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LYME NEUROBORRELIOSIS AS INITIAL EXPRESSION OF LYME DISEASE IN AN ELDERLY PATIENT

Emídio Mata[1], Bárbara Lage Garcia[1], André Pereira[2], Joana Rego[2], Flávia Santos[2], Carlos Fernandes[2], Jorge Cotter[2]

[1] Department of Cardiology, Unidade Local de Saúde de Alto Ave, Guimarães, Portugal
[2] Department of Internal Medicine, Unidade Local de Saúde de Alto Ave, Guimarães, Portugal

Corresponding author's e-mail: emidiomata@hotmail.com

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ABSTRACT

Background: Lyme disease (LD) is a multisystemic infection caused by *Borrelia burgdorferi* and transmitted by *Ixodes* ticks, affecting the skin, nervous system, heart and joints. Neuroborreliosis (LNB), a nervous system manifestation of LD, occurs in 10–15% of cases and may present with neurological symptoms at varying stages.

Case description: We present the case of an 84-year-old man, admitted to the emergency department following a seizure, with fever and oropharyngeal erythema. After the administration of penicillin for presumed tonsillitis, a generalised skin rash developed and spontaneously resolved after 4 hours. Within 24 hours, two well-defined round erythematous lesions were observed on the neck and shoulder. Due to new onset of confusion and lethargy a lumbar puncture was performed, revealing polymorphonuclear pleocytosis, elevated protein levels and normal glucose. An empirical ceftriaxone course was started for suspected neuroborreliosis. Neuroborreliosis was diagnosed based on the clinical presentation of fever and neurological changes, with supporting cutaneous manifestations and compatible *Borrelia burgdorferi* serology. The initial rash was interpreted as a Jarisch–Herxheimer reaction, and the two skin lesions were classified as erythema migrans. After completing treatment, the patient made a full recovery.

Conclusion: This case underscores the diagnostic complexity of LNB as an initial manifestation of LD, particularly in elderly patients. Early neurological symptoms, often preceding classic cutaneous signs, may lead to diagnostic delays. This highlights the importance of maintaining clinical suspicion for LD, given the limitations of serological and cerebrospinal fluid (CSF) testing. Prompt recognition and intervention are essential to prevent progression and ensure favourable outcomes.

KEYWORDS

Lyme disease, Lyme neuroborreliosis, *Borrelia* infections, Lyme meningoencephalitis

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LEARNING POINTS

- Lyme disease can present with neurological symptoms such as neuroborreliosis (LNB) before typical cutaneous signs, complicating diagnosis, especially in older adults. Early detection relies on clinical suspicion and cerebrospinal fluid (CSF) analysis, even when serology and PCR may be negative.
- Serum IgM antibodies can aid diagnosis, but their absence does not rule out LNB. CSF analysis often shows non-specific findings, and PCR testing has low sensitivity. The Jarisch–Herxheimer reaction, seen after treatment, can mimic an allergic response and should be recognised.

INTRODUCTION

Lyme disease (LD) is a tick-borne bacterial infection, caused by *Borrelia burgdorferi* spirochaetes. It is transmitted by the tick *Ixodes ricinus*, with a prevalence estimated at 12%[1,2]. As a multisystemic disease, it can affect the skin, the nervous system, the heart-conducting tissue and the joints, in different stages of the disease. Neuroborreliosis (LNB) can occur in both early and late LD, and may include involvement of central and peripheral nervous systems, occurring in up to 12% of cases of LD[3]. As a result of the low incidence of LNB, this diagnosis is hardly considered as a probable source of neurologic signs, with diagnostic delay and prognostic implications. We present a case of an 84-year-old man with LNB as a first presentation of LD.

CASE DESCRIPTION

An 84-year-old male presented to the emergency department (ED) after a seizure and fever. In the days leading up to his ED visit, the patient experienced myalgia and odynophagia, without any other symptoms.

He had a personal history of hypertension, dyslipidaemia, type 2 diabetes and benign prostatic hyperplasia. His medications included atorvastatin and dutasteride. The initial physical assessment unveiled fever (40°C) and an erythematous oropharynx, without purulent exudates or any rashes. The patient was disoriented in space and time, but without focal neurological deficits or meningism. Standard laboratory tests revealed rhabdomyolysis, acute kidney injury and elevated inflammatory markers *(Table 1)*.

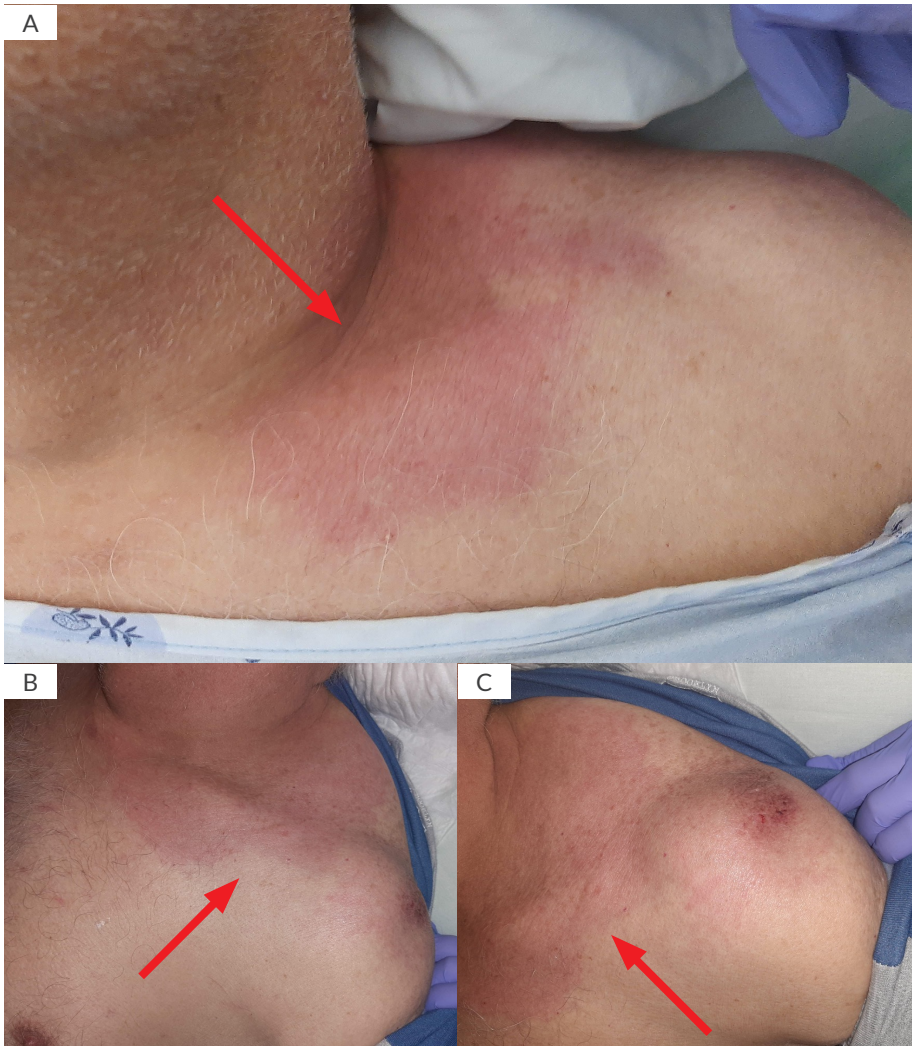

Figure 1. Erythema migrans. An 84-year-old male patient diagnosed with Lyme disease presenting with erythema migrans and its progression during the first days of hospitalisation. A) Day 1: well-defined, non-pruritic, round erythematous lesion on the patient's neck (red arrow); B and C) Day 4: progression of erythematous lesion (red arrows).

Cerebrospinal fluid analysis	Value	Reference values
Leucocytes (cell/µL) Polymorphonuclear (%) Mononuclear (%)	85 83 17	< 5
Glucose (mg/dL)	81	-
Proteins (mg/dL)	86.9	15–40
PCR panel (*Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, herpes simplex virus 1, herpes simplex virus 2, human herpes virus 6, parechovirus, varicella zoster virus, *Cryptococcus neoformans*, *Cryptococcus gattii*, *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Borrelia miyamotoi*, *Borrelia hermsii*, *Anaplasma phagocytophilium*, *Coxiella burnetii*, *Flaviviridae*, *Ehrlichia chafeensis*, *Ehrlichia muris*, *Babesia microti*, *Babesia divergens*, *Rickettsia spp*)	Negative	-
Streptococcus pneumoniae antigen	Negative	-
Cerebrospinal fluid cultures *	Negative	-
Blood sample analysis	**Value**	**Reference values**
Erythrocyte ($\times 10^6$/µl)	4.78	4.5–5.9
Haemoglobin (g/dl)	15	14–18
Haematocrit (%)	43	41–53
Leucocytes ($\times 10^3$/µl)	11.2	4.8–10.8
Erythrocyte sedimentation rate (mm/hr)	43	0–30
C-reactive protein (mg/l)	474.7	<3
Ferritin (ng/ml)	3,106	22–322
Procalcitonin (ng/ml)	4.23	-
Glucose (mg/dl)	122	74–106
Urea (mg/dl)	132	15–39
Creatinine (mg/dl)	1.49	0.7–1.30
Myoglobin (ng/ml)	2,715	14–106
Antibody anti-*Borrelia* IgM (Index)	104.4	Positive >22
Antibody anti-*Borrelia* IgG (AU/ml)	< 0.5	Negative <10
PCR panel (*Borrelia burgdorferi*, *Borrelia miyamotoi*, *Borrelia hermsii*, *Anaplasma phagocytophilium*, *Coxiella burnetii*, *Flaviviridae*, *Ehrlichia chafeensis*, *Ehrlichia muris*, *Babesia microti*, *Babesia divergens*, *Rickettsia spp*)	Negative	-

* Cultures of cerebrospinal fluid included media for *Mycobacterium ssp.* polymerase chain reaction (PCR).

Table 1. Cerebrospinal fluid and blood sample analyses. Detailed overview of the laboratory analyses, which includes elevated inflammatory markers, rhabdomyolysis, acute kidney injury and polymorphonuclear pleocytosis in cerebrospinal fluid.

A brain CT scan showed no acute lesions, and a full-body CT scan revealed no respiratory, abdominal or pelvic source of infection. The electrocardiogram indicated new-onset atrial flutter with variable conduction.

The patient received a single penicillin intramuscular injection for presumed tonsilitis. After the fever subsided in the ED, the patient became oriented and was admitted to the medical ward. One hour after penicillin administration, the patient experienced a full-body, non-pruritic mild scaling erythematous macular rash, which vanished spontaneously after four hours. Within 24 hours, the patient developed fever and exhibited lethargy and confusion, even during afebrile periods. Physical examination uncovered two well-defined, non-pruritic round erythematous lesions on the neck and right shoulder *(Fig. 1A)*, with centrifugal growth, in the first days of hospitalisation *(Fig. 1B and C)*.

As a result, neuroborreliosis was suspected and a lumbar puncture was performed. Cerebrospinal fluid (CSF) revealed proteinorachia with polymorphonuclear pleocytosis and normal glucose levels *(Table 1)*. A CSF polymerase chain reaction (PCR) panel for tick-borne disease and viral and bacterial pathogens was negative, as were CSF cultures and a PCR panel for tick-borne diseases in the admission blood sample. Serological testing for syphilis was conducted

using a reverse sequence screening approach, starting with a treponemal test via chemiluminescence immunoassay (CIA) in blood, complemented by a venereal disease research laboratory test in CSF, ruling out syphilis. Empirical antibiotherapy was initiated with a course of ceftriaxone at a meningeal dosage (2 g bid). A brain MRI showed no significant alterations, and an electroencephalogram ruled out epileptiform paroxysms or focal slowing, suggesting that the patient's symptoms were not due to seizures or localised brain dysfunction. A high titre of serum *B. burgdorferi* immunoglobulin M (IgM) antibodies, with negative immunoglobulin G (IgG) *(Table 1)* in combination with the previously described cutaneous manifestations supported the diagnosis of LD. IgM *B. burgdorferi*-specific antibodies results were obtained using CIA.

The initial rash, initially mistaken for a drug allergy, was a Jarisch–Herxheimer reaction, and the two additional skin lesions were identified as erythema migrans (EM). The diagnosis of neuroborreliosis was based on the CSF analysis, seizure episode and elevated IgM titres for *Borrelia*, despite negative PCR results and the absence of significant findings on an electroencephalogram or imaging. Within 8 days of treatment, the patient showed a recovered mental status, with reduced inflammatory markers and sustained apyrexia. On day 15 of hospitalisation, the patient developed pseudomembranous colitis, leading to ceftriaxone discontinuation on day 18 and initiation of vancomycin. After 28 days the patient was discharged to a rehabilitation centre which led to a complete recovery within four months.

DISCUSSION

LD is an infectious disease, caused by *B. burgdorferi* as a result of a tick bite, typically from *I. ricinus*. Notably, only about 40–50% of patients recall having been bitten[4]. In Europe, the most common genospecies are *Borrelia afzelii* and *B. garinii* and there are approximately 65,500 cases reported annually[5]. Clinical manifestations are dependent on the disease stage. In early and localised infection, the most common symptom is EM, often occurring at the bite site (80–89% of cases). EM appears as a painless, slowing expanding erythematous macule with a central clearing and red border, typically 7–14 days after the bite[1,5]. A second stage, indicating early disseminated infection, occurs days to weeks after the bite and is characterised by multiple EM (20%)[1], neurologic (15%) and cardiac manifestations (8%) such as atrioventricular blocks[5]. After weeks to years, late manifestations include acrodermatitis chronica atrophicans (1%) or neurologic manifestations (such as polyneuropathy, chronic encephalopathy and mood swings)[1,5]. LNB occurs when spirochaetes invade the nervous system, affecting up to 12% of patients within 1–12 weeks[3]. Early disease (<6 months) is the most common manifestation (95% of cases)[6,7] and includes cranial neuropathy (often seventh cranial nerve palsy), sensory radiculopathy and lymphocytic meningitis. Encephalitis is more prevalent in Europe due to the presence of B. garinii genospecies, which is more neurotropic[1]. CSF evaluation typically shows lymphocytic pleocytosis (>90% lymphocytes), moderately elevated protein levels and normal glucose levels[1,6,7].

The initial presentation of this case – seizure, fever and disorientation – was atypical because the patient's neurological symptoms preceded the cutaneous manifestations. Additionally, his advanced age contributed to the diagnostic challenge, as common infections such as tonsillitis can cause mental status changes at this age, potentially misleading clinicians. No tick bite was observed at the lesion site, though most LD patients do not recall a bite. The likely bite site was the neck's lateral or posterior skin fold, an area with limited visibility. While anecdotal evidence suggests transmission can occur in under 24 hours, the minimum duration for transmission remains unclear. Experimental data show spirochaetes can be transmitted in under 16 hours and often in less than 24 hours[8].

According to the European Guidelines, a definite diagnosis of LNB requires three criteria to be met, while possible LNB is diagnosed with two. The three criteria are neurological symptoms, CSF pleocytosis and *B. burgdorferi*-specific antibodies in CSF. In this case, only two criteria were met, and diagnosis was based on clinical manifestations and CSF analysis[6]. Although LNB typically presents with lymphocytic pleocytosis in the CSF, the predominance of polymorphonuclear cells observed is an atypical finding. While this deviates from the usual presentation, the diagnosis remains supported by the overall clinical and laboratory evidence.

B. burgdorferi-specific antibodies in CSF were not isolated in this case, as intrathecal production of antibodies has low sensitivity in early disease stages. Molecular (PCR) testing in CSF and plasma has also low sensitivity (10–30%) and is not usually recommended, since there are few *B. burgdorferi* cells in CSF and plasma to allow for DNA detection[6,7].

Limitations to *B. burgdorferi* serology are low sensitivity and low specificity in patients with symptoms for < 6 weeks, and it cannot distinguish between active and inactive infection[1,5-7]. A thorough skin examination is essential for detecting EM without positive serology, especially in the early stages, though in this case it was not relevant. Another limitation of this diagnostic method is the geographical variations in *B. burgdorferi* genospecies, which can also limit antibody detection in laboratories.

In this case, a high titre of IgM (4.75-fold increase) was detected in plasma and not in CSF, but likely due to the early stage of the disease. A marked IgM titre elevation (more than 2.8-fold) can justify immediate therapy, regardless of lumbar puncture results[9]. As in this case, about 20–30% of patients show positive IgM and negative IgG within 30 days of infection onset, indicating acute infection. A minority of patients may take 6–8 weeks to seroconvert to IgG[2,5,10]. Therefore, if a patient has symptoms for over 2 months with only a positive IgM test, it is likely a false positive and should be disregarded. Two months later, IgG was positive, supporting the diagnosis. However, it is important to note

that serological testing after treatment is generally not recommended, as early treatment in EM patients may prevent detectable antibody response. Therefore, a negative result does not exclude the diagnosis[11].

Although some manifestations of Lyme neuroborreliosis (LNB) may go into remission spontaneously, antibiotic treatment prevents disease progression. Most literature reports improvement in neurological symptoms within weeks to months after antibiotic treatment[1]. Current guidelines recommend treating early LNB with IV ceftriaxone or PO doxycycline for 14–21 days, being equally effective[5-7]. This patient improved with IV ceftriaxone, showing total regression of neurological impairment after 18 days.

As stated, the patient exhibited a Jarisch–Herxheimer reaction, which is a self-limited acute event characterised by fever, headache, hypotension, tachycardia, flushing and rash[12]. It occurs in about 15% of patients within the first 24 hours of therapy and is caused by the release of toxins, and inflammatory interleukins and TNF-alpha due to increased phagocytosis of spirochaetes[1,5,12]. This reaction can often be mistaken for a drug allergic reaction, as seen in this case, highlighting the need for awareness of it.

CONCLUSION

This case highlights the diagnostic challenge of LNB as a first manifestation of LD, since its diagnosis relies on clinical suspicion. This is an unusual case, as LNB preceded the appearance of EM, whereas EM is typically the first manifestation with central nervous system involvement usually occurring days to weeks later. Laboratory tests have important limitations and CSF analysis often show non-specific and indirect clues, common to other aetiologies. Accurate interpretation of serology and PCR is crucial, as negative results do not rule out the diagnosis.

REFERENCES

1. Goldman L, Cooney KA, editors. Goldman-Cecil Medicine. 27th ed. New York: Elsevier Health Sciences; 2021.
2. Factsheet about Borreliosis European Centre for Disease Prevention and Control [updated 6 Mar 2016]. [accessed 2024 Aug 5]. Available from: https://www.ecdc.europa.eu/en/borreliosis/facts/factsheet.
3. Koedel U, Fingerle V, Pfister HW. Lyme neuroborreliosis-epidemiology, diagnosis and management. *Nat Rev Neurol* 2015;**11**:446–456.
4. Santos FV, Cipriano A, Abreu MA, Andrade C, Sarmento-Castro R. Neuroborreliose Tardia num Estudante em Programa Erasmus. [Late Neuroborreliosis in an Erasmus Programme Student]. *Acta Med Port* 2018;**31**:509–511.
5. Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, editors. Harrison's Principles of Internal Medicine. 21st ed. New York: McGraw-Hill Education; 2022.
6. Mygland A, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I; European Federation of Neurological Societies. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neuro* 2010;**17**:8–16, e1–4.
7. Lantos PM, Rumbaugh J, Bockenstedt LK, Falck-Ytter YT, Aguero-Rosenfeld ME, Auwaerter PG, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease. *Arthritis Care Res (Hoboken)* 2021;**73**:1–9.
8. Cook MJ. Lyme borreliosis: a review of data on transmission time after tick attachment. *Int J Gen Med* 2015;**8**:1–8.
9. Schneider C, Gielen J, Röth P, Albrecht P, Schroeter M, Fink GR, et al. Quantitative serological antibody testing for suspected neuroborreliosis. *J Neurol* 2020;**267**:1476–1481.
10. Clinical Testing and Diagnosis for Lyme Disease Centers for Disease Control and Prevention. [accessed 2024 Aug 5]. Available from: https://www.cdc.gov/lyme/hcp/diagnosis-testing/?CDC_AAref_Val=https://www.cdc.gov/lyme/diagnosistesting/index.html.
11. Aguero-Rosenfeld ME, Nowakowski J, Bittker S, Cooper D, Nadelman RB, Wormser GP. Evolution of the serologic response to Borrelia burgdorferi in treated patients with culture-confirmed erythema migrans. *J Clin Microbiol* 1996;**34**:1–9.
12. Dhakal A, Sbar E. Jarisch–Herxheimer reaction 2022 [updated 24 Apr 2023]. [accessed 2024 Aug 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557820/.