INTRODUCTION

Since the novel detection of specific autoantibodies to the N-methyl-D-aspartate receptor (NMDAR) associated with paraneoplastic encephalitis, anti-NMDAR encephalitis has been recognized as a relatively common neuroinflammatory syndrome [1]. This condition disproportionately affects children and young women, with approximately 50% of the affected female patients having tumors, most commonly ovarian teratomas [2]. The presentation of the disease often involves multistage progression of symptoms or a variety of overlapping manifestations, making early recognition challenging [3-7].

Herein, we report the case of a young female adolescent who initially presented with a mild headache, which progressed to...
psychiatric symptoms. She was subsequently diagnosed with anti-NMDAR encephalitis in conjunction with an ovarian teratoma.

**CASE REPORT**

A 15-year-old female adolescent with no significant medical history visited a secondary hospital with symptoms of itching, nausea, and headache 5 days prior to hospital admission. Two days before visiting the secondary hospital, she developed fever. An initial lumbar puncture and cerebrospinal fluid (CSF) analysis revealed a white blood cell count of 1,400 cells/µL, protein level of 127 mg/dL, and glucose level of 67 mg/dL, with lymphocytic pleocytosis suggestive of meningitis. Although no organisms were observed on the Gram stain, she was started on antibiotics, including vancomycin and cefotaxime. Subsequently, she developed psychiatric symptoms and exhibited language deficits, dysarthria, and hallucinations. Brain magnetic resonance imaging (MRI) raised suspicions of herpes simplex virus (HSV) encephalitis, prompting the initiation of acyclovir therapy.

Following a CSF analysis that showed improvement (400 cells/µL, protein 127 mg/dL, and glucose 68 mg/dL), but persistent psychiatric symptoms, the patient was transferred to our hospital for further evaluation and management. At the emergency room of our hospital, she presented with short-term memory loss, emotional lability, anxiety, and involuntary twitching, leading to suspicion of focal motor seizures. This prompted the administration of levetiracetam. Based on outside brain MRI readings, her antibiotic regimen and acyclovir for suspected HSV encephalitis were maintained. Due to worsening consciousness and respiratory difficulty, she was transferred to the pediatric intensive care unit for intubation and mechanical ventilatory support. Electroencephalography (EEG) showed non-specific cerebral dysfunction without focal lateralizing or epileptiform discharges. A review of the outside brain MRI demonstrated subtle hyperintensity in the bilateral hippocampi, bilateral temporal lobes, and bilateral insula in T2 weighted images and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1). These findings were highly suspicious for autoimmune encephalitis rather than HSV encephalitis, leading us to start intravenous methylprednisolone therapy (1 g) starting on the third day of hospitalization and lasting for 3 days, followed by intravenous immunoglobulin (400 mg/kg) for 5 days. Despite these treatments, the patient continued to exhibit abnormal movements and agitation, complicating the weaning from mechanical ventilation. Imaging evaluation for paraneoplastic syndrome on the seventh day of hospitalization revealed an ovarian mature cystic teratoma (Fig. 2), which was surgically resected on the ninth hospital day. Positive anti-NMDAR antibodies in the CSF confirmed the diagnosis of anti-NMDAR encephalitis on the 10th hospital day. Despite the surgical resection of teratoma, her symptoms persisted from the 13th hospital day. Plasma exchange was performed 10 times on a daily schedule based on the working days. However, the patient’s neuropsychiatric symptoms and dyskinesia did not improve. Furthermore, her severe orofacial dyskinesia led to the loss of

![Fig. 1. Brain magnetic resonance imaging. (A) T2-weighted and (B) fluid-attenuated inversion recovery imaging findings show subtle hyperintensity in the bilateral hippocampi, temporal lobes, and insula (arrows).](https://doi.org/10.32990/apcc.2024.00059)

![Fig. 2. Computed tomography of the abdomen and pelvis shows a 2.4-cm cystic mass (arrows) with a possible gross fat component in the left adnexa, suggesting a mature ovarian teratoma, left. (A) Coronal view. (B) Axial view.](https://doi.org/10.32990/apcc.2024.00059)
several teeth (the right maxillary middle tooth, lateral tooth, and left middle tooth (#11, 12, 21), and the left lateral tooth (#22)), tongue and lip lacerations, and damage to the endotracheal tube. Continuous chewing movements caused leakage in the endotracheal tube, necessitating a tracheostomy. Various medications, including midazolam, ketamine, haloperidol, quetiapine, tetra- benzine, and trihexyphenidyl, were used to manage her symptoms, albeit with limited success. Ultimately, rituximab therapy was initiated, along with continuous symptom monitoring and medication adjustments. Specifically, 500 mg of rituximab was administered once a week starting on the 29th day of hospitalization and lasting for 4 weeks. After 49 days of hospitalization, the patient showed clinical improvement and was transferred to a general ward for rehabilitation.

Follow-up brain MRI performed on the 90th day of hospitalization revealed a significant improvement of the previously noted subtle hyperintensity in FLAIR/T2 images, indicating a nearly resolved state of autoimmune encephalitis (Fig. 3). With gradual improvement, the patient was successfully weaned from mechanical ventilation, and the patient underwent tracheostomy removal. Following ongoing rehabilitation and recovery, she was discharged from the hospital with significant improvement in cognitive and neurological functions.

Over a 5-year follow-up, the patient’s anti-NMDAR antibody status became negative 4 years after disease occurrence and remained stable, and no recurrent tumor was identified. The patient achieved near-complete mental recovery, eventually attending university.

**DISCUSSION**

This case involved anti-NMDAR encephalitis presenting with typical symptoms that align with established diagnostic criteria. These criteria require the rapid onset of at least four out of six major symptom groups: abnormal psychiatric behavior or cognitive dysfunction; speech dysfunction, including pressured speech, verbal reduction, or mutism; seizures; movement disorders, dyskinesias, or rigidity/abnormal postures; decreased level of consciousness; and autonomic dysfunction or central hypoventilation. Diagnostic confirmation is supported by abnormal EEG and/or CSF findings, which may include pleocytosis or oligoclonal bands, after reasonably excluding other disorders [8,9].

Autoimmune encephalitis is the most common and treatable form of the condition, typically preceded by nonspecific prodromal symptoms such as headaches, low-grade fevers, or symptoms of an upper respiratory infection. These initial signs are followed within 2 weeks by profound neuropsychiatric manifestations, including short-term memory loss, language deficits, delusions, hallucinations, seizures, and disturbed consciousness [4,7,10,11]. Mechanistically, the characteristic psychiatric symptoms are believed to result from NMDA receptor hypo-function, which occurs when autoantibodies bind to the GluN1 subunit of the receptor, leading to its internalization [7,11,13].

NMDAR encephalitis is a rare paraneoplastic neurological syndrome. Notably, there is an association between NMDAR encephalitis and an underlying neoplastic condition, with approximately 38% of cases linked to ovarian teratomas [2,13]. Ovarian teratomas may contain both mature and immature neuronal tissues that express NMDA receptors, potentially contributing to the synthesis of autoantibodies. These antibodies can then cross-react with NMDA receptors in the neuronal system [7,11,13].

The diagnosis of this condition is based on typical clinical manifestations and the progression of symptoms. Brain MRI often reveals subtle T2 or FLAIR sequence hyperintensities in the hippocampal, frontobasal, insular, or basal ganglia regions in approximately 50% of cases. EEG may also show abnormal findings.
in up to 90% of cases [2,9]. The confirmative test is anti-NMDAR antibodies in the CSF or serum [10,14].

In this case, due to early suspicion and a positive confirmative test for anti-NMDAR antibodies in the CSF, a prompt diagnosis was made, including the detection of an ovarian teratoma. The primary treatment strategies include immunomodulation with high-dose steroids, plasmapheresis, and immunoglobulin. Rituximab and cyclophosphamide are considered as second-line therapies. Tumor removal is recommended as a crucial step for controlling the causal factor, which reportedly leads to rapid clinical improvement [9,14]. However, in this patient, despite aggressive management involving tumor resection and early initiation of immune therapy, the symptoms did not improve rapidly.

As well as psychiatric symptoms, focal motor seizures present at a relatively early period of the disease and sometimes overlap with movement disorders, such as ataxia, catatonia, choreiform movements, and dyskinesia during disease progression [10]. This overlap of abnormal movements and complex seizures can create clinical dilemmas and lead to misinterpretations, potentially resulting in the unnecessary over- or under-dosing of antiepileptic drugs or other medications used to control dyskinesia. Although the mechanisms behind these phenomena are not fully understood, they are thought to be related to receptor hyperfunction [13].

Dyskinesia is one of the most troubling symptoms of the disease, commonly presenting in most patients and often including orofacial dyskinesia [12]. The severe form of dyskinesia can lead to self-injury or rhabdomyolysis [15-17], necessitating the use of anesthetics or neuromuscular blockers in the intensive care unit setting. This patient exhibited a severe form of dyskinesia, particularly orofacial dyskinesia, which resulted in the loss of several teeth, lacerations to the lips and tongue, and significant mouth bleeding. Management was consistent with previous reports, employing sedatives, neuromuscular blockers, botulinum toxin, and immunomodulation [16,18]. Other researchers have suggested tramadol, benzodiazepines, or a mega-dose of diazepam for managing symptoms [14,15,19]. In this case, neuromuscular blockers, antipsychotics, and benzodiazepines were combined for symptom control. Although there is no definitive evidence-based gold standard treatment protocol for recovering from dyskinesia, given its incidence and significance, a consensus-based recommendation is required.

The prognosis is dependent on various factors. Approximately 80% of affected patients recover or continue to experience mild sequelae, while the remaining 20% may encounter severe deficits or die [2,10]. Favorable outcomes are associated with early diagnosis and the prompt initiation of immunomodulatory management, along with tumor elimination if feasible [20].

In conclusion, anti-NMDAR encephalitis is an antibody-mediated autoimmune disorder, often linked with paraneoplastic syndrome. The clinical presentation of this condition can vary significantly, and the overlapping symptoms and progression of the disease make early diagnosis difficult. Therefore, maintaining a high level of suspicion and conducting a thorough evaluation, which includes testing for NMDAR antibodies, is crucial for achieving a timely and accurate diagnosis.

The primary treatment approach involves immunomodulation. Should initial therapy prove unsuccessful, second-line treatments, including rituximab and/or cyclophosphamide, may be considered. Dyskinesia is a common symptom among patients with this condition; however, managing dyskinesia can be challenging. There is a need for evidence-based guidelines to effectively control this difficult aspect of the disease.

CONFLICT OF INTEREST
Seong Jong Park is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS
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