Clinical Case Discussion

A Case of Anti-NMDA Receptor Encephalitis Treated with ECT

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We describe the case of a 17-year-old male who presented with acute onset of seizures and malignant catatonia with psychosis, agitation, and hypermetabolism, who responded to electroconvulsive therapy (ECT). Soon after he began to respond, he was diagnosed with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis and then given immunosuppressive therapy. Anti-NMDA receptor encephalitis is an increasingly recognized autoimmune disorder that often presents with neuropsychiatric symptoms. The mainstays for treatment have been early diagnosis, tumor work-up and removal if found, and initiation of immunosuppressive therapy. Treatment response is often slow and residual symptoms common. In this case, ECT produced clinical stabilization before the underlying diagnosis of anti-NMDA receptor encephalitis was made and standard treatment initiated. We suggest that ECT may be highly beneficial for stabilizing life-threatening neuropsychiatric symptoms in this syndrome and should be considered as a potentially additive treatment to immunotherapy when rapid relief is sought.
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KEY WORDS: anti-*N*-methyl-D-aspartate, anti-NMDA receptor encephalitis, electroconvulsive therapy, catatonia, seizures, psychosis

CASE PRESENTATION

We report the case of a 17-year-old male who presented with altered mental status, seizures, catatonia, and autonomic disturbance who was later diagnosed with anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis and who underwent electroconvulsive therapy (ECT) for stabilization of symptoms before immunosuppressive therapy.

Case Report

Before the authors' involvement with this case, the patient, a 17-year-old male, was initially seen in the emergency room of another hospital and then admitted to that hospital, where much of his initial work-up was completed. He was then transferred to our children's hospital in a large academic center for further work-up and evaluation of new-onset confusion, seizures, and symptoms of catatonia. An extensive review of the outside medical records was performed. The records indicated that the patient developed seizures, described as tonic-clonic in nature, followed by somnolence and confusion. The family also reported episodes of agitation and confusion and they described an episode when the patient ran into traffic and subsequently collapsed.

A medical work-up was initiated in the emergency room of the first hospital. Baseline chemistry and complete blood count were normal, as were a noncontrast computed tomography of the brain and an electroencephalogram (EEG). Cerebrospinal fluid (CSF) studies demonstrated pleocytosis with negative Gram stain. At that time, viral encephalitis was considered in the setting of normal laboratory findings, nonfocal neurological examination, and a normal EEG. Because of a history of genital herpes, strong consideration was given to herpes simplex virus (HSV) encephalitis. Acyclovir was started pending additional CSF studies for HSV and the Venereal Disease Research Laboratory test. The patient was admitted to the medical service of the first hospital for further evaluation and treatment. The initial work-up was unremarkable, including thyroid profile, erythrocyte sedimentation rate, vitamin D level, basic chemistry panel, complete blood count, and computed tomography head

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imaging. The patient remained delirious with signs of catatonia and disorganization in behavior and thought processes. Lorazepam 2 mg intramuscularly every 2 hours was ordered as needed for severe agitation. He also received several doses of haloperidol, which produced dystonia and opsithotonos. Other antipsychotic agents, including risperidone, were also tried without significant improvement in symptoms. The patient was subsequently transferred to our children's hospital for further evaluation and treatment.

On his index admission to our medical unit, the patient was started on a regimen of anticonvulsants and antipsychotics, in addition to doxycycline and acyclovir. The patient continued to demonstrate ongoing seizure activity that did not respond to multiple anticonvulsants, including levetiracetam, phenytoin, and phenobarbital. He also continued to have episodes of agitation and confusion that did not respond to antipsychotic medications, including haloperidol, olanzapine, and quetiapine. Magnetic resonance imaging of the brain was completed and was negative. Serum studies, including HIV, Venereal Disease Research Laboratory, and cryptococcal antigen, were all unremarkable. CSF cultures, including HSV, were also negative. His clinical picture continued to decline.

The patient demonstrated autonomic instability with elevations in blood pressure, sinus tachycardia, hyperventilation, diaphoresis, and fever with decreased level of responsiveness, dystonic posturing, and notable orofacial dyskinesia. He continued to have seizures and intermittent bouts of agitation. Long-term video-EEG monitoring was performed and demonstrated "moderately abnormal" anteriorly dominant arrhythmic δ-activity indicative of a diffuse neuronal disturbance. However, long-term video-EEG monitoring did not demonstrate any electrographic seizures, interictal epileptiform features, or periodic charges (discharges, typically epileptiform in appearance, that occur at regular intervals in critical patients; the clinical significance of these periodic EEG patterns is uncertain). The final clinical correlation on the EEG report for this case report stated: "This finding is indicative of a diffuse disturbance of neuronal function, but is not specific in etiology and in no way diagnostic of 'frontal lobe epilepsy'."

With an inconclusive laboratory work-up, a nonfocal examination, negative imaging studies, and an unremarkable EEG, a primary psychiatric disturbance was considered with concern about possible conversion disorder with pseudoseizures. A psychiatry consultation was conducted, with findings of a labile mood with uncontrollable crying, repetition of phrases, posturing, purposeless motor movements, negativism, cataplexy, stereotyping, waxy flexibility, hyperverbal speech with loose associations, echolalia, and disorientation. Because of these symptoms of catatonia, 2 doses of lorazepam 2 mg were given as an acute challenge with no improvement; subsequent doses provided no further relief. A repeat trial of antipsychotic agents, including olanzapine and quetiapine, did not produce any benefit but rather was associated with notable clinical deterioration at higher doses. In view of the patient's declining course and his initial presentation with seizure-like episodes, followed by confusion and agitation, movement abnormalities, and autonomic disturbances with negative viral CSF studies and brain imaging, the neurology and psychiatry consultants considered anti-NMDA receptor encephalitis. With all other treatment modalities exhausted, including use of the NMDA antagonist memantine, ECT was recommended for the immediate and definitive treatment of the ongoing symptoms of catatonia that had not been responsive to benzodiazepines. As noted above, the patient in this case had had repeated occurrences of seizure-like episodes that did not respond to anticonvulsant medications. At the time he was evaluated in our facility, his EEG demonstrated predominantly posterior α rhythms that were indicative of a diffuse disturbance of neuronal function, but not epilepsy and at no point was the patient considered to be in status epilepticus. After the discontinuation of all anticonvulsant medications, the only barrier to eliciting a generalized seizure during ECT would be the active use of a benzodiazepine. However, this can be quickly and acutely reversed with the administration of flumazenil, which is routinely done if patients are taking these medications during a regular course of ECT. Even if there was some concern about epilepsy in this patient, it is well known that seizure threshold rises during a course of ECT in individuals with documented histories of epilepsy, likely related to increased γ-aminobutyric acid (GABA)-ergic transmission along with other inhibitory peptides. Several reports in the literature have documented the anticonvulsant actions of ECT, and ECT has even been proposed as an intervention for treatment-resistant seizure disorder and status epilepticus, provided that

appropriate precautions are taken (ruling out causes of the seizure activity such as space-occupying or hemorrhagic lesions and metabolic or substance-induced disturbances and appropriately adjusting anticonvulsant medications and electrical dosage of the ECT).[1–3]

The patient received 2 ECT treatments with bitemporal electrode placement. Seizure threshold was achieved using a stimulus dose titration at a pulse width of 1 ms, frequency of 40 Hz, duration of 2 seconds, and current of 0.8 mA. An adequate seizure was achieved at 47 seconds by peripheral limb monitoring and 91 seconds by EEG monitoring. During the patient's second ECT treatment, the dosing parameters were adjusted to twice the determined seizure threshold. Thus, the patient was maximally charged with a pulse width of 1 ms, frequency of 60 Hz, duration of 3 seconds, and current of 0.8 mA. The patient tolerated both ECT treatments well, and he demonstrated notable improvement in his catatonic symptoms, including autonomic instability, stereotyped behaviors, and agitation.

Before the patient's third ECT treatment, results of CSF studies were received, demonstrating the presence of anti-NMDA receptor antibodies. Because of improvement in the patient's catatonic symptoms and confirmation of the underlying medical disorder, additional ECT treatments were not pursued. Lorazepam was continued as needed, but the antipsychotic agents and anticonvulsants were discontinued, and the patient was started on immunotherapy with intravenous immunoglobulin. Whole-body imaging studies were pursued to locate possible tumorous lesions, and the studies were negative. The patient began to show gradual improvement in cognition and physical functioning with resolution of seizure activity, dysautonomia, and agitation. He was even witnessed by the authors playing basketball in the rehabilitation unit and showing remarkable improvement. He was subsequently transferred to an outside pediatric hospital for ongoing treatment and physical rehabilitation. No additional follow-up information was available at the time of this report.

DISCUSSION

Dalmau and colleagues first identified paraneoplastic encephalitis in 2005.[4] At that time, the syndrome was reported in women with ovarian teratomas with the detection of an unknown antibody predominantly in the cell membrane of hippocampal neurons.[4] It was identified as an immune-mediated paraneoplastic syndrome resulting in an encephalitic process affecting limbic function. It was later recognized that the immune response was specifically associated with NMDA receptors that are usually expressed on teratomas of the ovaries or testicular tumors.[5] However, more recent studies have demonstrated that many patients with this disorder may not have a clinically detectable tumor, and that children can also be affected.[6,7] Because, in their initial stages, most paraneoplastic disorders are triggered by small tumors, it is possible that an immune-mediated antibody response may shrink or eliminate the tumor by antibody binding and complement-mediated cytotoxicity.[8] This may be a possible explanation for why a tumor might not be found in some patients. The strong association between antibody production and the presence of a teratoma or other neoplasms suggests that the syndrome may be triggered by cross-reaction between the antibodies produced in response to the presence of a tumor and antigenically similar synaptic proteins within the central nervous system.[9]

Conventional NMDA receptors are tetrameric complexes composed of heteromers of the NR1 subunit (which binds glycine) and the NR2 subunit (which binds glutamate).[7] Both subunits are required to make a functional receptor. These receptors are expressed on neurons throughout the brain, with the highest densities found in the amygdala, hypothalamus, prefrontal cortex, and hippocampus. NMDA has a role in synaptic transmission, dendritic sprouting, memory, and learning, and it mediates excitotoxicity which is associated with resulting dysfunction that has been seen in stroke, dementia, and epilepsy and the low activity seen in schizophrenia.[10–12] Studies using phencyclidine and ketamine have demonstrated the similarity between NMDA antagonist-induced symptoms and symptoms observed in schizophrenia, a finding which suggests that NMDA hypofunction may lead to secondary dopaminergic dysregulation.[13] The role of NMDA receptors and the similarities seen between schizophrenia-spectrum disorders and anti-NMDA receptor encephalitis may point to a common underlying pathophysiology.[14]

After the initial identification of this disorder in 2005, many case reports and studies of anti-NMDA receptor encephalitis have been published that suggest that this disorder is not rare.[15] The exact incidence of anti-NMDA receptor encephalitis is unknown, but based on the rapid accrual of patients and increasing numbers of case reports, it seems to be more frequent than any other known paraneoplastic encephalitis.[16] However, it appears that the rate of positive anti-NMDA receptor results in all cases of new-onset psychosis is still low. Larger studies are needed to estimate the true incidence of anti-NMDA receptor encephalitis.

The key features of this disorder include its rapid onset and progression of symptoms. About 70% of patients have a nonspecific flu-like prodrome, consisting of headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms.[16] These symptoms are followed by the development of a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements and autonomic and breathing instability. Because of the presentation of abnormal mental status, a psychiatric disorder is often considered initially, and patients may present to behavioral and mental health facilities. However, these patients frequently have an increased mortality and morbidity risk if not treated promptly, and they will usually require the level of care provided in an intensive care unit. Despite the severity of symptoms, it has been reported that up to 75% of patients recover after receiving immunotherapy and, when appropriate, tumor removal. However, 25% are left with memory, cognitive, and motor deficits, and, in rare cases, patients can die of the disorder.[17] In a large observational study published by Titulaer et al in 2013,[18] the researchers evaluated data from 501 patients with anti-NMDA receptor encephalitis who were followed for at least 4 months (median follow-up, 24 mo; range, 4 to 186 mo). Of the 501 patients, 472 patients (92%) received first-line immunotherapy with steroids and/or intravenous immunoglobulin, 251 (53%) of whom showed improvement within 4 weeks. Of the 221 patients who did not improve with first-line treatment, 125 (57%) received second-line immunotherapy with rituximab and/or cyclophosphamide, which resulted in a better outcome in those patients than in those who did not receive such immunotherapy. During the first 24 months, 394 of the 501 patients achieved a good outcome and 30 patients died. At 24-month follow-up, 203 (81%) of 252 patients had a good outcome. Recovery can take >18 months.[18]

As noted in a case report by Wilson et al,[19] many of the studies to date that have looked at treatment algorithms for anti-NMDR encephalitis have focused on immunotherapy, with only a few reports looking at treatment of the psychiatric manifestations of the disease. In the case of a 14 year old with anti-NMDA receptor encephalitis, Wilson and colleagues used immunotherapy to treat the primary immune-mediated encephalitis along with ECT and high-dose benzodiazepines to manage the symptoms of malignant catatonia. They hypothesized that ECT might reverse the effect of antibodies on the brain, which provides protection until immunotherapy and tumor removal successfully stop antibody production.[19]

In the case presented here, a young man with acute behavioral and mental disturbance, seizures, and fairly rapid decline was treated briefly with ECT for symptoms of malignant catatonia. The patient was subsequently diagnosed with anti-NMDA receptor encephalitis after CSF studies returned that were positive for anti-NMDA receptor antibodies. This case is notable in that well over 4 weeks of evaluation and work-up by internal medicine, neurology, infectious disease, and psychiatric services at 2 different facilities were completed before an accurate diagnosis was made and a sustainable treatment modality was initiated. This case highlights the need for greater recognition of this autoimmune syndrome to avoid costly and potentially deleterious treatment choices.

An argument can be made that ECT, a well-known treatment modality for catatonia as the most malignant and iatrogenic form of neuroleptic malignant syndrome, can be beneficial in stabilizing the dysautonomia, hypermetabolism, and agitated and psychotic states associated with anti-NDMA receptor encephalitis while a primary diagnosis and treatment are initiated. However, the appropriate role of ECT in the supportive management of severe cases such as the one described here has yet to be determined, and there is a relative dearth of information concerning the effective management of the behavioral and psychiatric symptoms associated with this disorder. Many case reports concerning

anti-NMDA receptor encephalitis published over the last 5 years have discussed the use of antipsychotic medications, benzodiazepines, and ECT in the management of the clinical symptoms, including associated catatonic symptoms. However, there are no established guidelines for optimal neuropsychiatric care of this syndrome.[20] As in the case described here, several reports have described benefits of ECT in the phase of symptoms associated with agitation, psychosis, social withdrawal, abnormal movements, and autonomic instability. These disturbances can be characteristic of the behavioral, cognitive, and psychiatric signs and symptoms associated with catatonia, a syndrome that is all too often underrecognized and thus undertreated. Although for decades catatonia has commonly been ascribed to schizophrenia, it is more commonly seen in affective disorders and medical and neurological disorders.[21] It has been hypothesized that disorders such as neuroleptic malignant syndrome represent drug-induced malignant catatonia[22]; Prader-Willi syndrome is a clinical GABAergic genetic-endocrine model of catatonia; Kleine-Levin syndrome represents a periodic form of adolescent catatonia; and anti-NMDA receptor encephalitis is an autoimmune type of catatonia.[23]

ECT and high-dose benzodiazepines are well established as effective treatment modalities for catatonia. Research has focused on the neurochemical pathways in which they work. It has been proposed that catatonia results from dysregulation in the glutamate, GABA-A, and dopamine pathways.[21] However, the specific brain or body system that can fully explain catatonia's pathologic mechanism or resolution with treatments such as ECT still remains unknown. Current research in populations such as those with anti-NMDA receptor encephalitis, neuroleptic malignant syndrome, and other autoimmune, viral, and neurological disorders provides an opportunity to further study the mechanisms, symptom presentation, and response to therapies such as ECT in these disorders.

Anti-NMDA receptor encephalitis is a disease that may be considerably underdiagnosed and should be considered more often in patients with encephalitis of unknown origin. As noted by Dalmau et al,[16] this disorder should be suspected in any individual younger than 50 years of age, and especially in children and adolescents, who develop rapid changes in behavior or psychosis and/or movement abnormalities, seizures, autonomic instability, and hypoventilation. Supportive findings would include CSF lymphocytic pleocytosis or oligoclonal bands, EEG with infrequent spikes with slow, disorganized, sometimes rhythmic activity that is not associated with most abnormal movements, and magnetic resonance imaging of the brain that is most often normal or shows transient Fluid-Attenuated Inversion Recovery (FLAIR) or contrast-enhancing abnormalities.[16] Despite the severity of the symptoms, the disorder is treatable and potentially reversible. The prognosis depends on early recognition, prompt immunomodulatory therapy, tumor removal when found, and the initiation of treatments to address the psychiatric manifestations of this disease. The case presented here also highlights that ECT can be done safely and effectively to treat the symptoms of catatonia and/or malignant catatonia that are often seen in these disorders.

COMMENTARY by David A. Kahn, MD

This journal has published previous case reports on anti-NDMA receptor encephalitis,[24] as well as the use of ECT in delirium due to Huntington disease, a neurological illness.[25] We are now able to add the report by Jones and colleagues to an emerging literature on the use of ECT for acute anti-NMDA receptor encephalitis, specifically for catatonic delirium.

In addition to the case by Wilson et al[19] cited by Dr Jones and colleagues in discussing their case, I was able to find 4 other detailed reports of similar patients. In the case described by Wilson and colleagues, steroids were begun for suspected herpes simplex encephalitis with no improvement. A course of ECT was begun along with high-dose lorazepam. After 5 treatments with only slight improvement, a dermoid cyst tumor was removed. ECT continued for 9 more treatments, while immunotherapy with rituximab and immunoglobulin was added. The patient gradually improved, received rehabilitation, and was well at 1-year follow-up. Matsumoto et al[26] described an 18-year-old man who made a full recovery from catatonic delirium after 13 ECT treatments (laterality not specified) together with antipsychotics but no immunotherapy. The presence of anti-NMDA

receptor antibodies was confirmed by lumbar puncture before treatment began. Braakman et al[27] treated a delirious, psychotic patient for presumed viral encephalitis with a course of 7 bilateral ECT treatments after failure of lorazepam and methylprednisolone. The patient's psychiatric symptoms resolved quickly, although it took a year for his cognitive function to return to baseline. After his treatment, archived CSF was found to be positive for anti-NMDA receptor antibodies; no further immunotherapy was given. Lee et al[28] reported the case of an 11-year-old girl with psychotic delirium. Treated at first with antipsychotics, she developed neuroleptic malignant syndrome with catalepsy. She deteriorated despite treatment with lorazepam, diphenhydramine, and bromocriptine. She improved quickly in all domains with 8 bilateral ECT treatments but still had some residual motor difficulties. She was then found to have an ovarian teratoma which was surgically removed. Her remaining motor symptoms largely cleared, and aside from mild short-term memory problems, she resumed normal functioning. She was not tested for anti-NMDA receptor antibodies but her diagnosis was paraneoplastic limbic encephalitis, presumed to be caused by antibody formation. Mann et al[29] reported the case of a 14-year-old girl with rapid onset of psychosis and delirium progressing to mutism. After 6 weeks of work-up, she was found to have anti-NDMA receptor antibodies. She failed to improve with 3 days of intravenous immunoglobulin, then a week of risperidone treatment, and finally a partial trial of rituximab. Because of progressively worsening catatonia, ECT was finally started (laterality not specified) with rapid though only partial improvement, leaving residual mood lability and sleep disturbance. She then received a series of immunotherapies as well as risperidone and lorazepam, making a gradual recovery with some residual cognitive problems 8 months after the onset of symptoms.

What is most interesting in these reports was that the response to ECT was frequently independent from the response to the usual standard treatments (ie, immunotherapy or tumor removal). Intravenous immunoglobulin was not even employed in 3 of the 5 cases, yet improvement with ECT was substantial. As Jones and colleagues mention, ECT may well have a direct disease-modifying effect in anti-NMDA receptor encephalitis. If this is the case, ECT might improve outcomes over standard therapy alone (immunotherapy and/or tumor removal). A recent review in the *Lancet* cited by Jones described outcomes in 501 cases collected internationally.[18] This review focused entirely on sequential immunotherapies and tumor removal, with no mention of ECT. Outcomes were "good" in about 81% of patients over a 24-month follow-up period. Improvements were gradual, with persistence of symptoms in many patients for a year or more. Only half the patients were actually symptom free at 24 months; nearly a third still had some symptoms or mild disability, both included in the "good" outcome category. Although these outcomes are indeed positive, the case reports of ECT in anti-NMDA receptor encephalitis suggest that it may have direct benefits that could accelerate and solidify clinical resolution if used more often in conjunction with standard approaches.

In conclusion, my reading of the outcome data, coupled with the handful of available case reports, is that ECT should be considered more often for its potential disease-modifying effects in anti-NMDA receptor encephalitis. It warrants further study as a companion to surgical and immunological therapy in the acute care of this very serious but often reversible cause of delirium, psychosis, and catatonia.

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