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Seizure semiology in leucine-rich glioma-inactivated protein 1 antibody-associated limbic encephalitis

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ABSTRACT

Objective: The objective of this study was to advance the characterization of seizure semiology in leucine-rich glioma-inactivated protein 1 (LGI1) antibody-associated limbic encephalitis (LE).
Methods: Eighteen patients diagnosed with LGI1 LE were identified. Seizure semiology, demographic features, MRI and fluorodeoxyglucose positron emission tomography (FDG-PET), electroencephalograms, and outcomes following immunotherapy were evaluated.
Results: Patients were divided into the following groups based on seizure semiology: faciobrachial dystonic seizure only (FBDS-only, n = 4), epileptic seizure without FBDS (Non-FBDS, n = 6), and FBDS plus epileptic seizure (FBDS+, n = 8). In the group with Non-FBDS, the majority of patients (5/6) manifested mesial temporal lobe epilepsy (MTLE) like semiology (i.e., fear, epigastric rising, staring, and automatisms) with a frequency of 7 ± 5 times per day and a duration of 15.3 ± 14.3 s. In the group with FBDS+, the distinctive symptom was FBDS followed by epileptic events, especially automatisms (7/8), with a frequency of 16 ± 12 times per day and a duration of 13.0 ± 8.0 s. In these cases, 67% and 50% of the patients showed abnormalities on MRI and FDG-PET, respectively, and the mesial temporal lobe structures were most often involved. Ictal discharges were observed in 0/4, 6/6, and 8/8 of the patients in the groups with FBDS only, Non-FBDS, and FBDS+, respectively. The temporal lobe was mainly affected. Immunotherapy had favorable therapeutic effects.
Significance: The LGI1 LE should be considered as one disease syndrome with a series of clinical manifestation. Identifying types of unique semiology features will facilitate the early diagnosis and the timely initiation of immunotherapy.

1. Introduction

Autoantibodies against the extracellular domains of the voltage-gated potassium channels (VGKC) complex protein, leucine-rich glioma-inactivated protein 1 (LGI1), and contactin-associated protein-2 have been described in patients with limbic encephalitis (LE), neuromyotonia, and Morvan syndrome [1–3]. In patients suffering from LE, LGI1 is the most commonly targeted VGKC-complex protein. It has been shown that identifying LGI1 antibody has a better sensitivity and specificity than VGKC-complex antibody testing in providing a diagnosis and rationale of immunotherapy for autoimmune diseases [4]. Amnesia, confusion, and seizure are the main symptoms of LGI1-related LE [5]. Recently, another distinctive symptom involving brief, very frequent episodes that typically involve dystonic posturing of the hemiface and ipsilateral arm (faciobrachial dystonic seizures, FBDS) has been described. Faciobrachial dystonic seizure is currently viewed as pathognomonic for the presence of LGI1 antibodies [6,7]. Accordingly, identifying this semiology may alert neurologists to the possibility of further LE.

However, it is unclear whether FBDS is 100% predictive of LGI1-positive LE. Therefore, combining FBDS with seizure into a comprehensive semiology analysis may be beneficial for clinical diagnosing LGI1 LE.

Abbreviations: LGI1, leucine-rich glioma-inactivated protein 1; LE, limbic encephalitis; FBDS, faciobrachial dystonic seizure; Non-FBDS, epileptic seizure without FBDS; FBDS+, FBDS plus epileptic seizure; MTLE, mesial temporal lobe epilepsy; VGKC, voltage-gated potassium channels.

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Few previous studies have (i) focused on the seizure semiology in patients with LGI1 LE, (ii) described whether there are other distinctive semiologies of seizure in addition to FBDS, and (iii) clarified the differences in epileptic semiology between patients with LGI1 LE and those with classic mesial temporal lobe epilepsy (MTLE). To explore these questions, we conducted a retrospective study over a period of 4 years during which we evaluated the clinical data for 18 patients with LE with positive LGI1 antibodies.

2. Material and methods

2.1. Patients

In all, eighteen patients with LE diagnosed with positive LGI1 antibodies from October 2011 to October 2015 in our center were enrolled. Commercially available postfixed sagittal mouse brain sections and cell-based biochips assays (Euroimmun, Lóbeck, Germany) were used to evaluate the serum titers of antibodies associated with autoimmune encephalitis. The biochips consist of human embryonic kidney (293) cells transfected with plasmids encoding the following antigens (subsequent fixation with the substances given in brackets): LGI1, $GABA_BR$, *N*-methyl-D-aspartate receptor (NMDAR, consisting of NR1 subunits only), contactin-associated protein-like 2 (CASPR2), and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR). The protocol for indirect immunofluorescence followed the instructions given by Euroimmun (FA 112d-1, immunoglobulin G [IgG]). The stained biochips were examined under a fluorescence microscope (Eurostar 3 Plus, Euroimmun, Germany). All of the patients received a 1.5/3.0 T MRI scan and a 24-hour EEG recording using the 10–20 system of scalp electrode placement. Clinical information was obtained by reviewing the patients' charts and the database. Patients/relatives received retrospective telephone/personal interviews. Before the follow-up, all of the subjects signed an informed consent form which was reviewed and approved by the ethics committee of Beijing Tiantan Hospital. Emphasis was placed on seizure semiology and video-EEG data, which were reviewed by two neurologists (attending doctor Chao Chen and senior doctor Xiao-Qiu Shao) who were experienced epilepsy professionals.

2.2. Statistical methods

Descriptive statistics were applied to analyze the distributions of demographic and clinical data. *t*-Tests and nonparametric tests were performed to analyze continuous variables, and Chi-square tests or Fisher's exact tests were used for discrete variables. All of the data were analyzed using SPSS software (SPSS, version 18.0 for Windows; SPSS Inc., Chicago, Illinois, USA).

3. Results

For this series, the mean age at symptom onset was 47.0 ± 14.4 years, the average time from symptom onset to diagnosis was 4.7 ± 6.4 months, and the gender ratio (male/female) was 4:5. All the patients were suffering from cognitive complaints (amnesia, confusion, or disorientation). One-third of the patients had sleep disturbance, and 44% showed hyponatremia (Table 1).

3.1. The patients were divided into three groups based on semiology of seizure

Eighteen patients were divided into the following three groups—only FBDS attack (FBDS-only), epileptic seizure without FBDS (Non-FBDS), and FBDS plus epileptic seizure (FBDS+) (Table 1 and Supplementary Table 2). There were no significant differences in the demographic data among these three groups. The groups with Non-FBDS and FBDS+ had a relatively longer average time from symptom onset to diagnosis than the group with FBDS-only, although this relationship was not significant.

Table 1
General clinical features of 18 patients with LGI1 antibody-positive LE.

	Limbic encephalitis (n = 18)	FBDS-only (n = 4, 22%)	Non-FBDS (n = 6, 33%)	FBDS+ (n = 8, 44%)
Median age at symptom onset, years	47.0 ± 14.4	45.0 ± 11.8	43.5 ± 15.9	50.6 ± 15.3
Median time from symptom onset to diagnosis, months	4.7 ± 6.4	1.9 ± 1.3	5.2 ± 5.3	5.8 ± 8.6
Male:female	8:10	1:3	3:3	4:4
Amnesia, n (%)	18 (100)	4 (100)	6 (100)	8 (100)
Confusion/disorientation, n (%)	17 (94)	4 (100)	5 (83)	8 (100)
Sleep disorder, n (%)	6 (33)	0 (0)	2 (33)	4 (50)
MRI abnormalities, n (%)	12 (67)	2 (50)	6 (100)	4 (50)
Hyponatremia, n (%)	8 (44)	2 (50)	2 (33)	4 (50)

FBDS = faciobrachial dystonic seizure; FBDS-only = only FBDS attack; Non-FBDS = epileptic seizure without FBDS; FBDS+ = FBDS plus epileptic seizure.

In the group with FBDS-only (n = 4), all of the patients showed typical symptoms of FBDS, with short episodes (2.1 ± 0.7 s), and high frequency FBDS attacks (40 ± 17 times per day). In case 3, the FBDS attacks were frequently triggered by changes in posture (Fig. 1A–E), and the other patients showed no auras.

Six of the patients were included in the group with Non-FBDS. The majority of these patients (5/6) manifested symptoms that were similar to MTLE (i.e., fear, epigastric rising, staring, and automatisms). In the remaining patient (case 7), the semiology was arm numb and soreness. Occasional episodes of GTCS were observed in two patients (cases 10 and 11), but neither was a major episode. In this group, the mean seizure frequency was 7 ± 5 times per day, which was lower than the frequency in the group with FBDS-only (7 ± 5 vs. 40 ± 17, $P < 0.05$), and the duration of seizure was 15.3 ± 14.3 s. This group of patients was easily diagnosed as MTLE, ignoring the cause of autoimmune encephalitis. The following illustrative case from our center was suspected to be autoimmune encephalitis until the presurgical evaluation conference. Before that, the patient was treated for refractory MTLE and about to undergo anterior temporal lobectomy.

Case 9 was a 17 years old female. Before the seizure onset, the patient first felt discomfort and then appeared facial expressions of fear, accompanied by short-term confusion. The whole process lasted for 5–20 (12.5 ± 7.5) s. The patient was treated with oral oxcarbazepine 1200 mg and Topamax 200 mg daily. There were still 3 times seizure attacks per day. Ictal EEG revealed rhythmic slow activities developing to spike and waves rhythm in left anterior temporal and frontal region (Fig. 2A). Magnetic resonance imaging documented the left hippocampal high intensity signal on T2/Flair weighted images (14 months after disease onset) (Fig. 2B, C). After a diagnosis of LGI1 LE, the patients started to receive oral prednisolone 60 mg per day (15 months after disease onset). After 3 days of treatment, the patient achieved seizure freedom. Twenty months after the disease onset, MRI-documented left hippocampal abnormalities disappeared (Fig. 2D, E).

Eight of the patients were included in the group with FBDS+. The major semiology of this group was FBDS combined with other epileptic events and took place in a single attack. The most common phenotype in this group is the first occurrence of FBDS-like dystonia followed by other symptoms (89%). For case 15 and case 17, FBDS plus epileptic seizure is their primary type of episode (64% and 64%). However, these two patients occasionally have other types of attack such as epileptic seizure followed by FBDS (5% and 12%), sole FBDS (5% and 12%), and sole epileptic seizure (26% and 12%) (Supplementary Table 2). The vast majority patients of this group (7/8 cases) exhibited FBDS plus automatisms (e.g., hand groping, soliloquizing, and oral-automatisms), and one (case 11) displayed a dystonic posture and subsequent ipsilateral