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Late-Onset Anti-$GABA_B$ Receptor Encephalitis

Clinical Characteristics and Outcomes Differing From Early-Onset Patients

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Abstract

Background and Objectives

Existing evidence indicates anti-$GABA_B$ receptor encephalitis ($GABA_B$R-E) seems to occur more commonly later in life, yet the age-associated differences in clinical features and outcomes are not well determined. This study aims to explore the demographic, clinical characteristics, and prognostic differences between late-onset and early-onset $GABA_B$R-E and identify predictors of favorable long-term outcomes.

Methods

This is an observational retrospective study conducted in 19 centers from China. Data from 62 patients with $GABA_B$R-E were compared between late-onset (aged 50 years or older) and early-onset (younger than 50 years) groups and between groups with favorable outcomes (modified Rankin scale (mRS) ≤ 2) and poor outcomes (mRS >2). Logistic regression analyses were applied to identify factors affecting long-term outcomes.

Results

Forty-one (66.1%) patients experienced late-onset $GABA_B$R-E. A greater proportion of males, a higher mRS score at onset, higher frequencies of ICU admission and tumors, and a higher risk of death were demonstrated in the late-onset group than in the early-onset group. Compared with poor outcomes, patients with favorable outcomes had a younger onset age, a lower mRS score at onset, lower frequencies of ICU admission and tumors, and a greater proportion with immunotherapy maintenance for at least 6 months. On multivariate regression analysis, age at onset (OR, 0.849, 95% CI 0.739–0.974, $p = 0.020$) and the presence of underlying tumors (OR, 0.095, 95% CI 0.015–0.613, $p = 0.013$) were associated with poorer long-term outcomes, whereas immunotherapy maintenance for at least 6 months was associated with favorable outcomes (OR, 10.958, 95% CI 1.469–81.742, $p = 0.020$).

Discussion

These results demonstrate the importance of risk stratification of $GABA_B$R-E according to age at onset. More attention should be paid to older patients especially with underlying tumors, and immunotherapy maintenance for at least 6 months is recommended to achieve a favorable outcome.

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Glossary

CBA = cell-based assay; **GABAB** = gamma aminobutyric acid–B; **GABABR** = gamma aminobutyric acid–B receptor; **GAD65** = glutamic acid decarboxylase 65; **ICU** = intensive care unit; **IQR** = interquartile range; **IVIG** = intravenous immunoglobulin; **mRS** = modified Rankin scale; **NMDAR** = N-methyl-D-aspartate receptor; **OR** = odds ratio; **KCTD16** = potassium channel tetramerization domain–containing 16; **PKC-γ** = protein kinase C gamma; **SCLC** = small cell lung cancer; **SOX1** = Sry-like high-mobility group box 1; **TBA** = tissue-based assay; **Tr/DENR** = delta/notch–like epidermal growth factor–related receptor; **Zic4** = zinc finger protein 4.

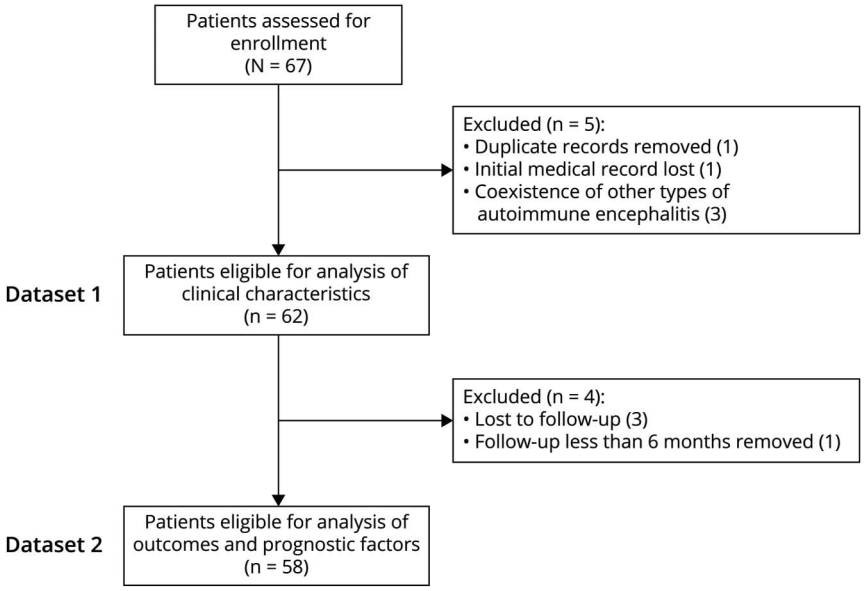
Anti-gamma aminobutyric acid–B receptor encephalitis ($GABA_BR$-E) is a recently recognized autoimmune disease entity of the CNS characterized by seizures, confusion, memory deficit, and psychosis. Since the first description in 2010,[1] an increasing number of cases with $GABA_BR$-E have been identified, and the landscape of clinical, immunologic, and neuroimaging manifestations is still expanding.[2-6] However, systemically investigating the clinical picture and long-term outcomes of this disease remains challenging owing to most prior reports available with small sample sizes. Recently, age-associated differences in clinical characteristics and outcomes have been determined in several autoimmune diseases such as neuromyelitis optica spectrum disorders,[7] myasthenia gravis,[8] and anti-NMDAR encephalitis.[9,10] Prior studies have implied that $GABA_BR$-E seems to occur more commonly later in life.[1-3,6] However, the demographic, clinical, and prognostic differences between late-onset and early-onset $GABA_BR$-E have not been well determined till now. Although several smaller series have identified risk factors of poor outcomes such as older age and tumor diagnosis,[2,5,11] these findings still require further confirmation in larger cohorts. To address these questions, we conducted this observational, retrospective, multicenter study involving 62 patients with $GABA_BR$-E to provide a systematic investigation of the clinical picture of this rare CNS autoimmune disease, particularly for further clinical refinement focusing on age-associated differences. In addition, we aimed to determine the predictive factors for favorable outcomes.

Methods

Patients and Data Collection

Demographic and clinical information for this observational, retrospective, multicenter study were collected from 19 centers in China. As shown in Figure 1, a total of 62 patients admitted between February 2015 and April 2022 fulfilling diagnostic criteria for $GABA_BR$-E[12] were included into dataset 1 and divided into early-onset (age at onset younger than 50 years) and late-onset (age at onset 50 years or older) groups. The medical records of all included patients were retrospectively reviewed. Data on sex, age at onset, smoking history, symptoms at presentation, results of auxiliary laboratory tests, brain MRI manifestations, EEG findings, admission to intensive care unit (ICU), immunotherapy regimens, and clinical relapses were collected. Admission or

Figure 1 Flowchart Diagram of the Included Patients With $GABA_BR$-E



transfer to ICU was mainly due to refractory status epilepticus or serious complications such as severe pneumonia. Clinical relapse was defined as new onset or worsening of symptoms occurring after an initial improvement or stabilization for at least 2 months. A follow-up was performed by face-to-face or telephone interview at 3 months after the initial presentation, and the modified Rankin scale (mRS) was used to evaluate the short-term clinical outcomes. Favorable outcome was defined as mRS score ≤2 and poor outcome as >2. The last follow-up was completed by outpatient or telephone interviews in May 2022, and mRS scores were assessed again to evaluate the long-term clinical outcomes. Fifty-eight patients completing the last follow-up and of at least 6 months were included into dataset 2 for further analyses of clinical outcomes and prognostic factors (Figure 1).

Screening for Anti-$GABA_BR$ and Other Paraneoplastic Antibodies

For diagnosing and enrolling those with $GABA_BR$-E in this study, cell-based assays (CBAs) were used to detect antibodies to $GABA_BR$ in the serum and/or CSF. In patients with serum-only reactivity, tissue-based assays (TBAs) were conducted with rat or monkey brain sections to further confirm positive results. Meanwhile, those with coexisting CSF antineuronal antibodies suggestive of autoimmune encephalitis such as anti-NMDAR encephalitis were excluded from our cohort. Moreover, serum or CSF samples were tested by CBAs or immunodot assays for paraneoplastic antibodies to Hu, Yo, Ri, CV2, Ma1, Ma2, SOX1, GAD65, Tr/DNER, Zic4, Titin, PKC-γ, recoverin, and amphiphysin.

Statistical Analysis

Statistical analyses were performed using SPSS 23.0, and figures were generated using GraphPad Prism 8.0. Categorical data were presented as number with percentage and continuous data as median with interquartile range (IQR). Intergroup differences were evaluated by chi-square or Fisher exact tests for categorical data and by Student *t* test or Mann-Whitney *U* test for continuous data with normal or skew distribution. Kaplan-Meier curves were generated for the discovery of tumor according to age at onset, and the differences were compared by the log-rank test. Binary logistic regression analyses were performed to identify predictors of a favorable clinical outcome. Variables with $p < 0.1$ from the univariate regression analysis were included in the subsequent multivariate analysis. Two-sided p values <0.05 were considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Committee of Tangdu Hospital (approval number K202112-18), and informed consent was waived based on the retrospective and observational nature of this study.

Data Availability

Anonymized data will be made available by request from the corresponding author.

Results

Demographic and Clinical Characteristics According to Age at Onset

As summarized in Table 1, 41 (66.1%) of 62 patients experienced late-onset $GABA_BR$-E. Males were predominant (male-to-female [M/F] ratio, 3.6:1) in the late-onset group, in contrast to a slight female predominance (M/F ratio, 0.8:1) in the early-onset group. Figure 2 shows the age-associated distribution of male and female patients. Overall, the age at onset ranged from 7 to 75 years, and the highest incidence was in the age group of 50–59 years. The most common symptoms at onset were epileptic seizures (54 cases, 87.1%), including 47 cases of generalized tonic-clonic seizures, 2 cases of complex partial seizures, and 5 cases of partial seizures with secondary generalization. Status epilepticus presented in 19 (35.2%) of 54 patients. Psychosis was another frequent symptom presented in 34 (54.8%) patients. The most common type was behavioral alterations recorded in 26 (76.5%) cases, followed by agitation in 25 (73.5%) cases, hallucinations in 5 (14.7%) cases, depression in 3 (8.8%) cases, delusions in 2 (5.9%) cases, and anxiety in 1 (2.9%) case. Although the incidences of psychiatric symptoms did not differ between early-onset and late-onset groups, however, the latter group underwent a worse disease status, showing a higher mRS score at onset and higher ICU admission rate than the former group ($p = 0.045$ and 0.035, respectively).

Sixty-one patients received brain MRI scans at onset, and 24 (39.3%) revealed abnormal manifestations. The most frequently involved area was the temporal lobe, followed by the frontal lobe and the insular lobe. Of 53 patients with EEG results available, 45 (84.9%) showed abnormal findings including epileptic discharges in 26 cases and slow waves in 19 cases. The frequencies of abnormal MRI and EEG findings did not differ between early-onset and late-onset groups (Table 1).

Antibodies to $GABA_BR$ were detected in serum and/or CSF samples of all the enrolled patients. Of them, 58 (93.5%) patients underwent antibody testing in the serum and CSF, with positive responses in both samples in 49 (84.5%) cases, only in the serum in 6 (10.3%) cases, and only in the CSF in 3 (5.2%) cases. Generally, antibodies to $GABA_BR$ seem to have a slightly higher positive rate in the serum than in the CSF (95.2% vs 88.7%) in our cohort, but early-onset and late-onset patients showed no significant differences in the positive rates and antibody titers in both the serum and CSF. In addition, the CSF profile did not differ between late-onset and early-onset groups.

Seven (11.9%) patients experienced 1 clinical relapse during the follow-up, with a median time from onset to relapse of 6 (IQR 4–22) months. Relapses occurred in 5 cases undergoing oral prednisone tapering; of them, 2 cases were combined

Table 1 Demographic, Clinical Features, and Immunotherapy in Patients With $GABA_BR$-E According to Age at Onset (Aged 50 y or Older or Younger Than 50 y)

	Total cohort (n = 62)	Late onset (n = 41)	Early onset (n = 21)	*p* Value
Sex ratio (M:F)	41:21 (2.0:1)	32:9 (3.6:1)	9:12 (0.8:1)	0.006[i]
Age at onset (y), median (IQR)	56.0 (45.8–63.3)	60.0 (56.0–65.5)	41.0 (30.5–46.5)	N/A
Smoking history, n (%)	23 (37.1)	17 (41.5)	6 (28.6)	0.320
Interval from onset to diagnosis (d), median (IQR)	13.5 (7.0–31.3)	13.0 (7.5–23.0)	22.0 (6.5–32.0)	0.352
Symptoms at initial presentation, n (%)				
Seizures	54 (87.1)	35 (85.4)	19 (90.5)	0.705
Psychosis	34 (54.8)	21 (51.2)	13 (61.9)	0.424
Memory deficit	19 (30.6)	14 (34.1)	5 (23.8)	0.403
Confusion	15 (24.2)	11 (26.8)	4 (19.0)	0.498
Fever	7 (11.3)	3 (7.3)	4 (19.0)	0.214
Headache	4 (6.5)	1 (2.4)	3 (14.3)	0.108
Speech disturbance	1 (1.6)	1 (2.4)	0 (0)	1.000
Ataxia	1 (1.6)	0 (0)	1 (4.8)	0.339
Diplopia	1 (1.6)	0 (0)	1 (4.8)	0.339
mRS score at onset, median (IQR)	3 (2–4)	3 (2–4)	2 (1–4)	0.045[i]
Admission to ICU, n (%)	23 (37.1)	19 (46.3)	4 (19.0)	0.035[i]
Abnormal brain MRI, n (%)[a]	24 (39.3)	15 (36.6)	9 (45.0)	0.528
Temporal lobe	20 (32.8)	12 (29.3)	8 (40.0)	0.402
Frontal lobe	4 (6.6)	3 (7.3)	1 (5.0)	1.000
Insular lobe	3 (4.9)	2 (4.9)	1 (5.0)	1.000
Parietal lobe	2 (3.3)	1 (2.4)	1 (5.0)	1.000
Occipital lobe	1 (1.6)	1 (2.4)	0 (0)	1.000
Cerebellum	1 (1.6)	0 (0)	1 (5.0)	0.328
Abnormal EEG, n (%)[b]	45 (84.9)	29 (90.6)	16 (76.2)	0.240
Epileptic discharges	26 (49.1)	15 (46.9)	11 (52.4)	0.695
Slow activity	19 (35.8)	14 (43.8)	5 (23.8)	0.139
Antibody status				
Positive in the CSF, n (%)[c]	54 (90.0)	37 (92.5)	17 (85.0)	0.390
Titer in the CSF, median (IQR)[d]	1:32 (1:10–1:100)	1:100 (1:15–1:100)	1:32 (1:2–1:100)	0.091
Positive in the serum, n (%)[c]	57 (95.0)	37 (94.9)	20 (95.2)	1.000
Titer in the serum, median (IQR)[e]	1:66 (1:32–1:100)	1:100 (1:32–1:100)	1:32 (1:32–1:100)	0.398
CSF analysis, median (IQR)				
Opening pressure (mmH_2O)[f]	140 (110–180)	140 (110–180)	145 (108–181)	0.979
WBC (/μL)[g]	11 (5–29)	14 (6–30)	9 (2–20)	0.255
Pleocytosis, n (%)	46 (78.0)	32 (82.1)	14 (70.0)	0.332
Protein (mg/L)[h]	389.7 (300.0–480.0)	396.7 (320.0–514.2)	311.3 (282.5–467.5)	0.130
Elevated protein, n (%)	18 (35.3)	14 (40.0)	4 (25.0)	0.298

Continued

Table 1 Demographic, Clinical Features, and Immunotherapy in Patients With $GABA_BR$-E According to Age at Onset (Aged 50 y or Older or Younger Than 50 y) *(continued)*

	Total cohort (n = 62)	Late onset (n = 41)	Early onset (n = 21)	*p* Value
Tumor, n (%)	21 (33.9)	20 (48.8)	1 (4.8)	0.001[j]
Immunotherapy, n (%)	60 (96.8)	40 (97.6)	20 (95.2)	1.000
Steroids	51 (82.3)	36 (87.8)	15 (71.4)	0.160
IVIG	47 (75.8)	30 (73.2)	17 (81.0)	0.498
Immunosuppressants	15 (24.2)	10 (24.4)	5 (23.8)	0.960
Plasma exchange	1 (1.6)	0 (0)	1 (4.8)	0.339
Length of hospital stay (d), median (IQR)	17.0 (13.8–25.2)	17.0 (13.5–26.5)	17.0 (13.5–25.5)	0.970
Relapse, n (%)[g]	7 (11.9)	4 (10.5)	3 (14.3)	0.691

Abbreviations: ICU = intensive care unit; IQR = interquartile range; IVIG = IV immunoglobulin; mRS = modified Rankin scale; WBC = white blood cell.
Early onset was defined as an onset age younger than 50 y, and late onset was defined as an onset age 50 y or older. CSF pleocytosis was defined as WBC ≥5/μL, and an elevated protein was defined as ≥ 450 mg/L. Immunosuppressants include rituximab, azathioprine, mycophenolate mofetil, and cyclophosphamide.
[a] Analysis of 61 patients with results available.
[b] Analysis of 53 patients with results available.
[c] Analysis of 60 patients with results available.
[d] Analysis of 49 patients with results available.
[e] Analysis of 52 patients with results available.
[f] Analysis of 56 patients with results available.
[g] Analysis of 59 patients with results available.
[h] Analysis of 51 patients with results available.
[i] $p < 0.05$.
[j] $p < 0.01$.

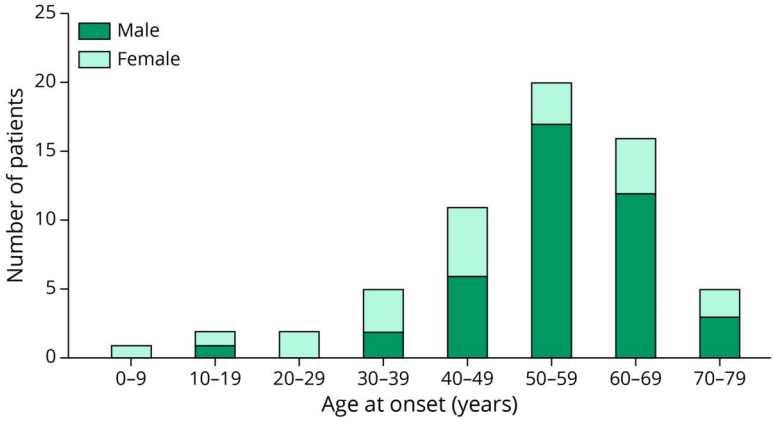
with rituximab maintenance therapy. Other 2 patients experienced relapses 22 months and 24 months, respectively, after the discontinuation of immunosuppression. Four (10.5%) late-onset and 3 (14.3%) early-onset patients experienced clinical relapses, with no age-associated differences in the rate of relapsing patients observed (Table 1).

Additional Paraneoplastic Antibodies and Tumor Association

Paraneoplastic antibodies were tested in 23 serum and 14 CSF samples. Seven late-onset patients had at least 1 additional autoantibody in sera, including anti-Hu (n = 3), anti-SOX1 (n = 3), anti-GAD65 (n = 2), antiamphiphysin (n = 1), antirecoverin (n = 1), and anti-Zic4 (n = 1). Especially, 2 patients had triple paraneoplastic antibodies in sera, with anti-Hu, anti-SOX1, and anti-GAD65 for 1 case and anti-Hu, anti-SOX1, and anti-Zic4 for the other. Besides, 1 case had CSF anti-SOX1 and anti-Hu antibodies and another had CSF anti-SOX1 antibodies. Of note, no paraneoplastic antibodies were detected in early-onset patients.

Of the 7 patients with additional paraneoplastic antibodies, concurrent lung cancers were found in 4 patients. Specifically, 1 had anti-Hu, anti-SOX1, and anti-GAD65 antibodies, 1 had

Figure 2 Distribution of Patients With $GABA_BR$-E According to Age at Onset and Sex



anti-Hu, anti-SOX1, and anti-Zic4 antibodies, 1 had anti-SOX1, and another had antirecoverin antibodies. Of the other 3 patients without concurrent tumors, 1 had anti-Hu, 1 had antiamphiphysin, and another had anti-GAD65 antibodies.

Underlying Tumor and Its Relevance to $GABA_BR$-E

Tumors were found in 21 patients and occurred more frequently in the late-onset group than in the early-onset group (48.8% vs 4.8%, $p < 0.001$, Table 1; eFigure 1, links.lww.com/NXI/A861). Generally, lung cancer was the most frequent type and detected in 18 (85.7%) cases. Of them, 11 (64.7%) had pathologically confirmed small cell lung cancer (SCLC), 1 (5.9%) had lung adenocarcinoma in situ, 2 (11.8%) had lung cancer with the pathologic type not available, 3 (17.6%) had radiographically diagnosed lung cancer without a final pathologic confirmation, and 1 (5.9%) had pulmonary epithelioid hemangioendothelioma. In addition, 1 case had pathologically confirmed gastric cancer (previously reported[13]), 1 had esophageal cancer, and 1 had laryngeal cancer. No significant differences in the incidence of each type of tumor and in the use of tumor-associated treatments were observed between late-onset and early-onset groups (eTable 1). Of note, 10 patients were found to have tumors at the diagnosis of $GABA_BR$-E, and other 11 were found during the follow-up with a median interval from encephalitis diagnosis to discovery of tumors of 5.0 (IQR 2.0–12.0) months.

Immunotherapy and Follow-up mRS Profiles

Overall, 60 (96.8%) patients received immunotherapy that was given after a diagnosis of $GABA_BR$-E had been made or was initiated as an empirical treatment before diagnosis. Table 1 summarizes immunotherapy profiles in detail (steroids, IVIG, plasma exchange, rituximab, azathioprine, cyclophosphamide, and mycophenolate mofetil alone or in combination), and no differences in the use of each regimen were observed between early-onset and late-onset groups. The distributions of mRS scores at disease onset, 3-month follow-up, and the last follow-up are shown in Figure 3, and the proportions of cases with mRS scores ≤2 were 35.5% (22/62), 81.0% (47/58), and 72.4% (42/58), respectively. Until the last follow-up, 13 (22.4%) had died of underlying tumors or serious complications of encephalitis, and all of them were late-onset cases.

Predictors of Favorable Clinical Outcomes

Table 2 outlines the comparisons between patients with favorable and poor outcomes, where 58 patients with a follow-up of at least 6 months (median, 27.0 [IQR, 12.8–38.5] months) were included. Patients with favorable outcomes had a younger age at onset, lower mRS score at onset, lower ICU admission rate, lower incidence of tumors, and greater proportion with immunotherapy maintenance for at least 6 months than those with poor outcomes (all p values <0.05). In the univariate logistic regression model, age at onset (odds ratio [OR] 0.880, 95% CI 0.811–0.955, $p = 0.002$) and presence of underlying tumor (OR 0.067, 95% CI 0.017–0.260, $p < 0.001$) were negatively associated with favorable outcomes, whereas immunotherapy maintenance for at least 6 months was positively associated with favorable outcomes (OR 4.400, 95% CI 1.278–15.152, $p = 0.019$). Subsequent multivariate analysis indicated that a younger age at onset, absence of underlying tumors, and long-term immunotherapy maintenance were the main independent prognostic factors for favorable outcomes (Table 3).

Discussion

By enrolling a Chinese cohort of 62 patients with $GABA_BR$-E in this study, we conducted a thorough analysis of the clinical picture of this rare autoimmune disease, and key findings include the following: (1) the first evidence regarding age-associated differences in the demographic, clinical characteristics, and outcomes associated with $GABA_BR$-E are provided, (2) the spectrum of clinical and immunologic manifestations

Figure 3 Distribution of mRS Scores at the Initial Presentation, 3-Month Follow-up, and the Last Follow-up

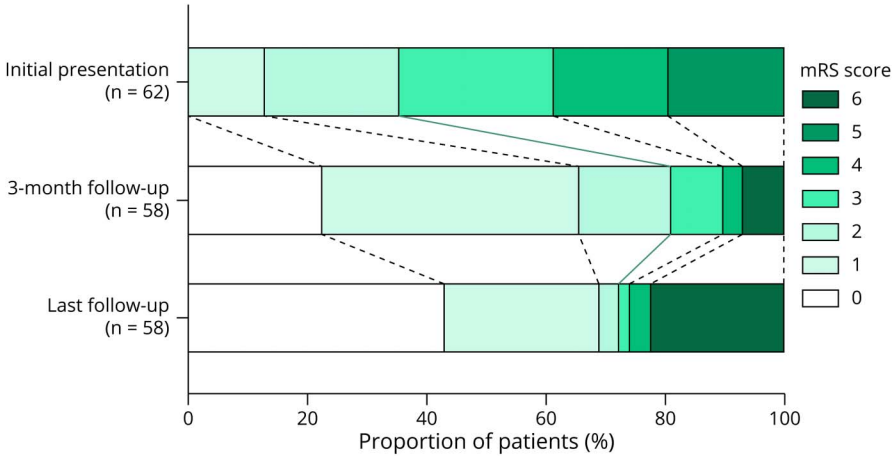


Table 2 Comparison of Demographic and Clinical Features of $GABA_BR$-E Patients With Favorable and Poor Outcomes

	Favorable outcome (n = 42)	Poor outcome (n = 16)	$Z/t/\chi^2$ value	*p* Value
Sex ratio (M:F)	27:15 (1.8:1)	11:5 (2.2:1)	0.102	0.749
Age at onset (y), median (IQR)	50.0 (40.5–58.3)	64.0 (59.0–70.5)	−4.212	<0.001[i]
Smoking history, n (%)	14 (33.3)	7 (43.8)	0.544	0.461
Symptoms at presentation, n (%)				
Seizures	36 (85.7)	14 (87.5)	0.031	1.000
Psychosis	21 (50.0)	11 (68.8)	1.647	0.199
Memory deficit	12 (28.6)	7 (43.8)	1.212	0.271
Confusion	9 (21.4)	3 (18.8)	0.051	1.000
Fever	5 (11.9)	2 (12.5)	0.004	1.000
Headache	4 (9.5)	0 (0)	1.637	0.567
Speech disturbance	1 (2.4)	0 (0)	0.388	1.000
Ataxia	1 (2.4)	0 (0)	0.388	1.000
Diplopia	1 (2.4)	0 (0)	0.388	1.000
mRS score at onset, median (IQR)	3 (2–4)	4 (2–5)	−2.128	0.033[h]
Admission to ICU, n (%)	11 (26.2)	9 (56.3)	4.634	0.031[h]
Abnormal brain MRI, n (%)[a]	15 (36.6)	8 (50.0)	0.860	0.354
Abnormal EEG, n (%)[b]	30 (81.1)	13 (92.9)	1.065	0.419
Antibody status, n (%)				
Positive in the CSF[c]	34 (85.0)	16 (100.0)	2.688	0.168
Titer in the CSF, median (IQR)[d]	1:32 (1:3.2–1:100)	1:100 (1:32–1:265)	−1.923	0.054
Positive in the serum	41 (97.6)	14 (87.5)	2.419	0.181
Titer in the serum, median (IQR)[e]	1:32 (1:32–1:100)	1:66 (1:31–1:100)	−0.247	0.805
CSF analysis, n (%)				
Pleocytosis[f]	30 (75.0)	12 (80.0)	0.151	1.000
Elevated protein[g]	10 (28.6)	7 (50.0)	2.027	0.193
Tumor, n (%)	7 (16.7)	13 (81.3)	21.391	<0.001[i]
Immunotherapy, n (%)	41 (97.6)	15 (93.8)	0.521	0.479
Maintenance ≥6 mo	28 (66.7)	5 (31.3)	5.926	0.015[h]
Relapse, n (%)	6 (14.3)	1 (6.3)	0.705	0.660

Abbreviations: ICU = intensive care unit; IQR = interquartile range; IVIG = IV immunoglobulin; mRS = modified Rankin scale; WBC = white blood cell.
A favorable clinical outcome was defined as an mRS score ≤2 at last follow-up, and a poor clinical outcome was defined as an mRS score >2. CSF pleocytosis was defined as WBC ≥5/μL, and an elevated protein was defined as ≥450 mg/L.
[a] Analysis of 57 patients with results available.
[b] Analysis of 51 patients with results available.
[c] Analysis of 56 patients with results available.
[d] Analysis of 45 patients with results available.
[e] Analysis of 50 patients with results available.
[f] Analysis of 55 patients with results available.
[g] Analysis of 49 patients with results available.
[h] $p < 0.05$.
[i] $p < 0.01$.

is further expanded based on the discoveries of several novel types of underlying tumors and additional paraneoplastic antibodies not previously reported, and (3) a younger age at onset, absence of underlying tumors, and long-term immunotherapy maintenance serve as the independent predictors of favorable outcomes.

Table 3 Logistic Regression Analysis of Factors Associated With Favorable Outcomes in Patients With $GABA_BR$-E

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Sex, male vs female	0.600 (0.164–2.192)	0.440		
Age at onset (y)	0.880 (0.811–0.955)	0.002[b]	0.849 (0.739–0.974)	0.020[a]
Smoking history, yes vs no	0.500 (0.155–1.613)	0.246		
mRS score at onset	0.628 (0.385–1.023)	0.062	0.701 (0.267–1.838)	0.470
Admission to ICU, yes vs no	0.355 (0.107–1.175)	0.090	0.424 (0.050–3.612)	0.432
Abnormal brain MRI, yes vs no	0.742 (0.229–2.401)	0.618		
Abnormal EEG, yes vs no	0.390 (0.043–3.538)	0.402		
CSF pleocytosis, yes vs no	0.750 (0.175–3.209)	0.698		
Elevated CSF protein, yes vs no	0.343 (0.092–1.276)	0.110		
Tumor, yes vs no	0.067 (0.017–0.260)	<0.001[b]	0.095 (0.015–0.613)	0.013[a]
Long-term immunotherapy, yes vs no	4.400 (1.278–15.152)	0.019[a]	10.958 (1.469–81.742)	0.020[a]
Relapse, yes vs no	2.000 (0.218–18.333)	0.540		

Abbreviations: ICU = intensive care unit; mRS = modified Rankin scale; OR = odds ratio.
Long-term immunotherapy was defined as maintenance for at least 6 mo.
[a] $p < 0.05$.
[b] $p < 0.01$.

In this study, the extensive coverage of age at onset ranging from 7 to 75 years and the highest incidence between the age group of 50 and 59 years indicate the vulnerability to $GABA_BR$-E across all ages especially the older age group. Consistent with prior reports,[2,3,14-16] male individuals are more prone to $GABA_BR$-E than female individuals (M/F, 2.0: 1). More notably, we observed a more obvious male predominance in the late-onset group, in contrast to a slight female predominance in the early-onset group. We found no significant differences in the clinical characteristics, MRI and EEG findings, and immunotherapy profiles between the 2 groups. However, special attention needs to be paid to late-onset patients, given the worse disease status demonstrated by the higher mRS score at onset, higher ICU admission rate, and higher risk of death in this subgroup.

A potential association of $GABA_BR$-E with neoplasms has been noticed since the first description in 2010.[1] Tumors were detected in approximately 50% of patients in most prior studies mainly focusing on the Caucasian population,[1,2,17] and this high oncologic association is reinforced by a recent systematic review.[15] However, in our cohort, a lower frequency of tumors (21/62, 33.9%) was determined, which is similar to those in other 3 Chinese cohorts ranging from 27.3% to 33.3%.[3,5,16] One possibility might be taken into account that with a longer follow-up, the frequency of tumors will increase, given the finding that the maximum interval from encephalitis diagnosis to discovery of tumor was 28 months in our cohort. Meanwhile, we conducted a pooled analysis involving 247 Chinese patients from previously reported cohorts[3,5,6,14,16,18-23] and our cohort and found tumors in 92 cases, with an estimate incidence rate of 37.2%. The lower incidence of tumors in Chinese patients with $GABA_BR$-E implies the possible involvement of differences across race and ethnicity; this hypothesis needs further verification in a larger sample size of Chinese patients with a longer follow-up. Consistent with prior reports,[1-3,15,24] lung cancer especially SCLC is the most frequent type of neoplasm in our cohort. Although lung cancer occurred more frequently in the late-onset group (17/41, 41.5%) than in the early-onset group (1/21, 4.8%), no difference in the proportion of smokers was observed between the 2 groups, thus eliminating to some degree tobacco's contribution to lung cancer occurrence in the context of $GABA_BR$-E. In addition, other types of tumors such as pulmonary epithelioid hemangioendothelioma, esophageal cancer, and laryngeal cancer were identified for the first time, and the potential mechanisms underlying this complex oncologic association require future investigation. Of note, tumors occurred more frequently in the late-onset group than in the early-onset group and are associated with poorer long-term outcomes in the multivariate regression model, highlighting the importance of broader and longitudinal screenings for underlying tumors in patients with $GABA_BR$-E.

In recent years, coexisting paraneoplastic antibodies have been increasingly reported in $GABA_BR$-E, implying the complexity of immunopathogenesis underlying this disease. The most frequently reported are anti-Hu and anti-SOX1,[15] and similar findings were observed in our cohort though not all patients had received paraneoplastic tests. More notably, 2

additional paraneoplastic antibodies, anti-recoverin and anti-Zic4, were detected for the first time though their pathogenic effects remain undetermined. In clinical practice, caution is needed when discussing the implications of paraneoplastic antibodies in the context of $GABA_BR$-E, given the fact that tumor association varies from paraneoplastic antibodies detected.[25-27] In this study, 3 patients with SCLC had anti-Hu and anti-SOX1 antibodies alone or combined, and these are considered true positives, given the high association of >85% with cancers.[25] Considering anti-GAD65 is a lower-risk antibody with cancer and anti-Zic4 primarily associated with Hodgkin lymphoma,[25,27] the 2 antibodies in the setting of SCLC are believed to be incidental. In another patient with lung adenocarcinoma in situ and antirecoverin antibodies, their close association is well identified despite the sensitivity of antirecoverin in lung cancer being less than 20%.[28] Moreover, it is of note that the remaining 3 patients without concurrent tumors each had anti-Hu, anti-amphiphysin, and anti-GAD65 antibodies in the serum. The absence of tumors and specific clinical presentations increased the likelihood of false positives for these antibodies, but anti-Hu and anti-amphiphysin, the 2 reported antibodies having high association with cancers,[25,29] draw increasing concerns about the subsequent occurrence of new malignancy in these patients.

Regarding the prognosis of $GABA_BR$-E, the mRS scores at 3 months after the initial presentation were evaluated as short-term outcomes and scores at the last follow-up (median, 25.0 months) as long-term outcomes. Overall, 81.0% (47/58) of patients achieved a favorable short-term outcome, but the proportion decreased to 72.4% (42/58) when considering the long-term outcome. This decrease is mainly attributed to the increased mortality because a growing number of patients had died of underlying tumors with the prolonged follow-up. Based on the nature of this autoimmune diseases, immunotherapy has been extensively recommended for $GABA_BR$-E in addition to symptomatic treatments such as antiepileptic therapy, and it has brought a good prognosis for most patients.[1-3,5,19,30] In this study, nearly all patients (56/58, 96.6%) were treated with immunotherapy, so we could not compare the long-term outcomes between patients with and without immunotherapy. Although the proportions of patients receiving immunotherapy were comparable between groups with favorable and poor outcomes, a greater proportion of patients with immunotherapy for at least 6 months was observed in the former group than in the latter group, suggestive of the necessity of long-term immunotherapy maintenance for this disease. Compared with patients with poor outcomes, those with favorable outcomes have a younger age at onset, lower mRS score at onset, lower ICU admission rate, and lower frequency of tumors. Thus, it is not surprising that several of these parameters negatively correlated with favorable outcomes in the univariate logistic regression model. Further multivariate regression analysis revealed that a younger age at onset and absence of tumors together with long-term immunotherapy maintenance were the independent prognostic factors for favorable outcomes. Therefore, long-term immunotherapy and more frequent tumor screenings should be recommended in those late-onset patients to achieve a better long-term prognosis for this subgroup.

There are several limitations to this study. First, given the nature of this retrospective multicenter cohort study, there was a lack of the unified recommendation regarding the coverage of examinations when diagnosing $GABA_BR$-E. As a result, not all the results of auxiliary tests of interest were available from the enrolled patients, thus to a certain extent affecting the analysis of disease picture. Second, we notice that the treatment strategies and timing of treatment initiation were inconsistent although nearly all patients received immunotherapy in this study, which might contribute to different clinical outcomes theoretically. This possible effect needs to be investigated subsequently. Third, the paraneoplastic antibody panel to be detected varied among centers. Thus, it is a pity that we could not evaluate the positive rate of each additional autoantibody in the whole cohort. A recent study has reported that patients with $GABA_BR$-E also had antibodies targeting potassium channel tetramerization domain–containing (KCTD)16, an intracellular $GABA_BR$-accessory subunit. This is particularly true for patients with small cell lung carcinoma.[4] Unfortunately, KCTD16 antibodies were not tested because of the absence of coverage by the paraneoplastic antibody panels used in this study. To address these limitations, additional prospective multicenter studies with rigorous design, large sample size, and sufficient clinical data of interest are warranted in the future.

In conclusion, our study demonstrated for the first time the demographic, clinical, and prognostic differences between late-onset and early-onset patients with $GABA_BR$-E, proposing the necessity of risk stratification according to age at onset. Special attention should be paid to those with an older onset age and underlying tumors, for whom immunotherapy maintenance for at least 6 months should be recommended to improve the overall prognosis of this rare CNS autoimmune disease.

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Appendix *(continued)*

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Late-Onset Anti-GABA$_B$ Receptor Encephalitis: Clinical Characteristics and Outcomes Differing From Early-Onset Patients

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