Lyme Disease

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Lyme disease, caused by the spirochete bacterium Borrelia burgdorferi, has become a significant public health concern due to its increasing incidence and potential long-term complications. It is the most common tick-borne illness in the Northern Hemisphere, predominantly affecting North America, Europe, and Asia.[1,2] The prevalence of Lyme disease has been steadily increasing over the past decades, with an annual incidence of approximately 476,000 cases in the United States, and more than 200,000 cases in western Europe [7,12, 14] The disease is more prevalent in rural areas with high deer and rodent populations. Figures for the number of cases of Lyme disease in Ireland are not available as only a more severe form of the disease known as neuroborreliosis is monitored as a notifiable disease. However, it is estimated that around 200 people in Ireland have a positive blood test for Lyme disease annually. The distribution of Lyme disease is influenced by environmental factors, climate change, and changes in human behaviour. It manifests in various stages, with diverse clinical features making diagnosis challenging, and complications that can involve multiple organ systems. [1, 2]

Lyme disease can affect anyone but is most common among hillwalkers, hikers, campers, and others whose leisure activities or work takes place in heathland, light woodland and other grassy areas or brings them in contact with certain animals e.g., deer and sheep. Summer and autumn months are the time when most cases occur.[12] Only a small number of individuals will develop Lyme disease following a tick bite, however, early identification with prompt and appropriate antibiotic therapy is important to minimise the likelihood of the development of late-stage infection and/or long-term complications.[11]

Prevention

Lyme disease from an infected tick bite can usually be prevented if the tick is removed within 24-36 hours. If the tick remains on the skin, it should be carefully removed as soon as possible. To remove a tick, a fine tipped tweezers or a tick removal tool can be used. Grasp the tick as close to the skin as possible, pulling slowly upwards, taking care not to squeeze or crush it. Dispose of the tick once removed and clean the bite with soap and water and/or antiseptic. Testing of removed ticks is not recommended as the presence of Borrelia is not a reliable predictor of the development of infection in humans.[11]

Pathophysiology

Lyme disease is primarily transmitted to humans through the bite of infected Ixodes ticks, particularly the black-legged tick (Ixodes scapularis) in North America and the sheep tick (Ixodes ricinus) in Europe. The tick must be infected with the spirochete bacterium Borrelia burgdorferi to transmit the disease. When an infected tick bites a human, the spirochetes

present in the tick's saliva can enter the skin through the bite wound. Borrelia burgdorferi then migrates outward in the skin, forming a characteristic rash known as erythema migrans (EM). If left untreated, the bacteria can disseminate throughout the body via the bloodstream or lymphatic system. [1, 2]

The host's immune response plays a critical role in the pathophysiology of Lyme disease. Innate immune cells, such as macrophages and dendritic cells, recognise the presence of the spirochetes and initiate an inflammatory response. They release pro-inflammatory cytokines and chemokines, attracting more immune cells to the site of infection. The activation of the immune response triggers an inflammatory cascade. Inflammatory cells, including neutrophils, lymphocytes, and monocytes, infiltrate the infected tissues. This immune response contributes to the characteristic signs and symptoms observed in Lyme disease, such as redness, swelling, and pain. [1,2]

Borrelia burgdorferi can invade various tissues, including the skin, joints, heart, central nervous system, and others. The bacteria can adhere to extracellular matrix components, evade immune detection, and form protective structures called biofilms, allowing them to persist within the host for prolonged periods. In some cases, the immune response against Borrelia burgdorferi can result in an aberrant inflammatory response and immunopathogenesis. This can lead to tissue damage, particularly in the joints, heart, and nervous system. Autoimmune-like mechanisms have been proposed as a potential explanation for persistent symptoms observed in some individuals. Individual variations in the immune response and genetic predisposition may influence the pathophysiology of Lyme disease. Some individuals may develop more severe manifestations or persistent symptoms due to differences in their immune response or genetic susceptibility. [1,2]

Clinical Presentation

Lyme disease presents in three stages: early localised, early disseminated, and late stage. The first two stages are part of the early infection, and the third stage part of a persistent or chronic disease. Early localised disease is characterised by the presence of erythema migrans (EM), a characteristic skin rash. Early disseminated disease can involve multiple organ systems, including the nervous system, heart, and joints. Late-stage Lyme disease can lead to persistent symptoms, such as arthritis, neurological impairments, and cognitive difficulties. [4]

The most common and first presenting sign of Lyme disease is the erythema migrans rash, which is found in 70% - 80% of cases and appears at the site of the tick bite as an expanding, erythematous skin lesion, measuring 5 cm or larger in diameter. The lesion may present as homogeneous erythema or display a targetoid appearance. The appearance of the rash occurs one to two weeks after the initial tick bite. The rash tends to expand for a few days, and concentric rings may be visible. If left untreated, the rash persists for 2 to 3 weeks. About 20% may have recurrent episodes of the rash, and multiple lesions are not uncommon. At the same time, flu-like symptoms may be present. The fever is low-grade and may be associated with myalgia, neck stiffness, and headache. Visual problems include eye redness and tearing. About

30% of patients with the rash will have no further progression of symptoms.[4] It is important to be aware that a rash that is not erythema migrans can also develop as a reaction to a tick bite. However, this rash usually develops and recedes within 48 hours from the time of the tick bite. [11]

<table>
<tr><th colspan="2">Erythema migrans versus bite reaction</th></tr>
<tr><th>Image: erythema migrans</th><th>Image: bite reaction</th></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td>Features:
Usually NOT itchy, hot or painful.
Flat, red macule or papule at bite site.
May appear from 3 days to 30 days after tick bite and lasts for several weeks</td><td>Features:
Usually hot, itchy and painful
Often raised papule, central punctum.
Usually develops and recedes within 48hrs</td></tr>
</table>

https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/skin-soft-tissue/lyme-disease/

Stage 2 early disseminated Lyme disease usually develops 3-12 weeks after the initial infection. Features may include fever, general malaise, neurological features (headache and dizziness), muscle pain, and cardiac symptoms (chest pain, palpitations, and dyspnoea). Cranial neuropathy may present as diplopia. Eye pain and keratitis have also been reported. Knee, ankle, and wrist joints are often involved. Symptoms may last 12-20 weeks, but recurrence is rare. Often when a single joint is involved, it may be mistaken for septic arthritis. About 20% of patients have CNS involvement, including encephalopathy, meningitis, and cranial nerve neuropathy. Bell's palsy can occur in about 5% of patients. When meningeal symptoms are present, lumbar puncture is required to rule out other causes. Encephalopathy presents with deficits in concentration, cognition, memory loss, and changes in personality. Extreme irritability and depression are common.[4, 6]

Late-stage Lyme disease (Stage 3) may occur many months or years after the initial infection, but usually occurs within 12 months of the infection. Typical features include rheumatological and neurological involvement. Many patients may not have a history of erythema migrans. However, they may present with aseptic meningitis, Bell's palsy, arthritis, or dysesthesias. Cognitive deficits are common. The key feature of late-stage Lyme disease is arthritis which tends to affect the knee. Neurological and psychiatric symptoms mimic fibromyalgia.

Radicular pain is common. Borrelia encephalomyelitis is rare and can present with ataxia, seizures, hemiparesis, autonomic dysfunction, and hearing loss. Acrodermatitis chronica atrophicans is typically seen in older women and tends to occur on the dorsum of the hands and feet. Cardiac involvement may present with arrhythmias or transient heart block. Conduction abnormalities are not uncommon, but most cases are isolated, rarely last more than a few days, and patients do not usually require permanent pacing.[4, 5]

Diagnosis

Diagnosing Lyme disease can be challenging due to its diverse clinical presentation and the limitations of current diagnostic tests.[10] The initial step in diagnosing Lyme disease involves a thorough clinical evaluation, including medical history, examination, symptoms, and exposure to tick-infested areas. The presence of characteristic signs, such as erythema migrans (EM) rash, can provide important diagnostic clues. However, not all patients develop a rash or exhibit typical symptoms, making clinical evaluation alone insufficient for diagnosis.[3,4,8] Erythema migrans should be diagnosed and treated without laboratory testing as antibodies to Borrelia bacteria take several weeks to develop. Serological testing is not indicated before or after antibiotic treatment of erythema migrans. [11]

Two-tiered serological testing is widely used to support the diagnosis of Lyme disease. The first step involves an enzyme immunoassay (EIA) or an immunofluorescence assay (IFA) to detect antibodies against Borrelia burgdorferi. If the initial test is positive or equivocal, a confirmatory test such as Western blotting is performed.[8, 13]

EIA/IFA tests detect antibodies, specifically immunoglobulin M (IgM) and immunoglobulin G (IgG), against Borrelia burgdorferi. However, false-positive results can occur due to cross-reactivity with other infections or autoimmune conditions. Western blot analysis is performed to confirm the presence of specific antibodies against various B. burgdorferi proteins. It provides more specificity but can yield false-negative results during the early stages of infection when antibody levels are low. [8, 13]

PCR is a molecular diagnostic technique used to directly detect the genetic material (DNA) of Borrelia burgdorferi in patient samples. PCR is particularly useful in detecting early-stage Lyme disease when the bacterial load is higher, such as in skin biopsy samples or in cerebrospinal fluid (CSF) for suspected neurological involvement. However, the sensitivity of PCR can vary, and false-negative results are possible, especially in blood samples.[3,4,8]

Laboratories in Ireland generally follow the laboratory testing recommendations of the US Centres for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA), the European Federation of Neurological Societies (EFNS) and the British Infection Association (BIA). The antibody tests used in Ireland are made by commercial companies and meet strict quality criteria. Irish laboratories have their own quality assurance methods to make sure the tests are working correctly as well as being accredited by the Irish National Accreditation Body (INAB) to perform the test correctly. [13]

Emerging diagnostic approaches, such as Next-Generation Sequencing (NGS), hold promise for improving the accuracy of Lyme disease diagnosis. NGS allows for the comprehensive analysis of microbial DNA in patient samples, enabling the detection of multiple pathogens simultaneously. This approach has the potential to identify Borrelia burgdorferi and other co-infecting pathogens that may contribute to Lyme disease symptoms. However, NGS is still a research tool and not widely available in routine clinical practice.[3,4.8]

It is important to note that diagnostic tests for Lyme disease have limitations, including the possibility of false-negative or false-positive results. Clinical judgment based on the overall presentation and consideration of the patient's history, symptoms, and potential exposure is imperative.[10] Ongoing research continues to explore new diagnostic methods and approaches to enhance the accuracy and early detection of Lyme disease. [3,4.8]

Treatment

The choice of treatment depends on the stage of Lyme disease. Early localised disease is usually treated with oral antibiotics, such as doxycycline or amoxicillin. Early disseminated or late-stage disease may require intravenous antibiotics. Treatment durations vary based on the severity of symptoms and involvement of different organ systems. Adjunctive therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics, may be employed to manage pain and inflammation. [4, 9, 10]

Erythema migrans should be diagnosed and treated without laboratory testing as antibodies to Borrelia bacteria take several weeks to develop. The risk of Lyme disease is very low if a tick has been attached less than 36 hours, however, if the tick has been attached for longer than 36 hours or if it is not possible to ascertain the duration of the tick attachment post-exposure prophylaxis should be considered. All patients symptomatic of Lyme disease should be treated with appropriate antibiotics. [11] Antibiotics are not recommended, however, where Lyme disease has previously been adequately treated (post-Lyme disease syndrome) as there is no demonstrable clinical benefit from prolonged antibiotic therapy and the risk of harm outweighs the benefit. Supportive management should be offered. [11]

Some individuals may experience a Jarisch-Herxheimer reaction in response to antibiotic treatment for Lyme disease. Jarisch-Herxheimer is an acute febrile illness which can cause an exacerbation of symptoms such as fever, chills, muscle pain, headache. The reaction is self-limiting, usually resolves within 24 -48 hours, and does not usually warrant stopping treatment.[11]

Post-exposure prophylaxis			
Drug	**Dose**	**Duration**	**+/- Notes**
Doxycycline	**Children under 12 years:** **4.4mg/kg** as a single dose Max. 200mg dose **Adults and children over 12 years of age:** 200mg as a single dose	Single dose	See additional information section below for: 1. Safety statement on use of doxycycline in children 2. Sample calculation for paediatric dosing & administration advice
• As infection risk is low & Lyme disease is readily treatable once symptoms develop, watchful waiting in case of contraindication to doxycycline (e.g. in pregnancy) is recommended instead of prophylaxis. • There is no data available to support the use of amoxicillin as an alternate prophylactic antibiotic.			

https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/skin-soft-tissue/lyme-disease/

Antibiotic treatment for Lyme disease			
Early onset/ erythema migrans without evidence of disseminated disease			
Drug	**Dose**	**Duration**	**+/- Notes**
1st choice			
Doxycycline	**Children aged 8-12 years:** **2.2mg/kg** every 12 hours (max 100mg every 12 hours) **Adults and children over 12 years of age:** 100mg every 12 hours	10 days	**Contraindicated in pregnancy** Take with a glass of water and sit upright for 30 minutes after taking. Can take with food or milk if gastritis is an issue. Avoid excessive sunlight or artificial UV light due to risk of photosensitivity. Advise use of sunscreen/sunblock. Absorption of doxycycline significantly impaired by antacids, iron/calcium/ magnesium/zinc-containing products and should be separated by at least 2 hours.
First alternative (1st line choice in pregnancy and children under 8 years of age)			
Amoxicillin	**Children under 12 years:** 30mg/kg every 8 hours (max. 500mg every 8 hours) **Adults and children over 12 years of age:** 500mg every 8 hours	14 days	Not suitable in penicillin allergy Liquid preparations available (sugar- free): 250mg/5ml 125mg/5ml
Second alternative			
Azithromycin	**Children 6 months - 12 years of age*:** 10 mg/kg every 24 hours (max 500mg every 24 hours) Children > 45kg dose as per adults. **Adults and children over 12 years of age:** 500mg every 24 hours	7 days	Liquid preparation available: 200mg/5ml (contains sucrose) To be taken one hour before or two hours after food/antacids. *Children under 6 months seek specialist opinion.
Early disseminated disease or later stage infection			
Refer to microbiology or infectious disease specialist			

https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/skin-soft-tissue/lyme-disease/

The use of doxycycline in children under 8 years of age is unlicensed in Ireland. Safety data from research in Europe and the US in recent years has provided reassurance that short courses of doxycycline are safe in children under 8 years of age and are not likely to produce either dental discoloration or enamel hypoplasia. This has been endorsed by the American Association of Paediatrics (AAP Red Book 2018) and Children's Health Ireland (CHI) Group.[11]

Prognosis

Treatment is usually curative for early cases of Lyme disease; however, it may be complicated due to late diagnosis, antibiotic treatment failure, and concomitant infection with other tick-borne diseases such as ehrlichiosis, babesiosis, and immune suppression. Approximately 5% of patients have lingering symptoms of fatigue, pain, or joint and muscle aches after treatment, known as post-treatment Lyme disease syndrome, lasting 6 months or more. Chronic Lyme disease is generally managed like fibromyalgia or chronic fatigue syndrome. [4, 9]

Lyme disease remains a significant health concern, necessitating awareness among healthcare practitioners and the general population. Early recognition, accurate diagnosis, and timely treatment are essential to prevent complications. Ongoing research efforts are focused on improving diagnostic methods, understanding the pathogenesis, and developing novel therapeutic interventions. Preventing Lyme disease relies on personal protective measures, including wearing protective clothing, applying insect repellents, performing tick checks after outdoor activities, and modifying the environment to reduce tick populations. Vaccination against Lyme disease is an area of active research and development.

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