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Misdiagnosis of Lyme disease: when not to order serologic tests

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Because of widespread public concern about Lyme disease and the erroneous belief that it commonly may present with vague, nonspecific symptoms without accompanying objective physical signs, the use of serologic tests to rule out Lyme disease has become very common in the evaluation of patients with such nonspecific symptoms as fever, malaise, arthralgia and fatigue.[1] Many studies document both interlaboratory and intralaboratory variability in the results of widely used serologic tests for Lyme disease.[2-6] These reports emphasize the need for serologic tests with excellent sensitivity, specificity and reproducibility. Less well-documented in the literature are the pitfalls that arise from overuse of serologic tests in patients with a low probability of having Lyme disease, even tests performed at reference laboratories, that are more accurate and more reproducible than those done by most laboratories that use commercial kits. A number of investigators have documented the high proportion of patients seen at referral centers that are misdiagnosed as having Lyme disease;[1, 7] this can be attributed at least in part to the indiscriminate use of serologic tests. The purpose of this report is to illustrate how widespread use of serologic tests for Lyme disease can frequently lead to misdiagnosis.

Sensitivity is the proportion of persons with a positive test among persons with disease; specificity is the proportion of persons with a negative test among persons without disease. A reasonably good serologic test for Lyme disease might have a sensitivity of 95% and a specificity of 90%.[8] Using these values we calculated the positive and negative predictive values for such a test in a theoretical sample of 10 000 persons, of whom 1% have Lyme disease. This theoretical prevalence of 1% is even higher than the annual incidence rate in most areas in which Lyme disease is endemic.

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The positive predictive value of a test is the proportion of persons with disease among all those with a positive test for the disease; the negative predictive value is the proportion of persons without disease among all those with a negative test for the disease.[8] We also calculated the predictive values of the results of the same test in samples with higher prevalences of disease.

The results are shown in Table 1. Under circumstances of a 1% prevalence of disease, the predictive value of a positive test is only 8.7%, and of all the positive tests for Lyme disease 91.3% were false positive results. The results of applying this test (with the same 95% sensitivity and 90% specificity) to samples with disease prevalences of 10 and 50%, respectively, are also shown.

Erythema migrans, the characteristic rash of Lyme disease, is pathognomonic. However, Lyme disease can present with less specific, objective signs such as arthritis, neurologic abnormalities (cranial nerve palsies, meningitis) or heart block, all of which may also be accompanied by very nonspecific symptoms such as myalgia, headache and fatigue. In these cases the diagnosis of Lyme disease is supported by serologic evidence of infection with *B. burgdorferi.* However, because of widespread anxiety about Lyme disease, the use of serologic tests for Lyme disease has become very common in the workup of patients with a low probability of having Lyme disease. Indeed the impetus to order

TABLE 1. Predictive value of a diagnostic test with 95% sensitivity and 90% specificity in samples with different prevalences of Lyme disease

Prevalence of Disease (%)	Test Result	Present	Absent	Total
1*	Positive	95	990	1085*
	Negative	5	8910	8915
	Total	100	9900	10 000
10†	Positive	950	900	1850†
	Negative	50	8100	8150
	Total	1000	9000	10 000
50‡	Positive	4750	500	5250‡
	Negative	250	4500	4750
	Total	5000	5000	10 000

* Positive predictive value = 8.7%; negative predictive value = 99.9%.
† Positive predictive value = 51.4%; negative predictive value = 99.4%.
‡ Positive predictive value = 90.5%; negative predictive value = 94.7%.

a serologic test for Lyme disease often may come from the patient and not from the physician. In one review of the use of serologic tests for Lyme disease in a health maintenance organization in California, 35% of the 117 tests for Lyme disease were obtained because of a request by the patient.[9]

For the clinician who is caring for an individual patient, the key characteristic of a diagnostic test is its predictive value: if a test is positive, how likely is it that the patient has the disease?[10] One percent of our first theoretical sample had Lyme disease, and the serologic test for Lyme disease had a positive predictive value of only 8.7%. In fact in a group of patients with only nonspecific, subjective symptoms, even in endemic areas, the proportion that has Lyme disease is probably substantially less than 1%. If serologic tests for Lyme disease are used indiscriminately as a screening test for such patients, the positive predictive value could be even lower. In 1994 the reported incidence rate of Lyme disease in Connecticut, the highest reported in any state, was only 61.8 cases/100 000 (0.062%).[11] In Wisconsin in 1987 the reported incidence rate of Lyme disease was 7.5 cases/100 000 population (0.0075%), yet in 1988 more than 1200 tests for Lyme disease per 100 000 population were performed.[12]

Table 1 demonstrates how the positive predictive value of a test with <100% specificity is critically dependent on the prevalence of disease in the sample being tested (as per Bayes' theorem).[10] In a sample of the same size (10 000) as in the first example, with a diagnostic test that has 95% sensitivity and 90% specificity, if the proportion of patients with disease in the sample is 10%, the positive predictive value of the test is 51.7%; if the proportion of patients with disease in the sample is 50%, the positive predictive value of the test rises to 90.5%. Thus if the test is used in a sample of patients with a higher probability of having Lyme disease (e.g. patients with objective physical signs, such as subacute arthritis of the knee), rather than in patients with nonspecific symptoms and a low probability of having Lyme disease, a positive serologic test for Lyme disease is more meaningful.

These examples illustrate the need for judicious use of serologic tests for Lyme disease to ensure that the predictive value of a positive test is high. There is little doubt that widespread, inappropriate use of serologic tests for Lyme disease is one important reason for the high proportion of patients who are incorrectly diagnosed as having Lyme disease. At one large referral center patients were prescreened by phone and were referred elsewhere if it seemed they were unlikely to have Lyme disease. Nevertheless in a report from that center, 57% of patients who were evaluated were ultimately found not to have Lyme disease, and another 20% had had Lyme disease in the past but the symptoms that led to the referral were not caused by Lyme disease.[1] Nonetheless in the appropriate clinical setting, when the index of suspicion for disease is high and the symptoms and signs are consistent with Lyme disease, serologic tests for antibodies to *B. burgdorferi*, using laboratory tests with excellent sensitivity and specificity, can help support or exclude the diagnosis.

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