Steroid Use in Lyme Disease-Associated Facial Palsy Is Associated With Worse Long-Term Outcomes

Nate Jowett, MD; Robert A. Gaudin, MD; Caroline A. Banks, MD; Tessa A. Hadlock, MD

Objective: The purpose of this study was to determine whether differences in long-term facial function outcomes following acute Lyme disease-associated facial palsy (LDFP) exist between patients who received antibiotic monotherapy (MT); dual therapy (DT) with antibiotics and corticosteroids; and triple therapy (TT) with antibiotics, corticosteroids, and antivirals.

Study Design: Retrospective cohort.

Methods: All patients with a prior diagnosis of unilateral LDFP who presented to our center between 2002 and 2015 were retrospectively assessed for inclusion. Two blinded experts graded static, dynamic, and synkinesis parameters of facial functions using standardized video documentation of facial function.

Results: Fifty-one patients were included. The mean time of assessment following LDFP onset was 15.1 months (range 0.3–84 months). Significantly worse facial outcomes were seen among those who received DT and TT as compared to those who received MT, most pronounced among those assessed 12 months or later following onset of LDFP (Dynamic—P = 0.031, post hoc MT vs. TT: mean difference [MD], 15.83; 95% confidence interval [CI], 1.54–30.13; P = 0.030. Synkinesis—P = 0.026, post hoc MT vs. TT: MD, 21.50; 95% CI, 0.68–42.32; P = 0.043, post hoc MT vs. TT: MD, 19.22; 95% CI, 2.23–36.22; P = 0.027).

Conclusion: An association between corticosteroid use in acute LDFP and worse long-term facial function outcomes has been demonstrated. Care should be taken in differentiating viral or idiopathic facial palsy (e.g., Bell palsy) from LDFP.

Key Words: Corticosteroids, Lyme disease, facial paralysis, synkinesis, outcomes, glucocorticoids, prednisone, neuroborreliosis, facial palsy, facial nerve, Borrelia burgdorferi, facial spasm, nerve regeneration.

Level of Evidence: 4.

INTRODUCTION

Lyme disease (LD) is the most common vector-borne human illness in the Northern hemisphere.1 Caused by spirochaetes of the Borrelia genus (B. burgdorferi in North America; primarily B. afzelii and B. garinii in Eurasia), the incidence is increasing. Recent figures estimate 300 thousand yearly cases in the United States alone.2 Lower motor neuron facial palsy (FP) is a common manifestation of early acute neuroborreliosis, occurring in 7.5% to 10% of previously untreated LD cases.3–5

The clinical presentation of LD-associated facial palsy (LDFP) involves a rapid-onset loss of tone across all facial zones of the affected side, resulting in flaccid FP, with gradual recovery over the following weeks to months.6 Although the two largest studies of outcomes following LDFP found that most patients recover normal facial function, 16% to 23% will have residual deficits.3,4 Clinically, this is seen as permutations of hypo- and hyperactivity with undesirable coactivation of facial muscles (i.e., synkinesis); it is known as postparalysis or nonflaccid FP (Fig. 1).6 Such dysfunction results from aberrant neuronal regeneration, where axons extend to mimetic muscles other than those they ought to innervate.7,8 It is unknown why—despite prompt appropriate antibiotic therapy—aberrant regeneration occurs in some patients following acute LDFP while others fully recover. The purpose of this study was to determine whether differences in long-term facial function outcomes following acute LDFP might exist between patients who received antibiotic monotherapy and those who received concurrent corticosteroids.

MATERIALS AND METHODS

The institutional review board at the Massachusetts Eye and Ear approved this study. Patients with a prior diagnosis of LDFP who presented to our center between January 2002 and August 2015 were assessed for inclusion. The majority of patients presented with postparalysis facial dysfunction. Patients meeting Centers for Disease Control and Prevention (CDC) 2011 case definition criteria for confirmed LD (FP in addition to erythema migrans with known tick exposure, or FP in addition to laboratory evidence of infection consisting of a positive cerebrospinal fluid antibody test or positive two-tier serology testing) were included.9 Exclusion criteria were prior episode of FP, inappropriate documentation of initial treatment, inappropriate antibiotic therapy (i.e., onset delayed by > 14
days following onset of FP; or agent, route, or duration of therapy inconsistent with the Infectious Disease Society of America guidelines, recent botulinum toxin administration, and absent video documentation of facial function. Cases with bilateral involvement were excluded because normal contralateral hemifacial function is required for accurate outcomes grading.

In addition to history, physical examination, imaging, and laboratory findings pertaining to the period of acute LDLP, documented variables included age, gender, type and timing of initial pharmaceutical management, and comorbidities (diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, hypothyroidism, mood disorders, tobacco and alcohol use). Facial function was graded using the previously validated eFACE facial grading system by two facial reanimation surgeons blinded to management, based on video documentation of a standardized sequence of volitional facial expressions on initial presentation to our institution (Fig. 2).

**Statistical Analysis**

Patients were grouped by initial pharmaceutical management, consisting of antibiotic monotherapy (MT); dual therapy (DT) with concurrent antibiotics and corticosteroids; or triple therapy (TT) with concurrent antibiotics, corticosteroids, and antivirals (acyclovir or valacyclovir in all cases). Demographics, comorbidities, and timing of antibiotic therapy with respect to LDLP onset were compared between groups. Facial function was compared between groups using static, dynamic, synkinesis, and composite eFACE scores for four time periods following onset of LDLP (less than 3 months or greater than 3, 6, or 12 months).
months. One-way analysis of variance (ANOVA) with Dunnett’s post hoc (with MT group as control) was used where normality and homogeneity conditions were met, as respectively assessed using the Shapiro-Wilk test and Levene statistic. Welch ANOVA with Dunnett T3 post hoc was used for comparisons meeting normality conditions but demonstrating inhomogeneous variance between groups. The independent-samples Kruskal-Wallis test was used for nonparametric ratio data, and the chi-square test for nominal data with pairwise significances was adjusted using the Bonferroni correction. Tests were performed using IBM SPSS Statistics (v22, IBM Corp., Armonk, NY), with significance level ($\alpha$) set at 0.05 (two-tailed).

RESULTS

Figure 3 demonstrates the flow of patients included in this study. Of those with confirmed unilateral LDFP, 17 (25%) were excluded due to inadequate documentation of initial therapy, inadequate antibiotic therapy, a prior episode of FP, or absent video documentation. Of the 51 patients included, the mean age was 39.6 years (range 6–72 years), with a male-to-female ratio of 1.04:1 and a right-to-left side ratio of 0.70:1. All patients reported complete or near complete flaccid FP at time of onset (i.e., House Brackmann Scale12 V or VI). The mean time of video documentation of facial function following LDFP was 15.1 months (range 0.3–84 months). Fifteen patients presented within 3 months; 17 presented between 3 and 12 months; and 19 presented 12 months or later following onset of LDFP.

The diagnosis of LD as the cause of the acute FP was made on initial presentation in 16 of 18 patients who received MT, in all 17 cases of those who received DT, and in six of 16 cases of those who received TT (MT vs. DT, $P = 0.471$; MT vs. TT, $P = 0.006$). Ten patients were initially incorrectly diagnosed with Bell palsy (BP) and two with Ramsay Hunt syndrome. Of these 12 patients, six described myalgia and six described frontal headaches, with two describing a rash consistent with erythema migrans on initial presentation with acute FP. Four of these 12 patients did not report a rash, headache, or myalgia. Of these, one described prodromal general malaise; one described severe facial pain; and two presented solely with acute facial paralysis and...
retroauricular pain, features that are clinically indistinguishable from BP. Of the 49 patients who reported initial symptoms (e.g., erythema migrans, headache, myalgia, fever), the mean time between initial symptom onset and LDFP onset was 6.8 days (range 0–42 days). Eight patients recalled a tick bite; of these, the average time from the bite to LDFP onset was 17 days (range 9–21 days).

Thirteen patients (25.5%) had already been diagnosed with LD and were taking appropriate antibiotics at the time of FP onset; of these, three patients were taking them for at least 1 week. Serology was reported in 41 of 51 (80.4%) patients. Of these, 26 patients were sent within 24 hours of the development of acute FP, with 19 (80.8%) returning positive and five (19.2%) returning negative for LD by enzyme immunoassay (EIA). Repeat serology returned positive by EIA in all five cases, with confirmatory Western blot (WB) positive for immunoglobulin M (IgM) and negative for immunoglobulin G (IgG) in two cases (sent 1 week following FP onset), and positive for both IgM and IgG in the remaining cases (sent 13 days or later). Of the nine patients whose serology was sent 48 hours or more prior to the onset of FP, four were negative (sent between 3 and 10 days prior) and five were positive by EIA and confirmatory WB, with IgM positive for all five and IgG positive in one (sent between 2 and 5 days prior). Of the four patients initially negative, three underwent repeat serology, with two returning positive by EIA and WB (sent between 1 and 20 days after FP onset) and one

Fig. 3. Study flowchart. Of the 88 patients assessed for inclusion, 68 had confirmed Lyme disease; 51 of these met criteria and were included in the present study. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
returning negative again by EIA (sent 4 days prior to FP onset). All six patients whose serology was sent 48 hours or later following FP onset were positive for LD by EAI and WB (sent between 2 and 16 days later).

Lumbar puncture (LP) was reported in 15 (29.4%) patients; all cases demonstrated lymphocytic pleocytosis with elevated protein and normal glucose. Lumbar puncture was performed within 24 hours of FP onset in 11 of these cases; samples from two of these patients underwent polymerase chain reaction for *B. burgdorferi* DNA, returning positive in one and negative in the other. Nine patients underwent magnetic resonance imaging (MRI); of these, four patients were imaged within 24 hours of LDFP onset. Of these four scans, all were performed without use of intravenous contrast; two scans were read as normal; and two demonstrated nonspecific scattered periventricular and subcortical white-matter T2 hyperintensities. Two patients underwent MRI with gadolinium contrast of the temporal bones within 5 weeks of FP onset, with enhancement of the facial nerve (FN) demonstrated along the labyrinthine, internal auditory canal, and tympanic segments seen in both. Enhancement extended to the mastoid segment in one patient and was demonstrated by the contralateral FN in the other patient despite clinically unilateral weakness.

Three patients underwent MRI imaging with contrast of the temporal bones long after LDFP onset; of these, ipsilateral FN enhancement was seen in two patients (one imaged at 4 months and the other at 8 months) and was not seen in one patient (imaged at 24 months).

The prevalence of examined comorbidities did not differ between groups. Figure 4 illustrates facial outcomes and timing of antibiotic therapy with respect to LDFP onset. No significant differences in static facial appearance at any time point were appreciated between treatment groups (Fig. 4 A). Differences between groups were detected for dynamic facial movements and measures of synkinesis, becoming significant 6 months following LDFP onset (Fig. 4 B,C), with differences in facial function composite scores between groups already seen among those presenting 3 months or later following LDFP onset (Fig. 4 D). Where differences existed, post hoc comparisons consistently showed worse outcomes for those who received DT or TT as compared to those who received MT. There was no difference in the timing of initiation of appropriate antibiotic therapy with respect to LDFP onset between MT and DT groups; a difference did exist for the TT group, with patients in this group demonstrating a significant delay in receiving appropriate antibiotics (Fig. 4-E).

Table I summarizes statistical tests, mean differences, and confidence intervals for facial function outcome measures. Interrater reliability of expert eFACE scoring of facial function was high (Static parameters—ICC = 0.817; 95% confidence
interval (CI), 0.697–0.893. Dynamic parameters—ICC = 0.939; 95% CI, 0.895–0.965. Synkinesis parameters—ICC = 0.879; 95% CI, 0.794–0.930; composite score; ICC = 0.874; 95% CI, 0.787–0.927; P < 0.001 for all).

**DISCUSSION**

No established role for corticosteroids in the setting of acute LD or LDFP exists.\(^{13,14}\) Heretofore, consensus that corticosteroid use in patients with LDFP receiving appropriate antibiotics has not shown clear benefit or harm has been based on two retrospective studies. The larger of these studies, published over 30 years ago by Clark et al.,\(^3\) demonstrated no difference in facial outcomes among 101 patients with LDFP who received antibiotics alone, concurrent antibiotics and steroids, steroids alone, or no treatment whatsoever. This study was limited by the failure to properly document the follow-up period, with the text suggesting that most patients were followed for less than 6 months. However, postparalysis synkinesis does not usually become apparent until several months following nerve insult,\(^{15}\) progressing in severity until a permanent plateau of dysfunction is reached at 12 to 18 months. Early in recovery, patients may appear to have regained relatively normal facial function prior to the development of severe facial synkinesis. This study was further limited in that facial outcomes were assessed using the crude six-point House-Brackmann Scale,\(^{12}\) which provides only enough resolution to distinguish normal (I) from near-normal facial function (II), moderate (III) from severe (IV) facial impairment, and a flicker of movement (V) from no movement (VI). In practice, the scale is reduced to four points when looking at long-term outcomes because all patients who develop LDFP will subsequently regain obvious facial movement.

The second study, published by Kalish et al. more than 15 years ago,\(^4\) examined long-term outcomes of 31 patients, 15 of whom received antibiotics and 16 of whom did not. Of those who received antibiotics, nine received concurrent corticosteroids, implying that six patients received antibiotics alone. Considering the small sample size, a lack of significant differences in outcomes among the groups could be attributed to the small sample size. However, it is also possible that corticosteroids provide no added benefit or harm in the setting of LDFP receiving appropriate antibiotics. Further work is necessary to determine whether corticosteroids should be used in patients with LDFP receiving appropriate antibiotics.
size, and the fact that facial function was assessed on a crude binary scale comprising presence or absence of facial weakness, the failure of this study to detect a difference in outcomes between groups is unsurprising. Of note, the Kalish et al. study found that 14 of 16 patients (87.5%) who did not receive antibiotics went on to develop Lyme arthritis, compared to two of 15 (13.3%) patients who did. Antibiotic therapy is always indicated to prevent this devastating long-term rheumatic complication.16

With no established role, why were corticosteroids prescribed to nearly two-thirds of the patients in the present study? Three reasons are likely: misdiagnosis, semantics, and ongoing mystery surrounding the pathophysiology of LDFP. Because corticosteroids are the standard of care for acute viral facial paralysis, it is not surprising that they were prescribed to nearly all patients who were initially misdiagnosed as having such. That LDFP can occur without preceding symptoms was recognized over 30 years ago; that LDFP can occur prior to the development of a measurable antibody response was recognized nearly 25 years ago.17 In this study, all patients were either positive for LD by laboratory testing or had reported at least one symptom consistent with viral FP, such as a rash, frontal headache, myalgia, severe facial pain, or general malaise at the time of LDFP onset. The overall sensitivity of a thorough history and physical examination, combined with EIA screening for the diagnosis of LDFP, likely approaches 100%.

Semantics warrants discussion: Facial palsy is a symptom that may be associated with Lyme disease; LDFP is not BP. Bell palsy is a clinical diagnosis of exclusion for which strong clinical evidence supports early systemic corticosteroid therapy in patients with moderate-to-severe weakness.18,19 Unfortunately, substitution of the term Bell palsy (which is a diagnosis) for the FP that may occur as a symptom of LD occurs frequently in the literature,17,20,21 and even on the CDC website on the topic.22 The incorrect use of such terminology leads to confusion among treating clinicians and could very well impact management.

That strong clinical and radiologic similarities exist between BP and LDFP may further confuse management, causing some to assume similarity of the underlying pathophysiologies and to infer that corticosteroids ought to benefit both conditions. However, important clinical and pathophysiologic differences exist. Bell palsy is a distinct mononeuropathy of the FN, for which strong evidence points to viral reactivation in sensory neuron cell bodies within the geniculate ganglion,23 and subsequent spread of the viral infection to FN Schwann cells. The result is a massive inflammatory infiltration of the nerve,24 thought to result in edema and ischaemic neural compression within the fallopian canal,25,26 subsequent Schwann cell death and demyelination; Wallerian degeneration; and in severe cases, damage to neural sheaths and subsequent development of synkinesis. Use of corticosteroids to dampen the host’s inflammatory response in the setting of viral FP is logical and supported by level 1a evidence.18,19

In contrast to Bell palsy, direct infection of the facial nerve is unlikely to play a major pathophysiologic role in LDFP because the spirochete is rarely found in neural tissues.20,27–31 The peripheral neuropathy of LD is a mononeuropathy multiplex with electrophysiology and biopsy findings consistent with an axonal neuropathy.29,32,33 Peripheral nerve biopsies in humans and non-human primates (NHPs) with LD have demonstrated multifocal Wallerian degeneration and axon loss, with perivascular inflammatory infiltrates—most concentrated in the epineurium—characterized by a high percentage of lymphocytes and plasma cells, without evidence of necrotizing vasculitis or primary demyelination.20,27,28,31,32–36 The inflammatory infiltrate in the absence of spirochete invasion that occurs in peripheral nerves in patients with LD points to autoimmunity as the underlying pathophysiology of LDFP.

Although cell-mediated autoimmunity or edematous compressive neuropathy occurring secondary to the inflammatory infiltration are plausible pathophysiologies, clinical and molecular evidence exist to support humoral autoimmunity as the root cause of LDFP. First, the inflammatory infiltrate seen in peripheral nerves in patients with LD contains a high proportion of plasma cells whose primary function is immunoglobulin production. Antibody and complement deposition have been demonstrated in neural tissue from humans and NHPs with neuroborreliosis.20,39 Serum of patients with LD has been shown to contain IgM antibodies to B. burgdorferi that cross-react with human axonal antigens,30,37,38 and higher levels of antiganglioside IgM antibodies have been shown in serum of patients with neuroborreliosis as compared to those with predominantly cutaneous and articular involvement.39 Animal models have shown that these antibodies are triggered by B. burgdorferi infection and bind to homologous antigens in the nodes of Ranvier,40 potentially explaining the mechanism underlying the diffuse axonal neuropathy that is seen in LD.41 IgM-specific mimicry is supported by clinical evidence of FP that often develops before any measurable IgG response, of FP that develops days or weeks after the initiation of appropriate antibiotic therapy and resolution of other symptoms, and by the frequent failure of corticosteroids to improve symptoms of LD neuropathy in the absence of antibiotic therapy.36

If LDFP is a humoral immune neuropathy, corticosteroid therapy may be ill-advised. Evidence has demonstrated that oral corticosteroids may delay recovery in Guillain-Barré syndrome.42–44 In NHP models of neuroborreliosis, corticosteroid monotherapy was found to increase spirochetal load in neural tissues29,45 and impair anti-B. burgdorferi isotype switching, resulting in higher IgM and lower IgG levels in the serum of immunocompromised animals as compared to infected immunocompetent controls.45 These findings provide possible explanations for the failure of corticosteroids to improve neuropathy symptoms in LD, and for why patients who received concurrent corticosteroids in the present study demonstrated worse long-term facial outcomes as compared to those who received antibiotics alone. Although delay in diagnosis and subsequent initiation of antibiotic
therapy may partially account for the worse outcomes seen among those who received TT in this study, such a delay in antibiotic treatment was not present for those who received DT, whose outcomes were similarly morbid.

Caution is warranted in interpreting the present findings because this study is retrospective, biased by patient self-selection to our center, and biased in that the sample population is principally representative of the smaller subset of LDPP patients who develop post-paralysis FP. In addition, the proportion of patients prescribed antibiotics alone versus concomitant corticosteroids for LDPP in the general population is currently unknown.

CONCLUSION
The present findings support caution in the use of corticosteroids in acute LDPP. A prospective study utilizing high-resolution facial grading scales and blinded expert observers to compare outcomes between treatment groups is required. Further work should seek to elucidate the pathophysiology of LDPP.

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