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Tetracycline Therapy for Chronic Lyme Disease

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Two hundred seventy-seven patients with chronic Lyme disease were treated with tetracycline for 1 to 11 months (mean, 4 months); the outcomes for these patients were generally good. Overall, 20% of the patients were cured; 70% of the patients' conditions improved, and treatment failed for 10% of the patients. Improvement frequently did not take place for several weeks; after 2 months of treatment, 33% of the patients' conditions were significantly improved (degree of improvement, 75%–100%), and after 3 months of treatment, 61% of the patients' conditions were significantly improved. Treatment outcomes for seronegative patients (20% of all patients) were similar to those for seropositive patients. Western immunoblotting showed reactions to one or more *Borrelia burgdorferi*–specific proteins for 65% of the patients for whom enzyme-linked immunosorbent assays were negative. Whereas age, sex, and prior erythema migrans were not correlated with better or worse treatment outcomes, a history of longer duration of symptoms or antibiotic treatment was associated with longer treatment times to achieve improvement and cure. These results support the use of longer courses of treatment in the management of patients with chronic Lyme disease. Controlled trials need to be conducted to validate these observations.

The clinical spectrum of illness caused by *Borrelia burgdorferi* has been known since the early 1900s, even though the causative organism was not identified until 1982 [1–3]. In Europe, the disease was described in primarily neurological terms [4], whereas in the United States (where the disease was first described as a cluster of cases of arthritis occurring in young children in Old Lyme, CT), the emphasis initially was placed on the joint manifestations [5]. Indeed, the case definition of the Centers for Disease Control and Prevention (CDC) includes arthritis but not arthralgias and other neurological symptoms [6]. It has since become recognized that chronic symptoms consisting of fatigue plus musculoskeletal pains, paresthesias, and other neuropsychiatric dysfunctions are typical symptoms of chronic Lyme disease [7–9].

Laboratory support for the diagnosis of Lyme disease beyond the erythema migrans phase has suffered from a lack of sensitive and definitive tests: ELISAs have been unreliable [10, 11]; western immunoblotting has been more sensitive but more difficult to perform and standardize; and PCR analysis of DNA is insufficiently sensitive [12]. Furthermore, none of the laboratory tests can be used to estimate the extent of infection, its prior duration, or its prognosis.

The treatment of chronic Lyme disease is also inadequately defined. Although recommendations have been made for 1 month of treatment [13], there have been no trials to test or support this view. Most physicians practicing in this area believe that a longer duration of treatment is needed to effect significant improvement or cure [14]. Because of our initial positive experience with tetracycline therapy for patients with symptoms compatible with those of chronic Lyme disease [15], many subsequent patients were treated with this antibiotic. The results of tetracycline treatment for 277 patients seen between 1988 and 1995 are reported here.

Patients and Methods

Patients were seen at the University of Connecticut's Lyme Disease Clinic (Farmington, CT) between 1988 and 1993 and at Boston University Medical Center (Boston) from 1993 to 1995. The patients described herein are those whose symptoms existed for >3 months with or without a history of tick bite (29% with known bite) or rash (44% with known rash). Inclusion criteria were a combination of at least two of three sets of major symptoms: fatigue, neurological complaints (e.g., paresthesias, cognitive dysfunction, and radicular pains), and musculoskeletal complaints (e.g., arthralgias, myalgias, and weakness). Many patients had other symptoms such as visual and auditory disturbances, palpitations, and gastrointestinal and genitourinary dysfunction (the combination of major symptoms and other symptoms has also been noted in other studies [7–9, 14]).

All patients were evaluated for alternative diagnoses such as rheumatoid arthritis, systemic lupus erythematosus, and other neurological disorders. Fibromyalgia and/or chronic fatigue had been diagnosed for some patients; if these patients met the clinical inclusion criteria, they were offered a trial of tetracycline therapy.

Serological evaluations from 1988 to 1993 included ELISA and western immunoblotting conducted at the University of Connecticut Health Center (Farmington, CT); those evaluations from 1993 to 1995 included IgM capture assays and western immunoblotting conducted by BBI/North American Laboratories (New Britain, CT). Both laboratories have rigid quality

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control programs and have participated in the evaluation of laboratory tests for Lyme disease [10]. Western immunoblotting was considered to be positive if there were one or more reactions to proteins specific to *B. burgdorferi* (i.e., 23 kD, 31 kD, 34 kD, 39 kD, and 83 kD); reactions to several specific proteins were found for most patients, and reactions to at least two proteins (e.g., 23 kD and 41 kD) were found for all patients.

Patients were treated with tetracycline hydrochloride (500 mg three times daily) before or between meals. The treatment was continued until the patient's symptoms resolved or the patient's condition improved. For those patients whose symptoms completely resolved, treatment was generally continued for one more month. For those patients whose conditions improved but whose symptoms did not resolve, treatment was generally continued for one to two more months before stopping or changing therapy. For those patients for whom treatment failed, therapy was continued for at least 3 months before being judged a failure.

A treatment cure was defined as the absence of symptoms for 1 year or more following cessation of therapy; significant improvement was defined as having recovered ≥75% of previous normal function, as assessed by the patient. The conditions of patients whose symptoms resolved completely by the end of treatment but who subsequently had relapsing symptoms after tetracycline therapy was discontinued were considered significantly improved but not cured; these patients usually relapsed within 2–6 weeks following therapy.

Results

Serological reactivity and treatment outcome. A total of 277 patients were treated with tetracycline for 1 month or more. A comparison of the results of EIA and western immunoblotting for these patients is shown in table 1. Overall, EIA or western immunoblotting was positive for 81% of the patients. EIA was positive for 29% of the patients, and western immunoblotting was positive for 81% of the patients. Whereas EIA was positive for 0.8% of the patients for whom western immunoblotting was negative, EIA was negative for 52% of the patients for whom western immunoblotting was positive.

Table 1. Comparison of the results of western immunoblotting and EIA for 254 patients with chronic Lyme disease.

	Western immunoblotting	
EIA	Positive	Negative
Positive	72 (28)	2 (0.8)
Negative	133 (52)	47 (18.5)

NOTE. Data are number (%) of 254 patients for whom the serological test was positive.

Table 2. Comparison of treatment outcomes of chronic Lyme disease according to serological results.

	No. (%) of patients with treatment outcome		
Serological test, result	Cure	Improvement	Failure
EIA			
Positive	10 (14)	51 (74)	8 (12)
Negative	34 (22)	105 (70)	12 (8)
Western immunoblotting			
Positive	38 (20)	137 (71)	18 (9)
Negative	10 (26)	25 (66)	3 (8)

A comparison of treatment outcomes according to seropositivity or seronegativity is shown in table 2. There were no significant differences in treatment outcomes between those patients for whom western immunoblotting or EIA was positive and those patients who were seronegative.

Age, sex, and treatment outcome. The age of patients treated with tetracycline ranged from 13 to 75 years (mean, 39 years). There were no differences in treatment outcomes according to age (data not shown). Two-thirds of the patients were female; there was a tendency to fewer cures (14% vs. 32%, respectively) and more failures (11% vs. 7%, respectively) for females than for males (table 3).

Duration of prior symptoms and treatment outcome. Patients whose symptoms had been present for >1 year had fewer cures and more treatment failures than did those patients whose symptoms had been present for <1 year (table 4). Patients with symptoms for >3 years fared poorer than did those with symptoms for either 1–3 years or <1 year. The duration of prior symptoms was also directly correlated with the time to onset of any improvement (i.e., the longer the duration of prior symptoms, the longer the time until any signs of improvement were noted; table 5). The mean time to onset of any improvement was 0.9 month.

The extent of improvement at 2 and 3 months after the initiation of tetracycline therapy is shown in figure 1. By 2 months of therapy, the mean degree of improvement was 50%–75%, with only one-third of the patients believing that their conditions had significantly improved (degree of improvement, 75%–100%); by 3 months, 61% of the patients believed that their conditions had improved ≥75%.

Table 3. Comparison of treatment outcomes of chronic Lyme disease according to sex.

	No. (%) of patients with treatment outcome		
Sex	Cure	Improvement	Failure
Male	27 (32)	51 (61)	6 (7)
Female	22 (14)	115 (75)	17 (11)

Table 4. Comparison of treatment outcomes of chronic Lyme disease according to duration of prior symptoms.

Duration (y) of prior symptoms	No. (%) of patients with treatment outcome		
	Cure	Improvement	Failure
<1	33 (28)	78 (67)	6 (5)
1–3	9 (15)	45 (75)	6 (10)
>3	7 (11)	43 (71)	11 (18)

Duration of treatment and treatment outcome. Patients were treated for as little as 1 month or as long as 11 months (median, 4 months). Most patients were treated for between 3 and 6 months. The duration of treatment was correlated with the duration of prior symptoms (data not shown).

Prior treatment and treatment outcome. Patients who were treated with any antibiotics at any time before the onset of tetracycline therapy had fewer cures (16% vs. 31%, respectively) and a generally poorer outcome than did those who were not previously treated (table 6). These poorer outcomes were not dependent on the duration of prior symptoms.

Treatment outcome and serological reactivity. The results of western immunoblotting for the first 86 patients studied before and after treatment are shown in table 7. Western immunoblotting was positive for IgM for 94% of the symptomatic patients, and IgM was the only antibody found for 36% of these patients. With successful treatment, the rate of IgM seropositivity decreased to 25%, compared with a rate of 69% for IgG seropositivity; 22% of the patients became seronegative.

Retreatment and treatment outcome. Ninety-eight patients who were cured or whose conditions were improved at the end of treatment but who had relapsing symptoms were retreated with antibiotics (table 8). Fifty of these patients were given another course of tetracycline therapy (cure rate, 28%; significant improvement rate, 70%). Of thirty-five patients treated with a combination of a macrolide and hydroxychloroquine, 74% were cured or believed that their conditions were further improved. Of 13 patients treated with iv ceftriaxone, one was cured, and 10 noted significant improvement in their conditions.

Table 5. Comparison of the onset of improvement of chronic Lyme disease according to the duration of prior symptoms.

Duration of prior symptoms (no. of patients)	Percent of patients with indicated time to improvement (w)							
	1	2	3	4	5–6	7–8	9–12	13–16
<1 y (122)	12	48	12	17	7	2	1	1
1–3 y (73)	5	26	24	24	16	4	1	0
>3 y (74)	1	28	9	24	23	9	5	1

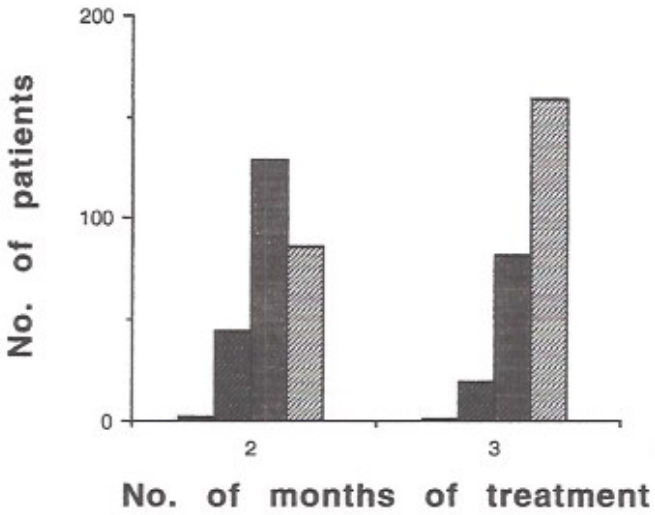

Figure 1. The number of patients with chronic Lyme disease whose conditions were improved at 2 and 3 months after the start of tetracycline therapy. The degree of improvement is indicated as follows: ■ = 0–25%; ▩ = 25%–50%; ▨ = 50%–75%; and ▩ = 75%–100%.

Discussion

The optimum criteria and methods for the diagnosis and treatment of chronic Lyme disease remain to be defined. Most practitioners use a clinical definition that includes a combination of symptoms and signs with or without positive serological support [14], but there are some who advocate a diagnosis that requires positive serologies [16]. A recommendation was made at a meeting of territorial public health officers in the fall of 1995 that western blotting be done only to confirm screening EIAs that reveal positive antibody titers [6]. According to our results and a physician survey [14], this approach would not diagnose >50% of the cases of chronic Lyme disease. Until better criteria are established, it would seem advisable to recommend that western immunoblotting, especially testing for IgM, be conducted for all patients who meet the clinical criteria.

IgM reactions may represent reactivation of latent disease or persistent infection and have been noted in other chronic infections (e.g., toxoplasmosis). Seronegative Lyme disease is a recognized entity [17–19] (K. Kezler, R. C. Tilton, M. Manak, and S. T. Donta, unpublished data), and our results demonstrate that patients with similar clinical symptoms who

Table 6. Comparison of treatment outcomes of chronic Lyme disease according to prior antibiotic treatment.

Prior treatment	No. (%) of patients with treatment outcome		
	Cure	Improvement	Failure
Yes	27 (16)	123 (73)	19 (11)
No	22 (31)	44 (63)	4 (6)

are seronegative have responses to antibiotic treatment that are not distinguishable from those of seropositive patients (including those who meet the current CDC criteria). These findings also suggest that circulating antibody responses are not the most relevant correlates of disease presence or activity. Until better diagnostic tests are available to document the presence and extent of infection, clinical criteria remain the mainstay of diagnosis.

The optimum treatment for chronic Lyme disease also remains to be delineated. No controlled clinical trials have been conducted to date, yet there appear to be strong opinions regarding the type and duration of any antibiotic therapy [20]. In contrast, there is a consensus that a 3- to 4-week course of therapy with a tetracycline or β-lactam antibiotic appears to yield a successful outcome of the earliest manifestation of Lyme disease (erythema migrans) [13]. Although it has yet to be established whether all or most cases of chronic Lyme disease are due to persistent infection, our results support the hypothesis that it is a persistent infection and provide the basis for a reasonable approach to its management.

The rationale for our use of tetracycline hydrochloride for the treatment of patients with chronic Lyme disease arose from several observations. One observation was that patients being seen in our Lyme disease clinic who had been previously treated with β-lactam antibiotics, including iv ceftriaxone, were not routinely cured or did not believe that their conditions were significantly improved, even after several months of therapy; serological tests for most of these patients were unequivocally positive. Another observation was that patients treated with doxycycline (100 mg twice daily) had some improvement in their conditions that was not sustained.

When the pharmacologic properties of doxycycline and tetracycline hydrochloride are compared, the absorption of doxycycline is sometimes better at comparable doses, but 500 mg of tetracycline three times daily achieves higher serum levels than does 100 mg of doxycycline twice daily [21]. Because doxycycline is also highly bound to proteins (which accounts for its longer half-life), the amount of free drug available to diffuse into tissues is less than that of tetracycline [21].

A third observation was the hypothesis that chronic Lyme disease is a persistent intracellular infection. This hypothesis draws support from what is known about other chronic infections, which most, if not all, have an intracellular reservoir (e.g., *Chlamydia, Legionella, Leishmania, Rickettsia,* and *Mycobacterium tuberculosis* infections). An intracellular location could also explain the difficulties posed for β-lactam antibiotics as treatment of Lyme disease; this location is supported by data from a tissue culture model of *B. burgdorferi* infection in which ceftriaxone was ineffective against intracellular organisms [22].

Table 7. Results of western immunoblotting before and after treatment of chronic Lyme disease.

Result	No. (%) of patients with indicated result	
	Symptomatic (n = 64)	Asymptomatic (n = 32)
IgG	4 (6)	17 (53)
IgM	23 (36)	3 (9)
IgG and IgM	37 (58)	5 (16)
No antibody	0	7 (22)

Table 8. Comparison of treatment outcomes of chronic Lyme disease according to retreatment.

Retreatment	No. of patients with treatment outcome		
	Cure	Improvement	Failure
Tetracycline	14	35	1
Macrolide plus hydroxychloroquine	4	22	9
IV ceftriaxone	1	10	2

Our results show that a 3- to 6-month course of treatment is associated with cure or significant improvement in 80%–90% of patients with chronic Lyme disease. The most important determinant of treatment duration and outcome appears to be the duration of symptoms before tetracycline therapy (tables 4 and 5). Improvement was noted to begin as early as 1–2 weeks, but in patients with symptoms for >1 year, the onset of any improvement frequently did not occur before 4–6 weeks of therapy had been given. It would not then be surprising if both patients and physicians would conclude that this mode of therapy was ineffective when there was no improvement after 3–4 weeks of therapy. This slow rate of improvement may correlate best with organisms for which the rates of multiplication and metabolism are slow, as is known for *B. burgdorferi* [23]. We speculate that the frequently noted cycles of improvement and relapse could be consistent with the varying metabolic activities of a heterogeneous population of spirochetes.

Our results also show that tetracycline is apparently effective in resolving symptoms associated with CNS function (i.e., cognition and emotions); these symptoms are probably secondary to encephalopathy. Recent studies with nonhuman primates have demonstrated that the CNS, especially sensory functions, is the main target of *B. burgdorferi* infection [24]. In this setting, tetracycline penetration would not appear to be a major limitation, as it might be in meningitis.

Our results suggest that the outcome for patients with symptoms compatible with those of chronic Lyme disease is generally good when tetracycline is administered for 3–6 months. Although this approach is relatively simple and inexpensive, it needs to be validated by controlled clinical trials comparing longer terms of therapy with short terms of therapy. Of great interest as well would be trials comparing the outcome of iv β-lactam therapy with that of tetracycline treatment.

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