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Commentary

Post-treatment Lyme borreliosis in context: Advancing the science and patient care

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The most common tickborne disease in both Europe and the United States, Lyme borreliosis (LB) can range from mild to severe forms of illness. If not recognized and treated during early localized disease, which typically presents as a large, slowly expanding erythema migrans rash, the *Borrelia* spirochete can disseminate, causing diverse pathologies including cranial neuritis, carditis, meningitis, and acute arthritis. Although most patients with LB recover completely when treated with antibiotics, some report persistent symptoms of fatigue, pain, or cognitive impairment lasting months or even years [1]. Because these symptoms are also ubiquitous in the general population, drawing a clear association between these lingering symptoms and treated LB has remained elusive.

In this issue, Ursinus and colleagues attempt to disentangle post-LB symptoms from prevalent background conditions by comparing symptoms over the course of a year across three main cohorts: patients being treated for acute, physician-confirmed LB; people reporting a recent tick bite but without a LB diagnosis; and a randomly selected cohort drawn from the general population [2]. They find that fatigue, pain, and cognitive complaints lasting more than 6 months were common in all cohorts. Approximately 1 in 5 persons in the general population cohort reported such symptoms, similar to the 30% estimated in a recent large population-based study [3]. Symptoms were significantly more common and more severe, however, in the treated LB cohort. The absolute difference was small, only 6% and 4% greater than among the general population and tick bite cohorts, respectively. Nonetheless, these percentages can equate to a substantial burden in areas where LB incidence is high.

The study by Ursinus and colleagues has several key strengths including a prospective design, appropriate reference cohorts and use of validated symptom scoring tools. Community engagement and an online mobile app, originally designed to increase citizen access to

tick bite prevention and reporting [4], was leveraged to enroll participants into the LB and tick bite cohorts. Notably, the study also included a fourth cohort comprised of patients with chronic symptoms self-attributed to unconfirmed LB. This is a group of patients who often report being neglected by the scientific and clinical community [5]; their inclusion provided an important opportunity to compare their symptoms with those of the other cohorts simultaneously using the same tools and metrics. Finally, the large sample of the study provided sufficient power to detect small but real increases in symptoms above those of the general population.

Previous studies have found that symptom persistence occurred more often among LB patients with severe presentations and longer delays before treatment [6]. In the current study, patients with disseminated LB reported a higher prevalence of fatigue and pain at enrollment than those with erythema migrans; however, these differences disappeared within 6 months. Among the fourth cohort with chronic symptoms self-attributed to unconfirmed LB, reported symptoms were significantly more prevalent, more severe, and associated with greater functional impairment throughout the 12-month study period, as compared to patients with confirmed LB. While confirming the suffering of these patients, these findings suggest that the two patient populations are fundamentally distinct, likely reflecting the inclusion of patients with other disease etiologies.

Several questions regarding post-LB symptoms remain [7]. First, are these specific to Lyme disease or do they occur with similar frequency following other acute infections? Second, assuming they are particular to LB, what is the mechanism? Are they the result of occult but persistent infection, or are they the product of post-infectious autoimmunity or immune dysregulation? Persistent symptoms after acute infectious disease are not uncommon and have been well described for many other etiologies, from Epstein Barr virus to COVID-19. Additional studies are needed to better understand whether genetic, immunological, or metabolic factors might predispose to persistent symptoms after exposure to certain infectious pathogens, and whether modifiable factors, such as lifestyle or anxiety, might have a role in potentiating symptoms [8].

The findings of Ursinus and colleagues support the perception that some patients experience persistent symptoms after receiving treatment for confirmed LB. They also confirm the challenges faced by providers attempting to distinguish symptoms related to Lyme disease from those that are prevalent in the general population. Without clarity regarding the pathophysiology of such complaints,

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clinicians should recognize their patients' lived experiences and promote evidence-based, multi-disciplinary support systems that strive to optimize patient function and quality of life.

The occurrence of persistent post-LB symptoms is yet another reminder of the urgent need for more effective prevention strategies for tickborne diseases. Encouraging individuals to employ daily preventive behaviors, such as applying repellent and performing tick checks, has proven insufficient as demonstrated by steadily increasing LB incidence. Similarly, environmental means of tick control have yet to demonstrate sufficient potency against human tick encounters or disease [9]. Fortunately, safe and effective vaccines for Lyme disease may be on the horizon [10], which could both reduce LB incidence on a population scale while averting long-term patient suffering.

Authors' contribution

GEM conceptualized and wrote the original draft. AFH and PSM reviewed and edited the manuscript.

Declaration of Interests

The opinions expressed in this commentary are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. We declare no competing interests.

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