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Review

Clinical characteristics, treatments, and outcomes of patients with anti-*N*-methyl-D-aspartate receptor encephalitis: A systematic review of reported cases

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ABSTRACT

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently recognized autoimmune disorder which is responsive to immunotherapy. However, the outcomes of different immunotherapies have not been defined and there have been few studies that carried out a comparison among them. To provide an overview of the clinical characteristics, treatments, and outcomes of anti-NMDAR encephalitis, we systematically reviewed the literature in the PubMed, Medline, Embase, Cochrane Library, BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), and Wan-fang databases. Eighty-three studies with a total of 432 patients were included. The median age was 22 years. Two hundred ninety-three (68%) patients were female, 87 (21%) of 412 patients had a tumor, including 68 (78%) patients with ovarian teratoma. Pediatric patients had a higher ratio of seizures to psychiatric symptoms as the initial manifestation ($p = 0.0012$), a lower proportion with a tumor ($p < 0.0001$) and CSF pleocytosis ($p = 0.0163$), and a better outcome ($p = 0.0064$) than adults. Patients who died had a higher proportion of CSF pleocytosis than the patients who survived ($p = 0.0021$). There were no significant differences among three first-line immunotherapy used alone ($p = 0.9172$) or among combinations of every two of them ($p = 0.3059$). With regard to the use of corticosteroid and IVIG, there were no significant differences between the outcomes of early combined treatment and sequential treatment ($p = 0.7277$), or between using corticosteroid first and IVIG first ($p = 0.5422$). Our findings suggest that the clinical characteristics and outcomes for pediatric patients were different from adult patients, and no significant differences were found among different immunotherapies.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently recognized autoimmune disorder in which auto-antibodies mainly target the NR1 subunit of the NMDA receptor leading to a series of complex neuropsychiatric symptoms [1–3]. In recent years, with the increased reports about anti-NMDAR encephalitis, the clinical characteristics of this condition have been summarized. It is a type of autoimmune encephalitis, presenting with psychiatric symptoms, behavioral dysfunction, seizures, speech disorder, cognitive impairment, movement disorder, decreased consciousness, autonomic instability or central hypoventilation. It is observed in patients of different ages and gender, with or without ovarian teratoma or other tumors [1,3,4].

Up to now, more than 1000 cases of anti-NMDAR encephalitis have been reported, which have increased in number with the increased clinical recognition of this disease. Therapeutic methods mentioned in reports mainly include tumor resection, symptomatic treatment, supportive care, and immunotherapy. First-line immunotherapy includes corticosteroids, intravenous immunoglobulins (IVIG), plasma exchange, plasmapheresis, and immunoabsorption. Second-line immunotherapy includes rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate [3,5–7]. Some papers have summarized the clinical features of autoimmune encephalitis, which provided practical clinical approaches to diagnosis of autoimmune encephalitis earlier, rather than completely rely on detection of autoantibodies [8,9]. Moreover, a meta-analysis in children found that earlier treatment of anti-NMDAR encephalitis leads to better outcomes [10]. However, studies that compare various immunotherapies and their therapeutic effects are scarce. Therefore, it is not easy to choose an appropriate treatment plan.

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To provide some practical guidance for clinicians and follow-up studies, we conducted a literature review to summarize clinical characteristics, treatments, and outcomes of patients with anti-NMDAR encephalitis, and attempt to find any differences among the outcomes of different immunotherapies.

2. Methods

2.1. Data collection

Two researchers performed a comprehensive literature search in PubMed, Medline, Embase and Cochrane Library using search terms 'Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis' OR 'anti-nmda receptor encephalitis' OR 'anti-nmdar encephalitis' to find articles published between January 1, 2005 and December 31, 2015. Three Chinese databases were also searched, including Chinese BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), and Wan-fang Database. The search was restricted to human beings but with no language limitations, although for articles in French, Swedish, German, Spanish, Danish, Dutch or Japanese, only their abstracts were consulted.

2.2. Data selection

All publications reporting at least two patients with a definitive diagnosis of anti-NMDAR encephalitis, by the detection of antibody, without any age, gender or race limit were selected for review and full-text analysis. Papers or cases conforming to one of the following criteria were excluded:

1) Single case reports;
2) Reviews, systematic reviews or meta-analyses;
3) Records without individual patient's information (minimum information for selection include age, sex, treatment, and outcome);
4) Records with only abstracts available in which needed information could not be obtained from these abstracts;
5) Studies about mechanism, diagnostic method, pathology, and questionnaire survey without information about treatment and outcome;
6) Cases that developed anti-NMDAR encephalitis during pregnancy or accompanied with other immune diseases of the central nervous system;
7) Cases without a definite diagnosis or which had conflicting or unclear descriptions.

In addition, for papers that contain overlapping data from the same agency, we chose the one containing the most cases. Eventually, 83 studies containing a total of 432 cases of anti-NMDAR encephalitis were included. The flow diagram for the study is shown in Fig. 1 and the excluded reasons of each record are presented in the supplementary material.

2.3. Data extraction and management

The following data were collected from all of the articles: authors, year of publication, number of cases included, patients' age, sex, initial symptoms (where available), with or without tumor and the type of tumor (where available), inspection results of cerebrospinal fluid (CSF) (where available), cranial magnetic resonance imaging (MRI) (where available) and electroencephalography (EEG) (where available), treatments, and outcomes. The outcomes were classified into 3 grades including "Full recovery", "Substantial improvement" and "Limited improvement or died". Patients were considered to have "Full recovery" if they were described to have "Full recovery" or "Nearly full recovery" or were able to return to all their activities or their modified Rankin Scale (mRS) score were determined to be 0 or 1; "Substantial improvement" if they were described to have "Improvement" or "Significant improvement" or returned to their homes with some deficits and were improving or their mRS score were determined to be 2–4; and "Limited improvement or died" if they had no distinct change in neurological status, or their mRS score were determined to be 5 or 6, or they died.

2.4. Statistical analysis

Statistical analyses were performed using SAS version 9.1. Age was analyzed as continuous variables using Wilcoxon Test, while gender, initial symptom, tumor type, CSF pleocytosis, abnormal EEG results, abnormal cranial MRI results, treatments, and outcomes were analyzed as categorical variables using Wilcoxon Test or the Chi-squared test. p value of 0.05 or less (two-sided) was considered to be significant.

3. Results

3.1. General clinical characteristics

Eighty-three studies with a total of 432 cases with a definite diagnosis of anti-NMDAR encephalitis were included. Eighteen were Chinese articles [11–28], seven were meeting abstracts [29–35], and the remaining fifty-eight studies were English articles from various countries, including America [36–47], China [48–55], the United Kingdom [56–60], Japan [61–65], Germany [5,6,66,67], Australia [68–71], France [72,73], Spain [74,75], Ireland [7,76], Brazil [77,78], Canada [79,80], India [81,82], Italy [83,84], Korea [85,86], Malaysia [87], Switzerland [88], Portugal [89], and the Netherlands [90]. It is notable that both the number of cases and papers have gradually increased over the years (Fig. 2).

Clinical characteristics are summarized in Table 1. Two hundred ninety-three (68%) patients were female. The median onset age was 22.00 years old ranging from 0.6 to 84 years. One hundred fifty-three (35%) of all 432 patients were younger than 18 years old, and 52 (12%) were 45 years old or older.

Eighty-seven (21%) of 412 patients whose information about tumor was available had one or two kinds of neoplasms, including 68 (78%) patients with ovarian teratoma, one of whom had an ovarian teratoma 30 years earlier and was detected to have a glioblastoma one year after the onset of anti-NMDAR encephalitis, 5 with lung cancer, 3 with breast cancer, and the remaining 11 patients had one of the following: mediastinal teratoma, ovarian fibroma, perineal schwannoma, ovarian carcinoma, thymic carcinoma, papillary thyroid carcinoma, sex cord stromal tumor, renal carcinoma, multiple neuroendocrine tumors along with ovarian tumor of unknown type, a pure seminoma in the left testis and a mixed germ cell tumor composed of seminoma and teratoma with small foci of embryonal carcinoma in the right, and mixed types of germ cell tumor (choriocarcinoma and teratoma) in the lung. Among the 87 patients with tumors, there were 79 female patients (277 available) and 8 male patients (135 available), which indicates that the proportion of female patients presenting with tumor was significantly higher than for male patients (29% vs 6%, $p < 0.0001$).

The initial symptoms of 227 patients were available. 147 (65%) of them presented with psychiatric symptoms, including anxiety, apathy, agitation, depression, delusion, suicide attempt, bizarre behavior, visual or auditory hallucinations as initial symptoms; 64 (28%) presented with seizures, 19 (8%) with cognitive impairment, 17 (7%) with speech disorder, 7 (3%) with autonomic instability, and 6 (3%) with movement disorder. Some of them had more than one initial symptom. For example, 13 patients had both psychiatric symptoms and seizures.

With respect to the inspection results, 186 of 320 (58%) patients had CSF pleocytosis (which refers to more than 5 cells/mm^3); 137 of 342 (40%) patients had abnormal MRI findings which included abnormal

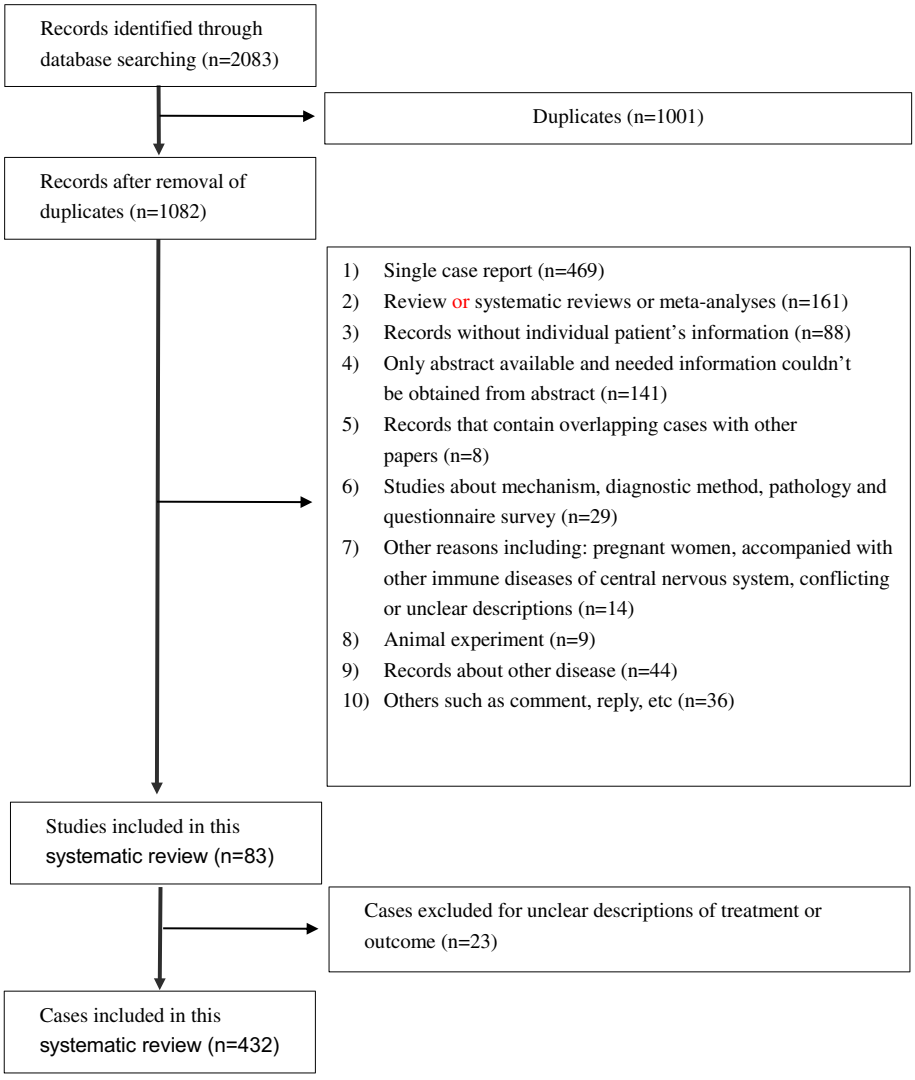

Fig. 1. Flow diagram for the systematic review.

signals in the cerebral cortex, hippocampus, insula, cerebral peduncle, cerebellum, gyrus cinguli, corpus callosum, corona radiata, basal ganglia region, or the periventricular white matter and 240 of 281 (85%) patients had abnormal EEG findings which included epileptiform activity, diffuse slow wave, and some other abnormalities which were not presented in detail.

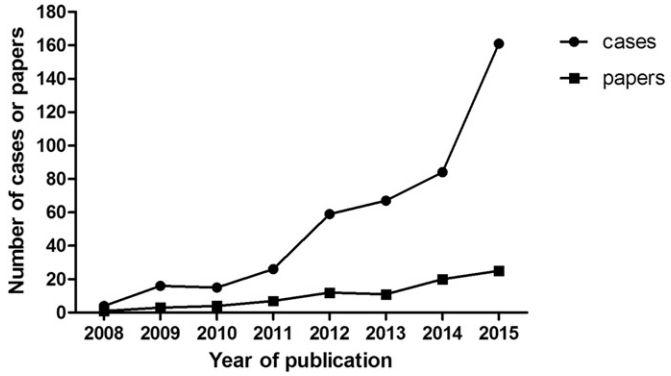

Fig. 2. The number of cases and papers included in our study by publication year.

According to the data, 190 (44%) patients had full recovery, 203 (47%) patients had substantial improvement, 13 (3%) patients had limited improvement, and 26 (6%) patients died. As shown in Table 2, the median age of patients who died was 29.00 years old (range from 5 to 84 years old), which was significantly older than patients who survived with a median age of 21.50 years old (range from 0.6 to 75 years old) ($p = 0.0006$). Moreover, we found that a higher proportion of patients who died had CSF pleocytosis than the patients who survived (90% vs 56%, $p = 0.0021$). The gender ratio, proportion of tumor, brain MRI abnormality, EEG abnormality, and treatment were not significantly different when comparing patients who survived with those who died.

3.2. Comparison between patients younger than 18 years old and those 18 years or older

Having compared pediatric patients (defined as younger than 18 years old) with adult patients (defined as 18 years or older), we found that pediatric patients had a higher ratio of seizures to psychiatric symptoms as the initial presentation (31:36 vs 33:111, $p = 0.0012$), a lower proportion with tumor (9% vs 27%, $p < 0.0001$) and CSF pleocytosis (49% vs 63%, $p = 0.0163$), and a better outcome ($p = 0.0064$) than adult patients. There were no significant differences in gender, and MRI and EEG results between pediatric and adult patients. Among the 13 pediatric patients

Table 1
Clinical characteristics of patients with anti-NMDAR encephalitis.

Item	Patients (%)
Number	432(100%)
Female	293(68%)
Age, y, median (range)	22.00(0.6–84)
<18	153(35%)
18–44	227(53%)
≥45	52(12%)
Tumor(information available for 412 patients)	87(21%)
Sex	
Female	79 of 277(29%)
Male	8 of 135(6%)
Type	
Ovarian teratoma	68(78%)[a]
Lung cancer	5(6%)
Breast cancer	3(3%)
Other tumors	11(13%)[b]
Initial symptoms[c] (information available for 227 patients)	
Psychiatric symptoms	147(65%)
Seizure	64(28%)
Cognitive impairment	19(8%)
Speech disorder	17(7%)
Autonomic instability	7(3%)
Movement disorder	6(3%)
CSF pleocytosis (>5 cells/mm^3) (information available for 320 patients)	186(58%)
Brain MRI abnormal (information available for 342 patients)	137(40%)
EEG abnormal (information available for 281 patients)	240(85%)
Treatment	
No immunotherapy	26(6%)
First-line immunotherapy alone	301(70%)
Second-line immunotherapy alone	1(0.23%)
First-line combined with second-line immunotherapy	104(24%)
Tumor resection	73 of 87(84%)
Outcome	
Full recovery	190(44%)
Substantial improvement	203(47%)
Limited improvement/died	13/26(9%)

[a] One of these patients had an ovarian teratoma 30 years earlier and a glioblastoma was detected one year after the onset of disease.
[b] Other tumors include each of the following: mediastinal teratoma, ovarian fibroma, perineal schwannoma, ovarian carcinoma, thymic carcinoma, papillary thyroid carcinoma, sex cord stromal tumor, renal carcinoma, multiple neuroendocrine tumors along with ovarian tumor of unknown type, a pure seminoma in the left testis and a mixed germ cell tumor composed of seminoma and teratoma with small foci of embryonal carcinoma in the right, and mixed and types of germ cell tumor (choriocarcinoma and teratoma) in the lung.
[c] Some patients had more than one kind of initial symptom, for example, 13 patients had both psychiatric symptoms and seizure.

who had a tumor, 12 (92%) had ovarian teratoma and the one remaining had mediastinal teratoma, while only 56 (76%) of 74 adult patients with tumor had ovarian teratoma (Table 3).

3.3. Treatment and outcome

There were various treatments used for anti-NMDAR encephalitis. The outcomes of different treatments are presented in Table 4. Among the 432 patients with anti-NMDAR encephalitis, 26 were not treated with immunotherapy and 406 were treated with immunotherapy, of which 301 had first-line immunotherapy alone, 104 had first-line immunotherapy combined with second-line immunotherapy, and 1 had second-line immunotherapy alone.

Because plasma exchange, plasmapheresis, and immunoabsorption have similar mechanisms and several studies did strictly distinguish them, in this systematic review, we classify them together as plasma therapy. Second-line immunotherapy includes rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate. There were no significant differences between the outcomes of patients who received immunotherapy and those who did not receive immunotherapy ($p = 0.7672$). In addition, 73 of 87 patients with tumor underwent tumor resection and 2 patients without tumor had a prophylactic ovariectomy or salpingooophorectomy. Among 87 patients with tumor, 39 (45%) had full recovery, 40 (46%) had substantial improvement, and 8 (9%) had limited improvement or died.

Having analyzed the outcome of patients that were treated with first-line immunotherapy, we found that among the 301 patients treated with first-line immunotherapy alone, 128 (43%) had full recovery, 148 (49%) had substantial improvement, and 25 (8%) had limited improvement or died. Among the 104 patients treated with a combination of first-line and second-line immunotherapy, 50 (48%) had full recovery, 43 (41%) had substantial improvement, and 11 (11%) had limited improvement or died, and no significant difference was found between them ($p = 0.5226$). With regard to using first-line immunotherapy alone, we comparatively analyzed not only the individual outcomes of using 3 first-line immunotherapies, but also a combination of any two of them. However, none of the comparisons yielded any significant differences.

The most common treatment was the combination of corticosteroid and IVIG. However, there were several different sequences used, including early combined treatment, and sequential treatment which can be divided into using corticosteroid first or using IVIG first. According to our data (Table 5), there were no significant differences between the outcomes of early combined treatment and sequential treatment ($p = 0.7277$), nor between using corticosteroid first and using IVIG first ($p = 0.5422$).

As several papers presented the outcome without a uniform standard, which would likely cause biases, we carried out a further analysis among 159 patients whose outcomes were estimated by mRS (Table 6). Similar to the above results, no significant differences were found

Table 2
Comparison between patients who survived and those who died.

Variables	All patients (n = 432)	Survived (n = 406)	Died (n = 26)	p value[b]
Age, y, median (range)	22.00(0.6–84)	21.50(0.6–75)	29.00(5–84)	0.0006*
Female	293(68%)	279(69%)	14(54%)	0.1312
Tumor	87 of 412(21%)	81 of 388(21%)	6 of 24 (25%)	0.6102
Ovarian teratoma	68(78%)	65(80%)	3(50%)	0.1153
Other tumors	19(22%)	16(20%)	3(50%)	
CSF pleocytosis (>5 cells/mm^3)	186 of 320 (58%)	168 of 300 (56%)	18 of 20 (90%)	0.0021*
Brain MRI abnormal	137 of 342 (40%)	132 of 323 (41%)	5 of 19 (26%)	0.2377
EEG abnormal	240 of 281 (85%)	222 of 261 (85%)	18 of 20 (90%)	0.7482
Treatment				
No IT	26	23	3	0.1998
IT[a]	406	383	23	
First-line IT alone	301	284	17	1.0000
First-line + second-line IT	104	98	6	
Second-line IT alone	1	1	0	

[a] Abbreviations: IT = immunotherapy.
[b] Fisher's exact test, except for age, which is Wilcoxon Two-Sample Test.
* $p < 0.05$.

Table 3
Comparison between patients younger than 18 years old and those 18 years or older.

Variables	All patients (n = 432)	Age < 18y (n = 153)	Age ≥ 18y (n = 279)	p value[a]
Age, y, median (range)	22.00(0.6–84)	12.00(0.6–17)	28.00(18–84)	
Female	293(68%)	104(68%)	189(68%)	1.0000
Tumor	87 of 412 (21%)	13 of 137 (9%)	74 of 275 (27%)	<0.0001*
Ovarian teratoma	68(78%)	12(92%)	56(76%)	0.2818
Other tumors	19(22%)	1(8%)	18(24%)	
Initial symptoms (Seizure: psychiatric symptoms)	64:147	31:36	33:111	0.0012*
CSF pleocytosis (>5 cells/mm^3)	186 of 320 (58%)	51 of 105 (49%)	135 of 215 (63%)	0.0163*
Brain MRI abnormal	137 of 342 (40%)	42 of 119 (35%)	95 of 223 (43%)	0.2039
EEG abnormal	240 of 281 (85%)	91 of 108 (84%)	149 of 173 (86%)	0.7291
Outcome				0.0064*
Full recovery	190(44%)	78(51%)	112(40%)	
Substantial improvement	203(47%)	69(45%)	134(48%)	
Limited improvement/died	39(9%)	6(4%)	33(12%)	

[a] Fisher's exact test, except for outcome which is Wilcoxon Test.
* $p < 0.05$.

between the outcomes of using first-line immunotherapy alone and the combination with second-line immunotherapy ($p = 0.3925$), or between corticosteroid and IVIG ($p = 0.6526$).

4. Discussion

Although the exact incidence of anti-NDMA receptor encephalitis is unknown, the increasing number of reported cases indicates that anti-NMDAR encephalitis may have a high morbidity. Therefore a systematic review of published papers about anti-NMDAR encephalitis is necessary and meaningful, to provide more practical information and guidance.

The result of this systematic review presents several findings regarding patients with anti-NMDAR encephalitis. The median age was 22.00 years old, which is similar to previous studies [1,3]. In terms of gender ratio in our studies, female patients accounted for 68%, which is lower than a previous multi-institutional study in western populations with a percentage of eighty [3]. However, in line with some previous studies in Asia populations which have not been included into our analysis, 47% in China [91] and 46% in Korea [92] were female patients, which were lower than the ratio in western populations. Therefore, we speculate that the dissimilarity of gender ratio is likely related to racial and regional differences. However, it is a pity that we could not carry out a comparison between them due to the absence of detailed demographic data. Further studies would be needed to identify those differences.

Previous studies showed that the clinical characteristics of patients in different age ranges had some distinctions, including symptom presentation, inspection results, and outcomes [3,93]. In the present study, it was found that pediatric patients presented a higher ratio of seizures to psychiatric symptoms as the initial symptom than adults ($p = 0.0012$) and a lower proportion with a neoplasm ($p < 0.0001$), which is consistent with previous studies [3]. But beyond that, our data showed that the proportion of those with CSF pleocytosis was lower ($p = 0.0163$) and the outcome was better ($p = 0.0064$) in pediatric patients. Furthermore, in comparing patients who survived and those who died, we found that patients who died had an older

Table 4
Comparison among the outcomes of different treatments.

Treatment[a]	Total	Full recovery	Substantial improvement	Limited improvement/died	p value[b]
Total	432	190	203	39	–
No IT	26	11	12	3	0.7672[c]
IT	406	179	191	36	
1st-line IT	405	178	191	36	
1st-line alone	301	128(43%)	148(49%)	25(8%)	0.5226[d]
CS alone	69	35	29	5	0.9172[e]
IVIG alone	59	28	26	5	
PT alone	2	1	1	0	
CS + IVIG	127	52(41%)	67(53%)	8(6%)	0.3059[f]
CS + PT	12	3	8	1	
IVIG + PT	5	1	3	1	
CS + IVIG + PT	27	8	14	5	
1st + 2nd line IT	104	50(48%)	43(41%)	11(11%)	0.5226[d]
CS + 2nd line IT	8	3	5	0	
IVIG + 2nd line IT	4	2	2	0	
PT + 2nd line IT	1	1	0	0	
CS + IVIG + 2nd line IT	48	30(63%)	13(27%)	5(10%)	0.0432[g]
CS + PT + 2nd line IT	6	1	4	1	
IVIG + PT + 2nd line IT	3	0	3	0	
CS + IVIG + PT + 2nd line IT	34	13	16	5	
2nd-line IT alone	1	1	0	0	

[a] Abbreviations: IT = immunotherapy, 1st-line IT = first-line immunotherapy, CS = Corticosteroid, IVIG = Intravenous immunoglobulins, PT = Plasma therapy, 2nd line IT = second-line immunotherapy including: rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate.
[b] Wilcoxon Test.
[c] Comparison between using immunotherapy and not.
[d] Comparison between first-line alone and a combination of first-line and second-line immunotherapy.
[e] Comparison among corticosteroid alone, IVIG alone, and PT alone.
[f] Comparison among corticosteroid plus IVIG, corticosteroid plus PT, and IVIG plus PT.
[g] Comparison between a combination of corticosteroid and IVIG and a combination of corticosteroid and IVIG plus second-line immunotherapy.

Table 5
Comparison among the outcomes of different sequences of CS and IVIG.

Outcome	Early combined treatment	Sequential treatment[a]		
		Total	CS first	IVIG first
Total	22	33	21	12
Full recovery	11(50%)	15(45%)	9	6
Substantial improvement	10(45%)	16(48%)	10	6
Limited improvement/died	1(5%)	2(6%)	2	0
p value[b]	0.7277[c]		0.5422[d]	

[a] Abbreviations: CS = Corticosteroid, IVIG = Intravenous immunoglobulins.
[b] Wilcoxon Test.
[c] Comparison between early combined treatment and sequential treatment.
[d] Comparison between CS first and IVIG first.

median onset age ($p = 0.0006$) and a higher proportion with CSF pleocytosis ($p = 0.0021$) than patients who survived. These results revealed that an older onset age and the presence of CSF pleocytosis might be associated with a poorer outcome.

Immune modulating treatment and tumor resection of patients with tumor are widely used and effective in controlling disease and preventing relapse [3,94]. In our study, the difference between the outcomes of using and not using immunotherapy had no statistical significance, because the disease condition of patients who were not treated with immunotherapy were more likely to be milder, thus affecting the result of the comparison. It is also difficult to estimate the severity of illness based on the information from literature as there were no objective evaluation standards. Previous studies showed that non-paraneoplastic patients with poorer outcome often had higher antibody titers, and the decrease of antibody titers was related to an improvement in the course of disease [1,95]. However, as few studies included in our review presented the data of antibody titers, it is hard to make an analysis between the outcome and antibody titers, and further clinical studies are needed. Furthermore, if antibody titers are related to the severity of illness and outcome, it may serve as an assessment standard to estimate outcome and match the severity of the patients' condition among comparison groups. Another factor that should have been taken into consideration is the duration of follow-up. However, only 202 cases have presented follow-up time. Their follow-up time range is large, from 0.5 to 108 months, and most of them only provided the outcome from the last follow-up. This made it difficult to include follow-up time in the analysis. But we have compared the follow-up times which are available from different treatments. Their outcomes have been compared in our analysis, and no significant differences were found between the follow-up times of different treatments (Table 7). Therefore, we evaluated outcomes based on the final result described in the literature.

Table 7
Comparison among the follow-up time of different treatments.[a]

Treatment	Number of cases available for follow-up time	Median time of follow-up, month (IQR)	Range, month	p value[b]
Total	202	10.5 (4–20.25)	0.5–108	
1st-line alone	122	9 (3–18.5)	0.5–108	0.0845
1st + 2nd line IT	66	12 (6–21)	1.5–63	
CS + IVIG	65	10 (4–15)	1–75	0.2603
CS + IVIG +2nd line IT	32	12 (6.25–15)	2–63	
CS alone	23	12 (3–48)	1–108	0.3445
IVIG alone	9	9 (3.5–26)	0.7–45	
CS + IVIG	65	10 (4–15)	1–75	0.1854
CS + PT	7	4 (3–10)	3–17	
Early combined treatment of CS and IVIG	18	7.5 (3.75–12)	1–16	0.2577
Sequential treatment of CS and IVIG	15	12 (3–18)	2–36	

[a] Abbreviations: IT = immunotherapy, 1st-line IT = first-line immunotherapy, CS = Corticosteroid, IVIG = Intravenous immunoglobulins, PT = Plasma therapy, 2nd line IT = second-line immunotherapy including: rituximab, cyclophosphamide, mycophenolatemofetil, azathioprine, and methotrexate, IQR = inter quartile range
[b] Wilcoxon Test.

Regarding whether there are differences among the outcomes of various immunotherapies, few studies have given a definite conclusion. To date, only a few articles made a comparison among immunotherapies. A multi-institutional study suggested that patients who were treated with second-line immunotherapy during the first episode of encephalitis had lower frequency of relapse [3]. According to our data, there was no significant difference between the outcomes of first-line immunotherapy used alone and a combination of first-line and

Table 6
Comparison among the outcomes (estimated by mRS) of different treatments.[a]

Treatment	Total	mRS(0–1)	mRS(2–4)	mRS(5–6)	p value[b]
Total	159	94	48	17	–
No IT	10	6	3	1	0.9482[c]
IT	149	88	45	16	
1st-line alone	119	68	38	13	0.3925[d]
CS alone	26	17	6	3	0.6526[e]
IVIG alone	33	19	11	3	
PT alone	0	0	0	0	
CS + IVIG	44	27	13	4	
CS + PT	3	1	1	1	
IVIG + PT	2	1	1	0	
CS + IVIG + PT	11	3	6	2	
1st + 2nd line IT	30	20	7	3	0.3925[d]
CS + 2nd line IT	0	0	0	0	
IVIG + 2nd line IT	2	2	0	0	
PT + 2nd line IT	1	1	0	0	
CS + IVIG +2nd line IT	19	14	3	2	0.4333[f]
CS + PT + 2nd line IT	0	0	0	0	
IVIG + PT + 2nd line IT	1	0	1	0	
CS + IVIG + PT + 2nd line IT	7	3	3	1	

[a] Abbreviations: IT = immunotherapy, 1st-line IT = first-line immunotherapy, CS = Corticosteroid, IVIG = Intravenous immunoglobulins, PT = Plasma therapy, 2nd line IT = second-line immutnotherapy including: rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate.
[b] Wilcoxon Test.
[c] Comparison between using immunnotherapy and not.
[d] Comparison between first-line alone and a combination of first-line and second-line immunotherapy.
[e] Comparison among corticosteroid alone and IVIG alone.
[f] Comparison between a combination of corticosteroid and IVIG and a combination of corticosteroid and IVIG plus second-line immunotherapy.

second-line immunotherapy ($p = 0.5226$). However, as the combination of corticosteroid and IVIG was the most commonly used method in first-line immunotherapy, we compared the combination of corticosteroid and IVIG with the combination of corticosteroid and IVIG plus second-line immunotherapy. The result suggested that the latter treatment had a higher proportion of full recovery ($p = 0.0432$). Because there is a limit to our extraction of exact information from literature, we could not make a specific comparison. Hence, it is difficult to estimate whether a combination of first-line and second-line immunotherapy has a better therapeutic effect than first-line immunotherapy alone. Further head-to-head studies are needed to confirm.

With respect to the three kinds of first-line treatment, information presented by previous studies is extremely limited. A study, which only presented preliminary data, suggested that therapeutic plasma exchange after steroids might have a better effect than corticosteroid alone [96]. However, as the sample size is small, the reliability is uncertain. In our studies, the outcomes of single first-line treatment and a combination of two or three kinds of first-line treatment were not compared, for the reason that physicians' decisions for further treatment would be directly affected by the therapeutic effect of the initial treatment, with a result that more severely ill patients would receive more treatment. But we had respectively carried out a comparison among three first-line immunotherapies used singly and a combination of any two of them. The results indicated that there were neither significant differences among the outcomes of three first-line treatments used singly nor a combination of any two of them. Furthermore, the analysis of 159 patients whose outcomes were estimated by a relatively objective standard (mRS), was basically consistent with the above result. Additionally, in some studies of other antibody-mediated autoimmune disorders, a meta-analysis suggested that IVIG might be more effective than corticosteroid for immune thrombocytopenic purpura (ITP) [97]. Another study indicated that corticosteroid and IVIG appeared to be equally effective in the treatment of Graves' ophthalmopathy but corticosteroid had more frequent and severe side effects [98]. To date, studies about the difference in effectiveness between corticosteroid, IVIG, and plasma therapy are still limited and inadequate inform best treatment strategies, and more randomized controlled trials with large samples to investigate the therapeutic effect and safety are needed.

With regard to the most common therapeutic regimen, which is corticosteroids combined with IVIG, there are currently no studies done to compare the optimal sequence of therapies. On the basis of our data, no significant difference was found between the outcomes of early combined treatment and sequential treatment. Additionally, in sequential treatment, the outcomes of prior use of corticosteroids or IVIG also showed no significant difference. As there were only a small number of studies that reported the specific sequences of these two treatments that were used, the sample size is small and the difference did not reach statistical significance. However, it can provide some guidance and indication for further study.

5. Conclusion

This systematic review suggests that pediatric patients presented a higher ratio of seizures to psychiatric symptoms as the initial symptom, a lower proportion with a neoplasm and CSF pleocytosis, and a better outcome. Patients who died had a higher proportion of CSF pleocytosis than the patients who survived. In addition, our study also found several trends in treatment response: firstly, no significant differences were found among the outcomes of three first-line immunotherapies used alone or a combination of every two of them; secondly, it was doubtful whether a combination of first-line and second-line immunotherapies is more effective than first-line alone; thirdly, there were neither significant differences between early combined treatment and sequential treatment nor using corticosteroid first or IVIG first. However, our study has its limitations. For example, currently there is no consensus to a standard for assessing the treatment outcome, and some patients' duration of follow-up were unclear, therefore we could only roughly divide the outcome into three classes according to the description, which would lead to some biases and reduce the significance of the findings. It also indicates that an applicable scale to assess the condition and outcome of anti-NMDAR encephalitis is needed. Moreover, as information was extracted from literature, treatment was not randomized and available information for analysis was often limited. Therefore, these findings should be interpreted with caution. Further clinical investigations with larger populations, based on strict design, would be necessary to confirm the findings and overcome the limitations of previous studies.

Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Ethical standard

The manuscript does not contain original studies or patient data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.12.019.

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