Successful Treatment of Refractory Dyskinesia Secondary to Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis With Electroconvulsive Therapy

To the Editor:

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is an autoantibody-mediated neurological disease characterized by psychiatric symptoms, altered consciousness, cognitive dysfunction, autonomic instability, and seizures.[1] It is well known that most patients with anti-NMDA receptor encephalitis respond to immunotherapy.[2] However, a small proportion of patients did not respond to immunotherapy and resulted in severe neurological deficit or death. Furthermore, the treatment for patients with immunotherapy-resistant encephalitis has not been established. To the best of our knowledge, we report the first case of anti-NMDA receptor encephalitis with prolonged and refractory dyskinesia, which was not improved by intensive immunotherapy and tumor removal but remarkably responded to electroconvulsive therapy (ECT).

A 27-year-old woman, who was previously healthy with no history of psychiatric illnesses, complained of headache and insomnia. For a few days, confusion, visual and auditory hallucination, and disorganized speech developed. Then, she was referred to our institute 10 days after the symptom onset because of the aggravation of psychotic symptoms followed by decreased consciousness. At the time of the emergency room visit, she was observed to be semicomatose without focal or lateralized signs in neurologic examination. Laboratory tests showed leukocytosis (white blood cell counts, 16,120/μL) with increased segmented neutrophils (83.5%). Electrolyte panel demonstrated mild hyponatremia (130 mmol/L) with a low serum osmolality (278 mOsm/kg). Other blood test results including liver function tests and serum creatinine level were normal. Cerebrospinal fluid (CSF) study revealed pleocytosis (59/mm^3) with lymphocytic predominance (89.8%), whereas protein and glucose levels were within reference limits. We tested for an extensive list of infectious pathogens including herpes simplex virus, but results were all negative. Brain magnetic resonance imaging with contrast enhancement was unremarkable. At the day of the admission, we tested neuronal autoantibodies from CSF and blood samples. A computed tomography scan of the abdomen and pelvis demonstrated 2-cm-sized, low-attenuated lesion suggesting ovarian teratoma. With a high suspicion of anti-NMDA receptor encephalitis, we immediately administered intravenous (IV) immunoglobulin for 5 days and surgically removed the ovarian mass on the fifth day of the hospitalization. The neuronal antibody panel was reported to be positive for NMDA receptor antibodies, which confirmed the diagnosis of anti-NMDA receptor encephalitis.

Despite the expeditious diagnosis, tumor removal, and IV immunoglobulin treatment, her consciousness did not improve, so the second-line immunotherapy with rituximab was initiated. After an episode of generalized tonic-clonic seizure, however, she developed hyperkinetic movements. Initially, they appeared as stereotypies with lip smacking and chewing movements as well as rhythmic, small-amplitude, flexion-extension movements of the hands and feet. As dyskinesia aggravated, however, they manifested as irregular, large-amplitude, choreic movements leading to flailing limbs, which were associated with rigidity. At that time, she was not exposed to neuroleptics or other dopamine antagonists, which might cause involuntary movements. Long-term video electroencephalography showed generalized irregular slow waves with delta brush signs, but there was no epileptiform or ictal discharges when the movements were observed. The abnormal movements did not respond to multiple antiepileptic drugs. As the disease progressed, she demonstrated severe rigidity and autonomic instability. Because benzodiazepines, especially lorazepam, are recommended as the treatment of choice in catatonia, we administered lorazepam and other benzodiazepines such as diazepam and clonazepam, but they had no effect on her condition. Subsequently, an atypical antipsychotic, olanzapine, was used to relieve catatonic symptoms. However, a few doses of olanzapine led to rhabdomyolysis with hypotension, which suggested neuroleptic malignant syndrome and inhibited further use of dopamine receptor blockers.

Refractory dyskinesia accompanied with rigidity was presumptively diagnosed with catatonia secondary to anti-NMDA receptor encephalitis. Uncontrolled dyskinesia resulted in tongue laceration and disrupted IV lines and endotracheal tubes. Accordingly, we were forced to start continuous infusion of cisatracurium, a neuromuscular blocker with little risk in patients with liver or renal dysfunction, to control her injurious movements. We assessed the cisatracurium requirement on a daily basis by temporarily reducing the dose by 0.5 to 1 μg/kg/min at a certain time of the day to evaluate her catatonia under medically induced paralysis. However, a dose of 4 μg/kg/min was persistently required, indicating that her clinical status did not change for several months despite 8 doses of rituximab. Finally, it was decided to start ECT for the treatment of ongoing dyskinesia and catatonia. She received bitemporal ECT with a schedule of 2 sessions per week. Electroconvulsive therapy was delivered with 1.0-millisecond brief pulse using a Mecta Spectrum 5000Q device (Mecta Corp, Lake Oswego, Ore). A total of 13 sessions were conducted. Twelve sessions were done using fentanyl 50 μg as anesthetic agent while she was in the intensive care unit. Because cisatracurium was continuously infused, we did not use other muscle relaxants. During the last session, propofol 70 mg and succinylcholine 70 mg were used. Stimulus dose ranged from 192 to 432 millicoulomb with 800-mA current. Seizure duration ranged from 33 to 63 seconds, which was measured by electroencephalographic monitoring. Response to ECT was noted after 3 sessions; cisatracurium requirement decreased to 3 μg/kg/min without aggravation of dyskinesia and rigidity. Thereafter, each session of ECT allowed sequential reduction of cisatracurium infusion rates. After the seventh treatment, continuous infusion of neuromuscular blocking agent was successfully discontinued. Moreover, she recovered alertness with spontaneous eye opening and was transferred to a general ward after 12 sessions of ECT. Her Glasgow Coma Scale score increased from 6 (E1, V1t, M4) to 13 (E4, V3, M6) after receiving ECT. Since then, her clinical status has been stable, and only minimal dyskinesia occurred temporarily when she had infections including pneumonia and urinary tract infection as complications related to prolonged hospitalization. Nevertheless, cognitive disabilities persisted with anti-NMDA receptor antibodies remaining positive in the CSF despite the additional immunotherapy.

The efficacy of ECT has been well established in several psychiatric diseases

such as treatment-resistant depression and schizophrenia. Regarding the treatment of anti-NMDA receptor encephalitis, there have been several case reports published in the literature.[3–5] They showed that ECT was mainly effective in the management of catatonia and psychosis resistant to antipsychotic medications. However, our case is distinguished from the previous reports in several aspects. First, her neurological conditions deteriorated despite early detection of autoantibodies and immediate treatment including tumor removal and immunotherapy, which was initiated within 2 weeks from the symptom onset. Second, dyskinesia, the major concern of the patient, was severe to the extent that continuous infusion of neuromuscular blocker was required to control self-injurious activities. Finally, the dramatic effect of ECT was obtained after prolonged clinical course, approximately 5 months, during which dyskinesia and catatonia did not respond to multiple immunotherapies. Taken together, these points emphasize the relatively distinct effect of ECT as compared with the severity and intractability of the catatonic symptoms in our case.

Our observation suggested that ECT could be used successfully as a last resort even after long-lasting courses with the failure of various immunotherapies. Therefore, ECT should be considered more often as a treatment option for life-threatening catatonia and medically refractory dyskinesia in patients with anti-NMDA receptor encephalitis.

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