The Canadian Journal of Neurological Sciences (2024), **51**, 325–327
doi:10.1017/cjn.2022.329

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Letter to the Editor: New Observation

Anti-N-Methyl-D-Aspartate Receptor Encephalitis Triggered by Lyme Disease

Yiu-Chia Chang[1], Adrian Budhram[1,2] and Daniel Wong[3]

[1]Department of Clinical Neurological Sciences, London Health Sciences Centre, Western University, London, Ontario, Canada, [2]Department of Pathology and Laboratory Medicine, London Health Sciences Centre, Western University, London, Ontario, Canada and [3]Department of Medicine, North York General Hospital, Toronto, Ontario, Canada

Keywords: Neurology – clinical; Neuroinfectious; Neuroimmunology; Neuroinflammation; Neurology – adult

A 70-year-old man presented with a complete right facial nerve palsy. Past medical history was only remarkable for hypertension and gastroesophageal reflux disease. He was diagnosed with an idiopathic Bell's palsy, for which he was treated with a course of prednisone and valacyclovir. He had complete resolution of facial weakness within 3 weeks of symptom onset. Four weeks after initial symptom onset, however, he became agitated and began exhibiting bizarre behavior, including inappropriately raising his voice at people and urinating on the side of the road. He then reportedly acutely developed incoherence and bilateral arm weakness, leading to local hospital admission. Head computed tomography (CT) was unremarkable, and his acute symptomology subsided so he was discharged back home. However, his family noted that he was repetitive and continued to have bizarre behavior. Over the next 3 weeks, he had four visits to the emergency room because of aggressive outbursts, such as yelling, pushing people, and hitting his own head. He was described as having pressured speech and was pacing the room. In addition, he also complained of headache. He had remained afebrile throughout these presentations. Unenhanced head magnetic resonance imaging (MRI) and routine electroencephalography (EEG) were unremarkable. For his agitation, he was initially prescribed lorazepam and sertraline and then switched to quetiapine, without significant response.

On his fourth admission, he had severe agitation requiring four-point restraints and treatment with haloperidol. He was assessed by the Neurology service, and aside from his behavioral change his examination including vital signs, orientation, cranial nerves, motor function, reflexes, sensation, and coordination were grossly intact. Formal bedside cognitive testing was not performed. Metabolic workup, including thyroid-stimulating hormone, vitamin B_{12}, liver function, and electrolytes, were normal, except for mildly elevated creatinine at 117 micromoles per liter. Rheumatologic workup only revealed a positive antinuclear antibody (ANA) at a titer of 1:80 with speckled pattern but was otherwise negative for extractable nuclear antigen, antimicrosomal antibodies, and anti-neutrophil cytoplasmic antibody. An enhanced thoracic, abdominal, and pelvic CT scan followed by whole-body positron emission tomography (PET)/CT found no evidence of malignancy. Enhanced head MRI did not reveal any acute abnormality. Repeat routine EEG was again unremarkable, without any epileptiform activity or focal slowing. Lumbar puncture for cerebrospinal fluid (CSF) evaluation showed normal glucose and protein, three white blood cells per microlitre, and negative oligoclonal bands. Extensive infectious workup, including testing for herpes simplex virus (HSV), varicella zoster virus (VZV), West Nile virus, fungi, acid-fast bacilli, and syphilis, was unremarkable except for serum detection of IgM and IgG antibodies against *Borrelia burgdorferi* by enzyme immunoassay and western blot. No CSF testing for *Borrelia burgdorferi* infection was performed. In retrospect, he recalled a tick bite 1 to 2 months preceding his facial nerve palsy. The Infectious Disease service was consulted and recommended daily intravenous ceftriaxone two grams for 4 weeks for possible nervous system Lyme disease, although his neuropsychiatric symptoms were considered to be atypical. No dramatic improvement was initially observed following administration of ceftriaxone. Comprehensive neural antibody testing for autoimmune encephalitis panel was performed and was positive for N-methyl-D-aspartate receptor antibody (anti-NMDAR) by fixed cell-based assay in CSF, confirming a diagnosis of anti-NMDAR encephalitis.[1] He was treated with IVIg 2 g/kg over 2 days and then a 5-day course of IV solumedrol 1000 mg. His neuropsychiatric symptoms began to improve within a week of treatment initiation, facilitating discharge from hospital. At 4-month follow-up, he was doing well according to family. Eight months after his original admission to the hospital, he developed agitation and pressured speech prompting clinical re-evaluation. However, brain MRI was again unremarkable, and repeat CSF evaluation including re-testing for anti-NMDAR was negative. On history, significant psychosocial stressors were identified that were felt to be the cause of his worsening. He improved with only low-dose clonazepam without immunotherapy and returned to his baseline within 2 weeks. At 1-year follow-up, the patient continues to do well, with no neuropsychiatric symptoms identified.

Corresponding author: Yiu-Chia Chang, University Hospital, 339 Windermere Road, London, ON N6A 5A5, Canada. Email: yiu-chia.chang@lhsc.on.ca

Cite this article: Chang Y-C, Budhram A, and Wong D. (2024) Anti-N-Methyl-D-Aspartate Receptor Encephalitis Triggered by Lyme Disease. *The Canadian Journal of Neurological Sciences* **51**: 325–327, https://doi.org/10.1017/cjn.2022.329

Table 1: Patients with anti-NMDAR encephalitis triggered by Lyme disease reported in the literature

	Martinez et al. 2018	Predkele et al. 2021	Chang et al. 2022
Age	32	74	70
Sex	Male	Male	Male
Symptoms indicative of Lyme disease	Low-grade fever	Left facial palsy and hypesthesia	Right facial palsy
Testing indicative of Lyme disease	Blood and CSF analysis revealed *Borrelia burgdorferi* IgM and IgG antibodies with elevated CSF antibody index	Blood and CSF analysis revealed *Borrelia burgdorferi* IgM and IgG antibodies with elevated CSF antibody index	Blood analysis revealed *Borrelia burgdorferi* IgM and IgG antibodies; CSF testing for Lyme disease not performed
Symptoms indicative of anti-NMDAR encephalitis	Behavioural changes, depression, memory loss, dysarthria, auditory hallucinations, irritability and aggressiveness	Behavioural and language changes, as well as memory impairment, balance impairment, and sleep disturbances	Behavioural change with agitation/ aggressiveness, pressured speech
Testing indicative of anti-NMDAR encephalitis	Positivity for anti-NMDAR by CBA in serum and CSF	Positivity for anti-NMDAR by fixed CBA in serum and CSF	Positivity for anti-NMDAR by fixed CBA in CSF
Time between onset of symptoms indicative of Lyme disease and anti-NMDAR encephalitis	Unclear; low-grade fever 4 weeks prior to hospital admission, although had onset of anti-NMDAR encephalitis symptoms preceding hospital admission	Unclear; symptoms indicative of Lyme disease noted at time of assessment for anti-NMDAR encephalitis	4 weeks
CSF profile	Inflammatory; 60 WBC/μL (98% lymphocytes)	Inflammatory; 79 WBC/μL (85% agranulocytes) and elevated protein of 1.924 g/L	Non-inflammatory
MRI findings	No acute abnormality	No acute abnormality	No acute abnormality
EEG findings	Diffuse delta slowing but no reported epileptiform activity	No reported epileptiform activity	No focal slowing or epileptiform activity
Treatments	Ceftriaxone, followed by plasma exchange then IVIG	Ceftriaxone, followed by IVMP	Ceftriaxone, followed by IVIG and then IVMP
Outcome	Initial worsening on ceftriaxone, with improvement following immunotherapy; recovered entirely 6 months after discharge from the hospital	Initially no marked improvement on ceftriaxone, with improvement noted after first 2 days of IVMP; marked improvement 10 days posttreatment and was discharged from the hospital, with mild residual fatigue and memory impairment	Initially no dramatic improvement on ceftriaxone, followed by improvement within 1 week of immunotherapy; returned to baseline 4 months after treatment, with transient worsening of behavior at 8 months that was attributed to psychosocial stressors and resolved without immunotherapy

CBA = cell-based assay; CSF = cerebrospinal fluid; EEG = electroencephalogram; IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; MRI = magnetic resonance imaging; NMDAR = N-methyl-D-aspartate receptor; WBC = white blood cell.

We herein present a patient who initially presented with facial palsy and serologic testing indicative of Lyme disease, followed by neuropsychiatric decline and CSF testing that confirmed a diagnosis of anti-NMDAR encephalitis. A number of pathologies have been reported as possible triggers for anti-NMDAR encephalitis, the most established of which are ovarian teratoma and HSV encephalitis.[2,3] In contrast, anti-NMDAR encephalitis following Lyme disease is exceptionally rare, with only two previous cases reported in the literature.[4,5] These two cases, along with our own, are summarized in Table 1. All patients had clinical symptoms indicative of Lyme disease within 4 weeks preceding or at the time of assessment for anti-NMDAR encephalitis. Interestingly, the two previously reported cases had an elevated *Borrelia burgdorferi* CSF antibody index suggestive of central nervous system Lyme infection. However, all patients had a neuropsychiatric decline that was more typical of anti-NMDAR encephalitis than neuroborreliosis and all lacked initial response to antimicrobial therapy but improved following immunotherapy, supportive of an autoimmune rather than infectious encephalitic process.[1,2,6] It is possible that *Borrelia burgdorferi* neuro-invasion may trigger anti-NMDAR encephalitis, like has been well described following HSV encephalitis.[3] Our findings suggest that CSF anti-NMDAR testing is warranted in patients diagnosed with Lyme disease followed shortly thereafter by subacute neuropsychiatric decline typical of anti-NMDAR encephalitis. In patients with anti-NMDAR encephalitis following Lyme disease, addition of immunotherapy should be considered to treat neuroinflammation possibly triggered by infection.

Funding. No funding was received for this manuscript.

Disclosures. Adrian Budhram reports that he holds the London Health Sciences Centre and London Health Sciences Foundation Chair in Neural Antibody Testing for Neuro-Inflammatory Diseases and receives support from the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO).

Yiu-Chia Chang has no disclosures to report.

Daniel Wong has no disclosures to report.

Statement of Authorship. YC drafted the manuscript.

AB reviewed the manuscript for intellectual content.

DW reviewed the manuscript for intellectual content.

https://doi.org/10.1017/cjn.2022.329 Published online by Cambridge University Press

References

1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15:391–404.
2. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157–65.
3. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol. 2018;17:760–72.
4. Predkele N, Mednieks J. Lyme disease and associated NMDAR encephalitis: a case report and literature review. Neurol Int. 2021;13:487–96.
5. Martinez HR, Olguin-Ramirez LA, Camara-Lemarroy CR. Lyme borreliosis as a trigger for NMDA receptor encephalitis? Neurol Sci. 2018;39:1815–7.
6. Halperin JJ. Nervous system Lyme disease. Infect Dis Clin North Am. 2015;29:241–53.

https://doi.org/10.1017/cjn.2022.329 Published online by Cambridge University Press