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# Case Reports

# Anti-NMDA Receptor Encephalitis in a 14-Year-Old Female Presenting as Malignant Catatonia: Medical and Psychiatric Approach to Treatment

Jo Ellen Wilson, M.D., John Shuster, M.D., Catherine Fuchs, M.D.

Anti-*N*-methyl-D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis has only recently been described. Acute psychiatric symptoms, seizures, memory deficits, decreased level of consciousness, and central hypoventilation associated with ovarian teratoma and cerebrospinal fluid inflammatory abnormalities, developed in four young women.[1] Anti-NMDAR encephalitis is increasingly recognized in children and adolescents. In one recent study, patients who were 18 years old or younger comprised 40% of all cases of anti-NMDAR encephalitis studied.[2] Algorithms for the treatment of anti-NMDAR encephalitis have been suggested; however, they focus mostly on immunotherapy and tumor resection and do not address the importance of targeting persistent signs of catatonia related to the physiologic mechanisms of anti-NMDAR antibodies on the brain.[3,4] Anti-NMDAR antibodies can persist in the cerebrospinal fluid (CSF) long after targeted immunotherapy, underscoring the importance of not only recognizing but also treating the downstream neuropsychiatric effects of these antibodies on the central nervous system.[5]

Malignant catatonia is an important neuropsychiatric phenomenon associated with significant morbidity and mortality. It consists of behavioral and motoric signs and is characterized by autonomic instability and death in about 10% of cases. The incidence rate of catatonia in the pediatric age group (18 years of age or younger) has been estimated to be 0.16 per million per year.[6] The incidence of malignant catatonia is even rarer. Electroconvulsive therapy (ECT) is generally safe and, at times, lifesaving for pediatric patients with malignant catatonia.[7–9] In its most severe forms, anti-NMDAR encephalitis is a model for malignant catatonia.[10]

We describe a case of an adolescent with anti-NMDAR encephalitis associated with ovarian teratoma and illustrate the importance of targeting both the immunologic and psychiatric manifestations of this unique disease process.

## *Case Report*

C.R., a 14-year-old African American female with a history of generalized fatigue and weakness, was diagnosed as having mononucleosis 3 months before presentation. After this diagnosis, C.R. experienced progressive weight loss, fatigue, weakness, and headache, followed by the onset of insomnia, agitation, echolalia, and bizarre posturing of her upper extremities. After taking a prescribed dose of zolpidem, she became combative and was taken to a local emergency room where she received an injection of haloperidol. This was followed by a prolonged period of somnolence and unresponsiveness. Her mental status at this hospital was described as "waxing and waning," with brief periods of arousal and verbalization punctuating a comatose state. She displayed no purposeful movements and required parenteral nutrition. During her initial hospitalization, C.R. underwent 3 magnetic resonance imaging (MRI) studies of her brain (all unremarkable), 2 lumbar punctures (one was remarkable for a white blood cell count of 43, differential not available), and

Received October 22, 2012; revised March 5, 2013; accepted March 6, 2013. From Vanderbilt University Medical Center, Nashville, TN; Alive Hospice, Nashville, TN. Send correspondence and reprint requests to Jo Ellen Wilson, M.D., Vanderbilt University Medical Center, South Nashville, TN; e-mail: jo.e.wilson@vanderbilt.edu

3 electroencephalograms (EEGs) (all normal). The working diagnosis was encephalitis of unknown origin, and valproic acid and acyclovir were administered to treat a possible of seizure disorder and herpes (herpes simplex virus) encephalitis. CSF study results, including bacterial cultures and enterovirus studies, were negative. As CSF herpes simplex virus testing was inconclusive; acyclovir was continued.

Ten days after initial presentation, C.R. was observed to have spells characterized by flexion of her arms and legs with eyes deviating to the right. The neurologist who was evaluating her recommended continuation of valproic acid and initiation of levetiracetam. Additionally, a left lower lobe aspiration pneumonia developed.

Twenty-five days after the initial presentation, C.R. was transferred to the Pediatric Intensive Care Unit at Monroe Carell Jr. Children's Hospital at Vanderbilt. At the time of admission, she demonstrated marked vital sign abnormalities including unstable blood pressures, tachycardia, decreased respiratory drive, and an elevated core body temperature. She exhibited a Glasgow Coma Score of 3 and epileptiform-like movements. Antibiotics for pneumonia and on antiviral treatment for presumed encephalitis were continued. Result of head computed tomography (CT) imaging was negative, and a 24-hour video EEG showed encephalopathy without epileptiform activity. Routine admission laboratory test results, including those of complete blood count, complete metabolic panel, liver function tests, and thyroid studies, were unremarkable. C.R. continued to have intermittent tachycardia, hypertension, and fever. She demonstrated intermittent brainstem reflexes, facial asymmetry, and lack of spontaneous movement or response to noxious stimuli. She had brisk reflexes with rigidity in all 4 extremities, *gegenhalten* in her upper extremities, and clonus in her ankles bilaterally.

A repeat brain MRI with magnetic resonance angiography was unremarkable. Neurology consultants noted that there was "evidence of brainstem dysfunction with hypertonia and clonus" while exhibiting posturing movements clinically inconsistent with seizures. Two doses of 2 mg of intravenous (IV) lorazepam brought about prompt resolution of facial grimacing and posturing.

On hospital day (HD) number 4 at Vanderbilt, the repeat herpes simplex virus PCR was negative and antivirals were discontinued. A trial of high-dose steroids and 2 courses of IV immunoglobulin were administered for a possible autoimmune process. Trials of clonidine and propranolol for vital sign abnormalities with presumed central storm were ineffective. From HD 4 through 11 she remained on advanced life support without significant clinical improvement. Possible transfer to hospice was discussed with the family.

On HD 11, C.R. underwent tracheostomy to protect her airway and a gastrostomy tube was placed. Repeat chest X-rays showed resolution of her pneumonia. Psychiatry was consulted to assess for possible psychosis or neuroleptic malignant syndrome. On examination, the predominant clinical features were posturing, facial grimacing, rigidity, mutism, and stupor. She had tachycardia and hypertension with mild temperature elevation. Neuroleptic malignant syndrome was thought unlikely because she had only received 1 dose of a neuroleptic more than a month before the psychiatric evaluation. Administration of the Bush-Francis Catatonia Rating Scale yielded a score of 21, consistent with malignant catatonia. Details of the score were as follows: immobility/stupor, 2; mutism, 3; staring, 1; posturing, 2; grimacing, 2; echolalia, 1; stereotypy, 1; verbigeration, 2; rigidity, 2; withdrawal, 3; and autonomic abnormality, 3. A trial dose of 0.5 mg of IV lorazepam led to slight improvement by opening her eyes and allowing the physical therapist to manipulate her legs. With a presumed diagnosis of malignant catatonia, C.R. was started on scheduled 1 mg of IV lorazepam q6h. On HD 12, lorazepam was increased to 3 mg q3h, resulting in more spontaneous eye openings. However, C.R. continued to have fever, tachycardia, and hypertension (with no clear medical explanation other than malignant catatonia). Emergent ECT was recommended. On HD 13, lorazepam was further increased to 3 mg q2h, followed by normalization of her vital signs. At this dose, C.R. exhibited "subtle improvement in muscle rigidity following each dose of lorazepam (but) became stiff again within 1–2 hours (following) each dose."

On HD 16, ECT was initiated. She exhibited more purposeful movements after her second ECT treatment. C.R. received 5 daily ECT treatments with only subtle improvements in her mental status and catatonic symptoms. Lorazepam was decreased to 12 mg/day to allow for improved seizure induction with ECT. On HD 19, CSF was collected for antibody analysis, which showed the following differentials: 7 nucleated cells, 15 red blood cells, 90 lymphocytes, and 10 monocytes.

On HD 20, C.R.'s rigidity had decreased sufficiently so that a chest, abdomen, and pelvis computed tomography scan could be obtained. The scan revealed a 5.5 × 5.0 cm cystic mass consistent with an ovarian

dermoid lesion. High-dose steroids were started because of concern for anti-NMDAR antibody–associated limbic encephalitis and C.R. underwent left salpingo-oophorectomy to remove the mass. Final operative pathology showed a mature teratoma with foci of glial, cortical, and cerebellar tissues.

Following tumor removal, C.R. slept minimally with frequent posturing and mannerisms; lorazepam was continued at 12 mg/day. ECT was held on HD 23 to see if removal of the mass would result in clinical improvement, and lorazepam was decreased to 9 mg/day. On HD 25, she exhibited gradual improvement in responsiveness and motor symptoms. Lorazepam was increased to 12 mg/day for vital sign abnormalities. On HD 27, ECT was restarted (sixth treatment) owing to continued autonomic instability.

On HD 28, the presence of anti-NMDAR antibodies was confirmed. High-dose steroids were continued and rituximab was initiated (4 weekly doses of 375 mg/m$^2$). C.R. was continued on lorazepam and thrice-a-week ECT. On HD 33, C.R. received IV immunoglobulin, and the following day she received her second dose of rituximab. On HD 36, following her tenth ECT treatment, C.R. was noted to blink her eyes in response to questions. On HD 38, following her 11th ECT treatment, she was observed initiating more purposeful movements, taking her first independent steps and throwing a ball back and forth to her mother.

ECT was continued and lorazepam was gradually lowered. By HD 43, she displayed more purposeful and goal-directed movements and she communicated that she was not talking because of her tracheostomy. Lorazepam was decreased to 7 mg/day and a steroid taper was initiated.

On HD 45, following her 14th ECT treatment, her catatonia was almost completely resolved. The tracheostomy tube was removed, and she began whispering words appropriately. On HD 48, C.R. received her third and final dose of rituximab and replacement IV immunoglobulin was continued. She progressively communicated more; on HD 50, lorazepam was decreased to 6 mg/day. The following day she was discharged to an inpatient rehabilitation facility. At 1-year follow-up C.R. had returned to her cognitive and physical baseline.

## *Discussion*

NMDARs have been linked to a variety of neuropsychiatric illnesses, playing a vital role in synaptic plasticity.[11] The NMDARs are heteromers of NR1 and NR2 subunits that bind glycine and glutamate, respectively. Hypoactivity at the NMDAR is associated with symptoms of schizophrenia; hyperactivity has been associated with epilepsy, dementia, and stroke.[11] Anti-NMDAR encephalitis has been associated with antibodies against the NR1 subunit of the NMDAR, it may be associated with ovarian teratoma and may lead to encephalitis, psychiatric manifestations, seizures, stupor, and central hypoventilation.[1,12] A number of cases have been reported in both genders, in patients aged 23 months to 73 years, and with and without tumors.[2,12]

In one large case series, 75% of patients with anti-NMDAR antibody–associated encephalitis recover or are left with only mild sequelae (median follow-up was 17 months); however, the other 25% remain severely disabled or die.[12] Diagnosis, if made, is often delayed, with a median time from symptom presentation to initial signs of improvement being around 6 weeks.[2] The reason for delay in diagnosis is complex but may be attributable to the lack of knowledge about the syndrome as well as the subacute presentation, which is characterized by profound psychiatric manifestations.[1] This often leads treating physicians to mistakenly diagnose a psychiatric condition rather than recognize a constellation of symptoms consistent with catatonia.[13,14] Our patient initially presented with behavioral dysregulation; this led to a delay in recognition of encephalitis, which was only considered after persistent mental status abnormalities and the discovery of a CSF pleocytosis.

Autonomic instability has been reported to be less severe in children as compared with adults; only 23% of patients in one case series experienced hypoventilation requiring mechanical support.[2] Some literature suggests that autonomic instability, which can occur with anti-NMDAR encephalitis, is a function of agitation rather than a symptom of catatonia.[2] However, our patient displayed persistent autonomic instability with hypoventilation, more consistent with malignant catatonia than nonspecific agitation. The severity of C.R.'s catatonic symptoms despite multiple medical interventions led the treating team to pursue ECT and lorazepam in a comprehensive effort to target her catatonic syndrome. She experienced normalization of her vital signs only after high-dose lorazepam (24 mg/d) was administered.

A significant percentage of patients with anti-NMDAR encephalitis exhibit physical manifestations consistent with catatonia, although the exact prevalence is unknown. The importance of recognizing and treating the catatonic

presentation is infrequently reported, and the role for ECT in managing catatonic presentations is rarely mentioned, with even fewer reports of ECT in patients with catatonia secondary to anti-NMDAR encephalitis.[1–4] Despite this, ECT is generally considered to be safe, even in medically compromised patients, and effective in treating 80% of cases of catatonia in the adolescent population.[7] ECT can be lifesaving in the setting of malignant catatonia, regardless of etiology; however, there are several barriers to routine implementation in the adolescent population. Fears regarding adverse side effects from ECT are widely considered despite the lack of published data on this topic.[7] Laws regulating ECT use in adolescents vary by state, affecting uniform implementation.

In a 2005 case report, Slooter et al. described a case of encephalitis complicated by malignant catatonia in a 13-year-old female.[15] ECT led to significant improvement in all components of her catatonic presentation.[15] The suggested treatment algorithms for anti-NMDAR encephalitis focus on medical treatment, including immunotherapies, most frequently methylprednisolone, IV immunoglobulin, and plasma exchange but neglect the management of the catatonic syndrome.[3,4] In a large case series, Dalmau et al. described the clinical characteristics of 100 patients with anti-NMDAR encephalitis[12]; only 3 were treated with ECT (without mention of the clinical response to this intervention).[12] In 2 separate studies, published by the same group, 81 and 419 patients were followed and only 2 patients were mentioned as having received ECT as a part of their treatment.[2,4] Dalmau et al. recommended that the treatment of anti-NMDAR encephalitis should initially focus on immunotherapy with detection and removal of a teratoma, if present.[4]

A few case reports suggest ECT either alone or in conjunction with other medical interventions may be effective in this population. Braakman et al. described a previously healthy 47-year-old man who was initially diagnosed with encephalitis lethargica (and was only later diagnosed with anti-NMDAR encephalitis), who failed to show clinical improvement with high-dose steroid pulse therapy and lorazepam.[16] He only achieved clinical remission following treatment with ECT.[16] A large case series reported only one response to ECT.[2] In one case report, ECT was reported to be useful in ameliorating symptoms of catatonia; full recovery was limited until the underlying tumor was removed.[14] The complexity of the treatments reported in the literature suggests that an integrated symptom-based treatment should be considered in anti-NMDAR encephalitis.

Our patient only improved significantly after receiving immunotherapy and tumor removal as well as ECT and high-dose benzodiazepines. Our rationale was to use immunotherapy to address the primary immune-mediated encephalitis combined with ECT and high-dose benzodiazepines to manage the symptoms of malignant catatonia. C.R.'s symptoms of malignant catatonia did not resolve until pharmacotherapy was combined with ECT. The pattern of response in our patient raises the hypothesis that treatment of anti-NMDAR encephalitis requires both management of the effect of the antibody on the brain and prevention of the antibody production through a combination of surgical removal of the stimulating tumor when present and immunotherapy. The immunotherapy is thought to target both B cells and antibody production via rituximab and steroid treatment.[17] ECT and benzodiazepines potentially target the effects of the antibodies on the brain, providing management of symptoms until immunotherapy is effective. In animal models, ECT has been shown to upregulate NMDARs in the brain, potentially providing one explanation as to why ECT is effective in this population.[18] This case illustrates that symptom management with ECT is necessary in severe cases when benzodiazepines are not sufficient. ECT targets the effect of the antibodies on the brain, providing protection until immunotherapy and tumor removal successfully stop antibody production. We propose that the risk of catatonic symptoms remains until there is decay of antibodies in the system. If this hypothesis is correct, then treatment of anti-NMDAR encephalitis presenting with malignant catatonia should include a combination of immunotherapy with benzodiazepines or ECT or both.

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