Lyme Arthritis in a 12-Year-Old Patient after a Latency Period of 5 Years

S. Albert, J. Schulze, H. Riegel, V. Brade

Summary

Lyme arthritis (LA) may be confused with other rheumatic diseases, particularly in the absence of a history of erythema migrans (EM). We report the case of a 12-year-old patient who developed a large effusion of the right knee joint. The titer for antinuclear antibodies was 1:80 and the test for rheumatoid factor was negative. - Investigations for antibody response to *Borrelia burgdorferi* demonstrated remarkable elevation of IgG antibody and no specific IgM response. These results were confirmed by immunoblotting reactivity with the bands p83/100, p58, p43, p41, p39, OspA, p30, OspC, p21, and p17. We subsequently learned that the child had suffered a tick bite followed by an EM 5 years earlier and had been treated with trimethoprim/sulfamethoxazole at that time. The patient now was given intravenous ceftriaxone, 2 g daily for 14 days. In the absence of clinical improvement 3 weeks later a knee joint aspiration was performed which resulted in a positive polymerase chain reaction (PCR) test for *B. burgdorferi* DNA (OspA) in the synovial fluid. The patient fully recovered 2 months later without further treatment. The case indicates that the latency period between EM and onset of LA may last up to 5 years. In addition to serologic test methods, analysis of synovial fluid using PCR may be decisive for making the final diagnosis of LA.

Introduction

Lyme disease (LD) is a multisystem disorder caused by the spirochetes *Borrelia burgdorferi sensu lato* which are transmitted by various species of Ixodes ticks [1–3]. One of the chronic clinical manifestations of LD is Lyme arthritis (LA) which usually develops in the U.S.A. in about 60% of untreated LD patients within several weeks to 2 years after the initial infection [4–6]. We report a recent case of LA in a 12-year-old child who had presented clinically with an erythema migrans (EM) 5 years earlier.

Methods

Antinuclear antibodies (ANA) were determined by an indirect immunfluorescence assay on Hep-2 cells (LD Diagnostika, Heiden, Germany). The test for rheumatoid factor was an indirect particle agglutination assay (Mast Diagnostika, Reinfeld, Germany). To determine antibody titers against *B. burgdorferi,* enzyme-linked immunosorbent assays (ELISA) were performed separately for IgG and IgM (Enzygnost Borreliosis, Dade Behring, Marburg, Germany). As confirmatory tests, two Western immunoblots were performed, using a whole-cell lysate of a *B. afzelii* isolate (PKo) (Biosens, Oberhaching, Germany) as well as recombinant proteins of *B. afzelii* and *B. garinii* (Recomblot *Borellia burgdorferi,* Mikrogen, Martinsried, Germany). The interpretation criteria of the manufacturers were applied for evaluation of blot results. A positive IgG Western blot with the whole-cell lysate required at least two reactive bands consisting of the following proteins: p83/100, p58, p43, p39, OspA (p31), p30, OspC (p23), p21, p17. The recombinant immunoblot (IgG) was classified as positive in the presence of p100 and/or OspC and several other bands. A polymerase chain reaction (PCR) for the detection of *B. burgdorferi* DNA was carried out using primers specific for the OspA gene of *B. burgdorferi:* OspA1 (5'GGGAATAGGTCTAATATTAGCC3' 22 mer), position 177–189 and OspA2 (5'CTAGTGGTTTTGCCATCTT CTTTGA3' 24 mer), position 464–488 [7].

Case Report

The patient, a 12-year-old boy, developed a large effusion of the right knee joint on June 15, 1998 without having sustained a previous accident or injury. Two days later the boy's mother brought him to a general practitioner who arranged for a blood test for ANA. The titer for ANA, however, was only 1:80 and the test for rheumatoid factor was negative. After consultation with the laboratory, investigations for antibody response to *B. burgdorferi* were recommended. The results obtained by ELISA demonstrated a significant elevation of IgG antibody response to *B. burgdorferi* and no specific IgM response. The ELISA results were confirmed by immunoblot reactivity with nearly all of the common IgG bands (whole-cell blot: p83/100, p58, p43, p41, p39, OspA, p30, OspC, p21, p17; recombinant blot: p100, p41, p39, OspC, p41int, p18, see Fig. 1). It subsequently became known that the child had suffered a tick bite followed by an EM 5 years previously. At that time the child had been

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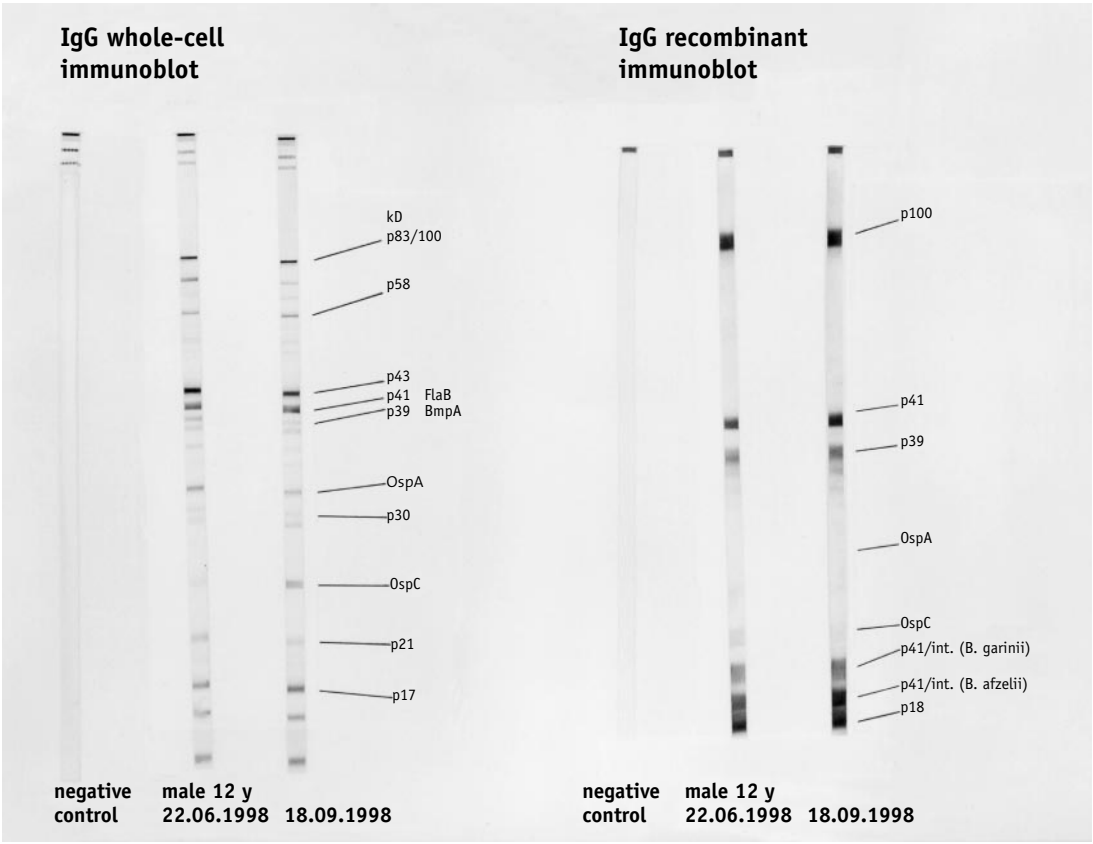

Figure 1
Whole-cell immunoblot and recombinant immunoblot of a 12-year-old male patient with Lyme arthritis. There are no significant changes seen during serological follow-up (after three months).

treated with trimethoprim/sulfamethoxazole. On June 25, 1998, the patient was administered intravenous ceftriaxone, 2 g daily for two weeks. In the absence of clinical improvement – three weeks after the onset of treatment the child still was walking on crutches – the physician untertook a knee joint aspiration, obtaining 90 ml of synovial fluid and injecting 10 mg intra-articular prednisolone.

The results of the investigations of the synovial fluid (SF) were as follows: white blood cell count 2,000/ml (normal value < 200) with 68% polymorphonuclear leukocytes, positive ragocyte cells, protein 5.6 g/dl, no cultural growth of *B. burgdorferi* in modified BJK medium or other microorganisms on conventional media, and positive PCR for *B. burgdorferi* DNA (OspA). In spite of intravenous antibiotic treatment, the patient still had a swollen knee joint two months after the onset of the illness. Four weeks later, however, the boy displayed no symptoms apart from a small residual effusion which was detectable only by ultrasound. Moreover, he had become accustomed to the crutches which in turn had led to a certain "careful posture". Nonetheless, the patient recovered shortly thereafter and could walk without crutches. On September 18, 1998, another blood sample was tested in the same run with the initial serum obtained three months previously. Nevertheless, there were no significant chances in the antibody titers against *B. burgdorferi* (see Fig. 1).

Discussion

As one of the late manifestations of LD, LA presents clinically as a monoarthritis or oligoarthritis with an intermittent course. Commonly affected sites are the large joints, most typically in the form of gonarthritis. Joint inflammation and effusion are the usual clinical symptoms [4]. LA may be mistaken for an acute bacterial septic arthritis or recurrent "pauciarticular rheumatoid arthritis", particularly when there is no previous history of EM [8–11]. *Eichenfield* et al. reported on 25 children with oligoarthritis associated with LD: 13 (52%) had no history of EM and only 12 (48%) remembered receiving tick bites. Ten children were hospitalized for presumed septic arthritis, seven of them with no known history of skin lesions. Another four patients had been diagnosed for as long as three years as having juvenile rheumatoid arthritis until the correct diagnosis was made and they could be cured by antibiotic therapy [10]. In our patient, who initially was thought to suffer from rheumatoid arthritis or collagenosis, the serologic results showed an elevated IgG antibody response revealing immunologic evidence of exposure to *B. burgdorferi.* The serological test results, therefore, in combination with the clinical signs of monoarthritis, led to the accurate diagnosis of LA. One must consider, however, that serologic testing is limited insofar as it is incapable of distinguishing between active and inactive disease. Accordingly, no positive indirect test method should be used to diagnose LD in the absence of such clinical find-

ings [12–14]. In the present case, the diagnosis was confirmed additionally by PCR analysis which identified DNA of *B. burgdorferi* in the synovial fluid. The sensitivity of PCR is higher than that of cultures because the presence of DNA in dead organisms as well as in viable organisms can be detected; the detection rate in synovial fluid in LA patients is about 50–70% [15]. After an adequate antibiotic therapy (i.e. intravenous ceftriaxone 2 g daily for 14 days, or, alternatively oral doxycycline 2 × 100 mg for 30 days), 90% of the LA patients become asymptomatic within 2–3 months, as could also be observed in our patient. In only 10% of the patients, LA may persist in spite of antibiotic treatment so that a second antibiotic regimen should be prescribed [16].

Reportedly, in the U.S.A., approximately 60% of untreated patients infected with *B. burgdorferi* suffered attacks of arthritis that may recur for years, the onset of symptoms after an EM rash ranging from several days to two years [4]. Our patient who had been bitten by a tick followed by an EM five years previously, must be classified as "untreated" insofar as trimethoprim/sulfomethoxazole does not have an effect on *B. burgdorferi*. The long latency period of five years seems remarkable and stands in contradiction to the observations of *Steere et al.* [4]. Furthermore, one should be aware that only about 30–50% of the patients with LA may recall being bitten or suffering from an EM [10, 16]. Theoretically, then, our patient could have experienced a second, unnoticed infection within the last five years. On the other hand, there are a few other reports showing that LA may occur ≥ 4 years after the initial infection [17–19].

This case report indicates that a long latency period between initial infection with *B. burgdorferi* and the onset of LA may exist. If LA is suspected, investigation of synovial fluid by PCR (at least 5 ml are required) is recommended whenever possible in addition to serologic testing methods. Because LA patients remain seropositive for many years after antibiotic treatment a close serological follow-up alone usually is not sufficient for monitoring the patient's progress.

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