Reply to Seligman et al

To the Editor—In their letter [1], Dr Seligman et al point out inherent difficulties in studies of post-Lyme symptoms. These include the marked variability in the severity and duration of the pain
and fatigue symptoms that may follow Lyme disease, the relatively small number of patients who experience post-Lyme disease symptoms, and the probable multifactorial nature of the underlying pathogenetic mechanisms, which may include both microbial and host genetics. Moreover, such symptoms are common in the general population and may be unrelated to Borrelia infection.

We studied the largest group of patients available who were evaluated for erythema migrans, treated with 10–15 days of antibiotics, and followed prospectively for 1 year [2]. These patients were from Slovenia and predominately B. afzelii infection. The most common post-treatment symptoms were arthralgia, headache, and fatigue. These symptoms were mild-to-moderate in intensity, they were not incapacitating, and they usually resolved in most patients within months. Twenty-five of the 45 patients in our study who had post-Lyme disease symptoms had persistently elevated levels of interleukin 23 (IL-23), a cytokine that is important in the expansion and maintenance of Th17 cells, implicating dysregulated Th17 immune responses in the pathogenesis of post-treatment symptoms in these patients. Moreover, the magnitude of the IL-23 response appeared to be important. All patients with the highest IL-23 levels (>230 ng/mL) had post-Lyme symptoms. We also found elevated levels of Th17-associated mediators CXCL9 and CXCL10 in most patients, but they did not correlate with post-treatment symptoms. We did not find elevated serum levels of interferon α (IFNα) in our patients.

Dr Jacek and her colleagues studied quite a different group of patients [3]. They tested 19 patients from the United States with a history of Lyme disease a median of 6 years previously and who currently had neurocognitive impairment. Compared with control subjects, sera from their patients induced higher expression of IFNα response genes in WISH cell lines, suggesting that type-1 IFN responses may play a role in their neurocognitive symptoms. However, protein levels of IFNα in serum, cerebrospinal fluid (CSF), or cell supernatants were not determined. Thus, although both studies implicated immunologic mechanisms in some post-Lyme disease patients, the underlying mechanisms appear to vary between these 2 different patient groups.

We agree that both host and spirochetal genetics likely play a role in the immune responses implicated in the development of post-Lyme symptoms. In our previous work [4], a host TLR1 polymorphism in patients infected with the particularly virulent B. burgdorferi RST-1 (OspC type A) strain resulted in greater inflammation, more symptomatic early infection, and more frequent antibiotic-refractory Lyme arthritis. Thus, certain host risk alleles in combination with particular spirochetal strains predispose susceptible individuals to excessive inflammation and immune dysregulation. Unbiased, discovery-based approaches, such as whole exome sequencing and transcriptomics analyses, are powerful new techniques to identify other risk factors for disadvantageous immune responses. Identification of immune abnormalities holds promise for new treatment strategies for this challenging clinical problem.

References


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