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Ovarian teratoma-associated anti-N-methyl-D-aspartate receptor encephalitis: a clinical analysis of 5 cases

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ABSTRACT

Objectives: To analyse the clinical features, diagnosis, treatment, and prognosis of anti-N-methyl-D-aspartic acid receptor (NMDAR) encephalitis associated with ovarian mature teratomas.

Material and methods: Retrospectively analysed the clinical-laboratory data of five patients with anti-NMDAR encephalitis combined with ovarian teratoma at a single centre between March 2016 and June 2019.

Results: The mean age of the patients was 22.40 ± 2.89 years (range, 19–26 years). Five patients had premonitory fever symptoms, clinical manifestations of mental disorder or convulsions for starting, with varying degrees of involuntary movement. Brain MRI and electroencephalography lacked specificity, and cerebrospinal fluid resistance NMDAR antibody detection was the key to diagnosis. All patients experienced good outcomes in response to immunotherapy combined with ovarian tumour resection, with a median follow-up time of 36 months (range, 16–55 months). The MRS value of five patients decreased significantly half a year after surgery, and no encephalitis or ovarian tumour relapses were reported.

Conclusions: Anti-NMDA encephalitis caused by ovarian teratoma is mostly a non-specific clinical manifestation of neurological and mental abnormalities, which can be easily misdiagnosed and delayed, and doctors should fully recognise the disease, early diagnosis, and timely surgical intervention to improve the prognosis of patients.

Key words: anti-N-methyl-D-aspartate receptor (NMDAR); autoimmune encephalitis; ovarian teratoma; tumour resection; retrospective study

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is autoimmune encephalitis mediated by anti-NMDAR antibodies, which is the most common autoimmune encephalitis; anti-NMDAR encephalitis was first described in 2005, and its autoantigens were discovered in 2007 in 12 female patients who had ovarian teratomas [1]. Anti-NMDAR encephalitis has a higher incidence among younger females (75%) and is associated with ovarian teratomas, and clinical symptoms can be significantly improved after tumour removal. However, clinicians often ignored it owing to the lack of specific clinical symptoms.

Objectives

In this paper, five cases of anti-NMDAR encephalitis with ovarian teratoma were collected, summarised, and analysed in combination with relevant articles at home and abroad in recent years to strengthen the understanding of clinicians on this disease, reduce unnecessary missed diagnosis and misdiagnosis, and try to diagnose and treat as early as possible, which is beneficial to improve the prognosis of patients.

MATERIAL AND METHODS

We retrospectively analysed clinical data retrieved from the medical records of five patients diagnosed with anti-NMDAR encephalitis combined with ovarian teratoma between March 2016 and June 2019 at The First Affiliated Hospital of Fujian Medical University; all patients met the three diagnostic criteria of anti-NMDAR encephalitis proposed by Graus et al. in 2016 [2]: (1) positive anti-NMDAR antibody in cerebrospinal fluid; (2) at least three or more of the following in acute or subacute onset: ① abnormal

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Table 1. Clinical features of the five patients

Cases	Age [years]	The first visited department	Interval between onset and diagnosis [day]	Prodromal symptom	Clinical symptom
1	19	Neurology	12	Fever, diarrhea	Self-talking, confusion, sluggish, epilepsy
2	21	Neurology t	11	Fever, headache	Self-talking, disorientation, emotional instability
3	24	Psychiatry	14	Fever, myalgia	Confusion, limb twitch, dyskinesia, self-talking
4	23	Psychiatry	16	Fever, dizziness	Self-talking, agitation disorientation, auditory hallucinations
5	26	Neurology	13	Fever, diarrhea	Hypersomnia, epilepsy, depression, global amnesia, auditory hallucinations

Table 2. Imageological and laboratory examination of five patients

Cases	Ovarian tumour		Brain MRI	EEG examination		CSF examination	NMDAR antibody	
	Site	Size [cm]		Before surgery	Two weeks after surgery		CSF	Blood
1	Bilateral	3.0 (left) 4.5 (right)	Sinus inflammation	Diffuse δ waves	Compound wave of spines and slow spines	Negative	1:32	1:10
2	Right	5.8	Hyperechoic image of the left frontal lobe in FLAIR	Diffuse δ waves	Negative	Increased glucose Pressure 260 mmH_2O	1:100	1:100
3	Right	4.5	Negative	Diffuse δ waves	Compound wave of spines and slow spines	Negative	1:100	1:10
4	Left	4.0	Negative	Negative	Negative	Negative	1:64	1:32
5	Bilateral	5.5 (left) 6.0 (right)	Hyperechoic signal in the right prefrontal lobe in FLAIR	Diffuse δ waves	Compound wave of spines and slow spines	Increased protein Pressure 280 mmH_2O	1:100	1:64

mental behaviour or cognitive impairment; ② speech disorders; ③ epileptic seizure; ④ involuntary movement or movement disorders; ⑤ decreased level of consciousness; ⑥ central ventilation disorder or autonomic nervous dysfunction; (3) exclusion of other causes of encephalitis; in this study, all five patients met the three diagnostic criteria of anti-NMDAR encephalitis, and mature ovarian teratoma was confirmed by gynaecological imaging and postoperative pathology during hospitalisation. The medical records, laboratory and imaging examinations, and surgical pathology reports of the five patients were retrospectively reviewed. Data obtained from medical records included age, symptoms, medical history, laboratory and imaging characteristics, treatment options, prognosis, and follow-up data.

RESULTS

Clinical features

The clinical characteristics of the five patients are described in Table 1. Patient ages ranged from 19 to 26 years (mean 22.40 ± 2.89 years) at the time of diagnosis. All five patients had a fever and other prodromal symptoms more than 10 days from onset to diagnosis. The clinical manifestations were non-specific, including self-talking, confusion, sluggish, epilepsy, disorientation, emotional instability, limb twitch, and hypersomnia.

Imaging and laboratory findings

All five patients had undergone Craniocerebral, pelvic MRI, EEG and cerebrospinal fluid examination during hospitalization. Craniocerebral MRI, CSF examination and EEG of the 5 patients showed no specific changes; serum and CSF anti-NMDAR antibody showed positive changes; pelvic MRI indicated unilateral or bilateral ovarian masses (diameter 3.0~6.0 cm) (Tab. 2).

Treatment and outcome

Laparoscopic teratoma resection was performed in five patients based on hormones, immunoglobulins, plasma exchange, and immunotherapy. Postoperative pathology revealed a mature cystic teratoma of the ovary with glial cells. The clinical symptoms significantly improved postoperatively (Tab. 3).

Follow up

All five patients provided follow-up data, and none were lost to follow-up. The duration of the follow-up period ranged from 16 to 55 months, with a median follow-up

Table 3. Treatment and prognosis of five patients

Cases	Artificial ventilation	Medical treatment	Interval between diagnosis and surgery [day]	Pathology	Follow-up [six months after surgery]	mRS Score*		
						Peak admission	Two weeks after surgery	Half a year after surgery
1	No	Corticosteroids, IVIG, rituximab, plasma exchange	31	Bilateral mature teratoma (with glial tissue)	Poor memory, emotional instability	5	4	3
2	Oropharyngeal airway	Corticosteroids, IVIG plasma exchange	37	Right mature teratoma (with glial tissue)	Sluggish, involuntary limb movements	4	3	2
3	Trachea cannula	Corticosteroids, IVIG Cyclophosphamide	9	Right mature teratoma (with glial tissue)	Slow reaction, slow speech, tinnitus	4	3	1
4	Orpharyngeal airway	Corticosteroids, IVIG, rituximab	12	Left mature teratoma (with glial tissue)	Slow response, memory loss	4	2	2
5	Trachea cannula	Corticosteroids, rituximab, IVIG, cyclophosphamide	15	Bilateral mature teratoma (with glial tissue)	Emotional instability, slow reaction	5	3	3

time of 36 months. Five patients recovered half a year after surgery, with a few remaining symptoms, and the score of the Modified Rankin Scale was improved. No recurrence of symptoms or tumours occurred in five patients after surgery (Tab. 3).

DISCUSSION

Autoimmune encephalitis (AE) is a type of encephalitis mediated by autoimmune antibodies, anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common autoimmune encephalitis [3], anti-NMDAR encephalitis was first described in 2005 [4] and its autoantigens were discovered in 2007 [5]. Patients often present with six main symptoms, including psychiatric symptoms or cognitive dysfunction, seizure, speech dysfunction, movement disorder, decreased level of consciousness, and autonomic dysfunction or central hypoventilation. Prodromal symptoms such as headache, fever, nausea, and upper respiratory tract symptoms are observed in many patients. In 2010, Irani et al. divided the disease process into two stages. In the early stages, patients often experience mental symptoms, cognitive dysfunction, and seizures. In the late stage, there are decreased levels of consciousness, movement disorders, and autonomic nervous dysfunction, often in young women aged 12–45 years, most of whom have ovarian teratomas. A study [6] showed that 220 patients with anti-NMDAR encephalitis with tumours, most of which were mature cystic teratomas, but not all patients with ovarian teratoma had encephalitis symptoms. Gong et al. [7] performed a serum anti-NMDAR antibody test on ovarian teratoma patients without encephalitis, and the results were negative. Anti-NMDAR antibodies pass through the blood-brain barrier and specifically bind to the GLUN1 subunit of NMDAR on neurones of the central nervous system, thereby causing damage to the brain tissue in the corresponding parts [8]. This group of five cases with cerebrospinal fluid and serum NMDAR antibodies were positive; postoperative pathology prompted ovarian mature cystic teratoma and contained glial tissue, presumably for ovarian teratoma glial tissue in stimulating antibodies generated as antibody targets at the same time, to promote a series of nervous and mental symptoms. The severity and prognosis of encephalitis are related to the titre and decreased level of anti-NMDAR antibodies in the cerebrospinal fluid [9].

Ovarian teratoma NMDAR encephalitis is a type of disease resistance caused by severe encephalitis [10], sudden onset and rapid development, a short period that can deteriorate into severe mental disorders, and central respiratory failure, life-threatening [11]. Thankfully, it is a curable encephalitis. If timely treated, 80% of patients can recover within half a year because NMDAR antibodies and receptors bind to antigenic determinant internalisation, to reduce the number of receptors, and this effect is reversible [12]. Therefore, early diagnosis and treatment are the key factors affecting prognosis [13]. However, owing to the young age of onset, lack of specificity of clinical symptoms, and lack of characteristic changes in craniocerebral MRI and EEG, the time from onset to diagnosis is often long. The interval time from onset to diagnosis of five patients was more than 10 days, and even two were admitted to the psychiatric department for antipsychotic drug treatment and were transferred to the department for treatment after no improvement. Therefore, all patients suspected of viral encephalitis and psychiatric diseases, especially young female

patients, should be alert to the possibility of this disease, actively check anti-NMDAR antibodies in the cerebrospinal fluid and serum, and perform tumour-related indicators such as gynaecological imaging and tumour markers to assist in early diagnosis.

Anti-NMDAR encephalitis caused by ovarian teratomas mainly consists of immunotherapy and tumour resection [14]. Immunotherapy aims to inhibit antibody production and reduce their impact on receptors [15]. Plasma exchange (PE), high-dose steroids (such as methylprednisolone), and intravenous immunoglobulin (IVIG) as first-line therapy improved clinical symptoms in 53–80% of patients. However, no systematic comparison of the three first-line immunotherapy options has been performed. A long-term follow-up study showed that patients treated with IVIG after PE had better outcomes than those who received IVIG prior to PE [16], and a recent study showed that the PE group showed greater improvement in clinical symptoms than the non-PE group at one month and two months following treatment [17]. Considering that plasmapheresis can quickly remove autoantibodies and accelerate the improvement of patient symptoms, its early use is a better treatment option [18]. Second-line immunotherapy, such as rituximab and cyclophosphamide, can improve the prognosis of patients with unsatisfactory first-line treatment, while long-term immunotherapy, such as mecofenate, azathioprine, bortezomib, and tocilizumab are mostly used for patients with tumour-negative and recurrent cases. Although major patients respond well to immunotherapy, the response to first-line immunotherapy is often slow, and the blood-brain barrier may affect the efficacy of PE or IVIG. Further research is required to identify more effective therapies [15]. In young women, anti-NMDAR encephalitis is often associated with ovarian teratoma, and the frequency of tumours is higher than that in children and males. For female patients with clinically confirmed anti-NMDAR encephalitis, ultrasound, MRI and CT scans should be actively performed to screen for potential ovarian tumours, and tumour resection, such as adnexectomy or ovarian tumour excision, should be performed as soon as possible.

Seki et al. [19] found that when tumours were removed as early as possible in the early stages of the disease, the time of insufficient ventilation and involuntary movement was significantly shortened. Clinically, patients are in a serious condition, often accompanied by coma and ventilation dysfunction, and the risks of anaesthesia and surgery are high. However, surgery should be performed as soon as possible after the patient's condition is stable. In this study, two patients were in a coma for more than 10 days, but their symptoms did not improve after applying PE, IVIG, and high-dose steroid immunotherapy. Ovarian tumour resection was performed on the 15th and 13th days of coma, and the patient was awake on the 3rd or 4th days post-surgery. Tumour resection was a favourable prognostic factor, and the postoperative MRS score decreased significantly. Reports that invisibility teratoma of encephalitis patients wasn't found on the imaging , but was found after ovarian biopsy [20] or during follow-up [21]. Even reported recurrence of encephalitis symptoms after recurrence of ovarian teratomas, which is related to the reactivation of anti-NMDAR antibody in the teratomas [21]. Therefore, expert consensus recommends pelvic imaging examination every six months to a year after the onset of disease and follow-up for at least four years [14] for female patients older than 12 years with anti-NMDAR encephalitis and no clinical ovarian tumour. Tumour resection should be performed as soon as possible after an ovarian tumour is detected. In this group, the symptoms of five patients were significantly relieved after surgery, and three patients had no postoperative convulsions. All of them became clear within four days after surgery, and no recurrence of ovarian tumour and encephalitis symptoms were found during follow-up.

CONCLUSIONS

In summary, teratoma-associated anti-NMDAR encephalitis of the ovary is a curable disease with a sudden onset, rapid progression, and recurrence. In young women with uninduced mental symptoms, epileptic seizures, movement disorders, memory loss, and other clinical symptoms, clinicians should consider the possibility of this disease, conduct serum and cerebrospinal fluid anti-NMDAR antibody detection as early as possible, screen tumours, and actively conduct immunotherapy while removing tumours as early as possible**,** which is beneficial for improving clinical prognosis.

Author contribution statement

All authors contributed to the study conceptionand design. LiDan He and Xia Zhang collected and analyzed the patients medical data. LiDan He wrote and revised the manuscript. JianBo Wu critically evised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability statement

Data included in article/supplementary material/referenced inarticle.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Acién P, Acién M, Ruiz-Maciá E, et al. Ovarian teratoma-associated anti-NMDAR encephalitis: a systematic review of reported cases. Orphanet J Rare Dis. 2014; 9: 157, doi: 10.1186/s13023-014-0157-x, indexed in Pubmed: 25312434.
2. Gresa-Arribas N, Planagumà J, Petit-Pedrol M, et al. Human neurexin-3α antibodies associate with encephalitis and alter synapse development. Neurology. 2016; 86(24): 2235–2242, doi: 10.1212/wnl.0000000000002775, indexed in Pubmed: 27170573.
3. Dalmau J, Graus F. AntibodymMediated encephalitis. N Engl J Med. 2018; 378(9): 840–851, doi: 10.1056/nejmra1708712, indexed in Pubmed: 29490181.
4. Vitaliani R, Mason W, Ances B, et al. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol. 2005; 58(4): 594–604, doi: 10.1002/ana.20614, indexed in Pubmed: 16178029.
5. Dalmau J, Tüzün E, Wu Hy, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007; 61(1): 25–36, doi: 10.1002/ana.21050, indexed in Pubmed: 17262855.
6. Titulaer M, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12(2): 157–165, doi: 10.1016/s1474-4422(12)70310-1.
7. Gong S, Zhou M, Shi G, et al. Absence of NMDA receptor antibodies in patients with ovarian teratoma without encephalitis. Neurol Neuroimmunol Neuroinflamm. 2017; 4(3): e344, doi: 10.1212/NXI.0000000000000344, indexed in Pubmed: 28439526.
8. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011; 10(1): 63–74, doi: 10.1016/s1474-4422(10)70253-2, indexed in Pubmed: 21163445.
9. Thomas A, Rauschkolb P, Gresa-Arribas N, et al. Anti-N-methyl-D-aspartate receptor encephalitis: a patient with refractory illness after 25 months of intensive immunotherapy. JAMA Neurol. 2013; 70(12): 1566–1568, doi: 10.1001/jamaneurol.2013.3205, indexed in Pubmed: 24166348.
10. Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019; 18(11): 1045–1057, doi: 10.1016/s1474-4422(19)30244-3.
11. Zhang Le, Wu MQ, Hao ZL, et al. Clinical characteristics, treatments, and outcomes of patients with anti-N-methyl-d-aspartate receptor encephalitis: A systematic review of reported cases. Epilepsy Behav. 2017; 68: 57–65, doi: 10.1016/j.yebeh.2016.12.019, indexed in Pubmed: 28109991.
12. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci. 2010; 30(17): 5866–5875, doi: 10.1523/JNEUROSCI.0167-10.2010, indexed in Pubmed: 20427647.
13. Barry H, Byrne S, Barrett E, et al. Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. BJPsych Bull. 2015; 39(1): 19–23, doi: 10.1192/pb.bp.113.045518, indexed in Pubmed: 26191419.
14. Graus F, Titulaer M, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016; 15(4): 391–404, doi: 10.1016/s1474-4422(15)00401-9, indexed in Pubmed: 26906964.
15. Tanguturi YC, Cundiff AW, Fuchs C. Anti-N-Methyl d-Aspartate receptor encephalitis and electroconvulsive therapy: literature review and future directions. Child Adolesc Psychiatr Clin N Am. 2019; 28(1): 79–89, doi: 10.1016/j.chc.2018.07.005, indexed in Pubmed: 30389078.
16. Pham HP, Daniel-Johnson JA, Stotler BA, et al. Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apher. 2011; 26(6): 320–325, doi: 10.1002/jca.20311, indexed in Pubmed: 21898576.
17. Zhang Y, Liu G, Jiang M, et al. Efficacy of therapeutic plasma exchange in patients with severe refractory anti-nmda receptor encephalitis. Neurotherapeutics. 2019; 16(3): 828–837, doi: 10.1007/s13311-019-00725-4, indexed in Pubmed: 30868469.
18. Titulaer M, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12(2): 157–165, doi: 10.1016/s1474-4422(12)70310-1, indexed in Pubmed: 23290630.
19. Seki M, Suzuki S, Iizuka T, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry. 2008; 79(3): 324–326, doi: 10.1136/jnnp.2007.136473, indexed in Pubmed: 18032452.
20. Peery HE, Day GS, Doja A, et al. Anti-NMDA receptor encephalitis in children: the disorder, its diagnosis, and treatment. Handb Clin Neurol. 2013; 112: 1229–1233, doi: 10.1016/B978-0-444-52910-7.00045-3, indexed in Pubmed: 23622333.
21. Mitra AD, Afify A. Ovarian teratoma associated Anti-N-methyl-D-aspartate receptor encephalitis: a difficult diagnosis with a favorable prognosis. Autops Case Rep. 2018; 8(2): e2018019, doi: 10.4322/acr.2018.019, indexed in Pubmed: 29780755.