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Pediatric Lyme Arthritis: Clinical Spectrum and Outcome

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Summary: A cohort of children with Lyme arthritis was used to evaluate the clinical and serologic profile of the disease. During a 42-month period (June 1989 to December 1991), 44 patients (13 girls and 31 boys, ages 4–18 years) were included and followed for 6–36 months. Inclusion required the presence of arthritis, as well as positive serology. Thirty-four children with juvenile rheumatoid arthritis or spondyloarthropathy were used as a serologic comparison group. Five different patterns of arthritis were found. Preceding erythema migrans was seen in seven children. Antinuclear antibodies were positive in 30% of the patients. Three treatments were used and selected according to physician preference, patient age, and presence of extraarticular disease: amoxicillin, doxycycline, and ceftriaxone. Articular disease reached complete resolution in all patients within 2–12 weeks. Lyme arthritis in children may mimic other pediatric arthritides. Prognosis for children with clearly defined Lyme arthritis was excellent. **Key Words:** Lyme arthritis—Serologic testing.

Lyme disease is a growing clinical (6) and public health problem (9). The standard of practice in pediatric rheumatology has changed to accommodate this "new" entity in the diagnostic work-up of childhood arthritis. In our area, which includes Delaware, southern Pennsylvania and New Jersey, and northern Maryland, Lyme disease is among the three most common nontraumatic arthritides in children. The clinical manifestations of pediatric Lyme arthritis, and the long-term outcome of untreated patients have been reported (4,17). This study focused on the multiple articular forms of pediatric Lyme arthritis, the differential diagnosis with other pediatric arthritides, and the outcome of timely diagnosed and treated children.

In this study, a cohort of children with Lyme arthritis was used to evaluate the clinical and serologic profile of the disease and its outcome. During a 42-month period (from June 1989 to December 1991), 44 children with serologically confirmed Lyme arthritis were included and followed for 6–36 months for clinical and serologic assessment.

MATERIALS AND METHODS

Study population

In May 1990, all patients diagnosed with Lyme were enrolled in a longitudinal study. The aim was to gain insight on the articular outcome and serologic evolution of treated patients with Lyme arthritis. The protocol involved initial evaluation at diagnosis, including complete history, physical examination, Lyme serology, and electrocardiogram, and clinical and serological assessment at follow-up visits (1, 6 and 12 months). The clinical follow-up was consistently undertaken by three of the authors, and the serologic testing was performed at the same laboratory. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), and rheumatoid factor (RF) were also measured at the initial visit.

Inclusion in the present study required presence of synovitis confirmed by a physician on physical examination, positive Lyme serology by enzyme-linked immunosorbent assay (ELISA) and Western blot analysis at initial evaluation (5,10,11), and a minimum of 6 months follow-up from initial evaluation. Lyme arthritis patients diagnosed before May of 1990 who were subsequently followed in our Lyme disease clinic were also included in this study if they fulfilled the inclusion criteria.

Serologic testing

Antibodies to *Borrelia burgdorferi* were measured by ELISA and Western blot techniques at presentation and at each follow-up visit. The ELISA test was performed as previously described (5,10,11). Briefly, for the ELISA, patient sera were diluted 1:80 with phosphate-buffered saline (PBS) containing 0.7 mg/ml of soluble *Escherichia coli* an-

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tigens and added to microtiter wells containing a 10,000 *g* supernatant fraction of sonicated *B. burgdorferi*. Following incubation and washing, peroxidase-conjugated anti-human immunoglobulin G (IgG) antiserum (Cappel) was added to each well for a 30-min incubation. Wells were then washed, substrate (ABTS) added, and the optical density (OD) was determined using a Titertek multiskan at 405 nm. An OD of 0.2, which is equivalent to a titer of >1:80, was considered positive.

IgG and immunoglobulin M (IgM) antibodies to *B. burgdorferi* antigens were measured by Western blot analysis as follows (11). Spirochete antigens were prepared and separated by polyacrylamide gel electrophoresis (PAGE), using the method of Laemmli (8). Separated antigens were transferred from the PAGE gel to nitrocellulose strips using a Nova blot transfer system (LKB Laboratories). The nitrocellulose strips were then blocked with 0.5% bovine serum albumen (BSA), dried, and stored desiccated until needed. Patient sera were diluted 1:100 with blotting buffer and incubated at room temperature for 1 h. After washing, a 1:1000 dilution of biotinylated goat anti-human IgG or IgM (KPL) was added, and incubated for 1 h. The strips were then washed and a 1:1000 dilution of peroxidase-conjugated streptavidine (KPL) was added for a 1 h incubation. Substrate (4-chloro-1-Naphthol) was then added to visualize antibody binding, and reactivity was determined by comparison to controls.

Comparison population

Two groups of patients with recognizable rheumatic diseases were included for comparison: a juvenile rheumatoid arthritis (JRA) group consisted of children with pauci, poly or systemic forms who satisfied the American College of Rheumatology criteria (1), and a spondyloarthropathy group included patients with SEA syndrome (seronegativity, enthesopathy, arthritis) (12), psoriatic arthritis or juvenile ankylosing spondylitis.

Therapeutic options

Any of the following therapies were selected according to physician preference, patient age and/or presence of extraarticular disease: (a) oral amoxicillin 60 mg/kg/day (q 8 h) for 4 weeks; (b) oral doxycycline 100 mg (q 12 h) for 4 weeks for children >8 years of age; and (c) i.v. ceftriaxone 100–200 mg/kg/day up to 2 g/day for 2 weeks followed by 2 weeks of amoxicillin or doxycycline according to the patient's age. In some patients, antiinflammatory agents, including ibuprofen (30–40 mg/kg/day) and tolmetin (30 mg/kg/day) were added for a period of 15 days to 2 months. A second course of antibiotics (i.v. ceftriaxone) was given to those patients who showed persistent arthritis for ~1 month after the conclusion of the initial course or worsening of joint involvement during the first week of oral therapy.

RESULTS

Of the 44 children who satisfied the inclusion criteria, 13 were girls and 31 were boys. Two patients were black and the rest were Caucasian. Ages were 4–18 years (mean 9.2 years). Twenty percent of the patients recalled being bitten by a deer tick. Eighteen percent had single erythema chronicum migrans (ECM), and none had multiple ECM. Three neurologic complications were seen: one Bell's palsy, one aseptic meningitis, and one diffuse encephalopathy with an abnormal magnetic resonance image scan.

Five forms of articular involvement were observed, as follows:

1. Classical: episodic synovitis with involvement of one to four joints for <1 week, separated by asymptomatic intervals of at least 2 weeks (2 weeks to 6 months).
2. Acute pauciarticular ("pseudoseptic"): continuous involvement of one to four joints for <4 weeks.
3. Chronic pauciarticular (pauci–JRA-like): persistent arthritis in one to four joints for >4 weeks.
4. Migratory: involvement of three or more joints in a sequential pattern in which one "hot joint" predominates at any given time.
5. Polyarticular: involvement of five or more joints.

The frequency of each articular pattern is depicted in Fig. 1.

The intensity of serologic reactivity measured by ELISA titer and Western blot band count did not differ among the five subsets of articular presentation. Table 1 compares initial serologies in the Lyme and chronic arthritis populations. Follow-up sera (>6 months) was available in 25 patients. Anti-*Borrelia* antibody titers by ELISA decreased two- to fivefold dilutions in 22 patients, remained unchanged in two patients, and increased in one pa-

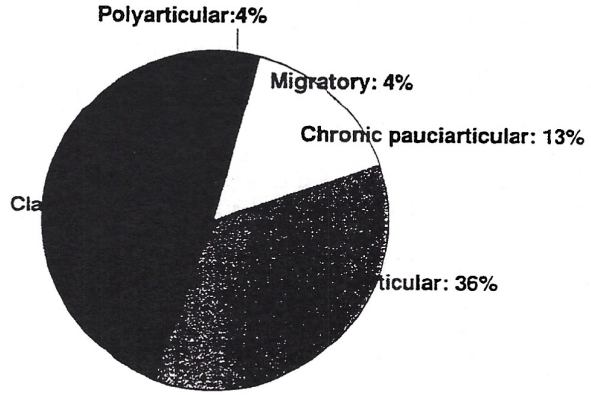

FIG. 1. Diagram showing the relative frequency of five different articular patterns seen in children with Lyme arthritis. Polyarticular: five or more joints involved; pauciarticular: one to four involved joints; acute: <4 weeks of symptoms; chronic: >4 weeks of symptoms.

TABLE 1. *Serologic results for the Lyme and comparison groups*

	Lyme arthritis (n = 44)	JRA/Spondyloarth. (n = 34)
ELISA		
Range	80–10240	<80–640
Mode	1280	<80
IgM Bands		
Range	0–4	0–1
IgG Bands		
Range	4–16	0–3
ANA		
Percent positive	28	50
Titer range	40–160	40–1280

tient. These latter three patients had similar disease duration and response to therapy. No sera became negative over time.

Sixteen patients received amoxicillin, 15 doxycycline and 13 ceftriaxone i.v. (see Methods). Follow-up was from 6 to 36 months (mean 20.9 months). In 39 patients, arthritis resolved before the end of therapy (88%); three patients were considered slow responders (resolution between 4 and 8 weeks after initiation of therapy) and two were deemed very slow responders (response between 8 and 12 weeks). The two very slow responders received retreatment.

DISCUSSION

This study describes the rheumatologic features, serologic findings, and articular outcomes of children treated for Lyme arthritis. We found five patterns of articular presentation, with the classic and acute forms occurring most commonly. With the exception of the classic (intermittent) arthritis, the other patterns mimicked the arthritis seen in other pediatric rheumatic diseases. In this regard, patients with the acute form of Lyme arthritis may be suspected to have septic arthritis or toxic synovitis. Children with the chronic form of Lyme arthritis have similar symptoms to pauciarticular JRA patients. Furthermore, ANAs, usually felt to be a confirmatory test for JRA, were detected in 30% of our Lyme patients. Indeed, the resolution of the arthritis after antibiotic intervention may be the only way to differentiate the chronic Lyme pauciarticular variant from JRA. The polyarticular form of Lyme arthritis, although rare in this series, has not been widely described in the literature. Again, the complete resolution of the symptoms with antibiotics is the strongest argument favoring the diagnosis of Lyme disease in such patients. These data, however, should be interpreted with caution. It is widely recognized that a small proportion of children with JRA and other pediatric arthritides may show a self-remitting course.

In endemic areas, Lyme disease is a common cause of acute arthritis in children. In the study of Eichenfield et al. (4), acute arthritis was seen in 56% of their patients. In the study of Cristofaro et al. (2), 25% of children had an acute arthritis. One-third of patients in our study presented in this way. Some of these children presented with fever and local findings compatible with septic arthritis. Three of them had the typical features of "toxic synovitis." This clinical overlap suggests that Lyme serology should be obtained in any patient with acute arthritis who lives in an endemic area.

Seventeen percent of our patients presented with chronic arthritis suggestive of JRA, and 30% of children in this series had positive ANAs. These data emphasize the need to consider Lyme disease as a diagnosis in all children with arthritis, even those with clinical and serologic criteria suggesting a diagnosis of JRA.

Care must be taken, however, not to overdiagnose Lyme disease in patients with arthritis and positive Lyme serology by ELISA, because patients with other forms of chronic arthritis and/or spondyloarthropathies may have a false-positive ELISA. We have previously reported on the increased specificity of Western blot analysis for the diagnosis of Lyme disease compared to the ELISA. In that and other studies, four IgG bands were required as one of the minimal criteria for positivity (7,8). In a previous study using JRA sera from an endemic area, 9% of the patients showed positive Lyme serology by ELISA (15), and no sera had more than four IgG bands on Western blot (this study required five bands for positivity). Sera from a nonendemic area showed 6% weakly positive ELISA and negative Western blots (13). In our comparison group (JRA and spondyloarthropathies), 22% had a positive ELISA, with titers as high as 1:640. However, when their sera were tested by Western blot, only one or two reactive bands were found in most of the patients (only one patient in that group had three IgG bands), and none of them had a clinical behavior compatible with Lyme disease at follow-up.

A clinical diagnosis of Lyme arthritis may be supported by the presence of extraarticular manifestations, although they are uncommon. Erythema migrans was detected in 72% of the 58 untreated children discussed by Szer et al. (17), in half the patients of Eichenfield et al. (4), and in one-third of the children in a previous report from our center (11). The current series showed only 18%. This finding may simply reflect a selection bias; however the apparent decrease in the frequency of a preceding rash in Lyme arthritis could be the result of earlier intervention by treating pediatricians. Perhaps early recognition and treatment of the disease creates a selection of patients without obvious rash who eventually evolve to a more advanced stage. Bell's palsy and aseptic meningitis were even less common than erythema migrans in this and other series of childhood Lyme arthritis (4,17).

Ten percent of adults with Lyme arthritis eventually develop chronic/recurrent synovitis despite antibiotic therapy (14). Certain human lymphocyte antigen (HLA) types may predispose to that adverse outcome (16). In children, the prognosis appears to be better (3,4). In his recent review article, Zemel (18) reported that in his patient population, 2% developed chronic arthritis (persistent arthritis for >6 months) and two patients required synovectomy. In our study, 88% of children were disease-free before the end of a 4-week antibiotic course, 7% required antibiotics for 8 weeks, and 5% required them for 12 weeks. The evolution of the ELISA titers supports the clinical observation of good response to therapy in most children; 22 of 25 sera showed a two- to fivefold decrease in the titer. However, none became negative during the follow-up period. No patient has yet shown evidence of recurrent articular disease.

This study shows that Lyme disease should be considered in any child from an endemic area who presents with arthritis, regardless of the articular pattern. Once a precise diagnosis is made and treatment is instituted, complete recovery is likely to occur.

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