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SCLC and anti-GABABR encephalitis: A retrospective analysis of 60 cases in China

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Abstract

Background: Anti-gamma aminobutyric acid B receptor (anti-GABABR) encephalitis is a rare autoimmune neurological syndrome observed in lung cancer patients. More research on the clinical characteristics of small cell lung cancer (SCLC) and anti-GABABR encephalitis should be carried out to improve diagnosis and treatment.

Methods: We retrospectively investigated the clinical characteristics, auxiliary examination results, and treatment responses in patients with SCLC and anti-GABABR encephalitis at Beijing Chaoyang Hospital from January 2010 to December 2020. The study also retrospectively analyzed cases of SCLC and anti-GABABR encephalitis well documented in China.

Results: A total of 60 cases of SCLC and anti-GABABR encephalitis were analyzed in the study, two in our hospital, and 58 previously reported in the literature. The male:female ratio was 3:1, with a median age at presentation of 61 years (range: 40–81 years). Twenty-eight patients initially presented with seizures, four with cognitive disorder, and three with psychiatric symptoms. The major symptoms were epileptic seizures ($n = 56$; 96.9%), cognitive impairment ($n = 47$; 81.0%), psychiatric disorders ($n = 45$; 77.6%), and conscious disturbance ($n = 32$; 55.2%). Fifty-five patients underwent immunotherapy, and 23 patients underwent oncologic treatment in the literature. After a median follow-up duration of 8.8 (range, 0.5–37.0) months, nine patients showed good outcomes (modified Rankin Scale score, mRS ≤2), eight patients showed poor prognosis (mRS > 2), and 18 patients died.

Conclusions: The clinical characteristics of SCLC and anti-GABABR encephalitis are seizures, cognitive impairment, and psychiatric disorders which affect middle-aged to elderly men in China. The long-term prognosis is relatively poor.

KEYWORDS
anti-GABABR encephalitis, limbic encephalitis, small cell lung cancer

INTRODUCTION

Limbic encephalitis (LE) is a rare neurological syndrome which selectively affects limbic system structures including the hippocampus, insular cortex, amygdaloid nucleus and cingulate gyrus. Patients often present with amnesia, psychological and behavioral disorder and epileptic seizures.[1] LE is an immune-mediated response associated with antineuronal antibodies, including neuronal nuclear antibody 1 (Hu), Ma2, amphiphysin, collapsin response mediator protein-5 (CRMP5),[2] voltage-gated potassium channel (VGKC) complex, N-methyl-d-aspartate receptor (NMDAR), and gamma aminobutyric acid B receptor (GABABR). Anti-GABABR encephalitis is a newly described form of autoimmune encephalitis associated with antineuron cell surface antigen antibodies.[3] Patients usually present with early and

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prominent seizures, cognitive impairment, psychiatric disorders, and conscious disturbance. In paraneoplastic cases of the disease, these patients usually harbor an underlying tumor, and small cell lung cancer (SCLC) is the most frequent neoplasm.[4–7]

Only a few cases of SCLC and anti-GABABR encephalitis have been reported to date, and the clinical manifestations and prognosis have yet to be investigated systematically.[8] In this study, we analyzed the clinical manifestations, auxiliary examination results, treatment strategies, and prognoses in patients with SCLC and anti-GABABR encephalitis in China, to improve the understanding of this relatively rare disorder.

METHODS

This observational retrospective study enrolled patients diagnosed SCLC and anti-GABABR encephalitis at Beijing Chaoyang Hospital from January 2010 to December 2020. Clinical information was obtained from hospitalization reports. The modified Rankin Scale (mRS)[9] was used to define favorable (score 0–2) and poor (score 3–6) functional outcomes. The study was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (No. 2016-ke-79). We also retrospectively collected cases of SCLC and anti-GABABR encephalitis in China, include Chinese National Knowledge Infrastructure (CNKI), Wanfang, Vip, Pubmed. Only reports on well-documented cases were considered. The data, including clinical characteristics, laboratory examination results, radiological and electroencephalogram (EEG) features, and treatment responses, were analyzed.

Statistical analyses were performed using SPSS 25.0 software (IBM-SPSS Inc.). Continuous variables were expressed as median (range and interquartile range). Categorical variables were described using frequencies (percentage, %).

RESULTS

Patients at our hospital

Two patients with SCLC and anti-GABABR encephalitis were recruited at our hospital. One patient was a 59-year-old woman who presented with memory deficit. Results of blood tests indicated that anti-GABABR antibody and anti-SOX1 antibody were positive. Pathological examination confirmed a diagnosis of SCLC, and she received platinum-based chemotherapy, intravenous immunoglobulins (IVIg), and antiepileptic drugs. The other patient was a 76-year-old man who presented with cognitive disorder. GABABR antibody was detected in the serum. He was diagnosed with SCLC in the right lung and received platinum-based chemotherapy. They both died 1 year later after diagnosis.

Patient characteristics

A total of 58 cases were reported in the literature between January 2010 and December 2020.[10–15] More details of the 60 patients (including the 2 patients at our hospital) are summarized in Table 1. The average age at presentation was 61 (range, 40–81) years, with a male/female ratio of 3:1. Twenty-eight patients initially presented with seizures, four with cognitive disorder, and three with psychiatric symptoms. The main symptoms were epileptic seizures ($n = 56$; 96.9%), cognitive impairment ($n = 47$; 81.0%), psychiatric disorders ($n = 45$; 77.6%), and conscious disturbance ($n = 32$; 55.2%). Ten patients exhibited sleep disorders, and 14 patients developed respiratory failure. A total of 55.0% were smokers. The median interval from symptom onset to diagnosis was 49 (range, 1–365) days. The patient characteristics are summarized in Table 2.

Laboratory tests

GABABR antibodies were detected in both serum and CSF samples in 38 patients, solely in serum in six patients, and solely in CSF in 10 patients; however, the detailed GABABR antibody test results of the other six patients was not clearly recorded in the literature (Table 3). Additional antibodies were identified; four had anti-Hu, two had anti-Yo, two had NMDAR, and one each had anti-amphiphysin, anti-SOX1, anti-ganglioside (GM1). Antinuclear antibody (ANA) positivity was observed in the serum samples of four patients, and five patients had antithyroid peroxidase (TPO) antibodies. Tumor marker neuron specific enolase (NSE) positivity in the serum was observed in eight patients. The CSF pressure was high (>180 mmH_2O, 60 mmH_2O–310 mmH_2O) in 12 (35.3%) cases at first spinal tap. An elevated leukocyte count was demonstrated in 31 cases (60.8%) (>8 cells/μl, range, 0–174 cells/μl) and an elevated protein level was noted in 29 cases (67.4%) (>40 mg/dl; range, 15.0–96.8 mg/dL).

Radiological examination and EEGs

There were 28 cases with lung localization reports following chest computed tomography (CT) scan. Thirteen cases (46.4%) had a lung mass on the right lung, and a lung mass was detected in 10 patients (35.7%) on the left lung, as well as hilar and mediastinal lymph node metastasis. Nine patients underwent positron emission tomography-computed tomography (PET-CT), and a hypermetabolic lung mass with lymphatic metastasis was revealed in six patients. All patients were diagnosed with SCLC following pathological biopsy and immunohistochemistry.

Brain magnetic resonance imaging (MRI) examination was performed in 47 cases and was unremarkable in

TABLE 1 Summary of the literature review on SCLC and anti-GABABR encephalitis

First author	Institution	Year	Journal	n
Linjia Guo	Beijing Shijitan Hospital, Capital Medical University	2015	Journal of Apoplexy and Nervous Diseases	1
Jiakai He	Xuanwu Hospital, Capital Medical University	2015	Chinese Journal of Neurology	1
Jieping Lu	Anhui Provincial Hospital	2016	Chinese Journal of Nervous and Mental Diseases	1
Haitao Ren	Peking Union Medical College Hospital	2016	Chinese Journal of Neurology	1
Lei Qiao	Peking Union Medical College Hospital	2016	Chinese Journal of Neurology	1
Jun Zhang	Xuanwu Hospital, Capital Medical University	2016	Chinese Journal of Neurology	2
Ying Shi	Affiliated Hospital of Hebei University	2017	Chinese Journal of Nervous and Mental Diseases	2
Chao Zhao	Tangdu Hospital, the Fourth Military Medical University	2017	China Medical Herald	1
Guifang Sun	The First Affiliated Hospital of Zhengzhou University	2017	Chinese Journal of Neurology	3
Cancan Wang	Zhengzhou University People's Hospital	2017	Chinese Journal of Neuromedicine	2
Song Qiao	Zhejiang Hospital	2017	International Journal of Neuroscience	3
Xueping Chen	West China Hospital, Sichuan University	2017	Neurological Research	3
Songbin Pan	Wuhan First Hospital	2018	Chinese Journal of Nervous and Mental Diseases	1
Ying Wang	The First Affiliated Hospital of Dalian Medical University	2018	Journal of Dalian Medical University	1
Junyan Liu	The First Affiliated Hospital of Harbin Medical University	2018	Chinese Journal of Nervous and Mental Diseases	1
Qinlan Xu	Beijing Tiantan Hospital, Capital Medical University	2018	Journal of Brain and Nervous Diseases	4
Junzhao Cui	Second Hospital of Hebei Medical University	2018	International Journal of Neuroscience	5
Qing Liu	Xuanwu Hospital, Capital Medical University	2019	Journal of Clinical Neurology	1
Junjie Dai	Ningbo City Medical Treatment Center Lihuili Hospital	2019	Chinese General Practice	5
Jingfang Lin	West China Hospital, Sichuan University	2019	Frontiers in Neurology	3
Yue Qiu	Huashan Hospital Affiliated to Fudan University	2020	Chinese Journal of Clinical Neurosciences	1
Minrui Dong	The First Affiliated Hospital of Zhengzhou University	2020	Chinese Journal of Neuroimmunology and Neurology	5
Benhai Yao	Affiliated Hospital of Zunyi Medical University	2020	Chinese Journal of Neuroimmunology and Neurology	1
Yi Li	Second Hospital of Hebei Medical University	2020	Journal of Clinical Neurology	1
Lina Li	Shenzhen Hospital, University of Hong Kong	2020	Chinese Journal of Neurology	4
Haibing Zhu	The First Affiliated Hospital of Gannan Medical College	2020	Chinese Journal of Geriatric Heart Brain and Vessel Diseases	2
Xiuhe Zhao	Qilu Hospital, Shandong University	2020	Experimental and Therapeutic Medicine	2

Abbreviations: GABABR, gamma aminobutyric acid B receptor; SCLC, small cell lung cancer.

TABLE 2 Clinical features of patients with SCLC and anti-GABABR encephalitis

Characteristics	No. of cases	Proportion (%)
Sex, M	44	75.9
Age, years, median (range)	61 (40, 81)	
40–49	7	12.1
50–59	15	25.9
60–69	28	48.3
≥70	8	13.8
Smoker	11	55.0
Symptoms of LE, *n* (%)		
Epileptic seizures	56	96.6
Cognitive impairment	47	81.0
Psychiatric disorders	45	77.6
Conscious disturbance	32	55.2

Abbreviations: GABABR, gamma aminobutyric acid B receptor; LE, limbic encephalitis; M, male; SCLC, small cell lung cancer.

12 (25.5%) patients. MRI demonstrated an involvement of the limbic system in 28 (59.6%) cases. The distribution was restricted to the left temporal lobe, insula and hippocampus in eight cases, right in four cases, and bilateral involvement was shown in 16 patients. Contrast enhancement of the adjacent meninges was observed in two patients. The lesions appeared hypointense on T1-weighted imaging (T1WI) and hyperintense on T2-weighted imaging (T2WI)/fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging. PET-CT of two patients detected hypermetabolism in the temporal lobe and hippocampus. Figure 1 shows the chest CT and brain MRI images of one patient.

A total of 34 cases reported EEG examinations. Temporal epileptiform discharges were confirmed in eight (23.5%) cases. Focal or global slow waves were observed in 15 (44.1%) patients, and 11 patients (32.4%) showed approximately normal EEG results. The detailed results of imaging and EEGs are presented in Table 3.

TABLE 3 Antibodies, CSF analyses, imaging findings, and EEG examinations in patients with SCLC and anti-GABABR encephalitis

Examinations	No. of cases	Proportion (%)
Anti-GABABR		
Antibodies in serum only	6	11.1
Antibodies in CSF only	10	18.5
Antibodies in serum and CSF	38	70.4
Earliest CSF		
Pressure (>180 H_2O)	12	35.3
WBC (>8 cells/μl)	31	60.8
Protein (>40 mg/dl)	29	67.4
Thorax CT		
Left lung	10	35.7
Right lung	13	46.4
Bilateral lung	3	10.7
Mediastin only	2	7.1
Brain MRI		
Normal	12	25.5
Left temporal lobe	8	17.0
Right temporal lobe	4	8.5
Bilateral temporal lobe	16	34.0
EEG		
Epileptic waves	8	23.5
Generalized or focal slowing waves	15	44.1
Roughly normal	11	32.4

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; GABABR, gamma aminobutyric acid B receptor; MRI, magnetic resonance imaging; SCLC, small cell lung cancer; WBC, white blood cell.

Treatment and prognosis

Fifty-five patients underwent first-line immunomodulatory therapy and 34 cases were treated with a combination of corticosteroids and IVIg, nine cases with corticosteroids alone, and 12 cases with IVIg alone, respectively (Table 4). Two patients were given at least one course of plasma exchange, and rituximab was administered in two patients. Twenty-three patients received treatment for the malignancy described in the literature. Furthermore, 31 patients received antiepileptic drugs or medication for psychiatric symptoms.

After a median follow-up duration of 8.8 (range, 0.5–37.0) months, 26 (52.0%) patients showed different degrees of recovery. Nine patients had experienced good outcomes (mRS ≤2), and the epileptic symptoms were well controlled. Eight patients showed poor prognosis (mRS >2), and there were no relapses on limbic symptoms observed during the follow-up periods. In addition, 18 patients died due to tumor progression or chemotherapy-related infection.

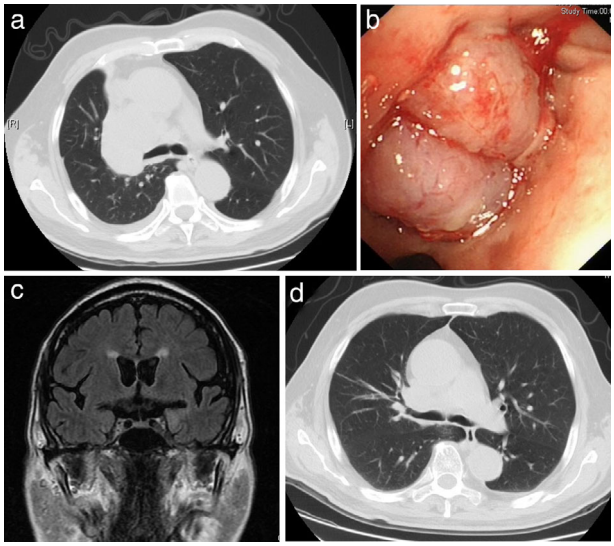

FIGURE 1 Chest CT, brain MRI, and bronchoscopic images of a 76-year-old male patient. (a) Chest CT showed one mass in the hilus of the right lung on the pulmonary window image. (b) Bronchoscopy showed a soft tissue mass in the upper lobe of the right lung. (c) Coronal sections of brain MRI FLAIR showed a high signal in the left hippocampus. (d) Chest CT showed the mass had significantly reduced after chemotherapy. CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

TABLE 4 Treatment of SCLC and anti-GABABR encephalitis

Treatment	No. of cases	Proportion (%)
Immunotherapy		
Corticosteroids alone	9	16.4
IVIg alone	12	21.8
Corticosteroids and IVIg	34	61.8
Cancer treatment	23	-
Antiepileptic drugs	31	-

Abbreviations: GABABR, gamma aminobutyric acid B receptor; IVIg, intravenous immunoglobulin; SCLC, small cell lung cancer.

DISCUSSION

Anti-GABABR encephalitis cases have been reported in the literature since 2010,[3] yet numerous studies only report a small number of cases.[4,5,8,16,17] Anti-GABABR encephalitis is often seen in SCLC. Our study provides the first detailed description of SCLC and anti-GABABR encephalitis, clinical characteristics, long-term prognoses, and anticancer treatment response rates of SCLC and anti-GABABR encephalitis in China. To the best of our knowledge, this is the largest case series of patients with this relatively rare disease currently available in the literature. However, as the disease information obtained from case reports was incomplete, this may have led to incomplete data analysis.

GABABRs are G-protein-coupled receptors belonging to typical inhibitory synaptic proteins in neurons, widely

distributed in the central nervous system, including the cerebral cortex, hippocampus, thalamus, and cerebellum.[18] They play critical roles in neurotransmitter transmission and synapse stabilization, and are primarily involved in learning, memory, and cognitive function.[19,20] The pathological features are believed to be immune-mediated, and include microscopic perivascular lymphocytic infiltration, neuronal cell loss, and reactive microglial proliferation of limbic structures. Around half of patients with anti-GABABR encephalitis have a final diagnosis of SCLC or neuroendocrine tumors.[7] Clinicians should eliminate the possibility of SCLC in patients with high anti-GABABR antibody levels. The detection of a tumor is usually established after the development of neurological symptoms.[6] Therefore, once a clinical diagnosis of anti-GABABR encephalitis is confirmed, screening for lung cancer is important. Long-term regular follow-up for tumor screening is recommended, even if no tumor is discovered at the time of presentation.[21] Similarly, in patients with SCLC accompanied by symptoms associated with LE, it is necessary to detect anti-GABABR antibody. GABABRs may be expressed in lung cancer tissues.[14]

Our study suggests that Chinese patients with SCLC and anti-GABABR encephalitis have similar clinical features as described in previous studies. This disease mostly affects middle-aged to elderly men.[3–5,8] Seizures are the initial and most prominent presentation. Indeed, seizures have been recognized as one of the major features of anti-GABABR encephalitis.[3,8] It should be considered as a possible diagnosis in middle-aged and older patients with refractory new-onset epilepsy. In the present study, almost all patients presented with typical limbic epilepsy, and had symptoms including seizures, cognitive dysfunction, confusion, personality changes, and psychiatric symptoms.[3] When these symptoms occur in combination with seizures, anti-GABABR encephalitis should be suspected, and comprehensive screening for antineuronal autoantibodies and tumors in both serum and CSF is essential. A strong suspicion might enable earlier diagnosis and lead to a better long-term outcome.

All the patients in our study had tested positive for anti-GABABR antibodies in serum and/or CSF. Consistent with previously reported cases, some patients also expressed additional autoantibodies in the serum, most commonly, anti-Hu, anti-Yo, NMDAR, SOX1, ANA, and TPO antibodies. The proportion of additional onconeuronal antibodies was previously reported to be in the range of 7%–40%.[3–5,16] These additional antibodies may very well reflect the disease association with autoimmunity or latent tumors, such as SOX1 antibodies associated with SCLC,[6] and are frequently associated with poor prognosis.[4] It has been suggested that testing for onconeuronal antibodies should be considered in all patients with anti-GABABR encephalitis. The effects of these antibodies on anti-GABABR encephalitis patient treatment response and prognosis require further investigation.

As for brain MRI, unilateral or bilateral medial temporal lobe and hippocampal changes were revealed in 28 patients, which is in accordance with the results of most prior studies.[3] Brain MRI did not provide unique or specific information useful for the diagnosis of anti-GABABR encephalitis, and 12 (25.5%) patients showed negative MRI findings in our study, which did not exclude the disease possibility and immunological testing should therefore be performed.[11] As far as we are concerned, brain MRI is more useful to rule out other disorders, such as tumors, that might lead to neurological symptoms. PET-CT might be more sensitive in the diagnosis and evaluation of anti-GABABR encephalitis, especially in patients with normal MRI findings.[8,22] Two patients in our study presented with hypermetabolism in the temporal lobe and hippocampus on PET-CT, and PET-CT could aid evaluations of both abnormal metabolism in the limbic system and the underlying neoplasm. More cases and research will be needed to determine the diagnostic value of PET-CT in this disease.

No agreement on the anti-GABABR encephalitis diagnostic criteria has been reached, with a high, incorrect preoperative diagnosis rate. The diagnosis requires a combination of clinical characteristic neurological syndromes, and the detection of specific anti-GABABR antibodies in the serum and/or CSF.[8,23] Furthermore, one could apply the criteria used for the diagnosis of other autoimmune encephalitides to anti-GABABR encephalitis, which consists of the presence of autoantibodies in the serum or CSF and a clinical response to immunotherapy.[24] Additionally, metabolic encephalopathy, neurotoxic drugs, inflammatory disorders, central nervous system tumors, and neurodegenerative disorders must be excluded.[23]

For the treatment of SCLC and anti-GABABR encephalitis, immunotherapy and antineoplastic therapy have been universally applied as first-line therapies.[3,4,25] Treatment with corticosteroids, IVIg and plasmapheresis, either alone or in combination, adding rituximab or cyclophosphamide as second-line therapies in refractory cases, is appropriate.[26] In our research, most patients received treatment with corticosteroids and IVIg. Previous studies have demonstrated that patients who received immunotherapy at initial presentation had better outcomes and lower rates of death than those who did not.[25] In comparison with traditional intracellular antigen antibody-related (e.g., anti-Hu) LE, anti-GABABR encephalitis usually shows a much better response.[3,4] The seizures caused by anti-GABABR encephalitis are usually refractory to antiepileptic medications, but respond well to immunotherapy.[27]

For patients with SCLC, treatment of cancer may also be necessary. In our study, 23 patients were reported to have received treatment for malignancy after diagnosis. Most patients experience improvement in neurological symptoms after systemic chemotherapy. Tumor therapy in most cases might lead to better neurological improvement than treatment with immunotherapy.[28] Patients with LE might have lower performance status scores owing to neurological disorders,[29] which was previously considered contraindicative for chemotherapy. Aggressive chemotherapy, despite slight reductions in tumor burden, might improve prognosis in this population.[28] However,

as the description of treatment and prognosis in the literature is unclear, our study did not provide more in depth analysis for SCLC-related clinical assessment, treatment, short-term effects, and outcome. Further studies are required to provide a detailed description of SCLC and anti-GABABR encephalitis, clinical characteristics, long-term prognoses, and anticancer treatment response rates of SCLC and anti-GABABR encephalitis.

At follow-up in the present study, 18 patients had died due to tumor progression or chemotherapy-related infection. Patients with SCLC and anti-GABABR encephalitis had a relatively poor prognosis. Few studies have focused on treatment responses and prognoses in patients with SCLC and anti-GABABR encephalitis. Previous studies have revealed that most patients with anti-GABABR encephalitis without cancer responded well to immunotherapy; however, patients with tumors have been reported to have lower survival rates.[4] The presence of status epilepticus or refractory seizures did not significantly affect survival. The prognosis might be worse for patients who were older at disease onset.[11] A large number of additional cases with long-term follow-up data to identify the optimal treatment and prognosis for this uncommon disorder should be addressed in more detail in the future.

In conclusion, SCLC and anti-GABABR encephalitis is a relatively rare disease. This disease in Chinese patients mostly affects middle-aged to elderly men and the major manifestations are seizures, cognitive impairment, and psychiatric disorders. Patients frequently express additional autoantibodies in the serum, most commonly anti-Hu, anti-Yo, NMDAR, SOX1, ANA, and TPO antibodies. MRI results reveal unilateral or bilateral medial temporal lobe and hippocampal changes, but negative findings do not exclude the disease possibility. Clinicians should make an appropriate early diagnosis and initiate immune therapy and possible antineoplastic therapy as soon as possible. Patients with SCLC and anti-GABABR encephalitis have a relatively poor prognosis. Additional studies are needed to provide more convincing data to establish a definite diagnosis and treatment strategy for clinical practice.

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CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

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