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EDITORIAL COMMENTARY

Posttreatment Symptoms in Lyme Borreliosis

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(See the Major Article by Wormser et al on pages 3118–24.)

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Lyme borreliosis (LB) is the most common vector-borne disease in the Northern Hemisphere, and its incidence is on the rise. Although the course of early LB is well described, the information on disease outcome remains limited. The first sign of infection is usually an expanding erythema migrans (EM) skin lesion, which is often accompanied with nonspecific symptoms. Comparisons of EM patients in the United States (US) and Europe revealed that such symptoms occur more frequently in the US than in Europe (60%–80% vs 30%–40%, respectively), which is likely a reflection of the different *Borrelia* species on the 2 continents. Regardless, treatment with appropriate antibiotic regiment for LB results in a favorable outcome in the vast majority of patients and treatment failure in terms of the infection and symptomology is relatively rare. Nonetheless, a subset of 5%–20% of patients continues to suffer from nonspecific symptoms, termed posttreatment Lyme disease symptoms (PTLDS), for months to years after antibiotics. The etiology of such symptoms is one of the most hotly debated yet poorly understood areas in LB.

A recent study of treatment efficacy in 1220 European patients with EM revealed that the proportion of patients with subjective symptoms attributed to LB decreases over time during the first year after antibiotic therapy for EM: from 31% before antibiotics, to 15% at 2 months, 10% at 6 months, and 6% at 12 months after start of antibiotics. Further stratification of patients revealed that the odds of incomplete response were higher in women (odds ratio [OR], 1.41), in older patients (OR, 1.95), and in patients who presented with disseminated disease (OR, 1.65). However, the strongest predictor of incomplete response was presence of LB-associated symptoms at enrollment (OR, 7.69). Despite these differences, the long-term outcome after start of antibiotics was generally excellent; 94% of patients were symptom-free 1 year after EM [1].

However, how about the 5%–20% of patients with PTLDS: what are the mechanisms involved, how to predict which patients will develop such symptoms, and how best to treat them? The rather strong association between LB-associated symptoms at enrollment and greater probability of PTLDS suggests that monitoring and studying such symptoms over the course of the illness provide important clues about pathogenesis and could also inform diagnosis and treatment. Yet, despite their association with preceding LB, these symptoms, which include myalgias, arthralgias, malaise, headaches, fever, and fatigue, are generally nonspecific, and with the exception of fever, they are subjective in nature, making them difficult to study. Moreover, similar symptoms are often present in other acute infections and chronic diseases, as well as in otherwise healthy population. Consequently, in designing studies on treatment outcome of LB, an important consideration is to first determine which symptoms to assess and attribute to LB; the criteria for their allocation; and how to assess their presence, severity, and duration.

A key challenge lies in how to determine if such symptoms are associated with preceding LB or not. Three European studies addressed this question by directly comparing symptoms in LB patients and control subjects who were followed systematically for 1 year to assess their posttreatment status [2–4]. The present study [5] is the first such study from the US. Since the clinical presentation and symptomology of early LB varies somewhat between North America and Europe [2, 6], the information from the US published in this issue of *Clinical Infectious Diseases* [5] is of special interest.

The approach taken by Wormser et al [5], which is sound, was to assess symptoms that are most commonly associated with EM and/or attributed to PTLDS. The authors selected 12 symptoms, of which 11 generally fulfilled this criterium. The only exception was cough, which was probably included as a "control" symptom that would not distinguish between LB patients and healthy controls. The frequency and severity of

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such symptoms were examined in EM patients and in matched control subjects followed prospectively for 12 months. At baseline, LB patients were more likely than controls to have symptoms, they had a higher number of symptoms, and their symptoms were more severe. However, as in European studies [2–4], at both 6 and 12 months, no significant differences were detected between patients and controls in the frequency or severity of these symptoms. This is intriguing given the differences in disease symptomology between the US and Europe and implies that despite different *Borrelia* genospecies and the clinical presentation of early LB, ultimately the prevalence and severity of PTLDS appear similar on both continents.

These findings suggest that although such symptoms accompany objective signs of LB and are usually perceived as being directly associated with LB, their presence does not convey specificity for LB, as they are also relatively common in the general population. This "noise" can be partly reduced by obtaining careful history of complaints prior to LB; for example, if symptoms appeared for the first time or were significantly increased with the onset of EM and no alternative explanation for their presence was found, such symptoms (new or increased) are more likely to be causally and not just temporarily associated with LB. Consequently, they better qualify as LB-associated symptoms than if similar problems had been present continuously or intermittently before the current illness. The situation is even more complicated for symptoms appearing after LB, because the majority of the general population has occasional headaches, joint and muscle pain, fatigue, and malaise, as well as a number of other conditions. Although the authors did not report on "new or increased symptoms," they did obtain additional information by asking participants at the 6- and 12-month visit whether a symptom had been present since the last study visit and if it lasted for at least 2 weeks. The duration of >2 weeks would likely exclude symptoms due to common respiratory, gastrointestinal, or other acute infections not related to LB.

The authors conclude that "the fact that similar types of persistent subjective symptoms also occur in control subjects, however, suggests that there are multiple potential etiologies for these symptoms, making it very challenging to be certain that the presence of symptoms consistent with PTLDS in a particular patient is correctly attributable to having had Lyme disease. An objective biomarker of PTLDS would be highly desirable to avoid misclassification of patients" [5]. This point is well taken and a growing number of studies have attempted to define objective biomarkers for PTLDS [7–9]. In general, such studies have implicated immune system abnormalities in greater disease severity during acute infection as well as post-Lyme complications. For example, in patients with EM, elevated levels of several inflammatory mediators associated with innate and Th1 adaptive immune responses correlated with more symptomatic early infection. Moreover, 2 studies, 1 in the US and 1 in Europe, evaluated inflammatory markers in EM patients followed systematically for 1 year to determine if such markers could predict PTLDS. Study in US patients demonstrated elevated levels of CCL19 in post-Lyme syndrome after EM [9], whereas the European study found elevated interleukin 23 levels in a subset of EM patients with post-Lyme symptoms [8]. In addition, antineuronal antibodies were associated with pain, neurocognitive, or fatigue symptoms years after LB [7]. However, none of these studies evaluated immune responses in the general population with such symptoms. Although dysregulated immune responses are likely a factor in at least some patients, thus far, there has not been consensus regarding a specific immune marker for PTLDS.

Given these findings, it may be necessary to first put this problem into a broader context of identifying biomarkers for such nonspecific symptoms in general. Demonstration of similar prevalence of "post-LB associated symptoms" in patients and control subjects, in both the US and Europe, raises questions regarding the specificity of these symptoms for LB. Moreover, the concept that the same symptoms may be initiated by different triggers implies that ultimately these symptoms are driven by similar mechanisms—that is, different stimuli induce similar pathways, resulting in analogous outcomes. Thus, it would be of interest to first identify biomarkers that would allow for early identification of those at greater risk for such symptoms not only after LB but also in the general population, and then try to identify markers that would be able to distinguish symptoms due to LB from other etiologies. Whether identification of such biomarkers is possible remains to be seen. However, at the very least, further studies of posttreatment symptoms after LB or other causes are needed to elucidate the pathogenesis of these conditions.

These findings also raise questions regarding appropriate treatment for patients suffering with PTLDS. Although persistent infection has been proposed as an explanation for post-Lyme symptoms after LB, 5 double-blind, placebo-controlled treatment trials in Europe and the US have not shown significant sustained amelioration of such symptoms with additional courses of antibiotics [10–13]. Moreover, microbiologic measures of infection in the postantibiotic period are usually negative. Additionally, as reported in this study and in previous European studies, the prevalence of LB-associated posttreatment symptoms is similar after EM and in healthy controls without a history of LB. Taken together, these studies imply that in the absence of evidence of infection, treatment of PTLDS should be symptom specific, and that further treatment with antibiotics for LB is likely to be ineffective and could be harmful.

In conclusion, the study by Wormser et al [5], as well as previous European studies, have made important contributions to the field both in terms of providing new information and a robust platform for study design; however, key questions regarding the etiology, diagnosis, and treatment of such conditions remain, and patients continue to suffer from adverse outcomes. This should serve as a stimulus and a foundation for future studies, which will need to involve additional comparison groups (eg, evaluation of patients with similar symptoms in other conditions) and well-defined clinical information, as well as the integration of the latest targeted and discovery-based experimental approaches to begin to decipher the etiology of PTLDS. It is important to note that post-Lyme complications can occur after other manifestations of LB. These complications may represent different syndromes involving different mechanisms than described here for nonspecific symptoms after EM, and they may require different study approaches optimized for each syndrome. For now, thorough clinical evaluation remains a critical component in the diagnosis, treatment, and follow-up of patients with LB.

Notes

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