# Early Diagnosis of Anti-*N*-methyl-D-aspartate Receptor Encephalitis in a Young Woman with Psychiatric Symptoms

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A previously healthy 21-year-old woman, transported to our medical emergency center for excluding organic brain disease, had undergone medical examination 9 days before for trembling in her left hand, which was caused by stress. The patient exhibited fever and strange behaviors, e.g., wandering around, babbling, and making smoking gestures; hence, psychiatric examination was performed.

The patient's Glasgow Coma Scale score was 4-3-5, and involuntary movement was observed. Cerebrospinal fluid examination revealed increased cell count; hence, we suspected anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis. We conducted an abdominal CT scan, which revealed a neoplastic lesion with calcification in the right ovary. Early steroid pulse therapy was started. On hospital day 25, she tested positive for anti-NMDA receptor antibodies; hence, anti-NMDA receptor encephalitis and concomitant ovarian teratoma was diagnosid. She underwent right adnexectomy; subsequently, immunotherapy was performed. The patient recovered and was discharged on hospital day 105.

Anti-NMDA receptor encephalitis is not uncommon; however, this disease must be considered for young encephalitis patients exhibiting psychiatric symptoms. If patients (aged  $\leq$  30 years) presents with encephalitis of uncertain etiology, psychiatric symptoms, seizures, movement disorders, or psychosis, clinicians should consider anti-NMDA encephalitis as a possible diagnosis. Clinical diagnosis should be waged early to ensure timely treatment.

Key words: Encephalitis, N-methyl-D-aspartate (NMDA) receptor, Psychiatric symptoms, Ovarian teratoma

## **INTRODUCTION**

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is form of encephalitis that develops through the action of NMDA receptor antibodies. Amongst patients aged ≤ **30 years, cases of anti-NMDA receptor en**cephalitis were nearly as common as viral encephalitis. It often occurs in young women and is accompanied by teratomas in various regions such as the ovaries. It causes psychiatric symptoms, involuntary movement of the face and limbs, disturbance of consciousness, and central hypoventilation.

We treated a patient with anti-NMDA receptor encephalitis who was hospitalized because of psychiatric symptoms. We strongly suspected this disease because of the patient's clinical course and her cerebrospinal fluid examination results. The presence of an ovarian teratoma led to a clinical diagnosis **and early treat**ment.

### **CASE REPORT**

Case: A 21-year-old woman.

Medical history, family history, life history, and history of overseas travel: No particular items of note. Chief complaint: Strange behavior

## History of present illness

The patient developed common cold symptoms, such as headache, 1 month previously. Nine days prior to admission, the patient visited her local doctor because of trembling in her left hand but returned home after a brain MRI scandid not reveal any abnormalities. Although the patient visited the same doctor again 2 days later, she was sent home after being diagnosed with a stress reaction. The following day and the day after, she visited a different local doctor, who recommended that she be examined at a psychiatric department. She underwent psychiatric examination because she developed a fever, was anxious, and began to exhibit strange behaviors such as wandering, babbling, and making smoking gestures. She was transported to our hospital's medical emergency center by ambulance for excluding organic brain disease.

# Status at arrival

The patient's Glasgow Coma Scale score was 4–3– 5, and the respiratory rate was 20 breaths/min. Her pulse rate was 110 beats/min, blood pressure was 124/60 mmHg, and body temperature was 38.2°C. The left and right pupils were 3 mm in diameter, equal and

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Fig. 1 Head CT image reveals no remarkable findings



Fig. 2 Brain MRI image reveals no remarkable findings



Fig. 3 CT image of the abdomen shows a right cystic adnexal mass with an internal focus of fat and high-attenuation material, suggesting an ovarian teratoma (white arrow)

round, and reacted quickly to light. Dyskinesia of the lips was observed. There was no clear limb paralysis, and no pathological reflexes were noted. Deep tendon reflexes were normal and Babinski's reflexes were not observed. No meningeal signs were apparent. Moreover, coordination and sensory disturbances as well as cognitive dysfunctions could not be determined due to the patient's conscious disturbances. No autonomic dysfunctions were observed.

## Laboratory findings at arrival

Peripheral blood and blood biochemical examination results revealed slight increases in the following parameters: WBC count,  $8100/\mu$ l; CPK, 2878 µl; GOT, 108 µl; GPT, 38 µl; and CRP, 0.20 mg/dl. When cerebrospinal fluid examination was conducted because of suspected encephalitis, the cell count was 31/mm<sup>3</sup>, with a significant increase in the number of lymphocytes; however, protein levels were found to be normal (19 mg/dL). Her thyroid function was normal, and there were no significant findings for any type of virus antibody titers. Head CT (Fig. 1) and brain MRI (Fig. 2) performed upon arrival showed no remarkable findings.

## Course after arrival at hospital

Because the patient was a young woman with encephalitis that developed from psychiatric symptoms, thoracoabdominal CT was conducted to search for teratomas considering the possibility of anti-NMDA receptor encephalitis. The abdominal contrast-enhanced CT (Fig. 3) revealed a  $44 \times 27$ -mm cystic lesion with calcification in the pelvis; the lesion appeared to be an ovarian teratoma. The patient was then admitted as the above findings led us to a clinical diagnosis of anti-NMDA receptor encephalitis with concomitant ovarian

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Table 1 Clinical course



## teratoma.

# Clinical course after admission (Table 1)

Steroid pulse therapy was initiated after the patient was admitted to the hospital. The patient stayed in the hospital on the second day, and tonic convulsive seizure of her superior limbs and body were observed. Tracheal intubation and respiratory management were implemented from hospital day 3 because of central hypoventilation. On hospital day 4, the patient developed general muscle hypertonia and intense dyskinesia in the mouth and lips. Moreover, she exhibited behaviors such as poking out of the tongue; therefore, she was administered propofol. Autonomic symptoms such as spasmodic hyperhidrosis, blood pressure fluctuations, and varying pulse rate appeared subsequently.

Blood serum and cerebrospinal fluid samples of the patient collected at the time of arrival were sent to Dr. Dalmau of the University of Pennsylvania, for measuring the levels of anti-NMDA receptor antibodies. On hospital day 25, we received information that the blood serum and cerebrospinal fluid samples tested positive for the antibodies; hence, this basis, the patient's diagnosis was confirmed to be anti-NMDA receptor encephalitis. On hospital day 26, enucleation of the ovarian tumor was performed. After the surgery, the patient underwent a third series of steroid pulse therapy and received high-dose intravenous immunoglobulins. Subsequently, her clinical course showed improvement, and respiratory support was withdrawn on hospital day 51. On hospital day 105, she was given an ambulatory discharge.

### Extracted samples (Fig. 4)

The cystic mass contained hair, lipid, and neural tissue. It was histopathologically diagnosed as a mature cystic teratoma.

#### DISCUSSION

Anti-NMDA receptor encephalitis is an autoimmune encephalitis first reported in 2007 by Dalmau et al. of the University of Pennsylvania [1]. In October 2008, clinical data from 100 cases, gathered from around the world, were published in Lancet Neurology [2]. This type of encephalitis often occurs in young women; the male:female ratio of this disease is 9:91, and the median age of patients is 23 years [2]. Psychiatric symptoms, involuntary movement of the face and limbs, disturbance of consciousness, and central hypoventilation are exhibited by patients with this disease. Patients follow a very similar course, gradually improving after progressing through common cold symptoms, a period of psychiatric symptoms, an immobile period, and a hyperactive period [3]. In the early phase, patients develop many different psychiatric symptoms; moreover, some cases of anti-NMDA receptor antibodies identified in patients with purely



Fig. 4 The cystic mass contains hair, lipid, and neural tissue. It was histopathologically diagnosed as a mature cystic teratoma.

psychiatric disorders have been reported [4, 5]. The complication rate for teratomas is reported to be 59%, and 95% of all teratomas are ovarian teratomas; additionally, mediastinal teratoma, orchioncus, small-cell lung carcinoma, and other tumors have been reported [6]. Definitive diagnosis is possible when anti-NMDA receptor antibodies are detected in the cerebrospinal fluid and blood serum.

If a teratoma is discovered, early tumor enucleation is effective [2]; further, steroid pulse therapy, gammaglobulin therapy, plasmapheresis, and immunosuppressant therapy have been reported to be effective [7–10]. However, the median duration of hospitalization was 2.5 months [11]. Although 75% of patients achieve complete recovery, complications often occur as the disease is serious and follows a prolonged course. The mortality rate is reported to be 7% [2].

The California Encephalitis Project (CEP) reported a total of 761 cases of encephalitis of uncertain etiology in individuals aged  $\leq 30$  years (the age group in which most anti-NMDA receptor cases occur) between September 2007 and February 2011 [12]. Etiology was identified in 79 of the 761 patients: anti-NMDA receptor encephalitis in 32, and viral encephalitis in 47 patients. Patients presenting with anti-NMDA receptor encephalitis were significantly more likely to exhibit seizures, movement disorders, language dysfunction, and psychiatric symptoms than those with viral encephalitis; moreover, they were less likely to demonstrate neck stiffness. Median values for white blood cell count and protein concentration in cerebrospinal fluids were lower in patients with anti-NMDA receptor encephalitis than in those with viral encephalitis; electroencephalograms were significantly, and more frequently, abnormal in individuals with anti-NMDA receptor encephalitis [12].

The patient in the present study was a 21-year-old woman who exhibited psychiatric symptoms, movement disorders, language dysfunction, and no signs of meningitis; samples of cerebrospinal fluids retrieved from this patient showed a significant increase in the number of lymphocytes. From these etiologies, we strongly suspected anti-NMDA receptor encephalitis and conducted an abdominal CT scan, which revealed a teratoma. We diagnosed this disease and started an early administration of steroid pulse therapy.

We were able to reach a definitive diagnosis when anti-NMDA receptor antibodies were identified in the patient's cerebrospinal fluid and blood serum. Over the course of the disease, the patient did require longterm artificial respiratory management because of central hypoventilation. Ovarian tumor enucleation was performed after a definitive diagnosis was made. The patient recovered over the course of approximately 2 months after steroid pulse therapy, and highdose intravenous immunoglobulin administration was conducted.

In cases where the patient is aged  $\leq 30$  years, and presents with encephalitis of uncertain etiology, psychiatric symptoms, seizures, movement disorders, or psychosis, the clinician should consider anti-NMDA receptor encephalitis as a possible diagnosis. This clinical diagnosis should be waged early to ensure timely treatment options.

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