

Pearls & Oy-sters: Electroconvulsive therapy in anti-NMDA receptor encephalitis

H.M.H. Braakman, MD
V.M.P. Moers-Hornikx,
MD

B.M.G. Arts, MD, PhD
R.M.M. Hupperts, MD,
PhD

J. Nicolai, MD, PhD

Address correspondence and
reprint requests to Dr. H.
Braakman, Department of
Neurology, Maastricht University
Medical Center, PO Box 5800,
6202 AZ Maastricht, the
Netherlands
h.braakman@mumc.nl

CLINICAL PEARLS The clinical picture of anti-NMDA receptor (NMDAR) encephalitis is highly characteristic; the presence of NMDAR antibodies confirms the diagnosis.

With its poor diagnostic criteria, encephalitis lethargica (EL) is a descriptive term for a melting pot of symptoms that likely represent multiple distinct disorders.

Sporadic EL is a diagnosis of exclusion, only to be made after appropriate exclusion of anti-NMDAR encephalitis and other (auto)immune phenomena.

INTRODUCTION NMDAR are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity. The receptors are heteromers of NR1 subunits that bind glycine and NR2 subunits that bind glutamate.¹ NMDA receptors are expressed on neurons throughout the brain; their highest densities are found in the amygdala, hypothalamus, prefrontal cortex, and hippocampus. Overactivity of NMDA receptors is a proposed underlying mechanism for epilepsy, dementia, and stroke, whereas low activity produces symptoms of schizophrenia.¹ Antibodies against NR1-NR2 heteromers can result in a characteristic neuropsychiatric syndrome, anti-NMDAR encephalitis.² Its characteristic clinical presentation resembles acute psychosis, with catatonia or, less frequently, memory deficits, followed by a rapid decline in the level of consciousness, central hypoventilation, seizures, involuntary movements, and autonomic instability. Although this syndrome was described recently,³ the ensuing report of numerous cases suggests that this is not a rare disorder.²

Anti-NMDAR encephalitis is a potentially fatal condition, although, if recognized timely, good treatment options exist. We present a case to illustrate that anti-NMDAR encephalitis should be considered in patients with acute psychosis, and that electroconvulsive therapy possibly adds an effective treatment option.

CASE REPORT A previously healthy 47-year-old man reported to the outpatient department. After an

upper respiratory tract infection, he had persisting malaise and excessive sweating. Over a 3-week period, he developed derealization, intense anxiety, and eventually auditory hallucinations consisting of various kinds of music. Neurologic examination and brain CT revealed no abnormalities, including no brain tumor. The consultant psychiatrist diagnosed psychosis with hallucinations of unknown origin. Three days later, the patient reported insomnia, disorientation, and suicidal thoughts. Neurologic examination showed disorientation in place, memory disturbances, bradyphrenia, restlessness, and excessive sweating. Our differential diagnoses included (infectious) encephalitis, mainly herpes simplex encephalitis, Creutzfeldt-Jacob disease, and, less likely, leptomeningeal metastases of an unknown primary tumor. Brain MRI demonstrated no abnormalities. CSF analysis revealed a pleocytosis of 30 cells/mm³ (normal value $\leq 5/\text{mm}^3$) with 100% lymphocytes and normal glucose and protein concentrations. The patient was admitted and received 10 mg/kg acyclovir 3 times daily based on a presumptive diagnosis of herpes simplex encephalitis. Microbiologic examination of CSF did not detect any viral or (myco)bacterial causative agents. Neither malignant cells nor the 14-3-3 protein were detected in the CSF. Based on these results, acyclovir was withdrawn.

After a few days, the patient developed paroxysmal sustained upward eye deviations, extreme agitation, dystonic posturing, rigidity, dyskinesias, dyspnea, and severe laryngospasms with saturation drops. These paroxysms were followed by periods of apathy and akinesia. Pathologic laughing and yelling eventually progressed to complete mutism. Based on the nonspecific and progressive clinical features, the differential diagnosis now included autoimmune, paraneoplastic, and postinfectious disorders. CSF and serum analysis showed intrathecal synthesis of multiple oligoclonal bands, with unique oligoclonal CSF bands. Antibodies against human basal ganglia antigens, paraneoplastic antibodies (anti-Hu, anti-

From the Departments of Neurology (H.M.H.B., V.M.P.M.-H., J.N.) and Psychiatry (B.M.G.A.), Maastricht University Medical Center, Maastricht; and Department of Neurology (R.M.M.H.), Orbis Medical Center, Sittard, the Netherlands.

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Yo, anti-Ma2), as well as antiganglioside antibodies could not be detected. Serum antistreptolysin and antistreptodornase titers were negative. Total body PET-CT revealed no abnormalities. EEG showed diffuse slow waves of bilateral frontal dominance, indicating diffuse encephalopathy. A second brain MRI again failed to demonstrate any abnormalities. Based on the clinical features including the extrapyramidal symptoms, oculogyric crises, psychiatric symptoms, cataplexy, mutism, respiratory failure, insomnia, and apathy, we eventually made a presumptive diagnosis of EL. IV administration of lorazepam up to 10 mg daily was initiated, as well as methylprednisolone pulse therapy (1,000 mg daily for 3 days). This therapy did not result in clinical improvement; therefore the psychiatrist referred him for electroconvulsive therapy (ECT). After 7 bilateral ECT treatments, he regained a normal level of consciousness; agitation, laryngospasm, mutism, hallucinations, catatonia, oculogyric crises, and extrapyramidal symptoms had disappeared. Without additional treatments, attention and memory deficits resolved over a 1-year time course and fatigue persists. At 2 years follow-up, he has returned to his former employment as a teacher.

Because the clinical picture resembled that of the recently reported anti-NMDAR encephalitis, we investigated this possible association. An archived CSF sample from his initial presentation was submitted to the University of Pennsylvania, where antibodies against NMDAR were detected in the sample; the final diagnosis was anti-NMDAR encephalitis.

DISCUSSION Exclusion of neurologic disease, including anti-NMDAR encephalitis, remains important in patients presenting with psychosis. The clinical features of anti-NMDAR encephalitis usually include a prodromal episode of fever, headache, or malaise, followed a few days later by mood and behavioral changes, and severe psychiatric symptoms suggestive of psychosis or catatonia.^{3,4} A psychiatric disorder is usually considered and patients are often admitted to psychiatric centers. Organic illness is considered only after patients develop seizures, autonomic instability, dyskinesias, or a decreased level of consciousness.³⁻⁵

MRI findings in anti-NMDAR encephalitis are diverse. In the majority of patients, no abnormalities are noted.² In some patients, transient cerebral, cerebellar, or brainstem hyperintensities have been noted, as well as transient contrast enhancement of the cerebral cortex, overlying meninges, or basal ganglia.² The EEG shows diffuse slowing or epileptiform activity.² CSF analysis reveals pleocytosis, elevated protein levels, oligoclonal bands, and anti-NMDAR antibodies. Anti-NMDAR encephalitis

predominantly affects young women, as it is generally a paraneoplastic phenomenon associated with ovarian teratoma. Associations with teratoma in the mediastinum and testes, as well as small-cell lung carcinoma, are rare.^{2,3} It has been postulated that ectopic expression of NR1 subunits by the nervous tissue contained in the teratoma itself contributes to breaking immune tolerance.² Still, in about half of the cases, anti-NMDAR encephalitis occurs in the absence of teratoma. Thus, other unknown immunologic triggers seem to be involved. The frequent prodromal flu-like symptoms in anti-NMDAR encephalitis are intriguing and possibly indicate a preceding viral infection. This preceding infection, and perhaps a genetic predisposition, could play additional roles in the initiation of the immune response. Microorganisms are an unlikely direct cause; extensive studies of CSF samples, brain biopsies, and autopsies failed to detect any microorganisms.²

Our patient was first diagnosed with sporadic EL. EL was a devastating epidemic of the early 20th century that killed an estimated 500,000 people worldwide.⁶ Nowadays, EL is still sporadically diagnosed. The etiology of EL remains unknown. The criteria for EL are poorly defined, and a clinical diagnosis of EL can be made if an acute or subacute encephalitis illness has at least 3 of the following features: 1) signs of basal ganglia involvement; 2) oculogyric crises; 3) ophthalmoplegia; 4) obsessive-compulsive behavior; 5) akinetic mutism; 6) central respiratory irregularities; and 7) somnolence and/or sleep inversion.⁷ Our patient met criteria 1, 2, 4, 5, 6, and 7, and was thus diagnosed with EL; this diagnosis was made prior to the first description of anti-NMDAR encephalitis as a separate clinical entity. After its description, the anti-NMDAR antibodies were detected in our patient's archived CSF sample. Many of the "idiopathic encephalitis," "encephalitis of unknown etiology," or "EL" cases may have in fact been anti-NMDAR encephalitis.^{8,9} Therefore, anti-NMDAR encephalitis should be excluded prior to diagnosing sporadic EL, which is mainly a diagnosis of exclusion.

Anti-NMDAR encephalitis can be severe and even fatal, but it is potentially reversible; most patients recover if the disorder is recognized and treated in time.² In anti-NMDAR encephalitis, a potentially treatable primary disease (e.g., teratoma) may be present. In fact, the most favorable outcomes occur with tumor removal, usually in combination with immunotherapy (IV steroids, IV immunoglobulin, or plasma exchange).^{3,10} Still, good clinical outcomes have been reported in patients treated with immunotherapy without tumor removal.^{4,11} Additional treatment with cyclophosphamide^{2,3,5} and rituximab^{2,12} has also proven to be effective in selected cases. Besides tu-

mor removal and immunotherapy, symptomatic treatment with antiepileptic drugs and benzodiazepines may partially relieve symptoms.^{4,12}

In our patient, ECT proved effective. In one previous case series, one patient was found to respond to ECT.¹³ Two patients have been reported with paraneoplastic catatonia and ovarian teratoma that partially improved with ECT, but full recovery was only attained after tumor removal.^{5,14} Still, the temporal association between ECT and recovery may have been fortuitous; the condition may have been self-limiting. However, our patient deteriorated clinically in a period of 10 weeks, and recovered in a period of 3 weeks after ECT was started. The mechanism of action of ECT remains largely unclear. Still, in animal models it has been shown to upregulate NMDA receptors.¹⁵ This may, in part, explain the efficacy of ECT in our patient.

Anti-NMDAR encephalitis has become an essential consideration in the diagnosis of subacute or acute encephalopathies with a clinical presentation of psychosis-like symptoms, particularly in young people. The diagnosis of EL can only be made after exclusion of anti-NMDAR encephalitis. We report dramatic recovery of our patient following ECT. Further clinical observation or studies in patients with anti-NMDAR encephalitis are needed to determine the relevance of our observation.

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DISCLOSURE

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