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Utilization of Tests for Lyme Disease Antibody at a University Hospital

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We performed a retrospective study on patients who had a positive screening antibody test result for antibody to *Borrelia burgdorferi* to determine the clinical indicators used by physicians to order this test. Eighty-two evaluable patients who were screen positive (indirect enzyme-linked immunosorbent assay) between August 1991 and March 1993 were included. Additional tests, isotype-specific capture immunoglobulin enzyme immunoassay and Western blot (immunoblot) analysis (immunoglobulin G), were performed on positive samples. Of 82 patients with a positive screening test result, 54 (66%) had no serologic evidence of Lyme disease on the basis of additional testing (positive predictive value, 34%). Only 28 of 82 patients (34%) had clinical indicators suggestive of Lyme disease. Antibody screening tests may provide misleading information if they are not accompanied by more specific assays. Inappropriate testing of patients without indications of Lyme disease is frequently performed, and the ordering practices of physicians should be reassessed.

The diagnosis of Lyme disease relies on both clinical and laboratory findings of infection. Over the past few years, it has become quite clear that serologic tests for Lyme disease are not optimal in terms of sensitivity and specificity (13). Furthermore, the lack of standardization of serologic tests has created difficulties in interpreting serologic tests performed in different laboratories (1, 9).

We noted that many of the patients with positive tests by indirect enzyme immunoassay (EIA) were not confirmed as being positive by alternative methods such as capture immunoglobulin EIA (cEIA) and Western blot (WB; immunoblot) analysis. To assess these discordant results, we performed a retrospective chart review of patients with a positive screening test result to determine (i) the correlation of the results of our EIA procedure with those of additional assays, (ii) the correlation of serologic test results with the patient's clinical findings, and (iii) the test ordering patterns among physicians at our institution.

(The study was presented in part at the 95th General Meeting of the American Society for Microbiology, Las Vegas, Nev., 27 May 1994 [11a].)

MATERIALS AND METHODS

We reviewed 111 charts on patients who had a positive screening antibody test result for Lyme disease from August 1991 through March 1993. Of these, screening EIA and additional assay results were available for 82 (74%) patients, and those data were included in the present study.

We classified patients as having an indication for testing for Lyme disease using a very liberal definition that included any one of the following: primary or secondary diagnosis of Lyme disease, treatment for Lyme disease, erythema migrans, cranial nerve palsies, meningitis, cardiac conductivity abnormalities or myocarditis, or arthritis of unknown etiology.

Serologic testing at our institution was performed with the API Lyme ELISA Test Kit (Analytab Products, Plainview, N.Y.) according to the manufacturer's instructions. The enzyme-linked immunosorbent assay (ELISA) detects both immunoglobulin M (IgM) and IgG antibodies. Additional tests were performed by Imugen Laboratories (Norwood, Mass.) by an isotype-specific (IgG, IgA, and IgM) cEIA and IgG WB analysis as described previously (2, 5). A patient was considered to have serologic evidence of Lyme disease if either the cEIA or WB result was positive. The sensitivity of cEIA (IgG/IgM) has been reported to be 67% during the acute phase of infection and 93% in the convalescent phase, with specificities ranging from 94% for IgG and 97% for IgM (2). The cEIA for IgA has been reported previously (14) for use in patients with early and late central nervous system disease. Interpretation of the WB result was as described by Dressler et al. (5), with the presence of at least 5 of the 10 most frequent IgG bands being required for a positive result. The sensitivity of WB analysis has been reported to be 83%, and the specificity has been reported to be 95% after the first weeks of infection (5).

Statistical analysis was performed by using InStat, version 2.02 (GraphPad, Inc., San Diego, Calif.).

RESULTS

The screening EIA results were compared with the cEIA and WB results. Of 82 patients that had either a positive or equivocal serologic EIA result, only 28 (34.1%) had additional serologic evidence of Lyme disease. Fifty-four patients with positive EIA results had negative cEIA and/or WB results (Table 1). We also correlated serologic results with clinical indications for patient testing (Table 1). Of 28 patients with clinical indications for Lyme disease testing, 19 (68%) had positive serologic evidence of Lyme disease by additional tests. Of 54 patients with no clinical indications for testing, 9 (16.7%) had positive serologic tests for Lyme disease by additional tests ($P < 0.0001$; odds ratio = 10.6; 95% confidence interval = 3.6 to 30.7).

Twenty-eight patients had serologic evidence of Lyme disease by cEIA and WB, and of these, only IgM was detected by cEIA in 15 patients; WB blot analysis was negative for these patients. Of these 15 patients, seven patients had clinical indications for testing and eight (53%) did not have any clinical evidence of Lyme disease. The primary diagnoses of the eight patients without clinical evidence of Lyme disease included hypertension, psychiatric illness, postviral syndrome, multiple sclerosis, psoriatic arthritis, torn rotator cuff, stage IV breast cancer with a skin rash, and rheumatoid arthritis.

The distribution of testing was analyzed by the source of test requests (Table 2). The majority of requests came from three major areas: internal medicine (19.5%), rheumatology (19.5%),

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TABLE 1. Correlation of screening EIA results with cEIA and WB serologic test results and clinical indicators for performing serologic testing

Parameter	No. of samples with the following cEIA or WB result:	
	Positive	Negative
Screen EIA result		
Positive	26	40[a]
Equivocal	2	14
Clinical indicators for testing		
Present	19	9
Absent	9[b]	45

[a] $P < 0.0001$ for the screening EIA by McNemar's pair test.
[b] Odds ratio, 10.6 (95% confidence interval = 3.6 to 30.1); for clinical indicators, $P < 0.001$ (Fisher's exact test).

and neurology (17%). The remaining sources were distributed among 19 different outpatient centers. A significantly higher proportion of nonindicated tests was requested from services other than the three major groups ($P = 0.014$). The diagnosis for patients without clinical indications for testing were varied and comprised various rheumatologic, dermatologic, neurologic, psychiatric, infectious, and miscellaneous causes (Table 3).

DISCUSSION

Lyme disease is now considered the most common vector-borne disease in the United States (13). The clinical manifestations of Lyme disease are varied, and consequently, many poorly described or understood conditions are ascribed to being caused by the agent of Lyme disease (13). An example is the recent conclusion by Fallon and Nields (6) that psychiatrists who work in an area where Lyme disease is endemic should include Lyme disease in the differential diagnosis of any atypical psychiatric disorder. Consequently, laboratory tests are frequently used as diagnostic tools when assessing patients for a diagnosis of Lyme disease. Laboratory tests that may aid in the diagnosis of Lyme disease include culture, antibody assays, and nucleic acid detection (10); however, antibody assays are the only practical methods for routine use.

The results of our retrospective study showed that the commercial antibody assay used in our laboratory correlated poorly with other independent antibody assays, with a positive predictive value of only 34%. Commercial assays are usually evaluated by using samples from patients representing a typical spectrum of disease, and thus, it is not surprising that almost all kit evaluations look fairly reasonable. Once the kits are used in general practice and are applied to patients for whom the test was not particularly designed or with a spectrum of disease not observed in controlled evaluations, test performance (i.e., sensitivity and specificity) may be different (7, 11). We suspect that the EIA used as a screening procedure in our study and other commercially available tests are subject to spectrum bias, as suggested by proficiency testing programs (1). The purpose of our study was not to specifically address the question of spectrum bias, because we did not examine all patients being tested for Lyme disease. However, our data showing a significant difference in confirmatory antibody test results for patients with clinical indicators (63%) versus those for patients with no clinical indicators (13.5%) suggest such a bias in test performance.

Only 28 of 82 patients with a positive indirect EIA screening

TABLE 2. Distribution of test orders by location and clinical indicators

Group	No. of patients	% of total	No. (%) indicated	No. (%) not indicated
Internal medicine	16	19.5	8 (50)	8 (50)
Rheumatology	16	19.5	8 (50)	8 (50)
Neurology	14	17	8 (57)	6 (43)
Other services	36	43.9	9 (25)	27 (75)[a]
Total	82	100	33 (40.2)	49 (59.8)

[a] Odds ratio, 3.27 (95% confidence interval = 1.3 to 8.5); $P = 0.014$ (Fisher's exact test) versus the three major services combined.

TABLE 3. Diagnoses for patients without clinical indicators for Lyme disease testing

Disease group and disease
Rheumatologic disorders
Painful L toe
Degenerative cervical vertebrae
Avascular necrosis of tibia
Rheumatoid arthritis
Cartilage degeneration
Lupus erythematosis
Joint nodules
Psoriatic arthritis
Torn rotator cuff
Dermatologic disorders
Bee sting
Actinic keratosis
Facial swelling postrhytidoplasty
Breast cancer with skin lesion
Infectious disease
Epstein-Barr virus infection
Disseminated gonorrhea
Viral illness[a]
Fever of unknown origin
Mycoplasma
Neurologic disorders
Headache, chiasmal field loss
Charcot Marie-tooth syndrome
Guillain-Barré syndrome
Neurosarcoid
Neuroretinitis exacerbation
Parkinson's disease
Cerebral vasculitis
Psychiatric disorders
Bipolar disorder
Depression
Akinetic rigid syndrome
Sleep disorder[b]
Sleep apnea
Presenile dementia
Gastrointestinal disorders
Fast gastric emptying
Idiopathic colitis
Miscellaneous disorders
Hematuria
"Courtesy" blood work

[a] A friend of the patient had Lyme disease.
[b] The son of the patient had Lyme disease.

test result had one or more clinical indicators suggestive of Lyme disease. The diagnoses for patients without clinical indicators suggestive of Lyme disease were quite varied and suggest that many physicians are uncertain of the clinical spectrum of Lyme disease. Of more general concern was the lack of rationale for performing serologic tests for Lyme disease and how the results would be used for patient management. While 48% of the nonindicated tests came from three major groups at our institution, 75% of the nonindicated tests were distributed among 19 other services. This suggests that there is less familiarity of the manifestations of Lyme disease among some physicians.

Few studies have examined physician practices related to serologic testing for Lyme disease. Steere et al. (15) found that 57% of patients referred to their Lyme disease clinic did not have Lyme disease and that for 45% of these patients a positive serologic test was performed at another laboratory. However, all of these patients were seronegative by the methods used in their laboratory (5). Ley et al. (8) recently studied Lyme disease serology utilization practices in a prepaid health plan in northern California. Of 117 patients studied, tests for 66 patients were ordered by a physician, tests for 41 patients were requested specifically by the patient, and the test requestor was unknown for 10 patients. Lyme disease was considered in the differential diagnosis for 27 of 66 patients (41%) tested upon physician request, while 39 patients (59%) had nonspecific complaints such as arthralgias, myalgias, and fatigue and testing was performed as part of a large battery of other laboratory tests. Of the tests requested by patients, many (n = 21) were requested because the patient reported a history of a tick bite. Twenty patients had no such history, and few had any symptoms of infection. Of all serum samples tested over a 1-year period (n = 422), only 9 (2%) were positive for antibodies against *B. burgdorferi*. Rose et al. (12) studied a pediatric population and found that 25 to 53% of patients without Lyme disease frequently had positive ELISA test results when the test was performed by commercial laboratories (but found) that the result could not be confirmed by in-house ELISAs or WB analysis. Sixty percent of patients referred to their Lyme disease clinic did not have Lyme disease by clinical and serologic testing criteria. Burdge and O'Hanlon (3) found that of 65 patients in British Columbia, where Lyme disease is not endemic, only 2 had probable Lyme disease and alternate diagnoses were likely for the majority of other patients. Twenty-eight patients (43%) had positive antibody test results by an indirect fluorescent-antibody assay. However, when additional antibody tests were performed, such as EIA and WB analysis, only five and two patients were positive by these tests, respectively. Non-Lyme disease-related diagnoses similar to those for our patients were found.

The purpose of our retrospective study was to assess the predictive value of a positive indirect antibody test (EIA) in our patient population. We did not determine whether patients with or without clinical indications for Lyme disease testing actually had Lyme disease. Thus, the true value of serologic testing in our population is still unclear. Additionally, we did not examine all patients tested regardless of their antibody status; thus, we cannot comment on the overall specificity or sensitivity of the EIA. Given the high proportion of nonindicated tests in patients who were antibody positive, we suspect that test ordering patterns would be similar for antibody-negative patients, as suggested by other studies (3, 8). Even with the use of additional serologic testing such as cEIA and WB analysis that should be more specific, results that were discordant with clinical findings were found, particularly by the IgM cEIA.

In conclusion, we found that screening of patients for Lyme disease antibody is frequently performed for patients without clinical indicators suggestive of Lyme disease. This has led to the overutilization of laboratory tests not specifically designed for screening such patients. As a result, the positive predictive value of this screening procedure is extremely poor compared with those of additional testing procedures. Physicians should consider limiting the use of antibody assays for Lyme disease to patients who have some history and clinical picture suggestive of Lyme disease. Although we could not accurately calculate the cost of the unnecessary testing performed in our laboratory, costs could be significantly reduced by limiting testing to patients with a reasonable likelihood of having Lyme disease. Furthermore, the treatment of Lyme disease is not benign, and costs may be significant (4, 12). Finally, in our experience, samples with positive results by indirect ELISAs should be tested by independent antibody tests such as cEIA and WB analysis before reporting the results. However, truly sensitive and specific confirmatory assays for Lyme disease need to be developed.

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