SCREENING FOR BIOMARKERS OF LYME-RELATED INFECTION


Incorporating fundus photography and visual evoked potential can facilitate diagnosis.

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Lyme disease (*Borrelia burgdorferi*) is an emerging vector-borne infectious disease that is highly prevalent in several US regions, including the Northeast, Upper Midwest, and Northern California.[1] The incidence of Lyme and associated diseases has increased in the past 2 decades with about 25,000 confirmed cases reported annually.[2] However, there are numerous indications that the number of cases is highly underreported; the US Centers for Disease Control and Prevention estimates that the actual number of cases may be closer to 300,000 annually.[3] There is no way to know exactly how many people are affected by Lyme-related infection because many are thought to be undiagnosed or misdiagnosed.

Lyme disease is delivered by a tick bite that inoculates the host with spirochetes. Lyme disease is the generalized term used for a variety of coinfections such as *Bartonella*, *Babesia*, and *Erlichia*. Lyme-related infections, or tick-borne infections, are more appropriate terms because they describe the condition as an infection and these terms acknowledge the variety of spirochete infections that are possible from a tick bite. Some more common tick-borne infections include: anaplasmosis, Rocky Mountain spotted fever, *Rickettsia helvetica*, Colorado tick fever, ehrlichiosis, and *Powassan*.

You're probably wondering what this has to do with optometry. Well, consider this: Tick-borne disease can cause complications including follicular conjunctivitis, bilateral corneal neuropathy, uveitis, iritis, retinal vasculitis, optic atrophy, and optic disc edema.[4] The infection also affects vision; however, symptoms are often mistaken for other problems associated with functional ocular disorders, balance, movement, and cognition.[2]

TABLE. SYMPTOMS OFTEN ASSOCIATED WITH TICK-BORNE DISEASE

- Difficulty converging the eyes to maintain alignment for reading
- Difficulty maintaining focus of the eyes for near vision activities
- Losing place when reading
- Blurring of vision that changes
- Dizziness
- Difficulty with attention and concentration
- Loss of comprehension when reading
- Difficulty with visual memory
- Avoiding looking at objects close to the face
- Difficulty with balance when walking
- Drifting when walking
- Feeling overwhelmed when in a busy, crowded environment
- Bumping into objects
- Light and glare sensitivity

Many individuals with tick-borne disease experience difficulty with reading, eyestrain and fatigue, intermittent diplopia, loss of comprehension, loss of place, headaches, dizziness, joint pain, blurred vision, photophobia, and discomfort in the neck and shoulders (Table). The infection can also affect balance and posture. Tick-borne disease may also affect personality and learning ability and can cause the onset of food allergies.[1,3]

VISUAL DYSFUNCTION

Tick-borne disease can cause dysfunction with the spatial visual process in the brain. This dysfunction causes interference in the balance between two visual processes in the brain. The imbalance causes functional vision difficulties such as convergence and accommodative insufficiency.

A compromise to the spatial visual process causes the patient's vision to isolate on detail. Reading is no longer fluent. Instead of the spatial visual process seeing the shape of several words before the higher process sees the letters, the patient begins to see the words as isolated details of letters. This is referred to as *focal binding*. It produces intensity within the visual process that interferes with comprehension and memory and produces fatigue, headaches, and visual fatigue.

The condition also affects patients in busy, moving environments. The world becomes overwhelming, and this produces anxiety and, in some cases, even panic attacks.

The early diagnosis and detection of tick-borne disease remains a challenge. Because tick-borne disease is considered "the great mimicker," it often causes misdirection leading to misdiagnosis.[4] Lack of diagnosis and treatment in the acute phase may result in a chronic and even neurologic advancement of the undiagnosed disease.

CASE EXAMPLE

A 12-year-old girl was referred to our clinic for a neuro-optometric evaluation because of her learning difficulties. Her parents reported delays in developmental milestones. She never crawled as an infant, and her speech was delayed. The patient had difficulties learning when she started school, and she was diagnosed with dyslexia when she was in first grade. She reported having difficulty seeing the board in class, having headaches and light sensitivity, losing her place while reading, avoiding near tasks, having difficulty tolerating busy crowded environments, and having poor balance and coordination.

The patient's parents also reported changes in social behavior and personality. She had also developed food sensitivities in the past 2 to 3 years. Her parents said they had never noticed a suspicious bull's-eye rash, but they

AT A GLANCE

- The diagnosis of Lyme-related infection is a challenge because many of its symptoms are shared with other diseases.
- Lack of diagnosis and treatment in the acute phase may result in a chronic and even neurologic advancement of undiagnosed disease.
- The incorporation of fundus photography, visual evoked potential, OCT angiography, and blood testing can enable early diagnosis of tick-borne infection.

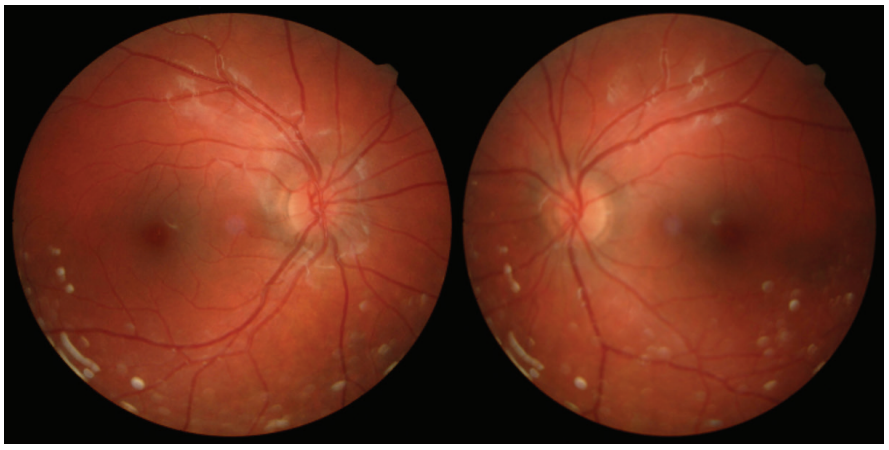

Figure 1. Fundus photos of the patient show peripapillary ischemia surrounding the ONH.

stated that the family had always lived in the Northeast region of the United States and enjoyed outdoor activities.

Previous Therapies

Because of her struggles in a traditional classroom setting, the patient was enrolled in an interactive learning center. Her pediatrician and school had suggested physical therapy (PT), occupational therapy (OT), and vestibular therapy to address her developmental delays. Her previous behavioral optometrist had recommended vision therapy (VT) due to the diagnosis of convergence and accommodative insufficiency, visual symptoms, and learning difficulties.

The patient completed PT, OT, vestibular therapy, VT, and neurological reorganization therapy. Some improvements had been noted in her learning and functionality, but she was still experiencing learning difficulties and visual fatigue. Little change had been detected in her convergence and accommodative insufficiency after VT was already completed.

Our Assessment

Upon our evaluation, the patient's entering distance BCVA was 20/20 OU. Extraocular muscles were full in all fields without pain, and her pupils were responsive with no afferent pupillary defect noted. However, pursuit tracking was jerky with fixation losses. The patient had a receded near point of convergence of 6"/10" and reduced stereoacuity of 140 seconds of arc on the random dot stereo test. Saccadic eye movements were reduced (unable to complete five rapid horizontal and vertical saccadic eye movements) both horizontally and vertically.

The patient's IOPs as measured with TonoPen (Reichert) were within normal limits at 11 mm Hg and 12 mm Hg. The refraction determined a low amount of hyperopia (+1.00 D) OU. Anterior segment findings were unremarkable. Posterior segment examination revealed a 0.25 cup-to-disc ratio OU. Close evaluation of the optic nerve head (ONH) showed an area of ischemia or atrophic changes that resembled a halo appearance around the ONH (Figure 1). This finding is uncommon in pediatric patients with no ocular disease. The disc was flat and distinct, but there was an obvious circumferential discoloration present bilaterally.

Biofilms and Ischemia

Padula and colleagues found that bilateral peripapillary ischemia is correlated statistically with Lyme-related infection.[2] The central retinal artery is approximately 50 µm in diameter, and the peripapillary capillary plexus decreases to approximately 15 µm. A spirochete is 15 µm in size and can easily pass through these vessels. However, when spirochetes are attacked by the body's immune system, they form *biofilms* as means of defense.

A biofilm is a collection of microorganisms. The spirochete embeds itself within the structure to avoid attack by the body's immune response. These biofilms are much larger than the spirochete. Although they pass through the larger central artery with no difficulty, it is suggested that they may be the cause of blockage in the small peripapillary plexus surrounding the optic nerve, thereby causing peripapillary ischemia.

Further Testing

OCT angiography (OCTA) was performed to evaluate the nerve fiber layer around the optic nerve and the patient's blood vessel density.[5] Results demonstrated a slight asymmetry between the right and left eyes, although the findings did not indicate significant deterioration of vessels (Figure 2). There may have been a pattern of reduction in retinal nerve fiber layer thickness, but at that time the findings were inconclusive.

A previous study using visual evoked potential (VEP) demonstrated that patients with active tick-borne infection have an increased (negative) amplitude for the N-75 (more than -5.0 µv).[2] This increased amplitude of the N-75 is correlated with increased symptoms related to binocular vision dysfunction and peripapillary ischemia. It was found that patients with potential active tick-borne disease demonstrated a statistically significantly higher amplitude for the N-75 compared with healthy patients. The study authors concluded that the N-75 is a biomarker that can be used to screen for tick-borne infections.

A binocular VEP was performed for this 12-year-old girl to evaluate the amplitude of the N-75, which was found to be -12.0 µv. This was a positive test for screening for

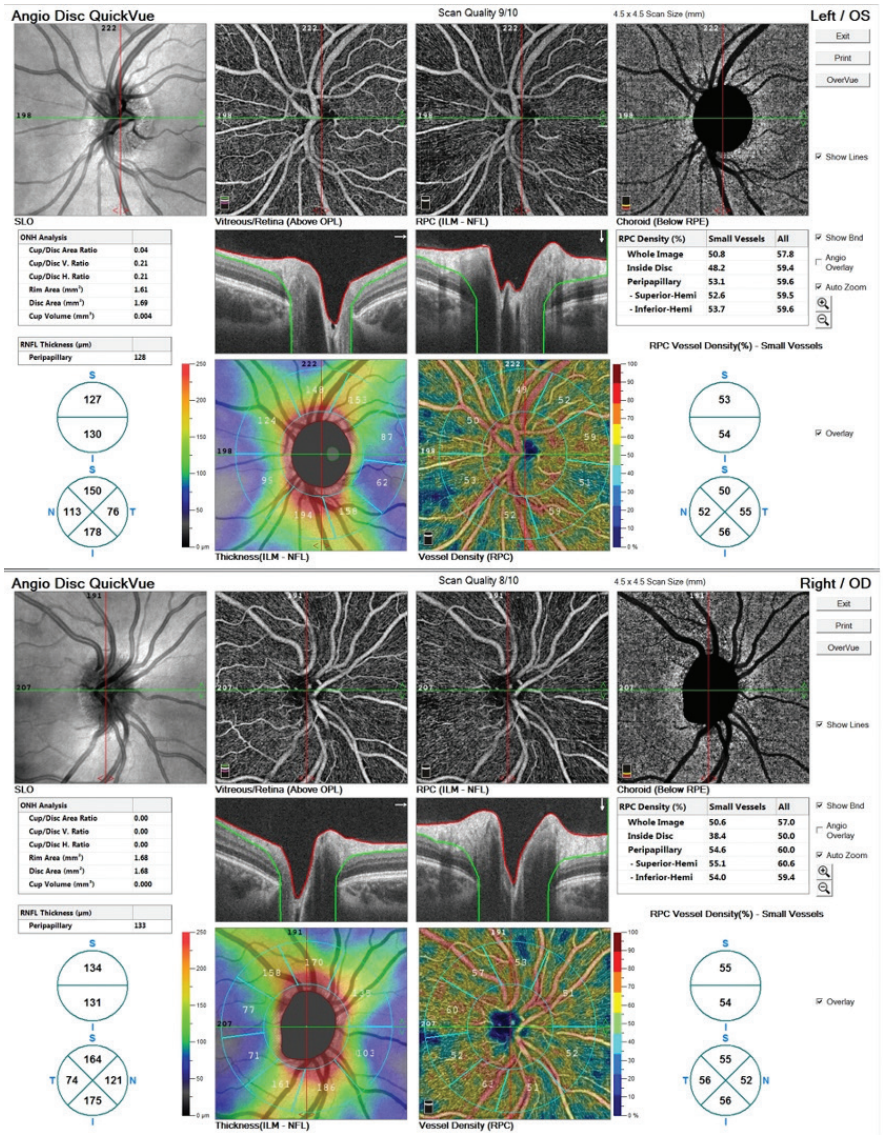

Figure 2. OCTA of the ONH, comparing retinal nerve fiber layer thickness and blood vessel density surrounding the ONH.

potential tick-borne infection. Further testing using prisms to affect the compromised spatial visual process was performed.

Post-Trauma Vision Syndrome

The binocular P-100 can be used to rule out compromise of the spatial visual process by testing with BCVA and then with 1.00-D to 1.50-D base-in prisms before each eye. If there is a compromise, the prism will support the spatial visual process, producing an increase in P-100 and a decrease in amplitude for the N-75.[2] This provides the differential diagnosis for a spatial visual processing dysfunction called *post-trauma vision syndrome* (PTVS) and demonstrates effective change by the prisms to be considered for prescription.[6,7]

The VEP binocular pattern reversal N-75 is an effective biomarker for screening Lyme-related disease.[2] The amplitude of the N-75 is sensitive to disruption or compromise of the spatial visual process delivered by the magnocellular system. The increased (negative) N-75 amplitude was found to be statistically significant in an experimental group with diagnosed tick-borne infection compared with controls.[2,7]

Differential Diagnosis

The patient was also diagnosed with spatial visual processing dysfunction and binocular vision dysfunction based on the VEP findings. Based on the biomarkers of peripapillary ischemia, a significant N-75 amplitude on the VEP (Figure 3), persistent visual symptoms, and binocular characteristics, it was decided to perform testing to rule out tick-borne infection.

The patient was provided a blood collection kit (IGeneX), along with orders to test immunoglobulin G and immunoglobulin M.

Results

IGeneX testing demonstrated positive results for *Borrelia burgdorferi*, *Babesia*, and *Bartonella* co-infections.

It was concluded that undiagnosed tick-borne disease had caused a spatial visual processing dysfunction that underscored the patient's binocular vision characteristics of convergence and accommodative insufficiency together with additional dysfunction with pursuits and saccadic fixations.

The patient was referred to a Lyme-literate physician, who started her on a course of multiple antibiotics and supplements.

Management

Treatment was started for spatial visual processing dysfunction with base-in prisms in each eye to affect the compromise of the spatial visual process. She was prescribed two pairs of prism lenses: one pair of continual-wear yoked prism lenses to affect vision, posture, and balance; and a near-prism prescription with a low plus power with 1.50-D base-in prisms for prolonged near work.[7]

The patient experienced improvement in convergence and accommodative insufficiency within several weeks. She also reported an improvement in her symptoms and noted a reduction

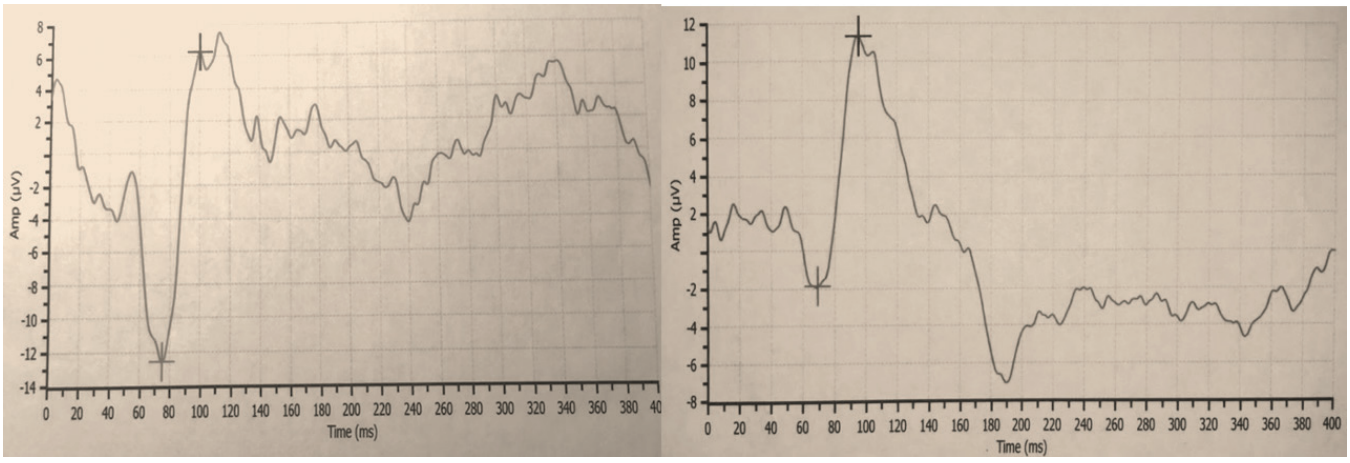

Figure 3. The N-75 from the patient (left) is compared to the negative deflection amplitude of the N-75 in a healthy individual (right).

in headaches and light sensitivity. Her parents observed improvement in her coordination and balance.

Patients with tick-borne infection must be monitored because the spirochetes often embed themselves in tissue within the body. Despite this, no antigens are present in the blood, which can cause false negative test results because the immune system will not produce antibodies without antigens. A patient's blood test can be negative, but reactivation of the infection can occur months or even years after the initial infection. Therefore, both vision and blood tests should be performed periodically to ensure systemic and visual health and visual processing efficiency.

Follow-Up

At the patient's initial progress check, she reported reduced eyestrain, improved reading ability, and better balance. Her convergence near point had improved to 4"/7" by means of the prism lenses affecting the spatial visual processing dysfunction. We recommended that she continue with the distance-prism glasses full time and near-prism lenses for prolonged near work.

She was still experiencing difficulties with visual skills, postural alignment, and balance, so we recommended neuro-visual postural therapy (NVPT) in conjunction with the continued use of the prism lenses. NVPT is a therapy to address the spatial visual processing dysfunction in addition to affecting the proprioceptive base of support.

The NVPT was provided for 10 visits, and a maintenance program was created for the duration of the patient's medical treatment. The course of antibiotics was continued for 6 months, and blood tests demonstrated no active infection.

BE ALERT FOR SYMPTOMS

Sudden onset of visual symptoms in conjunction with binocular dysfunction such as convergence and accommodative insufficiency can be characteristics of a tick-borne infection such as Lyme disease. Biomarkers of peripapillary ischemia and a VEP (negative) N-75 amplitude greater than -5.00 µV can be characteristics of a spatial visual processing dysfunction caused by tick-borne infection.

The incorporation of fundus photography, VEP, and OCTA can potentially enable early screening to rule out a tick-borne infection. This allows proper referral to a physician for medical treatment of Lyme-related disease and provides the clinician the opportunity to address the dysfunction in spatial visual processing through prescription of prism lenses and NVPT.

Vision is often affected by the infection. Symptoms are often mistaken for other problems associated with functional ocular disorders, balance, movement, and cognition.[5]

Due to the prevalence of visual symptoms associated with a tick-borne infection, the optometrist may be the first professional from whom a patient seeks help. Optometrists should be alert to the sudden onset of the symptoms and binocular characteristics of Lyme-related infection outlined in this article in order to screen for early diagnosis and appropriate treatment. ■

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