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LETTER TO THE EDITOR

Lyme borreliosis as a trigger for NMDA receptor encephalitis?

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Dear Editor:

NMDA receptor (NMDAR) encephalitis was initially described by Dalmau et al. [1] and is associated to a constellation of symptoms such as psychosis, memory deficits, seizures, abnormal movements, and autonomic dysfunction. In many patients, these autoantibodies occur in the setting of underlying tumor (teratomas), but in the remainder of patients, the immunopathogenesis remains unclear. Recent reports suggest that viral infections may trigger NMDAR [2], leading to speculation that mechanisms such as molecular mimicry and/or bystander activation may play a role.

A 32-year-old male was referred from a psychiatric hospital where he was hospitalized due to a gradual onset of behavioral changes, depression, memory loss, dysarthria, auditory hallucinations, irritability and aggressiveness. After 1 month of olanzapine, risperidone, clonazepam, valproate and biperiden treatment with no response, he was transferred to our care for neurologic evaluation. The past history was unremarkable; although, he frequently practices hunting in the countryside, and he reported a low-grade fever 1 month before admission. On admission, he was afebrile; he had general rigidity, rest-action tremor in upper limbs, psychomotor agitation, generalized myoclonus and signs of dysautonomia. A magnetic resonance imaging (MRI) was performed under sedation that showed no leptomeningeal contrast enhancement, temporal lobe involvement or ventricular enlargement. An electroencephalogram showed diffuse delta slowing but no seizure activity. Lumbar puncture on admission revealed 60 cells/μL (98% lymphocytes), protein 22.3 mg/dL and glucose 75 mg/dL. A working diagnosis of encephalitis was established, and the workup included viral, bacterial, mycobacterial and immunological studies. Blood and CSF Western Blot analysis revealed *Borrelia* IgM and IgG antibodies with CSF/blood antibody index > 1.19 and > 1.09, respectively (Table 1). Other infectious causes were ruled out, and IV ceftriaxone (2 g/day) was started. The patient developed stupor, severe dysautonomic derangements, severe rigidity, myoclonus and a tonic-clonic-generalized seizure. Endovenous lacosamide and valproate were started as anti-epileptics, and amantadine was added to manage rigidity. Five days later, blood and CSF revealed IgG and IgM antibodies against NR1 subunit of the NMDAR (cell-based assay) (Table 1). Laboratory test including other antibodies (Hu, Ri, Yo, anti-thyroglobulin, anti-peroxidase, anti-nuclear), HIV, VDRL and vitamin B_{12} levels were negative or normal. An enhanced abdominal, thoracic and pelvic computed tomography was normal. The diagnosis of anti-NMDAR receptor encephalitis was established. The patient was treated with plasma exchange followed by immunoglobulin 400 mg/kg of body weight every day during 5 days. One month after hospitalization, the extrapyramidal signs and seizures were under control and neurocognitive evaluation revealed MMSE score of 11, MOCA test in 12 and FAB score in 8. The patient was discharged, and 6 months later, he had recovered fully (MMSE and MOCA both 30 points). He was asymptomatic, and blood IgG and IgM *Borrelia* antibodies and IgG and IgM antibodies against NMDAR (NR1) were negative. He did not recall a tick bite or a skin lesion in the months preceding his initial symptoms.

Molecular mimicry and/or bystander activation has been proposed as a possible mechanism linking infections and some autoimmune encephalitis [2]. There are multiple reports that have described the development of NMDAR immunoreactivity and full-blown encephalitis after CNS infections with herpes simplex and Varicella-zoster virus [2]. Gable et al. described four cases of NMDAR encephalitis with serologic

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Table 1 Blood and CSF analysis to anti-NMDAR antibodies and *Borrelia* IgG and IgM antibodies, on admission and 1 month after treatment including plasma exchange. Other anti-neural antibodies were negative

CSF analysis on admission		CSF analysis in follow-up	
Anti-NMDAR antibody, positive (also in blood)		Not performed	
Western blot *Borrelia burgdorferi* IgG antibodies		Western blot *Borrelia burgdorferi* IgG antibodies	
Positive ≥ 5 bands		Positive ≥ 5 bands	
IgG P93 Ab	Absent	IgG P93 Ab	Absent
IgG P66 Ab	Present	IgG P66 Ab	Absent
IgG P58 Ab	Present	IgG P58 Ab	Absent
IgG P45 Ab	Absent	IgG P45 Ab	Absent
IgG P41 Ab	Present	IgG P41 Ab	Present
IgG P39 Ab	Absent	IgG P39 Ab	Absent
IgG P30 Ab	Absent	IgG P30 Ab	Absent
IgG P28 Ab	Absent	IgG P28 Ab	Absent
IgG P23 Ab	Absent	IgG P23 Ab	Absent
IgG P18 Ab	Absent	IgG P18 Ab	Absent
CSF/Blood antibody index > 1.09		CSF/Blood antibody index not performed	
Western blot *Borrelia burgdorferi* IgM antibodies		Western blot *Borrelia burgdorferi* IgM antibodies	
Positive ≥ 2 bands		Positive ≥ 2 bands	
IgM P41 Ab	Present	IgM P41 Ab	Absent
IgM P39 Ab	Present	IgM P39 Ab	Absent
IgM P23 Ab	Present	IgM P23 Ab	Absent
CSF/Blood antibody index 1.19		CSF/Blood antibody index not performed	

evidence of acute mycoplasma infection [3]. All patients were tumor-negative.

That infectious agent might account for the development of some of the tumor-negative cases of NMDAR encephalitis is an intriguing possibility. Lyme borreliosis (LB) is a tick-borne infection caused by *Borrelia burgdorferi* associated with erythema migrans and a flu-like illness; lyme neuroborreliosis (LNB) often presents with cranial neuropathies, radiculitis and, more rarely, encephalopathy [4]. We describe a young adult with a clinical phenotype of NMDAR encephalitis with no evidence of an underlying tumor but concomitant LNB.

LNB may have triggered the production of NMDAR antibodies leading to encephalitis. The absence of a tick bite, classical erythema migrans and cranial neuropathies in our case does raise some questions about a diagnosis of LNB, but we did have confirmation of intrathecal production of antibodies against *Borrelia*. Our region of Northeastern Mexico has a low prevalence of Western blot-confirmed seropositivity for LB (0.3%), although the Mexico-Texas border is considered endemic for the disease [5]. Chance alone would be an unlikely explanation for concomitant seropositivity for borreliosis and NMDAR in a patient with neurological signs and symptoms suggestive of encephalitis. However, that a common immune mechanism might be responsible for a false-positive *Borrelia*, serology remains a possibility.

Our patient responded well to antibiotic therapy and plasma exchange. It has been well established that *Borrelia* pathology is elicited by the host's innate and specific immune responses to surface proteins [4]. Neurological involvement in LNB may induce inflammation in peripheral/CNS structures probably releasing and presenting NMDAR epitopes to the immune system, breaking tolerance and initiating an autoimmune response [2, 4].If these events did indeed take place in our case, the precise immunopathogenic mechanisms remain unknown and warrant further study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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