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Cases of Lyme Borreliosis Resistant to Conventional Treatment: Improved Symptoms with Cephalosporin plus Specific β-Lactamase Inhibition

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ABSTRACT

We present four cases of verified late *Lyme borreliosis* with persistent symptoms and positive serology despite repeated courses of high-dose intravenous penicillin G and/or cephalosporins (including cefoperazone). The patients were now treated with cefoperazone 2 g plus sulbactam 1 g bid iv for 14 days. At the end of treatment, patients were symptom free and have remained so for the following 12 months. By then, IgG against *Borrelia burgdorferi* had decreased. It is concluded that the addition of β-lactamase inhibitors to intravenous treatment could be beneficial in Lyme disease refractory to conventional treatment.

INTRODUCTION

A NUMBER OF STUDIES have yielded ample evidence for therapeutic difficulties in late stages of Lyme borreliosis.[1–4] There have been reports that intravenous penicillin and/or cephalosporins may fail in up to 40% of patients with late Lyme disease.[1–3] The nature of the mechanism underlying this sometimes poor response to antibiotic treatment has not as yet been elucidated.

Similar therapeutic problems are seen in patients with late syphilis, another spirochetal infection (caused by *Treponema pallidum*). According to Stapleton *et al.*, resistance to penicillin, certain cephalosporins, and erythromycin could be accounted for by plasmid DNA seen in certain strains of the spirochete *Treponema pallidum*.[5,6]

Urban *et al.* have conducted an *in vitro* study of the effects of tazobactam (a β-lactamase inhibitor) on growth (with a little less potency than penicillin G) and penicillin binding proteins in *Borrelia burgdorferi* (tazobactam competes with penicillin in binding to a 94- and a 57-kDa membrane protein).[7] These authors demonstrated several proteins capable of binding labeled penicillin in this microorganism. Tazobactam affected PBPs and also inhibited growth in the presence of penicillin. While those findings do not indicate that an antibiotic resistance mechanism like β-lactamase is operating *in vivo*, the findings would still be consistent with such a possibility.

Following an earlier single case report,[4] we now present four cases of late Lyme borreliosis that have been refractory to repeated intravenous regimens of high-dose penicillin and cephalosporins (it is noteworthy that three of these patients had already received iv cefoperazone, but did not improve). However, all patients showed complete recovery after a combined therapy of intravenous cefoperazone and sulbactam (a β-lactamase inhibitor).

MATERIAL AND METHODS

Briefly, four patients (two female, two male; mean age 55) presented with stage II/III *Borrelia burgdorferi* infection in our Lyme disease Clinic with long standing well-diagnosed *Borrelia burgdorferi* infection (the diagnostic criteria for Lyme disease included a typical history of a well-documented, characteristic rash, secondary to a tick bite and consistent with erythema migrans, the best clinical marker for Lyme disease,[1,8] and objective involvement of three organ systems). Furthermore, a specific immunological reactivity to *Borrelia burgdorferi* was required (diagnostic details of *Borrelia burgdorferi* infection have been given.[1,8–10]). The patient's exact *Borrelia burgdorferi*-associated history was assessed following specific terms of reference consisting of 70 questions, diagnostic criteria, and assessments. Serodiagnosis was made

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using a commercially available enzyme-linked immunosorbent assay (ELISA) test kit [flagellar antigen; sensitivity 98%, specificity 99% according to the manufacturer (DAKO, Copenhagen, Denmark)]. Immunoblot (AccuBlot LYME, Whittaker, Cambridge, MA) is not performed routinely and has been performed in two of the patients (see Tables 1 and 2).

Other disorders capable of producing symptoms similar to those seen in Lyme borreliosis were excluded by exact assessment of the patient's history and by serological testing. Thus, the patients were screened for signs of autoimmune and rheumatoid disorders: tests for the rheumatoid factor, C-reactive protein, antistreptolysin (Latex), circulating immune complexes, antimitochondrial, antinuclear, thyroid antimicrosomal, antimyocardial, antibasalmembrane, and anti-smooth muscle antibodies were carried out. Seroimmunoreactivity against hepatitis A, B, and C, HCV, influenza A and B, *Mycoplasma pn.*, mumps, measles, cytomegaly, enterovirus, Coxsackie virus, Epstein–Barr virus, and syphilis (VDRL, TPHA) was assessed using standard laboratory tests.

TABLE 1. CLINICAL FINDINGS IN PATIENTS

	Symptoms	*Objective findings*	*History*
Case 1	Arthralgia Myalgia Palpitations Paraesthesia	Rubor and swelling of joints Episodes of supraventricular tachycardia ACA IgG positive in serum Immunoblot	ECM Flue-like symptoms Tick bite
Case 2	Myalgia Increased sensitivity to light Double vision Paraesthesias Balance problems Memory defects	Conjunctivitis Iritis Inflammatory signs in lumbar puncture Meningism Conjunctivitis ACA IgG positive in serum IgG positive in liquor	ECM Tick bite
Case 3	Arthralgia Myalgia Tinnitus Cephalea Paraesthesia Memory defects	Oligoarthritis Reduced left ventricular ejection fraction (46%) ACA IgG positive in serum Immunoblot positive	ECM Tick bite Episodic fever
Case 4	Arthralgia Myalgia Cephalea Problems with cognition Paraesthesia	Swelling of joints Meningism IgG positive in serum IgG positive in liquor Poliradiculitis	ECM Tick bite Iritis

TABLE 2. TREATMENT BEFORE AND CHANGES 6 MONTHS AFTER CEFOPERAZONE–SULBACTAM TREATMENT

	Treatment	*Serology*	*Resolution of symptoms*
Case 1	iv ceftriaxone Oral penicillin iv penicillin G iv cefoperazone	Serum IgG decreased	Complete resolution except right thumb
Case 2	iv penicillin G Oral amoxicillin iv cefoperazone	Serum IgG decreased	Complete resolution
Case 3	Oral roxithromycin iv penicillin G iv cefoperazone iv ceftriaxone Oral amoxicillin	Serum IgG decreased	Complete resolution
Case 4	Oral roxithromycin iv ceftriaxone iv penicillin G iv cefoperazone	Serum IgG decreased	Complete resolution

The duration of symptoms before admission to our department was 2–4 years. All patients had already been treated with iv penicillin, iv cephalosporins (including cefoperazone), and/or other antibiotics.

Measures of safety included a complete physical examination using vital sign recording methods, both prior to drug administration and again at the end of the administration period. A routine serum chemistry profile and a complete blood count were similarly carried out. Adverse effects were recorded. All patients were informed about the type of treatment and possible side effects and all agreed to be treated with this drug. Patients were followed up 6 and 12 months after treatment.

RESULTS

Patients reported a typical history of rash secondary to a tick bite consistent with erythema chronicum migrans. Furthermore, we found the following symptoms: neurological involvement (4 patients), joints (3), cardiovascular (2), muscular system (4), ophthalmic symptoms (2), acrodermatitis chronica atrophicans (3), and a marked decrease in memory performance (2). Tables 1 and 2 show patient details.

As a result of an earlier case of successful treatment with cefoperazone plus sulbactam,[4] we treated another four patients who had persistant symptoms and positive serology for more than 2 years, despite repeated courses of iv penicillin and cephalosporins (see Material and Methods and Tables 1 and 2). Three of these patients had already received cefoperazone without any improvement. Usually, the first course of iv treatment brought about transient improvement in symptoms, but none of the subsequent regimens had any marked therapeutic effect.

These four patients were then treated with cefoperazone–sulbactam (2 g/1 g bid iv for 14 days), which, in all patients, was followed by a typical Herxheimer–Jarish reaction. Within a week, all patients felt considerable improvement in their symptoms (Tables 1 and 2). At the end of the treatment, patients

were symptom free and remained so for the following year. In case 3, left ventricular ejection fraction (LV-EF) improved from 46 to 60% within 6 months after treatment. This is consistent with our earlier finding that in *Borrelia burgdorferi*-associated chronic heart failure LV-EF can improve upon antibiotic treatment.[11] Further objective physical findings were a marked improvement in acrodermatitis in all patients. No further swelling of joints was seen. Only one patient showed persistant swelling and joint pain in the right thumb, but symptoms as well as swelling disappeared in the other joints. IgG against *B. burgdorferi* were sampled before and 6 months after treatment. In all four patients IgG values decreased after 6 months.

DISCUSSION

Our findings suggest that in patients with late Lyme disease refractory to iv treatment with penicillin and cephalosporins, combined treatment with a cephalosporin plus sulbactam may be beneficial. For our first patient,[4] which is not included in the present work, sulbactam was added to cefoperazone 10 days after the onset of treatment and then caused a typical Herxheimer–Jarish reaction with subsequent improvement of all symptoms. This and the fact that these four patients remained symptom-free for 1 year thereafter were the first indications that *Borrelia burgdorferi* may be able to develop resistance against β-lactamase antibiotics. The hypothesis is further supported by the observation that patients recovered by taking cefoperazone–sulbactam, despite the fact that they did not respond to previous therapy with iv cefoperazone alone. However, one must consider other mechanisms of therapy failure in the above patients, such as persister state of the spirochete, possible sequestered site of the spirochete in the CNS where it might be protected from adequate concentrations of the antibiotic, a potential autoimmune cause of late disease in patients with certain HLA haplotypes, and other mechanisms of antibiotic resistance by certain strains of Borrelia. While the complete resolution of symptoms upon the addition of sulbactam could be coincidental, it is more difficult to argue that a decrease in IgG also occurs at the same time.

Penicillin, cephalosporins, and erythromycin have been widely used for many years for the treatment of human spirochetoses without the emergence of resistant spirochetal strains. However, experience with various bacterial pathogens serves to emphasize that resistance to penicillin and other antibiotics can suddenly appear after years of exquisite sensitivity. The finding of plasmid DNA in strains of *Treponema pallidum*, the reporting of several instances in which antibiotic treatment of syphilis and Lyme disease have failed, and the demonstration that a recent clinical isolate of *T. pallidum* is resistant to erythromycin all indicate that the pathogenic spirochetes do have the potential to develop antibiotic resistance.[4–7] While the findings by Urban *et al.* that the β-lactamase inhibitor, tazobactam, affects growth and penicillin binding proteins in strains of *Borrelia burgdorferi* does not necessarily imply that potential activity *in vivo* would be the result of inhibiting a β-lactamase, the findings would still be consistent with such a possibility.[7]

Late stages of *Borrelia burgdorferi* infection are sometimes difficult to treat and show poor response to iv antibiotics.[1–4] Many times, patients can be severely affected by neurological symptoms, cardiovascular problems,[11] and pain in different locations.

Although it is impossible to predict to which extent antibiotic resistance does ultimately constitute the key problem in dealing with chronic spirochetoses, the vigorous persuit of antibiotic alternatives for the control of human spirochetosis seems prudent.

The wide-spectrum "third-generation" cephalosporins have become well accepted for use against problem bacterial infections including *Borrelia burgdorferi* infection. These antimicrobial agents possess β-lactamase stability against clinically important enzymes. However, some bacterial β-lactamases have been demonstrated to hydrolyze these cephalosporins such as cefoperazone, cefotaxime, and, more rarely, the 7-methoxycephalosporins and ceftazidime.[12–14] To increase the stability to enzymes and, therefore, the already broad spectrum of these drugs, several have been combined with the penicillanic acid sulfone, sulbactam, which appears to be biologically and enzymatically more stable than clavulanate. It has clearly been shown that the use of the sulbactam–cefoperazone combination expands cefoperazone's antimicrobial activity, especially against plasmid-mediated β-lactamases.[12–14]

Although there is scant information on spirochetal plasmid-mediated β-lactamase activity,[4–7] especially as far as *Borrelia* is concerned,[7] the fact that several of the patients had already received cefoperazone without any signs of improvement, but completely recovered upon treatment with the same drug plus sulbactam, strongly argues in favor of a mechanism of resistance resulting from a sulbactam-sensitive plasmid-mediated β-lactamase. Further studies are certainly needed and β-lactamase activity remains to be shown in *Borrelia burgdorferi* cultures.

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