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EDITORIAL

The challenge of Lyme disease: tired of the Lyme wars

B.J. Kullberg*, A. Berende, J.W.M. van der Meer

Department of Medicine, Radboud University Nijmegen Medical Centre; and Nijmegen Institute for Infection, Inflammation, and Immunity (N4i), the Netherlands,
*corresponding author: tel.: +31 (0)24-361 88 19, e-mail: b.kullberg@aig.umcn.nl

Few diseases have aroused more emotional attention in the press and the public than Lyme disease. Discussions have not only focused on the increasing incidence[1] or the choice of appropriate treatment, but also on perceived inadequacy of serological testing and whether or not persisting fatigue, cognitive dysfunction and musculoskeletal pain are 'real disease' and related to persistent infection. Large numbers of patients with such symptoms attributed to Lyme disease seek medical opinions, but no consensus on approach or treatment exists.

In this issue of the Journal, Coumou *et al.* provide a review on several aspects of Lyme disease.[2] This review is extremely helpful for understanding the epidemiology and immunopathogenesis of the disease. Does it also provide a framework for the Dutch physician confronted with a patient with putative Lyme borreliosis, as the authors state? Probably not, since this publication precedes and potentially contradicts the revised national CBO Treatment Guidelines for Lyme Disease, which will be published later this year. The CBO guidelines, initially released in 2004, have been subject of much debate.[3] Whereas the guideline recommendations on prevention and treatment of early Lyme disease – the easy part – have been generally accepted, the lack of recommendations for the approach to patients with persistent symptoms after standard treatment of short duration has been criticised. The difficult diagnosis and paucity of studies of sufficient quality on this subject have prompted the 2004 CBO Guidelines Committee to refrain from addressing this subject in depth. In contrast, in the pending 2011 revision of the guidelines, recommendations may be expected on the approach to the patient with chronic fatigue and other persistent symptoms attributed to Lyme disease, including algorithms on possible persistence and empirical or second-line therapy. Therefore, the views by Coumou *et al.* in the present issue of the Journal cannot be viewed as a therapeutic guide replacing the revised 2011 CBO guidelines, which were developed according to the recommendations for evidence-based development of guidelines by a multidisciplinary committee, including the National Society for Lyme Patients (NVLP).[4]

Therapy of early uncomplicated Lyme disease or erythema migrans is usually successful, and a short duration of therapy (10 to 15 days) leads to cure in 84 to 95% of cases.[5,6] Indeed, for the large majority of patients, if correctly diagnosed and timely treated, Lyme disease is not an insidious illness. Reported failure rates in patients with late manifestations, such as arthritis or acrodermatitis chronica atrophicans, are considerably higher[7,8] and little is known about treatment success rates among patients with a delayed diagnosis or initiation of treatment. Treatment success rates in the latter groups invariably do not reach 100%, underscoring the need for more research to try and understand what is wrong in patients with persistent signs or unexplained symptoms after standard therapy.

Whether long-term treatment may be helpful for patients with unexplained symptoms after standard therapy for Lyme disease is currently unknown. The randomised studies that have been performed have been of questionable quality and were heavily underpowered to detect potential effects. Several trials[9,10] were prematurely discontinued due to slow recruitment and were only partially published: e.g., the publication by Klempner *et al.* did not report the primary endpoint of success in the intent-to-treat population, but just reported results in evaluable subgroups as small as 22 to 35 patients. Thus, whereas these studies did not reveal statistically significant differences between treatment groups, they cannot serve to rule out an effect of antibiotic therapy, due to their lack of power and failure to report the predefined endpoints.[9,10] Indeed, other studies of variable quality have

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suggested positive outcomes on some endpoints, such as persistent fatigue,[11] cognitive functioning[12] or treatment failures[13] in specific subgroups of patients with putative persistent infection, although these results were generally disappointing, and cannot be generalised.[11-13] Thus, there is a need for well-designed studies on this subject, rather than misusing outcomes of underpowered trials of disputed quality to either defend or deny the possible effect of antimicrobial therapy. A large randomised study to address this issue is currently being performed in the Netherlands.[14]

Serological testing for *B. burgdorferi* has been overemphasised, both by patients and physicians. Are these tests of abysmal quality, and are better serological tests available in other countries, as has been suggested in the lay press? Certainly not, but there is no need to conceal that the serological diagnosis of Lyme disease has its limitations.

As was demonstrated in a recent study from the Netherlands, the performance of serological assays is suboptimal.[15] In that study, eight commercially available ELISAs and five immunoblots were compared. The assays had a widely divergent sensitivity and specificity and a very poor concordance. ELISAs were positive in 34 to 59% of patients suspected of Lyme disease. Remarkably, there was very poor agreement between immunoblots, and their highly variable sensitivity and specificity further puts the much-advocated two-tier testing strategy into question. For example, a specific ELISA-immunoblot combination was able to confirm only 53% of positive ELISAs from patients suspected of Lyme disease, whereas another immunoblot confirmed 100% of the ELISA results.[15] These results underscore the notion that the outcome of serological testing is highly dependent on the commercial test kits chosen; hence the statement by Coumou *et al.* that serological tests have a 100% sensitivity for most manifestations of disease should be softened. This is not unusual, considering the fact that the development of a reliable test strategy for syphilis has required considerable efforts and is now based on a combination of tests, each with their own sensitivity, specificity and dynamics.

In addition, there is a clear need for the development of non-serology-based tests. Despite these shortcomings, not the quality of the assays but perhaps merely the incorrect interpretation of test results by both patients and physicians is the major hurdle. Importantly, as in many infections, antibodies persist for a long period of time, and possibly lifelong, after clinical cure of the infection.

Therefore, in addition to their limited sensitivity and specificity, it is clear that serological tests cannot be used to confirm or rule out the diagnosis of Lyme disease. Rather, serology may at most be helpful to increase or decrease the likelihood of disease in the context of the risk profile, the history, and the clinical signs and symptoms of an individual patient.

In their review, Coumou *et al.* provide a hypothetical case, in which the pre-test probability of Lyme disease is 0.5%. Not surprisingly, their calculations reveal that the predictive value of a positive test is very low. This confirms the textbook knowledge that screening tests for a disease with a likelihood of 0.5% are irrational. However, their example does not apply to patients with specific symptoms after a tick bite or erythema migrans, whose chance of having Lyme disease may be anywhere between 5 and 95%, depending on their individual situation.

Both patients and physicians should be aware of the limitations and the appropriate interpretation of serology, which is not different from many other infections. Thus, patients should not assume that the detection of antibodies indicates active infection. Likewise, physicians should not state that a failure to detect antibodies rules out disease. We have learned how to use a variety of tests, such as AST, Mantoux, Paul-Bunnel and Q-fever serology, with the cautious and professional interpretation of their limited predictive value, and we should be able to do so with Lyme serology, without misusing the results to convey personal viewpoints.

Why do doctors do their best to argue that patients consulting us about Lyme disease are overdemanding and should not be taken seriously? Clearly, many patients with aspecific symptoms do not have active Lyme disease, but this does not deny their concerns and their right to ask for a medical expertise. Patients with chronic fatigue and 'aspecific' symptoms, such as myalgia, impaired memory or concentration, headaches, or arthralgia, are often perceived as being annoying or overdemanding.[16] Most likely, doctors feeling insecure and powerless about patients with unexplained physical symptoms tend to blame their patients, especially if they express specific attributions and cognitions.

This leads to a strong tendency for circular reasoning, such as that stated by Coumou *et al.*: persistent infection as a cause of chronic symptoms after 'adequate treatment' is highly unlikely. Indeed, if 'adequate' signifies that the microorganism has been eradicated and the immune system has come to rest, the problem has been solved, but the issue rather is whether treatment has been 'adequate' or not in patients who continue to feel ill. In fact, authors using the term 'adequate treatment' suggest to be certain without further study that treatment has been successful and curative in 100% of cases, while actually referring to standard therapy for uncomplicated disease.

Likewise, designating such patients as having 'post-Lyme disease syndrome' (PLDS) incorrectly suggests a prior knowledge that the disease has been cured ('post' meaning after), before reasonable attempts have been

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made to rule out relapse or persistent infection. Whereas persistent infection may be highly unlikely in many patients, using deceitful terminology hampers a scientific and evidence-based approach. For this reason, the Dutch CBO 2011 Guidelines Committee has recommended not to use the term PLDS.

We agree with Coumou *et al*. that the term 'chronic Lyme disease' for persistent symptoms after so-called 'adequate' therapy is inappropriate, but this diagnosis cannot be rejected without a reasonable assessment whether patients do have persistent infection, post-infectious complaints, or rather a syndrome unrelated to Lyme disease. There are many diagnoses in infectious diseases, ranging from urinary tract infection to *Staphylococcus aureus* septicaemia, and from syphilis to Q-fever, where failure of primary therapy or late recurrences do occur in a minority of patients. There is general agreement that such patients deserve medical evaluation to rule out a potential relapse when having persistent or recurrent symptoms, and the approach to infection with *B. burgdorferi* should not be different. There is no place for circular reasoning ('Your treatment has been "adequate", so you can't have symptoms') or exaggerated assumptions ('standard therapy never fails', or 'our serological assay is 100% sensitive').

Does this mean that all patients presenting with chronic fatigue and arthralgias have persistent *Borrelia* infection? By no means, persistent infection by *B. burgdorferi* is probably rare, and many patients seeking information on Lyme disease most likely do not have a persistent infection. This is not different from the notion that not all patients presenting with a nodule have cancer, and not all patients with a sore throat have streptococcal angina.

Patients with chronic fatigue and persistent symptoms after having had a *B. burgdorferi* infection are persons who seek help and should not be turned away at the doorstep. We as doctors should not blame them for our limited capacity to address unexplained physical symptoms.

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