Physical Therapist Recognition and Referral of Individuals With Suspected Lyme Disease

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Abstract
The most commonly reported vector-borne and tick-borne disease in the United States is Lyme disease. Individuals with Lyme disease may present with a wide array of symptoms with resultant musculoskeletal, neurological, and cardiac manifestations that may cause them to seek physical therapist services. The symptoms may develop insidiously and with a variable presentation among individuals. Many persons with Lyme disease do not recall a tick bite or present with an erythema migrans rash, which is considered pathognomonic for the disease. Even if they do, they may fail to associate either with their symptoms, making the diagnosis elusive. It is important to diagnose individuals early in the disease process when antibiotic treatment is most likely to be successful. Physical therapists are in a unique position to recognize the possibility that individuals may have Lyme disease and refer them to another practitioner when appropriate. The purpose of this article is to (1) present an overview of the etiology, incidence, and clinical manifestations of Lyme disease, (2) review evaluation findings that should raise the index of suspicion for Lyme disease, (3) discuss the use of an empirically validated tool for differentiating those with Lyme disease from healthy individuals, (4) discuss the current state of diagnostic testing, and (5) review options for diagnosis and treatment available to individuals for whom referral is recommended.

Keywords: Decision Making: Clinical, Lyme Disease, Referral and Consultation
Introduction

The Guide to Physical Therapist Practice\(^1\) states that “As clinicians, physical therapists engage in an examination process that includes taking the history including a review of systems, conducting a systems review, and performing tests and measures to identify potential and existing problems. To establish diagnoses, prognoses, and plans of care, physical therapists perform evaluations, synthesizing the examination data and determining whether the problems to be addressed are within the scope of physical therapist practice or whether a referral to another health care provider is indicated.”\(^2\) As an ongoing process, the physical therapist must decide whether to treat the individual, refer the individual, or do both.\(^2\) This requires that the physical therapist recognize yellow and red flags in the individual’s history, medical screening, and physical examination that might indicate the presence of infection or disease. According to the United States Centers for Disease Control and Prevention (CDC), Lyme disease is the most commonly reported vector-borne disease in the United States.\(^3\) Individuals with undiagnosed Lyme disease may seek or be referred to physical therapist services due to musculoskeletal, neurologic, and cardiac impairments. Physical therapists should consider Lyme disease as a possible underlying cause for these impairments.

A variety of pathogens may be transmitted to the human host by the bite of an infected tick. According to the CDC, some of the most common tick-borne diseases in the United States include Lyme disease, babesiosis, ehrlichiosis, Rocky Mountain Spotted Fever, anaplasmosis, Southern Tick-Associated Rash Illness, Tick-Borne Relapsing Fever, and tularemia.\(^4\) The most commonly reported tick-borne disease in the United States is Lyme disease.\(^4\) While much of this article will focus on Lyme disease, it is not unusual for individuals with Lyme disease to be infected with other tick-borne pathogens, which may have varying manifestations.\(^5,6\)

Most cases of Lyme disease in the United States are caused by the bacterial species *Borrelia burgdorferi* (B. burgdorferi);\(^7\) which is transmitted by the bite of an infected blacklegged tick.\(^8\) The blacklegged tick or deer tick (*Ixodes scapularis*) is responsible for disease transmission in the northeastern, mid-Atlantic, and north-central United States, and the western blacklegged tick (*Ixodes pacificus*) spreads the disease on the Pacific Coast.\(^9\) The CDC estimates that approximately 476,000 Americans are diagnosed and treated for Lyme disease annually.\(^10\) Although most reported cases of Lyme disease occur in the Northeast, mid-Atlantic, and upper Midwest regions,\(^1\) the geographic distribution of high risk areas is expanding. A 2018 report by Quest Diagnostics shows that Lyme disease has been detected in all 50 states and in Washington, DC.\(^11\)

Untreated Lyme disease can produce an array of symptoms based on the stage of infection.\(^13\) Three stages of the disease are generally described,\(^14\)–\(^16\) including an early localized stage occurring days to 1 month after the tick bite, an early disseminated stage occurring weeks to months after the tick bite, and a late or chronic stage occurring months to years after the tick bite.\(^14\) The features of each stage may overlap, and some individuals will present with later features without having presented with earlier ones.\(^16\) Common symptoms of Lyme disease\(^17\) are listed in the Figure. Once inside the body, *B. burgdorferi* is able to disseminate quickly. A highly motile spirochete, it is capable of disseminating through blood vessels or the lymphatic system from the point of infection to infect any organ or tissue\(^13,18\) which may result in a broad range of symptoms.\(^19\) *Borrelia* are obligate parasites and must obtain the substances they need to live from their hosts, most of which can be found in collagen.\(^19\) As a result, *B. burgdorferi* bacteria prefer to reside in collagen-rich tissues such as skin, brain, muscle (including the heart), joints, and eyes.\(^20\) They also have a preference for myelin.\(^20\)

*Borrelia* spp. are known to manipulate the human immune system in several ways to perpetuate their own survival. The modulation of the immune response by the bacteria can suppress antibody production while increasing inflammation.\(^20\) Inflammation assists in breaking down tissues to make nutrients available for bacterial growth.\(^20\) Most of the resulting symptoms are due to inflammation,\(^20\) although the breakdown of tissues also gives rise to symptoms.\(^20\) Some genetically predisposed individuals develop an autoimmune response during this inflammatory process due to a cross-reaction between *borrelia*-specific antibodies and their own neuronal antigens.\(^21\) Because the internal terrain of each host is different, *B. burgdorferi* will manifest itself differently in every individual.\(^26\) Known as the “great imitator,” Lyme disease can produce a myriad of symptoms mimicking common illnesses such as chronic fatigue syndrome/systemic exertional intolerance disease, fibromyalgia, and autoimmune diseases such as rheumatoid arthritis, lupus, multiple sclerosis,\(^21\) and other multi-system illnesses.\(^3,17\)

Early Disease Manifestations

The early stage of Lyme disease may be characterized by the appearance of an erythema migrans (EM) rash and a viral-like syndrome.\(^14\) The EM rash, which is not always present, is an expanding red rash that develops at the site of the bite during the early stage after a delay of 3 to 30 days (average 7 days)\(^13\) or at sites remote from the initial bite once dissemination has occurred.\(^15\) The incidence of EM rash varies widely in the literature, ranging from 27% to 80%\(^13\). The appearance of the rash can be variable, with the classic “bull’s-eye” appearance being present in fewer than 20% of cases.\(^17\) The symptoms associated with the viral-like syndrome may include fever, chills, headache, fatigue, muscle and joint aches, swollen lymph nodes,\(^13\) neck stiffness,\(^23\) and anorexia.\(^25\) Dysesthesia as well as facial nerve dysfunction may also be present at this stage.\(^17\)

Musculoskeletal Manifestations

*B. burgdorferi* are capable of drilling into joint cartilage\(^20\) and are known to cause damage to collagen and elastic fibers.\(^26\) Arthralgias, myalgias, and migrating polyarthralgias are common features of early Lyme disease.\(^27\) Although arthritis typically does not occur until about 6 months after infection, it can occur as early as 4 days after initial infection.\(^15\) Arthritis is the most common manifestation of late-stage Lyme disease in the United States,\(^28\) and about 60% of untreated individuals will develop arthritis.\(^29\) Joint swelling may occur in the absence of pain. Joint pain and swelling may resolve or recur intermittently or become chronic and persistent.\(^15\) The typical presentation is intermittent attacks of monoarticular or oligoarticular arthritis.\(^29\) The large joints are often affected, especially the knees, but the ankle, shoulder, elbow, wrist, temporomandibular,\(^15,29\) hip, and sternoclavicular\(^29\) joints may be involved as well. Smaller joints can be affected although less...
**Neurologic Manifestations**

*B. burgdorferi* also has an affinity for the nervous system. Neurologic disease, occurring weeks to months after the tick bite, occurs in about 10% to 15% of untreated individuals in the United States. Refer to the Table for a summary of the neurologic manifestations of Lyme disease listed according to the part of the nervous system they affect. The classic triad associated with acute, early neurologic Lyme disease is lymphocytic meningitis, cranial neuropathy, and radiculoneuritis. Facial nerve palsy is a common neurological sign. Radiculoneuritis, a common peripheral nerve manifestation that can mimic a mechanical radiculopathy occurring in one or several dermatomes, is another possible manifestation. 

| Common Symptoms and Signs of Early Lyme Disease | Common Symptoms and Signs of Disseminated and Late Lyme Disease |
|-----------------------------------------------|---------------------------------------------------------------|
| Fatigue                                       | A cluster of spinal nerves can be affected as is the case with brachial plexopathies. | |
| Multiple red rashes (EMs)                     | Lumbar radiculopathy can also result, affecting organ function possibly causing constipation, difficulty with urination, and problems with blood pressure, heart rate, and autonomic function. A cluster of spinal nerves can be affected as is the case with brachial plexopathies. | |
| Severe headaches and neck stiffness           | Facial nerve dysfunction leading to weakness or paralysis of facial muscles (often mislabeled as Bell’s palsy). | |
| Neutrophilic symptoms—nervus pain, numbness, hot/cold sensations, tingling | | |
| Gastrointestinal symptoms—nausea, vomiting, laparic pain which may interfere with sleep | | |
| Psychiatric symptoms—including depression, anxiety, and mood changes | | |
| Cognitive dysfunction | | |
| Memory impairment | | |
| Light-headedness, fainting | | |
| Palpitations, or chest pain, shortness of breath | | |

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Cardiac involvement, if present, may occur weeks to months after the onset of infection and may occur asymptotically or can become so severe as to be life threatening. Lyme carditis occurs in about 1% of all cases of Lyme disease reported to the CDC according to national surveillance data collected between 2008 and 2018. Ciesielski et al. found cardiac manifestations to be present in 10% of individuals, which included palpitations, conduction abnormalities, myocarditis, left ventricular failure, and pericarditis. Woollf et al. found the incidence of electrocardiographic abnormalities to be 29% in pediatric individuals with definite Lyme disease. The most common clinical feature of Lyme carditis is atrioventricular conduction block due to dysfunction of the conduction system, but decreased cardiac contractility due to myopericarditis can occur as well. Additional cardiac abnormalities resulting in EKG changes have also been reported. Symptoms of Lyme carditis include light-headedness, fainting, shortness of breath, heart palpitations, and chest pain. According to the CDC, 11 cases of fatal Lyme carditis were reported worldwide between 1985 and 2019.

Evaluation

The vision statement for the physical therapy profession is that of transforming society by optimizing movement to improve the human experience. In working toward that vision and employing a movement dysfunction approach for physical therapy diagnosis, it is the responsibility of the physical therapist to be certain that individuals/clients are appropriate candidates for physical therapist services and to determine when referral to another health care practitioner is required. The diagnostic process involves evaluation of information obtained from the examination, including history, systems review, tests, and measures. The physical therapist must be able to recognize signs and symptoms of systemic disease that can mimic musculoskeletal, neuromuscular, and/or cardiac dysfunction that should prompt more specific screening, questions, and tests. Even with proper screening, some conditions may be missed because they are early in their presentation and are not yet recognizable; therefore, screening should be an ongoing process. As a result of the varied manifestations of Lyme disease, infected persons may experience any number of impairments, activity limitations, and participation restrictions that may cause them to seek physical therapist services. Given the preference of B. burgdorferi for collagen and nerve tissue, it seems likely that individuals infected with Lyme disease could seek physical therapist services to address impairments related to the musculoskeletal, neuromuscular, and cardiovascular systems. Impairments associated with the musculoskeletal system might include decreased joint mobility, motor function, muscle performance, and range of motion. Impairments associated with the neuromuscular system might include decreased or altered motor function and/or sensory integrity associated with the central or peripheral nervous systems, decreased motor control, loss of balance, gait disturbance, and, in the case of children, impaired neuromotor development. Due to the possibility of Lyme carditis, autonomic nervous system dysfunction, and the general deconditioning associated with the disease, individuals might seek services for impairments related to the cardiovascular system, including decreased aerobic capacity and endurance. Because physical therapists often see individuals frequently and at regular intervals, they are likely to be in a good position to recognize the possibility that a individual might have Lyme disease.

Examination should begin with a history. Individuals may report an insidious onset or unknown cause for their complaints such as joint pain in the absence of trauma. It is important to note that fewer than 30% of those infected with Lyme disease in the United States remember a tick bite and even those who remember one may not associate the bite with their symptoms. Some individuals may be asymptomatic in the early stages of the disease.

| Condition                  | Manifestations                                                                 |
|----------------------------|-------------------------------------------------------------------------------|
| Peripheral nervous system  | Facial nerve palsy, hearing loss, optic neuritis with visual changes, hyperacusis, pain behind the ear, altered taste, double vision, facial pain, tinnitus, eye movement disorders, and vestibulitis |
| Cranial neuritis           | Motor and sensory changes including pain, numbness, and tingling on one or both sides of the body |
| Radiculoneuritis           | Triad of meningitis, cranial nerve palsy, and intensely painful sensory radiculitis |
| Bannwarth syndrome         | Mononeuropathy, mononeuropathy multiplex, polyneuropathy, and autonomic neuropathy |
| Other                      | Neurologic Manifestations of Lyme Disease                                      |
| Central nervous system     | Sleepiness, decreased levels of consciousness, abnormal mood, confusion, cognitive changes, personality and behavioral changes, hallucinations, and seizures |
| Encephalitis               | Headaches, neck stiffness, nausea, vomiting, light sensitivity, or fever |
| Lyme encephalomyelitis     | Confusion and cognitive impairment; somnolence; severe psychiatric symptoms such as hallucinations, paranoia, and mania; paraparesis with sensory loss; abnormal body movements; impaired coordination; and seizures |
| Pseudotumor cerebri       | Headache following blurred and double vision, and, if untreated, optic nerve compression and visual loss can result |
| Encephalopathy             | Cognitive deficits, mild depressive symptoms, somnolence, headache, irritability, hearing changes, and possibly neuropathic symptoms occurring in the later stages of the disease |

Neuropsychiatric symptoms are also known to occur and may present as changes with cognition, and mood, and anxiety disorders.
symptoms associated with chronic Lyme disease develop gradually if immune function falters for any reason.\textsuperscript{20} These factors may make it even more difficult for individuals to make the association.

Similarly, individuals may not associate the EM rash with their symptoms. Not all infected individuals will develop a rash, and those that do may miss it because the rash is generally asymptomatic.\textsuperscript{17} It can also be missed when hidden from view in areas such as the hairline and scalp or on dark-skinned individuals.\textsuperscript{43} If the rash is visible, it may vary in appearance from the classic bull’s eye,\textsuperscript{13,17,43} most often presenting as an evenly red or reddish-blue lesion lacking the ring-within-a-ring pattern.\textsuperscript{43} Multiple skin lesions can occur in the disseminated phase.\textsuperscript{15,21,43} Rashes that differ from the classic bull's-eye appearance may go unrecognized and be mistaken for something else.\textsuperscript{19,21}

Symptoms in the early phase tend to be nonspecific and viral-like,\textsuperscript{42} so individuals may fail to report these constitutional symptoms, believing that they are unrelated. They may fail to disclose information about cognitive changes and behavioral or psychiatric manifestations for the same reason or due to embarrassment. As a matter of routine practice, physical therapists should ask individuals about any signs and symptoms they are experiencing regardless of whether the individual believes them to be related to the current problem.\textsuperscript{2}

Red flags noted on examination that would warrant further screening and testing could include the presence of symptoms that do not fit the expected mechanical or neuromuscular pattern\textsuperscript{2} such that the therapist is unable to alter (produce, worsen, reduce, or abolish) the symptoms by mechanical means. Symptoms that are not relieved by rest or positional change are a red flag as are symptoms that seem out of proportion to the injury or trauma or that persist beyond the expected time frame.\textsuperscript{2} Lyme radiculoneuritis, for example, should be considered in individuals in Lyme endemic areas who present with severe radicular pain in the trunk or limb without apparent mechanical cause.\textsuperscript{7} One of the hallmark features of Lyme disease is the migratory nature of the symptoms.\textsuperscript{44} This pattern may occasionally occur with other illnesses involving transient migratory arthritis,\textsuperscript{45} but, according to Horowitz, “only Lyme disease presents with persistent migratory pain, especially migratory nerve pain and paresthesias, which are not primary characteristics of these other illnesses.”\textsuperscript{44} Symptoms of Lyme disease may also be intermittent and change frequently.\textsuperscript{52} Individuals may report unprovoked pain that may interfere with sleep.\textsuperscript{17} The presence of constitutional signs and symptoms such as headache, fatigue, fever, sweats, chills, unexplained weight change (loss or gain), swollen glands, sore throat,\textsuperscript{21} and malaise\textsuperscript{17} should prompt concern regarding the possibility of systemic illness.\textsuperscript{3}

Individuals with postural orthostatic tachycardia syndrome may present with low blood pressure in standing and/or changing position with associated tachycardia, resulting in symptoms including dizziness, fatigue, and exercise intolerance.\textsuperscript{21} Therapists should always be alert to any pattern that may suggest a viscerogenic or systemic cause for symptoms,\textsuperscript{2} and the presence of a cluster of clinical symptoms associated with Lyme disease is certainly an important finding.\textsuperscript{44}

Additional factors may arise during the course of treatment that warrant further screening and may indicate the possibility of Lyme disease in addition to other illnesses. An individual who does not improve with intervention is always cause for concern.\textsuperscript{2} In response to physical therapist intervention, the individual may improve but then get worse, demonstrating a gradual, progressive, or cyclical pattern of symptoms.\textsuperscript{2} Additional signs and symptoms may develop, or the individual might become more willing to disclose them during the course of treatment.\textsuperscript{2}

**Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire**

Once the physical therapist suspects the possibility that the individual may have Lyme disease, the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire (HMQ)\textsuperscript{46} can be administered to identify whether the individual is likely to have Lyme disease. Horowitz defines Multiple Systemic Infectious Disease Syndrome as a syndrome involving Lyme symptoms that are worsened by additional tick-borne co-infections, such as babesiosis and Bartonella, as well as by the presence of other multiple overlapping factors. Some of the abnormalities are caused by Lyme disease and co-infections and others are not, but all factors affect the clinical course.\textsuperscript{21} Horowitz developed the questionnaire by including “a gestalt of symptoms” that he found to be associated with Lyme disease in his clinical practice, items related to the likelihood of exposure to Lyme disease, and items related to overall physical and mental health.\textsuperscript{44}

The questionnaire is comprised of 4 sections. Section 1 consists of a 38-point symptom checklist, including those that are most likely to be experienced by individuals with Lyme disease in clinical practice. Section 2, referred to as the Lyme incidence scale, consists of 10 items or incidents related to the likelihood of having Lyme disease. Items about migratory symptoms are also included. Section 3 contains 2 questions about overall physical and mental health. Section 4 creates a score based on 5 common Lyme symptoms that Horowitz observed to be linked to a higher probability of having Lyme disease. Each section is scored separately. The scores are then added together to create an overall HMQ score, which indicates the “probability as to whether an individual may suffer from Lyme disease and associated tick-borne disorders.”\textsuperscript{44}

A 2017 study\textsuperscript{44} supported the use of the HMQ as a valid, efficient, and low-cost screening tool for medical practitioners to decide if additional testing is warranted to distinguish between Lyme disease and other illnesses. The results of the study showed that the HMQ accurately differentiated between individuals with Lyme disease and healthy individuals.\textsuperscript{44} It can be completed independently by individuals or with the oversight of the physical therapist if needed.

**Referral**

Once the physical therapist has determined based on the HMQ score that referral to a qualified health care practitioner is recommended, this option should be discussed with the individual. Consistent with the emphasis on patient-centered care as articulated by the Institute of Medicine,\textsuperscript{47} the physical therapist should educate the individual and engage in shared decision making taking into account individual preferences, needs, and values. The steps taken to arrive at the recommendation for referral along with the underlying rationale and potential consequences of taking and refusing action should be explained in terms understandable to the individual.\textsuperscript{48} The individual should also be made aware that there are 2 sets of medical guidelines for the treatment of Lyme disease and be encouraged to seek further information.
in order to make an informed choice as to which health care provider to see for further evaluation.

Diagnostic Testing
As noted in the 2018 Report to Congress by the Tick-Borne Disease Working Group, an advisory body convened by the Department of Health and Human Services, diagnosing Lyme disease using currently available serologic tests is challenging. Individuals with an EM rash are considered to be infected without the need for a confirmatory test. Those who do not have an EM rash with a history of exposure and symptoms consistent with the disease are instructed to undergo the testing as recommended by the CDC. The current recommendation is to test blood for the presence of antibodies to Lyme disease bacteria using 2 steps. The first step uses a testing procedure called enzyme immunoassay or immunofluorescence assay. If the result of the first test is negative, no further testing is recommended. If the first test is positive, or indeterminate (sometimes called “equivocal”), the second step should be performed. The second step uses a testing procedure called an immunoblot, more commonly known as the Western blot, or an enzyme immunoassay. The overall test result is considered positive only when the first test is positive (or equivocal) and the second test is positive (or for some tests equivocal).

The 2-tiered testing method recommended by the CDC has been shown to be problematic. False seropositivity can occur especially in the presence of other diseases. False seronegativity has been extensively reported in the literature. Research indicates that the specificity of the 2-tiered test is approximately 99% and the sensitivity ranges from 53.7% to 57.6%. There are other direct and indirect tests available, but current Lyme testing lacks adequate sensitivity, which may leave many genuine cases underdiagnosed. The diagnosis of Lyme disease should be based on clinical signs and symptoms and supported by laboratory tests.

Medical Treatment Guidelines
Medical opinion about the diagnosis and treatment of TBD is divided into 2 schools of thought, each of which is reflected in a different set of guidelines. One set of guidelines has been authored by the Infectious Diseases Society of America (IDSA), and the other has been authored by the International Lyme and Associated Diseases Society. As outlined by the Tick-borne Disease Working Group 2018 Report to Congress, “The IDSA guidelines promote the diagnosis of Lyme disease through recognition of more specific objective manifestations of the disease and confirm the diagnosis by 2-tiered serologic testing except in cases of early Lyme disease with the erythema migrans rash, which constitutes a clinical diagnosis. The IDSA guidelines usually recommend 10 to 21 days of antibiotic treatment, except in cases of late arthritis where it may be longer. In contrast, the International Lyme and Associated Diseases Society guidelines promote the use of clinical judgment with an emphasis on both signs and symptoms of disease when diagnosing and treating tick-borne diseases and do not restrict the use of long-term use of antibiotics.

Summary
According to the CDC, the number of reported cases of tick-borne disease has more than doubled in the 13-year period between 2004 and 2016. The musculoskeletal, neurological, and cardiac manifestations of Lyme disease may cause infected persons to seek physical therapist services. Physical therapists often see individuals frequently and at regular intervals, positioning them optimally within the health care system to recognize individuals with undiagnosed Lyme disease. The HMQ can be a useful tool to assist with the recognition and referral of individuals with suspected tick-borne disease in the face of this growing threat.

Suggestions for Future Research
The medical management of acute Lyme disease typically involves antibiotic therapy. The medical management for those with persistent symptoms attributed to Lyme disease may also include antibiotics in addition to a wide variety of interventions that target multiple overlapping contributing factors. Individuals undergoing treatment for Lyme disease are generally advised to engage in physical activity to tolerance. The best practices for the physical therapist management of individuals with Lyme disease are not well described in the literature. Research is needed to examine the efficacy of physical therapist interventions directed toward improving the quality of life for those affected by this disease.

Acknowledgments
The author wishes to thank the following people for consultation and review of the manuscript: Holly Ahern, MS, MT(ASCP); Associate Professor of Microbiology, SUNY Adirondack; David J. Miller, PT, PhD; Professor Emeritus, Springfield College; and Julia Chevan, PT, PhD, MPH, OCS, Springfield College Department of Physical Therapy Chair. Special thanks to Richard I. Horowitz, MD, for his generosity in sharing his work.

Funding
There are no funders to report for this study.

Disclosures
The author completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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