Int J Clin Exp Pathol 2015;8(11):15474-15478
www.ijcep.com /ISSN:1936-2625/IJCEP0016950

Case Report

Anti-N-methyl-D-aspartate receptor encephalitis with occult ovarian teratoma: a case report

Shi-Xian Zhou, Yun-Mei Yang

Department of Geriatrics, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang, China

Received September 27, 2015; Accepted October 27, 2015; Epub November 1, 2015; Published November 15, 2015

Abstract: A 31-year-old female was admitted with headache, memory disturbance, abnormal behavior, incontinence, confusion, complex partial seizures, decreased oxygen saturation and increased temperature. Anti-NMDAR antibodies were positive in serum and cerebrospinal fluid. Subsequently, a regimen of immunotherapy that included intravenous immunoglobulins, methylprednisolone, plasma exchange and their combinations were used. But the treatment was ineffective. Though both transvaginal ultrasonography and abdominal CT scan contrast revealed left ovarian cyst, the patient had left oophorectomy. And during surgery we found a small cyst mass contained fat-like liquid with air in her left ovarian. Pathological examination demonstrated mature cystic teratoma accompanied with brain tissue. She has made gradual and steady improvement after surgery, but not fully recovery. By combining this case with previous studies of others, we further discuss the clinical characteristics, treatment and prognosis of the disease.

Keywords: Encephalitis, anti-n-methyl-m-aspartate receptor encephalitis, young women, ovarian teratoma, autoimmune

Introduction

Anti-N-methyl-M-aspartate receptor (NMDAR) encephalitis is an acute neuroautoimmune neurological disease. The disease was firstly classified as a paraneoplastic syndrome that primarily affects young women with ovarian teratoma [1]. Though the disease is increasingly recognized and it has been reported in males and females of all ages (from 8 months to 85 years old) [2, 3], it most commonly presents in young females of reproductive age. Anti-NMDAR encephalitis has also been diagnosed in patients who are suffered sex-cord stromal tumor, neuroendocrine tumor, teratoma of the mediastinum, small cell lung cancer or lymphoma [2, 4]. Even some patients who are not suffered tumors have been reported occurrence of the disease. Most reported patients with anti-NMDAR encephalitis are young women with ovarian teratoma.

The symptoms include psychotic encephalopathy, epilepsy movement and facial abnormalities, alterations of consciousness and central hypoventilation. The identification of anti-NMDAR antibodies is critical for the diagnosis of anti-NMDAR encephalitis as other clinical examination results are nonspecific. Early diagnosis of the disease is important.

We describe a 31-year old woman with anti-NMDAR encephalitis because of her clinical course and her cerebrospinal fluid and serum examination results. Treatment with the first-line therapy with intravenous immunoglobulins, methylprednisolone, plasma exchange and their combinations, the therapeutic effect is not obvious. By surgical exploration, a small ovarian teratoma was found and removed. The patient neurologic state gradually recovered after surgery. We also review the cases of anti-NMDAR encephalitis in young women that have been reported previously in the literature.

Case report

The patient is a 31-year-old female had a painless abortion. 5 days later, she complained of headache, accompanied by memory distur-

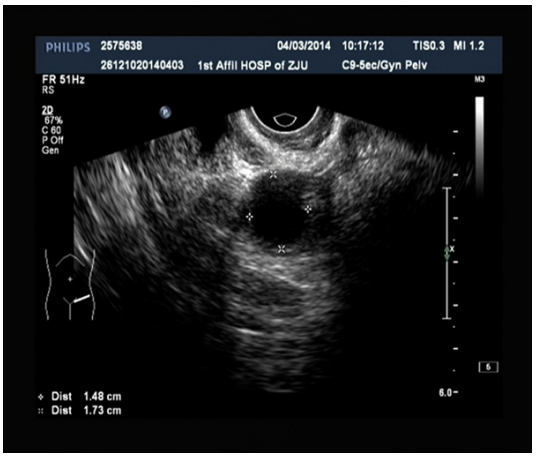

Figure 1. Transvaginal ultrasonography showed a cyst in the left ovary.

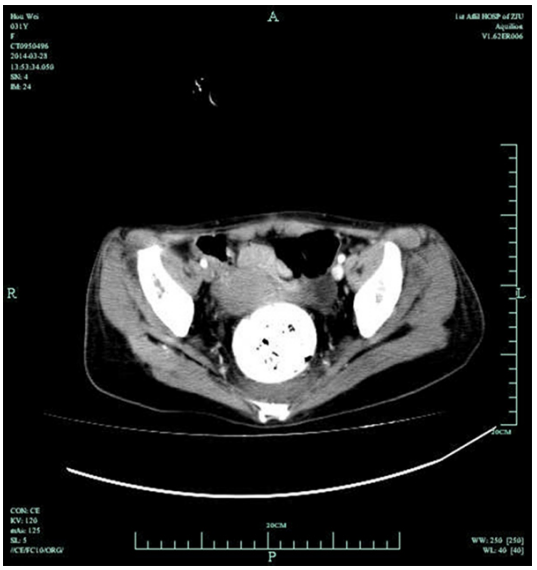

Figure 2. Abdominal contrast-enhanced CT scan showed the presence of a cyst in the left ovary, considering physiological cyst.

bance. Two days before admission, the families of the patient found she behaved abnormally, often talking to herself, laughing and cannot accurately answer questions. One day later, her shoulders shook violently but relieved after a few seconds. She began incontinence, and needed help to clean up. What is more, she became afraid of unfamiliar surroundings and has the eating problem.

When she was admitted to hospital, laboratory tests of antinuclear antibodies, extractable nuclear antigens (ENA) and other immunological parameters were normal. Polymerase chain reaction results of CSF and serum for herpes simplex virus, cytomegalovirus, Epstein-Barr were negative. Magnetic resonance imaging (MRI) of the brain was read as normal. Electroencephalography (EEG) showed diffuse slow waves, which revealed extensive damage to the cerebral cortex. A lumbar puncture was performed. Analysis of the cerebrospinal fluid showed mild lymphocytic pleocytosis (50/μl). Lymphocytic pleocytosis accounts for 60% of the total. There were also a protein of 0.26 g/L (normal: 0.15-0.45 g/L), and a glucose of 3.6 mmol/L (normal: 2.5-4.5 mmol/L). Treatments with acyclovir and Zyprexa were started for presumed viral encephalitis. However, the treatments have not improved her neurological states. Her state of confusion worsened. She demonstrated orofacial dyskinesias and involuntary movements of the four limbs. Immediately after, she became unconsciousness and had complex partial seizures repeated, accompanied by decreased oxygen saturation and increased temperature. Five days later, she was added endotracheal intubation and transferred to the Intensive Care Unit (ICU). In ICU, She continued receiving antiretroviral therapy. However the patient's condition has not improved. The frequency of attacks became higher and the lasting time of the attacks became longer. Cerebrospinal fluid was checked again and it showed a protein of 0.08 g/L, and glucose of 4.5 mmol/L, which was normal.

Combined with the patient's symptoms and signs, we strongly suspected anti-NMDA receptor encephalitis and conducted transvaginal ultrasonography and a contrast-enhanced abdominal CT scan (**Figure 2**), which all revealed left ovarian cyst. At the same time the NMDAR antibody were detected in the patient's serum and cerebrospinal fluid. NMDAR antibody titers were 1:10 (++) in serum, and 1:10 (+++) in cerebrospinal fluid. The presence of anti-NMDA receptor antibodies in the patient's cerebrospinal fluid and serum confirmed the suspected diagnosis of autoimmune encephalitis. A treatment with high-dose intravenous human immunoglobulin (400 mg/kg·d, 5 d), methylprednisolone (500 mg/d, 5 d), plasma exchange and their combinations were used. But the treatment is not satisfactory, the patient condition wasn't improved. Repeated transvaginal ultrasonography (**Figure 1**) and abdominal CT scan

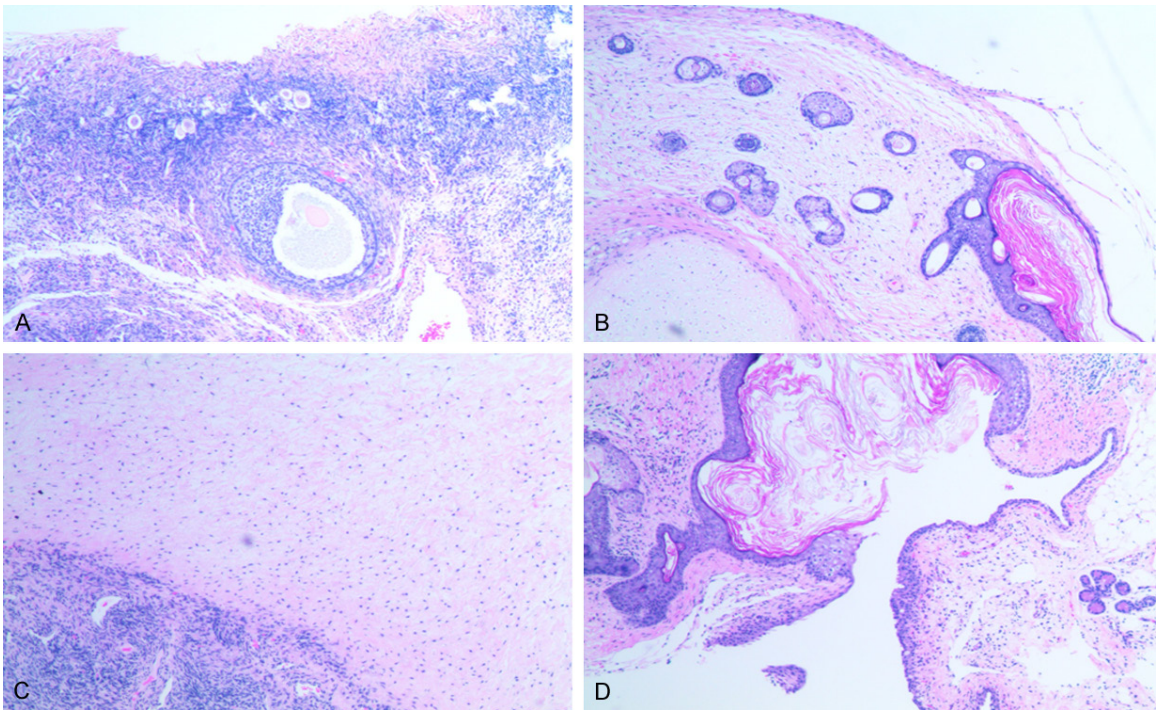

Figure 3. Pathological results: Ovarian tissue (A); Mature cystic teratoma accompanied with sweat glands (B), brain (C) and epithelium tissue (D).

(**Figure 2**) contrast revealed left ovarian cyst. Based on previous case report, post oophorectomy patient with negative imaging may have occult ovarian teratoma. Our patient had left oophorectomy, that during surgery we found a small cyst mass contained fat-like liquid with air in her left ovary. Pathological examination demonstrated mature cystic teratoma accompanied with brain tissue (**Figure 3**). She has made gradual and steady improvement after surgery. One year later; the patient was conscious and could obey simple orders such as to moving eyeball.

Discussion

Anti-NMDAR encephalitis is a serious yet treatable neuroautoimmune diseases first reported in 2007 by Dalmau et al. of the University of Pennsylvania [5]. The exact etiology and pathogenesis of anti-NMDAR encephalitis are still unclear. The latest study shows that the incidence of anti-NMDA receptor encephalitis may involve antibodies against NMDA receptor subunit GluN1 which exhausted NMDA receptor clusters of neurons, result in glutamate-mediated signal transduction dysfunction.

Most cases of anti-NMDA receptor antibody-positive encephalitis have been described in younger women with ovarian teratomas. However this case was interesting as it imaging examinations failed to find teratoma, but surgical exploration found the presence of ovarian teratoma.

Peery et al. described 4 different phases during an anti-NMDA receptor antibody-positive encephalitis: the prodromal phase, prodromal symptoms such as fever, headache, upper respiratory symptoms, vomiting, and diarrhea [4, 6, 7] were observed in 48-86% of patients within 2 weeks before hospital admission. It was followed by a period of psychiatric symptoms and/or seizure phase. Some patients develop drastic involuntary movements and spastic rigidity, and have high levels of creatine kinase [4, 8]. During the course of the disorder, most of patients have seizures, most commonly tonic-clonic seizures [4, 6]. After that, most patients develop an unresponsive phase and days or weeks later, autonomic instability often causes cardiac arrhythmia, hypotension, hypoventilation, and central hypoventilation, requiring intubation or pacemakers.

Results of traditional examinations including detections of CSF and serum, brain imaging, and EEG are nonspecific for anti-NMDAR encephalitis. The identification of anti-NMDAR antibodies is critical for the diagnosis of anti-NMDAR encephalitis, which positive will be basically confirmed. This is a case of 31-year-old female patient. Her serological examination showed no abnormalities and cerebrospinal fluid examination showed lymphocytosis, sugar chlorine protein normal. Cranial MRI examinations were normal. Diffuse slow waves were the main findings of EEG, which suggested that diffuse cortical damage. According to CSF, brain MRI and EEG results, she has been given antiviral treatment but her clinical course was more and more serious. The NMDAR antibodies were detected in the patient's serum and cerebrospinal fluid. The results in return confirmed the diagnosis of anti-NMDA receptor encephalitis. We started an early immunotherapy, but the patient condition was worse. Though both transvaginal ultrasonography and abdominal CT scan contrast only showed left ovarian cyst, we still suspected an occult ovarian teratoma. We decided an exploration surgery and the finding which had been confirmed pathologically met our expectation. After surgery she has made gradual and steady improvement, but she still requires long-term artificial respiratory management because of central hypoventilation.

Accumulating data suggest that tumor removal is a effective treatments for anti-NMDAR encephalitis. Dalmau et al. proposed that the tumor should be removed when present [9]. When tumor is not present, the first-line therapy with intravenous immunoglobulins, methylprednisolone and plasma exchange [10] can be used in sequence or in combinations. The second-line therapy with rituximab [11] (against CD-20 B-lymphocytes) or cyclophosphamide [12] can be performed when first-line therapy is invalid. Studies have shown that the patients with anti-NMDAR encephalitis who are unresponsive to first-line treatment, those who have received second-line treatment show better clinical results and lower recurrence rate than those who did not receive second-line treatment. Anti-NMDAR encephalitis is an immune-mediated neuronal dysfunction rather than irreversible degeneration, for the reason that it has a better prognosis after tumor resection and immunotherapy. Antibody levels are related to clinical outcomes. The level of anti-NMDAR antibodies in CSF and serum usually decreases when patients show substantial clinical recover [2, 4, 13, 14].

Anti-NMDA receptor encephalitis has been often mistaken as mental illness or viral encephalitis. The misdiagnosis has many causes, including the similarity of symptoms, such as fever, headache, vomiting, drowsiness, convulsions and even mental fatigue, as well as serum EB virus. In cases where the patients present with encephalitis of uncertain etiology, psychiatric symptoms, seizures, movement disorders, or psychosis, the clinician should consider anti-NMDA receptor encephalitis as possible diagnosis, especially if the patients were young females. At the same time we should actively looking for tumor and detecting anti-NMDA receptor antibodies as soon as possible. Studies have shown that early tumor resection could bring in better clinical outcomes [2, 15], particularly in the four months when the nervous system symptoms emerged [4]. Patients without tumors or lack of reaction to the first-line treatment, other treatments can be conducted, including rituximab and cyclophosphamide. By proper treatment, patients can slowly recover motor and cognitive function. The median duration of hospitalization is in the range of 2-2.5 months (range, 1-14 months) [4, 7]. Most patients can resume full or nearly full recovery. Recovery may take 2 years or longer, and not all the patients can return to their former levels of motor function and cognition [2, 4, 6, 16]. Thus, detection of anti-NMDAR antibodies for timely diagnosis, treatment and prognostic of patients has a very important significance.

Acknowledgements

The patient was admitted to the First Affiliated Hospital of Zhejiang University, where we treated her. We are deeply grateful to EUROIMMUN Medical Diagnostics (China) Co., Ltd, for helping us in the measurement of the levels of glutamate receptor antibodies. This study was supported by the National clinical key specialty construction project of geriatrics department and the key disciplines construction plan of Zhejiang province traditional Chinese Medicine (2012-XK-A20).

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Shi-Xian Zhou and Yun-Mei Yang, Department of Geriatrics, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang, China. Tel: +86-13567147276; E-mail: zhourexian@126.com (SXZ); yunmeiyang_0310@126.com (YMY)

References

[1] Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005; 58: 594-604.

[2] Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, Friese MA, Galea I, Kullmann DM, Beeson D, Lang B, Bien CG, Vincent A. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010; 133: 1655-67.

[3] Day GS, High SM, Cot B, Tang-Wai DF. Anti-NMDA-receptor encephalitis: case report and literature review of an under-recognized condition. J Gen Intern Med 2011; 26: 811-6.

[4] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008; 7: 1091-8.

[5] Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007; 61: 25-36.

[6] Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66: 11-8.

[7] Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, Dalmau J; Spanish Anti-N-methyl-D-Aspartate Receptor (NMDAR) Encephalitis Work Group. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013; 162: 850-856, e2.

[8] Turner MR, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: glycine and NMDA receptor antibodies. Neurology 2011; 77: 439-43.

[9] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10: 63-74.

[10] Pham HP, Daniel-Johnson JA, Stotler BA, Stephens H, Schwartz J. Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apher 2011; 26: 320-5.

[11] Ikeguchi R, Shibuya K, Akiyama S, Hino S, Kubo H, Takeda T, Shibata N, Yamamoto K. Rituximab used successfully in the treatment of anti-NMDA receptor encephalitis. Intern Med 2012; 51: 1585-9.

[12] Kashyape P, Taylor E, Ng J, Krishnakumar D, Kirkham F, Whitney A. Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with cyclophosphamide: the need for early aggressive immunotherapy in tumour negative paediatric patients. Eur J Paediatr Neurol 2012; 16: 74-8.

[13] Pruss H, Dalmau J, Harms L, Höltje M, Ahnert-Hilger G, Borowski K, Stoecker W, Wandinger KP. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010; 75: 1735-9.

[14] Seki M, Suzuki S, Iizuka T, Shimizu T, Nihei Y, Suzuki N, Dalmau J. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 2008; 79: 324-6.

[15] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10: 63-74.

[16] Gabilondo I, Saiz A, Galán L, González V, Jadraque R, Sabater L, Sans A, Sempere A, Vela A, Villalobos F, Viñals M, Villoslada P, Graus F. Analysis of relapses in anti-NMDAR encephalitis. Neurology 2011; 77: 996-9.