Lyme disease

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Introduction

This article includes discussion of Lyme disease, erythema migrans disease, Garin-Bujadoux-Bannwarth syndrome, Lyme borreliosis, neuroborreliosis, Lyme disease associated meningitis, cranial neuritis, radiculitis, and facial nerve palsy. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Lyme disease, a multisystem spirochetal infection responsive to antimicrobial therapy, continues to be the source of contentious but probably artificial debate. Some patient advocacy groups argue that there are large numbers of patients with chronic neurologic symptoms requiring long-term antibiotics. Studies now clearly show that individuals with the chronic symptoms referred to as “chronic Lyme disease” have neither neurologic disease nor Lyme disease and that these individuals do not benefit from treatment with long-term antibiotics. The author discusses the manifestations, pathophysiology, diagnosis, and treatment of Lyme disease.

Key points

- Lyme disease, infection with the tick-borne spirochete *Borrelia burgdorferi*, affects the central or peripheral nervous system in up to 10% to 15% of patients.
- Clinical phenomena associated with neuroborreliosis typically include cranial neuropathy (most often the facial nerve), radiculopathy, and lymphocytic meningitis.
- Serodiagnosis after the first month of infection has high sensitivity and specificity.
- Treatment with 2- to 4-week courses of oral antibiotics is curative in most; parenteral treatment is recommended either if there is evidence of parenchymal brain or spinal cord involvement or if objectively demonstrable active disease persists after appropriate oral treatment.
- Persisting difficulties after treatment, often referred to as “post Lyme disease syndrome”, may occur, but are not associated with nervous system infection and probably are no more common than in control populations.

Historical note and terminology

The term "Lyme arthritis" was first introduced in 1977 and was subsequently broadened to "Lyme disease" when it was recognized that the disorder commonly involved multiple organ systems in addition to joints (Steere et al 1977). However, the syndrome was described much earlier in the 20th century. In 1910, Afzelius first reported the typical cutaneous lesion, erythema migrans (formerly known as erythema chronicum migrans). In 1922, Garin and Bujadoux described tick bite-associated meningoradiculitis, the most typical neurologic presentation in this disorder (Garin and Bujadoux 1922). Following a more detailed description of this syndrome by Bannwarth, the notion that bites of *Ixodes* ticks could lead to a syndrome of lymphocytic meningitis with painful radiculoneuritis became widely accepted by European clinicians. The first reports of Lyme arthritis described cases of apparent juvenile rheumatoid arthritis among children in the region of Lyme, Connecticut (Steere et al 1977). Detailed epidemiologic studies led to the association of this disorder with bites of *Ixodes* ticks. In 1979, Reik and colleagues described a neurologic syndrome in American patients with Lyme disease virtually identical to that described by Garin and Bujadoux (Reik et al 1979). In 1983, the responsible spirochete, *Borrelia burgdorferi*, was identified as the causative agent in American patients with Lyme

disease (Benach et al 1983; Steere et al 1983). Shortly thereafter, a closely related agent was identified in European patients (Asbrink et al 1984). Subsequent work has both broadened the scope of the neurologic disorders recognized as associated with this infection (known collectively as "neuroborreliosis") and refined the microbiological understanding of the responsible organisms.

Clinical manifestations

Presentation and course

Lyme disease is a multisystem infectious disease. The most commonly affected organ systems are the skin, nervous system, joints, and heart. As many as 90% of infected patients develop the characteristic erythematous, macular, usually painless rash, typically evolving over days to weeks to become many centimeters in diameter (Gerber et al 1996).

Ten percent to 15% of patients will develop nervous system involvement that typically consists of all or part of the triad of lymphocytic meningitis (occurring in isolation in about 1% of CDC-confirmed cases) (Centers for Disease Control and Prevention 2009), cranial neuritis, and painful radiculitis (occurring in 4% of confirmed cases) (Reik et al 1979). Virtually any cranial nerve may be involved, although the seventh is the most common, being involved in 8% of CDC-confirmed cases. Lyme disease is 1 of the small number of disorders (along with sarcoidosis and Guillain-Barre syndrome) commonly associated with bilateral facial palsies. The painful radiculitis may precisely mimic a mechanical monoradiculopathy or may be more disseminated, causing an apparent plexitis (Wendling et al 2009) or even a diffuse disorder that may clinically resemble Guillain-Barre syndrome. Rare patients (probably no more than 0.1% of infected, untreated individuals) may develop a focal encephalomyelitis (Steinbach et al 2005) with prominent white matter involvement, often presenting with a myelopathic picture reported to occur in 7% of European patients with radiculitis (Schwenkenbecher et al 2017); no systematic data are available in U.S. patients. Studies of experimental infection in primates have demonstrated meningeal and radicular, but not CNS parenchymal, infection (Bai et al 2004).

Some patients will come to medical attention only when the disease becomes more chronic. Lyme arthritis is generally considered a subacute or late manifestation. This is typically an asymmetric, large joint (eg, knee, elbow, hip) recurring oligoarthritis (Steere et al 1977). The other common late manifestations are neurologic. At 1 extreme (fortunately rare), this may include a chronic encephalomyelitis, with focal abnormalities on neurologic examination and brain MRI scans (Halperin et al 1989). At the other neuroanatomic extreme, neurologic manifestations may entail a mild peripheral neuropathy that may present as a symmetric distal polyneuropathy, as a more focal mononeuropathy multiplex, or even as polyradiculopathy (Halperin et al 1990; Logigian and Steere 1992). A large proportion of experimentally infected primates develop a vasculopathic neuropathy (Elamin et al 2009), a mononeuropathy multiplex (England et al 1997; Roberts et al 1998) analogous to that seen clinically. Rarely demyelinating neuropathies have been reported in patients with this disorder (Muley and Parry 2009). A substantial number of patients with chronic *B. burgdorferi* infection will develop a mild confusional state in the context of symptomatic multisystem involvement, with difficulty with memory and complex intellectual tasks (Halperin et al 1988; Kaplan et al 1992). This may, in rare patients, be due to a mild encephalomyelitis but, almost always is due to the remote effects of systemic infection (ie, a metabolic encephalopathy) (Ogrinc 2013; Halperin 2014).

Table 1. Neurologic Disorders in Lyme Disease and their Pathophysiology Grouped by Pathophysiologic Mechanism

Peripheral nerve

- Mononeuropathy multiplex
  - Cranial neuropathy
  - Radiculopathy
  - Brachial plexopathy
  - Lumbosacral plexopathy
  - Diffuse/multifocal polyneuropathy
  - Motor neuropathy
  - “Guillain Barre-like” (not usually demyelinating)

Central nervous system

- Infection in subarachnoid space
  - Radiculitis
  - Cranial neuropathy
  - Meningitis (including pseudotumor-like presentation in children)
- Parenchymal infection
  - Encephalitis ("MS-like")
  - Myelitis
- Toxic/metabolic encephalopathy
  - Encephalopathy

Diagnosis requires combining clinical observations with laboratory data. Clinical diagnostic criteria (case definition) used by the Centers for Disease Control are useful but somewhat restrictive, being designed for surveillance purposes. These require either a physician-diagnosed erythema migrans, measuring at least 5 cm in diameter, or laboratory evidence of infection with *B. burgdorferi* (culture, significant change in antibody level, or a single demonstration of elevated levels of antibodies in CSF or serum) in combination with either (a) acute onset of otherwise unexplained heart block, (b) a relapsing large joint oligoarthritis, or (c) lymphocytic meningitis, cranial neuritis, radiculoneuritis, or encephalomyelitis. The last should be confirmed by demonstration of production of anti-*Borrelia* antibody in the CSF. In general clinical practice, acceptance of the diagnosis is reasonable if a patient has an epidemiologically plausible exposure, has had either an erythema migrans (early disease) or a positive serology (IgG antibodies should be demonstrable by 2-tiered testing in all patients with disease of more than 4 to 6 weeks duration), and has a clinical disorder within the realm of those reported to occur in this infection (Halperin et al 1996). The common causes of false-positive serology (eg, syphilis, polyclonal B cell expansion) must be excluded. In patients with positive serologies and atypical disorders, or with negative serologies and typical syndromes, the diagnosis is possible but must be entertained with caution.

Prognosis and complications

With appropriate antimicrobial therapy of early Lyme disease (erythema migrans), approximately 90% to 95% of patients will be completely cured. The exact rate of cure in patients with more chronic involvement is controversial but is probably in the range of 80% to 85% (Pfister et al 1989; Pfister et al 1991). Some patients will develop late sequelae despite early treatment, although prospective studies indicate that this is rare with adequate initial treatment (Wang et al 1998; Weitzner et al 2015; Wormser et al 2015a). These late manifestations may consist of chronic large joint oligoarthritis, which may be HLA-linked or, potentially more problematic, but fortunately rarely seen, chronic encephalomyelitis. Many patients with significant neurologic impairment can improve significantly if treated with appropriate antimicrobial therapy.

Controlled studies indicate that prognosis after treatment, even of later disease, is excellent (Kalish et al 2001; Ljostad 2012; Skogman 2012; Weitzner et al 2015). Although many have focused on persistent nonspecific symptoms following treatment of Lyme disease, labeling this "post Lyme disease syndrome," the existence of such an entity is questionable. In 1 study in Nantucket, an island with a stable permanent population and high incidence of Lyme disease, patients treated for Lyme disease were found to have more frequent subjective symptoms than controls, but no increase in objectively demonstrable rheumatologic, neurologic, or other clinical abnormalities (Shadick et al 1999). A study of patients reported to the Connecticut Department of Public Health as having Lyme disease compared them to matched case controls (Seltzer et al 2000). Treated patients reported a large number of subjective symptoms. However, the type, number, and severity of symptoms were indistinguishable from those reported by controls. Studies have confirmed this observation, again finding that although persisting symptoms are common among patients treated for Lyme disease, they are no more common in control populations (Cerar et al 2010; Skogman et al 2012). Even chronic fatigue, commonly thought of as a key element of post Lyme disease syndromes, does not appear to be a particularly common after effect (Wormser et al 2015b; Wills et al 2016). One plausible conclusion might be that receiving the diagnosis of Lyme disease heightens awareness of these subjective symptoms, but does not cause them, which is a form of anchoring bias (Halperin 2014). Importantly, multiple studies indicate these chronic symptoms are not associated with nervous system infection (Dersch et al 2016; Halperin 2016). Treatment trials further support this conclusion. It has been remarkably difficult to identify patients who meet the criteria for the diagnosis. More importantly, it is clear that additional antimicrobial therapy provides such patients no meaningful benefit (Hu and Klempner 2001; Klempner et al 2001a; Krupp et al 2003; Feder et al 2007; Fallon et al 2008; Halperin 2008; Berende et

al 2016).

Clinical vignette

A 38-year-old woman was seen in early October for new onset of facial palsy. She had been in excellent health until early August of that year when, while summering in a Lyme endemic area, she noted an expanding erythematous rash on her abdomen, ultimately about 8 inches in diameter and lasting about 3 weeks. This improved following treatment with an oral first generation cephalosporin, but she then developed 6 weeks of diffuse arthralgias and headaches. She next developed acute right facial paralysis, evolving over 24 hours, with retroauricular pain, hyperacusis, and decreased sense of taste. Past medical history was otherwise unremarkable, and examination was notable only for a complete peripheral right seventh nerve palsy.

She was treated with oral penicillin 2 g daily for 2 weeks. Although she improved, she had significant residual symptoms and underwent lumbar puncture. Fluid was completely normal. Serum Lyme ELISA was strongly positive, with the patient's value being 12.7 times the negative cut-off; the spinal fluid value, after appropriate correction, was identical to that in the serum. She then received 2 weeks of intravenous ceftriaxone and over the next month recovered completely.

Biological basis

Etiology and pathogenesis

Lyme disease is caused by spirochetes of the Borrelia burgdorferi sensu lato complex, transmitted by the bite of Ixodes ticks. Five members of this family (*B. burgdorferi sensu stricto, B. garinii, B. afzelii*, and strains found in Europe, *B. spielmanii* and *B. bavariensis* are pathogenic for humans, causing the predominant clinical forms of Lyme borreliosis (Margos et al 2013). In Europe, most cases with nervous system involvement appear to be caused by *Borrelia garinii* (B. garinii) (Ogrinc et al 2013) or the closely related strain *B. bavariensis* (Margos et al 2013).

Lyme disease is a multisystem infectious disease caused by a closely related group of spirochetes, known originally as *Borrelia burgdorferi* and now referred to as *Borrelia burgdorferi sensu lato*. *Borrelia burgdorferi sensu stricto* is the agent of North American Lyme disease; this strain and the other 4 occur in Europe. A distinct strain has been identified in 6 patients in the U.S. Midwest, with the suggested name *B. mayonii* (Pritt et al 2016). Lyme disease is a zoonosis, in which humans are an inadvertent host. The sole vectors are hard-shelled *Ixodes* ticks (*Ixodes scapularis* in most of the United States, *Ixodes pacificus* in California, and *Ixodes ricinus* in Europe). These ticks go through a 3-phase, 2-year (in temperate climates) life cycle, partaking of 1 blood meal in each phase. In the first phase, the larva, which is the size of a typewritten period, will typically feed on a small mammal, most often a white-footed mouse. If this host is already infected with *B. burgdorferi*, the tick can become infected. The tick will then mature into a nymph and subsequently have its second meal. If previously infected, the tick can now transmit spirochetes; if not previously infected, the tick again can acquire infection if it feeds on an infected host. Infection of the host takes time – typically, the tick must feed for at least 24 to 48 hours before the probability becomes high that the new host on which it is feeding will become infected with the Lyme agent. During this interval, ingested blood triggers proliferation of spirochetes in the tick gut. They then disseminate in the tick, reach its salivary glands and can then be injected into the host. Even in areas where a high proportion of ticks carry *Borrelia*, only about 5% of humans with identified *Ixodes* tick bites will become infected, only half of whom will be symptomatic (Wilhelmsson et al 2016).

The mature adult tick will subsequently take its third meal, preferring to attach to a large mammal such as a bear or deer, giving rise to the common names attached to these ticks; the "deer tick" in the northeast United States and the "bear tick" in the Midwest. Although other arthropod hosts have been shown to carry *B. burgdorferi* (horseflies, mosquitoes), the unique nature of the tick's feeding cycle is probably essential for hosts to become infected, making it highly unlikely that vectors other than *Ixodes* ticks would transmit Lyme disease in all but the most extraordinary circumstances.

The pathophysiology of peripheral nerve and brain involvement remains unclear (Rupprecht et al 2008; Ramesh et al 2015). The few available pathologic studies demonstrate multifocal perivascular inflammation in nerves (Halperin 2003; Eiffert et al 2004; Elamin et al 2009). MRI imaging suggests a similar process in brain and spinal cord. Although it has been impossible to demonstrate intact spirochetes in nerves or the brain, active infection is clearly an essential element, as elimination of organisms with antimicrobial treatment prevents further neurologic damage and typically

leads to significant improvement (Halperin and Logigian 2005). However, cytokines released in response to outer surface protein A (OspA) from *B. burgdorferi,* and even from nonviable spirochetes, can induce both astrocyte proliferation and apoptosis in vitro potentially amplifying the impact of infection with a small number of organisms (Parthasarathy 2013; Ramesh et al 2015). Studies suggest glia play an important role in this cytokine production (Myers et al 2009; Ramesh et al 2009). Interestingly, the in vitro production of cytokines induced in cultured astrocytes by Borrelia outer surface protein A is inhibited by the clinically effective antibiotics, doxycycline and minocycline (Bernardino et al 2009). Whether such mechanisms play a role in human disease and its response to treatment remains to be determined.

Epidemiology"

The Centers for Disease Control reports approximately 30,000 confirmed cases of Lyme disease annually in the United States (Centers for Disease Control and Prevention 2012). How accurately this reflects the actual incidence of this disorder is debated, although it probably includes the majority of cases that meet strict criteria. A study based on commercial laboratory testing suggested the actual number might be 10 times as high (Hinckley et al 2014); however, that estimate was based on the assumption that 85% of patients had just 1 test performed, which in the experience of many is a substantial underestimate. (If all patients had at least 2 tests, the estimate would decrease by half; a higher number of tests would further decrease this number.) Cases have been reported from 47 states, but enzootic cycles (ie, areas where infected ticks and hosts are known to be present) have only been reported from 19 states (Steere 1994) with only 16 states reporting more than 100 cases a year (Centers for Disease Control and Prevention 2012). Most cases cluster along the eastern seaboard from Maryland to Maine and in the upper Midwest (Wisconsin and Minnesota). In most of the United States, incidence is seasonal, with tick bites and infection occurring from spring through autumn, although in California a more uniform year-round distribution of acute infection is seen. The disease is prevalent in much of temperate Europe and Asia. Isolated cases have been reported from all continents except Antarctica.

Prevention

The best method to avoid becoming infected with *B. burgdorferi* is to avoid *Ixodes* tick bites. Standard recommendations include the wearing of light-colored, long-sleeved shirts and long pants tucked into socks when in tick-infested areas. Achieving this goal in young children in summer is problematic, at best. Extensive spraying of skin with tick repellants or acaricides is probably ill-advised, as these are partially absorbed and may be neurotoxic, particularly in small children. Spraying clothes with these agents, however, can be helpful. Because ticks must be attached for many hours before transmission is likely, a simple and thorough tick check at the end of the day will often suffice. Prophylactic antibiotics, specifically a single 200-mg dose of doxycycline (Nadelman et al 2001), can lessen the risk of infection following tick bites if in highly endemic areas (Shapiro 2014). However, the risk of significant adverse drug reactions must be weighed against the need to treat 50 patients to prevent 1 case of Lyme disease.

Outer surface protein A vaccines can provide some protection against infection and were approved by the U.S. Food and Drug Administration. However, limited demand, combined with litigation about possible immune-mediated complications led to its withdrawal from the market.

Efforts at reducing tick populations have had variable success. One feeding device that coats a deer's head and neck with acaricide while it feeds shows some promise for reducing local tick burden (Fish and Childs 2009).

Differential diagnosis

The differential diagnosis in patients with Lyme disease ranges from the remarkably simple to the quite complex. In patients with erythema migrans or a positive serology and part of the classic neurologic triad (meningitis, cranial neuritis, or painful radiculoneuritis), diagnostic confusion is unlikely. In patients with a subacute disseminated neuropathy, confusion with Guillain-Barre syndrome can be problematic, particularly with a facial diplegia. However, patients with severe Lyme-associated disseminated neuropathy frequently have a significant CSF pleocytosis. Some patients may develop a primarily motor polyradiculitis that can resemble a motor neuronopathy, particularly if subacute. Generally, evaluation of the CSF will differentiate among these entities.

One of the most difficult clinical dilemmas involves patients with encephalomyelitis. This very rare disorder can resemble clinically, and on MRI scan, a first episode of multiple sclerosis. Moreover, as in neurosyphilis and other

chronic CNS infections, patients with nervous system Lyme disease may have oligoclonal bands in the CSF as well as increased intrathecal immunoglobulin synthesis. However, patients with this as a manifestation of Lyme disease typically have more cells in the CSF and usually have demonstrable intrathecal production of anti-*B. burgdorferi* antibodies. Large, atypical appearing lymphocytes have been reported in the CSF as well. The most difficult situation occurs when a patient previously treated for suspected Lyme encephalomyelitis has a second attack; differentiating between inadequately treated Lyme disease and a new attack of multiple sclerosis may not be possible using generally available laboratory techniques.

Diagnostic workup

Laboratory diagnosis of Lyme disease is generally indirect. Although *B. burgdorferi* can be grown in vitro and can often be cultured from the typical cutaneous lesion (erythema migrans), sensitivity of CSF culture is no better than 10% even in the best of laboratories. The needed culture medium is not routinely available in most clinical microbiological laboratories, so even this is usually impractical. In the absence of the typical cutaneous lesion, serologic testing for immunologic evidence of exposure to *B. burgdorferi* is generally used and is subject to all the usual limitations of serologic diagnosis. Generally, several weeks are required following exposure before enough antibodies are present in peripheral blood for the response to be detectable. Particularly if infection has been present for an extended period of time, patients may continue to produce antibody for years following successful treatment. This makes it difficult to use antibody measurements either to differentiate between current infection and past exposure or to assess treatment response. As with other serologic tests, cross-reactions to other bacteria occur. Spirochetal disorders such as syphilis, relapsing fevers, and even periodontal disease due to Treponema denticola are particularly prone to cause false positives. However, other causes of polyclonal B cell stimulation, such as subacute bacterial endocarditis, have also been shown to produce cross-reactive false positives in ELISAs.

Increased specificity is provided by performing Western blots, which identify the specific antigens to which the patient's antibodies react. The CDC recommends the universal use of 2-tiered testing in which samples with positive or borderline ELISAs are confirmed by Western blot, interpreted by standard and well-validated (for North American patients) criteria (See Table 2). If 5 of the 10 specified IgG bands, or 2 of the 3 IgM bands are present in patients with long- or short-standing symptomatology respectively, the blot is considered positive (Dressler et al 1993). Importantly, patients with symptoms of more than 1 to 2 months duration should have a demonstrable IgG response; IgM results in any such patient are far more likely to be spurious than informative (Halperin 2013). This approach adds considerable specificity in patients with borderline or low positive ELISAs, but Western blots should not be used to increase sensitivity in individuals with negative ELISAs. The substantially greater strain variability among European Borrelia species to date has precluded the development of consensus criteria for European patients (Steere 2001; Branda et al 2011).

Table 2. Western Blot Criteria

IgG (5 of 10)	IgM (2 of 3)
18 kD	23 kD
23 kD	39 kD
28 kD	41 kD
31 kD	
39 kD	
41 kD	
45 kD	
58 kD	
66 kD	
93 kD	

Studies have investigated antibodies to another single antigen, C6, part of the VlsE lipoprotein of *B. burgdorferi*. C6 testing appears to be more reliable than 2-tier testing in European patients, where greater borrelia strain variability makes Western blot-based diagnosis more challenging (Schoen 2013). In US patients, C6 based assays may provide slightly greater diagnostic sensitivity but be slightly less specific than the 2-tier approach (Wormser et al 2013).

In general, serologic testing should only be performed when there is a reasonable pretest likelihood of Lyme disease (ie, when an epidemiologically plausible exposure occurs and the clinical symptoms are within the spectrum of those

known to be caused by this infection) (Nichol et al 1998). Indiscriminate serologic testing in other circumstances will result in more false than true positive results, with consequent unnecessary diagnostic confusion, patient apprehension, unneeded therapy, and treatment complications.

Early concerns about patients remaining seronegative beyond the first or second month of infection, particularly if given subcurative doses of antibiotics, have not been supported by subsequent studies. This observation is now believed to have been an artefact of the diagnostic technology available at that time.

When attempting to confirm central nervous system infection, the most useful and readily available technique is to examine cerebrospinal fluid, both for nonspecific markers of inflammation and for evidence of production of anti-*B. burgdorferi* antibodies within the central nervous system (Stiernstedt et al 1985; Halperin et al 1989). Current European guidelines require that patients have either a CSF pleocytosis or intrathecal antibody production to make the diagnosis of both possible and definite neuroborreliosis (Mygland et al 2010). Demonstrating intrathecal antibody production requires comparing specific CSF and serum antibody concentrations, adjusting for blood-brain barrier function, and correcting for the amount of antibody present in peripheral blood. Technically, this can be accomplished either with a capture assay or by measuring CSF and serum immunoglobulin concentration, diluting both fluids so that the final immunoglobulin concentration is identical, and then performing the Lyme-specific ELISA. Regardless of the technique used, it is essential that both CSF and serum antibody be measured and the 2 compared. Estimates of the technique's sensitivity vary between 50% in patients with more chronic syndromes (Logigian et al 1990) and 90% in acute CNS disease (Halperin et al 1991). Work suggests the specificity is over 95% (after excluding neurosyphilis) but suggests sensitivity may be lower very early in disease and, not surprisingly, in patients in whom the peripheral but not central nervous system is involved (Ljostad and Mygland 2008). One of the great shortcomings of this method is that, even after successful treatment, this measure of intrathecal antibody production may remain elevated for years.

Several other technologies have been applied in an effort to demonstrate bacteria directly. Many groups have applied the polymerase chain reaction to detect bacterial DNA. Diagnostic sensitivity in CSF is unfortunately low; a review by the Mayo Clinic lab, in which pretest probability was unknown, found PCR to be positive in just 0.06% of submitted CSF samples (Pritt et al 2016). The difficulty in specificity relates to eliminating the risk of contamination. Urine Lyme antigen assays are no longer commercially available and appear to be unreliable (Klempner et al 2001b). European work suggests that CXCL13, a B cell attracting chemokine, may be demonstrable in CSF very early in infection, potentially supporting the diagnosis (Rupprecht et al 2009). Unfortunately, similar elevations occur in other inflammatory disorders, including neurosyphilis and HIV (Marra et al 2010; Bremell et al 2013). This may provide a helpful if nonspecific marker of disease activity that may be helpful in following treatment response.

Management

Although some still debate what constitutes the optimal treatment of nervous system Lyme disease, the evidence supports several conclusions (Wormser et al 2006; Halperin et al 2007; Lantos et al 2010). In patients with early cutaneous disease, amoxicillin 1.5 g daily or doxycycline 200 mg daily for 2 to 4 weeks is generally effective. Erythromycin, although effective in vitro, is less efficacious in vivo. Some of the newer macrolides such as azithromycin or clarithromycin have some role, although they are probably less effective than amoxicillin or doxycycline. In patients with meningitis or other CNS infections, most centers in the United States have used meningeal doses of penicillin or third-generation cephalosporins with good CNS penetration, such as ceftriaxone (2 g daily) or cefotaxime (6 g daily) (Pfister et al 1989; Pfister et al 1991). Several studies have suggested that ceftriaxone and cefotaxime are about equally efficacious; most authorities in the United States consider them to be superior to penicillin. A meta-analysis of European studies comparing oral doxycycline to parenteral regimens in patients with Lyme meningitis or cranial neuritis suggests oral regimens are as effective in this population (Halperin et al 2007), an approach recommended by current European guidelines (Mygland et al 2010). The question has not been studied systematically in patients in the United States. Although there are strain differences between European and U.S. Borrelia, antimicrobial sensitivities are generally comparable. Until this question is rigorously tested in the United States, it is probably reasonable to use oral doxycycline in mildly-affected patients and ceftriaxone or cefotaxime in those with more severe CNS Lyme disease, pending further studies. However, 1 European study suggests oral doxycycline may be effective in parenchymal CNS neuroborreliosis as well (Bremell and Dotevall 2014).

Glucocorticoids, used in some patients concurrently with antibiotics to control radicular pain, or facial palsy, can be used, but with caution. No controlled clinical studies have been carried out, but animal studies suggest they may potentially play a role (Ramesh et al 2015).

Special considerations

Pregnancy

Anecdotal reports have described fetal loss and malformations in some women with untreated acute Lyme disease infection (tick bite, erythema migrans) during pregnancy (Lakos and Solymosi 2010), but no consistent congenital syndrome has been observed. Several large epidemiologic studies have indicated no increase in the frequency of adverse pregnancy outcomes in women who are found to be seropositive or are found to have other nonacute disorders associated with Lyme disease (Cartter et al 1989; ACOG Committee 1992; Strobino et al 1993; Strobino et al 1999). In women with acute infection during pregnancy, aggressive antimicrobial treatment is appropriate. Notably, use of tetracyclines such as doxycycline must be weighed carefully during pregnancy due to potential effects on bone and teeth, and some have suggested that use of ceftriaxone in the third trimester might be associated with fetal hyperbilirubinemia. High-dose ampicillin or penicillin is usually recommended in this setting.

Anesthesia

No data are present to address this issue. No evidence provides reason to believe that anesthesia would pose any additional risk for patients with Lyme disease.

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Lyme disease: 088.81

ICD-10:

Lyme disease: A69.2

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

none

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

Occupations involving extensive outdoor exposure

Differential diagnosis list

Guillain-Barre syndrome
Motor neuronopathy
encephalomyelitis
multiple sclerosis

Associated disorders

Confusional state
Peripheral neuropathy
Recurrent meningitis

Other topics to consider

Headache associated with meningitis, encephalitis, and brain abscess
Lyme disease: controversial issues
Molecular diagnosis of CNS infections
Recurrent meningitis
Vaccines for neurologic disorders
Vasculitic neuropathies