Borreliosis (Lyme Disease)

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Contents

Core Messages

- Lyme disease is a tick-borne illness caused by the spirochete *Borrelia burgdorferi.*
- Erythema migrans is an annular skin lesion that occurs in a large proportion of patients with Lyme disease and when present is highly suggestive of prior infection.
- A wide variety of opthalmic manifestations have been attributed to Lyme disease.
- The diagnosis of Lyme disease is based on a positive tick exposure history, supportive signs such as erythema migrans, arthritis, or uveitis, and positive laboratory confirmation.
- Serologic testing is very accurate after the first few weeks of infection, but its predictive value depends greatly on the clinical likelihood of infection.
- Oral antibiotics, such as doxycycline, are often efficacious in treating systemic disease, but intravenous antibiotics may be required to treat refractory CNS or ocular infections.
- The prognosis for recovery is best with early diagnosis and treatment, but good outcomes can also be achieved following treatment of later stages of infection.

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99.1 Definition

The expanding skin lesions known as erythema migrans (EM) were first described in 1909 in Sweden [116]. Over 65 years later, the characteristic "bull's eye" rash of EM was noted in a group of children in Lyme, Connecticut, all of whom subsequently developed an arthropathy and a constellation of systemic signs and symptoms referred to as Lyme disease [52, 94]. *Ixodes* ticks were soon implicated as the vector of Lyme disease, but it was not until 1982 that the spirochete *Borrelia burgdorferi* was identified as the causative agent [13]. Lyme disease typically begins with EM, a sign of localized infection (stage 1), followed thereafter by disseminated (stage 2) and persistent (stage 3) infection [23] if untreated.

99.2 Clinical Manifestations

99.2.1 General Disease

The three stages of Lyme disease each have characteristic physical findings. There is considerable overlap between the various stages, however, and involvement of a particular organ system is not limited to any single stage of disease.

Stage 1 disease develops approximately 3–30 days after the tick bite and is characterized by the development of an EM lesion at the site of inoculation in 60–80 % of patients [23, 49, 89, 91]. The typical EM lesion is annular and enlarges gradually, but there can be wide variability in the presentation [23, 100]. Because *Ixodes* ticks are small, approximately 50 % of patients have no recollection of a previous tick bite [100]. The EM lesion usually fades within 3–4 weeks.

Stage 2 disease occurs days to weeks after infection as the organism disseminates hematogenously to sites throughout the body [23]. The most common manifestations during stage 2 are cardiac, neurologic, and musculoskeletal [23, 49, 85]. Cardiac involvement can include atrial-ventricular block and myopericarditis, whereas neurologic findings can include headache, Bell's palsy, and lymphocytic meningitis, and musculoskeletal manifestations can include muscle pain, arthralgias, and arthritis. Stage 2 manifestations are usually self-limited, but may rarely be associated with severe morbidity or death.

Several months after the onset of infection, approximately 60 % of untreated patients develop arthritis, the most common manifestation of persistent, or stage 3, infection [23, 33, 49, 85]. Other late manifestations include ataxia, chronic encephalomyelitis, dementia, chronic fatigue, and a recurrence of EM.

99.2.2 Ocular Disease

Ocular manifestations of Lyme disease are uncommon and tend to occur in the later stages of infection [11, 58]. While a wide variety of ophthalmic manifestations have been attributed to Lyme disease, many of these associations have been based on isolated case reports wherein strict diagnostic criteria were not applied [8, 20, 29, 51, 69, 76, 96]. The true spectrum of ocular manifestations in patients with Lyme disease is therefore unknown. Findings, when present, are often bilateral.

Acute conjunctivitis occurs in approximately 10 % of patients with stage 1 Lyme disease [3, 39, 46, 60, 89, 91, 94] and is usually mild and self-limited, although it can sometimes produce pain and photophobia. Much less frequently, chronic follicular conjunctivitis, episcleritis, and scleritis have also been observed [24, 39, 44, 58, 60, 77, 114].

Stromal keratitis has been observed in stage 3, usually months to years following infection [3, 4, 6, 24, 33, 43, 59]. Focal nummular nonstaining corneal opacities can occur at different levels of the stroma. Such infiltrates can be peripheral or diffusely distributed throughout the cornea and may be associated with corneal edema and/or produce scarring, especially if left untreated. Lyme keratitis typically responds well to topical corticosteroids, suggesting an immune etiology [5, 43]. Although usually bilateral, unilateral interstitial keratitis can also occur [59].

Lyme disease can cause uveal inflammation in a variety of forms. The mechanism of inflammation is believed to result either from direct infection of the intraocular tissues or from an immune

reaction directed against the spirochetes. Iridocyclitis occurs commonly and may be observed with or without keratitis or granulomatous features, including large keratic precipitates and/or iris nodules [10, 24, 33, 39, 64, 107, 114].

Intermediate uveitis is one of the more common ophthalmologic manifestations of Lyme disease [12, 33, 39, 45, 56–58, 75, 98, 109]. Vitreous exudation can be heavy and may be associated with spillover anterior chamber inflammation [81]. Some authors have reported a good response to intravenous antibiotics [12, 98].

Several reports have described posterior uveitis, including choroiditis and neuroretinitis, in association with Lyme disease [9, 39, 40, 47, 56, 63, 81]. Exudative retinal detachment may also occur [7, 103, 109]. Choroiditis is often multifocal, can be unilateral or bilateral and observed with or without vitritis, and may appear similar to acute posterior multifocal placoid pigment epitheliopathy (APMPPE) [9, 26, 108].

Retinal vasculitis and perivasculitis can also occur in Lyme borreliosis [39, 56, 58, 87]. Late staining of the retinal vessels may be seen on fluorescein angiography. Retinal vascular occlusion, possibly secondary to occlusive vasculitis, has been reported [48, 58]. Secondary retinal pigment epithelium (RPE) changes [38] and RPE detachments have been described as well [42].

There have been several published cases of Lyme disease associated with severe panuveitis and endophthalmitis, some of which have involved identification of spirochetes within intraocular fluids [41, 92, 117]. Outcomes in these cases have generally been poor.

Cases of Lyme orbital myositis [15, 22, 31, 82] with associated extraocular muscle enlargement have been described and shown to improve radiographically following antibiotic treatment.

Neuro-ophthalmologic manifestations are relatively common in Lyme borreliosis [1, 3, 50, 118]. Facial nerve palsy, with the potential for corneal exposure, is the most common cranial neuropathy and is frequently bilateral. The prognosis for complete recovery tends to be excellent, however [18, 65]. Abducens nerve palsy may occur either as a result of direct invasion of the 6th cranial nerve or secondary to increased intracranial pressure [58]. Involvement of cranial nerves 3, 4, and 5 also occurs, although less commonly [78].

Optic nerve findings can include papillitis [10, 112], optic neuritis [35, 39, 47, 74, 83], optic neuropathy [14, 28, 59, 79, 106], and papilledema, usually resulting from meningitis with secondarily increased intracranial pressure [3, 47, 71, 73, 74]. Spirochetes resembling *Borrelia burgdorferi* have been identified in a temporal artery biopsy of a patient with sudden vision loss [68], suggesting that Lyme disease may also cause temporal arteritis.

Pupillary abnormalities described in patients with Lyme disease include paralytic mydriasis [39], Horner's syndrome [27], and tonic pupil [72]. A case of opsoclonus-myoclonus syndrome [66] and a case of Lyme amaurosis in a child have also been reported [2].

99.3 Etiology and Pathogenesis

Lyme disease is the most common tick-borne infection in the northern hemisphere [88, 104] and the most common vector-borne infection in the USA [49]. Endemic regions in the USA include the Northeast (from Massachusetts to Maryland), the Midwest (Wisconsin and Minnesota), and the West Coast (California and Oregon). Sporadic cases have occurred in almost every state, however [49, 101]. *B. burgdorferi* infection is also prevalent throughout Europe, particularly in Central Europe, the Baltic states, Austria, Sweden, Germany, Slovenia, and the Czech Republic. Lyme disease has also been described in South America, Africa, Australia, China, and Japan (Fig. 99.1) [17, 23, 36, 104, 113].

B. burgdorferi is transmitted by ticks of the *Ixodes ricinus* complex, which include *I. scapularis* (also known as *I. dammini*, the predominant tick vector in the USA), *I. pacificus* (Western USA), *I. ricinus* (Europe), *I. ovatus*, and *I. persulcatus* (Asia). These ticks can also transmit other diseases, including babesiosis and tularemia, which can complicate the course of borreliosis [97]. Ticks of the *Ixodes ricinus* complex have larval, nymph, and adult stages [23]. The nymph

Fig. 99.1 The global distribution of *Ixodes* spp. ticks able to transmit the agent of Lyme disease, *Borrelia burgdorferi* (Modified from Flipova [25]. Reproduced with permission from the CDC; http://www.cdc.gov/ncidod/dvbid/lyme/who_cc/)

form is the most aggressive and is responsible for transmission of infection to humans in early summer, when blood meals most often occur.

There are a variety of genospecies of *B. burgdorferi*, each with a predilection to cause particular disease manifestations. For example, *B. burgdorferi sensu strictu*, which is prevalent in the USA, tends to cause joint symptoms, potentially explaining why Lyme arthritis is more common in the USA than in Europe [95]. In addition, variability in host sensitivity, possibly as a result of different HLA typing, may explain why some individuals are subject to particular disease manifestations [93].

Borrelia burgdorferi is an extremely complex and adaptable organism [61]. The spirochete utilizes several pathogenic mechanisms, including both downregulation of immunogenic outer surface proteins during blood meals and movement to an intracellular location in order to survive in the presence of antibiotics [19, 32]. As a result, *Borrelia burgdorferi* is able to survive despite the intense inflammatory response it incites.

99.4 Diagnosis

The diagnosis of Lyme disease is based on clinical findings combined with an appropriate exposure history and positive laboratory confirmation [23, 39, 104, 105]. Tick exposure in an endemic region and the presence of EM are crucial to making a diagnosis [16]. However, EM is not present in every case, and laboratory testing is imperfect, thus complicating the diagnosis in many patients.

A positive skin culture of an EM lesion provides a definitive diagnosis of Lyme disease, but the diagnosis can usually be made without biopsy when EM is present [104, 110]. Culture of CSF and serum are less reliable and seldom useful [105].

Polymerase chain reaction (PCR) has been used to amplify *B. burgdorferi* DNA from tissue sites, such as synovial fluid and skin [80, 105]. There have also been reports of positive PCR results from the vitreous [30, 55] and conjunctiva [55]. Of note, PCR testing may identify the organism, but it does not necessarily indicate the presence of active infection.

Isolation and histopathologic identification of *Borrelia burgdorferi* from the vitreous cavity [54] and iris [69] are suggestive, but not diagnostic, of Lyme disease, since other spirochetes, such as *T. pallidum*, may appear similar histologically.

Serologic testing can be very useful in certain clinical situations, but may be misleading in others. It is appropriate to obtain antibody-based testing in patients from an endemic region with characteristic disease manifestations, such as intermediate uveitis [8, 34, 37, 57]. However, serologic testing is not indicated in a patient with EM because the lesion by itself is suggestive enough of disease and serologic results are likely to be falsely negative early in the course of infection [102]. Similarly, patients with a clinical history inconsistent with Lyme disease should not undergo serologic testing because of the high likelihood of obtaining a false-positive result.

A two-step approach to serologic testing, generally consisting of a sensitive antibody-based test, or ELISA, followed by a Western blot for patients with positive or borderline ELISA results, is recommended [23, 104, 105]. Antibody-based testing is often negative during the first few weeks after infection [39], but when performed, both IgG and IgM should be obtained. After about 1 month, the sensitivity and specificity of IgG testing alone are both greater than 95 % [104]. Thus, if serologic testing is negative in late stages of the disease, an alternative diagnosis should be sought [39]. False-positive testing can also occur, particularly in the presence of infection with other spirochetes, antibodies against which can be cross-reactive with *B. burgdorferi* [20, 51, 76, 86]. Seropositivity usually persists for years, and it is therefore often difficult to distinguish between active and latent infection [23].

99.5 Differential Diagnosis

Tuberculosis, syphilis, and sarcoidosis, with their protean manifestations, should always be considered in the differential diagnosis of Lyme disease. In particular, ocular syphilis and Lyme borreliosis seem to share many common features [39, 84, 117]. Interstitial keratitis and various types of uveitis, particularly intermediate and panuveitis, can occur in both ocular syphilis and ocular borreliosis. One case mimicking birdshot chorioretinopathy has been reported in association with positive Lyme serology [99]. In addition, a case of Lyme borreliosis in a patient with vitritis, serous retinal detachment, and lymphocytic pleocytosis was initially mistaken for Vogt-Koyanagi-Harada disease [7]. Lyme neuroretinitis [40] must be distinguished from other causes of neuroretinitis, such as *Bartonella henselae* infection. Other causes of intermediate uveitis and retinal vasculitis should be considered as well. Although highly suggestive, EM is not pathognomonic for Lyme disease [88] and may be observed in association with Lone Star tick (*Amblyomma americanum*) bites in the southern USA [53]. In addition, chemical reactions to tick and spider bites, drug eruptions, urticaria, and cellulitis may be mistaken for EM.

99.6 Treatment

Prevention strategies are aimed at limiting access of ticks to body surfaces and removing ticks early in order to reduce the transmission risk [67]. Treatment is most successful early in the course of infection [88, 115]. The majority of systemic manifestations of Lyme disease can be treated with orally administered antibiotics [23, 70, 88]. Doxycycline, 100 mg twice daily, is the first-line treatment for adults, but should be avoided in children less than 8 years of age and pregnant women [90]. Alternatives include amoxicillin, 500 mg three times daily, and erythromycin, 250 mg four times daily. A 2- or 3-week course of treatment has been suggested for localized and disseminated infection, respectively. However, a recent study failed to demonstrate a significant difference in efficacy between a 10- and 20-day course of oral doxycycline [111]. A 2- to 4-week course of intravenous therapy with ceftriaxone, 2 g daily (first choice), cefotaxime 2 g every 8 h, or penicillin G, five million units every 6 h, is recommended for patients with objective

neurologic abnormalities or high-degree atrial-ventricular block [90]. As with other spirochetal infections, antibiotic treatment can induce a Jarisch-Herxheimer-like reaction, including fever and tachycardia, in approximately 15 % of patients [21, 45, 50]. Coadministration of corticosteroids along with antibiotics has been advocated in order to prevent this reaction [50].

Treatment guidelines have not been well established for ocular manifestations of Lyme disease. Mild extraocular disease may respond to oral antibiotics, but inflammation may recur upon discontinuation [107]. If the response to oral antibiotics is not complete, intravenous treatment should be considered [62]. Intraocular complications, such as uveitis and optic neuritis, are best treated with a 2- to 4-week course of intravenous ceftriaxone [12, 98]. If clinical suspicion of Lyme disease is high, a trial of antibiotics should be considered even if serologic testing is negative. Topical corticosteroids can be useful adjuncts in the treatment of anterior uveitis and keratitis [5]. If appropriate antimicrobial coverage is employed, systemic and periocular corticosteroids can be added [89]. Corticosteroids may, however, increase the risk of antibiotic failure and recurrence [107].

99.7 Prognosis

Early diagnosis and treatment are associated with rapid resolution [23, 115], usually within 4 weeks. Although morbidity is somewhat higher, the majority of patients with late-stage disease still respond to treatment [32]. Evidence of chronic or recurrent intraocular inflammation should prompt consideration of an alternative diagnosis or more aggressive treatment with intravenous antibiotics [8].

Take-Home Pearls

- Intermediate uveitis, panuveitis, and optic neuritis are the most common ophthalmic manifestations of Lyme disease, but neuroretinitis, retinal vasculitis, and choroiditis, resembling APMPPE, may occur as well.
- Serologic testing is useful when the clinical presentation is suggestive of Lyme disease.
- Syphilis should always be ruled out in cases of suspected *B. burgdorferi* infection.
- Intravenous antibiotics are required in most cases of ocular involvement.
- The treatment of *B. burgdorferi* infection may be complicated by a Jarisch-Herxheimer-like reaction.

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