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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.

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