

Anti *N*-Methyl-D-Aspartate (NMDA) Receptor Encephalitis with Frustrated Diagnosis Course: A Case Report

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Abstract

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a rare disease with uncertain etiology and pathogenesis that affects young women. Its diagnosis can be delayed because of the nonspecific neuropsychiatric symptoms in the foreground. This article describes the details of a recent complicated case of a patient with this condition which is related to an ovarian teratoma. Correct diagnostic and prompt treatment of anti-NMDA receptor encephalitis remains a serious clinical challenge due to its unspecific manifestations and varying response to treatments. The information will be of interest to clinicians working with encephalitis patients.

Keywords

Anti-NMDA Receptor Encephalitis, Ovarian Teratoma

1. Introduction

Anti *N*-methyl-D-aspartate (NMDA) receptor encephalitis is an immune-mediated syndrome which is characterized by psychosis, seizures, sleep disorders, hallucinations and short-term memory loss [1] [2]. This syndrome has been predominantly described in young females (81%), and ovarian teratoma is the confirmed tumour associated with anti-NMDA receptor antibodies [3]. One multi-centre prospective epidemiological study demonstrated that anti-NMDA receptor encephalitis accounted for 4% of all encephalitis cases [4]. The signs and symptoms are often nonspecific, which makes the diagnosis difficult. Its diagnosis can be delayed because of the nonspecific neuropsychiatric symptoms in the foreground. Herein, the authors present a case of anti-NMDA receptor encephalitis with frustrated diagnosis course.

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2. Case Report

The patient, a 28-year-old maternal female from Guangdong province, suffered headache, insomnia and fever (ever the highest body temperature 41.0°C) since 7 January 2014. Upon the onset of the symptoms, she was once treated as an out-patient in a local clinic with unknown diagnosis and therapy and the symptoms were relieved. However, she appeared to be unresponsive with fewer words and became anxious since 13 February 2014.

After her hospitalization in a local countryside hospital, she was diagnosed as “anxiety” and given anti-anxiety treatment, yet the improvement was still dissatisfied. From 20 February 2014 on, during her hospital stay, she started to suffer frequent general tonic clonic seizures and was treated by depakine. Since 25 February 2014, the patient suffered from persistent consciousness. Skull CT revealed brain edema. She was given trachea intubation, along with anti-infection, dehydration, sedation and other treatment, but the condition was not improved.

Consequently, on 27 February 2014, she was transferred to a municipal hospital. Examination of cerebrospinal fluid (CSF) by lumbar puncture revealed no abnormalities in biochemical indicators. The CSF pressure was 120 mm H₂O, and leucocytes concentration was $45 \times 10^6/L$. Electroencephalographic (EEG) investigation revealed medium-diffused abnormalities with slow waves. The patient was initially diagnosed with viral encephalitis and treated with methylprednisolone (anti-inflammatory), human gammaglobulin, mannitol, phenobarbital, valproate, levetiracetam, and chloral hydrate (anti-epileptic). However, the symptoms did not improve, and the seizures worsened. On 24 March 2014, she was transferred to a provincial hospital. Brain magnetic resonance imaging (MRI) revealed bilateral symmetric abnormal signals in the lenticular nuclei areas. She was treated with similar diagnoses and therapies, but the mental and epileptic symptoms exacerbated (**Figure 1**).

On 14 May 2014 the patient arrived to the emergency room of the Neurology Department in our hospital for further diagnosis and treatment. After hospitalization, more detailed examination was undertaken. The parameters of routine blood test, blood clotting test, liver and kidney function test, blood glucose level, electrolytes level, routine urine and stool tests, erythrocyte sedimentation rate, and C-reactive protein were normal. The tests for infectious diseases (hepatitis B, syphilis, and human immunodeficiency virus) were negative. Immune indexes (antinuclear antibody, extractable nuclear antigen, and anticardiolipin) were within the normal range. EEG investigation revealed medium-diffused abnormalities. The treatment regiment described above was continued. On 22 May 2014, the lumbar puncture and the CSF examination were carried out again. The CSF pressure was 140 mm H₂O, leucocytes level was $2 \times 10^6/L$, and biochemical indicators were normal. Pandy’s test, tests for Gram-negative bacilli, Gram-negative cocci, acid-fast bacilli, and *Staphylococcus aureus*, and T-spot were negative. The immunoglobulin-G index was within normal limits and anti-aquaporin 4 antibodies were not detected.



Figure 1. Brain MRI revealed bilateral symmetric abnormal signals in the lenticular nuclei areas.

Diazepam and midazolam were terminated. Levetiracetam, chloral hydrate, phenobarbital, and clonazepam were prescribed for controlling the seizures. With regard to tumor markers, we noticed that CA125 (71.89 U/mL) was relatively high, so B-mode ultrasonographic investigations of pancreas, spleen, thyroid, and kidneys, and chest X-ray were performed. The additional imaging examination of pelvic computed tomography (CT) scan revealed a low density mass (15 × 10 × 17 mm) in the right ovary, consistent with the diagnosis of teratoma. The possibility of anti-NMDA receptor encephalitis was considered at this point. The second lumbar puncture and CSF examination were done on 30 May 2014. CSF was sent to the Laboratory of Neurology, Third Affiliated Hospital of Sun Yat-sen University to check for NMDA receptor antibodies. NMDA receptor antibodies test was positive in CSF (1:1), so the patient was finally diagnosed with anti-NMDA receptor encephalitis. The patient was sent to the Department of Gynecology. The laparoscopic cystectomy in the right ovary was performed on 18 June 2014. Postoperative pathological examination confirmed the diagnosis of mature cystic teratoma in right ovary. After surgery, the patient's frequency of seizures was reduced. However, due to severe pulmonary infection, the patient finally died of septic shock (Figures 2-4).

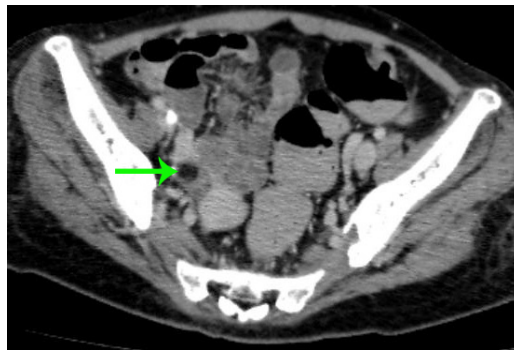


Figure 2. Pelvic CT scan revealed right ovary teratoma (arrow).

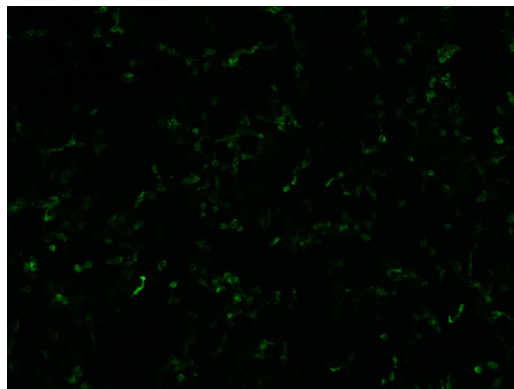


Figure 3. Indirect immunofluorescence of NMDA receptor antibodies.

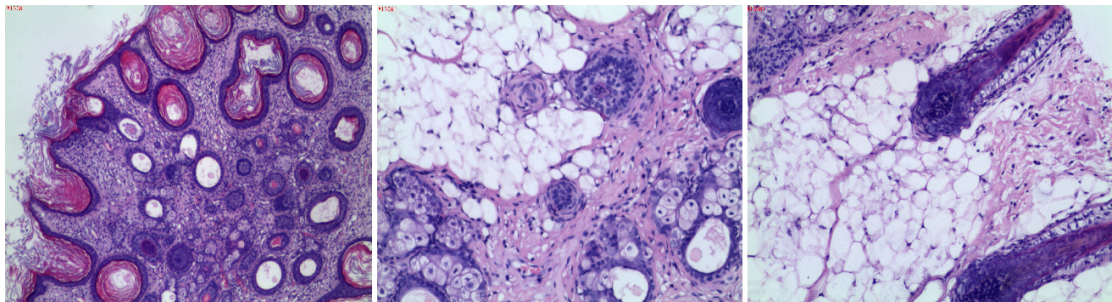


Figure 4. Postoperative pathological examination confirmed the diagnosis of mature cystic teratoma in right ovary.

3. Discussion

Our reported patient had the prodromal symptoms of headache and fever at the beginning. Days later, seizure symptom developed. After CSF examination, she was diagnosed as encephalitis. The treatment with antiviral and anti-inflammatory drugs did not improve the symptoms, which gradually got worse. During the active treatment, organic diseases were excluded by the first imaging examination. Eventually, anti-NMDA receptor encephalitis was considered, and the anti-NMDA receptor antibodies were detected in CSF confirming the definite diagnosis.

Encephalitis is an acute or chronic inflammatory disease of the central nervous system. Limbic encephalitis (LE) is an inflammatory condition related to the hippocampus, amygdaloid, and insular cortex, often defined by the clinical features of limbic dysfunction, evidence of CSF inflammation, and abnormalities in the limbic regions on electroencephalogram or MRI [5]. LE is subdivided into three categories depending on whether it is caused by viral infections, mediated by autoantibody, or concomitant to autoimmune diseases [6]. Though its rareness, classic LE is increasingly recognized, associated with anti-NMDA receptor antibodies [7].

Presentations can be variable, thus posing a challenge to clinicians in neurology and psychiatry settings. With symptoms and signs ranging from psychosis to mania to catatonia, clinicians may be prompted to consider primary mental health aetiology. The syndrome typically begins with a prodrome of cold-like symptoms, which can include nausea, vomiting, fever, headache, and fatigue [8]. This is followed by a spectrum of neuropsychiatric sequelae. Within the first month, nearly 90% of patients experience at least four of eight characteristic features: behavior/cognition problems, memory deficit, speech disorder, seizures, movement disorder, loss of consciousness, autonomic symptoms, and hypoventilation [9].

The pathogenesis of this disease is not clear, and different possibilities have been suggested. Some authors suggest that a tumor or a viral infection triggers the immunological response [10]. Most cases are probably immune mediated, the best evidence for which comes from the demonstration of antineuronal antibodies in the CSF and serum of patients. These antibodies react with neuronal proteins that are usually expressed by the patients' tumour, and their detection is the basis of useful diagnostic tests [11] [12].

At presentation, about half of the patients have abnormal MRI findings, most commonly increased signal on fluid-attenuated inversion recovery in the cerebral or cerebellar cortex without significant clinical correlation [2]. CT scans and ultrasound examinations are generally used to check for tumors, and ovarian teratoma is found in the majority of patients. On EEG examination, diffuse delta waves or epilepsy waves could be seen during no reaction stage and excessive movement stage [13]. CSF examination shows abnormalities, mainly in the form of nonspecific inflammatory reactions, in 80% of patients at early stages [10]. NMDA receptor antibodies could be detected in serum and CSF [8].

The differential diagnosis condition may present in the domain of either the neurologist or the psychiatrist, depending on whether psychiatric symptoms precede the neurological features, as is often the case. In the course of diagnostics, other viral and autoimmune diseases, metabolic, toxic, and other types of paraneoplastic limbic encephalitis (such as anti-AMPA receptor encephalitis [14] and anti-GABA receptor encephalitis [15]) should be excluded, and the presence of NMDA receptor antibodies should be confirmed in the serum and CSF. All patients should be examined for the presence of tumors, especially ovarian teratoma or testicular germ cell cancer.

Based on an extensive review, Dalmau and colleagues proposed an algorithmic strategy to guide treatment [8]. The first line of immunotherapy consists of corticosteroids, intravenous immunoglobulins, and plasma exchange (alone or in combination). The second line of immunotherapy (rituximab or cyclophosphamide or both) is usually needed in the case of a delayed diagnosis or in the absence of a tumor [8] [16]. Patients usually start to gradually improve within 2 - 3 weeks of tumor removal and immunotherapy. The persistence of high CSF antibody titers suggests the need for continuation of treatment. Compared with other types of paraneoplastic encephalitis, the prognosis for anti-NMDA receptor encephalitis is better [17]. Dalmau [8] reported that approximately 75% of patients recovered completely or only with minor disabilities. The rest of the patients remained serious ill or die.

4. Conclusion

Correct diagnostic and prompt treatment of anti-NMDA receptor encephalitis remains a serious clinical challenge due to its unspecific manifestations and varying response to treatments. The possibility of anti-NMDA receptor encephalitis must be considered on the condition when the treatment with antiviral and anti-inflammatory

drugs does not improve the symptoms, especially in young woman patients. Definite diagnosis requires anti-NMDA receptor antibodies detection in CSF or blood. Anti-NMDA receptor antibodies can be found well before the detection of tumor. The information will be of interest to clinicians working with encephalitis patients.

Conflict of Interest

This is a case report without any industry-sponsorship. All the authors report none to disclosures.

References

- [1] Tuzun, E. and Dalmau, J. (2007) Limbic Encephalitis and Variants: Classification, Diagnosis and Treatment. *Neurologist*, **13**, 261-271. <http://dx.doi.org/10.1097/NRL.0b013e31813e34a5>
- [2] Dalmau, J., Tuzun, E., Wu, H.Y., Masjuan, J., Rossi, J.E., Voloschin, A., *et al.* (2007) Paraneoplastic Anti-N-Methyl-D-Aspartate Receptor Encephalitis Associated with Ovarian Teratoma. *Annals of Neurology*, **61**, 25-36. <http://dx.doi.org/10.1002/ana.21050>
- [3] Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X.Y., Lai, M.Z., *et al.* (2008) Anti-NMDA-Receptor Encephalitis: Case Series and Analysis of the Effects of Antibodies. *The Lancet Neurology*, **7**, 1091-1098. [http://dx.doi.org/10.1016/S1474-4422\(08\)70224-2](http://dx.doi.org/10.1016/S1474-4422(08)70224-2)
- [4] Granerod, J., Ambrose, H.E., Davies, N.W., Clewley, J.P., Walsh, A.L., Morgan, D., *et al.* (2010) Causes of Encephalitis and Differences in their Clinical Presentations in England: A Multicentre, Population-Based Prospective Study. *The Lancet Infectious Diseases*, **10**, 835-844. [http://dx.doi.org/10.1016/S1473-3099\(10\)70222-X](http://dx.doi.org/10.1016/S1473-3099(10)70222-X)
- [5] Haberlandt, E., Bast, T., Ebner, A., Holthausen, H., Kluger, G., Kravljanc, R., *et al.* (2011) Limbic Encephalitis in Children and Adolescents. *Archives of Disease in Childhood*, **96**, 186-191. <http://dx.doi.org/10.1136/adc.2010.183897>
- [6] Asztely, F. and Kumlien, E. (2012) The Diagnosis and Treatment of Limbic Encephalitis. *Acta Neurologica Scandinavica*, **126**, 365-375. <http://dx.doi.org/10.1111/j.1600-0404.2012.01691.x>
- [7] McCoy, B., Akiyama, T., Widjaja, E. and Go, C. (2011) Autoimmune Limbic Encephalitis as an Emerging Pediatric Condition: Case Report and Review of the Literature. *Journal of Child Neurology*, **26**, 218-222. <http://dx.doi.org/10.1177/0883073810378536>
- [8] Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M.R. and Balice-Gordon, R. (2011) Clinical Experience and Laboratory Investigations in Patients with Anti-NMDAR Encephalitis. *The Lancet Neurology*, **10**, 63-74. [http://dx.doi.org/10.1016/S1474-4422\(10\)70253-2](http://dx.doi.org/10.1016/S1474-4422(10)70253-2)
- [9] Titulaer, M.J., McCracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., *et al.* (2013) Treatment and Prognostic Factors for Long-Term Outcome in Patients with Anti-NMDA Receptor Encephalitis: An Observational Cohort Study. *The Lancet Neurology*, **12**, 157-165. [http://dx.doi.org/10.1016/S1474-4422\(12\)70310-1](http://dx.doi.org/10.1016/S1474-4422(12)70310-1)
- [10] Hughes, E.G., Peng, X.Y., Gleichman, A.J., Lai, M.Z., Zhou, L., Tsou, R., *et al.* (2010) Cellular and Synaptic Mechanisms of Anti-NMDA Receptor Encephalitis. *Journal of Neuroscience*, **30**, 5866-5875. <http://dx.doi.org/10.1523/JNEUROSCI.0167-10.2010>
- [11] Posner, J.B. and Dalmau, J. (1995) Clinical Enigmas of Paraneoplastic Neurologic Disorders. *Clinical Neurology and Neurosurgery*, **97**, 61-70. [http://dx.doi.org/10.1016/0303-8467\(95\)00009-9](http://dx.doi.org/10.1016/0303-8467(95)00009-9)
- [12] Vitaliani, R., Mason, W., Ances, B., Zwerdling, T., Jiang, Z.L. and Dalmau, J. (2005) Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma. *Annals of Neurology*, **58**, 594-604. <http://dx.doi.org/10.1002/ana.20614>
- [13] Iizuka, T., Sakai, F., Ide, T., Monzen, T., Yoshii, S., Iigaya, M., *et al.* (2008) Anti-NMDA Receptor Encephalitis in Japan: Long-Term Outcome without Tumor Removal. *Neurology*, **70**, 504-511. <http://dx.doi.org/10.1212/01.wnl.0000278388.90370.c3>
- [14] Lai, M.Z., Hughes, E.G., Peng, X.Y., Zhou, L., Gleichman, A.J., Shu, H., *et al.* (2009) AMPA Receptor Antibodies in Limbic Encephalitis Alter Synaptic Receptor Location. *Annals of Neurology*, **65**, 424-434. <http://dx.doi.org/10.1002/ana.21589>
- [15] Lancaster, E., Lai, M.Z., Peng, X.Y., Hughes, E., Constantinescu, R., Raizer, J., *et al.* (2010) Antibodies to the GABA_B Receptor in Limbic Encephalitis with Seizures: Case Series and Characterisation of the Antigen. *The Lancet Neurology*, **9**, 67-76. [http://dx.doi.org/10.1016/S1474-4422\(09\)70324-2](http://dx.doi.org/10.1016/S1474-4422(09)70324-2)
- [16] Hachiya, Y., Uruha, A., Kasai-Yoshida, E., Shimoda, K., Satoh-Shirai, I., Kumada, S., *et al.* (2013) Rituximab Ameliorates Anti-N-Methyl-D-Aspartate Receptor Encephalitis by Removal of Short-Lived Plasmablasts. *Journal of Neuroimmunology*, **265**, 128-130. <http://dx.doi.org/10.1016/j.jneuroim.2013.09.017>
- [17] Byrne, S., McCoy, B., Lynch, B., Webb, D. and King, M.D. (2014) Does Early Treatment Improve Outcomes in N-Methyl-D-Aspartate Receptor Encephalitis? *Developmental Medicine & Child Neurology*, **56**, 794-796. <http://dx.doi.org/10.1111/dmcn.12411>