



## Clinical Studies

# A critical appraisal of the mild axonal peripheral neuropathy of late neurologic Lyme disease



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## ABSTRACT

In older studies, a chronic distal symmetric sensory neuropathy was reported as a relatively common manifestation of late Lyme disease in the United States. However, the original papers describing this entity had notable inconsistencies and certain inexplicable findings, such as reports that this condition developed in patients despite prior antibiotic treatment known to be highly effective for other manifestations of Lyme disease. More recent literature suggests that this entity is seen rarely, if at all. A chronic distal symmetric sensory neuropathy as a manifestation of late Lyme disease in North America should be regarded as controversial and in need of rigorous validation studies before acceptance as a documented clinical entity.

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Lyme disease is the most common tick-borne infection in both the United States and Europe with 300,000 cases estimated to occur annually in the United States (Hinckley et al., 2014; Nelson et al., 2015; Stanek et al., 2012; Wormser et al., 2006). Lyme disease is caused by various species of Lyme borrelia, known collectively as *Borrelia burgdorferi sensu lato* (Stanek et al., 2012; Wormser et al., 2006). Only *B. burgdorferi sensu stricto* and rarely *B. mayonii* (Pritt et al., 2016) cause Lyme disease in the United States, whereas in Europe most cases are caused by *B. afzelii* or *B. garinii* (Stanek et al., 2012; Wormser et al., 2006). The most common clinical manifestation is the characteristic skin lesion erythema migrans that occurs in approximately 80% of cases (Wormser et al., 2006). Other clinical manifestations may involve the heart, joints, and nervous system (Stanek et al., 2012; Wormser et al., 2006).

What has been referred to as early neurologic Lyme disease occurs in both the United States and Europe. Typical manifestations are cranial nerve palsy, especially seventh nerve palsy, lymphocytic meningitis, and painful radiculitis (Halperin, 2015; Hansen et al., 2013; Mygland et al., 2010; Ogrinc et al., 2016; Stanek et al., 2012; Wormser et al., 2006). These clinical manifestations are thought to occur within a few weeks or months of inoculation of Lyme borrelia into the skin by an infected tick. Some of these manifestations will improve coincident with antibiotic therapy, but the rate of recovery of others, such as facial

palsy, appears to be unaffected by antibiotic treatment (Clark et al., 1985). Studies in Europe have demonstrated that oral doxycycline is as effective as intravenous (IV) ceftriaxone for these clinical manifestations (Halperin et al., 2007; Ljostad et al., 2008).

Other neurologic conditions have been categorized by some as late neurologic manifestations (Table 1) (Fallon et al., 2008; Halperin et al., 1987, 1990; Hopf, 1975; Kindstrand et al., 1997, 2000, 2002; Kristoferitsch et al., 1988; Logigian and Steere, 1992; Logigian et al., 1990; Mygland et al., 2006, 2010; Steere et al., 1994; Wormser et al., 2006). Although it is somewhat arbitrary as to what time frame differentiates early from late onset neurologic manifestations of Lyme disease, neurologic manifestations that arise at the same time as, or after the onset of, recognized late manifestations, such as Lyme arthritis (Logigian et al., 1990; Steere et al., 1994) or acrodermatitis chronica atrophicans (ACA) (Stanek et al., 2012), certainly would be regarded as late neurologic manifestations. For example, more than 40% of patients with ACA develop a sensory peripheral neuropathy (Hopf, 1975; Kindstrand et al., 1997, 2000, 2002; Kristoferitsch et al., 1988; Mygland et al., 2006). Although this neuropathy may or may not be restricted to the limb with the ACA skin lesion, when the neuropathy occurs in a location other than the ipsilateral limb, it is typically less severe, indicating that it is usually not a symmetric distal neuropathy (Hopf, 1975; Kristoferitsch et al., 1988). The neuropathy that occurs in association with ACA does not respond to any form of antibiotic treatment, but (oral) antibiotic therapy will prevent further progression (Hopf, 1975; Kindstrand et al., 2002; Kristoferitsch et al., 1988).

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**Table 1**  
Manifestations of late neurologic Lyme disease.

| Manifestation         | Comment   |
|-----------------------|---|
| Encephalomyelitis     | Case definition requires inflammatory CSF and the presence of intrathecal antibody production to Lyme borrelia (Stanek et al., 2012; Mygland et al., 2010; Hansen et al., 2013). Although described in both Europe and the United States, appears to be more common in Europe (Wormser et al., 2006; Stanek et al., 2012). In United States is extremely rare and Powassan virus infection would need to be excluded, which in general has not been done, raising concerns over the validity of the diagnosis. Condition is chronic without improvement or resolution unless treated with antibiotic therapy. The term “chronic neurologic manifestation” may be more appropriate than “late onset neurologic manifestation”. |
| Radiculoneuritis      | Well recognized as an early manifestation in both Europe and the United States (Wormser et al., 2006; Stanek et al., 2012; Hansen et al., 2013; Ogrinc et al., 2016). Only reported as a late manifestation in the United States (Logigian and Steere, 1992; Logigian et al., 1990; Halperin et al., 1990) and concerns exist over the validity of the diagnosis for the same reasons as discussed for peripheral neuropathy (Table 2).   |
| Encephalopathy        | Poorly defined entity associated with objective cognitive dysfunction (Wormser et al., 2006; Halperin, 2015; Logigian et al., 1990). Pathogenesis thought to be either toxic-metabolic in patients with an inflammatory site of infection remote from the CNS, or due to a low grade encephalomyelitis but without evidence of inflammation in the CSF (Halperin, 2015). Only reported in the United States. Randomized, placebo-controlled trial in the United States did not find a durable benefit from a 10-week course of IV ceftriaxone (Fallon et al., 2008). This particular patient group, however, had already failed prior antibiotic therapy.   |
| Peripheral neuropathy | May present as a distal stocking-glove axonal neuropathy possibly due to a mononeuropathy multiplex (Wormser et al., 2006; Halperin, 2015; Logigian and Steere, 1992; Logigian et al., 1990; Halperin et al., 1987, 1990). Only found in the United States except for European patients with ACA (Mygland et al., 2006; Hopf, 1975; Kindstrand et al., 1997, 2000, 2002; Kristoferitsch et al., 1988). In conjunction with ACA, either exclusively involving just the extremity with ACA or with greater involvement of an extremity affected by ACA.   |

CNS = central nervous system.

In Europe, despite the fact that the second most common bacterial cause of Lyme disease there is *B. garinii*, a highly neurotropic strain of Lyme borrelia, a distal sensory peripheral neuropathy attributable to Lyme disease has not been well documented in any patients with Lyme disease except those with ACA (Hansen et al., 2013; Stanek et al., 2012). ACA is not seen in patients with Lyme disease acquired in the United States, most likely because the most common etiologic agent of ACA, *B. afzelii*, is not endemic in North America (Stanek et al., 2012). Nevertheless, a symmetric stocking-glove sensory peripheral neuropathy has been reported as a late neurologic manifestation of Lyme disease in the United States, often occurring in conjunction with, or even following, resolution of Lyme arthritis (Halperin et al., 1987, 1990; Logigian and Steere, 1992; Logigian et al., 1990; Steere et al., 1994). The objective of this paper is to provide a critical appraisal of this clinical entity.

Data regarding the symmetric stocking-glove sensory peripheral neuropathy manifestation of late Lyme disease in the United States are based on 4 publications from more than 20 years ago that report on 2 relatively small case series of predominantly adult patients (Halperin et al., 1987, 1990; Logigian and Steere, 1992; Logigian et al., 1990). The most common reported symptom is intermittent distal paresthesia (Halperin et al., 1987). The neurophysiologic abnormalities described were consistent with a large fiber axonal neuropathy (Halperin, 2015). Only 2 patients underwent a sural nerve biopsy, and the findings were described as “striking for the minimal nature of the abnormalities seen (Halperin et al., 1987).” The clinical course is said to be chronic, typically without progression of symptoms and signs over time, but also without spontaneous resolution (Logigian and Steere, 1992; Logigian et al., 1990).

There are, however, several confusing and some potentially conflicting features ascribed to this condition (Table 2) (England et al., 1997; Estanislao and Pachner, 1999; Halperin et al., 1987, 1990; Logigian and Steere, 1992; Logigian et al., 1990; Pachner, 2001; Roberts et al., 1998; Wormser et al., 2006). For example, the investigators involved with one of the case series have emphasized that the neurologic examination is most often completely normal (Halperin et al., 1987), whereas investigators from the other case series reported objective sensory abnormalities in the majority of patients (Logigian and Steere, 1992). In addition, investigators from one of the case series indicated that the condition rapidly responds to antibiotic therapy (Halperin et al., 1987), whereas the investigators from the other case series found that recovery of the neuropathy is slow and inconsistent, with the possibility of a clinical relapse despite treatment with IV ceftriaxone (Logigian and Steere, 1992). Surprisingly, sometimes this neuropathy develops in patients who have already been treated with an antibiotic known to have well-established efficacy for the treatment of Lyme disease, including even prior IV

antibiotic therapy with ceftriaxone (Logigian and Steere, 1992; Logigian et al., 1990). IV antibiotics are the recommended treatment (Wormser et al., 2006), but this recommendation is based on anecdotal evidence. No study has been performed that systematically compared oral with IV antibiotic treatment for this condition. The premise that every oral antibiotic, and especially oral doxycycline, would be ineffective for a peripheral neuropathy due to Lyme disease, whereas parenteral antibiotics would be highly and rapidly effective is implausible, given the successful outcomes following the use of these agents in other manifestations of neurologic Lyme disease (Bremell and Dotevall, 2014; Halperin et al., 2007; Ljostad et al., 2008; Wormser et al., 2006). The blood nerve barrier is not considered more impenetrable than the blood brain barrier, although more data on antibiotic penetration of the blood nerve barrier would be desirable (Kanda, 2013; Ubogu, 2013).

A noteworthy observation related to the symmetric stocking-glove sensory peripheral neuropathy of late Lyme disease in the United States is the rarity of documented cases in children (Belman et al., 1993; Gerber et al., 1996; Halperin et al., 1987, 1990). Children have a high incidence of Lyme disease and are at least as likely as adults to present with Lyme arthritis (Gerber et al., 1996). In addition, other manifestations of neurologic Lyme disease such as facial palsy or meningitis are relatively common and well documented in children (Belman et al., 1993; Gerber et al., 1996). Nevertheless, 2 pediatric neurologists and 4 pediatric infectious disease specialists with a cumulative 150 years in practice in a highly endemic area of southern CT have never seen a single child with this form of peripheral neuropathy due to Lyme disease (Personal communication, Eugene Shapiro, MD, 9/10/16).

A fundamental question is whether the symmetric stocking-glove sensory peripheral neuropathy associated with late Lyme disease has been appropriately validated (Hansen et al., 2013). Despite the not infrequent occurrence of Lyme arthritis (Avikar and Steere, 2015), cases of so-called distal peripheral neuropathy attributed to Lyme disease have not been seen at all by certain longstanding adult Lyme disease practices in the United States (Wormser et al., 2016), and some authorities have simply stated that cases appear to be rare or nonexistent (Halperin, 2015). Nevertheless, publications advising clinical evaluations for chronic, length dependent peripheral neuropathies often include in their recommendations diagnostic testing for Lyme disease (England et al., 2009; Watson and Dyck, 2015). Given the background rate of seropositivity to *B. burgdorferi* of 4–9% in certain high risk areas of the United States (Hilton et al., 1999; Krause et al., 1996, 2014), this is likely to lead to many cases of peripheral neuropathy incorrectly attributed to Lyme disease and may lead to subsequent unnecessary courses of IV antibiotics with the attendant risks of adverse effects from both the drug itself and from the IV catheter (Fallon et al., 2008), including possible alteration of the patient's microbiome and promotion

**Table 2**

Contrasting data or assertions regarding peripheral neuropathy in late Lyme disease.

| Topic   | Data or assertion  | Contrasting data or assertion   |
|---|--|---|
| Timing of occurrence  | Late onset manifestation (Halperin et al., 1987)   | Not necessarily late onset manifestation (Halperin et al., 1990)  |
| Frequency   | Up to 36% of late Lyme disease cases (Halperin et al., 1987)   | This entity is now seen rarely, if ever (Halperin, 2015)  |
| Typical symptom   | Paresthesias (Halperin et al., 1987)   | Paresthesias or pain (Logigian and Steere, 1992)  |
| Examination   | Typically normal (Halperin et al., 1987)   | Typically multimodal sensory loss in distal extremities (Logigian and Steere, 1992)   |
| CSF examination   | Typically normal (Halperin et al., 1987)   | Most often abnormal with an elevated protein level and/or intrathecal antibody to <i>B. burgdorferi</i> , but these abnormalities attributed to concomitant Lyme encephalopathy (Logigian and Steere, 1992)   |
| Treatment and response  | IV antibiotics lead to rapid resolution (Halperin et al., 1987)  | Response to IV antibiotics is slow, inconsistent, and potentially incomplete, and with possible relapses (Logigian and Steere, 1992; Logigian et al., 1990)   |
| Role of IV antibiotics  | Required (Wormser et al., 2006)  | No biologically plausible reason to believe that IV antibiotic treatment would be superior to oral doxycycline (Ljostad et al., 2008; Halperin et al., 2007)  |
| Will prior treatment of Lyme disease prevent development of peripheral neuropathy?  | Oral antibiotic therapy for Lyme disease may not prevent development of peripheral neuropathy (Logigian and Steere, 1992; Logigian et al., 1990; Steere et al., 1994; Halperin et al., 1987, 1990) | IV antibiotic therapy for Lyme disease may not prevent development of peripheral neuropathy (Logigian and Steere, 1992; Logigian et al., 1990)  |
| Concomitant Lyme encephalopathy   | Present in the majority of cases (Logigian and Steere, 1992)   | Not mentioned at all in other studies (Halperin et al., 1987)   |
| Electrophysiologic studies in nonhuman primates infected with <i>B. burgdorferi</i> | Abnormalities of peripheral nerves found by one group of investigators (Roberts et al., 1998; England et al., 1997)  | Such abnormalities were not found by a second group of investigators (Estanislao and Pachner, 1999; Pachner, 2001); it was suggested that the group that found these abnormalities had not performed rigorous baseline studies (Estanislao and Pachner, 1999) |

of antibiotic resistance. This approach may also lead to a delay in determining the actual diagnosis, as one of the authors (GPW) has witnessed with a young patient with neurologic dysfunction from B12 deficiency, who was treated for Lyme disease because of 2-tier IgG seropositivity to *B. burgdorferi* before the correct diagnosis was even considered. The patient developed worsening of his neurologic deficits during this time delay.

Another author (PGA) found only 2 patients with possible Lyme disease-related sensory peripheral neuropathy among 1261 patients referred to an academic medical center for consultation between 2000 and 2013. Neither of these 2 patients had a clear association or temporal onset with other objective findings of Lyme disease but both had 2-tier IgG seropositivity to *B. burgdorferi*. Both patients had normal cerebrospinal fluid (CSF) findings including negative results for intrathecal production of *B. burgdorferi* antibody. One patient received courses of doxycycline and ceftriaxone with no change in neuropathy characteristics over 239 days of follow-up. The other patient who was diabetic was treated with 60 days of doxycycline but had worsening of the neuropathy over 3183 days of follow-up. The lack of improvement or worsening despite antibiotic therapy argues against causality due to Lyme disease in these patients, and differs from the more favorable outcome described in prior reports from United States (Halperin et al., 1987, 1990).

Peripheral neuropathy is a common neurologic disorder with multiple causes (Watson and Dyck, 2015). The prevalence of peripheral neuropathy is 2.4% in the general population rising to an estimated rate of 8% in individuals older than 55 years (Watson and Dyck, 2015). In up to 25% of cases, no etiology is identified (Watson and Dyck, 2015). In addition, there is a decline in vibration sensation with normal aging. Almost 25% of individuals who are ≥65 years old have reduced or absent vibration sensation on physical examination (Watson and Dyck, 2015). The frequency of potential misdiagnoses of Lyme disease in

patients with peripheral neuropathy can be estimated based on the background rate of serologic reactivity to Lyme borrelia, which represents a combination of seroreactivity from symptomatic, as well as asymptomatic, prior infections (Hilton et al., 1999; Krause et al., 1996, 2014; Steere et al., 1998), plus the false positive rate of the testing per se (Table 3) (Dressler et al., 1993; Krause et al., 2014; Wormser et al., 2013). In the United States there are estimated to be 46 million adults at least 65 years of age (Administration on aging: aging statistics, n.d.). Assuming an 8% rate of peripheral neuropathy, at least 3,680,000 in this age group can be expected to have this condition. If the rate of false-positive results for serologic testing for Lyme disease is assumed to be 2%, as was recently reported (Krause et al., 2014), then at least 73,600 misdiagnoses of Lyme peripheral neuropathy may be expected just in this subset of the general population alone, if the evidence for the diagnosis was based only on serology and if all were tested for Lyme disease.

It is argued that the entity of distal symmetric peripheral neuropathy as a late manifestation of Lyme disease be systematically reevaluated and in such studies appropriately matched controls be included (Table 4). In a controlled study conducted in Norway, seropositivity to Lyme borrelia was found in 43 (21%; 95% CI, 15.3–26.7%) of 209 individuals with a chronic peripheral neuropathy (Mygland et al., 2006). However, 45 (18%; 95% CI 13.6–23.6%) of 247 healthy blood donors were also seropositive, a statistically insignificant difference  $P = 0.55$  (Mygland et al., 2006). In addition, the frequency of Lyme borrelia seropositivity among patients with peripheral neuropathy of unknown etiology was not significantly different from that of patients with peripheral neuropathy for whom the etiology (other than Lyme disease) had been identified (24/102 [24%; 95% CI, 15.7–33.0%] vs 19/107 [18%; 95% CI, 11.0–26.3%],  $P = 0.31$ ). Furthermore, 20 of the Lyme borrelia seropositive patients in this study who had a peripheral neuropathy were

**Table 3**

Estimated number of potential misdiagnoses of Lyme disease in 100,000 adult patients with peripheral neuropathy from various geographic areas in the United States.

| Geographic area                   | Background seropositivity rate for antibody to <i>B. burgdorferi</i> including false positives % (reference) | Number of potentially misdiagnosed cases per 100,000 persons with neuropathy |
|-----------------------------------|--|--|
| Long Island, NY                   | 4% (Hilton et al., 1999)   | 4000   |
| RI/MA                             | 9.4% (Krause et al., 2014)   | 9400   |
| RI                                | 7% (Krause et al., 1996)   | 7000   |
| Nonendemic areas for Lyme disease | 2% (Krause et al., 2014) (range, 0.5–5% [Wormser et al., 2013; Dressler et al., 1993])                       | 2000 (500–5000)  |

**Table 4**  
Potential future investigations to better understand whether a distal, symmetric peripheral neuropathy is a manifestation of late Lyme disease in the United States, and define appropriate management.

| Objective                               | Possible study design   |
|---|---|
| Establish the existence of this entity  | Evaluate the seroprevalence of IgG Lyme borrelia antibodies by 2-tier testing in patients with unexplained distal, symmetric peripheral neuropathy, compared with the seroprevalence in age, gender, ethnic group, and comorbidity matched controls from the same geographic area; in seropositive patients, consider sural nerve biopsy with application of molecular methods for detection of <i>B. burgdorferi</i> |
| Establish the benefit of antibiotics    | Conduct a randomized, double-blind, placebo-controlled treatment trial using ceftriaxone, with objective end points   |
| Establish the benefit of IV antibiotics | If IV ceftriaxone found to be efficacious, conduct a randomized, double-blind, controlled treatment trial comparing IV ceftriaxone with oral doxycycline  |

treated with ceftriaxone or tetracycline without any improvement (Mygland et al., 2006).

The few early studies in the United States that purported to show the existence of this entity were performed before the development of modern serodiagnostics (Centers for Disease Control and Prevention [CDC], 1995) and prior to a clear understanding of the clinical manifestations of *B. burgdorferi* infections. Thus, potentially serious methodologic concerns existed besides the lack of non-Lyme disease controls. Although all (Logigian and Steere, 1992), or nearly all, of the reported cases were thought to have other objective clinical manifestations of Lyme disease at, or prior to, the onset of the peripheral neuropathy, thus increasing the “pretest probability” of Lyme disease, none of the studies based the laboratory diagnosis of the patients described on 2-tier IgG seropositivity (Halperin et al., 1987, 1990; Logigian and Steere, 1992; Logigian et al., 1990). Such testing is now considered the standard of care (Centers for Disease Control and Prevention [CDC], 1995). Some of the patients regarded as having peripheral neuropathy as a manifestation of late Lyme disease were not seropositive by even a first-tier IgG test (Halperin et al., 1987, 1990; Logigian and Steere, 1992; Logigian et al., 1990). Some were only IgM seropositive and a few were only positive by a cellular diagnostic assay that has subsequently been shown to lack specificity (Zoschke et al., 1991). In addition, the concomitant evaluation for etiologies of peripheral neuropathy other than Lyme disease did not necessarily meet current diagnostic standards.

In conclusion, there is a substantial degree of uncertainty about the validity of the diagnosis of a distal, symmetric, large fiber, axonal peripheral neuropathy as a manifestation of late onset neurologic Lyme disease, especially when based on serology alone in the absence of any prior or additional concurrent objective manifestation of Lyme disease. This manifestation of late Lyme disease in the United States should be regarded as unproven, highly controversial, and in need of further rigorous studies to validate its existence and if it does exist, to establish appropriate management.

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