Reviewer's report

Title: Probable Late Lyme disease: An atypical manifestation of untreated Borrelia burgdorferi infection.

Version: 1 Date: 22 September 2011

Reviewer: Raphael Stricker

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General Comments
Aucott and colleagues present a retrospective case series of patients with persistent symptoms of Lyme disease and positive serology on commercial Lyme testing. The authors categorize these patients as having "probable late Lyme disease", which most closely resembles the "confirmed late Lyme disease" category that is based on CDC surveillance criteria. Considering the great controversy over the diagnosis of Lyme disease, the attempt by the authors to clarify the status of this group of patients is both laudable and worthy of publication. Several points require elaboration.

Major Comments
1. The authors cite the revised CDC surveillance case definition for Lyme disease (Reference 6) with objective symptoms supported by "positive IgG serology". It should be noted that Reference 6 refers to "IgG immunoblot seropositivity", and this term should be used throughout the manuscript. The problem with the revised CDC case definition is that the standard commercial laboratory approach involves two-tier testing with a screening IFA or ELISA followed by a confirmatory immunoblot. Thus it is unclear how the authors obtained the IgG immunoblot positivity in their patients. Were all patients screened with IFA or ELISA? Did the screening test have to be positive for an IgG immunoblot to be run? Or was the IgG immunoblot run without a screening test, contrary to the CDC-approved commercial test method? This needs to be clarified in the Methods section.

2. Assuming that screening tests were run, patients had commercial Lyme testing by "laboratories utilizing CDC interpretive criteria". It is important to note that the CDC-sanctioned two-tier test algorithm has a sensitivity of 46% or less in the USA (Stricker & Johnson, Minerva Med 2010;101:419-25, Table 1) and Europe (Ang et al, Eur J Clin Microbiol Infect Dis 2011;30:1027–32, Table 4). Thus the testing used in this study probably missed more than half the patients with Lyme disease. This should be stated somewhere in the Discussion.

3. The gender distribution in the five diagnostic categories is intriguing. As shown in Figure 2 and discussed in the manuscript, a male predominance was seen in the "Lyme groups", while a female predominance was seen in the "non-Lyme" and "indeterminate" groups. This distribution is consistent with the observation that commercial Lyme testing discriminates against women, who are less likely to
achieve the level of reactivity required for CDC surveillance positivity on the commercial Lyme immunoblot (Schwarzwalder et al, Gend Med. 2010;7:320–329; Stricker & Johnson, J Womens Health 2009;18:1717-18). This test bias may skew the results of the study, which might have been quite different if "gender neutral" testing was used (Engstrom et al, J Clin Microbiol 1995;33:419-27; Ma et al, J Clin Microbiol 1992;30:370-6).

4. The age distribution of patients is also of interest. The age of patients in the male-dominated "Lyme groups" appeared to be significantly higher than in the larger female-dominated "indeterminate" group (median 51 vs 42 years old). However, the median age in the "indeterminate" group matches the mean age reported in predominantly female patients with chronic neurologic Lyme disease (Stricker et al, Minerva Med 2010;101:1-7; Stricker et al, Int J Gen Med 2011;4:639-46). Thus there may be a larger group of younger, predominantly female Lyme patients who are not recognized by the diagnostically inappropriate CDC surveillance criteria and insensitive commercial Lyme testing. It follows that the 6% of patients who fall into the "probable late Lyme disease" category may be dwarfed by the missed cases of Lyme disease in the "indeterminate by CDC criteria" category.

5. The authors failed to report other Lyme-related information such as IgM immunoblot seropositivity and the results of coinfection testing. Positive IgM immunoblot results have been noted in patients with late Lyme disease (Porwancher et al, Clin Vaccine Immunol 2011;18:851-9, Table 3), and this testing would be helpful to confirm the etiology of "probable late Lyme disease" cases. Likewise the detection of other tickborne agents such as Babesia, Anaplasma, Ehrlichia, Bartonella and Rickettsia would support the presence of Lyme disease in these patients.

Minor Comments
1. The Conclusion is duplicated at the end of the Discussion section and should be deleted in that section.
2. Table 1: Male sex

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.