

Implications of Gender in Chronic Lyme Disease

Gary P. Wormser, M.D.¹ and Eugene D. Shapiro, M.D.²

Abstract

Background: "Post-Lyme disease syndrome" refers to prolonged subjective symptoms after antibiotic treatment and resolution of an objective manifestation of *Borrelia burgdorferi* infection (Lyme disease). "Chronic Lyme disease" is a vaguely defined term that has been applied to patients with unexplained prolonged subjective symptoms, whether or not there was or is evidence of *B. burgdorferi* infection.

Objective: To determine if the population of patients with chronic Lyme disease differs from the populations of patients with either Lyme disease or post-Lyme disease syndrome by examining the gender of patients with these diagnoses.

Methods: Data on gender were compiled in this cross-sectional study based on a systematic review of published studies of antibiotic treatment in United States patients with post-Lyme disease syndrome ($n = 184$) or chronic Lyme disease ($n = 490$), and on cases of adults with Lyme disease reported to the Centers for Disease Control and Prevention from 2003 to 2005 ($n = 43,282$).

Results: Patients with chronic Lyme disease were significantly more likely to be female than were patients diagnosed with either Lyme disease (odds ratio [OR] 2.42, 95% confidence interval [CI] 1.98–2.94, $p < 0.0001$) or with post-Lyme disease syndrome (OR 2.32, 95% CI 1.62–3.34, $p < 0.0001$).

Conclusions: Patients with chronic Lyme disease differ with regard to gender from those with either *B. burgdorferi* infection or post-Lyme disease syndrome. This finding suggests that illnesses with a female preponderance, such as fibromyalgia, chronic fatigue syndrome, or depression, may be misdiagnosed as chronic Lyme disease.

Introduction

THE TYPICAL OBJECTIVE MANIFESTATIONS of *Borrelia burgdorferi* infection (Lyme disease) include a characteristic skin lesion called erythema migrans, certain neurologic and cardiac manifestations, and pauciarticular arthritis, all of which usually respond well to conventional antibiotic therapy.¹ Despite resolution of the objective manifestations of Lyme disease after antibiotic therapy, a small minority of patients will continue to complain for more than 6 months of subjective symptoms that may include fatigue, musculoskeletal pain, difficulties with concentration or short-term memory, or all of these symptoms. The term "post-Lyme disease syndrome" has been used to refer to the subset of such patients who are functionally impaired.^{1–3} Although there has been variability in the particular criteria employed by different investigators to diagnose post-Lyme disease syndrome, there is general agreement on the absolute requirement for an antecedent infection with *B. burgdorferi*.^{1–4}

A small number of practitioners (often self-designated as Lyme-literate physicians) have introduced the term "chronic Lyme disease" to describe patients with similar kinds of subjective symptoms, with or without credible evidence (either clinical or from the laboratory) of a preceding or current infection with *B. burgdorferi*.^{4,5} Such patients often receive very prolonged courses of antimicrobial treatment as well as other less conventional therapies, although there is convincing evidence that these are without benefit.⁴ Reevaluation of patients who might have been labeled as having chronic Lyme disease at academic Lyme disease referral centers has consistently shown that the majority of such patients do not have post-Lyme disease syndrome and, indeed, have no credible evidence of ever having been infected with *B. burgdorferi*.^{4,6–8} Some of these misdiagnosed patients have instead had a variety of other treatable medical conditions, such as depression or rheumatoid arthritis.^{6,7} The appropriate diagnosis for many of the other patients has been fibromyalgia, chronic fatigue syndrome, or unexplained medical symptoms that do

¹Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla, New York.

²Departments of Pediatrics, Epidemiology and Public Health, and Investigative Medicine, Yale University School of Medicine and Graduate School of Arts and Sciences, New Haven, Connecticut.

not meet established criteria for either fibromyalgia or chronic fatigue syndrome.^{4,6-8}

Because there is no case definition or definitive laboratory test to identify patients with a diagnosis of chronic Lyme disease, systematic clinical evaluation of such patients is difficult. The diagnosis is based entirely on the clinical judgment of a Lyme-literate physician.^{4,5} Systematic assessments of such patients by other than Lyme-literate physicians have been limited to patients who have sought a second opinion from practitioners based at academic health centers and, thus, may not be a representative sample of such patients.⁶⁻⁸

In contrast to Lyme disease, which is more common in men,⁹ both fibromyalgia and chronic fatigue syndrome (conditions that may mimic symptoms of patients with chronic Lyme disease) are more common in women.¹⁰⁻¹³ If chronic Lyme disease is directly related to ongoing infection with *B. burgdorferi*, one might expect that the proportion of men and women who have this diagnosis would be similar to the proportions among persons diagnosed with Lyme disease in the general population, as well as among those with post-Lyme disease syndrome. On the other hand, if there is a substantial difference in the gender of patients with chronic Lyme disease, it is additional evidence that this disease is unrelated to infection with *B. burgdorferi*. To this end, we compared the gender of patients with chronic Lyme disease with those with either post-Lyme disease syndrome or Lyme disease reported to the Centers of Disease Control and Prevention (CDC).

Materials and Methods

Data on the gender of patients in studies of antibiotic treatment of chronic Lyme disease and all the controlled antibiotic treatment trials of patients with post-Lyme disease syndrome in the United States were tabulated.^{2,3,14-16} Studies were identified based on a review of the English language literature of publications listed in PubMed as of December 31, 2007, using the search term: 'chronic Lyme disease' and treatment. The bibliographies of selected articles found in the

search were also reviewed. The gender of adult Lyme disease patients in the United States was determined based on cases reported to the CDC.⁹ Odds ratios (ORs) and their associated 95% confidence intervals (CIs) were calculated using standard techniques. The statistical significance of differences between groups was determined using the chi-square test (two-tailed).

Results

Of the 43,282 cases of Lyme disease in persons ≥ 20 years of age reported to the CDC between 2003 and 2005 on which data about age and gender were complete (97% of reported cases), 20,755 were females (48.0%).⁹ Three clinical trials of antibiotic treatment of post-Lyme disease syndrome met the inclusion criteria; 90 of the 184 subjects in these studies (48.9%) were females (Table 1).^{2,3} The ratio of females/males did not differ significantly among the three studies ($p = 0.30$) and was not statistically significantly different from the ratio of females/males among the 43,282 cases of adults reported to CDC from 2003 to 2005 (OR 1.04, 95% CI 0.77-1.40, $p = 0.80$).

We were able to identify three studies of antibiotic treatment of patients with chronic Lyme disease (all of which were uncontrolled studies) (Table 1).¹⁴⁻¹⁶ The ratio of females/males did not differ significantly among the three studies ($p = 0.12$). Of the 490 subjects in the three trials of antibiotic treatment of patients with chronic Lyme disease, 338 (69.0%) were females. The proportion of females in the subjects with chronic Lyme disease differed substantively both from the proportion of females among subjects with post-Lyme disease syndrome (OR 2.32, 95% CI 1.62-3.34, $p < 0.0001$)^{2,3} and from that among reported cases of Lyme disease in adults in the United States from 2003 to 2005 (OR 2.42, 95% CI 1.98-2.94, $p < 0.0001$).⁹ The proportion of females in the 1997 report on chronic Lyme disease,¹⁴ which had the lowest proportion of females among all of the trials of patients with chronic Lyme disease, nevertheless had a significantly greater proportion of females than the proportions in the studies of post-Lyme disease syndrome (OR 1.91, 95% CI 1.27-2.89, $p = 0.001$)^{2,3} or

TABLE 1. GENDER OF PATIENTS IN THREE STUDIES OF ANTIBIOTIC TREATMENT FOR CHRONIC LYME DISEASE AND IN THREE CONTROLLED TREATMENT TRIALS OF POST-LYME DISEASE SYNDROME

First author	Reference Number	Time period of study	Year published	No. of females	Number of males	Female/Male ratio	Age of subjects in years	Comment
Chronic Lyme Disease								
Donta	14	1988-1995	1997	154	84	1.8	Mean 39	Gender not given for 39 subjects
Fallon	15	1993-?	1999	16	7	2.3	Mean 42.7	
Donta	16	1992-1997	2003	168	61	2.8	Median 41	Gender not given for 6 subjects
Total				338	152	2.2		
Post Lyme Disease Syndrome								
Klempner	2	1997-2000	2001	33	45	0.7	Mean 54-55	All subjects were seropositive ^a
Klempner	2	1997-2000	2001	28	23	1.2	Mean 51-52	All subjects were seronegative ^a
Krupp	3	1995-1997	2003	29	26	1.1	Mean 47-48	67% were seropositive ^a
Total				90	94	0.96		

in adults with Lyme disease reported to CDC from 2003 to 2005 (OR 1.99, 95% CI 1.51–2.51, $p < 0.0001$).⁹

Discussion

This study demonstrates that patients in studies of treatment of chronic Lyme disease are more likely to be female than are patients either in studies of treatment of post-Lyme disease syndrome or in adult patients with Lyme disease in the United States reported to the CDC between 2003 and 2005. Gender was neither an inclusion nor an exclusion factor in any of the studies nor were conditions that are known to be associated with female gender, such as fibromyalgia, if these conditions developed after the diagnosis of Lyme disease. These findings suggest that patients who are labeled as having chronic Lyme disease comprise a different population from patients who are symptomatic because of either current or past infection with *B. burgdorferi*. The findings are consistent with those of prior investigations in which patients with putative Lyme disease were reevaluated at academic Lyme disease referral centers.^{6–8} Those studies were the first to suggest that large numbers of patients were being inappropriately treated with often prolonged courses of antibiotic therapy for a presumptive infection with *B. burgdorferi* that they did not actually have. Many of the patients described in those reports would likely have been labeled as having chronic Lyme disease, although that term was not used as a diagnosis in those reports.

Why are patients who never had *B. burgdorferi* infection labeled with the diagnosis of and treated for chronic Lyme disease? One factor appears to be the use of diagnostic tests with extremely poor specificity. For example, in the two largest studies of patients with chronic Lyme disease considered here,^{14,16} the specificity of the criteria used by the investigators to interpret the immunoblots that confirmed the presence of antibody to *B. burgdorferi* was subsequently demonstrated by other investigators to be only about 60%⁴; the third study did not use 2-tier serological testing and did not specify what criteria were used to interpret immunoblots.¹⁵

Lyme disease may be one of the infectious triggers of fibromyalgia.^{7,17,18} In two small studies, the ratio of females/males in patients with fibromyalgia that followed Lyme disease was about 2:1,^{17,18} which is somewhat lower than this ratio in reports of patients with fibromyalgia in most other clinical settings (9:1).^{10,11} In another study, however, the ratio of females/males in patients whose fibromyalgia developed coincident with Lyme disease was >9:1.¹⁹

The predominance of females among patients with chronic Lyme disease in studies of antibiotic therapy may shed some light on the nature of the problem being misdiagnosed as chronic Lyme disease. Based on the experience of academic Lyme disease referral centers,^{6,7} it seems reasonable to surmise that many of these patients had fibromyalgia, chronic fatigue syndrome (reports about which indicate a female/male ratio of up to 3:1^{12,13}), depression (female/male ratio of about 2:1²⁰), or unexplained symptoms that did not meet criteria for either fibromyalgia or chronic fatigue syndrome (there is also usually a female preponderance in patients with unexplained symptoms that do not meet criteria for either fibromyalgia or chronic fatigue syndrome^{7,20–23}).

Our study has several limitations. One is the relatively small number of patients with post-Lyme disease syndrome who

were available to be analyzed. This is likely because very few patients actually develop significant long-term functional impairment after a true episode of Lyme disease. When investigators have sought to study patients with severe functional impairment after an episode of documented Lyme disease, it has been very difficult to identify such patients for enrollment into clinical trials.⁴ The vast majority of patients with chronic Lyme disease included in our analysis came from the practice of a single clinician and, thus, may not be representative of patients diagnosed by other practitioners. Data on the number of patients diagnosed annually with chronic Lyme disease in the United States do not exist. Given the inherent imprecision of the diagnosis of chronic Lyme disease, some degree of heterogeneity between different groups of such patients would be anticipated. Female preponderances of 1.5:1²⁴ and 1.6:1²⁵ were reported for 97 patients and 73 patients with chronic Lyme disease, respectively, in studies (which did not meet criteria for inclusion in our analysis) by other investigators who were studying laboratory testing in these patients.

In conclusion, the observed predominance of females among patients with chronic Lyme disease in studies of antibiotic therapy is consistent with the impression of numerous investigators that the term "chronic Lyme disease" is a misnomer.^{4,26,27} Chronic Lyme disease is clearly different from what has been referred to as "post-Lyme disease syndrome," although some patients with post-Lyme disease syndrome may carry a diagnosis of chronic Lyme disease.⁴ Evidence indicates that the majority of patients with chronic Lyme disease have never been infected with *B. burgdorferi* and, instead, suffer from a number of other diseases or symptom complexes that are often associated with a predominance of females.^{4,6–8,18,19}

Acknowledgments

The assistance of Cecil Encarnacion and Lisa Giarratano is greatly appreciated.

This publication was supported in part by CTSA grants UL1 RR024139, KL2 RR024138, and K24RR022477 (E.D.S.) from the National Center for Research Resources, a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on Re-engineering the Clinical Research Enterprise can be obtained from the NIH website.

Disclosure Statement

The authors have no conflicts of interest to report.

References

1. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;43:1089–1134.
2. Klemmner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* 2001;345:85–92.
3. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (Stop-LD). A randomized double-masked clinical trial. *Neurology* 2003;60:1923–1930.

4. Feder HM Jr, Johnson BJB, O'Connell S, et al. A critical appraisal of "chronic Lyme disease." *N Engl J Med* 2007; 357:1422-1430.
5. The ILADS Working Group. Evidence-based guidelines for the management of Lyme disease. *Expert Rev Anti-Infect Ther* 2004;2:533-557.
6. Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RI. The consequences of overdiagnosis and overtreatment of Lyme disease: An observational study. *Ann Intern Med* 1998; 128:354-362.
7. Steere AC, Taylor E, McHugh GL, Logigian EL. The overdiagnosis of Lyme disease. *JAMA* 1993;269:1812-1826.
8. Rose CD, Fawcett PT, Gibney KM, Doughty RA. The overdiagnosis of Lyme disease in children residing in an endemic area. *Clin Pediatr* 1994;33:663-668.
9. Centers for Disease Control and Prevention. Lyme disease—United States, 2003-2005. *MMWR* 2007;56:573-576.
10. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: The prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol* 1999;26:1570-1576.
11. Yunus MB. The role of gender in fibromyalgia syndrome. *Curr Rheum Rep* 2001;3:128-134.
12. Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. *Arch Intern Med* 1999;159:2129-2137.
13. Buchwald D, Pearlman T, Kith P, Schmaling K. Gender differences in patients with chronic fatigue syndrome. *J Gen Intern Med* 1994;9:397-401.
14. Donta ST. Tetracycline therapy of chronic Lyme disease. *Clin Infect Dis* 1997;25:S52-S56.
15. Fallon BA, Tager F, Fein L, et al. Repeated antibiotic treatment in chronic Lyme disease. *J Spirochetal Tick-Borne Dis* 1999;5:94-102.
16. Donta ST. Macrolide therapy of chronic Lyme disease. *Med Sci Monit* 2003;9:1136-1142.
17. Dinerman H, Steere AC. Lyme disease associated with fibromyalgia. *Ann Intern Med* 1992;117:281-285.
18. Sigal LH, Patella SJ. Lyme arthritis as the incorrect diagnosis in pediatric and adolescent fibromyalgia. *Pediatrics* 1992;90: 523-528.
19. Hsu VM, Patella SJ, Sigal LH. "Chronic Lyme disease" as the incorrect diagnosis in patients with fibromyalgia. *Arthritis Rheum* 1993;36:1493-1500.
20. Munce SEP, Stewart DE. Gender differences in depression and chronic pain conditions in a national epidemiologic survey. *Psychosomatics* 2007;48:394-399.
21. Petzke F, Gracely RH, Park KM, Ambrose K, Clauw DJ. What do tender points measure? Influence of distress on 4 measures of tenderness. *J Rheumatol* 2003;30:567-574.
22. Gran JT. The epidemiology of chronic generalized musculoskeletal pain. *Best Pract Res Clin Rheum* 2003;17:547-561.
23. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, MacFarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: Do they have common associated factors? *Int J Epidemiol* 2006;35:468-476.
24. Bayer ME, Zhang L, Bayer MH. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. *Infection* 1996;24:347-353.
25. Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. *Immunol Lett* 2001;76:43-48.
26. Sigal LH, Hassett AL. Contributions of societal and geographical environments to "chronic Lyme disease": The psychopathogenesis and aetiology of a new "medically unexplained symptoms" syndrome. *Environ Health Perspect* 2002;110:607-611.
27. Baker PJ. Perspectives on "chronic Lyme disease." *Am J Med* 2008;121:562-564.

Address reprint requests to:
 Gary P. Wormser, M.D.
 New York Medical College
 Division of Infectious Diseases
 Munger Pavilion Room 245
 Valhalla, NY 10595

E-mail: gary_wormser@nymc.edu