

## Simultaneous involvement of optic and abducens nerves by Lyme disease: Case report with review of the literature

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### Abstract

Ocular manifestations of Lyme disease (LD) remain a rare feature of the disease, but it may present a wide range of clinical presentations with different combinations. LD related optic neuritis or cranial nerve (CN) six palsy have been reported in the literature. However, this is the first case report of simultaneous involvement of CN 2 and CN 6 in a patient with LD. The diagnosis of LD can be challenging and initial laboratory tests can be a false negative. It is paramount important to repeat the diagnostic test if clinical suspicious is ongoing. With this case, we aim to increase awareness of clinicians for possible ocular manifestations of LD and its complex diagnostic process.

### Introduction

Lyme disease (LD) is an arthropod-borne disease caused by *Borrelia burgdorferi* and commonly seen in the Northern Hemisphere. Neurological manifestations of LD occur in 12% of these cases and can present as the only manifestation of the disease as early as 2-18 weeks after infection, and ocular manifestations can be seen in all three stages of the disease.<sup>1-6</sup> Ocular findings in LD are uncommon, but prior case studies and literature have reported conjunctivitis; keratitis; photophobia; periorbital edema; pupillary abnormalities; cranial nerves (CN) palsies of III, IV, VI; papilledema; optic neuritis; and optic atrophy.<sup>3,6-14</sup>

Optic neuritis (ON) is an inflammation of the optic nerve and is seen in various CNS etiologies, including demyelinating, autoimmune, inflammatory, infectious, and post-vaccination.<sup>10,15</sup> ON is usually associated with pain, and the patient usually has a history of rapid visual loss over hours to weeks, an afferent pupillary defect, or optic disc edema, in conjunction with either decreased visual acuity, visual field defect, or dyschromatopsia.<sup>15,16</sup> ON in LD is a rare finding, with a handful of reported cases documenting isolated nerve head involve-

ment.<sup>15,17,18</sup> Sixth-nerve innervated lateral rectus muscle and its palsy is hallmarked by double vision that worsens with horizontal gaze in the direction of the paretic lateral rectus muscle and can be an acquired lesion at any point along its path starting from the sixth nucleus located at the dorsal pons.<sup>19</sup> In adults, etiologies include idiopathic, inflammatory, trauma, tumors, vascular insults, and infectious.<sup>20</sup> Double vision as a result of palsies to cranial nerves III, IV, and VI have been reported numerous times in various literature associated with LD.<sup>12</sup> In this case report, we discuss an atypical case of possible LD presenting with ipsilateral left ON and left sixth-nerve palsy, along with pre- and post-treatment findings and literature review.

### Case Report

A 56-year-old female with past medical history of migraine headache and fibromyalgia presented on October 24, 2018 with continuous onset of left-sided hemifacial pain/headache for one week prior to the development of diplopia and blurry vision in her left eye. She claimed to have had tick exposure in June of 2018. The patient initially expressed a sudden and severe onset of a left temporal headache. The pain was described as sharp knives being stuck into her left temple/head and face extending to her nostril. This was associated with nausea without vomiting, which was atypical for her normal migraine attacks. She tried sumatriptan, but it was not effective. She experienced subjective changes in her taste and hyperalgesia to the left side of her face and ear as well as intermittent flashing lights and colors for an entire week. Roughly one week from the onset of the left hemifacial pain/headache, she had woken up to retro-orbital left eye pain and complained of double vision.

She saw her primary care physician (PCP) immediately, who prescribed promethazine and ketorolac, which provided minimal relief. She was started on a methylprednisone dose pack (4 mg tabs). C-reactive protein was checked and came back normal. Due to unresponsiveness to the treatments, she was referred to the emergency department (ED).

Her initial examination in the ED displayed a mild esotropia of the left eye in primary position and evidence of left lateral rectus palsy with subjective diplopia on left horizontal gaze. No other neurological deficits were noted. She was started on carbamazepine in the ED to treat for presumed trigeminal neuralgia, which subjectively helped her left hemifacial pain/headache

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mildly. She underwent clinical investigation with basic laboratory work, including comprehensive metabolic panel, blood cell count, and erythrocyte sedimentation rate, which all resulted in normal range values. She also underwent diagnostic imaging, including magnetic resonance venography (MRV) of head, which did not reveal cerebral venous sinus thrombosis, and magnetic resonance imaging (MRI) of brain with and without contrast, including thin cuts through the petrous ridge, which did not reveal any correlating pathology to her left lateral rectus palsy or headache.

Ophthalmology inpatient service was consulted, and examination revealed her visual acuity near with correction was 20/25 OD, 20/30 OS and tonometry was 17, 16 mm hg respectively. Confrontation visual fields were grossly full bilaterally. There was no afferent pupil defect. Motility was full on the right eye. The left eye had an obvious esotropia in primary position, and she had clear signs of left abducens paresis. Funduscopic exam of the right eye was normal, while funduscopic exam of the left eye revealed a blurring of the neuro-retinal rim and optic nerve that was consistent with ON. Further tests, including Lyme titers with band and myasthenia panel, were ordered. Due to history of previous tick bite, she was placed on doxycycline 100 mg twice a day, was discharged from the ED with an eye patch, and was ordered to follow up with her PCP, neurology, and neuro-

ophthalmology for the results of her remaining lab work and further medical management.

Two days later, she developed a nonspecific scalp rash and immediately followed up with her PCP. She still expressed left facial pain and headache. She continued to have double vision from her left abducens palsy and visual blurriness in her left eye. Her laboratory test reviewed by her PCP resulted in borderline seropositive acetylcholine (ACh) receptor binding antibodies of .56 (Positive:  $> \text{ or } = 0.50 \text{ nmol/L}$ ). Her Lyme antibody screen was negative at  $< 0.90$  ( $> 1.09$  is positive), but reflex IgG and IgM Western blot showed reactivity at 23KD IgG/IGM only. The decision was made to discontinue her doxycycline and to start her on valacyclovir 1gr per day for seven days for the nonspecific rash. She was told to follow up with neurology for further management of her headache associated with ocular manifestations.

During her follow-up examination with neuro-ophthalmology on November 1, 2018, the patient's nonspecific rash had improved after two days of valacyclovir, and she also expressed subjective improvement of facial/head pain. The neuro-ophthalmology examination showed esotropia in primary position and limited abduction of the left eye, 20/20 visual acuities bilaterally, no relative afferent pupillary defect bilaterally, and normal color test bilaterally. Funduscopic exam revealed mild disc edema in the left eye with no further abnormalities seen, especially from the vessels, disc, or macula. Humphrey visual field analyzer in the left eye revealed an inferior nasal step defect. Given her left ipsilateral hemifacial pain, left sixth-nerve palsy, and unspecified mild left optic neuritis, the neuro-ophthalmologist was concerned about poly-cranial neuropathies and recommended a lumbar puncture to check for cell count and protein, cerebrospinal fluid (CSF) Lyme antibodies, CSF VDRL, oligoclonal bands, herpes simplex virus polymerase chain reaction (PCR), herpes zoster virus PCR, and cytology. Pertinent results included mild pleocytosis of 22 cells (lymphocyte dominant), mild protein elevation of 49, and normal serum glucose. The remainder of laboratory work ups including nonreactive CSF Lyme antibodies, negative CSF VDRL, and absent oligoclonal bands were within normal limits.

The patient followed up in the neurology clinic on December 3, 2018 and no longer expressed left hemifacial pain/headache but still had diplopia from the left abducens nerve palsy with double vision on examination. The patient also expressed a vague intermittent tingling sen-

sation in bilateral feet, hands, and face, with a normal peripheral sensory nerve exam. She was put on pyridostigmine 60 mg q4 to empirically treat for ocular myasthenia, given positive serology. Simultaneously, she was started once more on doxycycline 100 mg bid to treat for LD, given her tick exposure, optic nerve involvement, and subjective complaints of paresthesias and dysgeusia. Myasthenia gravis panel serology was sent out from the December 3 neurology exam, which resulted on December 8 with negative ACh receptor binding, ACh receptor blocking and striated muscle antibodies.

The patient followed up with the neurology clinic on December 19, 2018, again without any further visual symptoms, and it was unclear if this improvement was a result of the pyridostigmine or doxycycline. The patient was then asked to discontinue her pyridostigmine and continue taking doxycycline to ensure that this was the result of tick-borne disease.

After a total of eight weeks on doxycycline, she remained asymptomatic and followed up on January 30, 2019 with an LD specialist, who repeated testing for Lyme antibody Western blot IgG/IgM. This time, she had a positive LD antibody IgM immunoblot reactive at 23KD, 39KD, and 41KD but negative LD antibody IgG immunoblot, which was only reactive at 23KD and 41KD. The LD specialist concluded that the patient had LD and asked her to continue doxycycline for two more weeks.

The patient, having been on doxycycline for 10 weeks, followed up with neurology on February 11, 2019 without any subjective visual and sensory complaints. She was asked to continue doxycycline for two weeks longer.

## Discussion

In this case report, we presented an atypical case of ipsilateral ON and sixth-nerve palsy possibly related to LD. In our case, the patient initially presented with left ipsilateral hemifacial pain/headache, left sixth-nerve palsy, and papillitis. Due to the unusual presentation, she was started on pyridostigmine and doxycycline. The patient's visual symptoms and sensory complaints had resolved both subjectively and clinically while on both medications, and this improvement warranted repeat serology for MG, which was negative. The patient was stopped on pyridostigmine and continued on doxycycline with no further ocular and sensory manifestations. Repeated Lyme serology revealed a positive immunoblot of

IgM reactive at 23KD, 39KD, and 41KD, and immunoblot for IgG was reactive at 23KD and 41KD. After 10 weeks of doxycycline, the patient continued to remain symptom free. To our best knowledge, this is first case report of LD related combined ON and abducens nerve palsy, which completely resolved with doxycycline treatment.

Laboratory confirmation of LD can be challenging. Typically, the CDC requires a two-step laboratory testing process for LD diagnosis, which includes enzyme-linked immunosorbent assay (ELISA) followed by a Western blot.<sup>21,22</sup> The initial blood work up showed a negative Lyme AB ELISA screen followed by a Western blot that revealed only one identical IgG/IgM band reactive at 23KD. Repeat serology three months later resulted in positive IgM blot reactivity at 23KD, 39KD, and 41KD and in positive five of the IgG blots.<sup>1,23</sup>

Bands that are reactive on an IgM blot after four weeks can sometimes lead to false positive results, but it has been established that seroconversion from IgM to IgG can sometimes take up to two months.<sup>1</sup> If one suspects neuroborreliosis, CSF for intrathecal production of antibodies to *B. burgdorferi* greater than 1.0 is considered a positive test, but it has been reported in case studies of early neuroborreliosis that CSF markers can be negative in 20–30% in the first six weeks.<sup>1,23</sup> For this reason, it is paramount important to repeat LD tests in cases, which initial LD tests are negative but clinical suspicious is continuing.

Unfortunately, there is not a direct link between Lyme seropositivity and ON. A few studies have examined the relationship between LD and ON.<sup>16,23</sup> Jacobson *et al.*<sup>23</sup> performed an investigation of 20 patients with newly diagnosed isolated ON who resided in a region endemic for LD, finding only four patients who had resulted in positive serology for LD. Three of these patients underwent CSF analysis, and two had CSF lymphocytic pleocytosis that remained unexplained after extensive evaluations for causes other than LD.<sup>15</sup> Lyme disease related CN 6 palsy is very rare. Few case reports<sup>8,10,19,20</sup> in the literature have been reported. The simultaneous involvement of CN 3 and CN 6 in a patient with LD was reported,<sup>8</sup> but the simultaneous involvement of CN2 and CN 6 was not reported previously. In our case, the patient presented both ON and CN 6 palsy.

Given the other neurological manifestations and ON, it appears that these cases of LD in addition to ON are trending to a diagnosis of exclusion. Therefore, a comprehensive investigation was performed to rule out other causes of ON in addition to sixth-

nerve palsy before beginning extensive treatment with doxycycline, which did show a favorable outcome.<sup>3,13,15,20,24</sup>

Neurological manifestations of LD in the past have shown highly effective responsiveness to ceftriaxone, cefotaxime, penicillin G, and doxycycline.<sup>4,14,15,24,25</sup> Prior cases of patients who failed oral regimens showed response to IV ceftriaxone, high-dose penicillin, and cefotaxime. Studies in Europe<sup>26-30</sup> have provided evidence that oral doxycycline can achieve effective concentrations in CNS and have been shown to be effective in Lyme meningitis, cranial neuritis, and radiculo-neuritis, as was the case in this patient.

## Conclusions

Ocular manifestations of LD remain a rare feature of the disease, but it may present a wide range of clinical presentations with different combinations. The unique part of this case is that the patient presented with simultaneous involvement of optic and abducens nerves. The diagnosis of LD can be challenging and initial laboratory tests can be a false negative. It is paramount important to repeat the diagnostic test if clinical suspicion is ongoing. With this case, we aim to increase awareness of clinicians for possible ocular manifestations of LD and its complex diagnostic process.

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