PAIN® 155 (2014) 1435–1438

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Topical review

Acute and chronic pain associated with Lyme borreliosis: Clinical characteristics and pathophysiologic mechanisms

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

1. Introduction

Lyme disease is a multisystem disorder caused by several related borrelial subspecies referred to generally as *Borrelia burgdorferi* [36]. It is transmitted by infected *Ixodes* ticks, and is the most common vector-borne infection occurring in endemic geographic areas in the temperate Northern hemisphere [5]. In the United States, where reporting is mandatory, documented infection occurred in 50,000 persons between 1982 (when the etiologic agent was first identified) and 1994 [33]. Since 1994, more than 500,000 new cases have been reported to the Centers for Disease Control and Prevention, averaging 20,000 to 30,000 cases per year [6]. Many more cases are never reported to the Centers for Disease Control and Prevention [28], suggesting that millions of United States inhabitants have had symptomatic Lyme infection.

Borrelia burgdorferi spirochete has tropism for skin, joints, nervous system, and heart causing substantial late morbidity, particularly when not diagnosed and treated promptly [4,33]. In past centuries, the spirochete *Treponema pallidum*, the causative organism in syphilis infection, was characterized by Sir William Osler as the "great imitator" [20] because of its ability to mimic a diverse array of clinical conditions. Today, *Borrelia burgdorferi* spirochete infection may be similarly missed because it is not considered in the differential diagnosis. Chronic pain resulting from arthralgia, neuropathy, or as a component of a fibromyalgia-like illness possibly induced by Lyme infection [9] occurred in 24% of United States confirmed and treated patients who had a prolonged (average 34 months) time to initial antibiotic treatment [33]. This may suggest that many people worldwide may suffer from chronic pain as a result of having contracted Lyme disease.

We performed a systematic review of the literature by searching "pain" and "Lyme disease" on PubMed. Our search criteria yielded 372 total references, including 280 English language references. The focus of this review is on the characteristics, possible etiologic mechanisms, and treatment of acute and chronic pain occurring in the setting of Lyme disease.

2. Acute pain

2.1. Musculoskeletal pain

Borrelia burgdorferi comprises a group of several species referred to as *Borrelia burgdorferi sensu lato* (ie, *Borrelia burgdorferi* in the general sense), and several subspecies including *Borrelia burgdorferi sensu stricto* (ie, in a strict sense), the cause of North American disease, and *Borrelia afzelii* or *Borrelia garinii*, the latter 2 subspecies being the infecting organisms in most cases in Europe [5]. *Borrelia afzelii* and *Borrelia garinii* have different organ tropisms than *Borrelia burgdorferi sensu stricto* [5], which may account for the higher prevalence of arthritis and lower prevalence of neurologic involvement in North America compared to European borreliosis (Fig. 1) [36].

Arthralgias are the most common form of pain associated with Lyme arthritis (Table 1). These occur early in the disease and affect 1 or a few joints [29]. Early musculoskeletal pain may involve bursae, muscles, tendons, or bones, and, similar to arthralgia, it is fleeting and migratory [29]. Involvement of 1 or a few large joints most often occurs weeks or months later and is self-limited, lasting only a few weeks [29].

In approximately 5% of cases, Lyme joint involvement may occur in the temporomandibular joint [23], mimicking the prevalent condition of temporomandibular joint dysfunction. Knee pain as a manifestation of Lyme arthritis may occur in up to 60% of North American cases of Lyme borreliosis [29]. Because Lyme arthritis can mimic a reactive arthritis or juvenile form of rheumatoid arthritis [36], serology combined with polymerase chain reaction (PCR) can be helpful in establishing the correct diagnosis. Yet each method has its shortcomings. For example, in endemic areas,

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http://dx.doi.org/10.1016/j.pain.2014.04.024

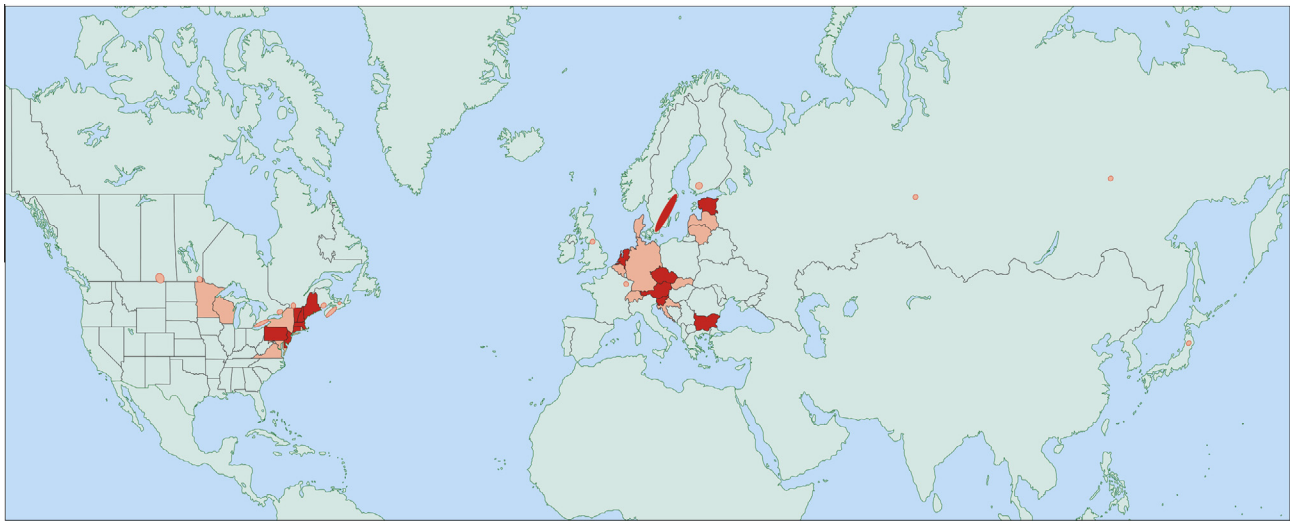

Fig. 1. Worldwide distribution of borreliosis endemic and highly endemic areas [6,21,35]. Light shading indicates region or country in which borreliosis is reported to be endemic, and dark shading indicates areas where borreliosis is reported to be highly endemic. Endemic = 10 confirmed cases per 100,000 population; highly endemic ⩾30 cases per 100,000 population.

Table 1
Acute and chronic pain after Lyme borreliosis.

Authors	Patients	Study design	Pain condition	Treatment outcomes; prevalence
Acute pain				
Dotevall et al. [10]	4 adults; LNB	Observational	Neuropathic (meningomyeloradiculitis) with lower-extremity paresis or cranial nerve palsy	Opioid analgesics effective short-term in 2/4; complete pain resolution in 3/4 with oral DOX, residual paresis in 1/4, cranial nerve palsy in 1/4
Steere et al. [36]	83 adults	Observational	Arthralgia, musculoskeletal, periarticular, arthritis	Early arthralgia(s) and arthritis respond to antibiotics
Lesnicar et al. [23]	2 adults	Observational	Temporomandibular joint	Complete resolution after IV CTX
Gorson et al. [15]	5 adults; acute LNB	Retrospective, case series	Flail arm, constant severe pain	Complete resolution in 5/5 with IV CTX in 4 and prednisone in 3
Ljostad et al. [24]	118; LNB	Randomized, double-blind; IV CTX vs oral DOX	Radicular	16/118 in both groups at 4 months
			Multisymptom, including persistent pain	29/118 in both groups at 4 months
				No significant between-group difference in residual symptoms
Chronic pain[*]				
Shadick et al. [33]	81	Retrospective, case-control	Nociceptive, arthralgias	23/38 LD vs 7/43 CTRL
			Neuropathic, burning with numbness/tingling	6/38 LD vs 1/43 CTRL
			Nociceptive, myalgias	3/38 LD vs 2/43 CTRL
Berglund et al. [4]	114	5-year follow-up of confirmed LNB	Neuropathic, paresthesias	4/74 adults, 1/40 children
			Neuropathic, radicular motor and/or sensory	3/74 adults, 0/40 children
			Fatigue, fibromyalgia, headache	22/74 adults, 6/40 children
Vrethem et al. [39]	229[†]	2.5-year follow-up of LNB; case-control	Nociceptive, chronic headache	17/92 LNB vs 3/90 LD
			Neuropathic, chronic paresthesias	20/92 LNB vs 7/90 LD
			Other chronic pain	14/92 LNB vs 2/90 LD
Fallon et al. [13]	57 (37 LD with memory impairment, 20 CTRL)	Randomized, double-blind; 10 weeks IV CTX vs PBO in previously-treated LD	Nociceptive, arthralgias	Primary analysis: cognitive improvement greater in CTX- vs PBO-treated LD patients at 12 (P = .053) but not 24 weeks Secondary analysis: LD patients with greater baseline joint pain had greater improvement in pain with CTX vs PBO at 24 weeks (P = .07)
Logigian et al. [27]	25	Retrospective, observational	Neuropathic (radicular, paresthesias)	12/25 radicular pain, 12/25 paresthesias

CTRL = control; CTX = ceftriaxone; DOX = doxycycline; IV = intravenous; LD = Lyme disease; LNB = Lyme neuroborreliosis; PBO = placebo.
[*] Chronic pain: >6 months in duration.
[†] Although 229 subjects were enrolled, only 182 completed the questionnaire.

seropositivity for *Borrelia burgdorferi* is common owing to a high rate of asymptomatic infection [7]. Although a positive synovial fluid PCR is highly correlated with untreated infection, synovial fluid PCR remained positive after antibiotic treatment in approximately 30% of Lyme arthritis patients, and it did not correlate with recurrent symptoms or evidence for persistent tissue infection [25].

2.2. Neuropathic pain

All 3 *Borrelia* species can infect the peripheral nervous system [5]. Acute pain is a central feature of acute nervous system involvement in Lyme disease. It has been characterized as having qualities of neuropathic pain, that is, radicular, deep aching, or lancinating pain, often worse at night [10], and associated with both sensory and motor findings [10,15] (Table 1).

Neuroborreliosis affects approximately 15% of people with acute Lyme disease, typically presenting with 1 or more components of the classic triad of meningitis, radiculoneuritis, and cranial neuropathy [3,4]. The diagnosis relies on a history of exposure to the organism, typical signs and symptoms together with a positive serology, and cerebrospinal fluid evidence for inflammatory changes and intrathecal production of specific *Borrelia* antibodies [17]. The history of a tick bite and of the characteristic skin rash, erythema migrans, may or may not be present. In North American neuroborreliosis, meningitis is more common than radiculoneuritis [16]. Headache is a frequent clinical manifestation in meningitis and may contribute to acute pain and chronic pain in a subset of patients showing residual symptoms [39]. Cranial neuritis can involve virtually any cranial nerve, but facial nerve palsy, often bilateral, occurs frequently, in at least 60% of cases [1]. Cervical, thoracic, and lumbosacral regions can be affected alone or in combination; typically asymmetric, with unilateral or bilateral involvement [1]. Interestingly, rhesus monkeys chronically infected with *Borrelia burgdorferi* develop mononeuritis multiplex with histopathologic features of multifocal axonal degeneration and regeneration and occasional perivascular inflammatory cellular infiltrates without vessel wall necrosis consistent with an immune-mediated mechanism for Lyme disease [12]. In patients with Lyme radiculoneuritis, sural nerve biopsies show perivascular endoneurial, perineurial, and epineurial lymphoplasmacytic infiltrates with axonal loss in the absence of vasculitis or demyelination [38].

Pain typically improves promptly within days to weeks after institution of antibiotic therapy, but neurologic deficits can resolve more slowly over weeks to months. The usefulness of opioids for the management of acute Lyme neuroborreliosis-related pain also has been described [10].

3. Chronic pain

3.1. Musculoskeletal pain

In approximately 10% of antibiotic-treated Lyme arthritis patients, a treatment-resistant form of chronic arthritis ensues that is unresponsive to subsequent courses of antibiotic therapy [29]. The presumptive cause of late, chronic disabling pain associated with *Borrelia* infection, although still debated in the literature [37], seems unlikely to be due to persistent joint infection with *Borrelia burgdorferi* [22]. Evidence suggests it may have an immunologic basis [36]; for example, the longer the *Borrelia* organism persists in the host, the more diverse the antibody response to *Borrelia* protein antigens [2].

A robust immune response to specific *Borrelia* antigens may be involved in the underlying mechanism of treatment-resistant Lyme arthritis, either through cross-reaction between specific anti-*Borrelia* antibodies and normal host synovial proteins [36] or through cytokine-mediated focal inflammation [31]. In several studies, persistent articular symptoms and signs were independently significantly associated with human leukocyte antigen DR4 and human leukocyte antigen DR2 haplotypes or with autoantibodies to the lipoprotein *Borrelia* antigen Osp A [18].

Early diagnosis and treatment of Lyme disease with antibiotics is vital in cases of Lyme arthritis, as discussed earlier. For management of chronic antibiotic-resistant Lyme arthritis, symptomatic relief with nonsteroidal anti-inflammatory drugs is the current mainstay of pain management. Persistent severe pain may necessitate more invasive interventions, such as synovectomy, to achieve a complete remission [36].

Persistent arthralgias occurring in the setting of a multisystem disease complex that includes fatigue, headache, chronic pain, and cognitive impairment may represent fibromyalgia, chronic fatigue syndrome, or posttreatment Lyme syndrome, which some investigators have suggested is triggered by prior Lyme infection [9] or maintained by low-grade persistent infection [37]. It is critically important to differentiate between late manifestations of untreated Lyme borreliosis and a late-appearing fibromyalgia-like condition in an adequately treated patient to avoid exposing patients to unnecessary risks associated with long-term antibiotic therapy [22]. An Infectious Diseases Society of America panel concluded that the risks of prolonged treatment with antibiotics in treatment-resistant forms of the disease outweigh the potential benefit for most patients [16,22]. It has been noted, however, that clinical trial results have been inconsistent with respect to whether a beneficial effect on fatigue or pain may occur for some patients [14].

3.2. Neuropathic pain

Chronic pain despite adequate antibiotic treatment of neuroborreliosis was reported by a substantial number of patients described by various investigators [4,13,26,33,39]. Three to 5 years after antibiotic treatment of neuroborreliosis, 29% of patients still complain of residual neurologic symptoms, including chronic pain (16%) and headache (18%) [4,39]. Chronic neuropathic pain after Lyme neuroborreliosis may be radicular and associated with sensory abnormalities such as paresthesias (Table 1). Corticosteroids were not consistently associated with benefit or harm after treatment of Lyme neuroborreliosis [15], whereas gabapentin improved neuropathic symptoms in 9 of 10 patients treated for chronic neuropathic pain after Lyme borreliosis [40].

Ljøstad et al. [24] reported that once-daily oral doxycycline (200 mg) was noninferior to once-daily intravenous (IV) ceftriaxone (2 g) in ameliorating overall clinical signs and symptoms of European neuroborreliosis at 4 months after randomized treatment. Chronic pain was 1 of several residual subjective complaints (malaise, fatigue, difficulty concentrating, memory problems) that occurred in the absence of objective findings in as many as 29 of their sample of 118 patients [24]. Chronic pain occurring as a component of a multisymptom complex that includes prominent fatigue and neurocognitive impairment may result from an exaggerated immunological response to *Borrelia burgdorferi* lipoprotein antigens such as Osp A [18] or enhanced Th-1 cytokine production in the central nervous system [11], leading to encephalopathy. On the other hand, a causative role for active infection is suggested by reports of untreated or inadequately treated patients with later-onset, chronic, painful radiculoneuropathy who do respond to antibiotic treatment [13,26,27].

Intravenous ceftriaxone is the preferred antibiotic choice in the United States for the treatment of neuroborreliosis [36]. A potential advantage of IV ceftriaxone compared with other antibiotics is that it has been shown to increase the expression of glutamate transporters at nerve terminals involved in mediating pain transmission [32]. This nonantibiotic-mediated effect may have contributed to

significantly reduced severe pain (after 12 and 24 weeks) in a randomized trial conducted by Fallon et al. [13] of 10 weeks of IV ceftriaxone for chronic encephalopathy. Of interest, several studies of long-term residual pain after Lyme neuroborreliosis have come from Europe [4,39], where it is more common to treat the disease with either oral doxycycline or IV penicillin G [19] than with IV ceftriaxone. Future clinical trials are needed to determine whether antibiotic regimens resulting in better short-term control of acute pain in neuroborreliosis may reduce the likelihood for development of chronic pain.

4. Pain and Lyme disease in children

Pain occurring in a young child may be the presenting symptom of Lyme disease affecting the nervous system. Neuroborreliosis is especially likely to occur in children, causing cranial neuritis and lymphocytic meningitis [8] but rarely radiculitis, which commonly occurs in adults [30]. For unknown reasons, neuroborreliosis is much less likely to cause long-term functionality-impairing symptoms in children [34] compared with adults after its treatment.

5. Conclusions

Substantial gaps exist in our understanding of the epidemiology and natural history of acute and chronic pain in Lyme disease. In addition, there is limited knowledge of the pathophysiologic mechanisms that contribute to the different types of acute and chronic pain associated with Lyme disease, including inflammatory, musculoskeletal, neuropathic, and mixed conditions. Prompt recognition and antibiotic treatment of Lyme disease is imperative in reducing the incidence of painful sequelae.

Conflict of interest statement

The views expressed in this article are those of the authors, none of whom have financial conflicts of interest related to the specific issues discussed in this article.

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