

Successful Oral Doxycycline Treatment of Lyme Disease—Associated Facial Palsy and Meningitis

Leif Dotevall and Lars Hagberg

From the Department of Infectious Diseases, Institute of Internal Medicine, Göteborg University, Göteborg, Sweden

Twenty-nine patients, aged 11–79 years (mean, 50 years), with Lyme neuroborreliosis, facial nerve palsy, and meningitis were treated with oral doxycycline (daily dose, 200–400 mg) for 9–17 days in a prospective, nonrandomized study. Facial paresis was bilateral in eight (28%) of the 29 patients. Twenty-six patients (90%) recovered without sequelae within 6 months, while three of the patients with bilateral facial palsy at admission had remaining paresis at follow-up. In five patients, contralateral facial paresis developed 1–12 days after initiation of therapy, and two patients were retreated with antibiotics. Posttreatment examinations of cerebrospinal fluid showed a marked decrease of inflammatory cells and protein concentrations compared with pretreatment levels in all followed up patients. The favorable clinical outcome agrees with findings of other reports on intravenous antibiotic therapy for Lyme disease–associated meningitis with facial palsy. Our conclusion is that oral doxycycline is an effective and convenient therapy for Lyme disease–associated facial palsy.

Cranial neuropathy is the most frequent objective neurological sign in Lyme neuroborreliosis and has been found in 47%–82% of patients with early neurological involvement [1]. Although *Borrelia burgdorferi* sensu lato may affect most cranial nerves, facial nerve paresis is the most common manifestation of infection. Unilateral or bilateral facial palsy has been described in 72%–92% of patients with cranial nerve affection [1, 2]. In previous Scandinavian studies of patients with Lyme neuroborreliosis, facial palsy was seen in 35%–51% of the cases [3, 4]. Lyme disease–associated facial weakness is often rapid in onset and is frequently accompanied by painful meningoradiculoneuritis, earlier described as Garin-Bujadoux-Bannwarth's syndrome [1]. Facial palsy in Lyme disease has often been viewed as peripheral neuropathy, although most patients have CSF abnormalities with lymphocytic pleocytosis and an increased number of plasma cells, increased CSF protein concentrations indicating blood-CSF barrier damage, intrathecal Ig production, and increased levels of a CSF glial protein marker (glial fibrillary acidic protein) [5]. These findings imply that the brain parenchyma is likely to be involved even in early Lyme neuroborreliosis.

A few major prospective, randomized trials of antibiotic therapy for Lyme neuroborreliosis in adult patients with facial palsy have been reported [6–10]. However, the optimal antimicrobial therapy for Lyme disease–associated facial palsy

remains unclear, as reflected by the wide range of reported treatment recommendations regarding first-line drugs, route of antibiotic administration, and duration of anti-infective therapy.

Doxycycline has been considered an alternative oral treatment of Lyme neuroborreliosis because of the pharmacokinetic properties of this lipophilic agent [11, 12]. The oral absorption is considered to be 95% [13], and it has been shown that plasma concentrations are equivalent when doxycycline is given by the oral compared with the parenteral route [14]. The doxycycline concentration in CSF has been found to exceed the highest reported MIC₉₀ for *B. burgdorferi* sensu lato when patients are treated by the oral route [11], and several studies have shown that good clinical responses occur when orally or intravenously administered doxycycline is used as treatment of Lyme neuroborreliosis [6, 10, 15].

In this nonrandomized, prospective trial, we studied the efficacy of oral doxycycline therapy for patients with Lyme disease–associated meningitis and facial palsy.

Patients and Methods

Patients and Inclusion and Exclusion Criteria

One hundred twenty consecutive patients with Lyme neuroborreliosis were admitted to the Department of Infectious Diseases, Sahlgrenska University Hospital/Östra, Göteborg, Sweden, between 1988 and 1996; these patients were included in the Lyme neuroborreliosis study at the department. Unilateral or bilateral facial palsy was found in 38 (32%) of these patients. The diagnostic criteria of Lyme disease in the CNS followed the guidelines of Halperin et al. [16]; these criteria included neurological symptoms compatible with neuroborreliosis, inflammatory CSF reactions, and immunologic signs of exposure to *B. burgdorferi* sensu lato with a serum and/or CSF positive for antibody, and/or verified erythema migrans.

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Reprints or correspondence: Dr. Leif Dotevall, Department of Infectious Diseases, Sahlgrenska University Hospital/Östra, S-416 85 Göteborg, Sweden (leif.dotevall@medfak.gu.se).

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Exclusion criteria for the doxycycline treatment study were age younger than 8 years, pregnancy, previous allergic reactions to doxycycline, and intravenous β -lactam therapy within 2 weeks before admission. Four of the 38 patients with facial palsy (three children [mean age, 6 years] and one adult) were not included in the doxycycline treatment study; these patients were treated with intravenous penicillin G.

Thirty-four of the adult patients with facial palsy were treated with oral doxycycline. Three patients with facial nerve palsy and positive borrelia serologies had normal results of CSF examinations and were excluded from the study. Two patients were lost to follow-up.

Thus, a total of 29 patients (11 women and 18 men; mean age, 50 years) with Lyme disease-associated facial palsy and meningitis who were treated with oral doxycycline were evaluated for efficacy of the treatment (table 1). In cases with complete facial paralysis, an otoneurological examination was performed at admission. None of the patients had diabetes or any other serious concomitant disorders. There was no history of recurrent facial palsy. All but two of the patients were seen by one of the two authors.

The patients were followed up at the Department of Infectious Diseases for 5–108 months (median, 30 months). Samples for borrelia serology, blood tests, and CSF analyses were obtained at enrollment and 6–8 weeks thereafter. Follow-up CSF examinations were approved by the ethics committee at Göteborg University, Göteborg, Sweden.

CSF and Serum Samples

CSF samples from all patients before the start of antibiotic therapy were analyzed. Twenty-six (90%) of the 29 patients underwent second lumbar puncture 33–102 days (median, 43.5 days) after treatment. CSF analyses included determination of cell counts, microscopic characterization of cells, bacterial cultures, determination of protein and glucose concentrations and albumin CSF/serum ratio, and isoelectric focusing.

Serum and CSF specimens were analyzed with a commercial ELISA for IgG and IgM antibodies to purified native *Borrelia burgdorferi* sensu lato flagellum (Dako, Glostrup, Denmark). The cutoff levels for corrected absorbance and the intraassay and interassay variations were in accordance with the manufacturer's recommendations. Specific western blotting (immunoblotting) or PCR assays were not done. Wassermann and VDRL (Venereal Disease Research Laboratory) tests were performed on serum samples from all patients.

Statistical Methods

The χ^2 test was used to examine the relationships between clinical outcome and uni- or bilateral facial palsy. Comparisons

between outcome and CSF findings, pretreatment duration, and age were made with the Mann-Whitney *U* test.

Results

Clinical Findings

Pretreatment characteristics, treatment data, and clinical outcome for the doxycycline-treated patients are shown in table 1. A previous tick bite was recalled by 11 patients (38%), and erythema migrans was found in 10 (34%). Most patients (86%) presented with painful meningoradiculoneuritis or a distinct feeling of discomfort followed by development of facial neuropathy several days later, consistent with the classical Garin-Bujadoux-Bannwarth's syndrome. Three patients were admitted to the hospital with general malaise, low-grade fever, and headache in addition to the facial palsy, while one patient (with bilateral facial paresis) experienced only slight general discomfort and no other neurological signs or symptoms.

Bilateral palsy was found in eight (28%) of the 29 patients with facial nerve paresis. Five of these patients developed contralateral facial palsy within 1–12 days (mean, 6.0 days) after the start of antibiotic treatment. In two other patients treated for Lyme disease-associated meningoradiculitis, unilateral facial paresis occurred during antimicrobial therapy. The other neurological manifestations, including radiculitic pain, resolved or decreased in intensity in all patients during antibiotic treatment. Neither pretreatment disease duration nor patient age was found to be associated with bilateral facial paresis.

CSF Changes

CSF cell counts before and after treatment are shown in table 1. For 26 patients who underwent a spinal tap at follow-up after a median 43.5 days, the mean lymphocyte count decreased from $240 \times 10^6/L$ to $12 \times 10^6/L$ during therapy. The mean pretreatment CSF protein concentration was 1,649 mg/L, and the mean posttreatment level was 536 mg/L. CSF cytology before treatment showed characteristic abnormalities with reactive lymphocytic pleocytosis and an increased number of plasma cells in all patients. Three or more oligoclonal Ig bands were noted by CSF protein electrophoresis and isoelectric focusing as a sign of intrathecal antibody production in 27 (93%) of the 29 patients. CSF glucose levels were normal in all patients. Neither pretreatment CSF cell counts nor pretreatment CSF protein concentrations were associated with the occurrence of bilateral palsy, although the two highest CSF protein values were found in patients with facial diplegia (patients 25 and 27).

Borrelia and Syphilis Serology

All patients had positive borrelia antibody tests in serum, CSF, or both. Twenty-seven patients (93%) had a positive

Table 1. Pre- and posttreatment data for patients with Lyme disease—associated facial palsy.

Patient no., sex	Age (y)	Duration before therapy* (d)	Facial palsy	Outcome	Pretreatment CSF finding		Posttreatment CSF finding		IgG and/or IgM antibody to <i>Borrelia</i> in	
					Lymphocyte count ($\times 10^6/L$)	Protein concentration (mg/L)	Lymphocyte count ($\times 10^6/L$)	Protein concentration (mg/L)	Serum	CSF
1, F	50	35	Unilateral	1	160	641	ND	ND	Positive	Positive
2, F	61	37	Unilateral	1	428	2,659	5	1,040	Negative	Positive
3, M	62	14	Unilateral	1	190	1,265	1	376	Positive	Positive
4, F	34	21	Bilateral	1	140	1,648	7	383	Positive	Positive
5, M	39	15	Bilateral	1	110	1,100	3	361	Positive	Positive
6, M	11	8	Unilateral	1	53	423	ND	ND	Positive	Positive
7, F	62	10	Unilateral	2	422	773	6	329	Positive	Positive
8, M	44	14	Bilateral	2	150	637	4	536	Positive	Negative
9, F	48	12	Unilateral	1	210	1,067	2	410	Positive	Positive
10, M	69	25	Unilateral	1	436	3,660	8	971	Negative	Positive
11, F	70	30	Unilateral	1	216	1,009	2	453	Positive	Positive
12, M	30	21	Unilateral	1	148	ND	8	392	Positive	Positive
13, M	31	21	Unilateral	1	442	1,531	7	340	Positive	Positive
14, M	29	60	Unilateral	1	1,100	1,874	18	565	Positive	Positive
15, M	67	45	Unilateral	2	30	788	7	657	Positive	Negative
16, M	68	18	Unilateral	1	64	750	7	451	Positive	Positive
17, F	48	30	Bilateral	3	608	3,260	45	664	Positive	Positive
18, M	51	30	Unilateral	2	291	2,584	9	640	Positive	Positive
19, M	36	13	Bilateral	1	214	2,700	41	744	Positive	Positive
20, F	19	14	Unilateral	1	271	2,450	16	388	Positive	Positive
21, M	73	40	Unilateral	1	55	768	14	458	Positive	Positive
22, F	64	16	Bilateral	3	10	387	3	284	Positive	Negative
23, F	49	30	Unilateral	1	88	783	11	459	Positive	Positive
24, M	41	20	Unilateral	1	23	528	2	310	Positive	Positive
25, M	33	20	Bilateral	3	564	4,800	38	622	Positive	Positive
26, F	79	45	Unilateral	1	109	1,436	32	660	Positive	Positive
27, M	53	14	Bilateral	1	300	4,000	4	760	Positive	Positive
28, M	62	14	Unilateral	1	24	1,364	3	687	Positive	Positive
29, M	67	5	Unilateral	2	104	1,289	ND	ND	Positive	Negative
Mean	50	23			240	1,649	12	536		

NOTE. Mean duration between first and second lumbar punctures was 43.5 days. 1 = no facial paresis at 2-month follow-up; 2 = no signs of facial palsy within 6 months; 3 = sequelae.

* Duration before therapy refers to neurological symptoms.

borrelia serology in serum, and 25 (86%) had a CSF test positive for antibody to *Borrelia*. All but one patient had negative Wassermann tests. The confirming *Treponema pallidum* hemagglutination assay and fluorescent treponemal antibody absorption test for IgM and IgG were negative for this patient.

Duration of Therapy and Adverse Effects

The duration of treatment with oral doxycycline was 9–17 days (mean, 10.8 days). The doxycycline dosage was 200 mg twice daily for 28 of 29 patients and 100 mg twice daily for one 11-year-old child. One patient experienced a Jarisch-Herxheimer reaction after the first dose of oral doxycycline.

Another patient developed transient hemiparesis during treatment, possibly an infection-triggered vascular ischemia. This patient recovered without any sequelae. Less than one-half of the patients complained of minor gastrointestinal irritation. No photosensitivity reactions were reported.

Retreatment

Two patients were retreated because of progression of facial palsy during doxycycline treatment. One of the patients, who had complete unilateral facial palsy at admission, developed contralateral paresis 12 days after the start of therapy and was given another course of oral doxycycline for 13 days. Another

patient (no. 10), who had meningitis and excruciating radicular pain but no signs of paresis at the start of treatment, developed unilateral facial palsy on the ninth day of antibiotic therapy. A second spinal tap on the same day showed a decrease in the CSF lymphocyte count from 436 to $93 \times 10^6/L$ in parallel with pronounced relief of the severe pain. He was treated with intravenous cefotaxime for 7 days. Both retreated patients recovered without sequelae within 8 weeks.

Clinical Outcome

Six months after treatment, 90% of the patients had no residual signs of Lyme disease–associated facial palsy (table 1). Three patients (10%) had remaining facial palsy with contracture at follow-up after 24 months, including one with only slight unilateral residual paresis. The clinical finding of facial diplegia was significantly correlated to residual symptoms ($P = .003$). None of these three patients needed occlusive glasses for the eyes after the initial months. The pretreatment durations of facial palsy did not differ between the patients with and without sequelae. Pretreatment disease duration, CSF cell count and protein level, and patient age were not associated with clinical sequelae.

Additional neurological symptoms were found in 12 of the patients at the follow-up examination. Eight patients (28%) experienced temporary subjective manifestations of paresthesias and hypoesthesias during the first months after therapy, while four patients (14%) had symptoms of fatigue and concentration impairment at a follow-up 6 months later. Objective sequelae were found only in one patient at a follow-up 6 months later (slight supranuclear arm paresis and partial facial diplegia) in addition to the two other patients with residual signs of facial palsy.

Discussion

In this nonrandomized, prospective treatment study during an 8-year period, all patients older than 10 years of age at the Department of Infectious Diseases, Sahlgrenska University Hospital/Östra, who had Lyme neuroborreliosis–associated facial paresis and meningitis were treated with oral doxycycline if the inclusion criteria were fulfilled. Oral doxycycline (200 mg twice daily) has been the recommended treatment of Lyme neuroborreliosis in adults at this department since 1987. In addition to clinical outcome, CSF cell counts and protein levels before and after treatment were analyzed. We found that oral doxycycline was effective and convenient treatment of Lyme disease–associated facial paresis.

B. burgdorferi has been regarded as the etiologic agent of peripheral facial palsy of otherwise unknown origin in 11%–20% of adult patients in Sweden [17–20]. In children, 33%–64% of the cases of facial paresis are caused by borreliosis [21–23]. Culture or characterization of the genospecies of the *Borrelia* spirochete was not done in this study. However, thor-

ough epidemiological investigations of *B. burgdorferi sensu lato* in ticks on migrating birds in Scandinavia showed that the subspecies *Borrelia garinii* was the most prevalent of the *Borrelia* genospecies [24]. Among European *B. burgdorferi* strains isolated in clinical studies, *B. garinii* has also been the most common subspecies found in CSF samples from patients with Lyme neuroborreliosis [25], implying that *B. garinii* was the probable etiology of most cases in this trial.

Of all clinical manifestations of Lyme neuroborreliosis, facial paresis is more easily objectively evaluated than other symptoms, such as radicular pain, sensory deficits, or encephalopathy. However, there are specific difficulties in assessing the efficacy of antibiotic therapy for the acute phase of Lyme disease–associated facial paresis. First, although antibiotic treatment appears to relieve neurological symptoms and contribute to the resolution of CSF inflammation, cranial neuropathy may still progress, with development of contralateral palsy up to a few days after the initial facial paresis (possibly due to an inflammatory response and the limited space in which the facial nerve is situated) [4]. Second, spontaneous recovery often occurs even without antibiotic therapy. Among adult patients presenting with peripheral idiopathic facial palsy (Bell's palsy), the recovery rate reported in five studies was 72%–83% [26]. The outcome of facial weakness in children seems to be better than that of facial weakness in adults [22].

In a well-defined Danish group of 95 patients with Lyme neuroborreliosis and facial palsy, of whom most were treated with intravenous penicillin G, 15% and 3% were found to have slight and severe posttreatment sequelae after unilateral palsy, respectively [4]. The corresponding rates among patients with bilateral palsy were 37% and 7%, respectively. The number of patients with severe sequelae agrees with the result of the present study.

Two patients were retreated because of progression of the symptoms at the end of the first antibiotic course. However, CSF analysis after the first treatment period for one of the patients showed a marked decrease in cell count and protein concentration as a sign of antimicrobial efficacy. The other patient was retreated with oral doxycycline. In all patients, the CSF cell count was either normalized or decreased to <30% of the initial value in a mean of 55.6 days after treatment.

CSF cell counts and protein concentrations are valuable means of assessing disease activity and the efficacy of antimicrobial treatment of Lyme neuroborreliosis. In another European study, improvement of these CSF parameters was shown to reflect clinical recovery in 37 patients treated with ceftriaxone intravenously for early and late Lyme neuroborreliosis [27]. Seventeen of these patients had facial palsy. The CSF findings for our patients treated with doxycycline were in accordance with those for the ceftriaxone-treated patients.

Oral treatment has several advantages. It reduces the number of visits to hospitals or outpatient clinics, and it is more cost-effective than parenteral antimicrobial administration. The use

of oral doxycycline in Lyme disease—associated facial paresis has previously been reported in one randomized study comparing intravenous penicillin G with oral doxycycline (200 mg daily) for 14 days [10]. Nine of 11 patients with facial paresis and Lyme neuroborreliosis were successfully treated with oral doxycycline, while two patients were found to have slight residual palsy. In the present study, the treatment duration was shorter (mean, 10.8 days) than in the previous trial, but the daily dose of oral doxycycline was higher (median, 400 mg). The rationale for the higher antimicrobial dose was the earlier observation that CSF doxycycline concentrations of 400 mg daily exceeded the estimated MIC for *B. burgdorferi* *sensu lato* in most cases [11]. Furthermore, steady-state levels of doxycycline are achieved faster with daily doses of 400 mg than with daily doses of 200 mg.

Oral doxycycline in a daily dose of 200 mg for 21 days was recently reported to be as effective as parenterally administered ceftriaxone for 14 days for patients with acute disseminated Lyme disease, but the study did not include patients with meningitis [28]. Questions have been raised concerning oral therapy for disseminated Lyme disease. Some investigators have proposed that neurological sequelae might be more frequent with oral antibiotics than with parenteral antibiotics [29]. This would certainly be the case if oral β -lactam antibiotics or other antimicrobial agents with insufficient penetration into brain parenchyma are used in Lyme disease in the CNS. The pharmacological properties of different antimicrobials must be considered, both to prevent risks of inadequate oral treatment of CNS infections and to avoid unnecessary, expensive, and risky therapies with intravenously administered antibiotics.

The older tetracyclines have less favorable pharmacokinetic properties than doxycycline, and since they are less lipid soluble, they do not reach as high tissue concentrations in the CNS [30]. Furthermore, residual neurological symptoms after antibiotic therapy have often been attributed to ongoing infection, without confirmation by thorough analyses and repeated CSF examinations. Infection-triggered immunologic processes, as well as permanent tissue damage caused by the initial infection, might be alternative explanations for residual neurological dysfunction.

We conclude that oral doxycycline is an effective and convenient alternative to intravenous antibiotic therapy for Lyme disease—associated facial paresis and meningitis. Randomized trials of oral doxycycline vs. intravenous ceftriaxone are needed for further evaluation of the optimal treatment of Lyme neuroborreliosis.

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