



Value of Patient Population Selection and Lyme Borreliosis Tests

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Regarding the paper entitled “Serological diagnostics of Lyme borreliosis: comparison of universal and *Borrelia* species-specific tests based on whole-cell and recombinant antigens” by P. Kodym et al. (1), we congratulate the authors and wish to add further comments.

It is worth noting that neuroborreliosis can present with meningoradiculitis.

Performing the cerebrospinal fluid (CSF) analysis is, in our opinion, particularly relevant in patients presenting with a clinical symptomatology suggestive of central neurological involvement, such as acute meningoradiculitis. However, some patients might exclusively suffer from peripheral neurological impairment, namely, in the chronic forms, the so-called “persistent polymorphic symptomatology after tick-bite” (PPSTB) or “posttreatment Lyme disease syndrome” (PTLDS). Such patients often report clinical signs, including paresthesia, dysesthesia, and neuropathic pain. This clinical syndrome has been well described by Rebman et al. (2) and, unfortunately, was not considered in the article by Kodym et al.

In the case of persistent borrelia disease, the neurological involvement form is most often peripheral; this explains the normality of the CSF sample.

Since a final diagnosis cannot be made by lumbar puncture (3), clinical examination, the exclusion of other diagnoses, and additional biological tests and examinations (an electromyogram can be useful) are mandatory. In such a chronic case, serological tests might lack sensitivity, and this has been stated by published articles and meta-analyses (4–6). The chronicity of the disease may be partly explained by the host’s autoimmunity and also by the particular organization of *Borrelia* into persisters: the biofilms and transformations into resistant “round bodies” (7–9). This hypothesis is controversial, mainly because the studies were made *in vitro*. These persisters show resistance to many antibiotic treatments that are usually active against *Borrelia* species. The immune evasion of pathogenic organisms and immunosuppression induced by *Borrelia* (marked by a deficiency in the TH2 response and the lack of a humoral response) may also explain both the reality of a chronic form and the false-negative serological results (10).

Interestingly, the clinical symptomatology of patients may not correlate with the biological diagnosis (serology/PCR). First, patients with positive results may experience little or no improvement with any antibiotic therapy. Second, in some patients with negative biologic results, clinical improvements and setbacks corresponding strictly to the administration and interruption of antibiotics may resemble the chronic persistence of a *Borrelia* event (11). The search by PCR for *Borrelia* and other coinfection agents may be helpful and can be performed in various media (2). Therefore, because of these strong biological limitations, Blanc et al. (12) and the recent High Authority of Health

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(Haute Autorité de Santé [HAS]) 2018 French report advocate useful and valuable antibiotic testing (for 1 month) when the clinical symptomatology is suggestive of Lyme diagnosis (2) whatever the results of biologic testing. Also, it is interesting to note that some migrant erythema cases could be caused by pathogens other than *Borrelia* (13).

Moreover, there is evidence that there is healthy carriage (14–16). Steere et al. concluded that the asymptomatic infection is, in fact, uncommon. However, owing to some difficulties in finding *Borrelia in vivo* by current microbiology techniques, it is difficult to be certain about the prevalence of such healthy carriers. The latter could be more numerous than expected because of changes in their lifestyles (hiking in the countryside, along trails, etc.). The selection of the control population reported in the article by Kodym et al. is therefore debatable. On the one hand, for all of the reasons mentioned above, it is obvious that there is no reliable random reference sample in the general population. On the other hand, the “sick patients” sample does not appear to be reliable in this article because this might exclude a too-large population of patients (including patients presenting with a chronic form) who often present with negative serological tests. Therefore, in our opinion, it seems impossible to reliably calculate any sensitivity and specificity for the biological tests for Lyme borreliosis.

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