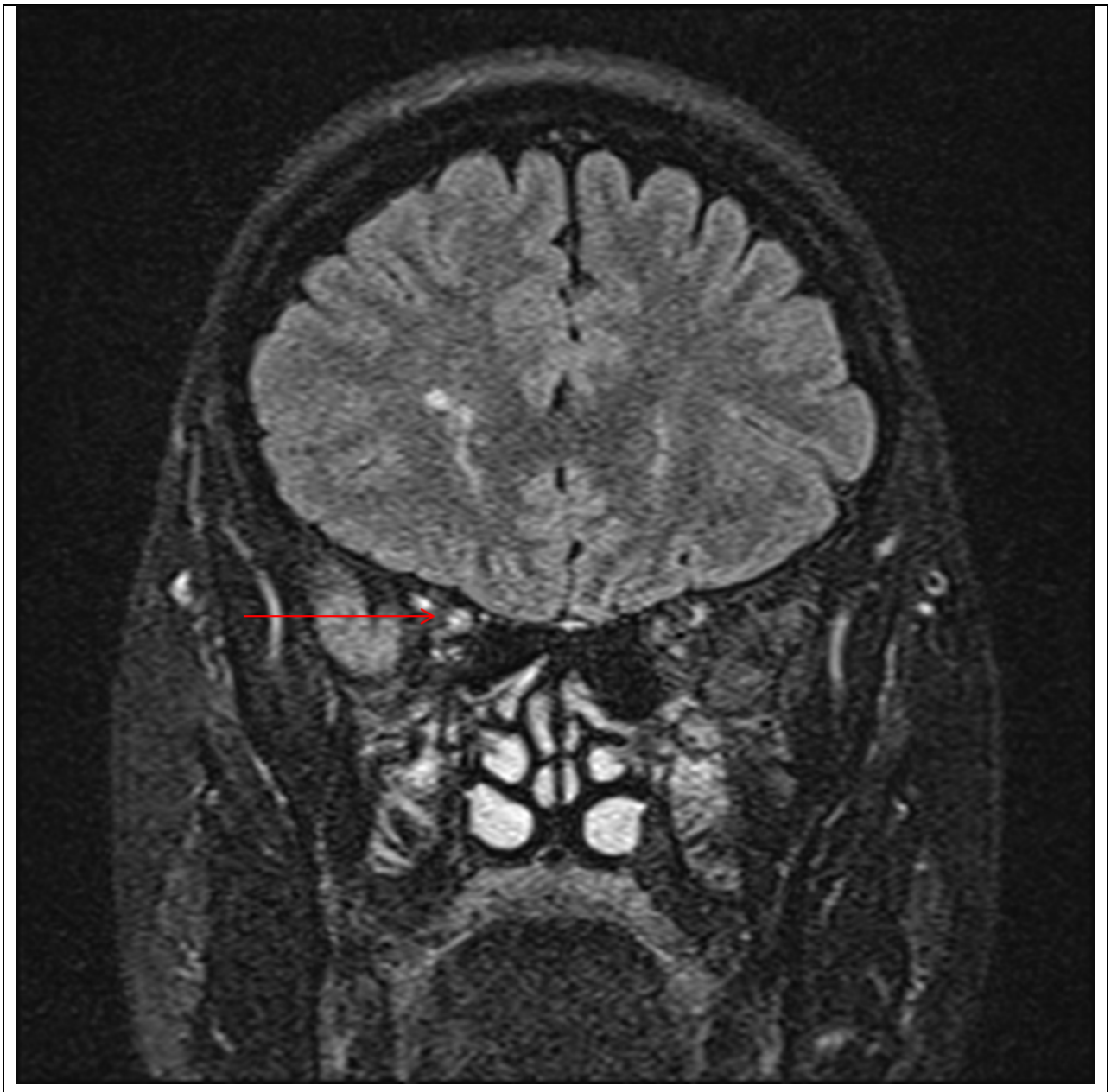

Figure 5: Coronal T2 – FLAIR sequence showing enhancement of the right optic nerve (arrow)

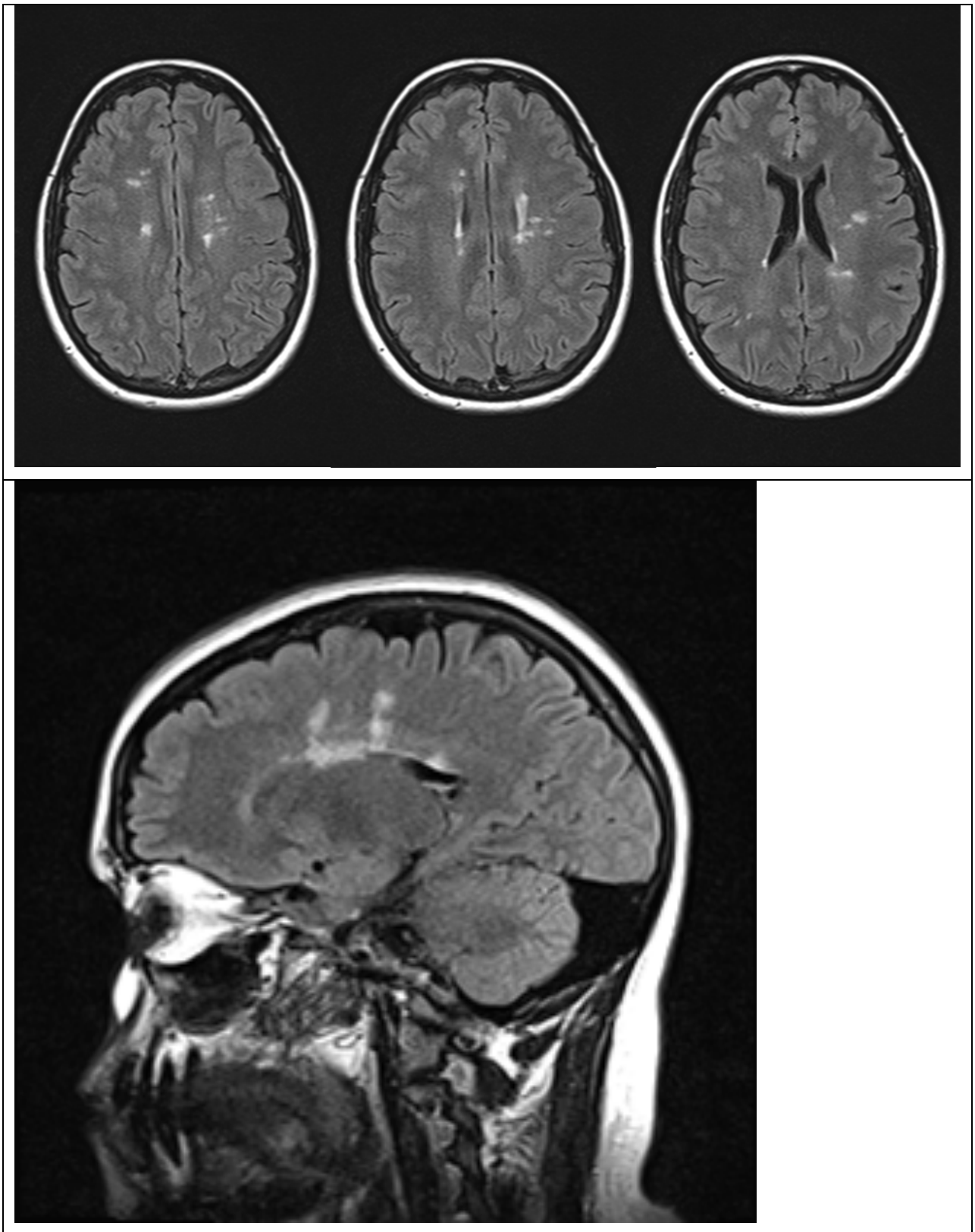

Figure 6: Axial (A) and sagittal (B) T2 – FLAIR sequence showing multiple "Dawson's Fingers": vertically oriented ovoid periventricular white matter lesions.

Diagnosis: Optic neuritis of the right eye with a prior bout of optic neuritis in the left eye

Discussion:

Optic neuritis is defined as inflammation of the optic nerve, which can be anterior, in which optic disc swelling is visible, or more commonly retrobulbar, in which inflammation is posterior to the globe without optic disc edema. The etiology of optic neuritis can be secondary to demyelination, vasculitis (such as secondary to systemic lupus erythematosus), infection (such as syphilis or post-viral optic neuritis, most commonly seen in children) or a granulomatous process (such as Wegener's granulomatosis or sarcoidosis). Demyelination may be isolated or associated with multiple sclerosis (MS) (Thurtell, 2012).

Presenting symptoms include subacute vision loss over a few days to 2 weeks, with recovery typically beginning by one month with the majority of recovery completed by two months. Pain with eye movement is seen in 92% of patients, and often precedes visual loss. Decreased color vision and color desaturation with loss of contrast is common, and is often more severe than Snellen acuity loss. Patients may describe phosphenes (light flashes with eye movement) or photisms (light induced by noise, smell, taste or touch) (BCSC Section 5 - Chapter 4, 2011).

Exam findings of optic neuritis include decreased visual acuity ranging from 20/20 to no light perception. A relative afferent pupillary defect is usually present unless optic neuropathy is bilateral. Optic disc edema is seen in about one-third of adult patients, although subtle disc edema can be seen in a higher percentage of patients if OCT is used. Visual field testing can show various nerve fiber bundle defects. In a study of 448 patients with acute optic neuritis, 48.2% of affected eyes had diffuse visual field loss, 20.1% of eyes had altitudinal or other nerve fiber bundle-type defects, and 8.3% had central or cecocentral scotomas (Keltner, 1993). Please refer to Keltner et al. for exemplary images of the visual field defects typically seen with acute optic neuritis. Of note, our patient's case is typical in all clinical respects except for her visual field defect; most patients have one of the patterns of visual loss listed above, whereas our patient's visual field had a mild relative paracentral defect.

Several eponymic signs and symptoms of demyelinating disease can be sought. Pulfrich's phenomenon represents an altered perception of motion; to a patient with unilateral optic neuritis, a swinging pendulum appears to trace an elliptical pathway rather than its true single-plane oscillation. This is due to a conduction delay in one optic nerve, causing a slowing in neuronal transmission compared with the other optic nerve (BCSC Section 5 – Chapter 6, 2011). Uhthoff's phenomenon describes worsening of vision or other demyelinating disease symptoms with physical activity or elevation in body temperature. L'Hermitte's sign describes an electrical "shock-like sensation" that runs down the spine and into the upper extremities with forward flexion of the neck (BCSC Section 5 – Chapter 14, 2011).

Optic neuritis should follow its typical course or other causes should be sought. Typically, optic neuritis worsens over days to several weeks, stabilizes and gradually improves over one to two months. If there is no substantial spontaneous improvement by one month, others causes should be considered. Further workup may include CSF studies of cell count, glucose, protein, VDRL and electrophoresis evaluating for oligoclonal bands. VDRL and FTA-ABS for syphilis, Lyme disease antibody titers, chest X-ray and serum angiotensin-converting enzyme levels for sarcoidosis and ANA for systemic lupus erythematosus and vasculitic disorders should be considered (BCSC Section 5 - Chapter 4, 2011).

MRI of the brain is performed when optic neuritis is suspected. If there are one or more white matter lesions typical for multiple sclerosis, a course of IV methyl prednisolone followed by an oral tapering dosage is considered (see below). When ordering brain MRI scans, the FLAIR (fluid-attenuated inversion recovery) sequence should be obtained, and gadolinium contrast should be used to look for active lesions in which the blood- brain barrier has broken down. Fat suppression should be used for sequences looking at the orbits. Demyelinating lesions in the brain are seen as periventricular, ovoid hyper-intensities in the white matter,

which are best seen on T2-weighted or FLAIR images (Thurtell, 2012). There is no role for CT scanning in optic neuritis. If there is uncertainty about the diagnosis of optic neuritis, MRI of the orbits with fat suppression and gadolinium are performed.

According to the Optic Neuritis Treatment Trial (Optic Neuritis Study Group, 2008), patients with no brain lesions on MRI had a 25% risk of progression to multiple sclerosis within 15 years, as compared to a 72% risk of progression in the same time period in patients with at least one demyelinating lesion seen on MRI. In this study, patients with normal MRIs who had not developed multiple sclerosis by year 10 had only a 2% risk of developing the disease by year 15. The highest rate of conversion to multiple sclerosis occurred in the first 5 years. Patients had a lower risk of developing future multiple sclerosis if they had a normal baseline MRI, were male, had optic disc swelling, no pain, or if exam showed no light perception vision, peripapillary hemorrhages or retinal exudates, as these are atypical features of optic neuritis. Recovery of vision was not found to be related to the presence of pain, optic disc swelling or severity of visual loss. At 10 years, recovery of visual acuity to ≥ 20/20 and ≥20/40 occurred in 74% and 92% of optic neuritis patients respectively, although most patients remain aware of residual abnormalities in contrast sensitivity, light brightness, visual field or color vision. Only 3% of patients had visual acuity worse than 20/200 in the Optic Neuritis Treatment Trial at 10 years. Recurrence of optic neuritis in the same eye or fellow eye is not uncommon, occurring in 35% of patients at 10 years according to the Optic Neuritis Treatment Trial.

Treatment for optic neuritis is based on the Optic Neuritis Treatment Trial protocol (Beck, 1992), which used IV methylprednisolone 250 mg q 6 hours x 3 days, followed by oral prednisone 1 mg/kg/day for 11 days. This therapy was shown to speed recovery by 1-2 weeks, although there was no long-term benefit for vision. In the group of patients with 2 or more white matter lesions, 16 % of optic neuritis patients who were treated with this corticosteroid regimen developed multiple sclerosis, compared with 36% of untreated optic neuritis patients over a two year period. However, this difference equalized by year 3 of the trial (Beck, 1993). Interestingly, patients treated with oral prednisone had a higher rate of recurrence of optic neuritis and therefore is not recommended.

In patients with newly diagnosed optic neuritis, the question of a diagnosis of multiple sclerosis is often raised. In 15-20% of cases, optic neuritis is the initial manifestation of multiple sclerosis. Since it is important not to incorrectly give a patient the diagnosis of multiple sclerosis and commit the patient to lifelong disease modifying treatment, the best and safest criteria for diagnosing multiple sclerosis requires two or more clinical events typical for multiple sclerosis that are separated in time and space with related MRI lesions, as shown in Table 1 (adapted from Ropper, 2009). Table 2 (adapted from McDonald, 2001) shows the McDonald criteria for the diagnosis of multiple sclerosis, applying the classic multiple sclerosis criteria to specific clinical situations. The McDonald criteria were developed for use in research protocols, which remains their most appropriate use. Recurring optic neuritis in the absence of other clinical or laboratory manifestations is not sufficient diagnosis of multiple sclerosis; autoimmune optic neuritis should be considered.

The Controlled High-Risk Subjects Avonex Multiple sclerosis Prevention Study (CHAMPS) (O'Connor, 2003), evaluated patients without clinically definite multiple sclerosis who are at high risk for developing the disease, based on a single demyelinating event. The single demyelinating event could be any one or more of: optic neuritis, spinal cord syndrome, or brainstem cerebellar syndrome, and 2 or more white matter lesions on MRI. This study found that patients treated with Avonex® (interferon beta-1a) were 44% less likely to develop clinically definite multiple sclerosis or to have progression of disability than those treated with placebo over a two-year period. The BENEFIT study showed similar results for Betaseron® (interferon beta-1b) (Kappos, 2007). Initiating immuno-modulating therapy in patients with a single demyelinating event remains controversial however, as this often means a lifetime of therapy in patients that may have a benign disease course without treatment. Many neurologists will follow the patient with repeat brain MRI every six months and decide on treatment based on the presence of the demyelinating activity observed.

Table 1: Diagnosis of multiple sclerosis based on dissemination in time and space (adapted from Ropper, 2009).

Dissemination in Time	Dissemination in Space
Any new cerebral or spinal T2 lesion on follow-up MRI at any time	One or more lesions in 2 or more characteristic sites: • periventricular, juxtacortical, posterior fossa, spinal cord • excluding symptomatic brainstem and cord lesions

Table 2: Diagnosis of multiple sclerosis based on the McDonald criteria (adapted from McDonald, 2001).

Clinical Presentation	Additional Data Needed for Multiple Sclerosis Diagnosis
Two or more attacks; objective clinical evidence of 2 or more lesions	None
Two or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by MRI *or* 2 or more MRI-detected lesions consistent with MS plus positive cerebrospinal fluid (CSF) *or* await further clinical attack implicating a different site
One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI *or* second clinical attack
One attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI *or* 2 or more MRI-detected lesions consistent with MS plus positive CSF *and* dissemination in time, demonstrated by MRI *or* second clinical attack
Insidious neurological progression suggestive of multiple sclerosis	Positive CSF *and* dissemination in space, demonstrated by 1) 9 or more T2 lesions in brain *or* 2) 2 or more lesions in spinal cord, *or* 3) 4-8 brain plus 1 spinal cord lesion *or* abnormal visual evoked potential associated with 4-8 brain lesions, or with fewer than 4 brain lesions plus 1 spinal cord lesion demonstrated by MRI *and* dissemination in time, demonstrated by MRI *or* continued progression for one year

In the case above, as is customary in our eye clinic when a patient presents with optic neuritis and has one or more typical demyelinating lesions on brain MRI, we treat based on the Optic Neuritis Treatment Trial protocol. We give 3 daily doses of 1 gram IV Solu-Medrol® (methylprednisolone sodium succinate), followed by 1 mg of oral prednisone per kilogram of body weight per day for 11 days (rounded to the nearest 10 mg) followed by a tapering regimen of prednisone consisting of 20 mg on day 15 and 10 mg on days 16 and 18. Treatment should begin within 8 days of the onset of visual symptoms. We consulted neurology for evaluation for treatment with immuno-modulating therapy for multiple sclerosis, based on 2 episodes of optic neuritis (showing dissemination in time) and multiple periventricular white matter lesions (showing dissemination in space).

Differential Diagnosis:
• Optic neuritis
  o Secondary to demyelination
  o Secondary to infectious causes: Lyme disease, syphilis, tuberculosis
  o Secondary to vasculitis such as lupus
• Neuromyelitis optica (Devic's Disease)
• Compressive optic neuropathy
• Infiltrative optic neuropathy from granulomatous disease or malignancy
	Signs:
	• Decreased visual acuity
	  o 20/20 to no light perception
	• Visual field defect
	  o Diffuse visual field loss most common, followed by altitudinal or other nerve fiber bundle-type defects
	• Relative afferent pupillary defect
	• Optic disc edema – about one-third of adults
	• Pulfrich's and Uhthoff's phenomena

Symptoms: • Subacute vision loss – over 1-2 weeks, with spontaneous recovery over weeks to months • Pain with eye movement • Decreased color vision	**Treatment:** • IV methylprednisolone 250 mg every 6 hours x 3 days, then • Oral prednisone 1 mg/kg/day for 11 days, then • Taper off over next 4 days

Summary: This case describes a 40 year-old female with subacute onset of decreased vision in the right eye, associated with pain with right eye movement, 0.3 – 0.6 relative afferent pupillary defect OD, and a fundus exam notable for temporal pallor OS. Her diagnosis is retrobulbar optic neuritis of the right eye. In retrospect, the patient had similar symptoms in the left eye one year prior that had resolved spontaneously, which is presumed to be from a prior episode of optic neuritis. During the workup of this episode, she was found to have multiple periventricular white matter lesions on MRI, consistent with a diagnosis of multiple sclerosis.

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