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Seronegative Chronic Relapsing Neuroborreliosis

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Abstract
We report an unusual patient with evidence of *Borrelia burgdorferi* infection who experienced repeated neurologic relapses despite aggressive antibiotic therapy. Each course of therapy was associated with a Jarisch-Herxheimer-like reaction. Although the patient never had detectable free antibodies to *B. burgdorferi* in serum or spinal fluid, the CSF was positive on multiple occasions for complexed anti-*B. burgdorferi* antibodies, *B. burgdorferi* nucleic acids and free antigen.

Introduction

The nervous system manifestations of Lyme disease have usually been described as responsive to appropriate antibiotic therapy, and without relapses. We describe a patient with Lyme disease manifested by episodic peripheral and cranial motor and sensory neuropathies, and central nervous system deficits. Progressive neurologic symptoms and signs led to six courses of intravenous antibiotic therapy in the last 5 years. Each time, initiation of therapy promoted a Jarisch-Herxheimer (J-H) reaction with fever, acute encephalopathy and abrupt neurologic deterioration. Although the patient's serum was consistently negative for free antibody to *Borrelia burgdorferi* (Bb), there was laboratory evidence of active infection in the cerebrospinal fluid (CSF) even after intense prolonged antibiotic therapy. The patient had lived in New York City for the last 40 years and her only known exposure to Bb was on a camping trip through the countryside in France and Switzerland in the summer 1981.

Methods

The Bb blastogenesis test was performed by Dr. David Volkman [1]. Intrathecal Bb antibody synthesis was demonstrated in Dr. John Halperin's laboratory [2]. PCR analyses were done in the laboratories of Halperin [3], Luft [4], and Marconi [5]. Dissociation of CSF immune complexes and Western blots for antibodies to Bb [6] and Bb antigen identification by ELISA and Western blot [7] were done by Dr. P.K. Coyle. HLA typing was performed by Dr. Edwin Dwyer [8].

The following tests were performed by MetPath Laboratories (Teterboro, N.J.): C1qBA, Raji assay, HTLV-I antibody, IgG subclasses and T lymphocyte profile. The other tests were done in the hospital's routine laboratory.

Case History

In January 1989, a previously healthy 58-year-old woman presented with 3 months of right shoulder girdle weakness, atrophy and radicular pain. Electromyographic studies demonstrated right C4 and C5 radicular dysfunction, with C4–C8 paraspinal denervation. Routine laboratory tests were normal or negative, including that for Lyme antibodies. In February 1989, mild distal weakness of the right hand and atrophy of the right hypothenar eminence were noted. Right hand weakness increased and right iliopsoas weakness developed, with right-sided hyperreflexia. Sternocleidomastoid weakness and a positive Romberg sign appeared. MRI studies of the head, cervical cord and brachial plexus were normal, as was a cervical myelogram.

Despite the negative serology for Lyme disease, in April 1989 a Bb blastogenesis test was strongly positive with a stimulation index of 50 [1]. CSF obtained as an outpatient showed only a slightly elevated protein (table 1). However, stored spinal fluid was subsequently shown to be positive for Bb-specific antigens by ELISA and Western blot (table 1) [7]. A decision was made to treat for possible seronegative Bb infection, and the patient was hospitalized for intravenous antibiotics. Twelve hours after initiating ceftriaxone the patient became confused, and then stuporous, with a temperature of 39.2°C. The time course was consistent with a J-H reaction and those symptoms resolved spontaneously in 48 h. She improved and was discharged to complete 3 weeks of intravenous ceftriaxone. Three months later she developed right anterior uveitis followed by two episodes of bilateral keratitis. In August 1989 she developed right pulsatile tinnitus and loss of taste with dysgeusia.

In December marked left tongue atrophy was noted. The patient was therefore hospitalized for a second course of intravenous ceftriaxone. Another J-H reaction occurred 24 h after starting antibiotics and then spontaneously cleared. The patient was treated for 8 weeks, with gradual improvement and was able to return to work. Spinal fluid from this admission that had been stored at –70°C was in retrospect shown to contain Bb nucleic acids by PCR [5] and Bb antigen by ELISA and Western blot [7].

In May 1990, she experienced severe right retro-orbital pain with a tender, engorged right temporal artery. Visual evoked potentials demonstrated right monocular delay. Two months later she developed a progressive right hemiparesis. CSF obtained at this time showed intrathecal synthesis of IgA antibody to Bb [2], and was positive by PCR for Bb nucleic acids in 2 different laboratories (table 1) [3, 5]. During the third hospitalization in July 1990 she was retreated with ceftriaxone. Twenty-one hours after antibiotic was started she developed blurred vision in her right eye followed by stupor. This was again considered to be a J-H reaction and she was treated with 1 g solumedrol i.v., followed by 250 mg every 6 h. Visual acuity returned to normal within 4 days. Following 2 weeks of intravenous ceftriaxone, doxycycline 200 mg p.o. b.i.d. was continued for 19 weeks. The patient's right hemiparesis continued to improve and no new neurologic symptoms developed while on doxycycline.

Within 2 weeks of stopping doxycycline the patient developed vertigo. Two months later, she experienced bilateral facial paresthesias and numbness of the mucous membranes of her mouth and gingiva. On examination there was absent sensation of the buccal and gingival mucous membranes, diminished sensation in the fifth cranial nerve V1–3 distribution and depressed corneal reflexes. Repeat lumbar puncture at this time revealed a protein of 75 mg/dl, and Bb-specific OspA antigen by ELISA and Western blot (table 1) [7]. The patient was hospitalized a fourth time and given intravenous cefotaxime 2 g every 8 h. Within 24 h of starting antibiotics, she developed multifocal myoclonic jerks and became unresponsive, with a dense right hemiparesis. This J-H reaction occurred despite premedication with 80 mg prednisone followed by 20 mg every 6 h. The patient was given 1 g of solumedrol i.v. followed by 250 mg every 6 h. Twelve hours later, 30 h after starting antibiotics, the patient was able to speak and the hemiparesis had improved. On day 21 agranulocytosis was noted so cefotaxime was discontinued, and 200 mg p.o. b.i.d. of doxycycline was started. While receiving this second course of doxycycline, the patient developed vertigo, experienced increasing hypesthesia of her face and burning paresthesias and numbness of her legs to mid-thighs.

Table 1. Supportive laboratory findings for Bb infection in the CSF

Dates	Hospital admissions	Protein mg/dl	Cells per mm³	PCR	Intrathecal antibody	Bb antigens	Bb specific IC
03-31-89	Office	56	3			OspA	
04-05-89	Office						
04-21-89	Pre-Rx 1	50	0				
09-08-89	Office						
12-28-89	Pre-Rx 2	40	0	+[a]		OspA	
01-16-90	Office						
06-04-90	Office						
07-16-90	Pre-Rx 3	38	0	+[a,b]	IgA 1:14[b]	OspA	IgG
07-18-90	36 h post-Rx 3	42	0	+[b]		OspA	IgG
08-13-91	Pre-RX 4	75	0			OspA	
09-10-91	Pre-Rx 5						
04-16-92	Office	52	1			OspA	
08-03-92	Pre-Rx 6	56	1	+[a,c]		OspA	IgG

Many of these studies were obtained retrospectively on CSF that had been stored at –70°C.
PCR performed in laboratories of Dr. R. Marconi[a], Dr. J. Halperin[b] and Dr. B.J. Luft[c].
Bb antigens (ELISA and/or Western blot) and specific immune complex (IC) dissociation studies by Dr. P.K. Coyle.

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According to Dr. Coyle she was blocked from publishing in US journals. So they went to a European journal. KVF 5/6/2020

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She was hospitalized for the 5th time in September 1991. To prevent another severe J-H reaction, she was premedicated with Motrin and 1 g of solumedrol in the 24 h prior to being given 2 g of i.v. ceftriaxone. There was only a mild J-H reaction with confusion and dysarthria. She was discharged on the 4th day and continued on 2 g daily of ceftriaxone for 2 weeks followed by 3 g of pulse ceftriaxone for 2 days of each weeks for 9 weeks. Episodes of fever, chills and arthralgias after the third pulse of antibiotic were considered to be serum sickness-like reactions and were initially controlled by 800 mg p.o. of Motrin. Progressive chills, fever and arthralgias necessitated discontinuation after 9 cycles in early December (fig. 1).

In the spring of 1992 the patient developed trigeminal sensory neuropathy, progressive diffuse paresthesias and leg numbness. Neurologic examination suggested mononeuritis multiplex. Spinal fluid was reexamined and the findings were consistent with persistent Bb infection (table 1). The patient declined admission until August, when she experienced exertional dyspnea. An EKG was normal and there was normal excursion of the right diaphragm. Right chest wall motion was limited due to an intercostal neuropathy. The patient declined EMG testing. She was again premedicated with 250 mg i.v. solumedrol and 400 mg p.o. ibuprofen every 6 h for 24 h before beginning antibiotics. She had only a mild J-H reaction and was discharged to continue 2 weeks of 2 g i.v. ceftriaxone, followed by 500 mg b.i.d. of oral clarithromycin. The latter was begun in August 1992 and the patient has had gradual regression of the sensory symptoms. No further new symptoms or deficits have occurred in the ensuing 22 months.

Negative tests included antibodies to HIV, HTLV-1, FANA and VDRL. Serum complement (C3, C4), ESR, quantitative immunoglobulins, IgG subclasses and the T-lymphocyte profile (CD4, CD8, CD4/CD8 ratio) were normal. Elevated C1qBA titers for immune complexes paralleled her clinical course (fig. 1). The Raji assay for immune complexes was negative.

Complete HLA typing was A2, A24, B35, B39 Bw6, Cw4, Dr2, DQw1 [8]. Paired serum and spinal fluid specimens taken at the time of each lumbar puncture were stored at –70°C. The spinal fluid PCR from 12/28/89 and the antigen capture ELISA and Western blots from 3/20/89, 12/28/89, 7/16/90, 7/18/90 and 6/13/90 were done retrospectively in the spring of 1993 (table 1).

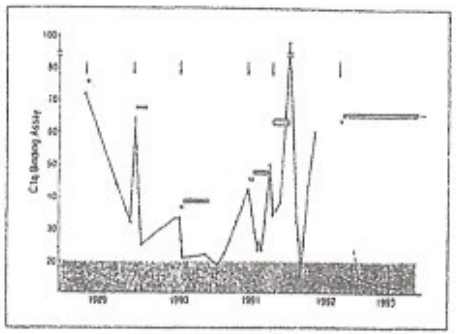

Fig. 1. Serum immune complex levels by C1q binding assay. Normal values are less than 20 (shaded). Arrows indicate hospitalizations. Narrow horizontal rectangles indicate antibiotics, as follows: solid bar – ceftriaxone; solid bar with open circle – cefotaxime; vertical shading – doxycycline; horizontal shading – ceftriaxone 'pulses', with serum sickness reaction; diagonal shading – clarithromycin.

Discussion

We describe a previously healthy woman with a 5-year history of a relapsing and remitting neurologic disorder involving the central nervous system (CNS) and multiple peripheral and cranial nerves. We believe this to be an unusual case of seronegative Lyme disease, though she did not have a recognized tick bite or erythema migrans. The patient's clinical involvement is compatible with that reported for neuroborreliosis. During her 5-year course, despite extensive evaluations, there has been no evidence of another disease such as multiple sclerosis, sarcoidosis, collagen-vascular disease or an occult infection. Severe J-H reactions, with acute encephalopathy, fever and worsening motor deficits, occurred repeatedly within 24 h of starting antibiotics [9]. During the last four admissions these symptoms were attenuated by premedication with Motrin and high dose intravenous glucocorticosteroids. Each course of antibiotics produced a therapeutic response, with temporary arrest of neurologic progression. During two prolonged courses of antibiotics no new manifestations developed. The patient has now been on p.o. clarithromycin for 22 months, and no new symptoms or deficits have occurred during this time.

Several experimental laboratory tests support infection with Bb (table 1). Before therapy in 1989 the patient had a strongly positive lymphoproliferative response to Bb (stimulation index 50) [2], a value more than 10 SD above the mean. When the stimulation index is more than 3 SD above the mean, positive results have had a 95% specificity [10]. When serum and spinal fluid immune complexes were dissociated, they contained antibodies that reacted on Western blot with OspA, B, and flagellar antigens from Bb [6]. Spinal fluid PCR assays, performed in three different laboratories, have been positive for Bb nucleic acids [3–5]. Intrathecal synthesis of IgA antibodies to Bb was demonstrated in the CSF in July 1990 [2]. Bb-specific OspA antigen was demonstrated by antigen capture ELISA and Western blot in CSF specimens that had been obtained and stored at –70°C prior to 5 hospitalizations [7], including the last admission in August 1992.

This patient's serum and CSF antibody negativity was attributed to immune complex formation. After dissociating the complexes, antibody to Bb antigens could be demonstrated [6]. CSF Bb antigen was demonstrated repeatedly in 7 spinal fluids [7]; such antigen excess could bind available antibody. Serum I-C levels roughly paralleled her clinical course, peaking before each course of antibiotics (fig. 1) and declining rapidly after antibiotic therapy. The striking clinical improvement after antibiotic therapy, coincident with a precipitous drop in the C1qBA titer and normal ESR, suggest that these changes were a result of therapy and unlikely related to a primary immune complex disease. Furthermore, the C1qBA has been within the normal range for the past 17 months while the patient has has been receiving clarithromycin. Previous studies have shown that persistently elevated serum I-C levels after Bb infection are associated with a higher incidence of cardiac and neurologic involvement [11]. The findings in this patient and others suggest that circulating I-C may confound efforts at serologic diagnosis using free antibody-based tests [6]. The use of experimental studies such as PCR, antigen detection, intrathecal antibody synthesis and fractionation of I-C may provide evidence for Bb infection in such seronegative cases. Before undertaking repeated empiric courses of antibiotic therapy, we attempted to establish the diagnosis by the use of these assays.

There is anecdotal evidence that pulse cefotaxime has succeeded in eradicating Bb in chronic relapsing Lyme disease [12] but cefotaxime could not be given to this patient because agranulocytosis followed its previous use on the 4th hospitalization. Therefore, after the fourth relapse, the patient was treated with 9 weekly pulses of ceftriaxone. However, pulse therapy had to be stopped when the symptoms of serum sickness were no longer controlled by premedication with 800 mg Motrin. The serum sickness reaction was accompanied by an abrupt rise in the C1q binding assay to 98.3 µg/l (normal less than 20), that rapidly returned to normal when the antibiotic was discontinued (fig. 1). Nine pulses of ceftriaxone did not eradicate Bb.

This is a very unusual example of Bb infection. It is not known why this previously healthy patient was not cured by successive courses of intense and prolonged antibiotic therapy. In a limited study of patients with Bb encephalomyelitis, all were HLA Bw6 positive; the 6 who were also DQw1 positive had no response to treatment or had relapsing disease [2]. Our patient was typed as HLA Bw6 and functionally homozygous for DR2, DQw1 [8]. It is possible that homozygosity (or hemizygosity with a null allele) for this HLA genetic type might predispose to a chronic relapsing course. Despite evidence for CNS infection with an elevated spinal protein level, this patient never had a CSF pleocytosis. Thirty seven percent of patients with subacute encephalopathy reported by Logigian had no spinal fluid pleocytosis [13]. Benach et al. [14] showed that I-C may block the Fc receptors on neutrophiles and monocytes, and prevent phagocytosis of spirochetes. This patient has had increased serum I-C levels throughout her illness (fig 1) and may therefore have been unable to contain and kill or prevent the dissemination of the Bb spirochete.

The PCR analysis of her CSF in August 1992 gave significant amplification products only with the specific primer sets for genomic group 3 (previously referred to as genomic group VS 461), which has heretofore been identified only in Europe and Asia [5]. This patient may have acquired Bb during a 3-week camping trip through the countryside of France and Switzerland in 1981. If so, there was a latent period of 7 years before the onset of neurologic symptoms, which is more typical of neuroborreliosis described in Europe than in the United States [15, 16]. Among eight European countries, the incidence of erythema migrans was lowest in Switzerland, whereas neurologic manifestations were reported there in 62% of patients with Lyme disease [17].

Before her 6th hospital admission this patient had received four courses of ceftriaxone, one of cefotaxime and two of doxycycline (of 19 and 8 weeks). Increasing right hemiparesis and dyspnea with right intercostal muscle weakness prompted her 6th admission to the hospital. Following intravenous ceftriaxone for 2 weeks, it was decided to place the patient on long-term therapy with clarithromycin. Although there is no information on the penetration of clarithromycin into the CNS, it achieves high concentrations within macrophages [18] a known sanctuary for the Bb spirochete [19]. The clinical response to clarithromycin in this patient has now been sustained for over 22 months.

Intracellular pathogens are notoriously difficult to treat and cure [20]. In experimental animals, Bb is relatively insensitive to humoral antibodies and is eradicated in vitro only by prolonged incubation with relative high doses of antibiotics [21, 22]. Survival of Bb in humans, despite aggressive antibiotic therapy has been previously reported [2, 22]. We believe this to be an example of a patient with chronic relapsing Bb infection. It is important to evaluate unusual patients like this thoroughly in order to determine the effectiveness of prolonged oral antibiotics as a therapeutic option.

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Book Review

Maurizio Versino, Daniela Zambarbieri (eds)

Ottorino Rossi Award Conference

International Workshop on Eye Movements

Pavia, June 13–14, 1994

The book was published in June 1994 for the Ottorino Rossi Award Conference, a neurological symposium held in Pavia every year. This year the topic was the neurology and neurophysiology of eye movements, and Prof. David Zee from the Johns Hopkins University in Baltimore was awarded for his fundamental contributions in this field.

Once the reader has found the table of contents, which unusually is placed before the author index at the end of the book he will find many contributors acknowledged worldwide for their publications on eye movements.

The book includes several sections: the main lecture by Prof. Zee deals with disorders of adaptive control of eye movements and clinical implications. The Invited Lectures are review articles (with some original experimental data) on the saccadic and the vestibular system. The Short Communication section includes original experimental data from Italian researchers. A small Abstract section consists of 5 very short, but self-consistent papers.

This is a very up-to-date introductory book on the saccadic and vestibular eye movement systems.

Finally, the book is available for free upon request from one of the editors at the following address: Fondazione Istituto Neurologico C. Mondino, Via Palestro 3, I–27100 Pavia (Italy).

Otmar Meienberg, Binningen