Characteristics of Lyme optic neuritis: a case report of Lyme associated bilateral optic neuritis and systematic review of the literature

Yezhong Lu¹ and Ramin Zand²*

Abstract
Optic Neuritis is rare in Lyme borreliosis. The current knowledge of optic nerve involvement in Lyme borreliosis relies solely on case reports. The aim of this systematic review was to characterize and investigate the associated factors of optic neuritis in Lyme borreliosis. We further presented a very rare case of isolated bilateral optic neuritis in a Lyme seropositive patient.

Background
Lyme borreliosis, caused by Borrelia burgdorferi, is the most frequent reported vector-borne disease in the United States [1, 2]. Steere et al., (1977) first introduced clinical characteristics of Lyme borreliosis as recurrent, asymmetric, short attacking arthritis, and often precede in skin lesions [3]. Lyme borreliosis can affect multiple systems and has various manifestations that occur in stages. The clinical course of Lyme borreliosis begins with skin lesions [4]. Neurological, cardiac, musculoskeletal and rheumatological presentation usually develop in 2nd and 3rd stage of the disease [2, 5–7]. However, presentations in each chronological stage has not been always consistent [8].

Kauffmann & Wormser (1990) was first to describe a case which the uniocular uveitis progressed to panophthalmitis and loss of vision due to Lyme borreliosis [9]. Ocular involvement is usually seen in the 2nd or 3rd stage of the disease. Although relatively uncommon, it could manifest multifariously such as conjunctivitis, keratitis, uveitis, periorbital oedema, cranial nerve II, III, IV, VII palsies, papilledema, reversible Horner’s syndrome, cotton wool spot, vascular occlusion, and optic neuritis [9–17]. Optic neuritis is rare in Lyme borreliosis; therefore, it is often overlooked in the differential diagnosis.

The goal of this systematic review was to characterize and investigate the associated factors of optic neuritis in Lyme borreliosis. We further presented a very rare case of isolated bilateral optic neuritis in a Lyme seropositive patient.

Methodology
A systemic review of Lyme optic neuritis cases characteristics was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. The electronic database Google Scholar was the primary source for article identification and PubMed was used for supplement. Articles were searched from database inception to July 2021 and identified through Keywords “Optic Neuritis”, paired with “Lyme disease”, “Lyme Borreliosis”, “Case report” and “Erythema Migrans”. MeSH term “Lyme Disease” paired with “Optic Neuritis” was used for search in PubMed. Accessible articles in English language were appraised and assessed via case report guidelines (CARE) by one individual and reference lists were scanned for additional studies of potential relevance.

*Correspondence: rzand@geisinger.edu
² Department of Neurology, Neuroscience Institute, Geisinger Health System, Danville, PA, USA

Full list of author information is available at the end of the article
Articles that include elements of clinical assessment/diagnosis of optic neuritis and Lyme borreliosis (positive 2 tier serology tests), therapeutic interventions and outcome were included. Demographics, clinical findings, treatment, and treatment outcomes are listed in Table 1 and Table 2.

We also presented a very rare case of isolated bilateral optic neuritis in a Lyme seropositive patient. The written consent was obtained from the patient to present her illness.

**Case presentation**

A 48 years old female with the past medical history of multiple sclerosis (MS), presented to her primary care physician in December 2019, with fever and sore throat. Three weeks later, patient returned and reported development of photophobia, eye pressure sensation, blurry vision, pain with eye movements for more than 3 weeks and noted central scotoma during the morning prior to her visit. Patient’s MS was first diagnosed in 2006. She has had relapses in 2010 and 2018, which both mainly presented as fatigue and difficulties in walking. Patient was on Copaxone (2006–2009), Gilenya (2010–2018) and currently treated with Ocrelizumab.

She did not report any new neurological deficit except blurry vision. Her fundus exam and optical coherence tomography (OCT) revealed bilateral disc edema, and peripapillary retina nerve fiber layer thickening OU (Fig. 1). Her visual acuity (Snellen linear chart) was 20/40 OU, intraocular pressures (non-contact) were 19 (mm Hg) OD and 18 (mm Hg) OS, Ishihara test resulted 8/8 OD and 7/8 OS, confrontational visual field full, and pupils equal round and reactive to light. Magnetic resonance imaging (MRI) of the orbit showed thickened and increased T2 signal of the optic nerve. MRI along with fundus exam confirmed the diagnosis of bilateral optic neuritis (Fig. 2). MRI of the brain showed similar burden of supratentorial and infratentorial T2/Fluid-attenuated inversion recovery (FLAIR) hyperintensities lesions compatible with her known MS, and no new lesions identified. Anti- Borrelia IgM were both positive in serum and cerebrospinal fluid (CSF) and was confirmed by western blot following a positive ELISA test (15 reports), other etiology leading to optic neuritis (2 reports), no English version of the text (3 reports), and diagnosis of optic neuropathy other than optic neuritis (3 reports) (see Fig. 3). Total of 10 reports and 11 patients with optic neuritis and Lyme borreliosis were included in this review [18–27].

The patients’ age ranged from 33 to 67 years (median 48 years), 5 were male and 6 were female. Seven cases were from Europe and 5 were from North America. The most common symptoms reported are related to optic neuritis – blurry vision (11 cases), headache (7 cases), scotoma (3 cases) and painful ocular movement (3 cases). Besides visual complaints, 4 reported neurological symptoms – paresthesia (3 cases) and ataxia (1 case); 3 reported arthralgia; and 3 reported nonspecific symptoms – fatigue, weakness, and myalgia.

The most common signs found are bilateral optic disc edema (8 cases) and relative afferent pupillary defect (2 cases). Erythema migrans was diagnosed in 2 of the total patients. Eight patients did not recall having tick bites. Moderate vision loss (better than 20/200) was observed with majority of the patients (9 cases).

Ten out of 11 patients have CSF study (see Table 2). They all revealed a normal opening pressure and glucose level. Common laboratory findings were elevated cerebrospinal fluid protein levels (6 cases), and mononuclear pleocytosis (4 cases).

The patients all responded well with combination of corticosteroid and antibiotic therapy, or antibiotic
| Cases                          | Age/Sex | Tick Bite | Erythema Migrans | Signs and Symptoms | Fundus | Imaging/Testing | Treatment | Treatment outcome               |
|-------------------------------|---------|-----------|------------------|-------------------|--------|----------------|-----------|---------------------------------|
| Cruz, et al. (2020) [18]      | 48/M    | Does not recall | Unreported       | 1. Blurry vision OD  
2. Inferior visual field defect  
3. RAPD OD  
4. Photopsia | 1. Pale optic disc  
2. Edema of inferior quadrant OD  
3. Hyperemia and diffuse edema OS | MRI: unremarkable  
VEP: delayed bilaterally  
VF: generalized deficit on the right eye and a left inferior scotoma | Ceftriaxone | Improved, lost to follow up due to patient relocation |
| Jha, et al. (2018) [19]       | 46/F    | Does not recall | Unreported       | 1. Progressive blurry vision > 3 wks.  
2. Upper respiratory symptoms  
3. Paresthesia  
4. Nausea  
5. Weakness  
6. Bilateral lower extremities paresthesia | 1. Bilateral optic head edema  
2. Hyperemia  
3. Optic disc edema | MRI: nonspecific white matter hyperintensities  
VF: Cecocentral defects OU | Doxycycline | Patient did not return for follow up |
| Wang, et al. (2017) [20]      | 50/F    | Does not recall | Pruritic rash on neck, chest, and right lower extremities | 1. Right sided headache  
2. Unspecified eye pain  
3. Blurry vision OD | 1. Optic head edema OD | MRI: enhancement of right optic nerve  
Ceftriaxone  
Methylprednisolone | Improved in symptoms  
MRI shows resolution of findings |
| Burakgazi and Henderson (2016) [21] | 59/F | Does not recall | Shoulders extending to midback, part of chest, left shoulder and right cheek | 1. Blurry vision OD for 3–4 wks  
2. Fatigue and generalized joint pain | 1. Optic head edema OD | MRI: unremarkable  
VF: unspecified visual field defect  
VA: 20/30 OD, 20/20 OS | Doxycycline | Improved visual deficits and symptoms |
| Tzoukeva, et al. (2014) [22]  | 42/F    | Does not recall | Absence          | 1. Progressive blurry vision OS  
2. Painful ocular movement  
3. Left RAPD  
4. Decreased color vision | Unremarkable | MRI: typical lesion characteristics of MS  
Medaxone  
Cefprozil | Methylprednisolone  
Cefprozil | Normalized |
| Qureshi, et al. (2016) [23]   | 43/M    | Does not recall | unreported       | 1. Headache  
2. Paresthesia  
3. Nuchal rigidity  
4. Kernig and Brudzinski sign  
5. Seizure episodes | 1. Posterior uveitis  
2. Bilateral papillitis | MRI: diffuse hyperintensities involving suprat and infratemporal cortical sulci consistent with diffuse leptomeningoencephalitis | Doxycycline  
Ketorolac | Normalized |
| Cases                              | Age/Sex | Tick Bite | Erythema Migrans | Signs and Symptoms                                      | Fundus                 | Imaging/Testing | Treatment          | Treatment outcome                           |
|-----------------------------------|---------|-----------|------------------|--------------------------------------------------------|------------------------|-----------------|-------------------|---------------------------------------------|
| McVeigh and Vakros (2012) [24]    | 48/M    | Denies recent bites, but had sustained bites previously | Absence | 1. Bilateral loss of visual acuity  
2. Painful ocular movements  
3. Photophobia  
4. Visual distortion  
5. Ataxia  
6. Headache | 1. Uveitis  
2. Bilateral disc swelling  
3. Splinter hemorrhage OD | Unspecified | Oral Steroid  
Ceftriaxone  
Doxycycline  
Amoxicillin | Normalized (Mild pallor of the left disc) |
| Blanc et al (2010) [25]           | 63/F    | Yes       | Unreported       | 1. Blurry vision OD  
2. Headache  
3. Arthralgia | 1. Uveitis  
2. Bilateral disc swelling  
3. Splinter hemorrhage OD | Unspecified | Ceftriaxone | Visual acuity improved to 20/80 |
| Blanc et al (2010) [25]           | 48/F    | Yes       | Denies           | 1. Arthralgia  
2. Headache  
3. Blurry vision | 1. Bilateral papillitis | MRI: 3 nonspecific lesions on T2 FLAIR and T2 weighted VEP: delayed bilaterally VA: 20/200 OD | Ceftriaxone  
Methylprednisolone | Visual acuity improved to 20/20 |
| Santino et al (2009) [26]         | 33/M    | Unspecified | Unspecified     | 1. Right central scotoma  
2. Blurry vision | 1. Bilateral papillitis | VA: 20/100 OS | Methylprednisolone  
Ceftriaxone | Visual acuity improved to 10/10 OU |
| Krim et al (2007) [27]            | 67/M    | Yes       | Right arm        | 1. Fatigue  
2. Myalgia  
3. Neck radiculopathy  
4. Facial weakness  
5. Ptosis  
6. Diplopia  
7. Fever  
8. Peripheral right facial palsy  
9. Right arm paresis  
10. Retrobulbar pain  
11. Diminished color perception OD | 1. Bilateral uveitis | MRI: unremarkable VEP: delayed OD VF: central scotoma OD VA: 5/10 OD 8/10 OS | Ceftriaxone  
Corticotherapy | Neurological symptoms resolved, and visual acuity improved to 10/10 OU |

*MRI: Magnetic resonance imaging, VA: Visual acuity, VEP: Visual evoked potential, VF: Visual field*
therapy alone. Of the 5 patients treated with solely antibiotic therapy, except 2 who did not return for follow up, the rest showed improvements or resolution of symptoms. The 6 patients who received combination therapy also showed improvements or normalization of the symptoms.

## Table 2  Cerebrospinal Fluid (CSF) Analysis of the reported cases

| Cases                          | CSF protein | CSF cell count |
|-------------------------------|-------------|----------------|
| Cruz, et al. (2020) [18]      | Elevated (185.4 mg/dL) | Elevated white cell count (177 cells/mL) lymphocytic predominance |
| Jha, et al. (2018) [19]       | Normal      | Normal         |
| Wang, et al. (2017) [20]      | Normal      | Elevated (20 red cells, 2 white cells) |
| Burakgazi and Henderson (2016) [21] | Elevated (55 mg/dL) | Normal   |
| Tzoukeva, et al. (2014) [22]  | Not performed | Not performed |
| Qureshi, et al. (2016) [23]   | Elevated (94 mg/dL) | Elevated white cell counts (288 white cells) lymphocytic predominance (98%) |
| McVeigh and Vakros (2012) [24] | Unreported  | Elevated       |
| Blanc, et al. (2010) [25]     | Elevated (0.49 g/l) | Normal         |
| Santino, et al. (2009) [26]   | Elevated (0.64 g/l) | Normal         |
| Krim, et al. (2007) [27]      | Elevated    | Elevated white cell count lymphocytic predominance |
|                              | Elevated (1.11 g/l) | Elevated white cell count (21/mm³) lymphocytic predominance (95%) |

**Discussion**

Optic Neuritis has been reported in both the US and Europe in patients with neuroborreliosis or positive Lyme serologies, however the relationship remains elusive due to insufficient knowledge and multiple confounding variables [12, 28–30]. Majority of the cases in the literature showed compelling clinical signs of Lyme borreliosis, however, did not meet the confirmatory diagnosis criteria according to Centers for Disease Control and Prevention (CDC) [31]. The relationship between Lyme borreliosis and optic neuritis has been controversial. In a retrospective study, Sibony et al., 2005, reported prevalence of 4% of optic neuritis patients with positive Lyme serology was possibly secondary to Lyme borreliosis [32]. But in another cohort study of 81 patients with neuroborreliosis, 27% reported to have delayed visual evoked potential, which suggests that prevalence of visual involvement in Lyme disease could be higher [33, 34].

Diagnosis of Lyme borreliosis is established based on clinical presentation with supportive findings from laboratory testing [31]. Laboratory diagnosis of Lyme borreliosis is established through enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antibodies against *Borrelia burgdorferi*. In patient with positive ELISA response, western blots were performed to confirm the specificity of the antibodies [31]. Immunoblot requires at least 2 of 3 signature bands (23kDa, 39kDa, 41kDa) for a positive IgM and at least 5 of 10 signature bands (18kDa, 23kDa, 28kDa, 30kDa, 39kDa, 41kDa, 45kDa, 58kDa, 66kDa, 93kDa) for a positive IgG [35].

The diagnosis of Lyme borreliosis remains challenging. Serology tests results are frequently misinterpreted leading to misdiagnosis and can lead to serious morbidity. Despite having high sensitivity, ELISA results could be
confounded by delayed immune response, false positivity, and high prevalence of asymptomatic seropositivity in endemic areas [4, 32, 36, 37]. In addition, the diagnosis is made difficult by long incubation period and symptoms mimicking a wide range of disease processes, such as fibromyalgia, syphilis, Alzheimer’s and autoimmune

![Fig. 2](image)

**Table 3** Summary of findings in the patient

|                      | Serum IgG/IgM Elisa | Serum IgG WB bands (kD) | Serum IgM western blot bands (kD) | CSF Glucose (mg/dL) | CSF protein (mg/dL) | CSF WBC (cells/mm$^3$) | CSF RBC (cells/μL) | CSF IgG Bands (kD) | CSF IgM Bands (kD) |
|----------------------|--------------------|-------------------------|-----------------------------------|---------------------|---------------------|-----------------------|-------------------|-------------------|-------------------|
| Patient              | 6.9                | 23,39,41,93             | Negative if not detected or fewer than 5 of 10 significant bands | 75                  | 133                 | 4                     | 0                 | 3,41,93           | 23,39             |
| Normal Value         | <0.91              | 23,39,41                | Negative if not detected or less than 2 bands | 45–70               | 15–45               | 0                     | –                 | –                 | –                 |
disorders [36–41]. Due to the limitations, Lyme borreliosis is frequently misdiagnosed or delayed in diagnosis. The CDC reports 30,000 cases of Lyme borreliosis annually from 2008 to 2014, but estimates true incidence is much higher [42]. The public health burden of Lyme borreliosis continues to grow substantially each year [43]. It is crucial for clinicians working in endemic regions to be aware and recognize of signs and symptoms of Lyme borreliosis.

The pathophysiology of Lyme borreliosis in various organs at different stages remains controversial due to infrequency of finding of *Borrelia burgdorferi* via direct testing [41, 44]. *Borrelia burgdorferi* has been successfully cultured from various tissues, like blood and synovial fluid, and also immune privileged sites like the eyes and brain, but the mechanism of entry remains unclear [9, 45, 46]. Current evidence suggests pathogenesis in the central nervous system is via direct cytotoxicity, neurotropism and production of neurotoxic and proinflammatory mediators [47–53]. Unlike other bacterial infections which elicit neutrophil infiltration in the CSF, *Borrelia* species produce lymphocytic pleocytosis and enhanced intrathecal antibody production [54, 55]. Optic nerve involvement in Lyme borreliosis has been rare and causal relationship has been difficult to prove. Currently, there is no clinical guidelines as when Lyme borreliosis should be considered in optic neuritis.

In this review, we collected cases that have demonstrated strong evidence of causal relationship of Lyme borreliosis and optic neuritis in attempt to characterize the nature and clinical presentations of optic neuritis involved in Lyme borreliosis. Importantly, there are few limitations and concerns need to be highlighted. Despite all the cases collected in this review having positive 2 tier Lyme serology (Table 1), majority of cases could still remain idiopathic (absence of tick bites and erythema migrans); the cause of the symptoms could be associated with undiagnosed underlying demyelinating conditions such as multiple sclerosis which will require a long term follow up to establish the diagnoses [56]. Additionally, 4 of 10 cases with CSF analysis revealed normal CSF cell count which led to
questions of whether there are other underlying etiologies. Regardless of the differences and limitations, there are few pertinent features that deserves considerations. Majority of the cases present with features of atypical optic neuritis that deviate from the characteristics of typical idiopathic demyelinating optic neuritis. Typical optic neuritis commonly presents with acute, painful, and self-limiting unilateral visual loss [57–59]. Our findings conclude Lyme optic neuritis usually presents with bilateral optic nerve head swellings, and painless, moderate (better than 20/200) and progressive visual loss. Common CSF analysis reveals elevated protein and mononuclear pleocytosis. These atypical features may provide a clue, however attention to presentations, detailed history taking, and correct interpretation of lab values are paramount for making the correct diagnosis and preventing future implications.

Additionally, our results indicate that these patients respond well to antibiotics and have good prognosis. Antibiotic therapy (14 to 21 day course) has been shown to be effective in treating Lyme borreliosis [60]. Antibiotics usually include doxycycline for adults, and amoxicillin or cefuroxime for adults, children, pregnant or breast feeding women [7]. Systemic corticosteroid without concomitant antibiotics should not be used in treatment of ocular Lyme disease [7]. For all antibiotics regimen, treatment failures and relapses have been reported, prolonged courses of therapy are not recommended. For treatment failures, underlying diagnosis should be reconsidered [38].

Finally, we present a case demonstrated a strong causal relationship of optic neuritis and Lyme borreliosis. Our patient’s optic neuritis could be reflective of her diagnosis of relapsing remitting multiple sclerosis. However, her presented symptoms were atypical for the patient’s MS due to absence of other neurological symptoms, and atypical compared to her flare ups in the past. Additionally, optic neuritis from multiple sclerosis is usually unilateral with normal or mild pupillary disc edema [40, 61, 62]. Initially, it was suspected that her condition was secondary to alternative inflammatory process such as neuromyelitis optica or myelin oligodendrocyte glycoprotein antibody demyelination due to bilateral involvement of her optic discs, but was later on ruled out by laboratory work up [63, 64]. CSF lymphocytic pleocytosis in the absence of meningeal signs, along with recent finding of ticks, positive serum Lyme antibodies and confirmatory test for Lyme borreliosis suggest her optic neuritis was secondary to Lyme borreliosis. Patient was administered IV ceftriaxone for the management of Lyme borreliosis, and steroid was given due to the degree of the swelling. Patient’s symptoms normalized after her treatments.

Conclusion
Clinicians working in the endemic areas should consider Lyme borreliosis in patients presents with bilateral optic nerve head swelling, and painless progressive visual loss. Inadequate early treatment of Lyme borreliosis increases the likelihood of late manifestation and leads to relapses. Lyme borreliosis patients with optic neuritis respond well to antibiotics and have good prognosis.

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Authors’ contributions
R.Z developed the study design and concept of the study, contributed to analysis and interpretation of the findings, and revised and approved the final manuscript. Y. L collected the articles and wrote the main manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
Data can be shared with other investigators upon request and execution of a data-sharing agreement.

Declarations

Ethics approval and consent to participate
The authors confirm that all methods were carried out in accordance with Geisinger Institutional Review Board (IRB) guidelines and regulations. All experimental protocols were approved by Geisinger institutional Review Board. The written consent was obtained from the patient to present her illness. Authors attest that informed consent for study participation was obtained from all subjects in the study.

Consent for publication
We obtained signed consent from the patient for the personal or clinical details to be published in this study.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Geisinger Commonwealth School of Medicine, Scranton, PA, USA. 2 Department of Neurology, Neuroscience Institute, Geisinger Health System, Danville, PA, USA.

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