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BRIEF REPORT

An Unusual Cluster of Neuroinvasive Lyme Disease Cases Presenting With Bannwarth Syndrome in the Midwest United States

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Bannwarth syndrome (BWS), an infrequent manifestation of neuroinvasive Lyme disease (LD) characterized by radiculopathy, neuropathy, and lymphocytic pleocytosis, is more commonly documented in Europe than North America. Here, we describe a cluster of 5 neuroinvasive LD cases with BWS in the upper Midwest United States between July and August 2017.

Keywords. Lyme disease; neuroborreliosis; Bannwarth syndrome; neuroinvasive; Garin-Bujadoux-Bannwarth syndrome.

Garin-Bujadoux-Bannwarth syndrome (Bannwarth syndrome [BWS]) is an uncommon manifestation of neuroinvasive Lyme disease (LD) caused by infection with members of *Borrelia burgdorferi* sensu lato (Bbsl) complex and is more frequently described in patients with Lyme disease in Europe as compared with the United States [1]. BWS is characterized by painful radiculopathy, neuropathy, varying degrees of motor weakness and facial nerve palsy, and cerebrospinal fluid (CSF) lymphocytic pleocytosis.

Over 3 weeks between July and August 2017, Mayo Clinic campuses in Minnesota and Wisconsin identified 6 patients from the upper Midwest with Lyme neuroborreliosis (LNB), 5 presenting with BWS. Here, we present the findings of these 5 patients.

CASES

Patient 1

A 61-year-old male with daily tick exposure presented with progressive back pain, upper torso and extremity paresthesias, right-sided facial droop, and blurry vision in the right eye. Four weeks prior, the patient observed an erythema migrans (EM) rash, treated with 5 days of twice-daily doxycycline. CSF and serum were submitted for LD serologic testing using the standard 2-tiered testing algorithm and interpretive criteria (applied to serum) [2]. LD antibody index (AI), comparing the level of anti-Bbsl IgG in CSF and serum for determination of pathogen-specific IgG intrathecal antibody synthesis, was also performed [3]. LD IgM immunoblot was positive in serum, IgM and IgG antibodies to *B. burgdorferi* senso stricto (*B. burgdorferi*) were detected in CSF, and LD AI was elevated at 5.28 (reference range, 0.6–1.29), which, alongside CSF lymphocytic pleocytosis (77 white blood cells [WBCs], 86% lymphocytes), led to a diagnosis of LNB/BWS (Table 1). The patient demonstrated significant neurologic improvement following 4 weeks of intravenous (IV) ceftriaxone.

Patient 2

A 62-year-old female presented with subacute onset of lower extremity weakness, progressing to flaccid paralysis over a 3-week period, alongside radiating low back and abdominal pain with associated numbness. A magnetic resonance image (MRI) of her spine showed diffuse inflammation of the cauda equina. CSF analysis was remarkable for lymphocytic pleocytosis (363 WBCs, 74% lymphocytes), elevated protein (649 mg/dL), and a high LD AI of 40.2. A *Borrelia* spp. real-time polymerase chain reaction (RT-PCR) assay was positive for *B. burgdorferi* in CSF (Table 1) [4]. The patient was diagnosed with LNB/BWS and discharged on a 4-week course of IV ceftriaxone. The patient reported improved mobility, though she still required extensive assistance 2 months post-treatment.

Patient 3

A 65-year-old female presented with subacute progressive ascending weakness and lower extremity paresthesias. Brain and spine MRI imaging were negative; however, CSF evaluation demonstrated lymphocytic pleocystosis (46 WBCs, 92% lymphocytes), elevated protein (113 mg/dL), and an LD AI of 2.49. The patient was positive for IgM and IgG antibodies to *B. burgdorferi* in serum, with both antibody classes also detected in CSF (Table 1). The patient was diagnosed with LNB/BWS and initiated on a 4-week course of IV ceftriaxone, and she reported significant improvement 2 weeks later.

Patient 4

A 29-year-old male developed fever, myalgias, chills, headache, fatigue, and a transient erythematous rash on his trunk in mid-June 2017. Two weeks thereafter, he developed right foot drop, Trendeleberg gait, lower extremity radiculopathy, and painful L5-S1 paresthesias. Over a 10-week period, he experienced constitutional symptoms, including a 15-pound weight loss. MRI of

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Table 1. Patient Characteristics and Exposures

Pt. No.	Age/Sex	Recalls Tick Bite/Other Tick Exposure?, State	CSF WBC/mcL, % Lymphocytes	CSF Glucose, mg/dL[e]	CSF Protein, mg/dL	CSF *B. burgdorferi* Serology			Serum *B. burgdorferi* Serology			
						C6 ELISA[a]	IgM Bands Detected[b]	IgG Bands Detected[b]	C6 ELISA[a]	IgM Bands Detected[b]	IgG Bands Detected[b]	*Borrelia* spp. IgG Antibody Index[c]
1	61/M	Y/Y (MN)	77 (86%)	72	158	Pos	23	18, 41	Pos	23, 39, 41	18, 23, 41, 45	5.28
2	62/F[d]	Y/Y (IA)	363 (74%)	60	649	Pos	23, 39, 41	18, 23, 30, 39, 41, 45, 58, 66, 93	Pos	23, 39, 41	18, 23, 30, 41, 66, 93	40.2
3	65/F	N/Y (WI)	46 (92%)	50	113	Pos	23, 41	18, 23, 41	Pos	23, 39, 41	18, 23, 30, 39, 41, 45, 66	2.49
4	29/M	Y/Y (MN)	ND	ND	ND	ND	ND	ND	Pos	23, 39, 41	18, 23, 39, 41, 58, 93	ND
5	69/M	Y/Y (MN)	142 (88%)	58	133	Pos	41	18, 23, 41	Pos	23, 29, 41	18, 23, 39, 41, 45	ND

Abbreviations: ND, not done; Pos, positive.

[a]C6 *B. burgdorferi* (Lyme) ELISA (Immunetics, Marlborough, MA).

[b]*Borrelia* IgM and IgG ViraStripe Immunoblots (ViraMed Biotech AG, Planegg/Steinkerchen, Germany).

[c]Lyme IgG Antibody Index performed using the anti-*B. burgdorferi* sensu lato IgG ELISA (Euroimmun Inc., Mountain Lakes, NJ) in CSF and serum and calculated according to Reiber and Lange method. Reference range is 0.6–1.29, interpreted as "Negative" for species-specific antibody synthesis (3).

[d]Patient was positive for *B. burgdorferi* by RT-PCR in CSF (4).

[e]Reference range: 0–35 mg/dL

the lumbar spine showed nonspecific enhancement of the cauda equina roots. The patient was seropositive for both IgM and IgG to *B. burgdorferi*; an LP was refused (Table 1). Based on clinical presentation, imaging studies, and seropositivity to *B. burgdorferi*, the patient was diagnosed with LNB/BWS and initiated on IV ceftriaxone. At a 2-week follow-up, the patient indicated complete resolution of symptoms.

Patient 5

A 69-year-old male presented with low-grade fevers, nausea, vomiting, diffuse arthralgias, headache, loss of smell, and blurry vision in the right eye. These symptoms were accompanied by neck and right upper extremity pain in a radicular pattern. The patient was seropositive for IgM and IgG antibodies to *B. burgdorferi* in serum, with both immunoglobulin classes also detected in CSF, which showed a lymphocytic pleocytosis (142 WBCs, 88% lymphocytes) (Table 1). An LD AI was not performed due to limited specimen volume. The patient's constellation of symptoms, alongside CSF findings, led to a diagnosis of LNB/BWS, and IV ceftriaxone was initiated. Following completion of treatment, the patient reported complete resolution of all symptoms.

DISCUSSION

LD is predominantly caused by 3 members of the *B. burgdorferi* sl complex: *B. burgdorferi* is responsible for the majority of cases in North America, whereas *B. afzelii* and *B. garinii* are predominant in Europe and Asia [5, 6]. Approximately 300 000 cases of LD are estimated annually in the United States [7]. LD can involve numerous organ systems, including the central nervous system (CNS), the peripheral nervous system (PNS), or both, with approximately 10% of untreated patients developing PNS involvement [5, 8]. While the clinical manifestations of LNB vary, the triad of painful radiculopathy, cranial neuropathy, and lymphocytic pleocytosis, often occurring in early-onset neuroinvasive LD, are encompassed by BWS [9]. Additionally, patients with LNB and BWS often experience paresis and show enhancement of the spinal nerve roots in the lower spinal cord and/or cauda equina on imaging [10]. While the precise incidence of BWS in the United States is unknown, literature suggests that LNB associated with BWS is more frequent in Europe, where it is primarily associated with *B. garinii* infections [1, 10].

In this brief communication, we report that among 6 patients with LNB identified over a 3-week period in 2017, 5 presented with PNS involvement (primarily axonal in nature) consistent with BWS. This is an unexpectedly high incidence at our facility as compared with prior years, in which 1 or 2 cases of LNB with BWS are typically suspected annually.

All 5 patients presented with symptoms including upper or lower extremity radiculopathy and/or paresthesias. Typically, BWS is associated with limited radicular pain, as observed for 2 patients presented here. The more widespread peripheral neuropathy observed for the remaining 3 patients in this series is

somewhat atypical. Additionally, 2 patients developed visual disturbances and nerve root enhancement in the cauda equina or lumbar spine, and 1 presented with Lyme disease–associated facial nerve palsy. Four patients underwent CSF collection showing significant lymphocytic pleocytosis and high protein, consistent with BWS. The absence of CSF evaluation for patient 4 is a limitation for definitive LNB classification, although his presentation with improvement following treatment strongly supports the presence of neuroinvasive disease. Importantly, 4 out of 5 patients showed rapid response to antimicrobials, as expected with LNB. For the fifth patient, although symptomatic improvement was noted, the prolonged symptoms may be a result of a concomitant neurologic process, though an alternative explanation has not yet been identified.

While definitive laboratory diagnostic criteria have been well-established for non-neuroinvasive LD, diagnostic testing guidelines are not as well defined for confirmation of LNB in the United States. Detection of IgM and/or IgG class antibodies to *B. burgdorferi* by immunoblot in CSF is often performed, although there are no specific criteria established for interpretation of banding patterns in CSF. Also, due to the possibility of passive immunoglobulin diffusion across the blood-CSF barrier or the presence of serum antibodies in CSF as a result of a traumatic lumbar puncture, detection of antibodies to Bbsl in CSF does not solely confirm intrathecal synthesis [8]. Anti-Bbsl intrathecal antibody synthesis can be established by determining a pathogen-specific IgG AI. The AI is a ratio of the level of pathogen-specific IgG antibodies in CSF:serum following normalization for total IgG in both specimen sources. An AI ratio of ≥1.5 is considered indicative of true, pathogen-specific intrathecal antibody synthesis [3]. The diagnostic sensitivity of the LD AI is variable (range, 55%–100%), largely dependent on the duration of symptoms prior to specimen collection [11]. Importantly, although offered through a limited number of reference laboratories in the United States, determining an LD AI is included in diagnostic and management guidelines for neuroinvasive LD from both the Infectious Diseases Society of America and the European Federation of Neurological Societies [6, 11]. In this case series, all 3 patients with sufficient CSF for LD AI testing were positive, with AI ratios ranging from 2.49 to 40.2. Finally, while definitive evidence of neuroinvasive LD includes detection of Bbsl nucleic acid in CSF, only 1 patient with LNB/BWS was RT-PCR positive in this series. This is consistent with previous studies showing that the sensitivity of RT-PCR in CSF for Bbsl is low, with a median sensitivity of 22.5% [12].

CONCLUSIONS

We report 5 cases of LNB with BWS in the upper Midwest United States. While this suggests an increased incidence of this presentation in our region, BWS associated with LD is not currently a reportable disease, and comparison with prior years is not possible. It remains prudent, however, for clinicians to be aware of this infrequent and possibly increasing clinical manifestation of LNB in the United States. The constellation of neurological symptoms, particularly when associated with a recent or suspected tick bite in an LD-endemic region, should prompt clinical evaluation for LNB and assessment for BWS as this syndrome may be more common than previously presumed in North America.

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