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Lyme Disease Neuroretinitis: A Case Report and Review of Immunologic Workup

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Abstract

Background: Lyme disease is an infection caused by a bacterial spirochete of the *borrelia* genus. The human vector is from a tick bite by an infected tick of the *ixodes* genus, commonly referred to as the deer tick or black legged tick. The incidence of Lyme disease is increasing in the United States. Once infected, Lyme disease manifestations usually depend on the stage of infection with late stage infection often causing debilitating illness.[1]

Case Report: Neuroborreliosis refers to *borrelia,* causing neurological infection and can occur as acute or late manifestation of Lyme disease. Neuroretinitis is a rare but reported manifestation of neuroborreliosis. Lyme diagnosis requires a two-step serologic test to meet CDC guidelines for Lyme confirmation.[1] Testing may be negative early in disease but may turn positive as the disease progresses.

Conclusion: Presented is a case where treatment decisions were made based on equivocal Lyme testing results.

Keywords

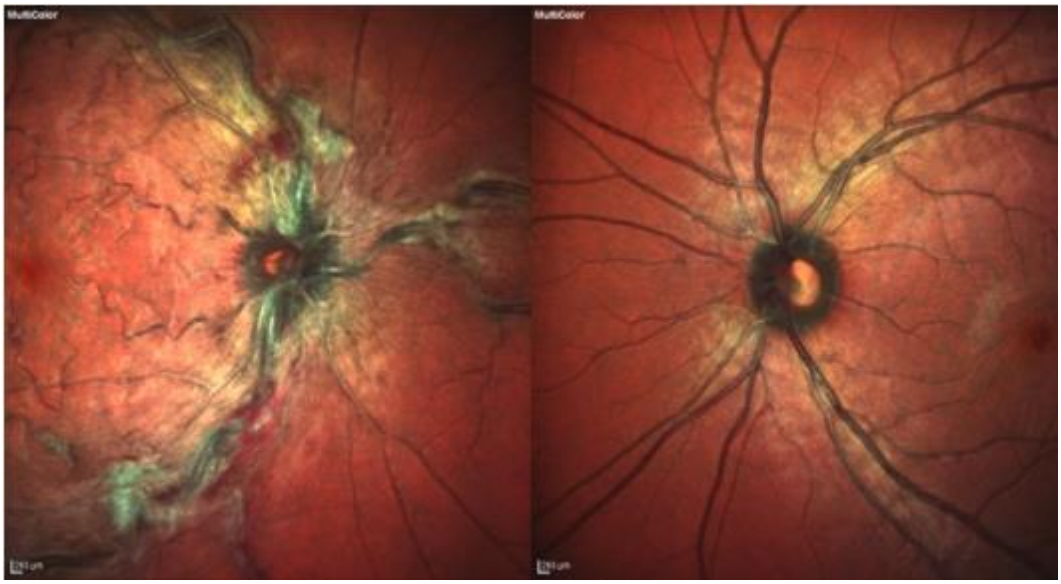
Lyme Disease, Neuroretinitis

INTRODUCTION

Neuroretinitis is characterized by inflammation of the optic nerve and neural retina. Findings usually include inflammation of the optic disc and peripapillary vasculature. Increased vascular permeability may result in hemorrhages, retinal edema, and exudates often forming a macular star.[1] Neuroretinitis generally presents unilaterally with acute painless vision loss, dyschromatopsia, relative afferent pupillary defect, and visual field defects, most commonly central field defects.[1,2] Neuroretinitis is attributed to a myriad of disorders such as infectious agents, autoimmune disorders, inflammatory, or idiopathic causes.[3] The range of etiologies can cause a diagnostic conundrum in some cases, as testing may leave a provider with only a suggestive causative agent. Vision and other symptoms often improve with resolution of the neuroretinitis. Presented is a case of neuroretinitis as the initial and only symptom with a resultant high enzyme-linked immunoassay testing for Lyme disease. Lyme disease is an infection caused by a bacterial spirochete of the *borrelia* genus. The incidence of Lyme disease is increasing in the United States. Once infected, Lyme disease manifestations usually depend on the stage of infection.[4] Neuroborreliosis occurs when *borrelia* infects the central nervous system. Neuroretinitis is a rare but reported manifestation of neuroborreliosis.[4]

CASE REPORT

A 24-year-old Hispanic male presented with decreased vision and light sensitivity in the right eye for the previous five days. Most bothersome to the patient was a tiny scotoma just to the right of fixation in his right eye. He claimed his left eye was normal. The patient took no systemic medications and denied alcohol or illicit drug use. He claimed that he was feeling fine and denied recent viral infections, insect bites, or associated systemic symptoms. He denied contact with cats but has two dogs. The patient lives in South Texas, denied recent travel, and does not eat sushi or uncooked meats. His blood pressure measured in the left arm was 148/98 mm Hg. His uncorrected visual acuity (VA) was 20/20 in each eye. Entrance testing was normal except for a mild right afferent pupillary defect (APD). The intraocular pressures were 10 mm Hg in each eye. The anterior segment examination was unremarkable. A dilated fundus examination revealed optic disc edema with peripapillary hemorrhages and hemorrhages in the vascular arcades, cotton wool spots in the superior and inferior arcades, white blood cells in the vitreous, and retinal vascular tortuosity and congestion, in the right eye. The left eye fundus examination was unremarkable with clear vitreous, normal appearing retinal vasculature, and a normal appearing optic disc with a C/D ratio of 0.3. (Figure 1)



Right **Left**

Figure 1 Image of right and left eyes taken with Heidelberg Spectralis Tracking Laser Technology. Note the optic disc edema right eye with retinal hemorrhages, cotton wool spots, and vascular congestion compared to the non-effected left eye.

A Spectral Domain Ocular Coherence Tomography (OCT) (Heidelberg Engineering Inc., Franklin, MA, USA) A-Scan vertically oriented through the optic nerve demonstrated optic disc swelling, epipapillary infiltrate, and inflammatory cells above the optic nerve. (Figure 2) The macula and perimacular area of the right eye were thickened relative to the left eye. (Figure 3) Visual fields (Humphrey 30-2) (Carl Zeiss Meditec, Dublin, CA) demonstrated an enlarged blind spot right eye with superior arcuate loss extending supranasal from the blind spot. The left eye visual field was normal. (Figure 4)

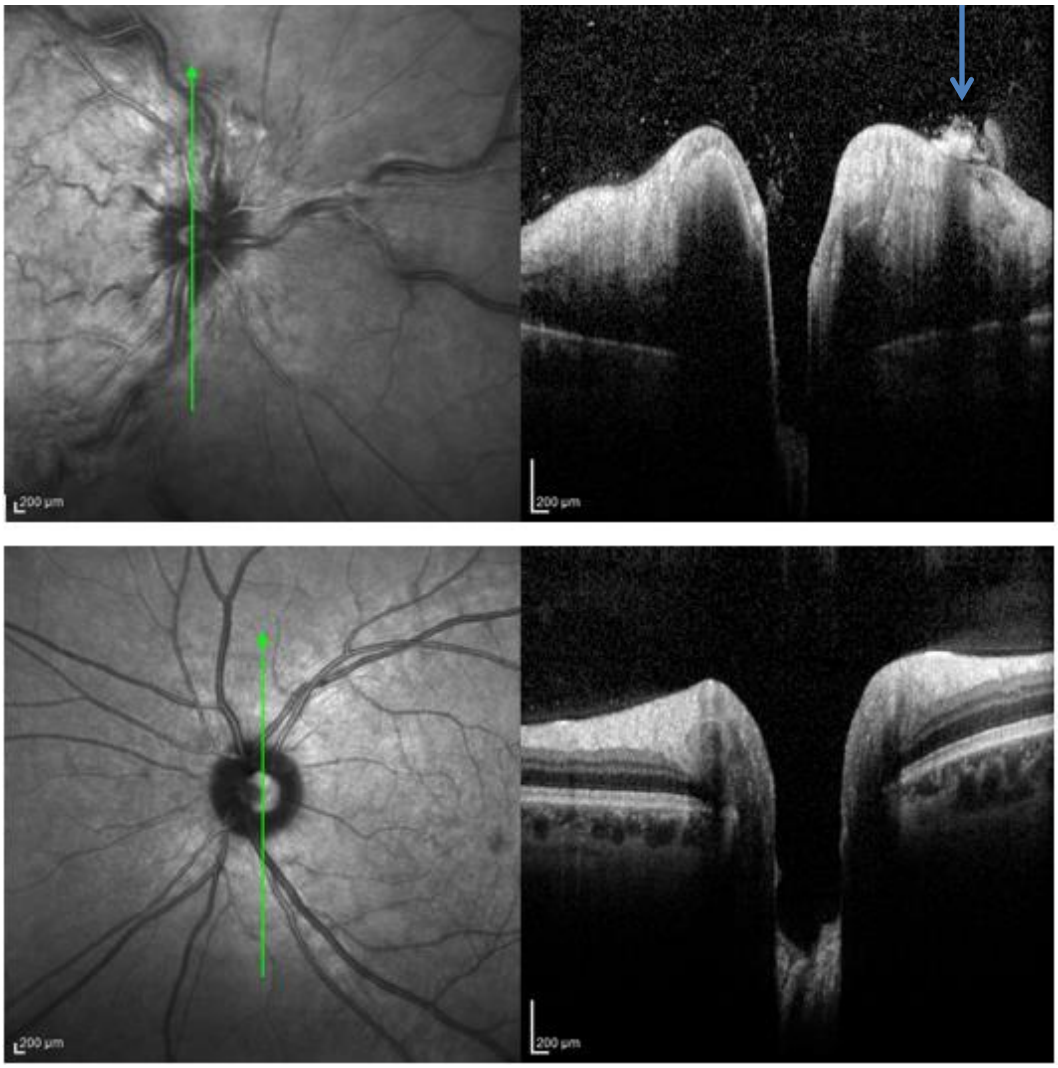


Figure 2: Heidelberg Spectralis OCT A-scan image of vertical slice through the optic nerve of the right eye (above) and left eye (below). Note the right eye optic disc swelling, inflammatory cells in the vitreous, and epipapillary infiltrate (blue arrow) abutting the optic nerve.

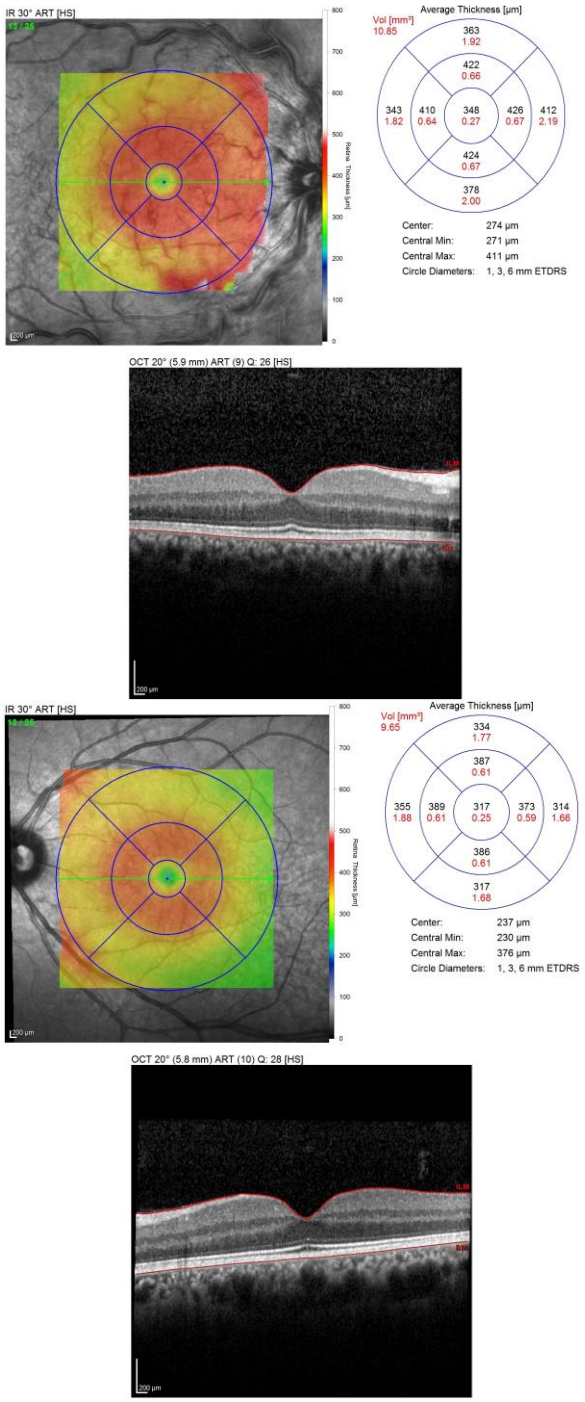


Figure 3 Heidelberg Spectralis OCT Macular Thickness Map of the right and left eyes. Note the general macular thickening of the right eye with a central thickness of 348 microns versus 317 microns left eye.

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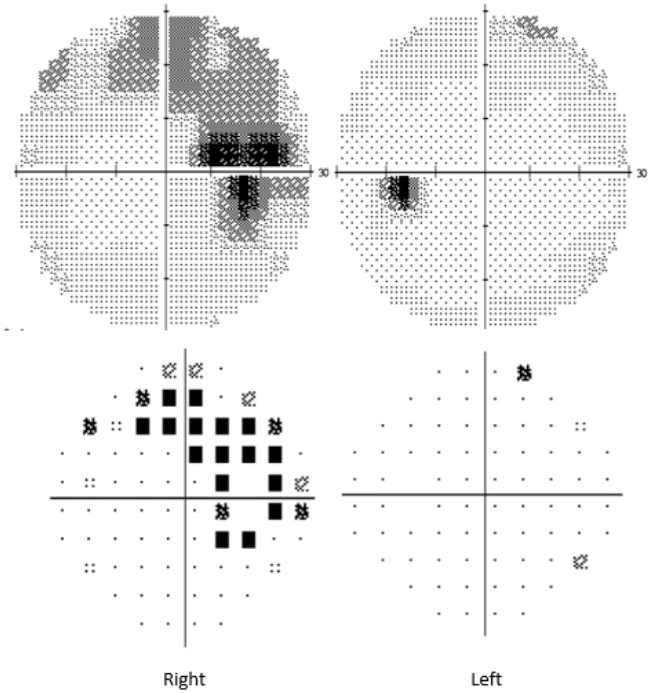

Figure 4 Humphrey Visual Field Grayscale map and Pattern Deviation of the right and left eyes. Right eye has an enlarged blind spot with superior arcuate loss extending supranasal from the blind spot.

The presentation of the unilateral ocular features with no other obvious organ system involvement was suggestive of neuroretinitis. The differential diagnosis included retinal vein occlusion with or without hyperviscosity syndrome, anterior ischemic optic neuropathy, hypertensive retinopathy with optic disc edema, papillitis, and infective/infiltrative neuroretinopathies. Other authors describe using spectral domain OCT to identify 'epipapillary infiltrates' (EI) which are accumulations of inflammatory cells on the surface of the optic nerve. Epipapillary infiltrates precede the formation of a macular star and have only been reported in neuroretinitis. Epipapillary infiltrates have not been reported in other forms of optic disc edema.[5] Unilateral presentation is not expected with hypertensive retinopathy or papilledema, and cells in the vitreous are not found in ischemic optic neuropathy, making these etiologies unlikely.

Diagnostic labs including CBC with differential, ESR, CRP, Bartonella titers, enzyme-linked Immunoassay Lyme titers, FTA-ABS, C-ANCA, P-ANCA, ANA, ACE, Lupus anticoagulants, protein c activity, protein s activity, and serum homocysteine levels were ordered. Treatment was withheld pending results of our initial diagnostic testing.

Lab results were available when the patient returned to the clinic one week later. All measurements were interpreted as either negative or in normal ranges except the enzyme-linked immunoassay (EIA) total Lyme antibody which was positive. Based on the clinical findings and EIA positive results for *B. burdorferi*, a presumptive diagnosis of Lyme neuroretinitis was made. Treatment consisting of doxycycline monohydrate 100 mg tablets twice daily was initiated. Western blot immunoglobin IgM and IgG for *B. burgdorferi* immunoassays were ordered to confirm Lyme disease. The patient was scheduled to return in two weeks.

After two weeks of treatment, the patient returned for follow-up and review of the Western blot immunoassays. The immunoassay results were equivocal with one IgG positive band, and one IgM positive band. However, the neuroretinitis was significantly improved with less optic disc edema and improving retinitis. Due to the improved clinical findings, despite the equivocal testing, the patient was continued on doxycycline monohydrate 100 mg BID. At seven weeks treatment, VA remained 20/20 in each eye and the right APD had resolved. The subjective blurring of vision with scotoma to the right of fixation in the right eye had improved but not completely resolved. The optic disc swelling, vascular congestion, retinal ischemia, and retinal hemorrhages had nearly resolved; there remained one cotton wool spot below the optic nerve with very subtle optic disc swelling. The OCT images comparing baseline to seven weeks clearly demonstrate less neuroretinitis and retinal vasculitis. (Figure 5).

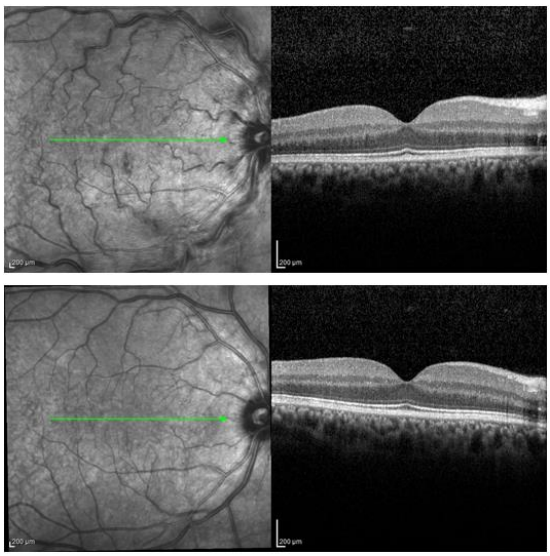

Figure 5 Images of right eye taken with Heidelberg Spectralis OCT. The image above is baseline and below after week seven of treatment. Note the improved retinal vasculitis with resolution of retinal hemorrhages and the decreased optic disc swelling.

The patient was evaluated five times in the first seven weeks but was subsequently lost to follow-up until returning nine months after the initial presentation. At nine months there was no evidence of neuroretinitis. Resolution was confirmed at the one year follow up when the visual acuity was stable at 20/20 in each eye, with no recurrence. At this point, the patient had no visual complaints. The pupil reactions were equal with no APD. OCT scans indicated a stable right eye with no optic disc swelling or retinal vasculitis. See figure 6 for image comparison of baseline to one year later. Images of OCT vertical a-scan through the optic nerve of the right eye compared to the left eye demonstrate relatively equal optic nerve thickness and profile. (Figure 7) The visual field in the right eye returned to near normal with a mild decrease in mean standard deviation right -2.41db compared to -0.83db left eye. (Figure 8)

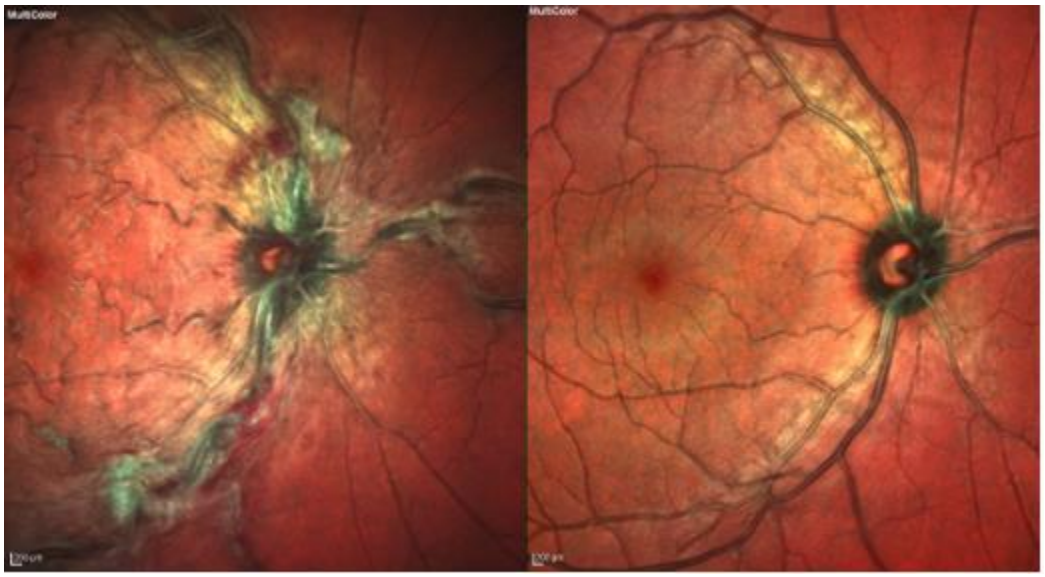

Figure 6 Baseline and one year later image of right eye taken with Heidelberg Spectralis Tracking Laser Technology. Note the resolved neuroretinitis.

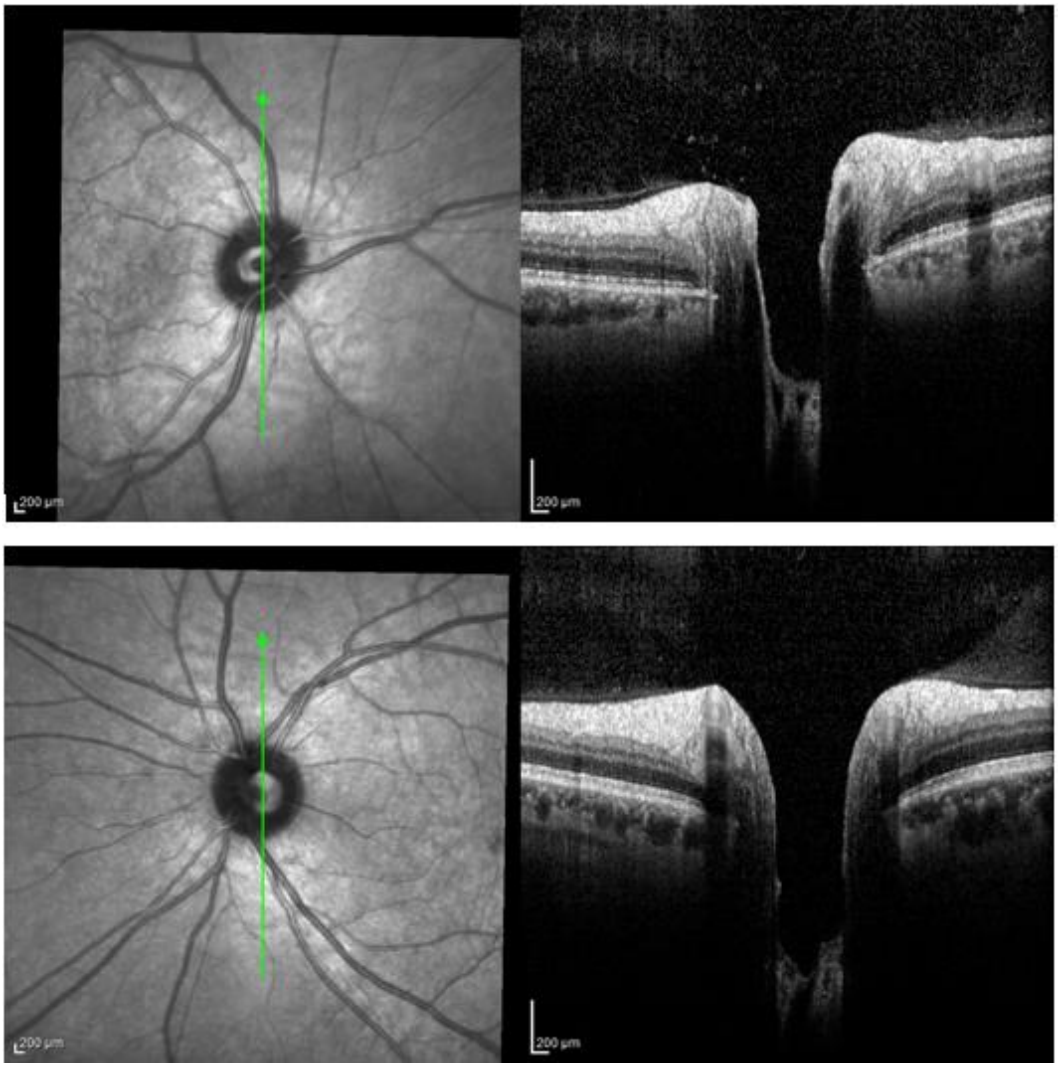

Figure 7 Heidelberg Spectralis OCT A-scan image of vertical slice through the optic nerve of the right eye (above) and left eye (below). Both optic nerves appear to be relatively equal in thickness. Note that the right eye experienced resolution of the epipapillary infiltrate.

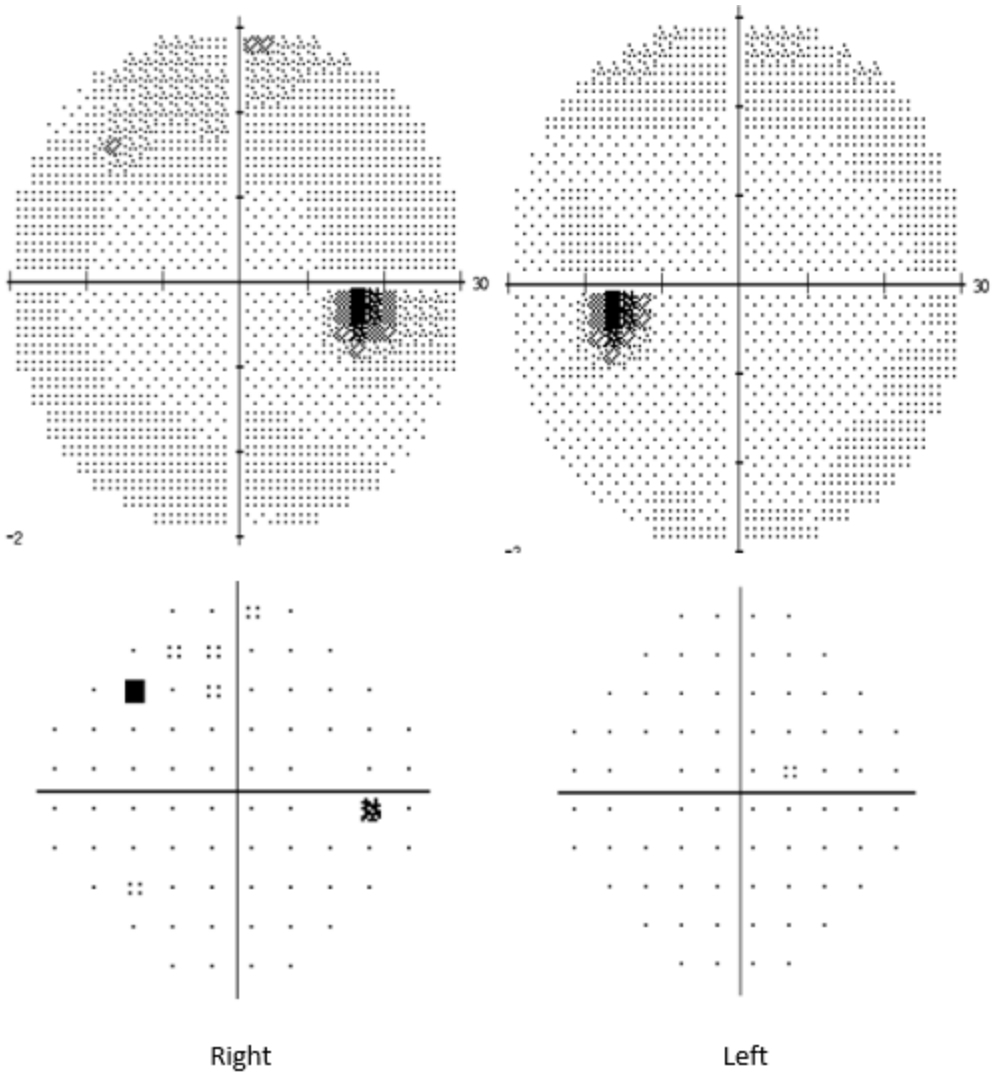

Figure 8 Humphrey Visual Field Grayscale map and Pattern Deviation of the right and left eyes. The right eye experienced significant improvement relative to the baseline visual field taken during the acute neuroretinitis.

Discussion

Neuroretinitis is generally defined as optic disc and peripapillary retinal inflammation. Neuroretinitis often presents with a classic triad of decreased visual acuity, optic disc edema, and macular star. The macular star forms later in disease process, classically 2-6 weeks after the onset of inflammation, therefore, may be

absent in early disease.[3,6,7] Visual field defects in neuroretinitis most commonly include a mild central or cecocentral scotoma.[6] A relative afferent pupillary defect (RAPD) is common, but not always present. Neuroretinitis causes are numerous, including infectious and non-infectious processes, as well as several masqueraders that must be ruled out. Many pathogens and classes of pathogens are suspected of potentially causing neuroretinitis including bacterial, viral, fungal, and parasitic disease. A thorough history including travel, dietary, social, sexual activity, exposure to pets or animals, previous viral illness and medical history (paying attention to lymphadenopathy), fever, and headache aids and helps steer the diagnostic work-up. Cat scratch disease, *Bartonella henselae,* is the most frequently identified infectious cause of neuroretinitis accounting for approximately two-thirds of identifiable infectious cases.[3,7-10] Spirochete disease such as syphilis and Lyme disease are both widely disseminated via the circulation including into the neural and ocular tissues with significant similarities in the common presenting ophthalmic and neurologic symptoms.[8]

Non-infectious processes such as sarcoidosis, inflammatory bowel disease, Behçet's disease, Voygt-Koyanagi-Harada syndrome and other systemic inflammatory disorders have been implicated in neuroretinitis.[3,7,9] Neuroretinitis with no identifiable cause is termed idiopathic and accounts for over half of all cases.[8] Idiopathic neuroretinopathy typically presents in young adults (8-55 years) who experience a painless vision loss; unilateral is much more common than bilateral. Over half of cases report a previous flu-like illness affecting the upper respiratory tract.[9]

Neuroretinitis generally has a good visual prognosis with spontaneous resolution. Idiopathic neuroretinitis is reported to spontaneously resolve over several weeks with 66% having visual acuity of 20/20 or better and 31% between 20/40 and 20/20.[8] There are rare patients who experience recurrent idiopathic neuroretinitis with progressive loss of visual acuity and visual field with each inflammatory episode. It is proposed that the vision loss in recurrent disease is due to optic disc vasculitis leading to optic neuropathy while the vision loss in non-recurrent disease is due to reduced macular function which generally resolves. Corticosteroid treatment (either orally or intravenously) does not seem to provide an outcome improvement. The role of long-term immunosuppressive therapy is not firmly established but azathioprine appears to decrease the rate of recurrence.[9]

Masqueraders of neuroretinitis include malignant hypertension, diabetic papillopathy, anterior ischemic optic neuropathy, retinal vein occlusions, idiopathic intracranial hypertension, arteriovenous malformations, optic neuritis, and juxtapapillary tumors.[3] These entities should be considered in the diagnosis and management plan.

Lyme disease is an infectious manifestation by spirochetes of the *Borrelia* genus. The human vector for infection is via the bite of an infected *Ixodes* tick. According to the CDC, *Ixodes* scapularis is most prevalent in the Northeast, but tick colonies are documented in every state in the eastern half of the United States. *Ixodes* pacificus is predominantly found in the Western United States.[11,12] Both species of the *Ixodes* tick are capable of harboring and transmitting *Borrelia burgdorferi* which causes Lyme disease.[11-13]

Lyme disease is the most common vector borne disease in the United States and Europe.[12-14] According to the CDC, in the United States, there are approximately 300,000 diagnosed cases of Lyme disease each year. While a helpful diagnostic tool, a known tick bite is not required for diagnosis if the infected person is known to have been in a tick endemic area.[15,16] The most common initial presentation of Lyme disease is a tick bite followed by a local rash known as erythema migrans, yet approximately 10-40% of patients never develop a rash.[13,15] Lyme disease is recognized as having three distinct stages (Table 1). [17,18]

Table 1: Stages of Lyme disease

Lyme disease stages		
Stage	Phase	Time frame
1	Early localized disease	1-4 weeks
2	Early disseminated infection	1-4 months
3	Late persistent Lyme disease	>4 months

After initial infection, the spirochete can disseminate via blood circulation to any tissue or organ. The spectrum of Lyme manifestation commonly presents as dermatologic, neurologic, rheumatologic, and cardiac disease. Details of the stages and myriad of possible symptoms of Lyme disease are discussed elsewhere.[4,15] The spirochetes may pass the blood-brain barrier in the first weeks after infection potentially causing neurologic disease.[19] Central nervous system involvement is referred to as Lyme neuroborreliosis (LN). Lyme neuroborreliosis manifests in approximately 12%-15% of Lyme disease cases and is reported as early as 2-18 weeks after infection.[20-22] Lyme neuroborreliosis commonly causes meningitis, cranial nerve palsies and radiculoneuritis. Facial nerve (CNVII) palsy is the most common cranial nerve involved with LN and is bilateral in up to 25% of affected individuals.[22]

For serologic confirmation of Lyme disease, the CDC suggests a two tiered serologic testing consistent of a sensitive enzyme immunoassay (EIA) or immunofluorescent assay followed by a reflex Western immunoblot test.[23] The

second tier immunoblot test detects IgM and/or IgG antibodies against specific *B. burgdorferi* surface proteins. The CDC recommends the immunoblot interpretation as positive if ≥2 of 3 bands on IgM are visible with equal or greater intensity to control bands, or ≥5 of 10 IgG bands are present.[12,23] Some drawbacks of the two tier testing are low sensitivity in early disease and subjective interpretation of immunoblots. Both the EIA and immunoglobulin (Ig) testing are indirect tests that detect host response to a known causative organism. Because of varying host immune responses, the antibody detection in early Lyme disease may be low with a testing sensitivity below 40% but climbing to 70-100% in disseminated or late Lyme disease.[24] It is recommended that IgM antibodies are only tested for in the first 4 weeks of disease duration.[1,11,16,23] If the two tier serology testing is negative in early Lyme disease, confirmation may be possible by retesting later in the disease, when a more robust antibody response has developed.

In the patient presented, the initial EIA total Lyme antibody test was 1.67 (reference ≥1.10 positive). Treatment with doxycycline was justified based on the initial clinical picture and the positive initial screening for Lyme disease. Western immunoblot for Lyme IgM and IgG were ordered to confirm the diagnosis. As part of the diagnostic work-up, fluorescein angiogram (FA) was considered but not performed. FA does not specifically differentiate Lyme neuroretinitis from other neuroretinitis. However, FA may be useful differentiating neuroretinitis from masqueraders. In neuroretinitis, FA usually shows leakage with optic disc and peripapillary staining in the mid-venous and late phases of the angiogram. The staining will usually be greatest corresponding to segments of the optic nerve with greatest edema. In neuroretinitis, the peri-macular capillaries do not leak, the macular edema and star formation are due to leakage from the papillary vascular hyperpermeability.[8] Visual evoked potentials (VEP), especially multi-focal VEP, are sometimes useful in diagnosing demyelinating disease or other forms of optic nerve disease that may cause a conduction defect.[25] VEP measurements have utility concerning documentation and monitoring of a defect, but the clinical utility of VEP may be hampered due to non-specific results with lack of standardization between varying equipment and limited clinical availability. In this case a VEP was not ordered, but VEP is another reasonable consideration, however, not required for diagnosis and management.

Neuroretinitis is not a common presentation of Lyme disease, but it has been reported.[18,26-28] Treatment goals are to relieve symptoms and prevent disease progression. Doxycycline 100 mg BID is an established, effective treatment for neuroborreliosis and with treatment, Lyme disease generally has a good clinical prognosis.[15,29] Alternatives to doxycycline include the beta-lactim antibiotics (azithromycin, cefuroxime, penicillin G, ceftriaxone) used for 14-21 days.[15,30] These drugs have good central nervous system penetration and are proven effective

against *Borrelia.* For this patient, the Western immunoblot results were not available for 10 days after starting treatment with doxycycline, but when available, this patient had weakly positive IgM and IgG response on Western immunoblot, but not enough positive bands to be a confirmatory diagnostic by CDC criteria. The patient was improving, so treatment with doxycycline was continued despite the equivocal Western immunoblot test. No further diagnostic tests were performed. Corticosteroids are a possible adjunctive therapy but were not prescribed due to the patient's clinical improvement with doxycycline alone. The patient ultimately experienced resolution of the neuroretinitis. At one year, there had been no recurrence of neuroretinitis or other systemic manifestation of Lyme disease. Visual function had returned to near normal with the patient reporting no symptoms and both eyes had 20/20 visual acuity. Visual field testing at one year revealed mild overall depression with the right eye relative to the left (mean standard deviation right eye was -2.41 db compared to -0.83 db left). Western immunoblot testing has lowest sensitivity during early Lyme disease, prior to a robust host antibody reaction, and it is not uncommon for neuroretinitis due to Lyme disease to occur in the early disseminating stage.[27] This patient did not report recent travel to a high risk area such as the northeast or upper mid-west United States but Lyme has been reported in Texas.[4] The patient lives within ten miles of the Mexican border. There is evidence that Lyme disease may be under-reported in Mexico where Lyme is not a mandatory notifiable disease as it is in the United States. A study conducted at three hospitals (one pediatric and two general hospitals) in Mexico City recruited neurological patients screening for cranial neuritis, radiculoneuritis, meningitis and encephalomyelitis. A total of 606 patients (403 adults and 203 children) were evaluated. *B. burgdorferi* infection was the most common diagnosis being found in 168 (27.7%) of the patients.[31] This suggests that Lyme may be more prevalent in the Mexican border region than currently thought. If the patient had not responded to treatment with doxycycline, an alternative antibiotic could have been trialed; alternative diagnoses are always considered in the case of treatment failure.

As of now there is no reliable direct measurement for Lyme disease due to the usually low concentration of spirochetes in blood or other body fluids. Polymerase chain reaction (PCR) testing carries a low sensitivity due to generally low spirochete numbers in body fluids and is further complicated by a lack of well-developed gene targets and methodology. Direct culture of *B. burgdorferi* is possible but has low sensitivity, and culturing requires special medium. Culture growth can take weeks, decreasing its clinical usefulness in acute disease. Another FDA approved test for Lyme, the C6 Lyme ELISA, is a single enzyme-linked immunosorbent assay test for the VIsE protein and amino acid protein (C6peptide). When compared to standard two tier serological testing, the C6 Lyme ELISA appears to have increased sensitivity in early Lyme disease, including early

neuroborreliosis, especially when erythema migrans is present, but has lower specificity than standard two tier testing.[32] This case presented a treatment dilemma since the initial EIA total Lyme antibody was positive but the confirmatory Western immunoblot tests were equivocal. Standard treatment targeting Lyme neuroborreliosis led to resolution of disease. We lack a reliable and fast single-tier test for the diagnosis of Lyme disease. At present, the CDC recommends two tier testing, EIA, or immunofluorescent assay followed by a reflex Western immunoblot test as the standard.

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