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Late-onset anti-*N*-methyl-D-aspartate receptor encephalitis in China

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ABSTRACT

Purpose: This study aimed to summarize the clinical characteristics and outcome of late-onset anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis in China.
Method: All cases of people with a definitive diagnosis of anti-NMDAR encephalitis in West China Hospital between June 2012 and April 2017 were retrospectively reviewed. The demographics, clinical characteristics, and outcome of those patients (age ≥ 45 years old) were summarized. Comparisons were conducted between older (≥45 years old) and younger (18–44 years old) adults.
Result: Eighteen (12%) of 151 people were ≥45 years old, 9 of whom (50%) were female. Psychiatric symptoms were the most common clinical manifestations of older adults and presented in all individuals. At the last follow-up, 14 (78%) of them had a good outcome (modified Rankin Scale: 0–2) and one (6%) died. Compared with 121 younger adults, older adults had a higher proportion of presenting memory deficit as the initial symptom (17% vs. 2%, $p = 0.023$), longer interval from onset to admission (30 vs. 13 days, $p = 0.013$), and longer interval from onset to diagnosis (42.5 vs. 24 days, $p = 0.045$). No older adults' condition was accompanied with teratoma compared with 75% of younger adults with tumor ($p = 0.032$). And older adults had a tendency to have a lower rate of positive NMDAR antibody (Ab) in serum (28% vs. 52%, $p = 0.053$).
Conclusion: Delayed admission and diagnosis are more common in older adults than in younger adults. A comprehensive consideration of all symptoms and early screening of NMDAR Ab, especially in cerebrospinal fluid, is necessary and beneficial to differential diagnosis.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disease caused by autoantibodies that target the NR1 subunit of the NMDAR [1,2], which often presents as psychiatric symptoms, seizures, memory deficit, speech impairment, movement disorders, autonomic instability, central hypoventilation, or decreased consciousness and often responds to immunotherapies [3–6]. A wide range of ages (range: 0.6 to 84 years old) can be affected, but it is most common in children and young adults [3,6,7].

Many studies have focused on pediatric anti-NMDAR encephalitis, involving extensive countries and races, and several previous studies found that symptoms and response to treatment can be different between children and adults [3,6,8–11]. Studies of older adults are scarce. However, as for older adults (≥45 years old), one multi-institutional study, mainly involving Europeans and Americans, reported some differences between younger adults and older adults regarding clinical characteristics and outcomes [12]. Until now, no study that focused on the characteristics of older adults in China was published. However, previous studies about anti-NMDAR encephalitis indicated that some distinctions are likely found among people from different races and regions [5,6,13]. Therefore, a study to present the characteristics and outcomes of older adults with anti-NMDAR encephalitis in China is necessary and practical.

This study aimed to summarize the clinical features, treatment, and outcome of older adults (age ≥ 45 years) with anti-NMDAR encephalitis in China and compare them with younger adults (age = 18–44 years).

2. Materials and methods

2.1. Patients

Cases of people who were admitted to the West China Hospital between June 2012 and April 2017 with a definitive diagnosis of anti-NMDAR encephalitis were reviewed. Diagnosis was based on clinical features and confirmed by positive anti-NMDAR IgG antibody (Ab) in cerebrospinal fluid (CSF) and/or serum. Serum and CSF samples of suspected cases were sent to Peking Union Medical College Hospital, China, or to Oumeng Biotechnology Corporation, Beijing, China, for testing. All samples were assessed by indirect immunofluorescence using EU 90 cells, and the method was previously reported in detail [5]. Concurrently, other auto-Abs, including Abs to contactin-associated protein-like 2, leucine-rich glioma inactivated 1, gamma aminobutyric

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acid beta receptor and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor in CSF, and/or serum were also screened; and only individuals with negative results for all these other Abs were included in the study.

2.2. Standard protocol, approval, and consent

This study was approved by the Ethical Committee of West China Hospital, Sichuan University, on human experimentation protocols. Written informed consent was obtained from the individual, the individual's family, or his/her representatives.

2.3. Data extraction and management

People aged ≥45 years at the onset of anti-NMDAR encephalitis were defined as having late-onset anti-NMDAR encephalitis (older adults), and those aged 18–44 years were defined as younger adults. Demographics, clinical manifestations, results of auxiliary examinations, treatment strategies, and outcomes were extracted. Electroencephalogram (EEG) results were considered abnormal if focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush was recorded. Cerebrospinal fluid results were considered abnormal if white blood cell count (>5/mm^3) and/or protein (>0.45 g/L) were elevated. An anti-NMDAR antibody titer in CSF ≥1:100 was defined as strongly positive. Individuals were screened for an underlying tumor by tumor markers and magnetic resonance imaging (MRI), ultrasound examination, and contrast-enhanced computed tomography of the chest, abdomen, and pelvis. All individuals were followed up by telephone or outpatient clinic visits. Outcomes were evaluated at the final follow-up using the modified Rankin Scale (mRS). Good outcome was defined as mRS score: 0–2, and poor outcome was defined as mRS score: 3–6. Relapse of encephalitis was defined as new onset or worsening of symptoms occurring after an initial improvement or stabilization of at least 2 months [3].

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 21.0. Univariate analyses were performed to compare gender, prodromal symptoms, initial symptoms, other symptomatic presentations, tumor findings, abnormal EEG results, abnormal brain MRI results, abnormal CSF results, strongly positive NMDAR Ab in the CSF, positive NMDAR Ab in the serum, treatment (immunotherapy and tracheotomy), interval from onset to admission, interval from onset to diagnosis, interval from onset to receiving immunotherapy, length of hospital stay, maximum mRS during hospitalization, duration of follow-up, treatment outcomes, and rate of relapse between older adults and younger adults or between females and males in older adults. Duration of follow-up, interval from onset to admission, interval from onset to diagnosis, interval from onset to receiving immunotherapy, and length of hospital stay were analyzed as continuous variables using the Wilcoxon test, while the remaining variables were analyzed as categorical variables (Fisher's exact test or the chi-squared test). A two-sided p-value < 0.05 was considered to be statistically significant.

3. Result

During the period of interest, 151 people were diagnosed as having anti-NMDAR encephalitis, among whom 18 (12%) were ≥45 years old, 103 (68%) were 18–44 years old, and 30 (20%) were younger than 18 years old. Detailed clinical information of older adults is presented in Table 1.

3.1. General clinical manifestation of older adults

Among 18 older adults, 9 (50%) were female; median age was 51.5 years old (range: 45–78 years, mean ± standard deviation: 54.17 ± 9.488). Median interval from onset to admission into our hospital was 30 days (range: 2 days to more than half a year), and median interval from onset to diagnosis was 42.5 days (range: 10 days to more than half a year). Ten (56%) individuals had prodromal symptom, including fever, headache, rhinorrhea, cough, dizziness, and vomiting. Thirteen individuals (72%) presented with psychiatric symptoms as their initial symptoms, three (17%) with memory deficit, and another two (11%) with seizure. Psychiatric symptoms (including psychosis, delusions, hallucinations, agitation, aggression, and catatonia), memory deficit, and seizure were the relatively common clinical manifestations of older adults, which presented in 100%, 79%, and 72% of individuals, respectively. Three (17%) of them had an underlying tumor, including one with fibroadenoma of the breast, one with hamartoma of the kidney, and the other with adrenal adenoma. None of them had teratoma. Two of them had tumors detected during hospitalization for encephalitis, and one of them was detected 2 years ago.

3.2. Ancillary examination

All 18 people had positive anti-NMDAR Ab in CSF; nine (50%) of them had strongly positive anti-NMDAR Ab in CSF, but only five (28%) were positive in serum. Ten (59%) of 17 people with available brain MRI had abnormal results, including five with increased signal on T2-weighted images (T2WI) and/or fluid-attenuated inversion recovery images (FLAIR) (one in the temporal lobe; one in the hippocampus and basal ganglia; one in the temporal lobe, hippocampus, insular lobe, occipital lobe, and thalamus; one in the frontal lobe and parietal lobe; one in the frontal lobe, parietal lobe, and thalamus), two with increased signal on T2WI and/or FLAIR and contrast enhancement (one in the temporal lobe, insular lobe, and cingulate gyrus; one in the temporal lobe, hippocampus, amygdala, insular lobe, and frontal lobe), one with obvious brain atrophy especially in the frontal lobe, temporal lobe, and hippocampus, and two with contrast enhancement and thickening of meninges.

Eleven (79%) of 14 individuals whose EEG results were available had abnormal findings, including nine with focal or diffuse slow or disorganized activity without epileptic activity, one with diffuse slow and epileptic activity, and one with extreme delta brush. Fourteen (78%) individuals had abnormal CSF findings, including 12 (67%) with pleocytosis and eight (44%) with increased protein concentrations.

3.3. Treatment and outcome

The median length of hospital stay was 22 days (range: 13–63 days). During hospitalization, 17 individuals received immunotherapy, and one person refused immunotherapy. The median interval from onset to receiving immunotherapy was 40 days (range: 10 days to more than half a year). Seven individuals were treated with intravenous immunoglobulin (IVIG, 0.4 g/kg per day for 5 days) alone, one patient was treated with intravenous methylprednisolone (MTP, 1 g/day for 5 days) alone, and nine patients received a combination treatment of IVIG and MTP. Two (11%) of them had tracheotomy for hypoventilation, and one was transferred to an intensive care unit (ICU) because of disease progression. None was treated with plasma exchange, a second-line immunotherapy, or underwent resection surgery of the tumor.

With a median follow-up duration of 13.5 months (range: 8–30 months), at the last follow-up, 14 (78%) of them had a good outcome (mRS: 0–2), seven of whom (50%) made a full recovery (mRS: 0). Four (22%) had a poor outcome (mRS: 3–6), and of those, one died of refractory status epilepticus. The sequelae include memory deficits (seven individuals), psychiatric symptoms (four individuals), seizure (one individual), and decreased consciousness (one individual). Two people

Table 1
Clinical information for older adults.

No.	Sex/age (year)	Interval form onset to diagnosis (days)	Prodromal symptom	Initial symptom	Other symptoms	Tumor	Max mRS/ICU/Tracheotomy	IT	Interval form onset to receive IT (days)	Last mRS (duration of follow up in months)
1	F/45	57	Headache, dizziness, and vomiting	Seizure	Psy, Se, Mov, DC	No	5/no/no	IVIG	57	1 (14)
2	F/45	40	Fever, and rhinorrhea	Psychiatric symptoms	Psy, Se	No	4/no/no	IVIG, MTP	40	1 (10)
3	M/45	48	No	Psychiatric symptoms	Psy, Se, Mov, Aut, DC, CH	Fibroadenoma of breast	5/yes/yes	IVIG, MTP	44	0 (8)
4	F/46	39	No	Psychiatric symptoms	Psy	No	4/no/no	IVIG	39	0 (21)
5	M/46	14	No	Psychiatric symptoms	Psy, Se, Me, Sp, DC	No	5/no/no	MTP, IVIG	11	2 (8)
6	M/49	34	No	Memory deficit	Psy, Se, Me, Mov, Aut, DC	No	5/no/no	IVIG	34	4 (19)
7	F/49	13	No	Memory deficit	Psy, Se, Me, Mov, DC, CH	No	5/no/yes	MTP, IVIG	20	1 (15)
8	M/51	12	Headache and fever	Seizure	Psy, Se, Me, Aut, DC, CH	No	5/no/no	IVIG	12	0 (15)
9	M/51	10	Headache and fever	Psychiatric symptoms	Psy, Se, Me, Mov, DC	No	5/no/no	MTP, IVIG	10	0 (18)
10	F/52	66	No	Psychiatric symptoms	Psy, Me	No	4/no/no	MTP, IVIG	66	0 (12)
11	F/53	53	Fever	Psychiatric symptoms	Psy, Se, Mov, DC	Hamartoma of kidney	5/no/no	IVIG	58	1 (18)
12	F/53	58	Headache and fever	Psychiatric symptoms	Psy, Se,	No	4/no/no	MTP, IVIG	58	0 (13)
13	F/56	58	Headache and fever	Psychiatric symptoms	Psy, Me	No	3/no/no	MTP	58	1 (13)
14	M/57	18	No	Psychiatric symptoms	Psy, Se, Me, Mov, DC	No	5/no/no	IVIG, MTP	19	6 (30.2[a])
15	M/62	86	Dizziness, cough, and fever	Psychiatric symptoms	Psy, Me, Sp, Aut	No	5/no/no	Untreated	Untreated	3 (15)
16	F/66	25	Cough and rhinorrhea	Psychiatric symptoms	Psy, Mov, Aut	No	4/no/no	IVIG, MTP	25	0 (12)
17	M/71	More than half a year	Headache	Memory deficit	Psy, Se, Me, DC	No	5/no/no	IVIG	More than half a year	5 (10)
18	M/78	45	No	Psychiatric symptoms	Psy, Se, Me, Sp, Mov, Aut	Adrenal adenoma	4/no/no	IVIG	45	2 (8)

Abbreviations: Aut = autonomic instability; CH = central hypoventilation; DC = decreased consciousness; F = female; ICU = intensive care unit; IT = immunotherapy; IVIG = intravenous immunoglobulin; MTP = methylprednisolone; M = male; Max = Maximum; Me = memory deficit; Mov = dyskinesias and movement disorders; mRS = modified Rankin Scale; Psy = psychiatric symptoms; Se = seizure; Sp = speech dysfunction.
[a] Time from onset until death (in months).

(11%) had a recurrence at 10 and 14 months, respectively, after the initial episodes.

3.4. Comparisons between older adults (≥45 years old) and younger adults (18–44 years old)

The comparative results between older and younger adults are summarized in Table 2 and Fig. 1. Older adults had a higher rate of present memory deficit as initial symptoms than younger adults (17% vs. 2%, $p = 0.023$), but the rate of memory deficit during the course of disease had no significant difference (79% vs. 82%, $p = 0.720$). Although the proportion of those whose disease was accompanied by tumor had no significant difference, the constituent ratio of tumor type was significantly different. No older adults had teratoma, while 75% of younger adults who had tumor had teratoma ($p = 0.032$).

Older adults had a greater tendency toward a lower rate of positive anti-NMDAR Ab in serum than younger patients (28% vs. 52%, $p = 0.053$). But there are no other significant differences among other ancillary examinations between the two groups.

Older adults had longer intervals from onset to admission to our hospital (30 vs. 13 days, $p = 0.013$) and from onset to accurate diagnosis (42.5 vs. 24 days, $p = 0.045$), and they tended to have a longer interval from onset to receiving immunotherapy (40 vs. 23 days, $p = 0.065$). But the severity (maximum mRS = 5, rate of being transferred to ICU), treatment (MTP, IVIG, and tracheotomy), outcome, and duration of follow-up had no significant difference.

3.5. Comparisons between females and males in older adults

Subgroup analyses were conducted between females and males among older adults (Table 3 and Fig. 2). Older male adults tended to be more likely to have maximum mRS = 5 during disease courses than females (89% vs. 33%, $p = 0.050$). But there were also no significant differences among other clinical symptoms, ancillary examination, and outcome between females and males among older adults.

4. Discussion

Our study presents some novel findings about late-onset anti-NMDAR encephalitis in China. Among 151 people with a definitive diagnosis of anti-NMDAR encephalitis, 18 (12%) are ≥45 years old. The proportion of older adults in this study was relatively higher than that in previous studies mainly involving Europeans and Americans, which reported that only about 5% of people with anti-NMDAR encephalitis were ≥45 years old [3,12]; however, it was similar to a systematic review of cases reported from various countries [6]. Moreover, in our study, males accounted for the same proportion as females among older adults, and there was also no significant difference in sex distribution between younger and older adults, which differed from previous studies in which older adults had a higher percentage of being male patients than younger adults [12]. Previous studies of Chinese and Korean patients showed that 46% to 63% of individuals with anti-NMDAR encephalitis were female, which was significantly different from studies about Western populations, reporting that about 79%–81% were female [3,5,13–15]. Therefore, we postulate that there were possible differences among different races on the sex and age distribution.

Previous studies indicated that children more frequently presented seizure as an initial symptom and less frequently presented psychiatric symptoms [6,15]. Our study found that the frequency of presenting seizure and psychiatric symptoms as an initial symptom had no significant difference between younger and older adults; however, older adults had a higher rate of presenting memory deficit as an initial symptom, which was similar to a previous study [12]. The potential mechanism of this difference is unknown and worth further studies. However, the atypical initial symptom was likely an important cause of delayed admission, diagnosis, and immunotherapy in older adults. On the one

Table 2
Comparisons between older adults and younger adults.

	Total, n (%)	Age ≥ 45 years, n (%)	Age = 18–44 years, n (%)	p values
Total	121	18	103	–
Age, years, median (range, mean ± SD)	29 (18–78, 32.12 ± 11.980)	51.5 (45–78, 54.17 ± 9.488)	27 (18–44, 28.26 ± 7.283)	–
Sex (female)	69 (57%)	9 (50%)	60 (58%)	0.514[a]
Prodromal symptoms	64 (53%)	10 (56%)	54 (52%)	0.806[a]
Initial symptom				
Psychiatric symptoms	73 (60%)	13 (72%)	60 (58%)	0.264[a]
Seizure	30 (25%)	2 (11%)	28 (27%)	0.236[b]
Memory deficit	5 (4%)	3 (17%)	2 (2%)	0.023[b]
Tumor	23 (19%)	3 (17%)	20 (19%)	1.000[b]
Teratoma	15 (65%)	0 (0%)	15 (75%)	0.032[b]
Other tumor	8 (35%)	3 (100%)	5 (25%)	
Abnormal EEG	84 of 98 (86%)	11 of 14 (79%)	73 of 84 (87%)	0.416[b]
Abnormal brain MRI	47 of 110 (43%)	10 of 17 (59%)	37 of 93 (40%)	0.145[a]
Abnormal CSF	81 (67%)	14 (78%)	67 (65%)	0.290[a]
Strongly positive Ab in CSF	63 (52%)	9 (50%)	54 (52%)	0.849[a]
Positive Ab in serum	58 (49%)	5 (28%)	53 of 101 (52%)[d]	0.053[a]
Interval form onset to admission, days, median (IQR)	14 (7.5–30)	30 (10–51)	13 (7–24)	0.013[c]
Interval form onset to diagnosis, days, median (IQR)	25 (15.5–40)	42.5 (17–58)	24 (15–38)	0.045[c]
Length of hospital stay, days, median (IQR)	24 (17–38.5)	22 (16–36)	24 (17–39)	0.710[c]
Interval form onset to receive IT, days, median (IQR), n = 117	25 (16–39)	40 (19.5–58)	23 (15.25–36.75)	0.065[c]
Maximum mRS (score = 5)	86 (71%)	11 (61%)	75 (73%)	0.312[a]
ICU	14 (12%)	1 (6%)	13 (13%)	0.691[b]
Treatment				
IVIG	109 (90%)	16 (89%)	93 (90%)	1.000[b]
MTP	72 (60%)	10 (56%)	62 (60%)	0.711[a]
Tracheotomy	18 (15%)	2 (11%)	16 (16%)	1.000[b]
Duration of follow-up, months, median (IQR)	15 (9–24)	13.5 (10–18)	16 (9–26.75)	0.316[c]
Good outcome	94 of 111 (85%)	14 of 18 (78%)	80 of 93 (86%)	0.472[b]
Death	9 of 111 (8%)	1 of 18 (6%)	8 of 93 (9%)	1.000[b]
Relapse	12 of 111 (11%)	2 of 18 (11%)	10 of 93 (11%)	1.000[b]

Abbreviations: Ab = *N*-methyl-D-aspartate receptor antibody; CSF = cerebrospinal fluid; EEG = electroencephalogram; ICU = intensive care unit; IQR = interquartile range; IT = immunotherapy; IVIG = intravenous immunoglobulin; MTP = methylprednisolone; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; SD = standard deviation.
[a] Chi-squared test.
[b] Fisher's exact test.
[c] Wilcoxon test.
[d] Two individuals were not tested for *N*-methyl-D-aspartate receptor antibody in serum.

hand, compared with psychiatric symptoms, which is the most common initial symptom of anti-NMDAR encephalitis [3,6], memory deficit is more inconspicuous and easy to ignore by patients, families, and outpatient doctors. On the other hand, memory deficit also can present during various other geriatric diseases such as Alzheimer's disease and vascular dementia [16,17], which cause a wider differential diagnosis. Consequently, older adults often experienced a longer duration from onset to admission into hospital and diagnosis, both in the present and

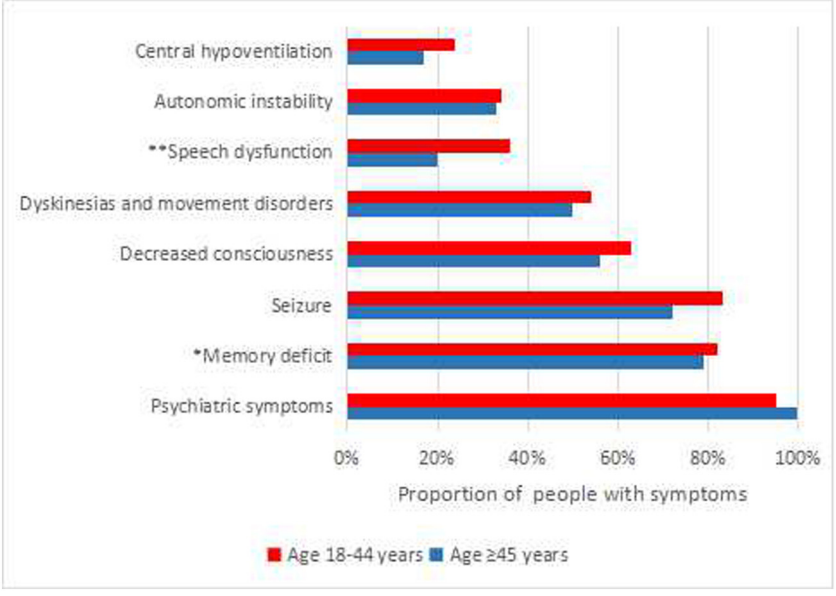

Fig. 1. Comparisons between older adults and younger adults among cumulative symptoms. The red bar represents older adults (age ≥ 45 years old, n = 18), and the blue bar represents younger adults (18–44 years old, n = 103). Fisher's exact test or the chi-squared test was used for statistical analysis, and no significant difference was found between the two groups. *Memory deficit was evaluated in 80 people (14 people: ≥45 years old; 66 people: 18–44 years old). **Speech dysfunction was evaluated in 101 people (15 people: ≥45 years old; 86 people: 18–44 years old). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Comparisons between female and male in older adults.

	Total, n (%)	Female, n (%)	Male, n (%)	p values
Total	18	9	9	
Prodromal symptoms	10 (56%)	6 (67%)	4 (44%)	0.637[a]
Initial symptom				
Psychiatric symptoms	13 (72%)	7 (78%)	6 (67%)	1.000[a]
Seizure	2 (11%)	1 (11%)	1 (11%)	1.000[a]
Memory deficit	3 (17%)	1 (11%)	2 (22%)	1.000[a]
Tumor	3 (17%)	2 (22%)	1 (11%)	1.000[a]
Abnormal EEG	11 of 14 (79%)	5 of 6 (83%)	6 of 8 (75%)	1.000[a]
Abnormal brain MRI	10 of 17 (59%)	5 of 8 (63%)	5 of 9 (56%)	1.000[a]
Abnormal CSF	14 (78%)	5 (56%)	9 (100%)	0.082[a]
Strongly positive Ab in CSF	9 (50%)	3 (33%)	6 (67%)	0.347[a]
Positive Ab in serum	5 (28%)	2 (22%)	3 (33%)	1.000[a]
Interval form onset to admission, days, median (IQR)	30 (10–51)	42 (23–51)	20 (7.5–56)	0.215[b]
Interval form onset to diagnosis, days, median (IQR)	42.5 (17–58)	53 (32–58)	34 (13–67)	0.354[b]
Length of hospital stay, days, median (IQR)	22 (16–36)	23 (16.5–30.5)	21 (15.5–51)	0.791[b]
Interval form onset to receive IT, days, median (IQR), n = 17	40 (19.5–58)	57 (32–58)	26.5 (11.25–44.75)	0.101[b]
Maximum mRS (score = 5)	11 (61%)	3 (33%)	8 (89%)	0.050[a]
ICU	1 (6%)	0 (0%)	1 (11%)	1.000[a]
Treatment				
IVIG	16 (89%)	8 (89%)	8 (89%)	1.000[a]
MTP	10 (56%)	6 (67%)	4 (44%)	0.637[a]
Tracheotomy	2 (11%)	1 (11%)	1 (11%)	1.000[a]
Duration of follow-up, months, median (IQR)	13.5 (10–18)	13 (12–16.5)	15 (8–18.5)	0.824[b]
Good outcome	14 (78%)	9 (100%)	5 (56%)	0.082[a]
Death	1 (6%)	0 (0%)	1 (11%)	1.000[a]
Relapse	2 (11%)	2 (22%)	0 (0%)	0.471[a]

Abbreviations: Ab = *N*-methyl-D-aspartate receptor antibody; CSF = cerebrospinal fluid; EEG = electroencephalogram; ICU = intensive care unit; IQR = interquartile range; IT = immunotherapy; IVIG = intravenous immunoglobulin; MTP = methylprednisolone; MRI = magnetic resonance imaging; mRS = modified Rankin Scale.
[a] Fisher's exact test.
[b] Wilcoxon test.

previous studies [12]. On the other hand, because previous studies indicated that anti-NMDAR encephalitis is often more common in young adults [3,6], screening of NMDAR Ab is easier to ignore in older adults with suspicious symptoms. One of our patients with memory deficit, delusions, hallucinations, agitation, aggression, and insomnia was given a misdiagnosis of vascular dementia for more than 1 year, as NMDAR Ab test was not conducted. Therefore, for older adults presenting with memory deficit and other suspicious symptoms, anti-NMDAR encephalitis should be considered, and further screening is needed.

In the present study, there was no significant difference on cumulative symptoms between the two groups; however, a previous study found that seizure was less common in older adults than in younger adults [12]. In other previous studies, occurrence of seizure also showed no significant difference between children and adults [3,14]. Further

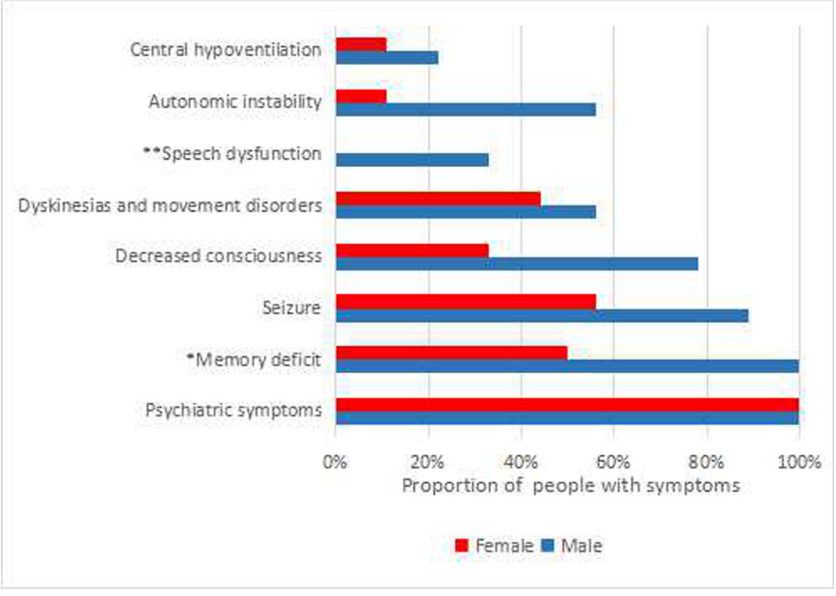

Fig. 2. Comparisons between females and males in older adults among cumulative symptoms. The red bar represents females (n = 9), and the blue bar represents males (n = 9). Chi-squared test was used for statistical analysis, and no significant difference was found between the two groups. *Memory deficit was evaluated in 14 people (6 female; 8 male). **Speech dysfunction was evaluated in 15 people (6 female; 9 male). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

studies are warranted to determine whether there are differences regarding the occurrence of seizure among different age groups. Another valuable finding is that, both in present and previous studies [12], all older adults would present psychiatric symptoms in the course of disease; thus, inquiring about psychiatric symptoms is also an important diagnostic clue for older adults. Furthermore, more than half of older adults would present abnormal results in EEG, brain MRI, and white blood cell count or protein concentration in CSF, which also had no significant difference from younger adults. Therefore, a thorough consideration of all symptoms and a comprehensive auxiliary examination can help clinicians make a definitive diagnosis and allow patients to receive appropriate treatment.

Teratoma has been proven to be significantly related to the occurrence of anti-NMDAR encephalitis [2,18,19] and is an important diagnostic basis [4]. However, in our study, none of the older adults had teratoma. Previous studies also reported that older adults were less likely to have teratoma and more likely to have carcinoma than younger adults [12,20]. Although a previous study found that NMDAR was expressed in breast cancer tissue from people with anti-NMDAR encephalitis [12], no older adults in this study underwent tumor resection; therefore, a random association due to the small size of sample cannot be excluded; also, the relationship between tumor and anti-NMDAR encephalitis cannot be identified, and further studies are needed.

In the present study, we found that older adults tend to have a lower rate of positive NMDAR Ab in serum than younger adults. We speculate that it is because the reliability and efficiency of the immune system in older adults was declining, which caused the weaker autoimmune response [21–23]. Therefore, in older adults who had suspicious clinical presentation, conducting an early NMDAR Ab test in CSF rather than only in serum is extremely necessary and crucial to clarify diagnosis and differentiate anti-NMDAR encephalitis from other diseases.

However, as opposed to previous studies that reported that older adults had possibly less severe conditions and tended to have a poorer outcome [12,20], in our study, older adults had a relatively lower rate of maximum mRS = 5 during hospitalization, being transferred to ICU, and good outcome at the final follow-up; but the severity and outcome between the two groups did not reach statistical difference. On the one hand, it was likely because our patients had shorter follow-up duration than those in previous studies, which caused the long-term outcome of our patients to be undiscovered. On the other hand, the small sample of older adults decreased the test's power and likely caused the false-negative result. Therefore, further studies with larger samples and longer follow-up duration are needed to confirm whether there are differences in the severity and outcome between the two groups.

Subgroup analysis in this study indicated that older male adults showed relatively more severe illness during hospital stay with a boundary p value, and the outcome at the final follow-up indicated that older female adults tended to have a better outcome, but the difference was not statistically significant. However, a similar difference between different sexes has also been reported in other autoimmune diseases, such as systemic lupus erythematosus [24,25]; the potential mechanism needs to be further investigated. However, as opposed to a previous study, which indicated that females had higher rates of tumor among adult patients [26], in this study, no statistical difference was found among rates of tumors in older adults of different sexes. This is likely because no older adults were found to have teratoma in this study, while in a previous study, female adults had a higher rate of having a tumor, mainly because more female adults had ovarian teratoma. Furthermore, previous studies also showed that there were some differences in clinical characteristics between female and male patients—for example, presenting psychiatric symptoms as the initial symptom was more common in female than male patients [5,26]; however, in this study, no significant difference was found in other clinical presentation and accessory examination between older adults of different sexes, possibly because of the diversity between age. But because of the limited sample of older adults in this study, the subgroup analysis results of sex should be interpreted cautiously, and further studies with larger samples are warranted.

Our study also had several limitations. Firstly, as no older adults with tumor underwent surgery, we were unable to test NMDAR in tumor tissue. Secondly, because of the small sample of older adults and shorter follow-up duration, comparative results should be interpreted with caution, and further investigations are warranted. Thirdly, because none of our older adults received plasma exchange and second-line immunotherapy, these treatments were not evaluated in this study. Fourthly, as all people included in the study were Chinese, our findings cannot be extended to other races. Lastly, the initial symptom was defined on the basis of the families' descriptions and the clinicians' expertise, which likely caused interpretative bias.

5. Conclusion

This is the first study to focus on older adults with anti-NMDAR encephalitis in China. And this preliminary study indicates that the proportion of older adults in China with anti-NMDAR encephalitis seems higher than that in studies mainly involving Europeans and Americans. Furthermore, compared with younger adults, people ≥45 years old need longer duration to admission and diagnosis, and they are more likely to present memory deficit as their initial symptom and less likely to have teratoma and positive NMDAR Ab in serum, which imply that a comprehensive consideration of all symptoms and early NMDAR Ab test in CSF in older adults with suspicious symptoms are vital for diagnosis. However, because of the small sample in this study, our findings should be carefully interpreted, and further studies with larger sample sizes are urgently needed to summarize the characteristics of older adults with anti-NMDAR encephalitis.

Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

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