Problems in comparing test strategies for detection of anti- antibodies

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Title: Problems in Comparing Test Strategies for Detection of Anti-*Borrelia* Antibodies.

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Sir,

We read with interest the article by Ang et al [1.], comparing different test strategies for anti- *Borrelia* antibodies using eight different ELISA's and five different immunoblots. The many discrepancies found in this study between the different tests makes one wonder what the relevance of *Borrelia* serology is and why laboratories perform any *Borrelia*-serology at all. However, given the design of the study these results could have been foreseen. Most importantly, information on the quality and diagnostic value of individual antibody assays is lacking.

Sera of patients suspected of Lyme disease are used in this panel as possible positives. However it is not stated in the paper which part of these sera were from patients with true infections by clinical criteria. Also no information is given whether samples are from patients with suspected early or late infection. Since 34 of the 59 sera from patients with suspected Lyme disease were from patients with skin manifestations and neurological symptoms it is plausible that a significant number of them had early Lyme disease. We wonder about the symptoms of the 10 patients classified in the category "other".

In patients with early Lyme the immune response could still be absent or in its early dynamic phase. In such sera the chance of finding discrepancies in test results between tests using different antigens is much higher than in sera of patients with late disease with a fully developed immune response against a broad spectrum of antigens. Also, depending on the rigidity of interpretation-criteria of immunoblot, in such "early" sera the sensitivity of ELISA may be higher than the sensitivity of immunoblot due to the smaller antigen-spectrum of the early immune response.

It is unclear how "indeterminate" results are judged by Ang et al. If indeterminate results are included among the positives, more discrepancies between assays can be expected.

In ELISA's, especially in those with whole cell antigens, false positive results are common, especially in IgM tests [2,3]. It has been advised to use IgM results only in early *Borrelia* infection and not in late infection [4.]. In this study, for analysis of ELISA results, the IgG and

IgM components have been taken together, therefore more aspecific results (because of IgM alone) are to be expected.

Ang et al. show that a number of sera react in certain immunoblots, but not in any ELISA: does this mean that in this case ELISA's lack sensitivity, or do some of the IgG or IgM immunoblots lack specificity? A conclusion can not be drawn due to lack of clinical data of included patients.

The authors conclude that commercial assays tested have a wide variety in sensitivity and specificity. However from this study it cannot be concluded whether the discrepancies are the result of insensitivity or of non-specificity of tests and which test or test-sequence would have the best performance in routine clinical practice. Are all tests bad? Or are some good and others bad? Correlating good with bad tests results in low kappa values.

To investigate which commercial test is most suitable for use as screening test or as confirmatory test, we think it is imperative to validate tests using sera from clinically well defined patients, with classical symptoms of Lyme disease, to evaluate IgM and IgG separately and to interpret the tests in relation to the manifestation of Lyme disease presented and the duration of disease at time of sampling.

References:

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