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Chronic infection in 'post-Lyme borreliosis syndrome'

From STEVEN E PHILLIPS, JOSEPH J BURRASCANO, NICK S HARRIS, LORRAINE JOHNSON, PATRICIA V SMITH and RAPHAEL B STRICKER*

Cairns and Godwin provide strong evidence that patients with Lyme borreliosis may have persistent fatigue, musculoskeletal pain, and neurocognitive difficulties despite 'adequate' antibiotic therapy.[1] The authors state that 'ongoing infection has not been excluded' in these patients with 'post-Lyme borreliosis syndrome'. Based on the evidence, we postulate that ongoing infection is the most likely explanation for chronic Lyme disease symptoms.[2–6]

Recent molecular, biochemical, and immunological studies of *Borrelia burgdorferi*, the causative agent of Lyme borreliosis, have demonstrated the complexity and elusiveness of this tick-borne spirochete.[3,6,7] The Lyme spirochete possesses functional properties that are found in other agents of chronic infection, such as *Mycobacteria*, *Brucella*, and *Treponema* species.[7] Thus it is highly likely that *B. burgdorferi* would evade both the human immune response and perfunctory antibiotic therapy to produce chronic infection in certain patients, especially those who initially go untreated owing to lack of recognition of the tick-borne disease or those who are coinfected with other tick-borne agents such as *Babesia, Anaplasma, Ehrlichia*, and *Bartonella* species.[3,6] In fact, the medical literature contains numerous examples of persistent human infection with *B. burgdorferi*.[3,6]

What is the evidence for 'post-Lyme borreliosis syndrome', defined as the persistence of symptoms in the absence of chronic infection with *B. burgdorferi*? Cairns and Godwin cite a study that found negative PCR testing in blood samples from 1800 patients with chronic Lyme disease. This study has been criticized for the lack of sensitivity of its non-nested PCR testing because it is highly unlikely that not a single patient in this Lyme disease cohort would have a positive PCR test.[3,5,6] Moreover, it is widely recognized that when minimal numbers of organisms are present in the blood, a negative blood PCR test does not exclude the presence of infection because rigorous tissue sampling may yield positive results.[8,9] For example, a necropsy study in dogs using PCR analysis of 25 tissue samples per dog demonstrated persistent infection after treatment.[9] Thus the argument that negative blood PCR testing excludes persistent infection is erroneous.

Cairns and Godwin also cite the hypothesis that infection with *B. burgdorferi* may trigger some autoreactive inflammatory processes leading to persistent symptomatology. Despite the attractiveness of this hypothesis, there is no convincing evidence to support it, and attempts to identify a candidate autoantigen have consistently failed.[3,6,10] The studies that have shown persistent inflammation in animal models of chronic Lyme disease have not excluded ongoing infection, and persistent

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infection with *B. burgdorferi* has been demonstrated in mice, dogs, and chimps with experimental Lyme disease.[3,6] Thus we are left with the strong assumption that chronic Lyme disease is caused by chronic infection with the Lyme spirochete.

As long as the medical community perceives chronic Lyme disease as an untreatable process that will somehow disappear with faith and prayer, patients with the debilitating symptoms of this disease will continue to suffer. Conversely, if the persistent symptoms described so elegantly by Cairns and Godwin are recognized as markers of chronic infection, then treatment of patients with chronic Lyme disease will become a logical approach, and the suffering of patients with chronic Lyme disease symptoms will be alleviated.

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Author's response to comments by Sigal and Hassett, Phillips *et al.*, and Shapiro *et al.*

From VICTORIA CAIRNS

In 1995, Sigal[1] wrote 'We must be aware of the mythology surrounding Lyme disease in our communities and counter with facts and the results of scientific studies'. To do this, we pooled the data from all scientific studies on random selections of patients who had had a diagnosis of Lyme borreliosis (LB) a few years earlier and, for comparison, random selections of subjects without LB from the general population. The prevalence of symptoms in LB patients was over and above the underlying prevalence of symptoms from other diseases such as fibromyalgia in the general population. Our meta-analysis[2] shows clearly that a small percentage of patients with LB have symptoms persisting for years. No other data have been provided that contradict this.

Inevitably, diagnoses based on subjective patient reports are prone to error, particularly of post-LB syndrome where the original diagnosis of LB may be in doubt. Steere *et al.*[3] concluded that a large proportion (57%) of patients referred to their Lyme Disease Clinic had not had LB, but these patients would not be representative if many were selected for referral because their diagnosis was uncertain. Fatigue, musculoskeletal problems and neurocognitive difficulties are relatively common in the general population, and, as pointed out by Shapiro *et al.*,[4] some LB patients with symptoms due to other disorders may misattribute them to post-LB syndrome. In their commentary Sigal and Hassett[5] report that many of the patients referred to their centre had fibromyalgia, and not post-LB syndrome. The pain following LB seems to be mostly roving, asymmetrical pain in the limbs, which is unlike the pain required for a diagnosis of fibromyalgia.[6] So, although fibromyalgia is often accompanied by fatigue and forgetfulness, it should usually be distinguishable from post-LB syndrome. Uncertainty and misdiagnosis in some patients does not mean that these two disorders are not distinct entities. There is clearly a potential for misdiagnosis of post-LB syndrome, and that is an important issue, but it was not the topic of our meta-analysis.

Sigal and Hassett report that many of the patients with post-LB syndrome referred to their centre had positive scores on depression and anxiety scales. Depression and anxiety scales often include symptoms such as fatigue, listlessness, slowed speech, difficulties in working, concentration and memory problems, muscle aches and pain, increased sweating, and weight changes, all of which may be symptoms of post-LB syndrome. And with the distress that often arises from such a chronic illness, it is not surprising if some patients have positive scores on these scales. They also state that this disorder is seen predominantly in women implying this is evidence that it has a psychological basis. Fibromyalgia and many autoimmune diseases are also seen more often in women. It cannot therefore be concluded from their observations that the persistent symptoms following LB are simply due to psychological disturbances.