Clinical Characteristics and Prognostic Analysis of Anti-LGI 1 Receptor Encephalitis in Northeast China

Qian Zhao  
Jilin University First Hospital

Mengmeng Li  
Jilin University First Hospital

yingxue lu  
Jilin University First Hospital

Weihong Lin (✉️ 1193148969@qq.com)  
Jilin University First Hospital

Research article

Keywords: Anti-LGI 1 encephalitis, Clinical features, electroencephalogram, treatment prognosis

DOI: https://doi.org/10.21203/rs.3.rs-40819/v1

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Abstract

Background: To investigate the clinical characteristics and prognosis of Anti-LGI1 receptor encephalitis.

Methods: This retrospective study enrolled forty-one patients with anti LGI1 receptor encephalitis diagnosed for the first time in the Department of Neurology, the first hospital of Jilin University from June 2015 to November 2019.

Results: There are twenty-two males and nineteen females, with a median age of fifty-four years. The first symptom of male patients showed cognitive impairment in nine (40.91%) cases, facial muscle dystonia in six (27.27%) cases. Of the female patients, seven (36.84%) patients had facial-arm dystonia-like seizures, six (31.58%) patients had cognitive impairment. Seven (18.42%) patients had abnormal tumor markers, but no tumor was found in all patients. Thirty patients (73.17%) had hyponatremia with a minimum of 115.4 mmol/L. Except for one patient, eighteen (45.00%) patients had normal cerebrospinal fluid indicators, twenty-two (55.00%) patients had abnormal cerebrospinal fluid indicators, eleven (50.00%) patients had elevated protein, and nine (40.91%) patients had elevated IgG, six (27.27%) patients' white blood cells increased, and four (18.18%) patients of increased pressure. Except for four patients, twenty-two (59.46%) patients had abnormal signals of hippocampus and temporal lobe, seventeen (77.27%) of them had bilateral abnormal signals of hippocampus, five (22.73%) cases had unilateral abnormal signals of hippocampus; eleven (29.73%) had lacunar cerebral infarction and ischemic focus; two (5.41%) cases of frontal and insular abnormal signals; one (2.70%) case of temporal and occipital abnormal signals; one (2.70%) case of white matter lesions. Except for one patient, the EEG showed twenty-seven (67.50%) cases of slow waves and focal discharges, (six (22.22%) of which were left-temporal spiked slow waves, and five (18.52%) were of right-temporal spikes Slow wave, four (14.81%) cases with double temporal sharpened slow wave, six (22.22%) cases with frontotemporal sharpened slow wave, one (3.70%) case with frontal sharpened slow wave, one (3.70%) case with Three-phase waves; In addition, four (10.00%) cases of fast activity increased; three (7.50%) cases of background α generalization). Patients received first-line immunotherapy except six patients who gave up treatment.

Conclusions: Anti-LGI1 receptor encephalitis is more common in middle-aged and older people. In male, the first manifestation is cognitive impairment, and the female is more common with the facial-arm dystonia-like seizures, and rarely can be manifested as discharge sensation, hallucinations and autonomic symptoms. Lumbar puncture pressure increased more than decreased; protein was significantly higher than leukocytes; EEG showed slow waves and focal discharges were more common, and abnormal background and normal EEG can occur. MRI shows that hippocampus and temporal lobe abnormal signal have the highest proportion. There is no significant difference in the prognosis of hormones, globulin, or both.

Background
Anti-LGI1 antibody-associated borderline encephalitis was previously thought to be an anti-voltage-gated potassium channel (VGKC) antibody against VGKC two related proteins, LGI1 and CASPR2 autoantibodies, LGI1 neurons Secreted proteins are mainly expressed in the hippocampus and temporal cortex, LGI 1 is secreted in the synapse, and is associated with two synaptic proteins of the catabolic factor and metalloproteinase domain (ADAM) family-presynaptic ADAM 23 and post-synaptic ADAM 22 interaction. Faciobrachial dystonic seizure (FBDS) is a specific symptom of anti-LGI1 antibody-related borderline encephalitis, manifested as frequent, transient dystonia-like involuntary movements on one arm and face and even lower limbs. The seizure time is short, generally only a few seconds, frequent seizures can reach dozens of times a day, may be accompanied by bilateral dystonia-like seizures, changes in consciousness, etc. Studies have shown that about 50% of patients exhibit these symptoms. We retrospectively analyzed the clinical data of forty-one patients with the first diagnosis of anti-LGI 1 receptor encephalitis admitted to the Department of Neurology at the First Hospital of Jilin University from June 2015 to November 2019. This study aimed to investigate the clinical characteristics and prognosis of anti-LGI1 receptor encephalitis in Northeast China.

Methods

Patients

The clinical data of forty-one patients diagnosed with anti-LGI 1 receptor encephalitis for the first time in the Department of Neurology at the First Hospital of Jilin University from June 2015 to November 2019 were selected.

The inclusion criteria are in accordance with the diagnostic points of the 2017 "Chinese Expert Consensus on the Diagnosis and Treatment of Autoimmune Encephalitis" [8]: (1) acute or subacute onset, progressive increase; (2) clinical compliance with marginal inflammatory brain, or manifested as FBDS; (3) The cerebrospinal fluid white blood cell count is normal or mildly lymphocytic inflammation; (4) head MRI: bilateral or unilateral medial temporal lobe abnormal signal, or no obvious abnormality; (5) abnormal EEG; (6) serum and (or) cerebrospinal fluid anti-LGI antibodies Positive.

Exclusion criteria: (1) No lumbar puncture during hospitalization, incomplete cerebrospinal fluid examination or clinical data; (2) Central nervous system infection caused by specific intracranial pathogens; (3) Recent history of thyroid disease, thyroid hormone replacement, or thyroid function and antibodies Lack of test results; (4) Immunosuppressive status (including long-term immunosuppressive therapy such as chemotherapy, organ transplantation, or cancer); (5) It is not the first time to diagnose anti-LGI 1 receptor encephalitis.

This study was approved by the local Ethics Committee. Written informed consent was obtained from each participant.

Data collection
Laboratory examination

All the samples collected were serum and cerebrospinal fluid samples from our hospital at the first attack and sent to Beijing Union Medical College Hospital for anti-neuronal antibody testing. It was confirmed that patients with serum and/or cerebrospinal fluid anti-LGI antibodies were positive.

General data collection

Retrospective analysis June 2015-November 2019 The clinical data of forty-one patients with the first diagnosis of anti-LGI 1 receptor encephalitis admitted to the Department of Neurology, the First Hospital of Jilin University. The clinical characteristics, laboratory examinations, imaging and electroencephalogram performance of patients were collected to evaluate the treatment effect and prognosis.

Results

Clinical characteristics

There are twenty-two males and nineteen females, with a median age of fifty-four years (range thirty-one to seventy-seven years). The first symptom of twenty-two male patients showed cognitive impairment in nine (40.91%) cases, facial muscle dystonia in six (27.27%) cases, mental behavior abnormality in four (18.18%) cases, two (9.09%) patients had seizures, one (4.54%) patient had unconsciousness, and one (4.54%) patient had hallucinations, dizziness, headache, nausea and vomiting, and head-like sensations. Of the 19 female patients, seven (36.84%) patients had facial-arm dystonia-like seizures, six (31.58%) patients had cognitive impairment, four (21.05%) patients had seizures, three (15.79%) patients had hallucinations, one (5.26%) patient had abnormal mental behavior, one (5.26%) patient had unconsciousness, and no (0.00%) dizziness, headache, nausea and vomiting, and head-like sensations. (Table 1 Table 2)
Table 1 Clinical characteristics of forty-one patients with anti-LGI 1 receptor encephalitis

| Clinical characteristics                                      | percentage                  |
|--------------------------------------------------------------|-----------------------------|
| Gender ratio (male: female)                                  | 22:19                       |
| Median age (years)                                           | 54                          |
| Hyponatremia at first visit                                  | 30/41(73.17%)               |
| Antibody positive                                           |                             |
| Blood positive                                               | 11/41(26.83%)               |
| Cerebrospinal fluid positive                                 |                             |
| Positive blood and cerebrospinal fluid                       | 30/41(73.17%)               |
| CSF indexes (except for one case unknown)                    |                             |
| Cerebrospinal fluid is normal                                | 18/40(45.00%)               |
| Abnormal cerebrospinal fluid                                | 22/40(55.00%)               |
| Increased protein                                            | 11/22 (50.00%)              |
| Increased white blood cells                                  | 6/22 (27.27%)               |
| Increased pressure                                           | 4/22 (18.18%)               |
| Increased IgG                                                | 9/22 (40.91%)               |
| Electroencephalogram (except one case without EEG)           |                             |
| Normal EEG                                                   | 4/40 (10.00%)               |
| EEG low voltage                                              | 1/40 (2.50%)                |
| Slow wave delivery (frontotemporal origin)                  | 27/40 (67.50%)              |
| Left temporal sharpened slow wave                            | 6/27 (22.22%)               |
| Right temporal slow-pointed slow wave                        | 5/27 (18.52%)               |
| Double temporal tip slow wave                                | 4/27 (14.81%)               |
| Frontotemporal pointed slow wave                             | 6/27 (22.22%)               |
| Forehead sharpened slow wave                                 | 1/27 (3.70%)                |
| Three-phase wave                                             | 1/27 (3.70%)                |
| Spike distribution                                           | 1/40 (2.50%)                |
| Low amplitude fast activity                                  | 4/40 (10.00%)               |
| Background generalization                                    | 3/40 (7.50%)                |
| MRI (except four cases exceptions)                           |                             |
| Clinical manifestation                                                                 | Male                  |
|---------------------------------------------------------------------------------------|-----------------------|
| Hippocampal anomaly signal                                                            | 22/37 (59.46%)        |
| Unilateral hippocampal anomaly signal                                                 | 5/22 (22.73%)         |
| Bilateral hippocampal anomaly signal                                                  | 17/22 (77.27%)        |
| Lacunar infarction and softening foci                                                 | 11/37 (29.73%)        |
| Frontal leaf Insular leaf abnormal signal                                             | 2/37 (5.41%)          |
| Temporooccipital abnormal signal                                                     | 1/37 (2.70%)          |
| White matter lesions                                                                  | 1/37 (2.70%)          |
| Abnormal tumor markers (except for 3 cases not checked)                               | 7/38 (18.42%)         |
| Tumor                                                                                 | 0/41 (0.00%)          |
| Treatment (except 6 cases of giving up)                                               |                       |
| Hormone                                                               | 11/35 (31.43%)        |
| Gamma globulin                                                                      | 9/35 (23.68%)         |
| Hormone combined with gamma globulin                                                 | 15/35 (42.86%)        |

Table 2 Clinical manifestations at the first attack

| Female                                                                 | Male                  |
|------------------------------------------------------------------------|-----------------------|
| Facial-arm dystonia (36.84%)                                           | 13/41 (31.70%)        |
| Cognitive impairment (31.58%)                                          | 15/41 (36.59%)        |
| Seizures (21.05%)                                                      | 6/41 (14.63%)         |
| Abnormal mental behavior (5.26%)                                       | 5/41 (12.20%)         |
| Unconsciousness 1/19(5.26%)                                           | 2/41(4.88%)           |
| Hallucinations (illusion, hallucinations, hallucinations) 3/19 (15.79%) | 4/41 (9.76%)          |
| Dizziness, headache, nausea and vomiting 0/19 (0.00%)                 | 1/41 (2.44%)          |
| Head discharge-like sensation and radiate one limb 0/19 (0.00%)        | 1/41 (2.44%)          |
Radiological examinations

Except for four patients with unknown MRI data, twenty-two (59.46%) patients had abnormal signals of hippocampus and temporal lobe, seventeen (77.27%) of them had bilateral abnormal signals of hippocampus, five (22.73%) cases had unilateral abnormal signals of hippocampus; Eleventh (29.73%) had lacunar Cerebral infarction and ischemic focus; Two (5.41%) cases of frontal and insular abnormal signals; on (2.70%) e case of temporal and occipital abnormal signals; one (2.70%) case of white matter lesions. (Table 1)

EEG examinations

Except for one patient who did not have EEG, the EEG showed twenty-seven (67.50%) cases of slow waves and focal discharges, (six (22.22%) of which were left-temporal spiked slow waves, and five (18.52%) were of right-temporal spikes Slow wave, four (14.81%) cases with double temporal sharpened slow wave, six (22.22%) cases with frontotemporal sharpened slow wave, one (3.70%) case with frontal sharpened slow wave, one (3.70%) case with Three-phase waves; In addition, four (10.00%) cases of fast activity increased; three (7.50%) cases of background $\alpha$ generalization; one (2.50%) case of sharp wave delivery; four (10.00%) cases of normal EEG. (Table 1)

Laboratory tests

Except for three unknown cases in the detection of tumor markers, seven (18.42%) patients had abnormal tumor markers, but no tumor was found in all patients. Thirty patients (73.17%) had hyponatremia with a minimum of 115.4 mmol/L during the first laboratory test on admission. Except for one patient with unclear lumbar puncture data, eighteen (45.00%) patients had normal cerebrospinal fluid indicators, twenty-two (55.00%) patients had abnormal cerebrospinal fluid indicators, Eleventh (50.00%) patients with abnormal indicators had elevated protein, and nine (40.91%) patients had elevated IgG, six (27.27%) patientys of white blood cells increased, and four (18.18%) patients of increased pressure. (Table 1)

Treatment and prognosis

All patients received first-line immunotherapy except six patients who gave up treatment. Fifteen (42.86%) patients had globulin and hormones, eleventh (31.43%) patients with hormones, and nine (23.68%) patients with globulins. After treatment, they all improved and were discharged from the hospital, but there was still a relapse. (Table 1)
Discussion

In 2010, Lai et al. [1] reported for the first time that anti-LGI 1 antibody-related encephalitis and anti-CASPR 2 antibody-related encephalitis were related to voltage-gated potassium channels. The first report was reported in 2013 from China[2]. Since then, the number of confirmed cases of anti-LGI 1 antibody-related encephalitis has also increased year by year, which may be related to the expansion of the known neuronal autoantibody spectrum and the gradual adoption of antibody testing. In recent years, the immunopathogenic mechanism of LGI1 antibody is still to be studied, and there are reports that it may be related to human leukocyte differentiation antigen (HLA) subtypes [3]. It has also been reported that patients with anti-LGI 1 encephalitis are more likely to develop autoimmune diseases than patients with other types of encephalitis, and found that autoimmune diseases do not affect the clinical process [4].

LGI-1 antibody encephalitis is most common in elderly men with a significant male predominance, and the disease is often a subacute attack, usually developing into complete encephalitis without treatment during the attack. The main clinical manifestations are FBDS, memory loss, hyponatremia, and good immunotherapy effect [5]. Other rare symptoms include autonomic dysfunction, including excessive sweating, bradycardia and sphincter dysfunction, and common behavior/personality changes, including irritability, obsessive-compulsive disorder, emotionalization, and insomnia [6]. FBDS and other epilepsy symptoms usually occur before cognitive impairment. This study reported forty-one cases of patients diagnosed with anti-LGI1 antibody-associated border encephalitis for the first time in our hospital. Reviewing the clinical data of the patients, the first manifestation of males was cognitive impairment, and females had the highest proportion of facial arm dystonia-like attacks, followed by Seizures, abnormal mental behavior, and hallucinations (phantom vision, olfactory auditory hallucinations), dizziness, headache, nausea, vomiting, autonomic symptoms, and abnormal discharge-like sensations in the head may be rare. To further confirm this difference, we need to further increase the sample size. Frequent seizures are also common, and it has been reported [7 8] that knocking out LGI protein genes can cause autosomal dominant temporal lobe epilepsy. Therefore, effective identification of seizures is helpful for early diagnosis of the disease. FBDS accounts for 50%, and the symptoms of non-FBDS attacks are diverse, usually focal attacks; general tonic clonic seizures are uncommon, usually appearing late in the disease. Recognizing this type of seizure with a relatively short duration may be difficult. Reasonable use of EEG is essential. Studies have shown that most of them appear sharp slow waves. Approximately 31.70% of patients in this study first showed FBDS, 67.50% EEG showed slow waves, focal discharges, temporal origins were more common, and even rare three-phase waves and the whole brain low voltage; 10.00% showed fast increased activity; 10.00% normal EEG; 2.50% manifested as sharp wave delivery; it has been reported [9] 60% of patients with head MRI showed bilateral temporal lobe high signal, 40% is abnormal signal in one hippocampus or normal, our The report is generally consistent with the above.

It has been reported in laboratory tests [10] that serum hyponatremia accounts for about 50%; patients with hyponatremia in this article account for 73.17%, with a minimum of 115.4 mmol/L, and hyponatremia is higher than previous reports. Report [11] shows that serum LGI1 antibody is easier to
detect than CSF LGI1 antibody. The double positives of blood and cerebrospinal fluid antibodies in this article are greater than those of pure blood positive, but there are no patients with positive cerebrospinal fluid positive in forty-one patients. According to the report, the serum LGI1 antibody is easier to detect than CSF LGI1 antibody. The specific mechanism still needs further study. CSF examination in patients with LGI1-associated encephalitis often indicates normal or only mild to moderate protein, increased cell count, and few intrathecal IgG synthesis [12]. In this study, we found that the pressure of lumbar puncture was normal for the first admission and the pressure increased higher than pressure reduction; protein is significantly higher than white blood cells. In this article, forty-one patients were found to have abnormal tumor markers, but no tumor was found. This is consistent with previous reports. There was no significant difference in the prognosis of thirty-five patients regardless of hormones, globulin or a combination of the two. Patients with seizures, especially FBDS combined with other types of epilepsy, when use immunotherapy, combined use of antiepileptic drugs is beneficial to patients.

**Conclusions**

Middle-aged and elderly patients have the above-mentioned clinical manifestations and hyponatremia. Regardless of whether there is abnormal signal on the cranial MRI, this disease should be considered, and the examination of cerebrospinal fluid LGI1 antibody and electroencephalogram should be improved. Anti-LGI1 encephalitis should be treated with immunotherapy in time to prevent recurrence, and attention should be paid to distinguish it from other autoimmune encephalitis. Proper identification of early-onset seizures is helpful for clinical diagnosis. Positive serum and/or cerebrospinal fluid LGI1 antibody is the main basis for diagnosis. Immunotherapy for the disease is effective, and the overall prognosis is good, and some patients may have residual memory impairment.

**Abbreviations**

CASPR2: contactin-associated protein-like2; CSF: cerebrospinal fluid; EEG: electroencephalogram; LGI1: leucine-rich glioma-inactivated 1; MRI: magnetic resonance imaging;

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the First Hospital of Jilin University. Written consent was obtained from each participant.

**Consent for publication**

Not applicable.
Availability of data and materials

All data used and/or analyzed during the study is available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors’ contributions

QZ collected and analyzed the clinical data and drafted the manuscript. ML and YXL participated in the study design and helped to draft the manuscript. WL reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all of the patients who participated in this study.

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