IDCases 27 (2022) e01443

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Acute Lyme neuroborreliosis with transient aphasia – Case report and review of current knowledge

Flávia Cunha[a,1,*], Joana Alves Duarte[b], Raquel Gonçalves[a]

[a] Infectious Diseases Department, Centro Hospitalar e Universitário de Coimbra, Portugal
[b] Internal Medicine Department, Centro Hospitalar e Universitário de Coimbra, Portugal

ARTICLE INFO

Article history:
Received 17 January 2022
Received in revised form 3 February 2022
Accepted 3 February 2022

Keywords:
CNS infection
Encephalitis
Lyme disease
Neuroborreliosis
Tick-borne encephalitis

ABSTRACT

Lyme borreliosis (LB) is a tick-borne infectious disease, endemic in the Northern hemisphere, with a polymorphic clinical spectrum (cutaneous, articular, and neurologic involvement). The variability of clinical manifestations poses LB as a diagnostic challenge. We describe a case of acute Lyme neuroborreliosis (LNB) in an adult female with a history of recent travel in Europe. There are few reports of acute LNB presenting as encephalitis in the literature. Suspicion for the diagnosis and prompt treatment seems to have a positive impact on patient outcomes.

Introduction

Lyme disease, the most common human arthropod-borne infectious disease in the Northern hemisphere, is caused by the spirochete *Borrelia burgdorferi* (Bb) sensu lato complex [1,2]. In Europe, the highest incidences of Lyme disease are found in Scandinavian countries and central Europe (Austria, Slovenia, and Germany) [2,3]. Lyme disease is spread by ticks infected with *Borrelia*, but different species of bacteria are found in endemic areas. In North America, the only known species responsible for human disease is *B. burgdorferi* sensu stricto, while in Europe at least five *Borrelia* species (*B. burgdorferi* sensu stricto, *B. garinii, B. bavariensis*, *B. lusitaniae, B. afzelii,* and *B. spielmanii*) can cause the disease [2,3].

Lyme disease is a multistage and multisystem disorder predominantly affecting the skin, but also involving the joints, heart, and peripheral and central nervous system (CNS) [1,2]. Neurological manifestations are reported in 10–15% of patients with Lyme disease in both Europe and the USA [4]. Early Lyme neuroborreliosis (LNB) generally develops within 2–18 weeks after infection and can be the presenting (or even the only) sign of Lyme disease. The most common manifestations of early LNB are painful meningoradiculitis and lymphocytic meningitis [5]. Other forms of CNS involvement, such as encephalitis and myelitis, are rare (below 5%) in patients with early LNB.

The diagnosis of LNB includes CSF study and serologic tests. Direct detection methods for *B. burgdorferi* are of limited use for the diagnosis of LNB [2]. The Centers for Disease Control and Prevention (CDC) recommend a two-test approach: screening test with enzyme-linked immunosorbent assay (ELISA), followed by a Western-blot [6].

Case report

A 44-year-old woman presented to the emergency department with transient aphasia, fluctuating level of consciousness, and fever in the last three days. She had also complained of headache with photophobia the week before. The patient was febrile at admission, alternating periods of aggressive behavior with prostration. Neurological examination revealed orofacial involuntary movements and global aphasia, but no motor deficits or pyramidal signs. Her past medical history was unremarkable, except for dyslipidemia, medicated. She lived in an urban area and had traveled to a village in Paris' surroundings two months before, where she performed trails in forest areas with some insect bites. She also recalls another insect bite in the woods last year, in the central region of Portugal. She did not remember identifying a tick. The patient's history was negative for erythema migrans.

Routine laboratory analysis showed lymphocytosis, elevated liver enzymes, and C-reactive protein (CRP). Blood and urine cultures were negative. Serological tests were positive for acute Bb infection.

* Corresponding author.
E-mail address: flavia.cunha12@gmail.com (F. Cunha).
[1] Present address: Praceta Mota Pinto, 3000–075 Coimbra, Portugal

https://doi.org/10.1016/j.idcr.2022.e01443
2214-2509/

Table 1
CSF findings, at admission and 48 hours later.

	Baseline examination	Post 48-hours	Reference values
Cells, mm^3	75 (mononuclear)	7 (mononuclear)	< $3/mm^3$
Proteins, mg/dL	138	75	15–40 mg/dL
Glucose, mg/dL	52	76	40–70 mg/dL
Lactate, U/L	29	–	–
Multiplex PCR testing for meningitis/encephalitis*	Negative		–
HSV-1 and HSV-2 DNA detection (by PCR)	Negative	Negative	–
RNA *B. burgdorferi*	–	Negative	–
Oligoclonal bands	–	Detected	–

CMV: Cytomegalovirus. DNA: deoxyribonucleic acid; HHV-6: Human herpesvirus 6. HSV-1: Herpes simplex virus 1. HSV-2: Herpes simplex virus 2. PCR: polymerase chain reaction. RNA: ribonucleic acid. VZV: Varicella zoster virus.
*This multiplex PCR testing includes the following microorganisms: HSV-1, HSV-2, CMV, Enterovirus, HHV-6 VZV, S. pneumoniae, H. influenza, L. monocytogenes, N. meningitidis, S. agalactiae, E. coli K1, C. neoformans/gattii.

Further studies excluded active infection with Epstein-Barr virus (EBV), Herpes simplex 1 and 2 viruses (HSV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), Hepatitis E virus (HEV), *Treponema pallidum, Toxoplasma gondii, Coxiella burnetii, Bartonella henselae, Rickettsia conorii*. Autoimmune workup was negative for ANAs, ANCAs, anti-ds-DNA, anti-SSA60, anti-SSB, RNP, Sm, Rcl70, JO1, C3, C4. Immunoglobulin levels were normal.

Cerebrospinal fluid (CSF) analysis showed a lymphocytic pleocytosis and elevated protein levels with no agent identification by culture or molecular method (Table 1). Magnetic resonance imaging (MRI) of the brain showed no acute vascular lesions or contrast enhancement of the meninges. Electroencephalography (EEG) showed an interhemispheric asymmetry with slow-wave activity in the left frontotemporal area, with no epileptiform activity. An acute lymphocytic meningoencephalitis was diagnosed and the patient was admitted to the Infectious Diseases department, under treatment with intravenous (IV) ceftriaxone 2 g bid, dexamethasone 10 mg QID, and acyclovir 750 mg tid.

CSF analysis was repeated forty-eight hours later, showing a decrease in lymphocyte cell count and a slightly elevated protein level (Table 1). Serological tests were performed in CSF second sample and revealed positive Bb-specific IgM antibodies. Polymerase chain reaction (PCR) for Bb in CSF was negative (Table 2). Oligoclonal bands were detected in the CSF. The diagnosis of acute neuroborreliosis was confirmed by a positive IgM Western-Blot (WB) in CSF, performed in the National Reference Laboratory, Instituto Nacional de Saúde Doutor Ricardo Jorge (Table 3).

Antibiotic treatment with iv ceftriaxone was carried out for 21 days. Neurological recovery of the patient was excellent since the first days of hospitalization. The patient maintains follow-up consultations in our outpatient clinic, with no symptoms of post-treatment Lyme disease syndrome.

Discussion

Acute Lyme neuroborreliosis presenting as encephalitis is an unusual form of the disease. Very few cases have been reported in the literature [7]. The neurological symptoms at admission raised suspicion of a CNS infection. An extensive investigation was performed, including lumbar puncture, brain MRI, EEG, and serology for other arthropod-borne infections.

Considering the epidemiology of our patient, we suspected *Borrelia burgdorferi* as a microorganism likely to be responsible for this episode, despite the absence of tick-bite lesions or erythema migrans. The time of infection was not clear at the beginning since there were two suspected possibilities for inoculation: (1) insect bite in summer about a year ago, in Portugal's central region, (2) insect bite in the countryside, in France, about ten weeks before the symptoms. However, the absence of suspicious symptomatic episodes before the one here reported leads us to consider the epidemiological link with the patient's stay in France.

The diagnosis of LNB should be based on a combination of patient history, clinical findings, CSF analysis, and serologic studies of serum and CSF. The presence of erythema migrans is not obligatory; cutaneous involvement is recalled in up to 50% of the cases [2]. The incubation period (eight weeks) is in the time interval usually considered in acute LNB [8,9]. The suspicion of LNB was supported by positive serology for *B. burgdorferi* sensu lato. An elevated IgM was detected in both serum and CSF, indicating an acute installation of the disease. These results were confirmed by a positive Western Blot in CSF, demonstrating an evolving humoral response in the CNS. A negative PCR does not exclude the presence of *B. burgdorferi* [2,10]; consequently, the use of a PCR assay to confirm LNB infection is not recommended [8]. Recently, a new diagnostic approach has been proposed by the Food and Drug Administration (FDA), named as the two-tier modified testing. This approach considers the use of a second sensitive enzyme immunoassay (EIA) in place of western immunoblot assay as an alternative for the serologic diagnosis of Lyme disease [11].

Treatment of LNB with antibiotics is recommended, to avert persistent neurological deficits [2,12]. Recommendations suggest the use of penicillin, ceftriaxone, cefotaxime, or doxycycline in LNB [9]. Recent studies showed non-inferiority of oral doxycycline compared to IV ceftriaxone [13,14]. Nevertheless, these studies include a reduced number of cases of LNB with CNS symptoms compared to LNB cases with peripheral nervous system (PNS) symptoms; the evidence is scarce in this topic, requiring further studies to better understand the effect of oral doxycycline-based regimens in LNB with CNS involvement. Recommended treatment duration is 14 days in acute

Table 2
Serologic results in serum and CSF.

Serology for *Borrelia spp*		
Serum		
Borrelia burgdorferi sensu latu		
IgG	< 5.0	Negative if < 10 UA/mL Positive if > 15 UA/mL
IgM	70.05	Negative if < 18 UA/mL Positive if > 22 UA/mL
CSF		
Borrelia burgdorferi		
IgG	0.62	Negative if < 2.5 UA/mL
IgM	4.59	Positive if > 3.5 UA/mL

CSF: cerebrospinal fluid; Ig: immunoglobulin

Table 3
Confirmatory tests for *Borrelia burgdorferi* in CSF.

Western Blot in CSF *Borrelia burgdorferi*	
Western Blot – Ig G	Negative
Western Blot – Ig M	Positive

CSF: cerebrospinal fluid; Ig: immunoglobulin

LNB and 21 days in late LNB [9,15]. In our case, we were not certain of the inoculation moment and disease evolution until WB confirmation of an acute process, therefore a 3-week treatment was performed. There is no sufficient data on the usage of steroids in LNB [9]; however, we considered that the anti-inflammatory effect of dexamethasone over cerebral parenchyma has contributed to an earlier neurological improvement in our patient.

Antibody titters generally decline after antibiotic therapy. Nonetheless, both IgM and/or IgG can remain positive for months or years after treatment [12,16]. *Borrelia*-specific antibodies do not help monitor treatment response and disease evolution [2].

This case illustrates the importance of a careful history, considering the type of exposure (rural areas, forests), together with the inflammatory CSF findings as suspicions to the diagnosis. With the actual massive traveling phenomena, though Portugal is not considered an endemic country, we should ponder Lyme neuroborreliosis in a patient with recent travel history to endemic countries and suspicion of CNS infection.

Consent for publication

The patient gave written consent for the publication of this case report.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

F.C. – Conception, and design of the study; acquisition of data; analysis and/or interpretation of data; drafting the manuscript; approval of the version of the manuscript to be published, J.A.D. - Conception, and design of the study; drafting the manuscript; approval of the version of the manuscript to be published. R.G. - revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published.

Acknowledgments

The authors thank Cristiana Lopes, from the Clinical Pathology Department of Centro Hospitalar e Universitário de Coimbra, for the help provided in the interpretation of serological results during the investigation.

Conflict of interest statement

The authors have no conflict of interest to declare.

References

[1] Rupprecht TA, Koedel U, Fingerle V, Pfister H-W. The pathogenesis of lyme neuroborreliosis: from infection to inflammation. Mol Med 2008;14(3–4):205–12.
[2] Koedel U, Fingerle V, Pfister H-W. Lyme neuroborreliosis – epidemiology, diagnosis and management. Nat Rev Neurol 2015;11(8):446–56.
[3] Schotthoefer AM, Frost HM. Ecology and epidemiology of lyme borreliosis. Clin Lab Med 2015;35(4):723–43.
[4] Halperin JJ. Diagnosis and management of Lyme neuroborreliosis. Expert Rev Anti Infect Ther 2018;16(1):5–11.
[5] Reik L, Streere AC, Bartenhagen NH, Shope RE, Malawista SE. Neurologic abnormalities of Lyme disease. Medicine 1979;58(4):281–94.
[6] Centers for Disease Control and Prevention. Recommendations for test performance and interpretation from the second national conference on serologic diagnosis of lyme disease. MMWR Morb Mortal Wkly Rep 1995;44(31):590–1.
[7] Schwenkenbecher P, Pul R, Wurster U, Conzen J, Pars K, Hartmann H, et al. Common and uncommon neurological manifestations of neuroborreliosis leading to hospitalization. BMC Infect Dis 2017;17(1):90.
[8] Eldin C, Raffetin A, Bouiller K, Hansmann Y, Roblot F, Raoult D, et al. Review of European and American guidelines for the diagnosis of Lyme borreliosis. Méd. Mal Infect 2019;49(2):121–32.
[9] Mygland Å, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European lyme neuroborreliosis: guidelines on neuroborreliosis. Eur J Neurol 2010;17(1):8–4.
[10] Rizzoli A, Hauffe HC, Carpi G, Vourc'h GI, Neteler M, Rosà R. Lyme borreliosis in Europe. Eur Surveill: Bull Eur sur Les Mal Transm = Eur Commun Dis Bull 2011;16(27):19906.
[11] Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of lyme disease. MMWR Morb Mortal Wkly Rep 2019;68(32):703.
[12] Djukic M, Schmidt-Samoa C, Nau R, von Steinbüchel N, Eiffert H, Schmidt H. The diagnostic spectrum in patients with suspected chronic Lyme neuroborreliosis - the experience from one year of a university hospital's Lyme neuroborreliosis outpatients clinic: suspected chronic Lyme neuroborreliosis and differential diagnosis. Eur J Neurol 2011;18(4):547–55.
[13] Bremell D, Dotevall L. Oral doxycycline for Lyme neuroborreliosis with symptoms of encephalitis, myelitis, vasculitis or intracranial hypertension. Eur J Neurol 2014;21(9):1162–7.
[14] Ljøstad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. Lancet Neurol 2008;7(8):690–5.
[15] Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the infectious diseases society of America. Clin Infect Dis 2006;43(9):1089–134.
[16] Topakian R, Stieglbauer K, Nussbaumer K, Aichner FT. Cerebral vasculitis and stroke in lyme neuroborreliosis. Cereb Dis 2008;26(5):455–61.