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Optometry Rounds

A Learning Resource for Optometrists from the School of Optometry & Vision Science, University of Waterloo, and the School of Optometry, University of Montreal

The Great Masquerader: Uncovering the Ocular Manifestations of Lyme Disease

By Michelle Steenbakkers, OD, FAAO, and Sarah MacIver, OD, FAAO

Although originally identified in Lyme, Connecticut, the condition now known as Lyme disease has since been diagnosed across Canada as well as in Europe and Asia. Optometrists can play a pivotal role by having an initial suspicion of Lyme disease in patients with some of the earliest presenting ocular symptoms in this condition. This issue of *Optometry Rounds* reviews the current state of knowledge specifically related to the systemic and ocular manifestations of this multifaceted condition.

> *"[Lyme disease] can look like any other disease and can affect almost any tissue of the eye, starting with the lids and working its way back to the optic nerve. It can create superficial inflammatory disease of the cornea. [The patient] can have neurotrophic disease that produces tissue loss. Most commonly [the eye care professional is] going to see inflammatory responses such as iritis, uveitis, retinitis, or optic neuritis."*
>
> – J. James Thimons, OD, FAAO,
> Editorial Board member, Primary Care Optometry News, Fairfield, Connecticut

Although Lyme disease is considered to be a relatively new medical condition, *Borrelia burgdorferi* bacteria (the tick-borne spirochete causing the disease) has been present for several millennia. The deoxyribonucleic acid (DNA) sequence of *B burgdorferi* was found in the 2010 autopsy of a 5300-year-old mummy found in the Italian Alps.[1] The first documented report that linked a tick bite to the development of a sensory radiculitis accompanied by meningitis dates back to the 1920s.[2] In 1975, the full syndrome now known as Lyme disease or Lyme borreliosis was recognized in a series of pediatric patients from Lyme, Connecticut, by Steere and Syndman.[3]

The first description of the ocular manifestations of Lyme disease, such as conjunctivitis and periorbital edema, were reported by Steere in the 1980s.[4] A number of isolated reports followed, documenting Lyme disease as causing blepharospasm, iridocyclitis, panophthalmitis, optic neuritis, and orbital myositis.[5,6] Lyme disease and its subsequent ocular manifestations mimic many other pathological conditions, and may be misdiagnosed and consequentially mismanaged. The clinical spectrum of ocular Lyme borreliosis continues to expand, making it crucial for optometrists to understand their role in the early detection, diagnosis, and long-term management of this condition.

Etiology and Epidemiology

Lyme disease is caused by specific spirochete bacteria of the genus *Borrelia*, including *Borrelia burgdorferi*, named after the medical entomologist Willy Burgdorfer. Burgdorfer isolated the species by DNA-DNA hybridization studies in 1982.[7,8] There are 3 genospecies, collectively known as *B burgdorferi* sensu lato (s.l.), which predominate as human pathogens: *B burgdorferi* sensu stricto in North America and Western Europe, and *Borrelia garinii* and *Borrelia afzelii* in Eurasia.[9] *B burgdorferi* s.l. is transmitted to humans via ticks and is the most commonly reported vector-borne disease in the Northern hemisphere. In 2008 there were 30 000 confirmed cases of Lyme disease in the United States (U.S.) compared to only 80 confirmed cases in Canada.[10-12] Lyme disease is substantially underreported to the U.S. Center for Disease Control (CDC) by as much as 6- to 12-fold.[13,14] Similar underreporting is believed to exist in Canada according to the Public Health Agency of Canada.[12] Using

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Figure 1: A map showing locations of known (red triangles) and suspected (blue triangles) Lyme endemic areas in eastern and (inset) central Canada. There are also known endemic areas in southern mainland and Vancouver Island, British Columbia, and cases have been reported as far east as Newfoundland. Reproduced from Public Health Agency of Canada. http://www.phac-aspc.gc.ca/id-mi/tickinfo-eng.php.

comparative data from the CDC, the estimated actual number of cases in Canada may currently be closer to 40 000.[15]

Owing to Canada's changing climate, the detection of ticks carrying Lyme disease has expanded from a limited area of Ontario (Long Point peninsula on the north shore of Lake Erie) to include areas of southern Quebec, Manitoba, northern Ontario, southwest Nova Scotia, and limited parts of Saskatchewan, Alberta, and British Columbia. Cases have also been reported in Newfoundland (Figure 1).[16] Following elevation of Lyme disease to reportable disease status in Canada, it has been noted that the incidence is increasing.[16] At present, personal protection such as wearing long pants, light-coloured clothing and inspecting for ticks after potential exposure in tall grass and woodland areas and education regarding the disease in endemic locations has been recommended as the best protection.

Stages of Systemic Lyme Disease

Lyme disease can present with a variety of symptoms (Table 1), and the disease itself shows 3 distinct stages.[17] The first stage is characterized by a skin lesion termed erythema migrans which has a "bull's eye" appearance (Figure 2). The lesion may expand to a diameter of >5 cm from the site of the tick bite.[18] Weeks to months after the initial infection, the patient may progress to stage 2: multiorgan involvement with a predilection for the cardiovascular system and the central nervous system. The third phase is chronic, occurring months after the initial onset. It can affect the patient's joints, peripheral nervous system, and subcutaneous tissues.

Table 1: Multisystem presenting symptoms of Lyme disease

Skin
- Benign tumour-like nodules
- Erythema migrans

Head, face, neck
- Headache
- Facial paralysis (eg, Bell palsy)
- Tingling of nose, cheek, or face
- Stiff neck
- Sore throat, lymphadenopathy
- Heightened allergic sensitivities
- Twitching of facial/other muscles
- Jaw pain/stiffness
- Change in smell, taste

Eye, vision
- Diplopia or blurry vision, vision changes
- Strabismus
- Conjunctivitis
- Photophobia
- Eye pain
- Periorbital swelling
- Floaters/spots in the line of sight

Ears, hearing
- Decreased hearing
- Tinnitus, pain in ears
- Sound sensitivity

Gastrointestinal system
- Nausea, vomiting
- Irritable bladder
- Unexplained weight loss or gain
- Loss of appetite, anorexia

Musculoskeletal system
- Joint pain, swelling, or stiffness
- Shifting joint pains
- Muscle pain or cramps
- Poor muscle coordination, loss of reflexes
- Loss of muscle tone, muscle weakness

Neurologic system
- Numbness and tingling
- Burning/stabbing sensations
- Burning in feet
- Limb weakness/paralysis
- Tremors or unexplained shaking
- Seizures, stroke
- Poor balance, dizziness, difficulty walking
- Increased motion sickness
- Syncope
- Encephalopathy (eg, encephalitis, encephalomyelitis, meningitis)
- Academic or work decline
- Difficulty with multitasking and organizing
- Auditory processing problems
- Word-finding problems

Respiratory/circulatory systems
- Difficulty breathing, night sweats, or unexplained chills
- Heart palpitations
- Diminished exercise tolerance
- Heart block, murmur
- Chest pain or rib soreness

General well-being
- Extreme fatigue
- Unexplained fevers, flu-like symptoms

Psychiatric
- Mood swings, irritability, agitation
- Depression and anxiety
- Aggressive behaviour, impulsiveness
- Suicidal thoughts
- Hyperemotional reactions
- Disturbed sleep
- Suspiciousness, paranoia, hallucinations
- Obsessive-compulsive behaviour
- Bipolar disorder/manic behaviour
- Schizophrenia-like state

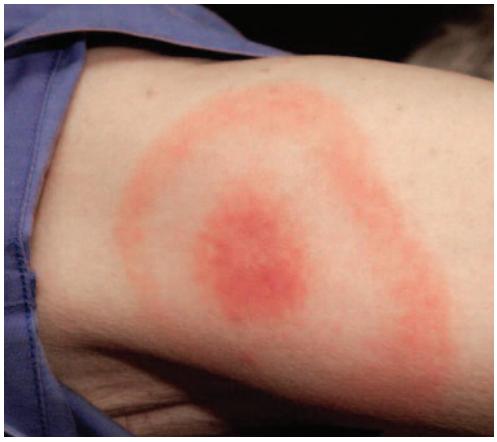
Cognitive
- Dementia, memory loss
- Poor school or work performance
- Attention deficit problems, distractibility
- Difficulty with concentration, reading, spelling
- Disorientation

Reproduction and sexuality – female
- Menstrual pain, irregularity
- Reproduction problems
- Extreme premenstrual syndrome symptoms

Reproduction and sexuality – male
- Testicular or pelvic pain

Other organ problems
- Thyroid dysfunction
- Liver inflammation
- Bladder and kidney problems

Figure 2: The pathognomonic "bull's eye" rash, known as erythema migrans, on the arm at the site of a tick bite in a patient with Lyme disease. Photo courtesy of James Gathany, Centers for Disease Control and Prevention. http://phil.cdc.gov/phil/home.asp. Photo ID# 9875, 2007.



A controversial aspect of the disease is the entity known as "late" or "chronic" Lyme disease. Certain patients develop a long-term or relapsing inflammatory reaction, including uveitis. It has not been established if patients with chronic Lyme disease represent antibiotic treatment failures, a persistence of the organism, infection with another tick-borne pathogen, or perhaps an autoimmune phenomenon.[30]

Ocular Manifestations

One of the first presentations of Lyme disease may be an ocular manifestation, which stresses the importance for all eye-care practitioners to consider Lyme disease in a differential diagnosis of red eye and/or vision loss. Ocular manifestations occur in 1% of cases of systemic Lyme disease.[19] Lyme borreliosis can cause a variety of ophthalmic conditions which can involve any of the ocular structures outlined in Table 2, usually presenting as an inflammatory event in the anterior and/or posterior segment, and can occur at any stage of Lyme borreliosis. Lyme disease resembles syphilis in that both have 3 stages of progression and both have ocular manifestations that can be described as great masqueraders, meaning that their ocular manifestations mimic other disease processes.[17] Lyme disease may imitate a number of other ocular conditions, including but not limited to Horner syndrome, oculomotor or trochlear nerve palsy, Rocky Mountain spotted fever, and sarcoidosis (Table 3).

Symptoms associated with ocular manifestations from Lyme disease are often nonspecific. Severe photophobia and ocular or periocular pain are reported by a considerable number of patients with a neuro-ophthalmological disorder or external ocular inflammation.[19] Other symptoms depend on the stage of Lyme disease and may present as pain, visual impairment, photophobia, diplopia and accommodative problems.[20]

Three Stages of the Ocular Manifestations of Lyme Disease

The ocular manifestations of Lyme disease can also be classified into 3 distinct stages.[17]

Table 2: Ocular manifestations in Lyme disease

STAGE 1

Anterior
- Conjunctivitis and related photophobia

STAGES 2 and 3

Anterior
- Anterior uveitis
- Episcleritis
- Keratitis
- Scleritis
- Symblepharon

Neuro-ophthalmic
- Bell palsy
- Cranial nerve palsies
- Internuclear ophthalmoplegia
- Papilledema

Posterior
- Branch artery occlusion
- Central retinal vein occlusion
- Chorioretinitis
- Cystoid macular edema
- Exudative retinal detachment
- Intermediate uveitis, pars planitis, vitritis
- Orbital myositis
- Peripheral multifocal choroiditis
- Retinal pigment epithelial detachment
- Retinal vasculitis

Stage 1

Ocular signs in stage 1 are typically isolated to the anterior segment and include a follicular conjunctivitis and related photophobia. Conjunctivitis is the most common ocular borrelial manifestation, reported in up to 10% of cases of Lyme disease,[21] and usually occurs within the first weeks of the initial infection.[4] Symptoms are often mild and transient: the patient may not seek consultation from an eye care professional. If the patient presents to an optometrist with a history of a persistent or transient conjunctivitis, the likelihood of Lyme disease must be evaluated through a complete history, including questioning of possible tick bite in an endemic area. The conjunctivitis is self-limiting and its resolution can provide false assurance that a prescribed topical antibiotic has led to resolution.

Failure to identify Lyme disease as the cause of conjunctivitis in the first stage of the disease can delay proper systemic treatment, allowing the disease to rapidly advance to stage 2, when the likelihood of a cure diminishes. The optometrist can play a critical role in suspecting Lyme disease at its earliest and most treatable stage, especially in the 20% of patients who do not develop the characteristic rash.

Stage 2

As the *Borrelia* spirochetes pass the blood-brain barrier, the most common complications are neuro-ophthalmic and include Bell palsy.[22] This may appear as part of the triad of Lyme neuroborreliosis: cranial nerve palsy, meningitis, and radiculopathy.[23-26] Bilateral facial nerve palsy in the general population is <2% of all cases of facial palsy;[27] however, Clark et al[28] found that of the 101 Lyme disease patients who presented with a facial nerve palsy (10.6% of the total study population), 25 (3%) were bilateral, making *B burgdorferi* the

Table 3: Ocular differential diagnosis of Lyme disease

- Bell palsy
- Viral conjunctivitis
- Herpes simplex
- Herpes zoster
- Horner syndrome
- Oculomotor nerve palsy
- Optic neuritis
- Rocky Mountain spotted fever
- Sarcoidosis
- Trochlear nerve palsy

most common infectious cause of this manifestation. Other neuro-ophthalmic signs include papilledema, where the patient may present with blurred vision, optic atrophy, optic or retrobulbar neuritis, or pseudotumour cerebri. Optic nerve presentations may be unilateral or bilateral and may be found as a solitary sign or associated with other neurologic manifestations. There is some evidence that children are more predisposed to optic nerve disease than adults.[29]

Late stage 2 and stage 3

The most severe ocular manifestations of the disease are seen at these stages. These manifestations often present as an inflammatory event in the anterior and posterior segment of the eye. The most common anterior segment manifestation is transient conjunctivitis, which can be significant and lead to symblepharon, episcleritis, keratitis, and anterior uveitis. Keratitis in the chronic stage of Lyme disease is usually bilateral, patchy, nummular stromal keratitis.[30]

Uveitis is most commonly intermediate in Lyme disease. It generally presents as a bilateral pars planitis associated with granulomatous iritis and vitritis. Many of these patients also have granulomatous keratic precipitates and posterior synechiae.[31] In 1985, Steere et al[32] described a patient in whom *B burgdorferi* spirochetes were isolated from the vitreous after severe panophthalmitis.

Posterior segment involvement is seen in the later chronic stages of the disease. Common posterior segment manifestations include chorioretinitis, exudative retinal detachment, retinal pigment epithelial detachment, cystoid macular edema, branch artery occlusion, central retinal vein occlusion, retinal vasculitis, peripheral multifocal choroiditis, orbital myositis and cranial nerve palsies.[19,33,34]

Neuro-ophthalmic Manifestations

It is important for optometrists to recognize the neuro-ophthalmic manifestations that may occur in Lyme disease. Approximately 10%–15% of infected individuals develop central nervous system involvement, most often meningitis.[35] The neurological disorders found in Lyme disease are collectively referred to as neuroborreliosis. Abnormalities of the cranial nerves are also a common nervous system manifestation of neuroborreliosis, occurring in 5%–10% of patients.[36] The most commonly affected is the facial nerve, occurring in 80% of Lyme disease cases with cranial nerve abnormalities. Lyme disease is one of the few disorders associated with bilateral facial palsies.[28,37] Other cranial nerve abnormalities associated with Lyme disease, including the oculomotor nerve, the abducens nerve, and the vestibuloauditory nerve, have been described in the literature.[38,39] Paralytic strabismus and diplopia associated with Lyme disease are most often secondary to abducens palsy.[25]

Internuclear ophthalmoplegia (INO), as the result of a lesion in the medial longitudinal fasciculus, has also been documented in Lyme disease.[38,40] Conjugate eye movements are affected in an INO. The connections between the paramedian pontine reticular formation-abducens nucleus complex and the oculomotor nucleus become dysfunctional. Gyllenborg and Milea[41] also reported a case of ocular flutter, described as bursts of horizontal saccadic intrusions, as the first manifestation of Lyme disease. If a patient presents with a sudden onset of diplopia, Lyme disease is important to include in the differential diagnosis.

Diagnostic Testing

As of 2009, healthcare professionals are required to report clinically confirmed and suspected cases of Lyme disease to the Public Health Agency of Canada.[42] Serological testing for *B burgdorferi* can be insensitive in very early Lyme disease. Possible reasons for false-negative blood test results include recent antibacterial or steroidal anti-inflammatory treatment prior to testing, an immunocompromised patient, or antigenic variability of *B burgdorferi*. The current Canadian standard for Lyme disease diagnosis includes the 2-tiered serological testing method consisting of enzyme-linked immunosorbent assay (ELISA) followed by Western blot to assist in diagnosis. When used alone, ELISA has limited specificity which is improved when used in conjunction with Western blotting.16 However, these 2 tests are not always reliable for a definitive diagnosis of Lyme disease.43

Management

Systemic

Although there have been many proposed management strategies and treatment protocols for systemic Lyme disease, the course of treatment often depends on the duration of undetected infection, the presence of co-infections such as *Babesiosis*, *Ehrlichiosis*, and *Bartonellosis*, and individual patient factors including the state of the patient's immune system.

Current treatment protocols for Lyme disease include the use of oral, intravenous, and intramuscular antibiotic medications. The treatment can be classified based on the stage of progression of the disease. Patients

in stage 1 of Lyme disease are treated with a 2- to 3-week course of oral antibiotics, including doxycycline and beta-lactams such as penicillin, amoxicillin, or cefuroxime. Doxycycline is often the preferred agent for oral treatment because of its activity against other tick-borne illnesses; however, it should not be used in pregnant women or children younger than 8 years.[44]

As the disease progresses to later stages, similar oral antibiotics are often used; however, the time course increases to 30 days. Parenteral antibiotic therapy may be required if the patient has a more severe presentation at this later stage, such as meningitis, neuroborreliosis, or carditis. Agents such as beta-lactam antibiotics for 2–3 weeks are initiated in the later stage. These include intravenous or parenteral beta-lactams such as penicillin G or cefotaxime, or the cephalosporin ceftriaxone.[44,45]

Ocular

The ocular management of Lyme disease can also be subdivided into the 3 stages of this condition. During stage 1, palliative treatment can be recommended, such as artificial tears for conjunctivitis and sunglasses for photophobia. Referral at the earliest stages of suspected Lyme borreliosis to an infectious disease specialist who is current in Lyme disease assessment and management is necessary to confirm the diagnosis. Remember that approximately 20% of patient with Lyme disease do not develop the typical annular rash.

In stage 2, facial nerve palsy is self-limiting but may require supportive therapy to prevent complications of exposure keratitis. Artificial tears may be recommended and tear gel or ointment in combination with eyelid taping may be suggested for overnight care. If dry eye and subsequent keratitis present with the facial nerve palsy, the patient may benefit from a short course of topical corticosteroids, such as fluorometholone 0.1% or loteprednol etabonate 0.5%.[46] Episcleritis can be managed with artificial tear lubricants and a topical nonsteroidal anti-inflammatory agent depending on the severity. The symptoms of transient diplopia, often secondary to an abducens palsy, may be relieved temporarily by Fresnel prisms or semi-occlusion on spectacle lenses. Anterior uveitis is managed aggressively with topical corticosteroids such as 1% prednisolone acetate, and topical cycloplegic agents such as 1% atropine or 5% homatropine, in conjunction with antibiotic agents.[20]

Patients with posterior-segment manifestations, including intermediate uveitis and neuro-ophthalmic manifestations, should be managed concurrently by an infectious disease specialist and an ophthalmologist. A treatment protocol for severe neuro-ophthalmic or posterior segment involvement in Lyme disease has not been established. Oral corticosteroids without concomitant antibiotics should not be used. A proposed management protocol includes a therapeutic 2- to 3-week trial of intravenous penicillin or ceftriaxone.[46,47] If the patient responds to treatment, the trial is considered successful and ocular Lyme disease is diagnosed with no further therapy required. Recurrences of Lyme uveitis, once adequate intravenous therapy has been given, can be treated with judicious corticosteroids.[46] The dosing regimens and therapies are continuously evolving with constant updates and new recommendations. Patients with Lyme disease are best co-managed by an infectious disease specialist who specializes in this condition and maintains a current state of knowledge.

Future Research

Investigation is ongoing to develop an effective, safe, and practical vaccine for the prevention of Lyme disease. A vaccine composed of a recombinant outer surface protein A (OspA) of *B burgdorferi* was approved by the U.S. Food and Drug Administration in 1998; however, it had several limitations and only an 80% efficacy rate and was discontinued in 2002.[26] An OspC is currently being investigated for future vaccine usage.[48] Future research is also aimed at developing a more sensitive and specific test for early detection of Lyme disease.

Conclusion

Lyme borreliosis should be considered in the differential diagnosis in the event of an acute ocular inflammatory condition such as a self-limiting follicular conjunctivitis at early infectious stages to later stage internuclear ophthalmoplegia, paralytic strabismus, diplopia, and retinal vasculitis. This is of paramount importance if the patient resides in an endemic area or has had recent travel to such a location. A thorough and complete history, including a possible asymptomatic tick bite, should be obtained. The recognition of stage 1 symptoms and directing a case history targeting the condition can potentially spare the patient a lifetime of chronic manifestations of Lyme disease.

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