The Epistemic Fallacy: Unintended Consequences of Empirically Treating (Clinically Diagnosed) Chronic Lyme Disease in a Soldier

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Abstract

We document a military patient presenting with a diffuse set of symptoms suggestive of chronic Lyme disease (CLD) and the subsequent empiric treatment and health complications arising therein. The lay medical community, spurred by the internet, has ascribed these diffuse symptoms to various illnesses including CLD without confirmatory serological evidence of any underlying disease. With a growing community of patient advocates, CLD has become an illness with broad and highly generalized list of clinical symptoms and an absence of agreed-upon confirmatory laboratory tests. Further complicating matters, diagnostic criteria and treatment protocols differ between the Infectious Diseases Society of America and the International Lyme and Associated Diseases Society guidelines. Clinicians also face serious challenges in diagnosing and treating patients who present with generalized symptoms and close to 50 diagnostic tests for Lyme disease available in North America. Further complicating the picture for military patients seeking medical confirmation of a disease and resolution of their symptoms, medical fitness boards use putative diagnoses as prima faciae evidence in disability. Here a military patient with a long list of complaints that defy any clear or easy diagnosis and treatment is discussed. However, these symptoms taken together with selectively summed notes in the medical record in the absence of convincing and clear laboratory confirmation are suggestive of CLD and its complications, but no resolution was ultimately reached. With the presumptive determination of a medical disability due to CLD by the medical board, the medical dismissal of this service member from active duty occurred.

Introduction

Patients with a variety of debilitating symptoms, but without clear diagnosis, find themselves desperately seeking guidance from practitioners for resolution of systemic complaints. They may press medical care providers for a diagnosis which can result in treatment in the absence of definitive laboratory identified disease, an issue which has broad consequences. This situation, which results from the limitations of diagnostic testing and treatment options faced by providers and patients suffering from chronic illness, affects a large community of patients across the country including members of the military and their families. Furthermore, many have been quick to jump to the conclusion of a Lyme disease (LD) diagnosis due to a common perception of unreliable and inconsistent testing.[1,2] This development has provided the opportunity for LD to become the scapegoat of a variety of systemic and otherwise undiagnosed illnesses. Additionally, protocols differ between Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS) guidelines and can lead to confusion in LD diagnoses.[3] For example, the IDSA, in alignment with the Center for Disease Control and Prevention (CDC), touts a clear decision-tree style, two-tier approach to the assessment and diagnosis of LD.[4] Alternatively, ILADS openly challenges the definitive aspects of the IDSA

approach and claims that its two-tier protocol does not adequately serve patients or providers.[5] Thus, it is critical to reiterate proper diagnoses really have an impact. It is the difference between initiating an appropriate intervention with positive improvement in symptom presentation or a patient whose condition inexplicably worsens to the point of disability.

During the medical review board process within the US Army, diagnoses can be rushed and based on empirical evidence in order to fit neatly into the diagnostic rating system utilized by the Army Physical Evaluation Board as well as Veterans Affairs. This process as well as the confusion between IDSA and ILADS protocols caused CLD to be focused on for this military patient, which led to years of various ineffective and damaging treatments. Ultimately, this patient ended up being empirically treated for clinically diagnosed CLD and lost his health and military career in the process.

Case Presentation

A 21-year-old male, Division I student-athlete patient presented with heart palpitations and frequent unprovoked adrenaline rushes and was sent to a health clinic in November 2015. Based on a normal cardiac exam, his symptoms were attributed to stress and no significant treatment was pursued. His condition continued to fluctuate in severity and symptomology, which led the treating physician to conduct the following serological testing and results in March 2016: Lyme disease—negative, thyroid peroxidase—negative, Epstein-Barr virus (EBV)—positive, and heterophile antibody test (monospot)—negative. At this point, the patient was diagnosed with EBV reactivation and prescribed rest and recovery. However, a few months later, in May 2016, he graduated and was commissioned but remained on medical hold since his symptoms had not subsided. At this time, he was prescribed further rest and recovery by another treating physician until symptoms resolved, at which point he could continue onto training. However, the patient never attended training since his persistent mononucleosis-like symptoms and history of traumatic brain injury from sports and military service caused concern for post-concussion syndrome.

The patient was seen by a team of health care providers who collaborated in assessing him with a final recommendation of rest and recovery. Hyperbaric oxygen therapy (HBOT) was also discussed, so the patient began HBOT therapy with a private physician. This therapy was discontinued after two sessions due to increasing symptoms (heart palpitations, flank pain, myalgia, neuropathy, etc). Searching for answers and now on active duty, in September 2016, the patient was seen by a new health care provider who requested follow on serological testing for LD. This test reported negative results, but the patient was clinically diagnosed with LD due to symptom presentation, potential for exposure in military training, and lack of other definitive findings.

The patient was subsequently treated with 30 days of doxycycline (150mg/day). Due to persistent neuro-immune symptoms after antibiotic treatment, the patient sought out a second opinion from a LD specialist. By December 2016, the specialist ordered multiple LD tests standard to the IDSA and the CDC requirements. All of the LD tests performed were negative, but another 30-day course of doxycycline (150mg/day) was prescribed. This treatment course led to worsening symptoms in much the same way as the HBOT did including joint pain, intermittent nerve pain, headaches, fatigue, cognitive difficulty, anxiety, mild depression, and increased chest and flank pain. These symptoms led the LD specialist in January 2017 to conclude that a Jarisch–Herxheimer reaction was occurring, so he had the patient submit a serum sample for further testing at an independent laboratory with non-traditional *Borrelia burgdorferi* (bacterial cause of Lyme disease) IGeneX testing.[6] The serological testing revealed the following results as defined by the lab: *Borrelia burgdorferi* IgG/M/A—low positive, *Babesiosis microti* IgG/M—low positive, and *Anaplasma phagocytophilum* (HGA) IgM—low positive. In response to these results, the LD specialist ordered another 30-day course of doxycycline at a larger dosage (300mg). However, the treatment was discontinued after 1 week because it caused increases in the patient's flank, nerve, and joint pain. Looking for further validation of the LD diagnosis, the LD specialist had the patient submit more follow up serological testing for *B. burgdorferi* via a different private laboratory, all producing negative results. The patient's symptoms persisted and continued to increase in severity including anxiety and depression, which prompted a recommendation to visit a physician practicing in functional medicine.

Upon review of the case and patient, this functional medicine physician initiated her own work-up focusing more on the potential of mycotoxicosis due to increased susceptibility with CLD and mold exposure within living and training environments. This included submitting a buccal sample for genetic testing[7] in April 2017, looking for genetic indications in general limitations in detoxification pathways. Results revealed a homozygous single nucleotide polymorphism (C677T: T/T) in the Methylenetetrahydrofolate Reductase (MTHFR) gene suggesting the patient may have low activity of the MTHFR enzyme, which is a key factor in metabolic detoxification.[8] Based on this result as well as the patient's

background history, the functional medicine specialist tested him in June 2017 with a mycotoxin urine panel, which revealed strong positive results for mycotoxicosis. This physician then made a diagnosis of mycotoxicosis in addition to the clinical LD diagnosis already received, and the patient started receiving weekly infusions of IV phosphatidylcholine (up to 10 amps), IV glutathione (1200 mg), and IV Leucovorin (10 mg), as well as subcutaneous methyl B12 (1000 ug) for the next 3 months.

The patient experienced minor improvements in fatigue and stamina before the treatment became too costly to sustain out-of-pocket and was terminated. Following shortly after treatment termination, in October 2017, the patient was retested by the functional medicine specialist with the mycotoxin urine panel yielding negative results. However, the patient was still symptomatic and worsening in other areas. At this same time, the patient was recommended to the Army Medical Review Board to determine medical fitness to continue serving as an active duty officer. Due to continued chronic fatigue-like symptoms into November 2017, the following tests were run by the functional medicine specialist as well as an Immunologist and Neurologist (both referred to the patient by the functional medicine specialist) up to January of 2018, while the patient continued to experience persistent symptoms: investigating abnormalities in C-reactive protein, Sjogren's antibody (Ab), hepatitis, anticardiolipin Ab, antineutrophil cytoplasmic Ab panel, antinuclear antibodies IFA, Lyme Ab, C6 *B. burgdorferi*, bartonella DNA PCR, West Nile virus PCR, TNF-alpha, sensory neuropathy Ab, vasoactive intestinal peptide, melanocyte stimulating hormone, total IgG and IgE, mannose binding lectin, tryptase, chromogranin, human leukocyte antigen B27, and C3a. All of these tests yielded negative results. However, abnormal elevations in inflammatory immune biomarkers, such as C4a were continually discovered during testing.

During this time, the patient was unable to perform moderate or strenuous physical exercise or cognitive activity due to the following symptoms: cognitive impairment affecting short-term memory and ability to focus, severe fatigue and post-exertion malaise, asthma and increasing allergic-type reactions with chemical and food sensitivities as well as histamine intolerance, and progression to heat/ultraviolet induced urticaria. Additionally, the patient struggled emotionally with anxiety, depression, environmental stimulation (such as bright and flashing lights and loud noises), and sensitivity to stress. As a result of all these tests, the patient was diagnosed with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) following resolved acute mycotoxicosis by the functional medicine specialist. However, ongoing investigation and findings continued in order to better understand the root cause of the CFS/ME. By February 2018, the Army Medical Evaluation Board found the patient unfit for military service, and he was subsequently medically retired in June 2018 receiving 100% Veterans Affairs disability rating for the following: "Lyme disease, mycotoxicosis, chronic fatigue syndrome, allergic rhinitis and vasomotor rhinitis (physical evaluation board (PEB) referred as chronic Lyme disease, mycotoxicosis and chronic fatigue syndrome)."

Discussion

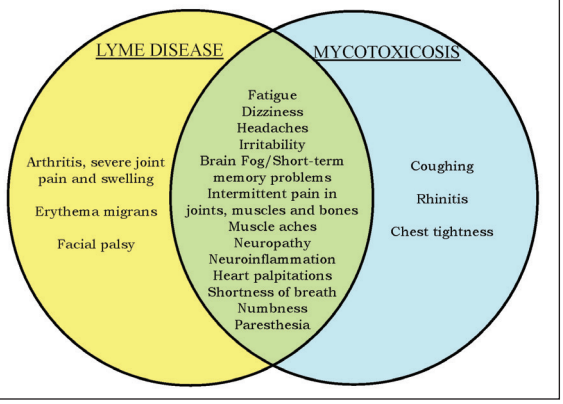
Here we present a set of complaints and diffuse symptoms commonly observed by medical practitioners. This presumptive case of CLD in the absence of clear and convincing laboratory confirmation and treatment guidelines, subsequent empiric therapy, and current practices by military medical boards resulted in the medical retirement of the service member. The current diagnosis and treatment of CLD is difficult at best for medical practitioners and may have serious unintended consequences for service members where military medical boards may make a presumptive determination of CLD and a recommendation for medical discharge in the absence of clear and convincing medical confirmation of disease.

This case shows how empirically treating and diagnosing symptoms can lead to a fishing expedition for the patient and multiple, unnecessary and potentially dangerous treatments. It also points to the importance of and need for clear testing/diagnosing guidelines. In this case, the numerous repeated seronegative results for *B. burgdorferi*, combined with the absence of erythema migrans and no known recent exposures, did not confirm a LD diagnosis. However, it is commonly accepted that LD, and, furthermore, CLD are clinically difficult to diagnose due to the sample type obtained for testing, the stage of the disease process, and the variations in the target type of the diagnostic assays used for detection.[1,2] Additionally, while both professional societies, IDSA and ILADS, continue to incorporate advances in laboratory-based diagnostic criteria or refinements in treatment regimes for LD, differences are pronounced, and patients are left with conflicting guidance. Furthermore, all of the currently available LD diagnostic tests have performance issues, which create concerns about the appropriate use and interpretation of these tests for both physicians and patients. So, when the low positive for *B. burgdorferi* on the non-traditional IGeneX test results were revealed, the LD diagnosis was believed to be solidified, especially when coupled with the presumed risk of the patient being exposed to *B. burgdorferi* infected

ticks because of his military duties.[9,10,11] These positive tests led to the preferred antimicrobial treatment for LD without any relief and, in fact, exacerbated the symptoms.

This worsening of symptoms prompted the subsequent testing of the patient for maladies to include mycotoxicosis. The patient had been exposed to mold in living and training locations, and there is a connection between CLD and increased susceptibility to other illnesses, including mycotoxicosis.[12,13] This susceptibility is thought to be because, although CLD patients may have antibodies to *B. burgdorferi* and generate memory B-cells to this pathogen, their humoral response is suppressed in the long term by the infection.[14] Additionally, although the symptoms of mycotoxicosis are dependent on the type of mycotoxin, length of exposure, age, sex, genetic predisposition, and prior health condition of the exposed individual, they include many of the same symptoms as CLD.[15] For this reason, it can be hard to distinguish between mycotoxicosis and LD when patients exhibit full-blown chronic symptoms of each (Figure 1).

Figure 1. Overlapping symptoms of Lyme disease and mycotoxicosis.



In regard to mycotoxicosis, the body's nonspecific immune defenses and detoxification pathways are typically able to eliminate mycotoxins as long as it is not suffering from some other chronic disorder or condition. In the case here, the patient had a MTHFR gene mutation. This specific mutation has been implicated in the MTHFR enzyme having a lower than normal activity with respect to methylation of protein intermediaries for a number of biochemical reactions in the body,[16] thereby potentially making exposure to mycotoxins much more difficult to control.

It is critical to highlight that while originating for different reasons, diagnoses such as CLD and mycotoxicosis share predominantly similar presentation of symptoms. This phenomenon is partly due to similar chronic activation of the immune complement system, in particular C3a and C4a, generating inflammation. In acute cases, spirochetes in LD and mycotoxins are both considered to be or to produce biotoxins, which perhaps leads to the shared symptomology. Complement proteins, C3a and C4a, are elevated in many LD patients. Symptomatic response to therapy in CLD often is associated with a decrease in C4a anaphylatoxins, whereas worsening symptoms often relates to an increase of this biomarker. Similarly, this inflammatory expression is seen following chronic mold exposure. Specifically, C3a levels will be normal while C4a levels will be elevated in mycotoxicosis.[17]

It is especially important to understand even the term chronic Lyme disease (CLD) can be confusing and refer to different patient populations that should not necessarily be grouped together. Four such populations include patients with post-treatment Lyme disease syndrome (PTLDS), patients with diffuse symptoms and unclear cause either diagnosed based on non-validated/unproven laboratory tests and/or clinical diagnosis, patients with an illness unrelated to *B. burgdorferi* infection, and patients exhibiting symptoms of late Lyme disease (encephalomyelitis, arthritis, etc.) who have antibodies against *B. burgdorferi*.[18] Of these four groups, most research and studies have been focused on PTLDS—how it is defined and possible causes.[19]

Ultimately, in the present case, it is unknown whether the military patient was initially exposed to *B. burgdorferi*, mycotoxins, or whether either of these two eventual diagnoses were actually responsible for initiating and progressing his illness. Yet, because of unreliable diagnostic testing and confusing standards for diagnosis, this patient was clinically diagnosed with LD and empirically treated for CLD and complications arising from it. This case serves as an example why it is extremely important to have clear guidelines surrounding a disease diagnosis and reliable, accurate diagnostic tests.

Conclusion

This case illustrates that an inappropriate clinical diagnosis and empirical treatment can be inherently detrimental to the health, safety, and well-being of the patient. Additionally, the amalgamation of perceived mistrust and limitations in LD testing combined with an eagerness to diagnose LD based on what may be considered "pseudoscience" is potentially harming patients with undiagnosed chronic illness. As far as the military's Medical Evaluation Board is concerned, a clinical diagnosis, whether confirmed with diagnostic tests or not, can result in removal of a service member from the military. This, along with the fact many chronic illnesses share

overlapping symptoms, beget the recommendation that resources be directed to further develop diagnostic tests and strategies to evaluate physical, neuro-cognitive, and behavioral symptoms alongside clinical testing in order to address the root cause of the illness. Potentially implementing genetic testing, immune complement (or other biomarker) testing, and imaging earlier in the diagnostic procedures of nonspecific and variable symptom presentation will lead to higher success rates in identifying predispositions, susceptibility, and co-infections as well as better inform effective and appropriate treatment. Ultimately, early detection and a more comprehensive understanding of and treatment plan for chronic conditions could help more service members return to being fit for duty, and restore the strength of our fighting force.

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