Case Report

Anti-NMDAR encephalitis: case report and diagnostic issues

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Case: A 20-year-old woman developed acute psychotic symptoms and altered level of consciousness. She presented with neck stiffness, tremulous arms, facial dyskinesia, and distension of the lower abdomen. Pelvic magnetic resonance imaging showed bilateral ovarian teratomas. Anti-N-methyl-D-aspartate receptor antibodies were detected in her cerebrospinal fluid.

Outcome: Resection of the tumors and immunotherapy were carried out. She gradually recovered and was discharged with few neurological deficits on the 105th day of hospitalization.

Conclusion: Our survey of 63 previous reports describing 92 cases revealed that 21.7% of the patients were sent to emergency departments and 59.8% of the patients were managed in intensive care units. Emergency physicians and intensivists should be aware of this disorder, as they may encounter undiagnosed disorders in patients with epileptic attacks, acute psychotic signs, dyskinesia, or hypoventilation in the course of the illness.

Key words: Anti-NMDAR encephalitis, immunotherapy, intensive care units, limbic encephalitis, teratoma

INTRODUCTION

LIMBIC ENCEPHALITIS IS often considered as an infectious disease caused by herpes simplex virus. The clinical manifestation is a set of specific features that present as psychiatric symptoms, dyskinesia, and epilepsy. Paraneoplastic limbic encephalitis seen in patients with some cancers is reported to present with similar conditions.[1] Recently, immunological mechanisms have been found to occur in the same pathological situation.[2] Antibody against N-methyl-D-aspartate receptor (NMDAR), which is a kind of glutamate receptor that contributes to memory and learning through the signal transmission in the central nervous system, is found to cause limbic encephalitis. Anti-NMDAR encephalitis was described in 2007.[3] Young women with ovarian teratomas typically develop acute encephalopathy and respond to treatment with tumor resection and immunotherapy, although approximately 25% of patients do not respond well and the mortality rate is 4%.[4] Early diagnosis, immediate immunotherapy, and tumor resection should lead to a better prognosis. Early signs of this disorder are similar to psychosis or some other type of encephalopathy, which may lead to a misdiagnosis by physicians. We report a case with clinical signs of encephalomeningitis in the course of this disorder.

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Received 4 Mar, 2014; accepted 1 May, 2014; online publication 8 September, 2014

CASE REPORT

A 20-YEAR-OLD WOMAN with no history of serious disease presented with a headache and fever 1 week before admission. She required emergency care in the psychiatric ward of a general hospital after experiencing hallucinations, agitation, and confusion for 3 days. Those signs were recognized as schizophrenia symptoms. She was transferred to our emergency department to determine whether there was an organic cause inducing the altered level of consciousness, assessed as E1V2M4 using the Glasgow Coma Scale. Her body temperature was 37.2°C. She also presented with neck stiffness, tremulous arms, facial dyskinesia, and distension of the lower abdomen. The patient was intubated and placed on a respirator in the intensive care unit (ICU) owing to her altered level of consciousness in the emergency room. We assumed that her illness was encephalomeningitis because of neck stiffness and altered level of

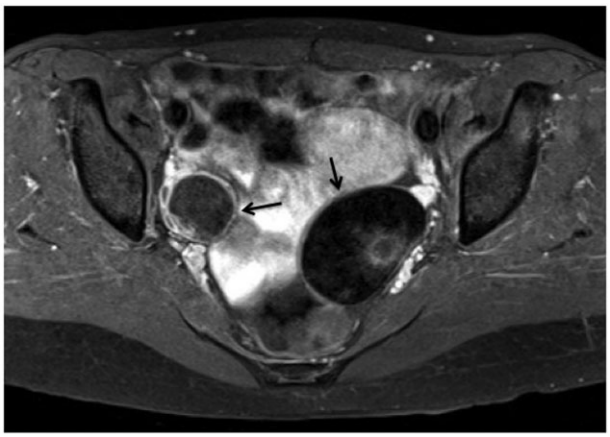

Fig. 1. Abdominal magnetic resonance imaging of a 20-year-old woman who developed acute psychotic symptoms and altered level of consciousness, and was diagnosed with anti-N-methyl-D-aspartate receptor encephalitis. The image shows bilateral ovarian teratomas (arrows).

consciousness, attributable to viral infectious encephalopathy, or limbic encephalitis mediated by the autoimmune system. Non-specific findings appeared on brain computed tomography and magnetic resonance imaging (MRI). Her electroencephalogram findings showed diffuse slow waves intermittently. A cerebrospinal fluid (CSF) examination revealed clear, colorless fluid, an initial pressure of 330 mmH_2O, a protein concentration of 33 mg/dL, a glucose level of 83 mg/dL, and 57 mononuclear cells/μL. Pelvic MRI showed bilateral ovarian teratomas (Fig. 1). Resection of the teratomas was carried out 5 days after admission as her illness appeared to be anti-NMDAR encephalitis and the level of consciousness was unchanged. Immunotherapy with corticosteroids started from 2 weeks after admission. As anti-NMDAR antibodies were detected in the patient's CSF, her condition was definitively diagnosed as anti-NMDAR encephalitis. Her consciousness gradually recovered from approximately the 30th day of hospitalization. She was transferred to the general medical ward on the 35th day, and was discharged with few neurological deficits on the 105th day. She returned to her normal daily activities approximately 3 months after being discharged.

DISCUSSION

AN INCREASING NUMBER of case reports of anti-NMDAR encephalitis since its description in 2007 suggest that it is not a rare disorder. The NMDA antibody is reported to cause 4% of encephalitis worldwide.[5] The identified number of patients with anti-NMDAR encephalitis is 400 over a period of 3 years. Although the typical patient is a young woman with teratomas, approximately 20% of anti-NMDAR encephalitis cases are men. More than 90% of these patients are under 42 years old. Patients between 12 and 45 years old are more likely to have tumors than the other patients.[6] Male patients with the disease have few tumors. The ratio of bilateral ovarian teratomas, detected in our patient, to all ovarian teratomas is 13.3% in the patients with anti-NMDAR encephalitis, according to our survey of 63 reports (Fig. 2). This ratio is not specific to anti-NMDAR encephalitis because the ratio of bilateral ovarian teratomas to all ovarian teratomas is known to be 10–15%.

The clinical phases of anti-NMDAR encephalitis can be described according to the classification of Iizuka et al.[7] Upper respiratory tract symptoms, fever, headache, nausea, vomiting, and diarrhea were detected as prodromal symptoms in approximately 70% of patients.[7] Our patient presented with fever and headache. Psychiatric symptoms, seen within 2 weeks, include anxiety, insomnia, fear, grandiose delusion, hyper-religiosity, mania, and paranoia. Inhibition of NMDAR, which worsens schizophrenia, causes acute psychosis at the early phase of the disorder. Our patient's condition had been misdiagnosed as acute psychosis and she was admitted to the psychiatric ward at the onset of this disorder. Misdiagnosis as psychosis or some other types of encephalopathy may occur, particularly in the early phase.

The phase of decreased responsiveness follows sequentially. Patients showing dissociative responses appear to have awareness, but show little responsiveness to nociceptive stimuli in this phase.[7] Agitation and catatonia can be observed simultaneously. Abnormal movements such as orolingual-facial dyskinesias, limb and trunk choreoathetosis, elaborate motions of the arms and legs, oculogyric crisis, dystonia, rigidity, and opisthotonic postures also occur.[8] These clinical signs may have been detected as neck stiffness

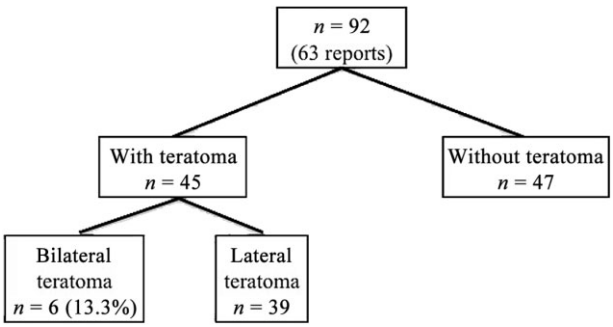

Fig. 2. Ratio of bilateral ovarian teratomas in anti-N-methyl-D-aspartate receptor encephalitis. The ratio of bilateral ovarian teratoma to all ovarian teratoma is 13.3% in the 63 previous reports examined.

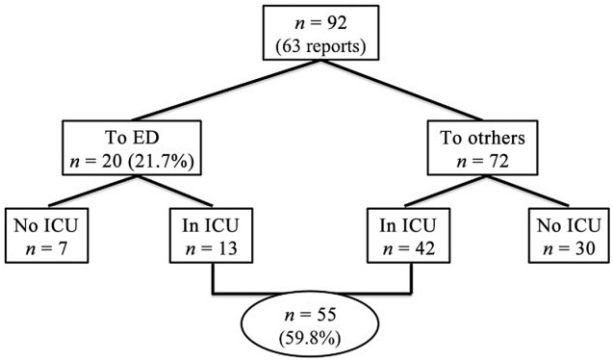

Fig. 3. Distribution of patients with anti-N-methyl-D-aspartate receptor encephalitis reported as treated in emergency departments (ED) and intensive care units (ICU). The ratios of the patients sent to the ED and managed in the ICU are 21.7% and 59.8%, respectively, in the 63 reports examined.

and altered level of consciousness in our patient, as few patients with anti-NMDAR encephalitis show signs of encephalomeningitis. Autonomic instability, including hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction are common manifestations at this phase. Patients with hypoventilation requiring respiratory support, or those with epileptic seizures, are managed in the ICU.[9] Our survey of 63 previous reports describing 92 cases revealed that 21.7% of the patients were sent to emergency departments and 59.8% of the patients were managed in ICUs (Fig. 3).

Brain MRI images of half of the patients show T2 or fluid attenuated inversion recovery (FLAIR) signal hyperintensity in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular region, basal ganglia, and brainstem, but are unremarkable in the other half.[10] Abnormal electroencephalograms, showing non-specific, slow, and disorganized activity, and sometimes with electrographic seizures, are seen in most patients. Moderate lymphocytic pleocytosis and normal or mildly increased protein concentration are abnormal findings in the CSF from more than 80% of the patients. Cerebrospinal fluid-specific oligoclonal bands are seen in 60% of the patients. These findings are not specific to anti-NMDAR encephalitis. Anti-NMDAR antibodies are detected in the CSF of most patients, although there are smaller amounts of these antibodies in serum.

Immunotherapy and the detection and removal of the teratomas should be the curative management of anti-NMDAR encephalitis, and such curative management, when started early, results in a better prognosis.[6,10] The first line of immunotherapy includes treatment with corticosteroids and i.v. immunoglobulins or plasma exchanges. The second line of immunotherapy is rituximab, cyclophosphamide, or both; this is usually needed for patients showing little or no response to the first line of immunotherapy. The presence of teratomas indicates a better prognosis. Although tumor removal and the first line of immunotherapy showed substantial improvement in 80% of the patients with a tumor, the first line of immunotherapy showed a similar degree of improvement in only 48% of those without a tumor. The second line of immunotherapy showed improvement in 65% of the patients, but it was not substantial. Overall, 84% of the patients with a tumor and 71% of those without a tumor showed substantial improvement.[4] Most patients with anti-NMDAR encephalitis require intensive care support, immunotherapy, and prolonged stays in hospital. Despite the severity of the disease, they respond to immunotherapy and/or tumor removal and recover gradually.

Patients with anti-NMDAR encephalitis recover gradually in the reverse order of symptom presentation. At least 3–4 months of hospitalization and several months of physical and behavioral rehabilitation are usually required.[10]

CONCLUSIONS

PATIENTS WITH ANTI-NMDAR encephalitis may show similar signs to psychosis or some other type of encephalopathy, including encephalomeningitis, in the early phase. Early treatment results in a better prognosis. Emergency physicians and intensivists should be aware of this disorder, as they may encounter undiagnosed disorders in patients with epileptic attacks, acute psychotic signs, dyskinesia, or hypoventilation in the course of the illness.

ACKNOWLEDGEMENTS

THE AUTHORS THANK Dr. Keiko Tanaka of Kanazawa Medical University for the measurement of anti-NMDAR antibodies. The authors are also indebted to Dr. Edward Barroga, Associate Professor and Senior Medical Editor of the Department of International Medical Communications of Tokyo Medical University for the editorial review of the English manuscript.

CONFLICT OF INTEREST

NONE.

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