GYNECOLOGY

Surgical outcomes in patients with anti-N-methyl D-aspartate receptor encephalitis with ovarian teratoma

Yi Dai, MD; Junji Zhang, MD; Haitao Ren, MBBS; Xingnan Zhou, MD; Juan Chen, MD, PhD; Liying Cui, MD; Jinghe Lang, MD; Hongzhi Guan, MD[1]; Dawei Sun, MD[1]

BACKGROUND: Anti—N-methyl-D-aspartate receptor encephalitis is an autoimmune encephalitis mediated by anti—N-methyl-D-aspartate receptor antibodies. Ovarian teratoma is closely related to anti—N-methyl-D-aspartate receptor encephalitis. However, the optimal treatment remains unknown, and strategies used for the diagnosis and therapy, including surgical intervention of ovarian teratoma, are debatable.

OBJECTIVE: The objective of the study was to study the clinical features of anti—N-methyl-D-aspartate receptor encephalitis with ovarian teratoma to further understand the disease.

STUDY DESIGN: This single-center prospective study included patients with anti-NMDAR encephalitis with ovarian teratoma from 2011 to 2016 who were admitted to Peking Union Medical College Hospital, Beijing, and discussed the clinical characteristics, treatment, and prognosis of the disease. The diagnosis of anti—N-methyl-D-aspartate receptor encephalitis was established preoperatively by identifying anti—N-methyl-D-aspartate receptor antibodies in the cerebrospinal fluid. Ovarian teratomas were suspected preoperatively by pelvic ultrasound and were diagnosed pathologically after laparoscopic detection and ovarian tumor resection. All patients were treated with first-line immunotherapy (steroids, intravenous immunoglobulin, and plasmapheresis), and when the therapy failed, they were treated with second-line immunotherapy (cyclophosphamide and rituximab). All patients were followed up regularly, and N-methyl-D-aspartate receptor antibodies, pelvic ultrasound, and neurological condition were monitored. Neurological symptoms were assessed using the modified Rankin Scale.

RESULTS: A total of 108 female patients with anti—N-methyl-D-aspartate receptor encephalitis were screened, of whom, 29 patients (26.9% of 108; mean age ± SD, 23.14 ± 6.59 years) had pathologically confirmed ovarian teratoma. The incidence of fever, decreased consciousness, arrhythmia, central hypoventilation, ventilator-assisted respiration, and intensive unit care (75.9%, 65.5%, 27.6%, 55.2%, 55.2%, and 58.6%, respectively) were significantly higher in patients with ovarian teratoma than in those without ovarian teratoma. The modified Rankin Scale at the acute onset in those 29 patients was 4.11 ± 1.20, which was also much higher than that in patients without ovarian teratoma (3.58 ± 1.08). Of the 29 patients with ovarian teratoma, 22 (75.9%) underwent laparoscopy during the acute onset of neurological symptoms. The mean diameter of the tumor was 4.61 ± 3.41 cm (SD), and the smallest tumor was only 1 cm in the unilateral ovary. All other cysts, except 4 bilateral cysts (13.8%), were unilateral. Only 1 patient was diagnosed pathologically with immature ovarian teratoma, while others had benign ovarian teratomas. In all, 28 patients (96.5%) had a good outcome (modified Rankin Scale ≤2) and 1 died. In the follow-up visit (mean duration, 37.69 months), the relapse rate of encephalitis in patients with ovarian teratoma undergoing laparoscopic cystectomy was 14.6%, whereas for those without ovarian teratoma, the relapse rate was 33.3%. The removal of ovarian teratoma was associated with reduced risk of relapse.

CONCLUSION: Patients having anti—N-methyl-D-aspartate receptor encephalitis with ovarian teratomas tend to present more severe neurological conditions. The diameter of the tumor in these patients is not very large and could be as small as 1 cm, and thus, careful exploration should be considered during surgery. Most of the ovarian teratomas in patients with anti—N-methyl-D-aspartate receptor encephalitis are mature. Early operative treatment is safe and effective because it is associated with reduced risk of relapse and complete recovery.

Key words: cerebrospinal fluid, diagnosis, female, laparoscopy, psychotic disorders, tumor resection

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was firstly identified by Dalmau et al[1] in 2007, and it is recognized as an autoimmune neurological disease that presents with acute to subacute psychiatric and/or neurological complaints. The disease is marked by new-onset behavioral changes that, at later stages, may develop into psychosis and catatonia, cognitive decline, seizures, progressive encephalopathy, and/or movement disorders, and automatic dysfunction including hypoventilation in severe cases.[2]

Anti-NMDAR encephalitis is the major component of autoimmune encephalitis. Ovarian teratoma is associated with anti-NMDAR encephalitis in female teens and adults because ovarian teratoma was reported as an underlying etiology in these anti-NMDAR patients, but most gynecologists do not identify the associated neoplasm.[3,4] Moreover, the strategies used for the diagnosis and therapy are debatable.

Peking Union Medical College Hospital (PUMCH) (Beijing, China) has become a referral center for this disease in China for detection of anti-NMDAR antibodies[4–11] because it was was the first to report laparoscopic ovarian tumor removal for encephalitis with ovarian teratoma in China in 2014.[12] Since then, an increasing number of patients from all over the country have been hospitalized in PUMCH. We studied the clinical features of anti-NMDAR encephalitis with ovarian teratoma in a

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AJOG at a Glance

Why was this study conducted?

With an aim to improve the understanding of the disease, this study determined the clinical features of anti−N-methyl-D-aspartate receptor encephalitis with ovarian teratoma.

Key findings

Patients with ovarian teratoma had more severe neurological conditions and higher modified Rankin Scale scores than those without ovarian teratoma.

What does this add to what is known?

Early removal of ovarian teratoma is safe and effective because it is associated with reduced risk of relapse and complete recovery.

prospective cohort of 29 patients to evaluate the clinical features associated with the disease, treatment strategies, and prognosis.

Materials and Methods

Patients and methods

Patients with anti-NMDAR encephalitis were prospectively recruited between June 2011 and May 2016.

The inclusion criteria were as follows: (1) acute onset of 1 or more of the 8 major groups of manifestations such as psychosis, memory deficit, speech disturbance, seizures, movement disorder, loss of consciousness, autonomic dysfunction, and central hypoventilation; and (2) cerebrospinal fluid (CSF) samples tested positive for NMDAR antibodies in cell-based assay (Euroimmun AG, Lübeck, Germany). Patients with other disorders were excluded.

All patients fulfilled the diagnostic criteria suggested by Graus et al.[13] The presence of NMDAR-immunoglobulin in CSF or serum samples was evaluated using a clinically validated, fixed cell−based indirect immunofluorescence test using BIOCHIPS (Euroimmun AG). The CSF samples were tested undiluted, whereas serum samples were diluted in a 1:10 ratio.

The enrolled patients underwent brain magnetic resonance imaging (MRI), electroencephalogram, and CSF examinations. All the patients were diagnosed and treated first by neurologists and were screened for systemic tumors. The patient data were recorded in detail in compliance with the protocol, including neurological and gynecological symptoms, physical signs, and laboratory exams before and after surgery.

The details recorded included co-occurrence of fever, headache, and arrhythmia; intensive care unit (ICU) admission; and other atypical symptoms. Demographic details such as age at onset of neurological symptoms, gender, disease course, and ancillary tests results including CSF tests results, brain MRI, and electroencephalography were also recorded.

The neurological status of the enrolled patients was evaluated using the modified Rankin Scale (mRS). The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is an established scale and has been used in previous studies on anti-NMDAR encephalitis for outcome and response measurement.[14,15]

Clinical improvement (good response) was defined as a decrease in the mRs $\geq$1 from that at the previous visit; a poor response was defined as no improvement in the mRS or as a mRS $\geq$4 for 4 weeks. Outcome was considered good with an mRS score of 0−2. Relapse of encephalitis was defined as the new onset or worsening of previous symptoms (mRS score increase $\geq$1) occurring after at least 2 months of improvement or stabilization.

This study protocol was approved by the Institutional Review Board of PUMCH (institutional review board number JS-890, ZS-1701). Written informed consent was obtained from all patients or their legal surrogate in accordance with the Declaration of Helsinki.

Gynecology evaluation and treatment

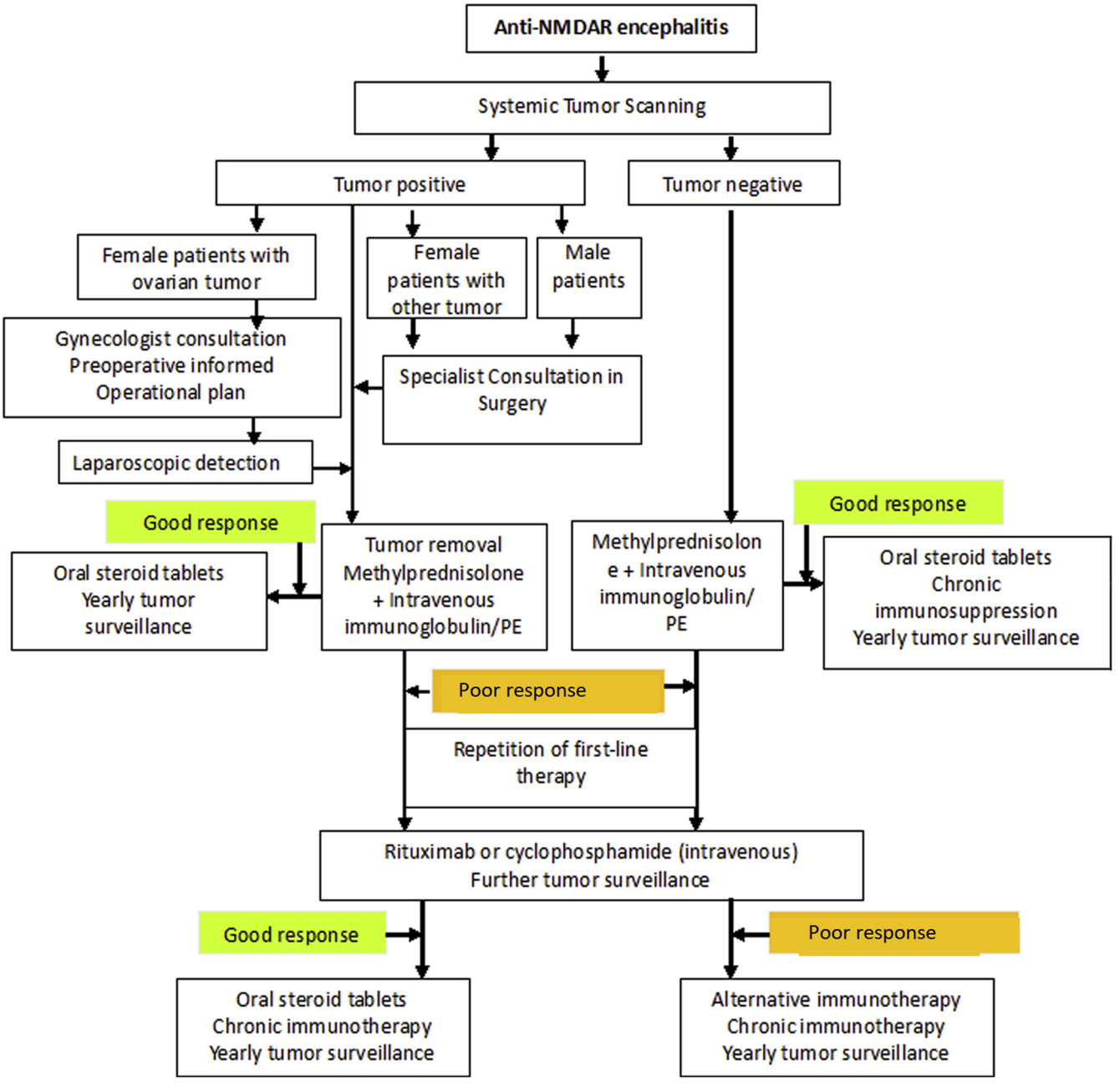
All patients underwent pelvic ultrasound for detection of uterine and/or ovarian tumor. Laparoscopic detection and cystectomy were performed in patients with suspected ovarian teratoma as shown by ultrasound. The decision to perform laparoscopic detection was made jointly by the neurologists and gynecologists. Because of the risks to patient fertility, informed surgical consent was obtained from all patients or their authorized representatives before surgery. Operative findings were recorded in detail.

Neurological treatment

Patients received combined immunotherapy, both before and after surgery. The treatment included first-line immunotherapy (steroids, intravenous immunoglobulin [IVIg], and plasmapheresis alone or combined). IVIg was administered at 20−25 g once daily for 4−5 days in 2−4 cycles. The observation period was 10−14 days. During IVIg infusion, allergy symptoms and thrombus were monitored along with blood glucose level and liver and kidney functions. The IVIg treatment was discontinued in the patients who developed adverse reactions such as erythema.

Pulse steroids therapy was administered with methylprednisolone (1 g for 5 days) and was gradually reduced to prednisolone at 60−80 mg/d. A gastric mucosal protective agent was used to prevent peptic ulceration or bleeding. Intravenous vitamin D and calcium supplements were provided to prevent osteoporosis. Additionally, adverse reactions to long-term treatment with large hormone doses such as Cushing's syndrome, edema, hypertension, and diabetes mellitus were monitored. When first-line therapy failed, the patients received second-line immunotherapy (rituximab and/or cyclophosphamide).

FIGURE 1
Treatment of anti-NMDAR encephalitis



The retrial of first-line therapy is an option in patients with little or no response to the initial immunotherapy. Chronic immunosuppression was mycophenolate mofetil or azathioprine for 1 year.

NMDAR, N-methyl-D-aspartate receptor; *IVIg*, intravenous immunoglobulin; *PE*, plasma exchange.

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The therapy plans were made by a neurologist. The treatment algorithm is given in Figure 1.

Follow-up

Patients were followed up at regular intervals (3, 6, 9, 12, 15, 18, and 24 months) after the disappearance of symptoms and discharge. Scoring for every symptom and the laboratory tests were included in the follow-up visit. Relapse of encephalitis was defined as the new onset or worsening of symptoms (mRS score increase $\geq$1) occurring after at least 2 months of improvement or stabilization.

Statistical analysis

Statistical Package for the Social Sciences version 20.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Baseline

FIGURE 2
Overall nonrelapse analysis in patients with and without ovarian teratoma

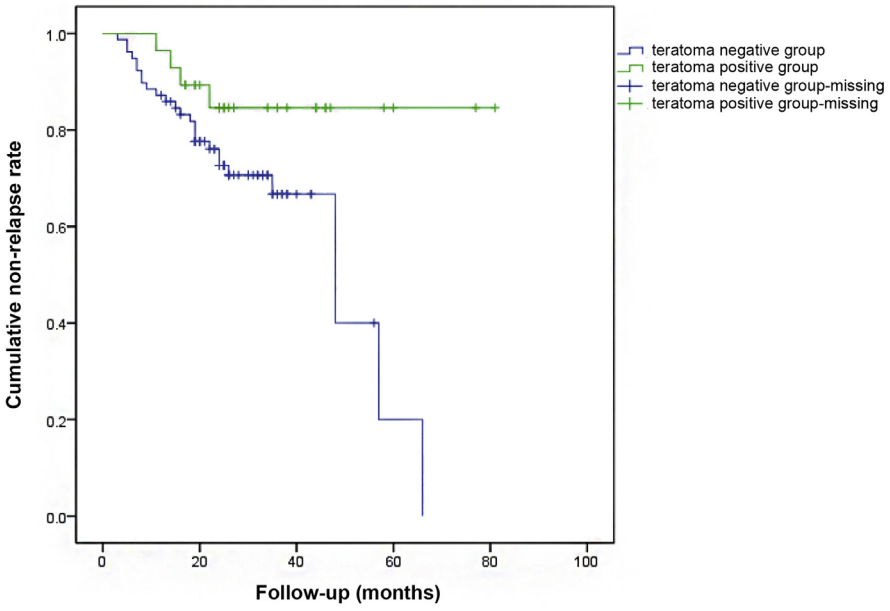

Figure shows the Kaplan-Meier plot for overall nonrelapse analysis in patients with ovarian teratoma removal and those without ovarian teratoma.

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parameters were presented using descriptive statistics. For categorical variables, we used Pearson's χ^2 test or Fisher exact test as appropriate, and for continuous variables, an independent-sample t test or the Wilcoxon signed rank test as appropriate was used.

One-way analysis of variance analysis was used to compare continuous variables across groups, and linear regression and binary logistic regression were used to control multiple confounders. Kaplan-Meier analysis was used to compare the relapse rates in the 2 groups at the follow-up visits. Statistical significance was set at $P < .05$.

Results

A total of 108 female patients were diagnosed with anti-NMDAR encephalitis from 2011 to 2016. After pelvic ultrasound, ovarian cysts suspected as ovarian teratomas were found in 31 patients. All patients underwent laparoscopic detection. Ovarian teratoma was confirmed by pathological diagnosis in 29 patients (26.9%). In 76 patients aged ≥18 years, 23 (30.3%) had ovarian teratoma, among 18 patients aged ≥14 to <18 years, 2 (11.1%) had ovarian teratoma, whereas in 14 patients aged <14 years, 4 (28.6%) had ovarian teratoma ($P = .254$).

Clinical features of anti-NMDAR encephalitis with ovarian teratoma

The mean age of patients was 23.14 ± 6.59 years, with the youngest patient being only 10 years old (prepuberty) and the oldest patient was 36 years old. A comparison of the general characteristics in the patients with anti-NMDAR encephalitis with ovarian teratoma and those without ovarian teratoma is presented in Table 1.

There was no significant difference in age, height, age of menarche, gravidity or parity, history of travel, animal contact, or infection between patients with anti-NMDAR encephalitis having ovarian teratoma and those without ovarian teratoma (Table 1). However, in their medical history, the patients with ovarian teratomas tended to have a more complicated history of gynecological surgery. Three patients had prior laparoscopy for ovarian teratoma, and 1 patient had a family history of teratoma (Table 1). None of the patients with ovarian teratoma had lower abdominal pain before onset, and none experienced acute torsion of ovarian teratoma.

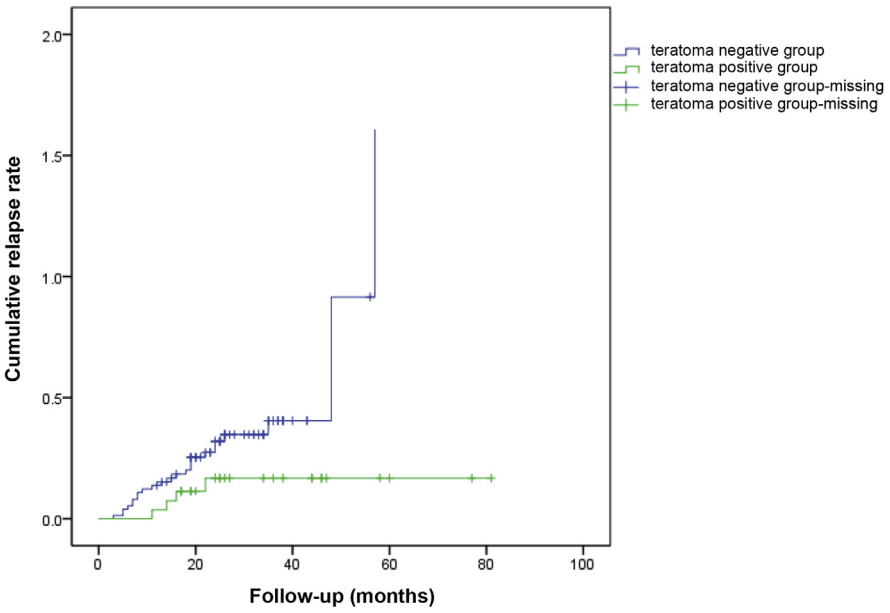
Table 2 lists all the neurological details of the patients having anti-NMDAR encephalitis with and without ovarian teratomas. The incidence of fever, decreased consciousness, arrhythmia, central hypoventilation, ventilator-assisted respiration, and ICU admission (75.9%, 65.5%,27.6%, 55.2%, 55.2%, and 58.6%, respectively) in patients with ovarian teratoma were significantly higher than those in patients without ovarian teratoma. Additionally, the mRS score at acute onset in patients with ovarian teratoma was 4.11 ± 1.20, which was also higher than that in patients without ovarian teratoma (3.58 ± 1.08).

Laboratory tests and findings during laparoscopic detection of the 29 patients

We detected serum cancer antigen 125, carbohydrate antigen 19-9, and serum alpha-protein and found the average level of carbohydrate antigen 19-9 to be higher than the normal range (Table 3). The diameter of the ovarian cyst ranged from 1 to 12 cm (Table 3). The majority of cysts were unilateral: 12 (41.4%) on the left side and 13 (44.8%) on the right side. Only 4 cysts (13.8%) were bilateral.

The pathological examination showed the presence of mature cystic ovarian teratomas in 28 patients and grade 1 immature ovarian teratoma in 1 patient who was followed up regularly by a gynecologist, and the patient experienced no relapse of the ovarian cyst. Neural tissue was detected by histochemical staining in 3 cases (10.3%). Of the 29 patients, 22 (75.9%) underwent laparoscopy during the acute onset of neurological

FIGURE 3
Relapse rate in patients with and without ovarian teratoma removal



Kaplan-Meier plot for analysis of cumulative relapse rate in patients with ovarian teratoma removal and those without ovarian teratoma is shown.

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symptoms, including 16 patients with severe central hypoventilation requiring ventilator-assisted breathing; 3 (10.3%) patients received laparoscopy after neurological symptoms were relieved; and 4 (13.8%) patients underwent laparoscopic teratoma removal after the first recurrence of symptoms. The latter 4 patients did not agree for tumor removal at the initial treatment in other hospitals. After recurrence, they were admitted in the PUMCH. All surgeries were performed successfully and safely with no postsurgical complications.

After laparoscopic resection, the patients continued neurological therapy. Only 1 patient died because of severe infection and respiration failure because of prolonged seizures. This patient had been treated in 2 different hospitals before admitting to the PUMCH. The death rates in patients with ovarian teratoma and those without ovarian teratoma were 3.4% and 1.3%, respectively. Table 3 presents the gynecological characteristics and findings of laparoscopic examination of the patients with ovarian teratoma.

Follow-up and relapse

The details collected at the follow-up visit included mRS score, detailed neurological symptoms, physical examination, medication, anti-NMDAR laboratory test, and pelvic ultrasound. The average follow-up time of 106 patients was 37.69 ± 12.04 months (range, 12−81 months).

Among 29 patients with ovarian teratoma, 28 patients (96.6%) reported a good outcome (mRS score ≤2) and 1 patient died. Among 78 patients without ovarian teratoma, 98.7% had a good outcome (mRS score ≤2; 1 death). One death was reported in both groups. The death rate in the 2 groups had no statistical significance. Other than the patients who died, only 4 of 28 patients with ovarian teratoma (14.3%) and 26 without ovarian teratoma (33.3% of 78) experienced relapse of neurological symptoms ($P = .043$ with the Fisher exact test and $P = 0.055$ with Pearson's χ^2 test). The odds ratio for risk of relapse in the ovarian teratoma group was 0.333 (95% confidence interval, 0.105−1.062).

Ovarian teratoma removal was associated with reduced risk of relapse. Figure 2 presents the Kaplan-Meier plot for good prognosis and Figure 3 shows relapse (%) for the 2 groups. The mean time to relapse was 71.39 ± 4.463 months in patients with ovarian teratoma and 43.001 ± 3.401 months in patients without teratoma (log rank test, $P = .019$).

The gynecological follow-up did not observe ovarian cyst relapse in 29 patients. Furthermore, 2 patients with ovarian teratoma who underwent tumor removal became pregnant after recovery, including 1 patient with immature ovarian teratoma. The patient with immature teratoma delivered at term, and no relapse of neurological symptom or ovarian cyst was observed during the follow-up. No significant change in menstrual function was observed during the follow-up visit in patients who were not pregnant.

Comment

Principal findings

This study observed that ovarian teratomas present in patients with anti-NMDAR encephalitis are mostly mature, with a tumor diameter ranging from 1 to 12 cm. Furthermore, the neurological symptoms were more severe in patients with anti-NMDAR encephalitis and ovarian teratomas than in those without ovarian teratoma. Interestingly, tumor removal was associated with reduced risk of relapse and improvement of long-term prognosis in these patients.

Incidence of ovarian teratoma among female patients with anti-NMDAR encephalitis

Among 108 female patients with anti-NMDAR encephalitis admitted to the PUMCH from 2011 to 2016, only 29 patients had anti-NMDAR encephalitis complicated by ovarian teratoma as confirmed by pathological tests (incidence rate, 26.9%). Dr Dalmau reported that 11 of 12 female patients had concomitant ovarian teratoma and

TABLE 1
General characteristics in the patients with anti-NMDAR encephalitis with ovarian teratoma and those without ovarian teratoma

Parameters	Anti-NMDAR encephalitis with ovarian teratoma (n = 29)	Anti-NMDAR encephalitis without ovarian teratoma (n = 79)	*P* value
Age, y	23.14 ± 6.59 (range, 10–36)	23.51 ± 12.56 (range, 5–72)	.881
Height, cm, mean ± SD	162.75 ± 6.23	164.50 ± 4.80	.596
Age at menarche, y, mean ± SD	13.04 ± 1.10	13.48 ± 0.90	.049
Gravidarum, mean ± SD	0.75 ± 0.32	1.13 ± 0.59	.125
Pravida, mean ± SD	0.32 ± 0.14	0.55 ± 0.12	.475
History of mental behavior disorder, n, %	1 (3.4)	2 (2.6)	1.000
Travel history, n, %	0 (0)	1 (1.3)	.633
Animal touch, n, %	0 (0)	3 (3.8)	.387
Infection history, n, %	1 (3.4)	3 (3.8)	.387
Medical history of ovarian surgery	3 (10.34) cystectomy for ovarian teratoma in different lateral, 1 (3.4) unilateral oophorectomy for ovarian teratoma	0 (0)	.004
Medical history of other gynecology surgery, n, %	1 (3.4) cesarean delivery	1 (1.3) myomectomy, 1 (1.3) cesarean delivery	1.000
Other medical history, n, %	None	1 (1.3) appendectomy, 1 (1.3) lung cystectomy, 1 (1.3) of thyroiditis, 1 (1.3) Kawasaki's disease	.562
Family history of ovarian teratoma, n, %	1 (3.4)	0 (0)	.269

NMDAR, N-methyl-D-aspartate receptor.
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Titulaer et al[16] observed that the incidence of ovarian teratoma was 44.2% among women with anti-NMDAR encephalitis.[1]

In a study conducted by Florance et al,[17] the frequency of ovarian teratoma in patients with anti-NMDAR encephalitis was 56% in women aged >18 years, 31% in girls <18 years, and 9% in girls aged <14 years. The incidence rate of ovarian teratoma from our analysis (26.9%) was not as high as previously reported, that is, 30.3% (23 of 76, 30.3%) in patients aged ≥18 years, 11.1% (6 of 32, 18.8%) in patients aged ≥14 to <18 years, and 28.6% in patients aged <14 years, indicating a higher prevalence of ovarian teratoma in young women aged ≥18 years. However, there was no significant difference between the 2 groups.

The median age of the patients included in the current study was 23.14 ± 6.59 years (range, 10–36 years) and 23.51 ± 12.56 (range, 5–72 years) for patients with teratoma and those without teratoma, respectively.[18] In our data, the youngest patient with ovarian teratoma was 10 years old and the one without ovarian teratoma was only 5 years old.

Leel et al[19] reported the first case of anti-NMDAR encephalitis with ovarian teratoma in a 7 year old patient in the United Kingdom. Lesher et al[20] reported a case of teratoma in 15 year old female with anti-NMDAR encephalitis. Titulaer et al[14] reported 4 cases of females <12 years of age having tumors associated with anti-NMDAR encephalitis but without teratoma. Thus far, the youngest reported patient with anti-NMDAR encephalitis was only 8 months old.[16] Because patients with anti-NMDAR encephalitis are also predominantly young people, we did not find significant differences in the average age between patients with and without ovarian teratoma in the current study.

Gynecological and neurological symptoms in patients with ovarian teratoma

None of the 29 patients with ovarian teratoma reported lower abdominal pain before onset or acute torsion of ovarian teratoma. In the present study, the patients <14 years old had 28.6% risk of ovarian teratoma (4 of 14). Based on these observations, it may be concluded that ovarian teratoma exhibited few gynecological symptoms in these patients. Therefore, we believe that pelvic ultrasonography is necessary for all female patients, including preadolescent children, with NMDAR encephalitis to screen for ovarian teratomas.

In this study, all female patients were examined with pelvic ultrasound at the baseline. Because of ethical

TABLE 2
The neurological disorders in 108 female patients with or without ovarian teratoma

Parameter	Anti-NMDAR encephalitis with ovarian teratoma (n = 29)	Anti-NMDAR encephalitis without ovarian teratoma (n = 79)	*P* value	Odds ratio (95% confidence interval)
Fever (T_{max} >37.5°C)	22/29, 75.9%	40/79, 50.6%	.019	3.06 (1.18–7.99)
Headache	9/29, 31.0%	31/79, 39.2%	.434	
Mental and behavioral disorders	26/29, 89.7%	62/79, 78.5%	.185	
Memory impairment	14/29, 48.3%	41/79, 51.9%	.739	
Epileptic seizure	23/29, 79.3%	57/79, 72.2%	.452	
Decreased consciousness	19/29, 65.5%	34/79, 43.0%	.038	2.515 (1.037–6.098)
Involuntary movement	14/29, 48.3%	31/79, 39.2%	.399	
Ataxia	0/29, 0%	8/79, 10.1%	.074	
Speech disorder	16/29, 55.2%	40/79, 50.6%	.676	
Sleep disorder	15/29, 51.7%	31/79, 39.2%	.245	
Hyperhidrosis	18/29, 62.1%	48/79, 60.8%	.902	
Arrhythmia	8/29, 27.6%	9/79, 11.4%	.047	2.963(1.016–8.638)
Central hypoventilation	16/29, 55.2%	10/79, 12.1%	< .0001	8.492 (3.163–22.801)
Ventilator-assisted respiration	16/29, 55.2%	10/79, 12.7%	< .0001	8.492(3.163–22.801)
Intensive care unit	17/29, 58.6%	17/79, 21.5%	< .0001	5.167(2.073–22.801)
Modified Rankin score at onset	4.11 ± 1.20	3.58 ± 1.08	.032	

NMDAR, N-methyl-D-aspartate receptor.
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considerations, we could discuss only the possibility of laparoscopic exploration with patients and their families on detection of ovarian cysts during ultrasound. Therefore, no cases in which ovarian teratoma was identified under laparoscopy, but not seen in preoperative ultrasound scanning, were observed. However, from the results of this study alone, the incidence of ovarian teratoma was only 26.9%, and hence, we cannot conclude whether all female patients should be operated on for pelvic exploration.

Pelvic MRI may be more sensitive and specific in detecting ovarian teratomas than pelvic ultrasound; however, because of the high cost, longer examination time, and the need to move patients (many of the patients were in serious conditions and required respiratory support), it is difficult to complete pelvic MRI; only 4 patients underwent pelvic MRI. Pelvic nuclear magnetic resonance may be a better method for examination, but this needs to be evaluated in future studies.

In terms of neurological symptoms, the 29 patients with ovarian teratoma presented more severe conditions than those without ovarian teratoma. In addition, patients with ovarian teratoma had a higher mRS score at the acute stages than those without ovarian teratoma (4.11 ± 1.20 vs 3.58 ± 1.08). Therefore, the combination of anti-NMDAR encephalitis and ovarian teratoma may be associated with more severe neurological symptoms.

Role of immune system and neural tissue in anti-NMDAR encephalitis with concurrent ovarian teratoma

Paraneoplastic neurological syndromes are neurologic deficits triggered by an underlying remote tumor, which could explain the relationship between ovarian teratoma and anti-NMDAR encephalitis.[21] Previously, in a study conducted by Titulaer et al,[16] 94% of tumors associated with anti-NMDAR encephalitis were ovarian teratomas, 2% were extraovarian teratomas, and 4% were other tumors (including lung, breast, and testicular tumors [2 cases each]; 1 ovarian carcinoma, 1 thymic carcinoma, and 1 pancreatic cancer).

In addition, Tanyi et al[22] reported a case of anti-NMDAR encephalitis complicated by ovarian sex cord–stromal tumor. In another study, Yin et al[6] showed that resection of melanocytic nevi positively affected persistent recovery of patients with anti-NMDAR encephalitis.

Overall, ovarian teratoma is the most commonly implicated tumor of anti-NMDAR encephalitis. Ovarian tumors and nervous tissue share common antigens (eg, cdr2 and NMDAR), and autoimmune etiology is believed to be a probable mechanism of these neurologic disorders. Accordingly, neural tissue was found in ovarian teratoma tissue specimens from 3 of our 29 patients (10.3%). We plan to report the results of further immunohistochemical analysis of tissue samples from each patient in our subsequent research article.

TABLE 3
The gynecological characteristics and laparoscopic detection results of patients with ovarian teratoma

Parameter	Mean ± SD	Minimum, maximum
Cancer antigen-125, U/mL	27.15 ± 9.88	11.2, 51.28
Carbohydrate antigen 19-9, U/mL	60.75 ± 143.94	1.60, 756.50
Diameter of the ovarian cyst in laparoscopic detection, cm	4.61 ± 3.41	1, 12
Duration between surgery and onset, mos[a]	1.71 ± 0.33	0.5, 5

[a] The duration between surgery and onset in the 22 patients who underwent laparoscopic cystectomy in acute stages.
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Previously, Iemura et al[23] observed NMDAR-expressing neurons in 4 cases of ovarian teratoma associated with anti-NMDAR encephalitis, and the neurons were significantly densely aggregated. In a study by Day et al,[24] atypical neurons were observed in ovarian teratomas resected from patients with NMDAR but not in control patients with ovarian teratoma, reliably distinguishing ovarian teratomas associated with NMDAR encephalitis.

These findings indicate that abnormal neuroglial elements are closely related to immune infiltrates in ovarian teratomas resected from NMDAR encephalitis. Moreover, Tabata et al[25] reported that lymphocyte infiltration was more frequent in neuronal tissues obtained from ovarian teratomas in patients with NMDAR encephalitis than in those without encephalitis. These results suggest the immunological importance of the ovarian teratoma as the site of antigen presentation in anti-NMDAR encephalitis.[25]

Pathological status of ovarian teratoma associated with anti-NMDAR encephalitis

Furthermore, we found the average diameter of the ovarian cyst to be 4.61 ± 3.41 cm (1−12 cm range) and the smallest cyst to be only 1 cm. In a study conducted by Iemura, the size of ovarian teratomas was relatively smaller in encephalitis-associated cases than in control cases.[23]

Similarly, Mizutamari et al[26] reported a very small ovarian teratoma of 1.0 × 2.5 × 3.0 cm associated with anti-NMDAR encephalitis during pregnancy. Therefore, careful intraoperative exploration is very necessary in patients with anti-NMDAR having ovarian teratoma.

Except for 1 case of pathological grade 1 immature ovarian teratoma, all remaining cases were mature ovarian teratomas. Previous studies have mostly reported mature ovarian teratomas, and to the best of our knowledge, this study reports the first case of anti-NMDAR encephalitis complicated by immature ovarian teratoma in China. In a retrospective observation study conducted by Bost et al,[27] it was reported that immature ovarian teratomas represented only 11.8% of all ovarian teratomas in patients with NDMAR-Ab encephalitis and were directly associated with a higher risk of death.

Clinical implications and the timing of tumor removal

Early resection of ovarian tumors is a significant part of paraneoplastic neurological syndromes management and improves the outcome and decreases relapse.[23] Surgery and immunomodulatory treatment are considered the most important management procedures among patients with these conditions.[21]

Mizutamari et al[26] reported a successful outcome following detection and removal of a very small ovarian teratoma associated with anti-NMDAR encephalitis during pregnancy. Moreover, Florance et al[17] reported that full recovery occurred more frequently in patients who had an ovarian teratoma that was removed (5 of 8) than in those without an ovarian teratoma (4 of 23; $P = .03$). Among the 29 patients, 28 patients (96.6%) reported a good outcome and only 4 (14.3%) patients experienced relapse; tumor removal was associated with reduced risk of relapse in patients with teratoma as compared to patients without ovarian teratoma (33.3% of 78).

The mean time to relapse in patients with ovarian teratoma was longer than that in patients without teratoma. Hence, we believe that tumor resection is helpful for the long-term prognosis of NMDAR encephalitis. Screening for systemic tumors is recommended at the initial diagnosis of autoimmune encephalitis has been recommended in the published consensus and guidelines.[13,28,29]

Regarding the timing of the surgery, 22 of 29 underwent laparoscopic surgery during the acute onset of neurological symptoms, and all the surgeries had no complications. Except for 1 patient who died of infection because of prolonged assisted breathing, all other patients recovered with a good outcome after the operation. Therefore, we believe that laparoscopy is also safe for acute NMDAR encephalitis.

The only patient who died did so because of severe infection and respiration failure because of seizures and had been treated in 2 hospitals without surgical treatment before being transferred to our hospital.

Our findings also suggest that early surgical removal of tumors is important for relieving the severe condition in patients with anti-NMDAR encephalitis. Early treatment and a lack of ICU admission are reportedly predictors of good outcomes.[16] Because underlying tumors are the major cause of autoimmune encephalitis, tumor removal is an important part of initial treatment.

Many neurologists believe that ovarian teratoma, once detected, should be removed promptly in anti-NMDAR encephalitis patients; however, critical neurological and systemic complication should not be looked as contraindications for surgery.[28] But this view has not been widely accepted by gynecologists. The results of our study hope to arouse

gynecologists' attention to the importance of early removal of tumors.

Strength and limitations

Anti-NMDAR encephalitis is rare and mostly reported as case reports[30–32]; therefore, the clinical features of associated ovarian teratoma remain unknown.[30,33] To the best of our knowledge, this study presented the largest sample of patients having anti-NMDAR encephalitis with ovarian teratomas in 1 tertiary medical center in China and thus provided evident information on the clinical features of the disease that can be generalized to the population of these patients.

This study had a few limitations. First, although this was a prospective observational cohort study, the patients were not randomized, and hence, assessment could be biased. Second, the number of subjects allocated to the 2 study groups (patients with ovarian teratoma and those without ovarian teratoma) were highly varied. A comparison made using groups with a similar number of patients in future might provide more generalizable results.

Conclusions

Patients with anti-NMDAR encephalitis having ovarian teratomas tend to present more severe neurological conditions. Most ovarian teratomas in patients with anti-NMDAR encephalitis are mature. All females with NMDAR encephalitis, including the pediatric patient population, should undergo pelvic ultrasound for detection of ovarian tumor. In these patients, the diameter of the tumor is not very large and could be as small as 1 cm. Thus, careful exploration during surgery should be considered.

Early tumor removal might be effective in improving health outcomes of these patients and lower the risk of relapse and improve long-term prognosis; therefore, even small tumors should be removed as part of comprehensive treatment including steroids, immune therapy, and plasmapheresis. The reproductive function can be preserved through fertility-sparing surgery at the time of removal. ■

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Author and article information

From the Departments of Gynecology and Obstetrics (Drs Dai, Zhang, Zhou, Chen, Lang, and Sun) and Neurology (Mr Ren and Drs Cui and Guan), Peking Union Medical College Hospital, Beijing, China.

[1]These authors contributed equally to the manuscript.

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Corresponding author: Dawei Sun, MD. sundw@pumch.cn; or Hongzhi Guan, MD. guanhz@263.net