Long-term Assessment of Health-Related Quality of Life in Patients With Culture-Confirmed Early Lyme Disease

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(See the Editorial Commentary by Auwaerter on pages 248–50.)

The health-related quality of life of 100 subjects with culture-confirmed early Lyme disease enrolled in a prospective study with annual follow-up visits was evaluated using the 36-Item Short Form General Health Survey version 2 (SF-36v2) questionnaire at 11–20 years after diagnosis. The mean summary scores of physical and mental health were similar to those of the general population.

Keywords. Lyme disease; *Borrelia burgdorferi*; outcome; quality of life.

Lyme disease is the most commonly reported tick-borne infection in the United States [1]. The purpose of this study was to assess the long-term health-related quality of life in patients with culture-confirmed Lyme disease at 11–20 years after diagnosis based on the Medical Outcomes Study 36-Item Short-Form General Health Survey version 2 (SF-36v2), a widely used instrument in the study of Lyme disease and many other medical conditions [2–12].

METHODS

Two hundred eighty-three adult patients with erythema migrans, for whom the diagnosis was confirmed by recovery of *Borrelia burgdorferi* from culture of a skin or blood sample [13], were enrolled in a prospective study between 1991 and 2000; the subjects were asked to return annually to determine the long-term outcome of this infection [14, 15]. Patients who had concomitant possible neurologic or cardiac manifestations of Lyme disease were not excluded. At baseline, the patients were treated with antibiotics that are usually effective for *B. burgdorferi* infection [16]. The study was conducted in New York State and was approved by the institutional review board of New York Medical College.

During the years 2011–2013, the 100 participants who returned to the study center were assessed for their health-related quality of life by the self-administered SF-36v2; the SF-36 had not been used in our study prior to 2011. The standard form was used in which a 4-week time frame is specified for those questions that refer to a time interval. The SF-36v2 includes multiple scales that measure physical functioning, physical limitations on usual role-related activities, bodily pain, general health perceptions, vitality, social functioning, emotional limitations on usual role-related activities, and mental health [17]. These scales are used to calculate the 2 summary scores on the physical and mental components of the SF-36. Higher scores indicate better health-related quality of life. For each of the scales, the mean score for members of the general population has been normalized to be 50 ± 10. If our subjects' scores equalled the mean for the general population they were reported as 50; if they exceeded that of the general population they were reported as >50, and if they were less than that of the general population they were reported as <50. Only normalized values are reported in this study.

Statistical Methods

For continuous variables, independent sample *t* tests, assuming unequal variances, were used. For categorical variables, the Fisher exact test was used. Logistic regression was used to examine selected baseline characteristics jointly in distinguishing those subjects returning for the SF-36 evaluation and those who did not. Variables selected for this analysis were those that achieved a *P* value of .10 in univariable testing. Significance testing was conducted at a critical value of 5%. Analyses were conducted using Stata software, version 13.1 (StataCorp, College Station, Texas).

RESULTS

The mean age of the 100 subjects was 64.9 years (median, 64 years; range, 42–86 years) at the time of the SF-36 assessment;

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Table 1. Normalized 36-Item Short Form General Health Survey Results

Section	Normalized Score	
	Lyme Disease Patients	General US Population
Physical Component Summary	51.9	50
Mental Component Summary	52.8	50
Physical Functioning	51.3	50
Role Limitations, Physical	51.1	50
Bodily Pain Index	53.2	50
General Health Perception	53.1	50
Vitality	54.3	50
Social Functioning	52.2	50
Role Limitations, Emotional	50.9	50
Mental Health	53.2	50

52.0% were male. At the baseline visit, 81% had a single erythema migrans skin lesion and 19% had multiple skin lesions. When the SF-36 survey was conducted, the mean duration of follow-up since the diagnosis of culture-confirmed Lyme disease was 15.4 years (median, 16 years; range, 11–20 years). At least 24 (24%) of the subjects experienced an additional episode of early Lyme disease based on the development of the skin lesion erythema migrans during the follow-up period; such individuals were diagnosed clinically (with or without culture confirmation) and were retreated with recommended antibiotic regimens [16].

The mean summary scores of physical and mental health were virtually identical to the general population, as were the 8 subsurveys (Table 1). On the mental health survey, the percentage at risk for depression among the 100 subjects was also similar to the general population: 18% for the general population vs 16% of the 100 study subjects. Separate analyses stratified based on gender-by-age (35–44 years, 45–54 years, 55–64 years, 65–74 years, and ≥75 years) were also comparable to the norms for those subsets of the general population (data not shown).

Selected demographic variables and clinical features at time of presentation of the 100 subjects who returned to the study center during the time period when the SF-36 was administered were compared with those variables for the 183 subjects who did not return for this evaluation. As shown in Table 2, those who completed the SF-36 were older at time of study entry (49.1 ± 10.9 years vs 43.2 ± 13.4 years; $P < .001$), were less likely to be male (52.0% vs 66.7%; $P = .02$), and reported fewer symptoms at study entry (3.4 ± 2.9 vs 4.2 ± 3.1; $P = .03$). Participants and nonparticipants were similar on other Lyme disease–related characteristics at study entry, such as the proportion with multiple erythema migrans skin lesions.

A multiple logistic regression model containing the baseline characteristics of sex, age, and number of baseline symptoms was used to determine which of these variables were associated with completing the SF-36 evaluation, while adjusting for the other variables. In this model, all 3 factors remained significant. Although there was a significant difference in the number of baseline symptoms between those subjects who completed the SF-36 and those who did not, the mean difference was only approximately 1 symptom. Among symptomatic subjects, the proportion who were considered the most symptomatic with ≥6 symptoms was similar and substantial for both groups (24/81 [29.6%] among those who completed the SF-36 evaluation vs 56/155 [36.1%] for those who did not; $P = .39$). Adjusting for age and sex using logistic regression did not alter this finding ($P = .17$).

DISCUSSION

Erythema migrans is the earliest and most common clinical manifestation of Lyme disease, occurring in 70%–80% of patients [16]. The majority of US patients with erythema migrans will

Table 2. Comparison of Selected Variables for the 100 Subjects Who Underwent the 36-Item Short Form General Health Survey With the Other 183 Subjects Who Were Originally Enrolled but Did Not Return to the Study Center During the Time Period When the Survey Was Administered

Variable	Groups		*P* Value
	Subjects Who Underwent SF-36 Evaluation	Subjects Who Did Not Participate in the SF-36 Evaluation	
No. of subjects	100	183	
No. of males (%)	52 (52.0)	122 (66.7)	.02
Mean age ± SD at study entry (median [range])	49.1 ± 10.9 (49 [25–72])	43.2 ± 13.4 (42 [16–76])	<.001
No. with multiple erythema migrans at study entry (%)	19 (19.0)	45 (24.6)	.30
No. symptomatic at study entry (%)	82 (82.0)	155 (84.7)	.61
Mean No. of symptoms at study entry ± SD (median [range])	3.4 ± 2.9 (3 [0–10])	4.2 ± 3.1 (4 [0–11])	.03
Mean No. of days of illness until baseline visit ± SD (median [range])	5.4 ± 6.5 (3 [0–42])	6.8 ± 8.3 (4 [0–66])	.13

Abbreviations: SD, standard deviation; SF-36, 36-Item Short Form General Health Survey.

also have concomitant symptoms such as fatigue, musculoskeletal pains, headache, neck stiffness, and others. Although recommended treatment regimens have been uniformly successful in resolving the erythema migrans skin lesion, these other symptoms, although generally improved, may persist for ≥6 months in approximately 10% of patients (range, 0%–40.8% in 8 studies from the United States) [18]. For an undefined fraction of patients with posttreatment Lyme disease symptoms (PTLDS), the symptoms are so severe that they interfere with functionality. The specific subgroup of patients with symptoms of that level of severity was enrolled into 2 separate studies to determine if intensive retreatment with antibiotics might be beneficial [2].

The SF-36 health survey was employed in both of these retreatment studies [2] and in numerous other studies that have attempted to evaluate the outcome of Lyme disease patients [3–12]. In the 2 retreatment trials, it was found that the SF-36 scores of the Lyme disease patients with residual symptoms were less than that of the general US population [2]. The authors stated that "the deficits in physical health status as measured by the SF-36 were equivalent to those observed in patients with congestive heart failure or osteoarthritis and were more than 0.5 SD greater than the impairment observed with type II diabetes or a recent myocardial infarction" [2].

It is sometimes overlooked, however, that impaired functionality was an entry criteria for these retreatment trials [2, 19]. As a consequence, some have mistakenly concluded that all patients with PTLDS, or even all patients with Lyme disease, are at high risk to have residual impairment in their health-related quality of life.

The current study addressed the long-term health-related quality of life of patients with well-documented early Lyme disease, for which there is a paucity of data. The study demonstrated that at 11–20 years after diagnosis, the mean SF-36 scores of 100 patients with culture-confirmed erythema migrans were the same as for the general US population. These findings are remarkably similar to those of Kalish et al, who similarly studied 25 patients with Lyme disease using the SF-36 at 10–20 years after they had been diagnosed with erythema migrans and found normalized physical and mental component scores of 52 and 54, respectively [5].

A limitation of our study is that only 100 of the 283 subjects who were enrolled into this prospective study returned to the study center during the time period when the SF-36 was administered, raising a concern that there was selection bias. A comparison of the 100 subjects who completed the SF-36 survey with the other 183 subjects at the baseline visit showed that the frequency of symptomatic infection or of dissemination based on the presence of multiple erythema migrans skin lesions did not differ significantly between the 2 groups. However, those who did not return were more likely to be male and to be younger and to have approximately 1 more symptom on average on presentation. Whether these differences may have impacted our results is unclear. Neither male sex nor age at presentation increased the likelihood of persistent symptoms in a European study of patients with erythema migrans [20]. Furthermore, in our study there was no significant difference between those subjects who returned and those who did not in the proportion with >5 symptoms at the baseline visit. A prior analysis of a subset of the subjects enrolled in this study evaluated at multiple specified follow-up time points whether certain variables were associated with the development of PTLDS. A high number of baseline symptoms, most often averaging >5 per subject, was found to be associated with the development of PTLDS [13].

Another limitation of our study is that it was not directed at patients with extracutaneous manifestations of Lyme disease. Data from certain European studies have suggested that impairment in health-related quality of life may occur as a consequence of neurologic Lyme disease specifically [9, 11]. In addition, we did not evaluate patients using the SF-36 survey at an earlier time point after study entry.

In conclusion, subject to the limitations described above, our study has demonstrated that the long-term health-related quality of life of patients with culture-confirmed early Lyme disease, when assessed by the SF-36 survey, is on average similar to that of the general United States population.

Notes

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Disclaimer. The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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