Lyme Disease Presenting as Chronic Fatigue Syndrome

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ABSTRACT. *Objective*: Chronic Fatigue Syndrome (CFS) by definition represents a diagnosis of exclusion. Late stage or "Chronic Lyme" infection with or without "co-infections" is a difficult diagnosis to establish. The symptom complex of both conditions can be very similar. This case study represents an attempt to support serious consideration for a subpopulation of patients otherwise diagnosed with "CFS," as actually representing chronic Lyme disease.

Method: A case study is presented of a 33-year-old man, who for two years, was being managed as having CFS. However, after ~2 years of utilizing multiple modalities of management with limited success, the diagnosis of Lyme disease was reconsidered. Historical exposure risks to Lyme disease in this individual were high. He had prolonged exposure in the highly tick-infested mountains of North Carolina for 18 months, several years prior to becoming ill. More aggressive investigation confirmed the diagnosis of Lyme disease. Appropriate changes in management were associated with an improved level of functioning that was far in excess of what maximal management of CFS was able to achieve.

The features of CFS and chronic Lyme disease can be very similar and include the following.

Profound fatigue often associated with cognitive impairment. Other common symptoms related to both of these conditions include sleep disturbances, fibromyalgia, and dysautonomias. In pursuing clarification of this diagnosis, the author was exposed to a contrast in medical opinion regarding diagnostic tools and criteria that were perceived as creating

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potential barriers to the management of patients presenting with these symptoms.

Conclusion: Acceptance and awareness of the possibility that Lyme disease can present as CFS has important therapeutic and prognostic implications. doi:10.1300/J092v13n04_06

KEYWORDS. Lyme disease, chronic Lyme disease, chronic fatigue syndrome, CFS, fatigue

INTRODUCTION

Chronic fatigue syndrome is an entity defined by the Chronic Fatigue Syndrome Study Group as a chronically fatiguing illness that leaves an individual at a functional capacity of <50% of their pre-morbid state for > 6 months, such that other causes of chronic fatigue have been ruled out (1,2). This is felt to represent a multisystem process (3), manifesting with varying degrees of fatigue, pain, and cognitive dysfunction. Because there are no consistent, pathognomonic markers, CFS is a "diagnosis of exclusion." In essence, other forms of chronic fatigue need to be ruled out prior to establishing this diagnosis.

Lyme disease or Lyme borreliosis is a well-accepted process that has the distinction of being placed on the differentials for multiple syndromes. Unfortunately, there exists a significant degree of controversy in the literature, as to the diagnosis and management of Lyme disease. In the last 10 years, two standards of care have evolved for the diagnosis and treatment of Lyme disease (4,5). These standards are represented by the guidelines of the Infectious Diseases Society of America (IDSA) (6) and the guidelines of the International Lyme and Associated Diseases Society (ILADS) (7). As a result of this confusion, the identification of Lyme disease can often be wrought with difficulty. This, thus, can contribute to delay or frank inability in distinguishing between the enigmatic etiology of chronic fatigue syndrome, versus a subpopulation of CFS patients, who actually represent the infectious syndrome of chronic Lyme.

Case Study

In order to address the aforementioned diagnostic conundrum, the author presents the case of a 33-year-old male, who fulfilled established

criteria for CFS but was later characterized as fulfilling CDC criteria for Lyme disease. DB presented with an ~6-month history of progressive, debilitating fatigue with a questionable "event" in the fall of 2002, described as an episode of "severe fatigue" and "aches." His pre-morbid state was that of an active law enforcement official, who regularly participated in the martial arts. By the time he was seen by me, he was unable to function at all at work and barely with his ADLs. He had described several post- exertional "crashes" that left him bed-bound. Other symptoms included "profound unrefreshing sleep, cognitive fog, mild headaches, and nausea."

His past medical history was otherwise unremarkable. His only medication of significance when presenting to my office was florinef that had been initiated by a cardiologist ~2 weeks prior. The initial exam was significant for the lack of orthostatic change in either heart rate or blood pressure with a standing BP of 114/70 and HR of 68. A standard workup was only remarkable for a total testosterone level of (L) 210 (241-827 ng/dL). Testosterone replacement offered mild benefit to energy and a sense of well-being. Other labs, including HCV, HHV 6 by PCR, HIV and several tests for *Borrelia burgdorferi*, in keeping with CDC "two-tiered" analysis by ELISA, were all negative. Rheumatologic and metabolic studies were normal. Specialized labs included initial Insulin Like Growth Factor 1 of 224 ng/ml with an IGF BP3 of 4.7 mg/L and a ratio of 21, for which Acclydine was initiated. This, too, offered mild clinical benefits, particularly with respect to energy and loss of these benefits when the medication was not taken.

Another modality of therapy that was associated with mild clinical improvement included high dose Vitamin B12 (hydroxocobalamine) delivered by IM injection at 10,000 mcg three times weekly. November 2003 NK cell activity of 6.2% (4.5-20.4%) was associated with initiation of a six-month protocol of Immunivir (Isoprinosine), with minimal benefit.

In the summer of 2005, a reevaluation for the potential of tick/*B. burgdorferi* exposure was entertained. With this in mind, the patient recognized historically ~18 months of sustained high risk exposure. A laboratory reevaluation, going directly to Western blot technology (through Igenex labs) (8), revealed a positive IgM by CDC criteria (with the following positive bands: 2+ for 30 and 31 and 1+ for 18, 34, 39, 41, 45, 58, and 93) . The western blot IgG was "negative" (including 1+ bands for 30, 41, and 58 and indeterminate bands for 18, 31, 39, and 66). The Igenex and Medical Diagnostic Laboratory co-infection profiles were negative. The patient's diagnosis at that point was changed from CFS to chronic Lyme with "CFS-like" features and started on an ILADS approved

course of antibiotics. Within a month or two of starting antibiotics, the patient described a significant improvement in sleep, such that he no longer required prescription medication to initiate or maintain his sleep. Endurance and fatigue were described as being better, with extended windows of functionality "that I haven't had in years."

DISCUSSION

CFS is a diagnosis of exclusion. In essence, there are no "markers" that have been consistently established to definitively make the diagnosis of chronic fatigue syndrome. Lyme disease was first reported as an outbreak of juvenile rheumatoid arthritis by Steere et al. (9). Lyme disease is also felt to be a complicated multi-system disorder caused by the spirochete *B. burgdorferi* sensu lato complex (10,11) transmitted by *Ixodes dammini* and other related ixodid ticks (12,13). Following the introduction of *B. burgdorferi* into the skin by an infected tick, the organisms begin to spread both locally and systemically. Several days typically elapse before the appearance of the first sign of infection, that is, erythema chronicum migrans (ECM) or other less typical rashes (14). The time period during which the organisms are being disseminated to their target tissues and cells is approximately 2-4 weeks after inoculation. Approximately 4-6 weeks following the tick bite, the first systemic symptoms (other than multiple rashes) occur in some patients, usually in the form of "flu" (15). While the Lyme-"flu" symptoms can spontaneously resolve, patients can experience recurrent "flu." Soon after the onset of Lyme-flu, fatigue, arthralgias and/or myalgias may begin. In fact, as previously described, chronic or "late stage" Lyme disease can clinically be indistinguishable from chronic fatigue syndrome.

The organism *B. burgdorferii* has evolved multiple mechanism to elude host immune recognition. Given that the majority of diagnostics available to characterize this infection utilize different aspects of the immune response, it is not surprising to consider that present technology is far from ideal in allowing appropriate characterization of this infection. In essence, immune parameters are often falsely negative and this diagnosis is often not made (16-19).

ELISA has been shown to be an unreliable test in many patients with Lyme Disease, both in early infection and later disease. Nineteen studies performed by the group responsible for the Lyme disease proficiency testing for the College of American Pathologists (CAP), suggest that currently available ELISA tests do not have adequate sensitivity to meet the

"two-tiered" approach recommended by the CDC for surveillance (20). Over 75% of patients with chronic Lyme Disease are negative by ELISA, while positive by Western blot (20-22). The Western blot is recognized by the National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), as the most useful method for detecting *B. burgdorferi* antibodies currently available (23).

The issue of seronegativity is significant. Studies have ranged from 20% to 80% of documented Lyme disease patients having detectable serologic responses (7,20-22). PCR (polymerase chain reaction) is a highly sensitive means to detect microbial DNA or RNA. It was hoped that this technique would find an important role in the diagnosis of Lyme disease. Thus far, however, despite the specificity of this method, borrelial DNA or RNA has not been reliably detected in the blood, urine, or spinal fluid of patients with early or later forms of Lyme disease. Currently, the Western blot assay is the most reliable immunologic test (19).

There are several proposed mechanisms for the aforementioned difficulties in testing and eradication of *B. burgdorferi.* For one, the organism is felt to be sequestered in a protective niche, related to the tendency to reside within cells (25-27). Sites such as joints, eyes and CNS contain extracellular fluids (synovial and cerebrospinal) that do not circulate through conventional lymphatics. In essence, *Borrelia burgdorferi* can potentially reside in virtually immune protected environments. In doing so, the likelihood of the host's immune system mounting a consistently reliable immune response is minimized.

Surface antigenic modulation has been described by Schwan et al. (28). De Silva et al. confirmed this finding by comparing spirochetes in unfed versus fed ticks; immunofluorescent staining identified that OspA was present on spirochetes in unfed ticks but was lost after the blood meal (29). Henderson et al. also described this "on and off" switching of phenotype expression. *B. burgdorferi,* in essence, has the capacity to respond to the environment and create a more heterogeneous population (30).

Embers and colleagues described several other "survival strategies" of *B. burgdorferi* (31). These included induction of anti-inflammatory cytokines and the formation of immune complexes (antigen:antibody aggregates) that tie up host antibodies. Immune complexes may potentially decrease the likelihood that an immune response would be detected using present technology (32). In addition, *B. burgdorferi* has been shown to change to a cyst form (spheroplast L-forms) when exposed to a hostile environment (such as the lack of fatty acids in the growth medium) (33-35). *B. burgdorferi* has been shown to shift to cyst forms with *in vivo* exposure to beta-lactam antibiotics (36). In addition, cysts have

been shown to change back to spiral forms *in vivo* (37). As Brorson and Brorson describe, when neuroborreliosis is suspected, it is necessary to realize that *B. burgdorfferi* can be present in a cystic form. That this characteristic may very well "explain why cultivation of spinal fluid often is negative with respect to *B. burgdorferi*."

Given the myriad protective mechanisms that *B. burgdorferi* can utilize, it comes as no surprise that multiple authors have described evidence for the persistence of Lyme infection in patients who otherwise were felt to have been treated "adequately" according to the IDSA recommendations (38-44). In particular, Phillips and colleagues were able to actually culture *B. burgdorferi* in 43/47 (91%) of patients who had relapses after long-term oral and intravenous antibiotics. Interestingly, the mix of serologic findings was consistent with the relative inadequacy of present technology to identify this entity. In particular, although almost all cases had serologic evidence suggestive of infection with *B. burgdorferi,* few had positive ELISAs and only a little over half met CDC serologic criteria for Western blot positivity. Of the 47 patients 4 (9%) were positive by Lyme ELISA, 3 were equivocal by ELISA, 26 (55%) were positive by CDC criteria for Lyme Western blot. Of these 26 positive cases by CDC criteria 20 (77%) were IgM positive, 10 (38%) were IgG positive, and 4 (15%) were positive for both IgM and IgG.

The literature supports the potential of several "co-infections" that may be associated with Lyme disease. Although a more complete treatise on co-infections is beyond the scope of this report, the most likely agents to play this role include: *Ehrlichia sennetsu* (45-47), *Bartonella henselae* (48,49), and *Babesia microti* (45,50-52). Reports suggest that co-infections with one or more of these agents can both exacerbate the presenting symptoms of Lyme disease and decrease response to therapeutics.

CONCLUSION

Patients with symptoms that are consistent with chronic fatigue syndrome should be seriously evaluated for the potential of chronic Lyme infection. Common features in both conditions include profound fatigue, sleep, and cognitive impairment, along with fibromyalgia and dysautonomias, In addition, if chronic Lyme is determined to be present, then evaluation for the potential of co-infections with *Ehrlichia sennetsu, Bartonella henselae* or *Babesia microti* should be undertaken. In doing so, we are more likely to effectively reverse the chronic, often debilitating processes with which our patients are so often presenting.

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