

# **UCLA**

## **Proceedings of UCLA Health**

### **Title**

A Case of Anti-NMDA Receptor Encephalitis Diagnosed as Bipolar Disorder with Psychotic Features

### **Permalink**

<https://escholarship.org/uc/item/9n76v3fz>

### **Journal**

Proceedings of UCLA Health, 24(1)

### **Authors**

Hua, Duong Tommy

Dac Pham, Charles

### **Publication Date**

2020-08-27

## CLINICAL VIGNETTE

---

# A Case of Anti-NMDA Receptor Encephalitis Diagnosed as Bipolar Disorder with Psychotic Features

---

Duong Tommy Hua, MD and Charles Dac Pham, MD

### *Case Report:*

A 43-year-old female with diabetes, hypertension, and anxiety was brought in to the Psychiatric Emergency Room by family for strange behavior described as physically aggressive, repeating words, and inability to sleep. She attempted to drown herself with a hose, run into traffic, and was hearing voices that were telling her to kill herself. Family noted that the patient reported feeling depressed, nervous, and scared. Psychological stressors include her uncle's death two weeks prior to presentation and the witnessed suicide of a neighbor one year prior. The patient herself denied any previously diagnosed psychiatric conditions and denied any alcohol or drug use. Her medication list included metformin, lorazepam, ibuprofen, and simvastatin.

Her initial mental status exam was notable for restlessness, pressured speech, anxious affect, and tangential thoughts. She was also noted to have limited insight and judgment. Her complete blood count, basic metabolic panel, liver function tests, thyroid stimulating hormone, urine toxicology, and HIV test were negative.

She was placed on a 72-hour hold for danger to self and others, diagnosed as psychotic disorder – not otherwise specified, and started on olanzapine and clonazepam. She continued to show disorganization, agitation, psychosis, emotional lability, delusions, selective mutism, and bizarre behavior. Dystonia was also noted in the patient's neck and tongue. She did not clinically improve despite various medication adjustments during hospital days 4-22. Further collateral information later revealed that the patient had a prior episode of emotional lability, increased energy, and excessive shopping, three months before she was diagnosed with bipolar disorder with psychotic features.

On hospital days 23-26, the patient had a catatonic-like episode and developed findings consistent with sepsis, and given her

persistent encephalopathy, a lumbar puncture was performed. Analysis of the cerebral spinal fluid was remarkable for the presence of white blood cells (**Table 1**). She was initiated on empiric acyclovir. The patient continued to be non-communicative and minimally responsive with episodic fever and tachycardia. Neurology was consulted due to the lack of improvement in the patient's condition, for which a magnetic resonance imaging (MRI) of the brain, paraneoplastic panel including anti-N-methyl-D-aspartate receptor (anti-NMDAR), electroencephalogram (EEG), and computed tomography (CT) of the chest, abdomen, and pelvis were recommended.

On hospital day 31, the patient was started empirically on 1 g of intravenous methylprednisolone for 5 days for anti-NMDAR encephalitis due to the lack of improvement in mental status, episodes of severe dysautonomia, and otherwise extensive negative evaluation. On hospital day 35, the patient was noted to have increased tone in all extremities and dyskinesias in the face. By hospital day 36, the patient did not show signs of improvement so intravenous immunoglobulin (IVIG) 400 mg/kg was initiated for 5 days. On hospital day 38, the anti-NMDAR encephalitis antibody testing resulted as positive. On hospital day 42, due to the lack of clinical response, plasmapheresis was initiated for 5 treatments every other day.

By hospital day 49, the patient started to show signs of improvement in her mental status and returned to baseline by hospital day 58. The patient remained hospitalized due to severe deconditioning and initiation of rituximab 375mg/m<sup>2</sup> as an inpatient to prevent relapse, which was given on hospital day 66 and 73. The patient was discharged to home on hospital day 74 with plans for outpatient rituximab infusions. Eleven days after her hospitalization, the patient received a third dose of rituximab. She was subsequently lost to follow up after this visit.

**Table 1.**

Labs/Diagnostics in Chronological Order	Result
CT head without contrast	No acute intracranial abnormalities
Lumbar puncture	WBC – 16 cells/ $\mu$ L. Lymphocytes 96% Monocytes 4% RBC – 0 cells/ $\mu$ L. Protein - 21 mg/dL Glucose - 89 mg/dL Viral encephalitis panel - negative Opening pressure - 14 cm H <sub>2</sub> O Gram stain – negative Culture - negative
Anti-NMDAR antibody test	Anti-NMDAR antibody (NR1 subunit) – positive (hospital day 38)
MRI brain with and without contrast	Hyperintense signal on FLAIR sequence in the posterior aspect of the right cerebellum with asymmetric increased size of the adjacent sulci, suggestive of encephalomalacia and gliosis in the territory of the right PICA
CT chest, abdomen, and pelvis with contrast	Unremarkable
Paraneoplastic panel	Anti-Hu antibody – negative Anti-Ri antibody – negative Anti-Yo antibody – negative
EEG, 24-hour	In the awake state, a posterior dominant rhythm of 6-7 Hz and normal amplitude is present bilaterally. The alpha rhythm attenuates normally with eye opening. There is an excess of generalized theta and delta frequency slowing during the awake state. Normal sleep architecture in the form of vertex waves, sleep spindles, and K-complexes is seen. No epileptic discharges were noted. EEG is concerning for severe generalized encephalopathy.
Ultrasound of the pelvis	Unremarkable

## Discussion

About 70% of patients with anti-NMDAR encephalitis may experience a viral-like prodrome, including headache, low-grade fever, malaise, fatigue, nausea, vomiting, diarrhea, and upper respiratory tract symptoms.<sup>1-3</sup> Typically between a few days to two weeks, patients begin to develop psychiatric manifestations.<sup>3</sup> Patients can present with a wide spectrum of neuropsychiatric features, including bizarre behavior, anxiety, agitation, paranoia, delusions, visual and auditory hallucinations, short-term memory loss, difficulty with concentrating, seizure, decreased level of consciousness, catatonia, diminished response to stimuli, echolalia, dyskinesias (particularly orofacial), choreoathetoid movements, and autonomic instability, including cardiac dysrhythmias and fluctuations in temperature and blood pressure.<sup>1,2</sup> Patients will often be misdiagnosed with a primary psychiatric disorder at presentation similar to our patient.

There is a well-established association of anti-NMDAR encephalitis and teratomas, particularly ovarian teratomas. In a study of 91 female patients diagnosed with anti-NMDAR encephalitis, 56 were diagnosed with a tumor, 53 of which were ovarian teratomas.<sup>1</sup> Another study found that 220 out of 468 female patients with anti-NMDAR encephalitis had an underlying malignancy, 207 of which were ovarian teratomas and 4 of which were extra-ovarian teratomas. Other malignancies that

are rarely associated with anti-NMDAR encephalitis include neuroendocrine, lung, breast, thymic, pancreatic, and testicular.<sup>1,4</sup>

The diagnosis of anti-NMDAR encephalitis can be difficult, particularly at presentation. Patients are often diagnosed with a primary psychiatric condition, leading to delays in diagnosis. Table 2, which is adapted from a 2016 article by Graus et al,<sup>5</sup> outlines three different sets of criteria to establish the diagnosis of probable or definite anti-NMDAR encephalitis.

IgG antibody testing against the NR1 subunit of the NMDAR receptor is particularly useful for the diagnosis of anti-NMDAR encephalitis. Antibody testing can be performed on the serum and/or the CSF. In one study of 250 anti-NMDAR encephalitis patients, the sensitivity and specificity of antibody testing on the serum was found to be 85.6% and 100%, respectively; on CSF, it was found to be 100% in both sensitivity and specificity.<sup>6</sup>

A normal brain MRI can be seen in 50% of patients.<sup>3</sup> In our patient, hyperintensity on fluid-attenuated inversion recovery (FLAIR) was seen in the right cerebellum. In one study of 100 anti-NMDAR encephalitis patients, 55 had abnormal MRI's with most abnormalities occurring in the medial temporal lobes

(40%), followed by the cerebral cortex (31%) and cerebellum (11%).<sup>1</sup>

Lumbar puncture should be performed for CSF analysis in order to exclude alternative diagnoses. Lymphocytic pleocytosis or oligoclonal bands may be seen in the CSF.<sup>2</sup> In addition, anti-

NMDAR antibody testing can be done on the CSF, which is more sensitive than serum antibody testing.<sup>2</sup>

EEG may show non-specific findings such as diffuse slowing.<sup>2</sup> Slowed activity may be seen in about 77% of patients and epileptic activity may be seen in about 23% of patients.<sup>1</sup>

**Table 2. Three sets of diagnostic criteria (adapted from Graus, et al, 2016)<sup>5</sup>**

<p><b>Probable Diagnosis</b> Meets all 3 of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Rapid onset (within 3 months) of symptoms - at least 4 out of 6 of the major groups <ul style="list-style-type: none"> <li>Abnormal behavior or cognitive dysfunction</li> <li>Speech dysfunction</li> <li>Seizures</li> <li>Movement disorder</li> <li>Decreased level of consciousness</li> <li>Autonomic dysfunction</li> </ul> </li> <li>2. Laboratory studies – at least 1 <ul style="list-style-type: none"> <li>Abnormal EEG – focal or diffuse slowing or disorganized activity, epileptic activity, or extreme delta brush</li> <li>Abnormal CSF - pleocytosis or oligoclonal bands</li> </ul> </li> <li>3. Exclusion of other disorders</li> </ol>
<p><b>Probable Diagnosis</b> Meets all 3 of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Systemic teratoma</li> <li>2. At least 3 of the major group of symptoms (see above)</li> <li>3. Exclusion of other disorders</li> </ol>
<p><b>Definite Diagnosis</b> Meets all 3 of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Presence of IgG anti-GluN1 antibodies</li> <li>2. At least 1 of the major group of symptoms (see above)</li> <li>3. Exclusion of other disorders</li> </ol>

First line therapies include corticosteroids, immunoglobulins, and plasmapheresis.<sup>7</sup> In our case, due to lack of clinical response, we gave all three treatments consecutively, including methylprednisolone 1 gram once a day for five days, then IVIG 30 grams (400mg/kg) once a day for five days, then plasma-pheresis every other day for a total of five treatments. The patient started to show response to therapy after seven days from the first plasmapheresis and returned to baseline mentation after twenty days.

Second line therapy options are rituximab or cyclophosphamide.<sup>7</sup> In one study, when second line immunotherapy with rituximab or cyclophosphamide was used in combination with first line therapies, there was a significant reduction in relapse.<sup>4</sup> In our patient, we initiated rituximab (375mg/m<sup>2</sup>) in order to help prevent relapse of disease rather than failure of response to therapy. She received a total of three doses. Our plan was to provide a fourth dose of rituximab, but the patient was lost to follow-up.

In one study of 501 patients, 12% had a relapse of disease at 24 months.<sup>4</sup> The median time to first relapse is 20 months.<sup>8</sup> Eighteen percent of patients were found to have severe deficits at 17-month follow up and 47% had made full recoveries.<sup>1</sup>

Among patients being treated for anti-NMDAR encephalitis, mortality is estimated to be 7% at 24 months.<sup>4</sup> Median time from disease onset to death was 3.5 months.<sup>1</sup>

One study developed a scoring system to predict outcomes for 1-year functional status in patients diagnosed with anti-NMDAR encephalitis and included the following significant variables: need for ICU admission, no clinical improvement after four weeks of treatment, no treatment given within four weeks of symptom onset, abnormal MRI, and CSF WBC count > 20 cells/μL.<sup>9</sup> The most important variable was lack of improvement after four weeks of treatment, which conferred an odds ratio of 12.1. Each variable is assigned a point value of one and when added together, provided the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score. They found that for patients with NEOS scores of 0-1, 3% of patients had poor functional status versus 69% for patients with NEOS scores of 4-5. In our patient, her NEOS score was 2 (no treatment given within 4 weeks of symptom onset, abnormal MRI). Unfortunately, our patient was lost to follow up so we were unable to assess her functional status at 1 year.

## REFERENCES

1. **Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR.** Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* 2008 Dec;7(12):1091-8. doi: 10.1016/S1474-4422(08)70224-2. Epub 2008 Oct 11. PMID: 18851928; PMCID: PMC2607118.
2. **Ford B, McDonald A, Srinivasan S.** Anti-NMDA receptor encephalitis: a case study and illness overview. *Drugs Context.* 2019 Aug 30;8:212589. doi: 10.7573/dic.212589. PMID: 31516531; PMCID: PMC6726359.
3. **Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R.** Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol.* 2011 Jan;10(1):63-74. doi: 10.1016/S1474-4422(10)70253-2. PMID: 21163445; PMCID: PMC3158385.
4. **Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Florance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J.** Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol.* 2013 Feb;12(2):157-65. doi: 10.1016/S1474-4422(12)70310-1. Epub 2013 Jan 3. PMID: 23290630; PMCID: PMC3563251.
5. **Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J.** A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016 Apr;15(4):391-404. doi: 10.1016/S1474-4422(15)00401-9. Epub 2016 Feb 20. PMID: 26906964; PMCID: PMC5066574.
6. **Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, Gleichman AJ, Balice-Gordon R, Rosenfeld MR, Lynch D, Graus F, Dalmau J.** Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol.* 2014 Feb;13(2):167-77. doi: 10.1016/S1474-4422(13)70282-5. Epub 2013 Dec 18. Erratum in: *Lancet Neurol.* 2014 Feb;13(2):135. PMID: 24360484; PMCID: PMC4006368.
7. **Barry H, Byrne S, Barrett E, Murphy KC, Cotter DR.** Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. *BJPsych Bull.* 2015 Feb;39(1):19-23. doi: 10.1192/pb.bp.113.045518. PMID: 26191419; PMCID: PMC4495821.
8. **Gabilondo I, Saiz A, Galán L, González V, Jadraque R, Sabater L, Sans A, Sempere A, Vela A, Villalobos F, Viñals M, Villoslada P, Graus F.** Analysis of relapses in anti-NMDAR encephalitis. *Neurology.* 2011 Sep 6;77(10):996-9. doi: 10.1212/WNL.0b013e31822cfc6b. Epub 2011 Aug 24. PMID: 21865579.
9. **Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ.** A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. *Neurology.* 2019 Jan 15;92(3):e244-e252. doi: 10.1212/WNL.0000000000006783. Epub 2018 Dec 21. PMID: 30578370; PMCID: PMC6340387.