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ORIGINAL PAPER

A Case of Anti-NMDAR Encephalitis Induced by Ovarian Teratoma

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Abstract A young woman was received in the hospital with gradually worsening neurological symptoms consistent with encephalitis. After several cerebrospinal fluid examinations, infectious encephalitis (viral, bacterial, or linked to tuberculosis or parasites) and autoimmune encephalitis were ruled out. The possibility of autoantibody-mediated encephalitis was considered, and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) antibodies were detected in cerebrospinal fluid and blood, thus confirming the diagnosis of anti-NMDAR encephalitis. After initial successful treatment, the disease relapsed and the repeated ultrasound investigation revealed teratoma in the left ovary, which was not observed at initial examination. Tumor was removed by laparoscopic oophorocystectomy, and the treatment with hormones and gamma globulin was continued after the surgery. The patient's conditions were gradually improving after the treatment. Correct diagnostic and prompt treatment of anti-NMDAR encephalitis remains a serious clinical challenge due to its unspecific manifestations and varying response to treatments. This article describes the details of a recent complicated case of a patient with this condition. The information will be of interest to clinicians working with encephalitis patients.

Keywords Ovarian teratoma · Anti-NMDAR encephalitis · Cerebrospinal fluid

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Case Description

The patient, a 23-year-old nulliparous female university student from Anhui province, suffered from headache and persistent fever (body temperature 37.5 °C) without clear incentive since July 27, 2012. Upon the onset of the nonsense symptoms on August 4, the patient arrived to the emergency room of the Neurology Department in our hospital for diagnosis and treatment. Examination of cerebrospinal fluid (CSF) by lumbar puncture revealed no abnormalities in biochemical indicators. The CSF pressure was 250 mm H_2O, and leucocytes concentration was 30×10^6/L. The patient was initially diagnosed with encephalitis and treated with acyclovir (antiviral), dexamethasone (anti-inflammatory), mannitol, and glycerol fructose (for lowering the intracranial pressure). However, the symptoms did not improve, and the symptom of nonsense worsened. Consequently, the patient was hospitalized on August 5, 2012.

After hospitalization, more detailed examination was undertaken. Neurological signs were negative. 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 (ESR), and C-reactive protein (CRP) were normal. The tests for infectious diseases (hepatitis B, syphilis, and HIV) were negative. Tumor markers (CA125, CA19-9, CEA, AFP, CA50, CA724, CA211, neuron-specific enolase (NSE), and squamous cell carcinoma antigen (SCC)) and immune indexes (antinuclear antibody (ANA), extractable nuclear antigen (ENA), and anticardiolipin (aCL)) were within the normal range. Electroencephalographic (EEG) investigation revealed medium-diffused abnormalities. The treatment regiment described above was continued.

The mental symptoms exacerbated on August 6, with occasional symptoms of yelling and aggressive behavior

sometimes. The patient was treated with diazepam and chlorpromazine for calming, and olanzapine for controlling the psychotic symptoms. At 19:00 on August 10, the patient got sudden epileptic seizures, and she was treated by depakine and ganciclovir (instead of acyclovir). On August 11, the lumbar puncture and the CSF examination were carried out again. The CSF pressure was 113 mm H_2O, leucocytes level was 30×10^6/L, and biochemical indicators were normal. Pandy's test, tests for Gram-negative bacilli, Gram-negative cocci, acid-fast bacilli, and *Staphylococcus aureus*, T-spot, and the test for Japanese encephalitis virus IgM were negative. Subsequently, the patient experienced epileptic seizure every day from August 11 to 16. Olanzapine was terminated on August 16, and levetiracetam and depakine were prescribed for controlling the seizures. The possibility of anti-NMDA receptor encephalitis was considered at this point. From August 17 to 21, gamma globulin (20 g/day) was administered. The third lumbar puncture and CSF examination were done on August 20. CSF was sent to the parasitic disease office of the Chinese Disease Control and Prevention Center to check for parasites serum antibodies, and the results were negative. CSF and blood samples were also sent to the Peking Union Medical College Hospital to check for NMDAR antibodies. NMDAR antibodies test was positive in CSF and weakly positive in blood (1:50), so the patient was finally diagnosed with anti-NMDAR encephalitis.

The whole-body examination by PET-CT was performed. In addition, B-mode gynecologic ultrasonography and ultrasonographic investigations of pancreas, spleen, thyroid, and kidneys, chest X-ray, and brain MRI were performed. No abnormalities were found by any of the above examinations. Subsequently, the administration of antibiotics and antiviral drugs was stopped. From August 30, dexamethasone was terminated as well, and oral prednisone was prescribed instead. From August 31 to September 4, the second course of gamma globulin treatment (17.5 g/day) was done. Epileptic seizures were taken under control and psychotic symptoms gradually improved. On September 7, the Mini Mental State Examination (MMSE) score was 27 points (3 points deducted in memory), and the Montreal Cognitive Assessment (MoCA) score was 23 points (3 points deducted in recall, 2 points deducted in structure, and 2 points deducted in the logics of thinking). The patient was allowed to leave hospital on September 15. She continued taking prednisone (40 mg/day) which was gradually reduced by 5 mg every week until reaching 5 mg/day and then maintained on this level.

The EEG examination was done on November 7 for additional check, and the paroxysmal θ-wave was noted. Prednisone was stopped on November 8. After discontinuation of prednisone, the patient was able to speak more words, although there were periods of nonsense sometimes, as well as paroxysmal dizziness and occasional headaches. However, her memory loss was significant since the onset of illness (especially recent memories, the previous event were still remembered), so she was hospitalized again on November 17. From November 21, the patient became euphoric, noisy, and feverish at night. Anti-NMDAR encephalitis has relapsed. From November 21 to November 25, the patient was administered with the third course of gamma globulin (22.5 g/day) and methylprednisolone (500 mg/day). The fourth lumbar puncture and CSF examination were done on November 23. CSF and blood were sent to the Peking Union Medical College Hospital again to check the level of NMDAR antibodies. The antibody test was positive in CSF and weakly positive in blood (1:50). The additional imaging examination (B-mode gynecologic ultrasonography) revealed a high echogenic mass ($25 \times 28 \times 27$ mm) in the left ovary, consistent with the diagnosis of teratoma. Tumor markers such as CA125 and others were negative. The patient was sent to the Department of Gynecology. The laparoscopic cystectomy in the left ovary was performed on December 5. Postoperative pathological examination confirmed the diagnosis of mature cystic teratoma in left ovary. After the surgery, methylprednisolone was tapered to 60 mg/day, and prednisone (40 mg/day) was taken orally from December 13. From December 13 to 17, the patient was given the fourth course of gamma globulin (20 g/day). She left hospital on December 18.

In March 2013, after catching a cold, the patient experienced a paroxysmal memory decline. She often forgot that she did and even could not recognize the members of her families. With the progression of symptoms, she was hospitalized again on April 18. On April 22, the fifth lumbar puncture and CSF examination were done. CSF and blood were sent to the Peking Union Medical College Hospital again to check for NMDAR antibodies. NMDAR antibodies were positive in CSF and weakly positive in blood (1:20). From May 8 to 12, the patient was administered with the fifth course of gamma globulin (20 g/day). The EEG examination on May 9 revealed medium-diffused abnormalities.

Discussion

Encephalitis is an acute or chronic inflammatory disease of the central nervous system. Limbic encephalitis [1] is an inflammatory condition related to the hippocampus, amygdaloid, and insular cortex. Limbic encephalitis is subdivided into three categories depending on whether it is caused by viral infections, mediated by autoantibody, or concomitant to autoimmune diseases.

The exact etiology and mechanism of anti-NMDAR encephalitis is unknown. The disease is considered as an autoantibody-mediated, paraneoplastic form of limbic encephalitis. The tumor antigens are similar to the antigens expressed by the cells of nervous system. As a result, the antibodies attacking the tumor antigen could cause an inflammatory reaction in central nervous system, leading to the disease development [2]. The disease's long-term effects are caused by tumor indirectly. In 2005, Vitaliani et al. [3] discovered the presence of previously unknown antibodies in young female patients with benign teratoma. Subsequently, Dalmau [4] identified anti-NMDAR antibodies in serum and cerebrospinal fluid of patients with similar symptoms, and the detection of these antibodies became a basic approach in diagnostics of anti-NMDAR encephalitis.

The development of anti-NMDAR encephalitis usually follows five stages with distinctive clinical manifestations, although the boundaries between stages are not strict [5–9]: (1) Prodromal stage: at this stage, the symptoms are similar with usual cold or viral infections and include fever, headache, nausea, vomiting, and diarrhea for approximately 2 weeks. The symptoms of mental and behavioral abnormalities gradually develop at the same time; (2) Psychiatric symptom stage: this stage can easily be misdiagnosed as schizophrenia or short-term memory loss; (3) No reaction stage is characterized by performance which is dissociated and unresponsive, refusal to open the eyes, and the absence of response to painful stimuli and speaking. However, imitating of language and brain stem reflexes remains normal; (4) Excessive movement stage is associated with abnormal movements and dysfunctions of autonomic nervous system. Typical abnormal movements, which often persist, include abnormal movements of mouth, tongue, and face, dystonia, and dance-like movements. Autonomic dysfunctions are manifested as fever, tachycardia, bradycardia, excessive salivation, hypertension, hypotension, urinary incontinence, and erectile dysfunction; (5) Recovery stage is a gradual process with the opposite sequence of symptoms. With the autonomic function becoming stable, the patients wake up from coma, respiratory conditions and dystonia gradually improve, social behaviors and executive functions usually improved as well, and rehabilitation follows. Other manifestations of anti-NMDAR encephalitis may include central disorders of ventilator system and epilepsy.

Approximately half of the patients with anti-NMDAR encephalitis do not show abnormal signs on brain MRI. In the other half, abnormally high signals can be observed in T2 and FLAIR images in cerebellum, cortex, basal ganglia, brain stem, and spinal cord [4]. 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 [8]. Cerebrospinal fluid examination shows abnormalities, mainly in the form of nonspecific inflammatory reactions, in 80 % of patients at early stages [5]. Anti-NMDAR antibodies could be detected in serum and cerebrospinal fluid [10]. Most tumor markers are usually within the normal range.

The diagnosis of anti-NMDAR encephalitis has to be considered in patients aged less than 50 years, especially children, adolescents, and women, who show the signs of acute abnormal mental behaviors, posture and movement disorders (mainly abnormal movements of the mouth, face, and limbs), epilepsy, autonomic dysfunction, and ventilatory disorders. The MRI examination may produce normal results or abnormally high signals that briefly appear in the cerebral cortex, cerebellum, or medial temporal lobe. 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 [11] and anti-GABA receptor encephalitis [12]) should be excluded, and the presence of anti-NMDAR antibodies should be confirmed in the serum and cerebrospinal fluid. All patients should be examined for the presence of tumors, especially ovarian teratoma or testicular germ cell cancer.

The main treatments include tumor resection and immunotherapy. Currently, the corticosteroids, immunoglobulin for intravenous injection, and plasmapheresis are used as the first-line immunotherapy approaches. After tumor resection and immunotherapy, 80 % of patients have significant improvements in the symptoms. However, only 48 % of patients without tumors go into remission, the others still need to take the second-line immunotherapy treatment [10]. For the second-line therapy, rituximab, cyclophosphamide, or combination of these two drugs are used [13], and 65 % of patients experience significant relieve after the treatment.

Compared with other types of paraneoplastic encephalitis, the prognosis for anti-NMDAR encephalitis is better [14]. Dalmau [10] reported that approximately 75 % of patients recover completely or only with minor disabilities. The rest of the patients remain serious ill or die.

Our reported patient had the prodromal symptoms of headache and fever at the beginning. Eight days later, psychiatric symptoms have developed. After cerebrospinal fluid examination, she was diagnosed as encephalitis. The treatment with antiviral and anti-inflammatory drugs did not improve the psychiatric symptoms, which gradually got worse and culminated in epileptic seizure. During the active treatment, encephalitis linked to viral, bacterial, and parasitic infections or tuberculosis was excluded. Organic diseases were excluded by the first imaging examination. Eventually, anti-NMDAR encephalitis was considered, and

the anti-NMDAR antibodies were detected in cerebrospinal fluid and serum confirming the definite diagnosis.

After hormonal and gamma globulin treatments, the symptoms improved and discharged. After the discharge, the hormone doses were gradually reduced and then stopped. However, the disease relapsed and the patient went to hospital again. The second imaging examination revealed ovarian teratoma, and the laparoscopic cystectomy of left ovarian cysts was undertaken. Postoperative pathological examination confirmed the diagnosis of mature cystic teratoma in the left ovary. Hormone and gamma globulin treatments were undertaken continually after the surgery. The psychiatric symptoms of the patient gradually improved during the 1-year follow-up. However, the patient's memory remained affected.

Conclusion

Ovarian teratoma-related anti-NMDAR encephalitis is a rare disease with uncertain etiology and pathogenesis. The signs and symptoms are often nonspecific, which makes the diagnosis difficult. Definite diagnosis requires anti-NMDAR antibodies detection in cerebrospinal fluid and blood. Anti-NMDAR antibodies can be found well before the detection of tumor. The earliest possible detection of tumor, its surgical removal, and early immunotherapy allow to shorten the course of disease, improve the survival rates, and to limit the negative long-term consequences for the patients.

References

1. Seki, M., Suzuki, S., Suzuki, N., et al. (2011). Limbic encephalitis up to date. *Nippon Rinsho, 69*, 442–447.
2. Posner, J. B., & Dalmau, J. (1995). Clinical enigmas of paraneoplastic neurologic disorders. *Clinical Neurology and Neurosurgery, 97*, 61–70.
3. Vitaliani, R., Mason, W., Anees, B., et al. (2005). Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Annals of Neurology, 58*, 594–604.
4. Dalmau, J., Tfizfin, E., Wu, H. Y., et al. (2007). Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Annals of Neurology, 61*, 25–36.
5. Hughes, E. G., Peng, X., & Gleichman, A. J. (2010). Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *Journal of Neuroscience, 30*, 5866–5875.
6. Weiner, A. L., Vieira, L., McKay, C. A., et al. (2000). Ketamine abusers presenting to the emergency department: a case series. *Journal of Emergency Medicine, 18*, 447–451.
7. Stone, J. M., Morrison, P., & Pilowsky, L. S. (2007). Glutamate and dopamine dysregulation in schizophrenia—a synthesis and selective review. *Journal of Psychopharmacology, 21*, 440–452.
8. Iizuka, T., Sakai, F., Ide, T., et al. (2008). Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology, 70*, 504–511.
9. Dalmau, J., Gleichman, A. J., Hughes, E. G., et al. (2008). Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurology, 7*, 1091–1098.
10. Dalmau, J., Lancaster, E., Martinez-Hernandez, E., et al. (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurology, 10*, 63–74.
11. Lai, M., Hughes, E. G., Peng, X., et al. (2009). AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Annals of Neurology, 65*, 424–434.
12. Lancaster, E., Lai, M., Peng, X., et al. (2010). Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurology, 9*, 67–76.
13. Florance, N. R., Davis, R. L., Lam, C., et al. (2009). Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Annals of Neurology, 66*, 11–18.
14. Ishiura, H., Matsuda, S., Higashihara, M., et al. (2008). Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. *Neurology, 71*, 1921–1923.