

## LYME DISEASE IN CHILDREN IN SOUTHEASTERN CONNECTICUT

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## ABSTRACT

**Background** Although the incidence of Lyme disease is highest in children, there are few prospective data on the clinical manifestations and outcomes in children.

**Methods** We conducted a prospective, longitudinal, community-based cohort study of children with newly diagnosed Lyme disease in an area of Connecticut in which the disease is highly endemic. We obtained clinical and demographic information and performed serial antibody tests and follow-up evaluations.

**Results** Over a period of 20 months, 201 consecutive patients were enrolled; their median age was 7 years (range, 1 to 21). The initial clinical manifestations of Lyme disease were a single erythema migrans lesion in 66 percent, multiple erythema migrans lesions in 23 percent, arthritis in 6 percent, facial-nerve palsy in 3 percent, aseptic meningitis in 2 percent, and carditis in 0.5 percent. At presentation, 37 percent of the patients with a single erythema migrans lesion and 89 percent of those with multiple erythema migrans lesions had antibodies against *Borrelia burgdorferi*. All but 3 of the 201 patients were treated for two to four weeks with conventional antimicrobial therapy, which was administered orally in 96 percent. All had prompt clinical responses. After four weeks, 94 percent were completely asymptomatic (including the two patients whose parents had refused to allow antimicrobial treatment). At follow-up a mean of 25.4 months later, none of the patients had evidence of either chronic or recurrent Lyme disease. Six patients subsequently had a new episode of erythema migrans.

**Conclusions** About 90 percent of children with Lyme disease present with erythema migrans, which is an early stage of the disease. The prognosis is excellent for those with early Lyme disease who are treated promptly with conventional courses of antimicrobial agents. (N Engl J Med 1996;335:1270-4.)

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**L**YME disease has become a relatively common problem among children in areas of the country in which the disease is endemic.<sup>1,2</sup> However, there are few prospective studies of the disease among children in the United States.

Many parents fear that their children will acquire Lyme disease with complications that are difficult to treat and may become chronic, debilitating, or even fatal.<sup>3</sup> Consequently, they sometimes question whether intravenously administered antimicrobial agents would be better than orally administered agents and

whether prolonged therapy (i.e., lasting several months) would be better than conventional therapy (i.e., two to four weeks of amoxicillin or doxycycline) for their children. In addition, when children with early Lyme disease who have been treated with appropriate antimicrobial agents later have vague, nonspecific symptoms (e.g., headache, fatigue, and myalgia), their parents often worry that the antimicrobial therapy was inadequate and request that additional antimicrobial agents be prescribed. Although there are data on the persistence or recurrence of symptoms among adults with early Lyme disease, as well as on the risk of progression to late disease, there is very little such information about children.<sup>4,9</sup> To remedy this situation, we conducted a prospective, longitudinal, community-based cohort study of children with Lyme disease in southeastern Connecticut.

## METHODS

## Study Population

All children from five pediatric practices who were given a diagnosis of Lyme disease of recent onset were eligible to be enrolled in the study. The five pediatric practices are located in southeastern Connecticut, the area of the state with the highest reported incidence of Lyme disease (180 cases per 100,000 population in New London county).<sup>10</sup> The practices care for more than 40,000 children; the pediatricians in these practices are all experienced in the diagnosis and treatment of Lyme disease.

## Enrollment Criteria and Definitions

Before the study began, the participating physicians agreed on criteria for the diagnosis of Lyme disease based on the surveillance case definition established by the Centers for Disease Control and Prevention (CDC)<sup>11</sup>: an erythema migrans lesion ( $\geq 5$  cm in diameter) or clinical manifestations of either early disseminated or late Lyme disease with serologic evidence of infection with *Borrelia burgdorferi*. However, if a child had an expanding erythematous lesion consistent with the definition of erythema migrans that was less than 5 cm in diameter and the epidemiologic and other clinical findings were consistent with Lyme disease, the lesion could be classified as erythema migrans.

Early localized disease was defined as a solitary erythema migrans lesion with or without an influenza-like illness. Early disseminated disease was defined as multiple erythema migrans lesions

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or either neurologic disease (e.g., aseptic meningitis, cranial-nerve palsy, or peripheral neuropathy) or acute cardiac disease with serologic evidence of infection with *B. burgdorferi*. Late disease was defined as arthritis, encephalopathy, or polyneuropathy with serologic evidence of infection with *B. burgdorferi*.

The antimicrobial agents used to treat each patient were selected by his or her pediatrician. Treatment consisted of conventional antimicrobial therapy — either orally administered amoxicillin, doxycycline, erythromycin, or penicillin or intravenously administered ceftriaxone.

**Initial and Follow-up Evaluations**

At the time of enrollment, after informed consent had been obtained from a parent or guardian, demographic and clinical information about each patient was obtained by one of our specially trained research assistants through a telephone interview using a standardized form. Follow-up telephone interviews were conducted 1, 4, and 8 weeks and 6, 12, 18, and 24 months later. During these interviews, information was obtained from one of the child's parents or guardians about the persistence or recurrence of both specific (e.g., erythema migrans) and nonspecific (e.g., headache, myalgia, arthralgia, and fatigue) signs and symptoms during and after the completion of antimicrobial therapy. Information was also obtained about the possible progression from early to late Lyme disease.

The medical records of each patient were reviewed by one of our research assistants for the results of all physical examinations performed by one of the investigators during visits either for routine well-child care or for an acute problem that occurred after enrollment in the study. The results of these examinations were carefully analyzed for any objective evidence of Lyme disease.

To determine whether the patients had complied with the antimicrobial regimen, urine specimens collected from each patient on days 7 and 14 of treatment were tested for antimicrobial activity by a simple microbiologic technique.<sup>12</sup>

The patients were asked for a sample of blood at the time of enrollment (initial sample) and approximately eight weeks later (follow-up sample). All serum samples were stored at -70°C for later testing. Initial and follow-up samples from each patient were analyzed at the University of Connecticut Health Center in the same batch for concentrations of both IgM and IgG antibodies against *B. burgdorferi* with our own enzyme-linked immunosorbent assay.<sup>13</sup> We also analyzed all samples from each patient together for both IgM and IgG antibodies against *B. burgdorferi* using our own immunoblot assay.<sup>14</sup> The results were interpreted with the use of recently described criteria, and all positive results with the enzyme-linked immunosorbent assay were confirmed by immunoblotting.<sup>13,15</sup>

**Statistical Analysis**

For proportions, 95 percent confidence intervals were estimated by standard methods.<sup>16</sup> Relations between the stage of disease at presentation and the demographic and clinical variables were assessed with statistical tests appropriate for the type of variable, including one-way analysis of variance for the comparison of means and either the Wilcoxon or the Kruskal-Wallis test for the comparison of ordinal measures.<sup>17</sup> When the F value derived from analysis of variance was statistically significant, post hoc comparisons were made with the Tukey-Kramer HSD (honestly-significant-difference) test for multiple group comparisons.<sup>18,19</sup> Risk ratios and their 95 percent confidence intervals were estimated with Epi Info software (CDC, Atlanta). Contingency-table analyses were performed with the chi-square test or Fisher's exact test. P values (two-tailed) below 0.05 were considered to indicate statistical significance.

**RESULTS**

A total of 201 consecutive children with newly diagnosed Lyme disease were enrolled between April

1, 1992, and November 30, 1993. The patients ranged from 1 to 21 years of age (median, 7; mean, 7.8), and 65 percent were boys. One hundred thirty-two (66 percent) presented with early localized Lyme disease (i.e., a single erythema migrans lesion), 56 (28 percent) presented with early disseminated Lyme disease, and 13 (6 percent) presented with late Lyme disease (all with arthritis). The initial presentation was in June, July, or August for 89 percent of both those with early localized disease and those with early disseminated disease. The 13 patients with late Lyme disease presented at all times of the year, although 4 (31 percent) presented in October. The proportions of patients presenting with each stage of Lyme disease were similar for both years of the study. There was no association between the patient's age, sex, or race and the stage of Lyme disease at the time of presentation.

The initial clinical manifestations of Lyme disease in these patients are given in Table 1. Of the 201 patients, 179 (89 percent) presented with either a single erythema migrans lesion or multiple lesions;

**TABLE 1. CLINICAL MANIFESTATIONS OF LYME DISEASE AT THE TIME OF PRESENTATION IN 201 CHILDREN.**

| CLINICAL FINDING                  | STAGE OF LYME DISEASE        |                                |                  |
|-----------------------------------|------------------------------|--------------------------------|------------------|
|                                   | EARLY LOCALIZED<br>(N = 132) | EARLY DISSEMINATED<br>(N = 56) | LATE<br>(N = 13) |
|                                   | percentage of patients       |                                |                  |
| Single erythema migrans lesion    | 100                          | 2                              | 0                |
| Multiple erythema migrans lesions | 0                            | 84                             | 0                |
| Fever                             | 24                           | 45                             | 23               |
| Fatigue                           | 58                           | 80                             | 15               |
| Headache                          | 42                           | 70                             | 31               |
| Arthralgia                        | 33                           | 50                             | 100              |
| Neck pain                         | 26                           | 34                             | 8                |
| Nausea                            | 21                           | 36                             | 15               |
| Abdominal pain                    | 17                           | 18                             | 23               |
| Diarrhea                          | 16                           | 21                             | 0                |
| Myalgia                           | 16                           | 21                             | 38               |
| Sore throat                       | 12                           | 20                             | 15               |
| Cough                             | 8                            | 13                             | 0                |
| Rhinorrhea                        | 8                            | 11                             | 23               |
| Vomiting                          | 7                            | 25                             | 0                |
| Conjunctivitis                    | 5                            | 25                             | 8                |
| Facial palsy                      | 0                            | 11                             | 0                |
| Aseptic meningitis                | 0                            | 7                              | 0                |
| Arthritis                         | 0                            | 0                              | 100              |
| Carditis                          | 0                            | 2                              | 0                |
| Joint swelling                    | 0                            | 2                              | 100              |
| Numbness                          | 0                            | 2                              | 0                |
| Dysesthesia                       | 0                            | 2                              | 0                |

1 additional patient presented with a single erythema migrans lesion and a facial-nerve palsy. In 119 of the 132 patients (90 percent) who had a single erythema migrans lesion at the time of presentation, the lesion was at least 5 cm in diameter.

Of the 132 patients who had a single erythema migrans lesion at the time of presentation, 47 (36 percent) had had a recognized tick bite within the preceding month. However, in only 29 (62 percent) of these patients was the tick bite at the site of the erythema migrans. Of the patients who were examined often (every day or every other day) for ticks, 23 percent had had a recognized tick bite at the site of the erythema migrans, as compared with 13 percent of those who were examined occasionally (every three to seven days) and 6 percent of those who were examined rarely (less than once a week) ( $P < 0.01$ ). Patients who were rarely or never examined for ticks were more likely to present with late disease (16 percent) than patients who were examined more frequently (4 percent) (relative risk, 3.9; 95 percent confidence interval, 1.3 to 11.4;  $P < 0.03$ ).

The single erythema migrans lesions were on the head or neck in 26 percent of the patients who had them, on the arms or legs in 25 percent (legs in 17 percent and arms in 8 percent), on the back in 24 percent, on the abdomen in 9 percent, in the axilla in 8 percent, in the groin in 5 percent, and on the chest in 3 percent. Patients with lesions on the head or neck were significantly younger than those with lesions at other sites (mean age, 5.9 vs. 8.1 years;  $P < 0.01$ ); patients with lesions on the arms or legs were significantly older than those with lesions at other sites (mean age, 9.2 vs. 7.4 years;  $P < 0.04$ ).

#### Serologic Results

Of the patients with either single or multiple erythema migrans lesions from whom serum samples were obtained, the proportions with antibodies against *B. burgdorferi* in their initial and follow-up samples are shown in Table 2. Of the 96 patients with early localized Lyme disease from whom both initial and follow-up samples were obtained, 6 (6 percent) had IgM or IgG antibodies against *B. burgdorferi* in the initial specimen but not in the follow-up specimen and 5 (5 percent) had IgM or IgG antibodies against *B. burgdorferi* in the follow-up specimen but not in the initial specimen. Of the 25 patients with multiple erythema migrans lesions from whom both initial and follow-up samples were obtained, 6 (24 percent) had IgM or IgG antibodies against *B. burgdorferi* in the initial specimen but not in the follow-up specimen, and none had IgM or IgG antibodies against *B. burgdorferi* in the follow-up specimen but not in the initial specimen. All 11 patients with late Lyme disease from whom both initial and follow-up samples were obtained had IgG antibodies against *B. burgdorferi* in both specimens.

**TABLE 2.** PERCENTAGE OF PATIENTS WITH ERYTHEMA MIGRANS WHO HAD ANTIBODIES AGAINST *B. BURGDORFERI* AT ENROLLMENT AND AT FOLLOW-UP.\*

| ANTIBODY | ENROLLMENT                               |  | FOLLOW-UP                               |  |
|----------|--|--|---|--|
|          | SINGLE ERYTHEMA MIGRANS LESION (N = 118) | MULTIPLE ERYTHEMA MIGRANS LESIONS (N = 38) | SINGLE ERYTHEMA MIGRANS LESION (N = 99) | MULTIPLE ERYTHEMA MIGRANS LESIONS (N = 26) |
|          | percentage of patients                   |  |   |  |
| IgM      | 31                                       | 89   | 21                                      | 35   |
| IgG      | 19                                       | 58   | 28                                      | 62   |
| Either   | 37                                       | 89   | 39                                      | 69   |

\*The follow-up samples were obtained approximately eight weeks after enrollment.

#### Treatment

Antimicrobial agents were administered orally to 192 (96 percent) of the patients: 71 percent received amoxicillin, 27 percent received doxycycline, 1.5 percent received erythromycin, and 0.5 percent received penicillin. Orally administered antimicrobial agents were given for 14 to 35 days (median, 21); 94 percent received 20 to 28 days of therapy. The parents of two patients, each with multiple erythema migrans lesions, refused to allow antimicrobial treatment for their children. Ceftriaxone was administered intravenously to seven patients (3 percent); three of these patients had meningitis, two had a peripheral facial-nerve palsy, one had both meningitis and a facial-nerve palsy, and one had carditis. Intravenously administered antimicrobial agents were given for 10 to 30 days (median, 21); 86 percent of these patients received 10 to 21 days of therapy.

Among 137 patients initially treated with oral amoxicillin, treatment was switched to erythromycin in 3 and to doxycycline in 1 because of mild side effects, before the initial course of therapy was completed. Among the 51 patients initially treated with oral doxycycline, treatment in 3 was switched to amoxicillin because of mild side effects, before the initial course of therapy was completed. Among the seven patients initially treated with intravenous ceftriaxone, treatment was switched to intravenous ampicillin in one because of a rash, before the completion of the initial course of therapy. One patient received three 21-day courses of orally administered amoxicillin because of recurrent episodes of arthralgia.

#### Compliance

Of the 192 patients treated with orally administered antimicrobial agents, the urine strips obtained after one week of therapy were returned by 169 patients (88 percent); of these, 111 (66 percent) had

antimicrobial activity in their urine. The urine strips obtained after two weeks of therapy were returned by 153 of the 192 patients (80 percent) treated with orally administered antimicrobial agents; of these, 104 (68 percent) had antimicrobial activity in their urine.

#### Outcomes

None of the 145 patients with either early localized or late Lyme disease were hospitalized. Of the 56 patients with early disseminated Lyme disease, 4 (7 percent) were hospitalized (3 had aseptic meningitis and 1 had carditis) for one to nine days (median, three).

All 201 of the patients who were enrolled or their parents or guardians completed the follow-up telephone interview at 6 months, 97 percent completed the 12-month follow-up, 96 percent completed the 18-month follow-up, and 95 percent completed the 24-month follow-up. At the four-week follow-up, 94 percent of the patients were completely asymptomatic (including the two who had not received antimicrobial therapy), 5 percent continued to have nonspecific symptoms (e.g., arthralgia, myalgia, and fatigue), and 1 percent had a residual peripheral facial-nerve palsy. The nonspecific symptoms were mild and did not interfere with either play or school. By the six-month follow-up all the symptoms in all the patients except one had resolved. At long-term follow-up a mean of 23.3 months (range, 9 to 24) later, none of the patients had evidence of either chronic or recurrent Lyme disease. The parents of the child who was still symptomatic at 6 months continued to report mild, intermittent arthralgia without any objective signs of arthritis throughout the 24-month follow-up. This arthralgia did not interfere with either school or play, and it is not clear that there was any causal relation to Lyme disease.

Of the 201 patients, 178 (89 percent) had at least one follow-up physical examination 1 to 46 months (mean, 25.4; median, 25) after enrollment. No patient had documented evidence of either neurologic or rheumatologic complications from Lyme disease during any of these examinations.

#### Reinfections

Six patients had subsequent episodes of Lyme disease during the study. Of these patients, four initially presented with a single erythema migrans lesion and two presented with multiple erythema migrans lesions; all the subsequent episodes of Lyme disease consisted of either single or multiple lesions. Two of the six patients had neither IgG nor IgM antibodies against *B. burgdorferi* in the follow-up sample after the initial episode. However, one patient had both IgM and IgG antibodies and three patients had IgG antibodies against *B. burgdorferi* in the follow-up samples after the initial episode.

#### DISCUSSION

Limited data suggest that as compared with adults, children with Lyme disease are more likely to present with fever and arthritis and are less likely to present with erythema migrans.<sup>1,20,21</sup> Recent reports from Europe suggest that children with Lyme disease commonly present with either peripheral facial-nerve palsies or aseptic meningitis and are less likely to present with arthritis than with neurologic symptoms.<sup>22-24</sup> However, in this study, we found that almost 90 percent of 201 children with Lyme disease presented with erythema migrans, a proportion similar to that recently reported among adults in a prospective, population-based study.<sup>10</sup> We found, as did European investigators,<sup>25,26</sup> that erythema migrans was more likely to be on the head or neck in younger children and on the arms and legs in older children.

In this study, only about one third of the patients who presented with early, localized Lyme disease had had a recognized tick bite within the preceding month. In addition, the location of the tick bite in relation to the erythema migrans suggested that in 38 percent of these patients, *B. burgdorferi* had been transmitted from a different, unrecognized tick bite.

As in studies primarily of adults,<sup>24,27</sup> we found that only about one third of the patients with a single erythema migrans lesion had serologic evidence of *B. burgdorferi* at the time of presentation, whereas almost 90 percent of the patients with multiple erythema migrans lesions were seropositive. However, in contrast to these earlier reports, we found that one month after the completion of the antimicrobial therapy (eight weeks after enrollment), very few of the seronegative children had become seropositive.

The children in this study with early Lyme disease had prompt clinical responses to antimicrobial therapy; within approximately one week of completing their initial course of antimicrobial therapy, 94 percent were completely asymptomatic. As has previously been demonstrated in adults with Lyme disease,<sup>4,5</sup> the persistence of vague, nonspecific symptoms in these patients was not an indication of treatment failure. By six months after the initial course of antimicrobial therapy, all these symptoms had resolved in all but one patient, and only one patient was given additional courses of antimicrobial therapy.

Subsequent episodes of erythema migrans have been reported in patients who received appropriate antimicrobial therapy for their initial episode of erythema migrans.<sup>6,28</sup> It has been assumed that prompt initiation of antimicrobial therapy for early Lyme disease can depress the humoral immune response to *B. burgdorferi* while the patients' cellular immune responses may be left intact.<sup>29</sup> Such patients may be susceptible to reinfection after subsequent encounters with *B. burgdorferi*. Four of the six patients with second episodes of erythema migrans in this study had antibodies against *B. burgdorferi* in their serum

after the initial episode, suggesting that the antibody response to *B. burgdorferi* with episodes of erythema migrans may not provide protection against subsequent infection.

Whether treated with orally administered penicillin, amoxicillin, doxycycline, or tetracycline, 90 percent or more of adults with early Lyme disease are cured.<sup>4,5,7,8</sup> A recent retrospective cohort study of 63 children with physician-documented erythema migrans who had been treated appropriately found that none of the patients had evidence of problems attributable to Lyme disease 1 to 6 years (mean, 3.5) later.<sup>6</sup> In a prospective, controlled investigation of the cognitive skills of children treated for Lyme disease a mean of 24 months earlier, none of the 41 patients had impairment of cognitive functioning.<sup>9</sup>

With the exception of one patient who received multiple courses of antimicrobial therapy, one who received 5 weeks of antimicrobial therapy, and two whose parents refused to allow them to be treated, all our patients received a single, conventional (2-to-4-week) course of antimicrobial therapy, and at the time of the follow-up telephone interview and physical examination (a mean of 23.3 and 25.4 months later, respectively), none had evidence of either chronic or recurrent Lyme disease or of progression from early to late disease. We conclude that the prognosis for children with early Lyme disease who are treated with appropriate antimicrobial therapy is excellent.

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## APPENDIX

The following are other members of the Pediatric Lyme Disease Study Group: Drs. Frederic P. Anderson, Brenda K. Balch, Donald P. Buebendorf, Kenneth R. Burke, Nancy Czarkowski, Owen R. Ehrlich, Charles R. Esposito, Steven H. Forstein, Bernard A. Gisserman, Christopher W. Goff, Phyllis A. Hoffman, Dennis S. Long, David M. Rinzler, Charles H. Robinson, Dawn C. Torres, and E. Maurice Wakeman.

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