ANNALS of Clinical and Translational Neurology
Open Access
ANA American Neurological Association since 1875

RESEARCH ARTICLE

Seizure semiology: an important clinical clue to the diagnosis of autoimmune epilepsy

Rui-Juan Lv[1,2], Hai-Tao Ren[3], Hong-Zhi Guan[3], Tao Cui[1,2] & Xiao-Qiu Shao[1,2]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, 6 Tiantanxili, Dongcheng District, Beijing 100050, China
[2]China National Clinical Research Center for Neurological Diseases, 6 Tiantanxili, Dongcheng District, Beijing 100050, China
[3]Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

Correspondence
Xiao-Qiu Shao, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, 6 Tiantanxili, Dongcheng District, Beijing 100050, China.
Tel: +86 10 67098366;
Fax: +86 10 67098322;
E-mail: shaoxiaoqiu2000@163.com

Funding Information
This work was supported by grants from the National Natural Science Foundation of China (Nos. 81301119 and 81471327), the Beijing Municipal Administration of Hospitals' Youth Programme (No. QML20160504), the China Association Against Epilepsy-UCB Research Fund (No. CAAE-UCB2016008), and the National Key Technology Research and Development Program of the Ministry of Science and Technology of China (No. 2013BAI09B03).

Received: 12 August 2017; Revised: 29 November 2017; Accepted: 6 December 2017

Annals of Clinical and Translational Neurology **2018; 5(2): 208–215**

doi: 10.1002/acn3.520

Abstract

Objective: The purpose of this study is to analyze the seizure semiologic characteristics of patients with autoimmune epilepsy (AE) and describe the investigation characteristics of AE using a larger sample size. **Methods**: This observational retrospective case series study was conducted from a tertiary epilepsy center between May 2014 and March 2017. Cases of new-onset seizures were selected based on laboratory evidence of autoimmunity. At the same time, typical mesial temporal lobe epilepsy (MTLE) patients with hippocampal sclerosis (HS) were recruited as the control group from the subjects who underwent presurgical evaluation during the same period. **Results**: A total of 61 patients with AE were identified. Specific autoimmune antibodies were detected in 39 patients (63.93%), including anti-VGKC in 23 patients (37.70%), anti-NMDA-R in 9 patients (14.75%), anti-$GABA_B$-R in 6 patients (9.84%), and anti-amphiphysin in 1 patient (1.64%). Regarding the seizure semiology, no significant differences were noted between AE patients with autoantibody and patients with suspected AE without antibody. Compared to typical MTLE patients with HS, both AE patients with autoantibody and patients with suspected AE without antibody had the same seizure semiologic characteristics, including more frequent SPS or CPS, shorter seizure duration, rare postictal confusion, and common sleeping SGTC seizures. **Significance**: This study highlights important seizure semiologic characteristics of AE. Patients with autoimmune epilepsy had special seizure semiologic characteristics. For patients with autoimmune epilepsy presenting with new-onset seizures in isolation or with a seizure-predominant neurological disorder, the special seizure semiologic characteristics may remind us to test neuronal nuclear/cytoplasmic antibodies early and initiate immunomodulatory therapies as soon as possible. Furthermore, the absence of neural-specific autoantibodies does not rule out AE.

Introduction

Autoimmune epilepsy is an under-recognized condition without standardized management guidelines.[1] However, identifying an underlying autoimmune etiology for epilepsy is critical, as these patients may remain refractory to conventional antiepilepsy drugs (AEDs). An autoimmune cause has been increasingly recognized in the spectrum of limbic encephalitis characterized by cognitive impairment, especially memory impairment, behavioral changes, temporal lobe seizures, and sleep disturbances.[2] However, accumulating evidence supports an autoimmune basis for seizures in the absence of syndromic manifestations of limbic encephalitis for a subset of AED-resistant epilepsy cases.[3–8] Autoimmune epilepsy often does not respond to conventional antiepileptic treatment but might respond to immunotherapy. Therefore, expedited diagnosis is important for early initiation of immunotherapy which can slow, halt, or even reverse the epileptogenic process in these patients.[3,4,9]

When syndromic features of limbic encephalitis are absent, the diagnosis of autoimmune epilepsy is often delayed. Valuable clinical clues include acute or subacute onset, an unusually high seizure frequency, intraindividual seizure variability or multifocality, AED resistance, personal or family history of autoimmunity, or history of recent or past neoplasia.[3] Valuable supportive investigations to the diagnosis include the detection of neural autoantibody, the presence of temporomesial inflammation on magnetic resonance imaging (MRI) or fluorodeoxyglucose positron-emission tomography (FDG-PET), and cerebrospinal fluid (CSF) evidence of neuroinflammation.[3,10]

Neuronal autoantibodies are important diagnostic markers of autoimmune epilepsy. However, these biomarkers are only present in a proportion of patients with immunotherapy-responsive epilepsy.[11] Therefore, the suspicion of autoimmune epilepsy should be based predominantly on clinical seizure semiologic characteristics, being new and late onset, rapid deterioration in cognitive function in a short period of time, seizures resistant to treatment, and supportive laboratory and radiological investigations, rather than solely on biomarkers. Faciobrachial dystonic seizures (FBDS) are the most characteristic seizures seen in VGKC complex antibody encephalitis. These seizures are manifested by sudden onset of flexion contraction of one upper extremity, accompanied by contraction of the ipsilateral face, head, and neck.[12] These seizures, which typically last for approximately 1 sec, and occur multiple times per day, are present in approximately one fourth of VGKC complex antibody epilepsy patients.[11] Except for FBDS, patients with VGKC complex antibodies mainly experience mesial temporal lobe seizures, including simple partial seizures (SPS), complex partial seizures (CPS), and secondarily generalized tonic-clonic (SGTC) seizures.[13] By far, very few studies have analyzed the seizure semiologic characteristics of antibody-mediated autoimmune epilepsy in detail.

This study aims to compare the clinical seizure semiologic characteristics of autoimmune epilepsy with typical mesial lobe epilepsy (MTLE) with hippocampal sclerosis (HS) and describe the investigation characteristics of autoimmune epilepsy using a larger sample size.

Subjects and Methods

We recruited 39 autoimmune epilepsy patients with antibody (mean age = 50.44 years, SD = 13.81) and 22 suspected autoimmune epilepsy patients without antibody (mean age = 41.64 years, SD = 12.43) into our tertiary epilepsy center between May 2014 and March 2017. As a comparison for seizure semiologic characteristics, 22 typical MTLE patients with HS (control group, mean age = 28.23 years, SD = 9.01) were also recruited from subjects who underwent presurgical evaluation during the same period. These typical MTLE patients with HS were seizure free following standard anterior temporal lobectomy and amygdalohippocampectomy with a minimum follow-up of 1 year. The surgical pathology of these typical MTLE patients with HS was consistent with HS without dual pathology. Informed consent to participate in the study and to permit publication of clinical details was obtained from each subject enrolled. The study was reviewed and approved by the ethics committee of Beijing Tiantan Hospital affiliated to Capital Medical University in the People's Republic of China.

Cases of autoimmune epilepsy included in the study involved patients presenting with new-onset seizure, and at least two of the following: (1) CSF findings consistent with inflammation (elevated CSF protein [>45 mg/dL] and/or lymphocytic pleocytosis [>10/μL], elevated CSF immunoglobulin G [IgG] index and/or positive oligoclonal bands [OB]); (2) brain MRI or FDG-PET showing signal changes consistent with limbic encephalitis; (3) serum and/or CSF autoimmune/paraneoplastic antibodies which have been associated with autoimmune encephalitis in previous studies (any neuronal nuclear/cytoplasmic antibodies, such as anti-Hu, Yo, Ri, Ma2/Ta, CV2/CRMP5, amphiphysin, or any neuronal membrane antibody, including anti-NMDA-R, CASPR2, AMPA1-R, AMPA2-R, LGI1, and $GABA_B$-R); (4) new-onset seizures responsive to immunomodulatory therapies. Cases were excluded if there was evidence of another identified cause of the patient's seizures, such as (1) presence of CSF viral/bacterial/fungal antigens, antibodies, or DNA PCR which could explain underlying acute inflammatory brain parenchymal changes; (2) presence of metabolic abnormalities which could have precipitated seizures (severe renal or hepatic failure, malignant hypertension, or severe hypo-/hyperglycemia); (3) presence of brain structural lesions such as stroke, tumor, traumatic lesions, heterotopia, vascular malformation, abscess, or infectious lesion which could have precipitated the presenting seizures.

Cases selected based on inclusion and exclusion criteria without a prespecified antibody were further divided based on the presence or absence of high titers of thyroid peroxidase (TPO) antibodies (>100 IU/mL). Anti-TPO antibody was not included in the prespecified inclusion criteria due to its lack of specificity of antibody for autoimmune encephalopathy.[14]

Collection of patient seizure semiologic characteristics [including seizure type, symptomatic and electroencephalogram (EEG) duration of each seizure, seizure frequency, and SGTC seizure circadian rhythm (SGTC occurred during sleep or waking state)] as well as health

information, including epidemiological and demographic variables (age, sex, clinical presentation, symptoms, age at seizure onset, interval of presentation to diagnosis, laboratory tests, CSF analysis, type of antibodies, EEG findings, imaging, immunosuppressive therapies used, and neurological follow-up outcome) were performed by manual search of the electronic medical record system. We followed up the patients with autoantibody and those with suspected autoimmune epilepsy without autoantibody patients receiving immunomodulation. During follow-up, a 50% reduction of seizure frequency was considered a favorable clinical outcome and was termed the "responder rate" (RR).

All patients received 24-h video-EEG recordings with sphenoidal electrodes using the 10-20 system of scalp electrode placement. Recordings included both waking and sleeping states. Interictal FDG-PET was also performed to support the clinical diagnosis. Additionally, the Montreal Cognitive Assessment (MoCA) was performed to test for cognitive impairment.

Neuronal antibody measurement

All suspected autoimmune epilepsy patients underwent serum and CSF antibody testing. Serum and CSF samples were sent to the neurological immunology laboratory of Peking Union Medical College Hospital. Serum and CSF titers for the onconeural antibodies, anti-Hu, Yo, Ri, CV2/CRMP5, amphiphysin, and Ma2/Ta, and the neuronal surface antibodies, anti-NMDA-R, CASPR2, AMPA1-R, AMPA2-R, LGI1, and $GABA_B$-R, were measured using both cell-based assay and immunohistochemistry.

Seizure semiology and EEG findings measurement

Seizure semiology and EEG findings were first reviewed by two epileptologists (R.-J. Lv and T. Cui). Regarding the quantification data, for example, SPS or CPS duration, we used the average value of the results presented by two epileptologists. If there were disagreements between them, then the summarized results will be finally assessed by an experienced epileptologist (X.-Q. Shao). The epileptologists were blind to neuronal antibody test results.

Statistical analyses

Statistical analyses were performed using SPSS 21.1 for Windows (IBM, Armonk, NY). Quantitative variables were expressed as median or as *n* (%). Categorical variables were analyzed using the chi-square test. Distribution assessment of independent variables was performed using the Shapiro–Wilk test of normality. Normally distributed data were analyzed using the independent *t*-test, and non-normally distributed data were analyzed using the Mann–Whitney *U* test. A $P < 0.05$ was considered statistically significant. Binomial logistic regression was utilized to adjust for baseline characteristics.

Results

A total of 61 patients with autoimmune epilepsy were identified (antibody positive:negative = 39:22). Specific autoimmune antibodies were detected in 39 patients (63.93%), anti-VGKC in 23 (37.70%), anti-NMDA-R in 9 (14.75%), anti-$GABA_B$-R in 6 (9.84%) patients, and anti-amphiphysin in 1 patient (1.64%).

The demographics and test results of autoimmune epilepsy patients with autoantibody were shown in Table S1. The mean age of patients was 50.44 years and 32 patients (82.05%) were male. Patients with anti-VGKC included 21 patients with anti-LGI1 and two patients with anti-CASPR2 antibodies. FBDS only appeared in patients with anti-LGI1, among whom six patients (28.57%) had FBDS, consistent with a previous study.[11] Eight patients (20.51%) included in the study had an underlying malignancy: 2 had adenocarcinoma of the lung, 5 had small cell lung cancer, and 1 had hepatic mass (refused further investigation). Most patients (83.33%) with $GABA_B$-R antibody had underlying malignancies, which was consistent with previous reports.[15,16] The median time between symptom onset and diagnosis was 2 months (range = 0.5–24 months). The median time to clinic follow-up after hospital discharge was 14 months (range = 1–24 months). Electroclinical seizures were documented in 22 patients (56.41%) after admission. Of the 39 patients included, 12 (30.77%) had unilateral and 4 (10.26%) had bilateral temporal lobe onset, 7 (17.95%) had bilateral or focal slowing, while 8 (20.51%) had extra-temporal onset/multiple ictal foci. Two patients (5.13%) had only electrographic seizures without clinical correlation. Interictal discharges were present in nine cases (23.08%). Thirty patients (76.92%) had cognitive changes, 8 (20.51%) had personality changes and 9 patients (23.08%) had psychiatric changes. Seventeen (43.59%) patients had CSF findings consistent with inflammation. Twenty-four (61.54%) patients with antibodies had MRI changes concerning for autoimmune encephalitis, among whom 13 (54.17%) patients had amygdala and hippocampus high signals in MRI FLAIR sequence (Fig. 1). Nineteen patients (86.36%) with suspected autoimmune epilepsy without autoantibodies had similar MRI changes. However, typical MTLE patients with HS did not have amygdala involvement. Thirty-six patients (92.31%) achieved 50% reductions in

seizure frequency (RR) at the follow-up clinic visit after inpatient management of the acute episode. Thirty-three (84.62%) patients had complete seizure resolution as of clinic follow-up. Thirty-seven (94.87%) patients received immunomodulatory therapies, including high-dose corticosteroids (35.90%), IVIg (23.08%), or a combination of high-dose corticosteroids and IVIg (35.90%). Four patients with LGI1 antibody also received additional immunomodulation using mycophenolate (10.26%). There was no significant difference in RR at the time of follow-up with use of different immunomodulatory regimens. Of the two patients who did not receive immunomodulation, one patient ($GABA_B$-R) had died by the follow-up visit date. The second patient had anti-amphiphysin antibody, and did not show significant improvement in seizure frequency following initiation of lamotrigine treatment. There was no significant difference in seizure reduction based on gender, age, presenting symptoms (behavior change, memory loss, seizure, altered mental status, speech changes, or movement disorder), or type of antibody detected. However, patients without underlying malignancy achieved a better RR ($P < 0.05$). Having antibodies directed against neuronal cell membrane antigens versus neuronal nuclear/cytoplasmic antibodies did not significantly affect the RR. There was no significant relationship between RR and average pretreatment seizure frequency, number of AEDs used, or other clinical measures (CSF pleocytosis, interictal discharges or ictal EEG pattern, or pattern of MRI changes). Forty percent of patients with suspected autoimmune epilepsy without antibody received immunomodulatory therapies and achieved complete resolution of seizures or RR on clinic follow-up.

The seizure semiologic characteristics of patients with autoantibody and suspected autoimmune epilepsy without antibody were shown separately in Tables S2 and S3. When comparing the seizure semiologic characteristics, we excluded patients with anti-NMDA-R antibodies. Patients with anti-NMDA-R antibodies may present with diffuse encephalitis or encephalopathy and a distinct syndrome of acute onset severe epilepsy, neuropsychiatric change, choreoathetoid movements, dysautonomia, and hypoventilation.[13,17] These features may facilitate differentiation of these patients from other autoimmune epilepsy patients easily. Seven patients (23.33%) with autoantibodies had SPS. Patients with antibodies may also experience simple partial autonomic seizures manifested by unilateral piloerection or palpitations. Others describe their seizures as a brief ascending or descending "wave" passing through their body. These may be accompanied by brief periods of amnesia, presenting as CPS. One-half (50%) patients with autoantibodies also had CPS. The important and primary clinical manifestation of seizure was consistent with temporal lobe seizures. The seizures described above typically last several seconds and occur multiple times a day in affected patients, similar to FBDS. In the group of patients with autoantibody, 76.19% had sleeping SGTC seizures. In the group of patients with suspected autoimmune epilepsy without autoantibody, 71.43% had sleeping SGTC seizures.

The seizure semiologic characteristics of typical MTLE patients with HS were shown in Table S4. All MTLE patients with HS had CPS, which often lasted 2–3 min. Most patients had longer symptom duration than EEG duration, suggesting that most patients had postictal confusion after CPS. However, we found no obvious postictal

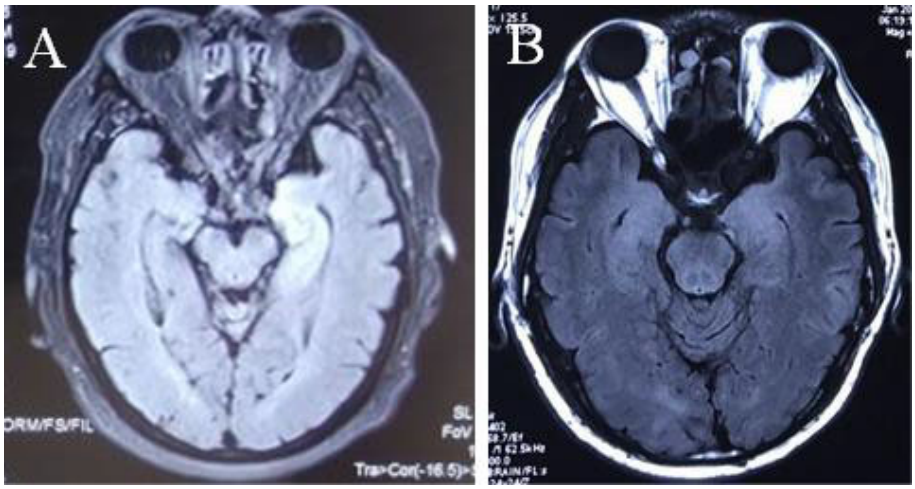

Figure 1. (A) Seventy years old male with LGI1 antibody: MRI showing left amygdala and hippocampus FLAIR hyperintensity. (B) Forty-nine years old male with LGI1 antibody: MRI showing bilateral amygdala and hippocampus FLAIR hyperintensities.

Table 1. Comparison between antibody-positive cases, antibody-negative cases, and MTLE-HS (control).

Variables	Number				
	Positive (n = 30)	Negative (n = 22)	P^1 value	Control (n = 22)	P^2 value
Seizure characteristic					
Age at onset (y), median[a]	58	45	0.320	13.5	<0.001
Duration of seizures (mo), median[b]	2	7.5	0.007	138	<0.001
Seizure type					
SPS	7	7		1	
SPS duration (sec), median[b]	8	7	0.456	30	NA
SPS frequency			NA		NA
Daily, *n* (%)	7 (100)	7 (100)		0	
Weekly, *n* (%)	0	0		1	
Monthly, *n* (%)	0	0		0	
CPS	15	16		22	
CPS duration (sec), median[b]	11	10	0.922	95	<0.001
CPS frequency[c]			0.484		<0.001
Daily, *n* (%)	14 (93.33)	16 (100)		0	
Weekly, *n* (%)	1 (6.67)	0		12 (60)	
Monthly, *n* (%)	0	0		8 (40)	
Postictal confusion, *n* (%)	0	0		18 (81.82)	
SGTC circadian rhythm[c]	23	14	0.705	8	0.002
Sleep, *n* (%)	18 (78.26)	10 (71.43)		1 (12.50)	
Awake, *n* (%)	5 (21.74)	4 (28.57)		7 (87.50)	

CPS, complex partial seizure; MTLE-HS, mesial temporal lobe epilepsy with hippocampal sclerosis; SPS, simple partial seizure; SGTC, secondary generalized tonic-clonic seizure; y, year; mo, month; NA, not available. P^1 antibody-positive cases versus antibody-negative cases; P^2 antibody-positive cases versus MTLE-HS.

[a]Independent *t*-test.

[b]Mann–Whitney *U* test.

[c]Chi-square or Fisher's exact test.

confusion in autoimmune epilepsy patients with autoantibody.

We compared the seizure semiologic characteristics between autoimmune epilepsy patients with autoantibody as well as those with suspected autoimmune epilepsy without autoantibody, autoimmune epilepsy patients with autoantibody, and typical MTLE patients with HS (shown in Table 1). Regarding the seizure semiologic characteristics including age of onset, SPS or CPS duration and frequency, and SGTC circadian rhythm, there were no significant differences between autoimmune epilepsy patients with autoantibody and suspected autoimmune epilepsy without antibody. Compared to typical MTLE patients with HS, both autoimmune epilepsy patients with antibody and suspected autoimmune epilepsy without autoantibody had the same seizure semiologic characteristics including more frequent SPS or CPS, shorter seizure duration, rare postictal confusion, and the occurrence of most SGTC seizures during sleep.

Discussion

The primary aim of this study was designed to compare the clinical seizure semiologic features of autoimmune epilepsy patients with those of patients with typical MTLE with HS. Additionally, we reported the clinical and auxiliary investigation characteristics and immunotherapy response of a larger cohort diagnosed with autoimmune epilepsy. Recurrent seizures were the early and predominant clinical manifestation among the patients of our report. In our report, 20% of patients had seizures as their exclusive presentation without other recognized clinical accompaniments of limbic encephalitis. Although the remaining 80% had additional neurological problems, including cognitive, personality, and psychiatric changes, they presented with the predominant concerns of high daily seizure burden. The majority of these patients came to see a doctor after enduring frequent seizures. Therefore, recognition of seizure semiologic characteristics may provide important clinical clues in the diagnosis of autoimmune epilepsy.

The diagnosis of autoimmune epilepsy requires a high level of suspicion at initial evaluation. Although the clinical presentations in our patients were heterogeneous, some general observations can be made. Data from the current study suggest that autoimmune epilepsy should be considered in the presence of one or more of the following: unusually high seizure frequency (often daily),

short duration of each seizure (often several seconds), SGTC seizures occurring during sleep, intraindividual seizure variability or multifocality, rare postictal confusion, initial resistance to AED, and favorable outcome of immunosuppressive treatment in combination with AEDs.

Regarding seizure semiologic characteristics, our work was similar to the findings of a study previously performed by Quek et al.,[3] including high seizure frequency and AED resistance. Our study analyzed the seizure semiology including seizure type and frequency, symptom and EEG duration of each seizure, and SGTC seizure circadian rhythm in detail. We found that most patients had daily seizure, each simple or complex partial seizure usually lasted several seconds, there was less postictal confusion compared with typical MTLE patients with HS, and SGTC seizures usually occurred during sleep. The reduced postictal confusion in autoimmune epilepsy patients compared to typical MTLE patients with HS may have been mainly because of the short CPS duration. The possible explanation was as follows. Our previous report and recent study showed that temporal lobe epilepsy (TLE) with enlargement of amygdala was highly suggestive of an autoimmune mechanism.[18–20] In antibody-positive autoimmune epilepsy patients with abnormal MRI exclusive of NMDA-R antibody, 63.16% had amygdala enlargement. 86.36% of suspected autoimmune epilepsy patients without autoantibody had similar MRI changes. However, typical MTLE patients with HS rarely had amygdala enlargement. One previous study mentioned that amygdala-kindled rats were more susceptible to epileptogenic effects during the subjective night.[21] This finding may partially explain the observed sleeping SGTC seizures, because the amygdala was involved in most of our patients. Additionally, the amygdala had cortical and subcortical connections with the posterior orbitofrontal cortex.[22,23] Therefore, seizures originating from the amygdala often spread via the orbitofrontal pathway with seizure semiology similar to frontal lobe seizure,[24] which were short, frequent, and nocturnal. This may explain our findings that SGTC seizures often occurred during sleep in autoimmune epilepsy patients. In contrast, abnormal electrical activity originating from the hippocampus often propagated from hippocampal head to hippocampal tail or to the contralateral temporal lobe. This finding may explain the different seizure semiologic characteristics between autoimmune epilepsy patients and typical MTLE patients with HS. This study is the first report that autoimmune epilepsy patients often had sleeping SGTC seizures. This finding still needs further exploration.

The overall duration of seizures of autoimmune epilepsy patients with antibodies is the least versus without antibody or in controls for the following reasons. The autoimmune epilepsy patients with autoantibody received early immunotherapy. Considering the risk and cost of immunotherapy, immunotherapy was delayed for suspected autoimmune epilepsy cases without antibody.

In some drug refractory epilepsies, identification of an underlying autoimmune etiology and initiation of immunomodulation might ultimately prevent unnecessary surgical intervention. Additionally, we found that the prevalence of autoimmune epilepsy secondary to neuronal cell surface antigen-specific antibodies appeared to be significantly higher than the prevalence of intraneuronal antigen-specific antibodies (typical paraneoplastic antibodies).

Similar to a previous report,[3] most of our patients (58.97%) had VGKC autoantibodies. LGI1 was the target antigen in 91.30% of our VGKC complex antibody-positive patients. Two patients had antibodies targeting CASPR2. It is well known that FBDS were reported to precede LGI1 antibody-associated encephalitis, suggesting that early immunotherapy could prevent the evolution to limbic encephalitis.[12,25] We identified similar FBDS in 6 (28.57%) of 21 LGI1-seropositive patients in this cohort, often accompanied by other seizure semiologies including SPS and CPS. The clinical characteristics of our study population differed from their studies somewhat, as our three largest antibody subgroups included VGKC, NMDA-R, and $GABA_B$-R. We found that $GABA_B$-R antibody was usually accompanied by small cell lung cancer (SCLC). Autoantibodies to plasma membrane proteins can also be paraneoplastic, but are, in general, immunoresponsive. The most common presenting symptom among our patients was seizure, as it was in theirs. None of our cases underwent epilepsy surgery, though several patients in their studies did.

Serological testing is most valuable as an aid to establishing the diagnosis of an autoimmune etiology. As illustrated in the patients we presented, other laboratory and radiological findings may be normal. Serial MRI findings were consistent with inflammation in most patients. When detected, these radiological findings supported the diagnosis of autoimmune epilepsy. However, MRIs were normal in approximately 40% patients. Cerebrospinal fluid was also normal in more than half of the patients despite the presence of an autoimmune neurological disorder. Hence, the presence of normal CSF or MRI does not exclude an immune-mediated process. Regarding seizure semiologic characteristics, we did not find a significant difference between autoimmune epilepsy patients with autoantibody and suspected autoimmune epilepsy patients without autoantibody. Therefore, failure to detect an autoantibody in patients presenting with a clinical picture suggestive of autoimmune epilepsy, including EEG, MRI, CSF, and other laboratory findings, does not rule out an autoimmune etiology. This finding may reflect the

yet undiscovered array of neuronal antibodies that could result in autoimmune epilepsy, consistent with the results with previous studies.[26,27]

Limitations of this study include the retrospective design and the limited range of autoantibody testing. Because GAD65 antibody testing was not available at the time of our study and because some autoimmune epilepsy patients may not have a recognized neurological autoantibody, the results still may represent an underestimate of the prevalence of autoimmune epilepsy. In addition, patients were enrolled at a specialized tertiary epilepsy center, making the study subject to referral bias.

Conclusions

This study highlights important clinical seizure semiologic characteristics of autoimmune epilepsy. Patients with autoimmune epilepsy had special seizure semiologic characteristics. For patients with autoimmune epilepsy presenting with new-onset seizures in isolation or with a seizure-predominant neurological disorder, the special seizure semiologic characteristics may remind us to test neuronal nuclear/cytoplasmic antibodies early and initiate immunomodulatory therapies as soon as possible. Furthermore, our study demonstrates that the recognition of a subset of autoimmune epilepsies may have dramatically changed the evaluation and management of new-onset seizures. The past decade has seen a dramatic increase in the discovery of neural-specific autoantibodies and their target antigens. Laboratory testing is now available for most of these autoantibodies to help establish a diagnosis and determine prognosis. Furthermore, the absence of neural-specific autoantibodies does not rule out autoimmune epilepsy.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (Nos. 81301119 and 81471327), the Beijing Municipal Administration of Hospitals' Youth Programme (No. QML20160504), the China Association Against Epilepsy-UCB Research Fund (No. CAAE-UCB2016008), and the National Key Technology Research and Development Program of the Ministry of Science and Technology of China (No. 2013BAI09B03).

Author Contributions

Lv and Shao contributed to the study concept and design, and critically revised the manuscript for important intellectual content. Lv, Shao, Ren, Guan, and Cui acquired the data. Lv, Cui, and Shao analyzed and interpreted the data. Lv drafted the manuscript. Lv provided statistical expertise. Lv, Ren, and Shao provided administrative, technical, and material support. Shao supervised the study.

Conflict of Interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. On behalf of all authors, the corresponding author confirms no conflict of interest.

References

1. Dubey D, Konikkara J, Modur PN, et al. Effectiveness of multimodality treatment for autoimmune limbic epilepsy. Epileptic Disorders 2014;16:494–499.
2. Gultekin S. H., M. R. Rosenfeld, R. Voltz, et al. 2000. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 123 (Pt 7):1481–1494.
3. Quek AM, Britton JW, McKeon A, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 2012;69:582–593.
4. Barajas RF, Collins DE, Cha S, Geschwind MD. Adult-onset drug-refractory seizure disorder associated with anti-voltage-gated potassium-channel antibody. Epilepsia 2010;51:473–477.
5. Majoie HJ, de Baets M, Renier W, et al. Antibodies to voltage-gated potassium and calcium channels in epilepsy. Epilepsy Res 2006;71:135–141.
6. Liimatainen S, Peltola M, Sabater L, et al. Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. Epilepsia 2010;51:760–767.
7. Peltola J, Kulmala P, Isojarvi J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. Neurology 2000;55:46–50.
8. Bien CG. Value of autoantibodies for prediction of treatment response in patients with autoimmune epilepsy: review of the literature and suggestions for clinical management. Epilepsia 2013;54(Suppl 2):48–55.
9. Irani SR, Buckley C, Vincent A, et al. Immunotherapy-responsive seizure-like episodes with potassium channel antibodies. Neurology 2008;71:1647–1648.
10. Hoffmann LA, Jarius S, Pellkofer HL, et al. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J Neurol Neurosurg Psychiatry 2008;79:767–773.
11. Toledano M, Britton JW, McKeon A, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. Neurology 2014;82:1578–1586.
12. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 2011;69:892–900.

13. Bakpa OD, Reuber M, Irani SR. Antibody-associated epilepsies: Clinical features, evidence for immunotherapies and future research questions. Seizure 2016;41: 26–41.
14. Olmez I, Moses H, Sriram S, et al. Diagnostic and therapeutic aspects of Hashimoto's encephalopathy. J Neurol Sci 2013;331:67–71.
15. Boronat A, Sabater L, Saiz A, et al. GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology 2011;76:795–800.
16. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA (B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010;9:67–76.
17. Gaspard N. Autoimmune Epilepsy. Continuum (Minneap Minn) 2016;22:227–245.
18. Lv RJ, Sun ZR, Cui T, et al. Temporal lobe epilepsy with amygdala enlargement: a subtype of temporal lobe epilepsy. BMC Neurology 2014;14:194.
19. Malter MP, Widman G, Galldiks N, et al. Suspected new-onset autoimmune temporal lobe epilepsy with amygdala enlargement. Epilepsia 2016;57:1485–1494.
20. Wagner J, Schoene-Bake JC, Malter MP, et al. Quantitative FLAIR analysis indicates predominant affection of the amygdala in antibody-associated limbic encephalitis. Epilepsia 2013;54:1679–1687.
21. Quigg M. Circadian rhythms: interactions with seizures and epilepsy. Epilepsy Res 2000;42:43–55.
22. Timbie C, Barbas H. Pathways for Emotions: specializations in the Amygdalar, Mediodorsal Thalamic, and Posterior Orbitofrontal Network. J. Neurosci. 2015;35:11976–11987.
23. Garcia-Cabezas MA, Barbas H. Anterior cingulate pathways may affect emotions through orbitofrontal cortex. Cereb Cortex 2017;27:4891–4910.
24. Durazzo TS, Spencer SS, Duckrow RB, et al. Temporal distributions of seizure occurrence from various epileptogenic regions. Neurology 2008;70:1265–1271.
25. Irani S. R., Stagg CJ, Schott JM, et al. 2013. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 136:3151–3162.
26. Sharma A, Dubey D, Sawhney A, Janga K. GAD65 Positive Autoimmune Limbic Encephalitis: a Case Report and Review of Literature. J Clin Med Res 2012;4:424–428.
27. Vincent A, Crino PB. Systemic and neurologic autoimmune disorders associated with seizures or epilepsy. Epilepsia 2011;52(Suppl 3):12–17.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Clinical characteristics of autoimmune-mediated epilepsy with autoantibody.
Table S2. Seizure semiologic characteristic of autoimmune-mediated epilepsy with autoantibody.
Table S3. Seizure semiologic characteristic and follow-up outcome of autoimmune-mediated epilepsy without autoantibody.
Table S4. Seizure semiologic characteristic of MTLE with HS.

