Three cases of antibody-LGI1 limbic encephalitis and review of literature

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Three cases of antibody-LGI1 limbic encephalitis and review of literature

Abstract: Antibody-LGI1 limbic encephalitis (LGI1-Ab LE) is an anti-neuronal surface antigen related autoimmune encephalitis, which clinically manifests through memory impairment, faciobrachial dystonic seizures (FBDS), epileptic seizures, behavior
disorders, and hyponatremia. Now, we reported three cases of LGI1-Ab LE. The clinical features of our patients presented with memory impairment, epileptic seizures, hyponatremia, and two patients presented with behavior disorders. All serum LGI1 antibodies were positive, whereas one patient LGI1 antibodies of cerebrospinal fluid (CSF) was negative. Gammaglobulin, hormone or both in combination were administered to them, the clinical symptoms improved significantly.

**Keywords:** Epilepsy, FBDS, hyponatremia, immunomodulatory therapy, LGI1-Ab positive, limbic encephalitis.

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**Introduction**

Limbic encephalitis (LE) is an autoimmune encephalitis involving the limbic system including hippocampus, amygdala, medial temporal lobe, insular lobe and cingulate cortex. LE is regarded as a disease associated with epilepsy, memory deterioration, behavioral disorders, and sleep disorders. It is also related to the paraneoplastic disease of antibodies in cerebellar cells. LE is associated with antibodies(Abs) to the voltage-gated potassium channel complex (VGKC), the Abs are mainly directed to the VGKC-complex proteins, leucine-rich glioma inactivated 1 protein (LGI1) or contactin-associated protein-like 2 (CASPR-2). Most of the involved Abs are LGI1 which is an anti-neuronal surface antibody, accounting for 30% of the LE-related Abs. LGI1-Ab LE is mostly non-paraneoplastic[1,2], and thought to be responsive to immunotherapy[3,4]. The typical features include: faciobrachial dystonic seizures (FBDS), cognitive decline, hyponatremia, LGI-1 antibody positive of Serum or CSF, and brain MRI reveals abnormalities in the medial temporal lobe or the hippocampus [5]. In this study, we
report three cases of LGI1-Ab LE, describe the characteristics of clinical manifestation, course of evolution, imaging manifestation and treatment outcomes.

Case 1

A previously healthy, 50-year-old female, initially presented with numbness of the upper left limb. She exhibited an untreated hyponatremia upon physical examination.

5 hours before admission, she developed to generalized tonic–clonic seizure. Simultaneously, she also showed absence seizures and experienced memory loss particularly her recent memory. Her score of Montreal Cognitive Assessment (MoCA) was 16, Mini Mental State Examination (MMSE) was 21. Routine EEG result was mainly slow waves in background. Serum sodium was 135.8mmol/L. Anti-SSA antibody 60kd, Anti-SSB antibody were positive. Tumor markers and paraneoplastic neuronal antibodies (Hu, Ri, Yo) were negative. Repeated CSF routine, cells, glucose, chloride, protein were within the normal range. Test of serum LGI1-Ab was positive (+++), while the CSF LGI1-Ab was negative, using the indirect immunofluorescence test (IIFT) (EUROIMMUN, FA 112d-1, Germany). Brain MRI (Fig. 1) showed abnormal signal in the left hippocampus region and the lesions was not enhanced. Magnetic resonance spectrum(MRS) showed the cholin(Cho) peak increased, and the N-acetyl aspartic acid (NAA) peak showed a decreasing trend in the left hippocampus. The bilateral hippocampus showed high signal on fluid-attenuated inversion recovery (FLAIR) sequence. She was treated with Methylprednisolone pulse therapy (500mg for 3 days and 250 mg for 3 days) combined with antiepileptic drugs(Sodium valproate and lamotrigine). After the immunotherapy, she no longer had epileptic seizure and had
improved memory. Her repeated score of MoCA was 20, and MMSE was 25. Prednisolone 60 mg daily oral treatment was administered subsequently with slow tapering after discharge. During a 90 days’ follow-up, there was no recurrent seizure two weeks after the drug was discontinued, but leaving mild memory impairment. Her MoCA scores were 24 and MMSE scores were 28.

Case 2

A 45-year-old woman was admitted to hospital with a witnessed generalised tonic clonic seizure. She experienced strangeness to familiar environment, and expressed some incomprehensible words related to her work. Cranial MRI revealed chronic ischemic changes in the deep white matter of the frontal and parietal regions. EEG result showed slow background activity and no epileptic waves. No apparent positive signs were found after she completed a nervous system examination, however her memory was impaired. Her score of MoCA was 14, MMSE was 22. She was treated empirically with phenobarbital sodium and sodium valproate. Serum tests indicated peroxidase (TPO) 158IU/ml, 679.10 IU/mL anti-thyroglobulin (TG), 121.0 mmol/L serum sodium. Chest, full abdominal and pelvic CT examination showed no signs of tumor. The levels of the CSF, cells, glucose, chloride and culture were normal. Tests of serum LGI1-Ab was positive(++) and CSF LGI1-Ab was also positive (++), examined by the indirect immunofluorescence test (EUROIMMUN, Germany). She was treated with intravenous immunoglobulin (IVIG) at a dose of 0.4 g/kg/day for 3 days combined with dexamethasone 10 mg/day. Prednisolone acetate oral treatment was administered subsequently with slow tapering. Repeat MRI(Fig. 2) revealed thickening swell signal of the right hippocampus structure. She responded quite well to the immunotherapy and
epilepsy was no recurrence. Her repeated score of MoCA was 22, and MMSE was 25. During a 90 days’ follow-up, neurological examination was essentially normal with the exception of mild memory impairment. Her MoCA score was 28 and MMSE score was 28.

Case 3

A 64-year-old male presented with a 7-day’s history of lag in response and balderdash. Nocturnal arm twitching was noted for half a month with visual hallucination. At the same time, family members also noted his recent memory was impaired. Cranial MRI revealed the hyper-intensity of the left medial temporal lobe, mild white matter ischemic change. His medical history was notable for hypertension for 2 years. A nervous system examination revealed his impaired memory and dullness of mind. His score of MoCA was 18, MMSE was 23. In the ward, he exhibited a paroxysmal involuntary twitch of the upper limbs and the right face. This condition was relieved within a few minutes, but was observed at a frequency of dozens times/day. He was treated with Sodium valproate. Reviewed cranial MRI (Fig. 3): left hippocampus appeared abnormal signal on T2/FLAIR sequence. Routine EEG showed slow background activity and sporadic sharp waves during wakefulness. Serum sodium was 132mmol/L. There was no obvious abnormality in lung CT examination. The levels of the CSF, cells, glucose, chloride and culture were normal. Test of serum LGI1-Ab was positive(+ +), while CSF LGI1-Ab was negative, examined by the indirect immunofluorescence test (EUROIMMUN, Germany). He was treated with intravenous immunoglobulin (IVIG) at a dose of 0.4 g/kg/day for 5 days, and continued oral Prednisone acetate 60 mg/day subsequently. Memory deterioration was alleviated, and
epileptic seizure was relieved after treatment. His repeated score of MoCA was 21, and MMSE was 26. During a 90 days’ follow-up, there was no recurrent seizure and his recent memory was impaired slightly, too. His MoCA score was 26 and MMSE score was 27. (table 1)

Discussion

LE, a clinicopathological entity with inflammatory lesion in the limbic system, is caused by a combination of antibodies and expressed proteins on the neuronal surface. VGKC-Ab is a kind of anti-neuronal surface antibody, including CASPR2-Ab, LGI1-Ab and other antibodies[6]. LGI1 is a secreted protein encoded by the Igl1 gene. It can interact with presynaptic membrane ADAM metallopeptidase domain 22 and presynaptic membrane ADAM metallopeptidase domain 23 to affect the signal transduction between the synapses by the VGKCs and postsynaptic membrane a-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors[7]. LGI1-Ab could destroy LGI1 involved in the function through a variety of mechanisms[8]. In this study, the average age of onset is 53 years old. Case 1, 2 were female, and case 3 is male. Ramanathan's[9] findings revealed that the average age of onset was 57 years old and 65% were male.

LE is resulting in a variety of clinical manifestations, epilepsy is the most common. The forms of attack can be varied. FBDS, which was recently described as a characteristic feature of LGI1-Ab LE[5], is short, frequent, and unconscious, together with dystonia, simple upper limbs spasm and contraction, and ipsilateral face twitch which is not long, 3 s, several times a day. Our cases all presented with seizures at onset, but had varying individual characteristics. Case 1 with paresthesia of left upper limb as the first symptom, we considered it as a simple partial seizure. Later, it
developed into generalized tonic clonic seizure. In addition, the patient also had absence seizures. Case 2 presented generalized tonic clonic seizure as the first symptom. Case 3 exhibited a paroxysmal involuntary twitch of the upper limbs and the right face, which was considered as FBDS. Some scholars speculated that FBDS is not really epilepsy. Minor improvements were noted after the regular use of antiepileptic drugs, but the FBDS remarkably reduced and ceased after treatment with immunomodulatory therapy[11]. However, Irani et al[12] thought that FBDS was a kind of epileptic seizure. So, currently on the FBDS is seizure or dystonia is controversial[24]. The possible relationship between FBDS and LGI1-Ab LE should be investigated in more detail.

Cognitive impairment is also the common neurological disorder in LGI1-Ab LE. Memory disorder, especially the recent memory impairment is the most prominent [13]. Majoie et al [6] found that 89% of LE patients with 8-month disease course had memory disorder. Malter et al[14] confirmed that the decrease in cognitive disorder was related to the disease course before immunotherapy. Therefore, in the acute phase of the disease, cognitive dysfunction may not occur. The MoCA and MMSE tests were done in all the patients, the results found that they all had mild cognitive dysfunction. 3 cases showed abnormal MRI signals in the unilateral/bilateral hippocampus. This indicated that abnormal structures in the hippocampus might be associated with memory disorder. Dysphrenia is also common clinical symptom of LGI1-Ab LE. The main manifestations are personality and behavior disorders, irascibility, anxiety, impulsive behavior, paranoia, and stupor; some patients mainly have visual hallucination[3,15]. Case 2 manifested as strangeness to familiar environmental, involuntary and incomprehensible words related to her work. Case 3 appeared as visual hallucination during hospitalization. Sometimes, the onset of symptoms may be delayed because they were treated in psychiatric hospitals. After immunotherapy, mental symptoms disappeared.
EEG is of great significance in the diagnosis of LGI1-Ab LE. Often, the onset of intermittent, EEG may be normal or appears focal slow or sharp wave, especially in the temporal frontal region. Cases 3 revealed epileptic waves, while case2 and 1 EEG shown non-specific slow waves in background, no epileptic waves. A video recorder, which is more helpful in the diagnosis of FBDS and differential diagnosis with movement disorders, is recommended.

It is an important basis for the diagnosis of LGI1-Ab LE that cranial MRI shows the abnormal signal of temporal lobe medial or hippocampus. For case 1, we found that the lesion of the left hippocampus spread to the bilateral hippocampus, showing a dynamic change. For case 2, repeated cranial MRI revealed swollen abnormal signal of the right hippocampus region. This indicated that the abnormal signals of lesion might be present in a normal course of the disease, rather than in the acute phase. Cranial MRI (Case 3)also showed abnormal signal of the left hippocampus. Irani et al [17] found that the LGI-Ab LE, without any immunotherapy, might gradually develop into hippocampus atrophy with related nervous system symptoms, so follow-up MRI scan and careful evaluation of the hippocampus area are recommended. PET-CT has been reported is beneficial for the early diagnosis and prognosis of LE. Irani et al revealed abnormal glucose metabolism in the temporal region or basal ganglia even when the MRI was normal[1]. Given the limited number of brain PET-CT studies in LGI1-Ab LE, more investigations are needed.

LGI-1 Ab positive of Serum or CSF is the specific indicator. The antibody titer of CSF is 1% -11% of serum according to Vincent et al[18]. We recommend that LGI1 antibody test should be performed on both serum and CSF if available. All serum LGI1 antibodies were positive, whereas one LGI1 antibodies of CSF were negative. The possibility of LE patients with positive LGI1 antibody, having tumors is
minimal[17,19]. It also supports the diagnosis of paraneoplastic encephalitis, if the CSF leukocytes were significantly increased or immunoglobulin abnormalities. We can not completely rule out the potential of tumor, it still needs a long-term follow-up for tumor screening, including CT scan of the chest and abdominal together with tests of tumor markers every six months or once a year, even if no tumor is discovered now.

Hyponatremia, due to the syndrome of inappropriate antidiuretic hormone secretion, is another characteristic feature of LGI1-Ab LE. 60% patients are persistent refractory hyponatremia, according to the literature[16]. It might be related to the simultaneous LGI1 expression of the hypothalamus and kidney[15]. But hyponatremia in other types of LE is rare. Whether LGI1-Ab LE is associated with hyponatremia, and whether the selective involvement of the kidneys and hypothalamus, need to be further studied. In this study, all patients had hyponatremia, and the serum sodium level increased as the condition improved. It is necessary to consider the presence of the tumor, especially small cell lung cancer, if there is intractable hyponatremia. In addition, Case 1 immune-related assay: anti-SSA antibody 60kd, anti-SSB antibody were positive. Case 2 serum test revealed anti-thyroid peroxidase antibody (An-TPOAb) was positive. It indicated that LE may be a comorbidity of other autoimmune disease.

Although there is no definitive standardized treatment, immunotherapy is strongly recommended, including first-line drug: methyl-prednisolone injection, immunoglobulin injection, plasma exchange and other immune support[20]. In the early stage, the patients are given the treatments of intervention, particularly immunoglobulin, and blood exchange combined with hormone therapy is better than simplex glucocorticoid[21]. Early treatment, according to individual treatment plan, can prevent disease progression and get good prognosis. After the immunotherapy, the clinical symptoms of 3 patients were improved in different degrees. Their cognitive levels have
also been significantly improved (table2 and table 3). Some studies suggest that
effective and long-term immunotherapy, which could prevent long-term complications,
including hippocampus atrophy and persistent memory damage, should be given[14].
Second-line drugs can be added to patients who did not respond well to the first-line
drugs or had a recurrence, including rituximab or cyclophosphamide[22]. In addition,
all the patients took the antiepileptic drugs. Therefore, we think that antiepileptic drugs
should be given to patients with epileptic seizures. This disease responds well to
immunotherapy and the prognosis is good[23].

In conclusion, LGI1 -Ab LE, which is an autoimmune disease, is rare clinically. A
high degree of vigilance is necessary to this disease. We suggest that LGI1-Ab LE be
considered in any patient with acute or subacute onset, cognitive dysfunction (especially
near memory impairment), various types of seizures, accompanied by mental disorders
and hyponatremia, MR showed the involvement of the limbic system. Brain MR
reexamination is necessary to confirm the diagnosis if the initial image is negative.
Differential diagnosis includes viral encephalitis, metabolic encephalopathy. It is
necessary to have LE-related antibodies tested. Early immunotherapy can significantly
improve the patient's neurological function, and effective and long-term immunotherapy
is also recommended. At the same time, we should also pay attention to the possibility
of potential tumors. For patients whose tumor screening is initially negative at present,
long-term follow-up on tumor screening and better identify the prognosis is also
important.
Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

References


   Neuropsychiatric Disease and Treatment 2017; 13: 1589-96.


Fig. 1 Cranial MRI of case 1.

Fig. 2 Cranial MRI of case 2.
Fig. 3 Cranial MRI of case 3.
Table 1. Demographic and clinical data of three cases of antibody-LGI1 limbic encephalitis

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Presenting</th>
<th>Results of EEO</th>
<th>Results of CSF</th>
<th>Serum EMG</th>
<th>Serum titers</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 F</td>
<td></td>
<td>Generalized tonic-clonic seizures, right hemiparesis</td>
<td>Bilateral hyperintensity</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>41 F</td>
<td></td>
<td>Generalized tonic-clonic seizures, right hemiparesis</td>
<td>Bilateral hyperintensity</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>64 M</td>
<td></td>
<td>Mental disorder, FBDs</td>
<td>Bilateral hyperintensity</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>30 mg/day</td>
</tr>
</tbody>
</table>

Abbreviations:
- EEO: Electroencephalogram
- EMG: Electromyography
- CSF: Cerebrospinal fluid
- MRI: Magnetic resonance imaging
- FBDs: Frontobrachial dyskinetic seizures
- FLAIR: Fluid-attenuated inversion recovery
Table 2. Changes of scores of MMSE before and after treatment and follow up

<table>
<thead>
<tr>
<th>MMSE</th>
<th>Case1</th>
<th>Case2</th>
<th>Case3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td>F</td>
</tr>
<tr>
<td>Orientation</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Registration</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Attention and Calculation</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Recall</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Language and Praxis</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>25</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations:

MMSE: Mini-mental state examination

B: before treatment

A: after treatment

F: follow up
**Table 3.** Changes of scores of MoCA before and after treatment and follow up

<table>
<thead>
<tr>
<th>MoCA</th>
<th>Case1</th>
<th>Case2</th>
<th>Case3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td>F</td>
</tr>
<tr>
<td><strong>Visuospatial/Executive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naming</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>attention</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>100 continuous reduction of 7</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Language</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Abstraction</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Orientation</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

**Abbreviations:**

MoCA: Montreal cognitive assessment scale

B: before treatment

A: after treatment

F: follow up