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Review

The conflict on posttreatment Lyme disease syndrome: a clinical mini review

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ABSTRACT

Is *Borrelia burgdorferi* responsible for the persistence of symptoms after the standard successful course of antibiotics in Lyme disease patients? This highly controversial issue, concerning the underlying mechanism of posttreatment Lyme disease syndrome (PTLDS), still seems to be a matter of intense conflict of opinion. PTLDS is the manifestation of nonspecific symptoms including fatigue, musculoskeletal pain, dysesthesias, and neurocognitive deterioration after the standard antimicrobial therapy administered to patients suffering from Lyme disease. In this article, we review the conflicting views and published highlights of recent human studies regarding PTLDS.

Key words: Antibiotic therapy; duration of therapy; Lyme disease; nonspecific symptoms; posttreatment Lyme disease syndrome

INTRODUCTION

There is no fundamentally widely accepted definition of posttreatment Lyme disease syndrome (PTLDS). This has led to confusion and controversies and to a lack of data on its incidence, prevalence, and pathogenesis. The most accepted definition is that PTLDS is the manifestation of nonspecific signs and symptoms such as fatigue, muscle pain, arthropathy, neuropathy, and cognitive dysfunction after the standard course of antibiotics that are administered to patients between 10 and 28 days depending on disease stage and severity. It is expected that this syndrome persists for at least 6 months. Additionally, all indicated known diagnostic workup regarding neuroborreliosis has to be negative.[1,2] A sufficient amount of data shows that patients with PTLDS have reduced life functioning than those without the syndrome,[3] or even when compared to patients with other chronic diseases.[4] Intuitively, the presence of PTLDS after recommended treatment is associated with significantly increased health care costs.[5]

NOT TO TREAT PTLDS

The Infectious Diseases Society of America (IDSA) reported that Lyme disease is not always properly diagnosed or treated and that some patients may continue to experience prolonged Lyme disease symptoms even after an intense chemotherapeutic regimen. The diagnosis of so-called "chronic Lyme disease", implying an ongoing infection, is not supported by scientific evidence and the treatment based on long-term chemotherapy is not recommended. Standard courses of antibiotics, between 10 and 28 days depending on the manifestation of Lyme disease, have been proven effective to cure the infection. These chronic symptoms may be due to persisting inflammatory responses to bacterial debris by genetically predisposed individuals after the resolution of the infection, as well as due to joint damages caused by the initial infection.[1] Some already treated patients

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rarely develop a facial nerve palsy or meningitis.[1,2,6] Cranial neuritis, in most cases, appears to be benign, and it is attributed not to a persistent infection but to residual, irreversible neurologic damage. Conversely, if Lyme meningitis was developed shortly after the completion of a course of oral antimicrobial therapy, the patient undergoes another cycle of treatment with either ceftriaxone or with a similar parenteral antibiotic.[6] The presence of such symptoms during the first several weeks to months after treatment most often appears to be due to a slow resolution of the inflammatory process associated with a highly prolonged or disseminated *Borrelia burgdorferi* infection. However, there is no scientific evidence that *Borrelia burgdorferi* persists in such patients.[1,2] Another study on patients with refractory late Lyme arthritis showed that these symptoms may persist for several years, but the incidence and severity of the symptoms do decrease over time, and the estimated number of individuals who continue to have recurrences is reduced by 10-20% each year.[7]

The use of antibiotic regimen for a long time is not recommended, in fact, it does not improve patient outcome. Instead, it can also promote the development of drug-resistant infections. Valid placebo-controlled randomized trials do not support long-term treatment for Lyme disease and have failed to demonstrate any benefit over placebo. In fact, these randomized clinical studies have shown that approximately one-third of patients benefit from placebo.[8,9] Additionally, there is no clear evidence supporting the hypothesis that Lyme disease is a chronic, actively infectious disease requiring ongoing antibiotic therapy.[2,10,11]

TO TREAT PTLDS

In 2014, the International Lyme and Associated Diseases Society (ILADS) published its own treatment guidelines[12] for the management of Lyme disease patients, after adopting the GRADE scheme.[13] Among others, ILADS guidelines address the issue of antibiotic retreatment in patients with persistent symptoms. After performing an individualized risk-benefit assessment, the initiation of a 4-6 weeks antibiotic regimen is recommended in previously treated Lyme disease patients. This is then followed by a reassessment which will determine whether modifications or discontinuation of the treatment is necessary. Even longer treatments may be chosen.[12]

Furthermore, ILADS is critical in interpreting the results of the 4 randomized control trials (RCTs),[8,9,14] based on which the IDSA and other authorities support the idea that there is no infectious mechanism underlying PTLDS. The 4 RCTs did not provide any positive results after antibiotic re-administration suggesting that this retreatment was not specific nor sustainable. In addition, in some cases, retreatment was associated with adverse events.[8,9,14] By analyzing these conclusions, ILADS raises issues on the bias, precision, consistency, and generalization of the results. Therefore, it can be concluded that current evidence supports persistent infection, although other mechanisms may coexist. In addressing this issue, ILADS also suggests that the potential benefits of retreatment are sufficient to support those physicians who wish to treat but cannot mandate retreatment.[12]

In 2012, two critical analyses of the 4 RCTs[8,9,14] were published. A first biostatistical review concluded that all primary outcomes in Klempner[8] and Krupp.[9] trials, except for fatigue in the Krupp trial, were likely underpowered.[15] In the same year, a reappraisal of US clinical trials highlighted the limited generalization of the results and the reduced likelihood of identifying significant treatment effects. This specific study concludes that antibiotic retreatment is potentially beneficial at least in a fraction of the PTLDS group. Thus, the recommendation of not re-administering antimicrobials should be carefully reconsidered. Additionally, it suggests that immune dysregulation as a contributor to pathogenesis should be taken into account in future studies.[16]

Interestingly, brain abnormalities were detected in chronic Lyme patients using neuroimaging based on single photon emission computed tomography. The authors concluded that the use of antibiotics with intracellular activity resulted in an increased resolution or improvement of clinical symptoms detected by imaging in 70% of patients over a 1-2 years period.[17]

COMMENT

The consequences of the lack of a worldwide accepted definitive diagnosis and the lack of an established treatment regimen include poor patient health, discomfort, additional expensive diagnostic testing, lack of health care effectiveness, and deterioration of the doctor-patient relationship.[18] Currently, PTLDS is the paradigm of this scenario.

In this situation, three challenging questions need to be addressed by the scientific community: First, how do we precisely define PTLDS? Second, how do we diagnose PTLDS? And third, is PTLDS a fully treatable condition?

There is a common believe that in order to define PTLDS, an expert panel and subsequently a consensus report seems to be the best solution. To address the

second and third questions, we need to consider the basic principles of pathogenesis and pathophysiology.

Postinfectious autoimmunity vs. persistent spirochetal infection still represents an open question. The hypothesis is that PTLDS may be a result of chronic *Borrelia burgdorferi* infection in combination with other tick-borne coinfections, and the mechanisms of "stealth pathology" utilized by the Lyme spirochete in evading the host immune response establishing infection in diverse both have been reported.[19-21] Additionally, it has been suggested that *borrelia* wall-deficient forms and biofilm formation may play a role in chronic infection.[19] Biofilms are polysaccharide-based structures which protect bacteria and thus promote persistence while their contribution to chronic infection pathogenesis is yet to be evaluated. Further studies on the underlying mechanism in the biofilm process would potentially facilitate the development of antibiotics that may counteract this phenomenon.[19] While clinical testing for Lyme disease remains critical, the use of proteomics and more novel tests are necessary.[19-21] Recently, a human study focusing on Xenodiagnosis to detect *Borrelia burgdorferi* infection has been published showing promising results regarding pathogenesis and diagnosis.[22] Is this the future? Whenever any new diagnostic test is developed, it must be compared to existing diagnostic methods to ensure that it is comparable to specificity and sensitivity before it can be widely implemented.

Analysis of the cerebrospinal fluid (CSF) in PTLDS patients may represent a solution.[1,2,19] The CSF analysis in chronic Lyme encephalomyelitis, a different nosological entity of PTLDS, is constantly showing a mild hyperproteinuria and lymphocytic pleocytosis. In chronic Lyme encephalomyelitis, cerebral magnetic resonance imaging is usually abnormal, showing subcortical or brainstem multiple sclerosis-like, inflammatory lesions. Meningeal gadolinium enhancement is sometimes the only result.[23]

The corticosteroids in neuroborreliosis are not widely recommended. There are no prospective trials that have addressed this question. The need for corticosteroids arises frequently in patients with facial nerve palsy, as some guidelines recommend for treatment of idiopathic facial nerve palsy, but others do not recommend the use of corticosteroids.[2,24] In literature, it has been reported that patients with Lyme arthritis who received steroids are more difficult to cure;[2,25] of note, steroids may well have been used in these patients due to a probably more intense disease or relevant complications. Available recommendations regarding nonspecific neurological symptoms do not exist. Thus, their management has to be assessed according to the best medical practice.

CONCLUSION

Nowadays, there are valid reasons to opt for long-term antibiotic therapy. However, it is critical to focus on the well-designed clinical trials in order to evaluate if a therapeutic intervention has an actual, beneficial effect in contrast to a resolution of symptoms which might spontaneously occur over time. The need for additional research to determine safe and effective treatments must be widely recognized by the scientific community to resolve this long controversy.

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Conflicts of interest

There are no conflicts of interest.

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