

Persistent PCR Positivity in a Patient Being Treated for Lyme Disease

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A 30-year-old white female presented with worsening clinical symptoms suggestive of Lyme disease while on antibiotic therapy. Results of enzyme-linked immunosorbent assay (ELISA) and of western blot tests for IgG and IgM antibody were equivocal. However, *Borrelia burgdorferi* DNA detected by the polymerase chain reaction (PCR) was detected in whole blood on two separate occasions, 1 month apart, while the patient was on oral doxycycline, 100 mg b.i.d. This report questions the significance of persistent *Borrelia burgdorferi* DNA in a patient who is not responding to antibiotic therapy.

INTRODUCTION

Lyme disease is transmitted to humans by ticks infected with *Borrelia burgdorferi* (Bb) (1). Illness usually begins with the appearance of the erythema chronicum migrans rash (ECM) and flu-like symptoms. Untreated multisystem complaints, including neurologic, cardiac, rheumatologic, and ocular, may occur soon after the bite or many months later (2). The characteristic onset of the disease may not be observed because of the absence of ECM. Failure to treat early may result in disseminated disease.

There is controversy in the medical community as to the length of initial therapy as well as the most appropriate antibiotic. This case report highlights the difficulty that primary physicians face in having to choose an antibiotic empirically. It also raises questions as to the significance of repeatedly reactive polymerase chain reaction (PCR) tests in a patient whose clinical course is worsening.

CASE REPORT

Before contracting a present illness, 30-year-old white female occupational therapist was healthy and active. She bicycled regularly in a Lyme endemic area. In early July 1994, she had 3 days of flu-like symptoms with a temperature of 101°F for three consecutive nights. At the end of August 1994, she developed fatigue, and could not ride her bicycle as long as she was used to. She did not recall either a tick bite or a rash. By the beginning of September 1994, she had trouble concentrating, experienced short-term memory problems, and was increasingly fatigued. She had bilateral knee pain without redness or swelling. She noted a lot of "crunching" in the joints. She went to see her primary physician. Tests for infectious mononucleosis and rheumatoid arthritis were all negative. Because she lived in an area endemic for Lyme disease and spent much time outdoors, the physician performed a Lyme disease antibody test in October 1994. The test was positive, and she was started on oral doxycycline, 100 mg b.i.d. for 30 days. Her symptoms persisted and antibiotic treatment was extended for a total of 3 months. At the end of this period, she felt better but reported that she was not "normal." Her physician felt that

additional treatment was unnecessary. In March 1995, the patient complained of recurrent frontal headaches, vertigo, shooting pains in her right ear, neck stiffness, pain near the paravertebral area of the upper thoracic spine, arthralgia, paresthesia of the right hand, and weakness in her thigh muscles. She felt heaviness in her chest and exertional dyspnea climbing a flight of stairs. She had memory problems, difficulty concentrating, and irritability when referred.

Her past medical history and physical examination were unremarkable. Lyme antibody tests were repeated at North American Clinical Laboratories. The IgG ELISA titer was 1:160, and the IgM < 1:160. The IgG test was interpreted as equivocal, and the IgM as nonreactive. The IgG western blot showed 50,41,23 Kda bands. The IgM blot showed a 31 Kda band. Both western blots were interpreted as equivocal. A PCR was done on whole blood (N.A.C.L.) and was positive. The PCR on whole blood utilized a 20 kb primer, which is a protein of the 350 kb Osp A sequence. Positive hybridization controls (HLA), DQ alpha negative controls, and inhibition controls were used in each PCR run. Amplified products were detected by both southern blotting and a nonradioisotopic DNA capture technique. Patient was restarted on oral doxycycline 100 mg b.i.d. The patient continued to have the same symptoms with exacerbations once a week while on the oral doxycycline. The PCR test on whole blood was repeated 1 month later while on doxycycline. It was again positive for Bb. After the second positive DNA-PCR test result, the patient was switched to intravenous Ceftriaxone 2 gm q.d. for 4 weeks. At the end of 2-1/2 weeks, she developed an allergic rash, and the I.V. therapy was discontinued. As of this writing, she is being continued on oral Biaxin (500 mg b.i.d.). The patient has improved significantly and is 95% better.

DISCUSSION

The patient described here received 100 mg of doxycycline orally twice a day for 30 days. Oral doxycycline has good absorption and good central nervous system (CNS) penetration due to its lipophilic affinity. However, the mean inhibitory concentration (MIC) of doxycycline in the CNS and other organs is not known and may not be high enough with the currently recommended dose to eradicate most strains of Bb (3, 4). It has been documented that the *in vitro* sensitivity of antibiotics to Bb does not correspond to treatment results (5). It has been

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previously reported that Bb may reside in privileged sites like macrophage (3) and fibroblasts (6, 7). The intracellular localization of Bb is believed (8) to make effective eradication of the organism very difficult (12, 13). In this case, extended doxycycline therapy did not eradicate the symptoms.

It has been reported that patients with arthralgia, myalgia, malaise, and evidence of dissemination, such as the patient in this case, were more likely to have recurrent symptoms after treatment (5). The longer the duration of Lyme disease before treatment the more frequent the residual symptoms may be (14). In one study, patients whose treatment was delayed had arthralgia, distal paresthesia, concentration difficulties, verbal memory deficit, and fatigue at a greater frequency than the control group (14) who received timely therapy.

The lack of response to therapy in a patient is very difficult to assess. It is hard to determine on clinical grounds alone when treatment has been adequate (12). Persistence of symptoms has been suggested to be caused by a mechanism other than chronic infection, and the lack of response to prolonged therapy has been attributed to permanent tissue damage, post Lyme disease syndrome, slowly resolving Lyme disease, or causes other than infection with Bb (14-16).

There have been few well-controlled clinical trials to determine the relationship between length of antibiotic therapy and adequacy of therapy. Similarly, little data are available on the choice of antibiotics and its relation to clinical outcome. It should not be assumed that failure to respond clinically to an antibiotic is a function of "post Lyme syndrome." It is possible that protracted symptoms may be a function of persistent infection due to Bb.

Preliminary results on 40 patients with late stage or post acute Lyme suggest that whole blood PCR is more sensitive than either serum or urine. Over 80% of patients with Lyme disease fitting the Centers for Disease Control (CDC) surveillance definition had at least one positive PCR (Tilton, RC, unpublished data). Other studies (17), however, reported that PCR positivity was usually restricted to the initial 7 to 10 days of infection. The detection of circulating DNA in this patient may indicate persistent infection or DNA released from lysed bacteria. The PCR in cerebrospinal fluid (CSF) is useful in identifying patients persistently keep infected with Bb as well as patients who may be refractory to antibiotic therapy (18, 19). At present, a reactive PCR should not be used to prove persistent infection nor a negative PCR considered a test of cure. However, this sensitive and specific test when positive indicates that Bb is present in the patient.

CONCLUSION

This case report points out the problems in choosing the appropriate antibiotic and the duration of therapy for LD. DNA

testing may be a useful laboratory test to determine either persistence of the bacterium in the host or the presence of lysed products from bacteria that were once viable. The duration of DNA positivity in a recovering patient or the frequency of DNA reactivity in a symptomatic patient is still unknown.

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