What's Different about Teratoma-Associated LGI1 Encephalitis? A Long-Term Clinical and Neuroimaging Case Series

Cun Li
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Hong-bin Cai
No.9 hospital of Wuhan City
Xu Zhao
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Xin-cong Xi
No.6 hospital of Shanghai City
Qing Zhou
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Hui-ya Luo
Huazhong University of Science and Technology Tongji Medical College
Zhou-ping Tang
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Huicong Kang (kanghuicong@163.com)
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
https://orcid.org/0000-0003-1585-8491
Heidi E. Kirsch
Epilepsy Center, University of California, San Francisco, California

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Abstract

Background Leucine-rich glioma-inactivated 1 (LGI1) encephalitis is clinically heterogeneous, especially at presentation, and though it is sometimes found in association with tumor, this is by no means the rule. The aim of this study is to report a case of teratoma-associated LGI1 encephalitis, to summarize a retrospective series of LGI1 encephalitis and compare them.

Methods Clinical data for 10 people with LGI1 encephalitis were collected. Patients were divided into those with and without associated teratoma, and compared for clinical characteristics. Microscopic pathological examination and immunohistochemical (IHC) assay of the LGI1 antibody were performed on teratoma tissue obtained by laparoscopic oophorocystectomy.

Results The LGI1 patient with teratoma was similar to the non-teratoma (NT) group in many ways: age at onset (average 47.3 in NT group); percent presenting with rapidly progressive dementia (RPD) (67% of NT group) and psychiatric symptoms (33%); hyponatremia (78%); normal cerebrospinal fluid results except for positive LGI1 antibody (78%); bilateral hippocampal hyperintensity on magnetic resonance imaging (MRI) (44%); diffuse slow waves on electroencephalography (EEG) (33%); good response to immunotherapy (67%); and mild residual cognitive deficit (22%). Her chronic anxiety and presentation with status epilepticus were the biggest differences compared with the NT group. Teratoma pathology was characterized by mostly thyroid tissue and IHC assay confirmed positive LGI1 expression.

Conclusion In our series, LGI1 encephalitis included common clinical features: RPD, faciobrachial dystonic seizures, behavioral disorders, hyponatremia, T2-MRI hyperintensity of hippocampus and residual cognitive deficit. We observed some differences in our case with teratoma, but a larger accumulation of cases is needed to improve our knowledge base.

Background

Autoimmune encephalitis (AE) is an immunopathologic encephalopathy mediated by auto-antibodies. Leucine-rich glioma-inactivated 1 (LGI1) encephalitis is the second most common AE following N-methyl-d-aspartate (NMDA) receptor encephalitis, and is characterized by rapidly progressive dementia (RPD), faciobrachial dystonic seizures (FBDS), hyponatremia, and T2 hyperintensity of bilateral hippocampus on magnetic resonance imaging (MRI)[1]. The diagnosis of AE is challenging because of heterogeneous clinical presentation especially early in the course of disease[2]. A large multicenter study of AE indicated that “typical” clinical features above were absent in a relatively large segment of cases: only 42% presented with RPD; only 47% suffered from FBDS; 35% had no hyponatremia and 26% showed normal structural MRI[3]. Therefore, LGI1 encephalitis was commonly misdiagnosed as its mimickers, including Creutzfeldt-Jakob disease (CJD)[4], herpes simplex encephalitis[5], Hashimoto’s encephalopathy[6], neurodegenerative disease[7] and stroke[8].

In the past few years, many researches have indicated correlations between the presence of tumors and paraneoplastic limbic encephalitis (PLE), an important subtype of AE. One study of the correlation of PLE

and tumor found that among 50 patients diagnosed with PLE, cancer of lung (50%, of which small-cell lung cancer (SCLC) accounted for 80%), testis (20%) and breast (8%) were the three most common tumors, alongside other rarer cancers like Hodgkin's disease (4%), ovarian teratoma (4%) and thymoma (2%)[9]. PLE is thought to be due to stimulation of an antibody-mediated immune response caused by tumor antigens that are cross-reactive with neural host antigens[10]. The most specific correlation is between NMDA encephalitis and ovarian teratoma[9]. In a descriptive clinical report including 81 patients with NMDA encephalitis, ovarian teratoma was found in 56% of patients > 18 years old, 31% of patients > 14 and < or = 18 years old and 9% of patients < or = 14 years old. No tumors were found in male patients[11]. However, the prevalence of tumor in voltage-gated potassium Channel (VGKC) encephalitis (including LGI1 or contactin-associated protein 2(Casper2)) was less than 10%[12], being more frequently seen in Casper2 encephalitis than in LGI1 encephalitis[12]. In one study, less than 10% LGI1 encephalitis was comorbid with tumors, including thymus, thyroid, lung and renal cell tumors[13, 14]. Even though tumors were detected in 13% of a series of 166 patients with LGI1 IgG positivity [15], to our best knowledge, no correlation between teratoma and LGI encephalitis has been reported to date.

Therefore, here we report a case of LGI1 encephalitis comorbid with ovarian teratoma; pathological association was indicated by immunohistochemistry showing positive expression of LGI1 in the teratoma tissue. The patient has been followed for 5 months since diagnosis in clinic, with neuropsychological evaluations, neuroimaging, electroencephalography (EEG) and serum antibody titers. The clinical features of a series of LGI1 encephalitis cases without ovarian teratoma were also summarized and compared with this rare case to explore the possible diagnostic clues to LGI1 encephalitis with and without teratoma.

Methods

Clinical data

Ten patients were diagnosed with LGI1 encephalitis at Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology (HUST) between January 2013 and July 2019. These included one patient with ovarian teratoma and nine without. Among the nine cases without teratoma, the average age at onset was 47.3 ± 15.6 years, and the sex ratio was 1:2 female:male.

Clinical data were abstracted from patient records, including acuity of onset, symptoms at onset and during disease course (e.g. seizures, cognitive dysfunction, psychiatric symptoms and sleep disorders), presence of comorbid tumor, serum sodium levels, cerebrospinal fluid (CSF) results, MRI, EEG, neuropsychological assessment ((Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Barthel Index (BI)), response to therapy and clinical course.

For the CSF results, we defined normal as cell count < 8 cells/mL, protein level ≤ 0.30 g/L. For onset, we defined acute within 2 weeks, sub-acute as 2 weeks to 2 months and chronic as > 2 months for the time

from onset to peak.

Neuroimaging Scanning Protocol

All MRI sequences were performed on the 3.0-T MR scanner (Discovery MR750, GE Healthcare, Milwaukee, Wisconsin) with a 32-channel phased-array head coil. All subjects underwent a standard structural brain scan, including axial T1-fluid-attenuated inversion recovery imaging (FLAIR) (TR/TE/TI 2991/24/868 ms, matrix size 320 × 320, FOV 24 × 24 cm^2, slice thickness 5 mm, gap 1.5 mm), T2-weighted FSE (TR/TE 4579/102 ms, matrix size 320 × 224, FOV 24 × 24 cm^2, echo train length 20, slice thickness 5 mm, gap 1.5 mm), T2-FLAIR (TR/TE/TI 8000/160/2100 ms, matrix size 256 × 256, FOV 24 × 24 cm^2, slice thickness 5 mm, gap 1.5 mm), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and a contrast-enhanced T1-weighted spin echo sequence in axial, sagittal and coronal planes following a bolus injection of 0.2 mmol/kg of Gd-DTPA. Some patients also underwent arterial spin labeling (ASL) using a pseudocontinuous labeling (pCASL) with a high level background suppression (TR/TE 4788/14.7 ms, post label delay (PLD) 1525 ms, slice thickness 4 mm, NEX = 3, time duration 4 min38s).

Pathological And Immunohistochemistry Examination Of Ovarian Teratoma Tissue

The tissue of teratoma was fixed by 4% paraformaldehyde, embedded by paraffin and sliced using a microtome. The sections were deparaffinized, dehydrated and subjected to hematoxylin and eosin staining.

Immunohistochemical analyses of teratoma tissue were performed using a rabbit polyclonal antibody against LGI1 (diluted 1:200, BIOSS, Beijing, China). The immunostaining protocol for LGI1 detection were described previously[16].

The study was approved by the HUST Committee on Human Research and all patients signed informed content to participate.

Results

Clinical presentation of LGI1 encephalitis with teratoma

The patient was a 48-year-old woman with past medical history of nodular goiter and suspected teratoma. She began to suffer from anxiety six months prior to diagnosis, and have been treated with anxiolytics with no effect and with gradual deteriorization. In the two months prior to admission, she had been hyperglycemic, and for the prior month had suffered from short term memory dysfunction and drowsiness.

She was admitted to the endocrinology department and once glucose control was established, she was transferred to the neurology department because of ongoing cognitive impairment. The patient frequently forgot whether she had taken her medication, where her bed was located in the hospital, and who had visited her. MMSE was 13 (details in Table 1) and she could not complete the MoCA because of irritability. Laboratory data after admission confirmed slightly decreased sodium level of 135.4 mmol/L (normal range 136–145 mmol/L) and potassium 2.87 mmol/L (normal range 3.5–5.1 mmol/L), increased glucose 12.48 (normal range 3.9–6.1 mmol/L), but normal complete blood counts, urinalysis, liver and renal function, myocardial infarction markers and coagulation functions. On day 6 after admission, lumbar puncture was performed with normal routine and biochemical testing results, except for elevated glucose level of 4.74 mmol/L (normal range 2.22–3.89 mmol/L), normal immunology. Autoimmune encephalitis antibody panel (including NMDA, LGI1, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 (AMPA1), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2 (AMPA2), gamma-aminobutyric acid-B receptor ($GABA_B$) and Casper-2) of serum and CSF was also performed. On day 7, she developed visual hallucinations, and routine EEG was performed showing diffuse slow waves. Brain MRI showed bilateral hippocampal hyperintensity on T2 and T2-FLAIR sequences. Methylprednisolone (200 mg/d, I.V.) and 2.5 mg olanzapine were given immediately with the diagnosis of possible AE.

Table 1
Neuropsychological assessment in LGI1 encephalitis case with teratoma

Scale	Time since admission				
	Day 6	Day 32	Month 3	Month 4	Month 5
MMSE					
Total	13	19	26	24	27
Orientation	5	7	10	9	9
Registration	2	3	3	3	3
Attention and Calculation	2	1	1	1	5
Recall	0	0	3	2	1
Language	4	8	9	9	9
MoCA					
Total	N/A	20	24	28	29
Visuospatial and Executive function	N/A	4	5	5	5
Animal naming	N/A	3	3	3	3
Attention	N/A	4	4	4	6
Language	N/A	3	3	3	3
Abstraction	N/A	2	1	2	2
Delayed recall	N/A	0	2	5	4
Orientation	N/A	4	6	6	6
HAMA			8	2	4
HAMD			12	0	3
N/A, MoCA was not performed because the patient was too irratated.					
MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; BI, Barthel Index; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive section.					

On day 8, she was transferred to intensive care unit (ICU) because of convulsive status epilepticus (SE) for 20 minutes unresponsive to diazepam (10 mg I.V.) twice and phenobarbital (200 mg I.M.) begun given 5 minutes after seizure onset. In the ICU, endotracheal intubation was followed by antibiotic therapy because blood oxygen saturation dropped to 70% and symptoms and signs of pneumonia were evident. Meanwhile, she was treated with midazolam, fentanyl and levetiracetam (LEV) initially followed by LEV monotherapy once she had been seizure-free for 24 hours. The diagnosis of LGI1 encephalitis was

confirmed by the detection of LGI1 antibody both in blood (1:32) and CSF (1:3.2), whereas other autoimmune antibodies were all negative. Considering her hyperglycemia and that seizures were controlled, methylprednisolone pulse therapy (MPT) was deferred; instead the dose was maintained at 200 mg/d with combined immunoglobulin ((0.4 mg/kg/d), I.V. 5 days) therapy. She was extubated on day thirteen at which point her vital signs were continuously stable.

After her seizures and pulmonary infection were well controlled, she returned from the ICU to the neurology ward with impaired cognitive function, visual hallucinations and irritability. We reduced the daily dose of methylprednisolone gradually with a transition to oral prednisone acetate, and continued drugs for control of seizures and psychosis. At day 25 after admission, the patient could answer simple questions and complained of stomachache (right lower quadrant). Considering her past history of suspected teratoma, ultrasound examination of uterus and appendages was performed and indicated a right adnexal mixed cystic-solid lesion. Further abdominal computed tomography (CT) indicated a possible teratoma in this region. Gynecologic oncologists recommended elective surgery after the LGI1 encephalitis was stable. One week later, neuropsychological assessment was performed with MMSE of 19 and MOCA of 20 (details in Table 1). She was discharged with continued oral prednisone acetate (10 mg/d), LEV (1500 mg/d) and olanzapine (1.66 mg/d).

At month 1 followup, the patient presented to the clinic with impaired short term memory and spatial disorientation, but no hallucinations. She was intermittently unaware of where she was and why she had come. Short term memory was impaired to the extent that she had to write down her daily plan and what she did every day in her notebook. She was partially reliant on a home caregiver. Repeated MRI (3 months after onset of memory dysfunction) showed reduced swelling of the bilateral hippocampus on T2 and T2-FLAIR sequence, slightly improved. Considering her improved LGI1 encephalitis, she was admitted to the gynecological oncology department for laparoscopic oophorocystectomy. Postoperative pathological examination confirmed the diagnosis of teratoma: part of the left ovarian tissue was filled with colloidal substance, most of which was goiter, and was consistent with mature teratoma. Positive staining for LGI1 was observed with the deepest staining in the thyrocytes.

At month 2 followup, her spatial disorientation was gone; she knew where she was and how to get back home when she went out, but she complained that she felt anxious when facing daily activities such as answering phone calls, and her short term memory was still bad. Neuropsychological assessment showed improved cognitive function with MMSE of 26, MOCA of 24 (details in Table 1) and a mild mood problem with HAMA of 8 and HAMD of 12. LGI1 antibody titer in blood was 1:32 at this time (one month after surgery).

At month 3 followup, her anxiety was greatly improved, but she still had short term memory impairment. EEG background had improved and showed focal, bilateral frontal slowing. Neuropsychological assessment showed very mild cognitive impairment and normal HAMA and HAMD scores (details in Table 1).

At month 4 followup, the patient's anxiety was totally relieved and she could live independently and return to work as her memory had gradually improved and she could recall what she had done without checking her notebook.

At month 5 followup, she complained once again of short term memory impairment during work, she frequently forgot where to find her working tools and documents. She was afraid of being alone and she preferred to stay at home with her family rather than having social contact. Neuropsychological assessment scores were 27 for MMSE, 29 for MOCA, 4 for HAMA, 3 for HAMD (details in Table 1), 8 for Alzheimer 's disease assessment scale (ADAS-Cog) (scored 5 for memory, 2 for word recognition and 1 for orientation) and 100 for BI. Repeated MRI including structural and functional sequences indicated improvement: hyperintensity on T2 and T2-FLAIR were now gone on the left hippocampus though still present on the right side without swelling; no progressive brain atrophy was observed; DWI and DTI were symmetric bilaterally and normal; ASL showed slightly decreased blood flow in her left temporal lobe.

Clinical manifestations in LGI1 encephalitis cases with and without teratoma

The clinical features of this case of teratoma-associated LGI1 encephalitis and of the nine other cases without teratoma are summarized in Table 2.

Table 2
Clinical characteristics of LGI1 encephalitis cases with and without teratoma

Clinical characteristics	LGI1encephalitis without teratoma (N (%))	LGI1 encephalitis with teratoma
Total Number	9	1
Female	3/9 (33%)	Yes
Age at onset (y, mean ± SD (range))	47.3 ± 15.6 (19–67)	48
Disease onset	9	Yes
Acute	6 (67%)	
Sub-acute	3 (33%)	
Chronic	0	
Clinical symptoms	9	Yes
Symptoms at onset	9	Yes
Behavioral disorders	2 (22%)	Yes
FBDS	2 (22%)	Yes
Cognitive impairment	1 (11%)	Yes
Behavioral disorders + Cognitive impairment	1 (11%)	Yes
RBD	1 (11%)	
Dizziness	1 (11%)	
Mood disorder	0	
Mood disorder + FBDS	1 (11%)	
Symptoms through entire disease course	9	
Seizures	8 (89%)	
Generalized convulsions	4/8 (50%)	
	3/8 (38%)	

Yes means the LGI1 encephalitis patient with teratoma had the symptom.

LGI1, leucine-rich glioma-inactivated 1; FBDS, faciobrachial dystonic seizures; RBD: rapidly eye movement behavior disorder; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI: magnetic resonance imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS: modified Rankin Scale.

* one patient died of pneumonia because of comorbid myasthenia gravis and one patient died of hepatic failure due to chronic schistosomiasis liver disease and hepatitis B, deteriorated after immunotherapy.

Clinical characteristics	LGI1encephalitis without teratoma (N (%))	LGI1 encephalitis with teratoma
FBDS	1/8 (13%)	
Focal seizures	0	
Status epilepticus	6 (67%)	
Cognitive impairment	3 (33%)	
Hallucinations	6 (67%)	
Sleep disorder	3/6 (50%)	
Insomnia	2/6 (33%)	
RBD	1/6 (17%)	
Drowsiness		

Yes means the LGI1 encephalitis patient with teratoma had the symptom.

LGI1, leucine-rich glioma-inactivated 1; FBDS, faciobrachial dystonic seizures; RBD: rapidly eye movement behavior disorder; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI: magnetic resonance imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS: modified Rankin Scale.

* one patient died of pneumonia because of comorbid myasthenia gravis and one patient died of hepatic failure due to chronic schistosomiasis liver disease and hepatitis B, deteriorated after immunotherapy.

Clinical characteristics	LGI1encephalitis without teratoma (N (%))	LGI1 encephalitis with teratoma
Ancillary test results	9	Yes
Evidence of tumor	0	Yes
Hyponatremia	7 (78%)	Yes
CSF	7 (78%)	Yes
Cell count < 8 cells/mL	7/7 (100%)	Yes
Protein < = 0.58 g/L	7/7 (100%)	Yes
Positive LGI1 antibody immunoassay	9 (100%)	Yes
Serum	2/9 (22%)	
CSF	2/9 (22%)	
Serum + CSF	5/9 (56%)	
EEG	6 (67%)	
Background slowing	3/6 (50%)	
Background slowing + epileptic discharges	1/6 (17%)	
Normal	2/6 (33%)	
MRI	9 (100%)	
Hippocampal lesion	8 (89%)	
Bilateral	4/8 (50%)	
Unilateral	4/8 (50%)	
Normal	1 (11%)	

Yes means the LGI1 encephalitis patient with teratoma had the symptom.

LGI1, leucine-rich glioma-inactivated 1; FBDS, faciobrachial dystonic seizures; RBD: rapidly eye movement behavior disorder; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI: magnetic resonance imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS: modified Rankin Scale.

* one patient died of pneumonia because of comorbid myasthenia gravis and one patient died of hepatic failure due to chronic schistosomiasis liver disease and hepatitis B, deteriorated after immunotherapy.

Clinical characteristics	LGI1encephalitis without teratoma (N (%))	LGI1 encephalitis with teratoma
Cognitive function evaluation results	6 (67%)	Yes
MMSE < = 24	3/6 (50%)	Yes
MOCA < = 26	1/6 (17%)	
Normal	2/6 (33%)	
Follow-up	8 (89%)	Yes
mRS evaluation	8 (89%)	Yes
<=2	6/8 (75%)	
> 2	2/8 (25%)	
Residual symptoms or death	8 (89%)	
No symptom	3/8 (38%)	
Short-term memory impairment	2/8 (25%)	
FBDS	1/8 (13%)	
Death*	2/8 (25%)	
Yes means the LGI1 encephalitis patient with teratoma had the symptom.		
LGI1, leucine-rich glioma-inactivated 1; FBDS, faciobrachial dystonic seizures; RBD: rapidly eye movement behavior disorder; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI: magnetic resonance imaging; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; mRS: modified Rankin Scale.		
* one patient died of pneumonia because of comorbid myasthenia gravis and one patient died of hepatic failure due to chronic schistosomiasis liver disease and hepatitis B, deteriorated after immunotherapy.		

Our case with teratoma shared many clinical features with those subjects without teratoma (NT group), including 1) age at onset of 48, near the average of 47.3 years in the NT group; 2) hyponatremia, as seen in 78% of the NT group; 3) normal CSF cell count and protein, as seen in 78% of the NT group; 4) positive LGI1 antibody, as seen in blood and/or CSF of all subjects; 5) hippocampal hyperintensity on MRI, as seen in 89% of the NT group; 6) slow waves on EEG, as seen in 33% of the NT group; 7) cognitive impairment and sleep disorder, seen in 67% of the NT group; 8) residual cognitive impairment > 1 year after admission, as seen in 67% of the NT group; and 9) only mild neurological disability during follow-up: the mRS score was 1 in the patient with teratoma, as compared to < = 2 in 67% of the NT group.

However, there are also four key points in which the patient with teratoma significantly differed from those without. First, she presented with chronic anxiety as a prominent symptom; only one patient in the NT group had anxiety as a symptom, and this was acute anxiety beginning simultaneously with FBDS.

Second, her anxiety was persistent, lasting until her most recent follow up (13 months from onset); the NT patient with acute anxiety had resolution of this feature by two months follow up. Third, the patient with teratoma developed convulsive status epilepticus during her course, but never had FBDS, as was seen in several of the NT group in both the acute stage of their disease and during follow up.

We followed the patient with teratoma for five months; one patient in the NT group was lost to follow up after discharge, but the other eight were followed for an average of 26.1 ± 12.0 months. After immunotherapy and removal of the teratoma, the patient with teratoma recovered, becoming seizure-free and living independently. Similarly, intravenous immunoglobulin (IVIG) and/or methylprednisolone pulse therapy treatment was effective in 78% of the NT group; one patient died of pneumonia because of comorbid myasthenia gravis and one patient died of hepatic failure due to chronic schistosomiasis liver disease and hepatitis B, deteriorated after methylprednisolone pulse therapy followed by oral azathioprine. None of the NT patients relapsed within the follow-up period.

Discussion

Unlike NMDA receptor encephalitis, LGI1 encephalitis is a subtype of AE with heterogenous clinical manifestations, rarely comorbid with tumor[12, 14]. To our knowledge, ours is the first reported case of LGI1 encephalitis with teratoma. By comparing this case with other cases of LGI1 encephalitis without teratoma in our center, we have derived several possible diagnostic biomarkers of LGI1 encephalitis in hopes of promoting its early diagnosis.

The mechanism of LGI1 encephalitis is mediated by pathogenic auto-antibodies, which directly attack presynaptic and postsynaptic protein complexes[2]. Although limited data indicates the correlation of tumor and LGI1 encephalitis, one study showed that less than 10% of patients have tumors, including thymoma, thyroid, lung and renal cell tumors[13, 14]. We think that LGI1 encephalitis was associated with the teratoma in our case for several reasons: 1) IHC staining confirmed the positive expression of LGI1 antibodies in the teratoma tissue; 2) pathological results indicated that teratoma tissue mainly consisted of thyroid gland, which is susceptible to immunological attack and easily promotes the generation of various antibodies as antigen[17] (additionally, thyroid cancer can be comorbid with LGI1 encephalitis[13, 14]); 3) after removal of the teratoma, her cognitive function recovered greatly; and 4) many reports about AE or PLE associated with ovarian teratoma have been published since 1998, including Yang Y.W. *et al*'s case of episodic dystonia highly consistent with characteristic FBDS described in LGI1 encephalitis today[18–24].

The most representative and high-incidence subtype of AE associated with teratoma was NMDA encephalitis; NMDA receptor-expressing neurons have been described in the neural tissue within teratoma, which was pathogenetic of NMDA encephalitis[25]. Unlike NMDA receptors, which are the extracellular domain of the GluN1 subunit[26], LGI1 is not a structural component of a receptor or ion channel, but is rather secreted by neurons, perhaps explaining why the incidence of tumor is much lower in LGI1 encephalitis compared with NMDA encephalitis. Nevertheless, LGI1 forms a trans-synaptic

complex with presynaptic proteins and is involved in synaptic transmission of neuronal excitability[27], so LGI1 encephalitis may still be comorbid with tumors such as teratoma.

Summary data from our case series indicates similar clinical manifestations as seen in many larger series. These specific manifestations are probably early diagnostic clues to LGI1 encephalitis, including, 1) acute or sub-acute onset of RPD in relatively older aged population[3, 28, 29], 2) FBDS[3, 28, 30], 3) hyponatremia[3, 29] and 4) hyperintensity of bilateral hippocampus on T2 and T2-FLAIR MRI[3, 28].

More importantly, our LGI1 encephalitis case with teratoma presented several specific features that might differentiate it from other subtypes of AE, but perhaps even other cases of LGI1 encephalitis without teratoma, and might therefore be clues. First of all, her chronic onset of anxiety has never been reported in other subtypes of AE by our best knowledge. For NMDA encephalitis, 86% of 100 cases presented headache, fever of a non-specific viral-like illness as prodromal symptom in one case series report[31], and in another study NMDA encephalitis patients developed psychiatric symptom and short term memory loss in less than two weeks[32]. 77% of 22 $GABA_B$ encephalitis patients presented isolated recurrent seizure at onset[33]. In 76 LGI1 antibody positive patients, only 2.6% presented isolated anxiety as initial symptom and the median duration time for isolated initial symptoms was 2 months[34].

Secondly, seizure is one of the most common symptoms of AE, but the clinical manifestation varies among different subtypes. The incidence of seizure in NMDA encephalitis and $GABA_B$ encephalitis is the highest, followed by LGI1 and AMPA encephalitis. Whereas the most typical seizure type with diagnostic specificity is FBDS in LGI1 encephalitis, seen in almost half of 39 confirmed cases, FBDS were not seen in our case with teratoma[3]. NMDA encephalitis has more seizure types at onset; a study of seven cases found that 43% had generalized tonic clonic seizures (GTCS), 43% had focal seizures and 14% had both simultaneously [35]. Seizure was relatively uncommon in AMPA encephalitis (20% of patients), typically GTCS[36]. SE is seen more often in GABA encephalitis, based on the limited literature: seen in 58% of one series of 12 $GABA_A$ encephalitis cases[37] and 27% in another series of 11 confirmed $GABA_B$ encephalitis subjects[38], compared with only 6% of 100 NMDA encephalitis patients[39] and 5% of 19 LGI1 encephalitis patients[40]). Interestingly, our case with teratoma developed SE on her 8th day of admission. We think there are two interpretations, 1) SE may be more typical in LGI1 encephalitis with teratoma and 2) the patient's immunotherapy started relatively late, one month after onset of RPD, facilitating the development of SE.

Thirdly, the persistent short term memory impairment and anxiety until 5 months following the acute disease stage in our patient was highly consistent with reported LGI1 encephalitis. One study found 62% of 85 LGI1/CASPR2-IgG-positive patients with central involvement had residual cognitive and personality disturbances[15]. Another study revealed that 23% of 76 patients with LGI1 antibody positive had moderate or severe cognitive impairment at two years follow-up[34]. Recovery from cognitive and neuropsychological symptoms is quicker and more complete in other forms of AE. 75% of 100 confirmed patients with NMDA AE showed full recovery (mRS 0, MMSE 29–30) or very mild functional deficits (mRS 1–2, MMSE 25–28) at median 17 months (range 1-194 months) follow-up[31]. Serial observation of

patients with $GABA_B$ encephalitis indicated that 35% recovered fully and 40% improved markedly, except for recurrent seizures in 50% of 20 cases comorbid with SCLC[41]. Our case suggested that the cognitive deficits in LGI1 encephalitis might need longer time to recover than those in NMDA or $GABA_B$ encephalitis.

Conclusion

Given our experience with our small LGI1 encephalitis cohort, we suggest that physicians should consider the diagnosis of LGI1 encephalitis, and screen for the existence of teratomas, in patients with chronic onset of mood disorders followed by RPD, SE and psychiatric symptoms. Early diagnosis is vital because immunotherapy was effective in LGI1 encephalitis and if instituted early might avoid deterioration and need for ICU management. Further illumination of specific clinical biomarkers of LGI1 encephalitis with teratoma will require collection of more cases.

Abbreviations

LGI1
leucine-rich glioma-inactivated 1,IHC:immunohistochemical, NT:non-teratoma, RPD:rapidly progressive dementia, MRI:Magnetic Resonance Imaging, EEG:electroencephalography, AE
autoimmune encephalitis, NMDA
N-methyl-d-aspartate, FBDS:faciobrachial dystonic seizures, CJD:Creutzfeldt-Jakob disease, PLE:paraneoplastic limbic encephalitis, SCLC:small-cell lung cancer, VGKC:voltage-gated potassium Channel, Casper2:contactin-associated protein 2, HUST:Huazhong University of Science and Technology, CSF:cerebrospinal fluid, MMSE:Mini-Mental State Examination, MoCA:Montreal Cognitive Assessment, HAMD:Hamilton Depression Scale, HAMA:Hamilton Anxiety Scale, BI:Barthel Index, FLAIR:weighted and fluid-attenuated inversion recovery imaging, DWI:diffusion-weighted imaging, DTI:diffusion tensor imaging, ASL:arterial spin labeling, pCASL:pseudocontinuous labeling, PLD:post label delay, AMPA1:α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1, AMPA2:α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2, $GABA_B$:gamma-aminobutyric acid-B
receptor, ICU
intensive care unit, SE:status epilepticus, LEV:levetiracetam, MPT:methylprednisolone pulse therapy, CT:computed tomography, ADAS-Cog:Alzheimer 's disease assessment scale, IVIG:intravenous immunoglobulin, GTCS:generalized tonic clonic seizures.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and Consent to participate

The study was approved by the HUST Ethics Committee on Human Research. All patients signed informed content to participate.

Consent for publication

All patients signed informed content for publication.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author's contributions

CL and HC collected all the clinical data. XZ performed and read all the MRI scans. XX and CL followed up the cases. QZ and HL did IHC assay of the LGI1 antibody. ZT provided advice on neuropsychological assessment. CL wrote the first draft of the manuscript. HCK and HEK contributed to main idea of the manuscript. All authors contributed to the revision of the manuscript and approved the submission.

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Figures

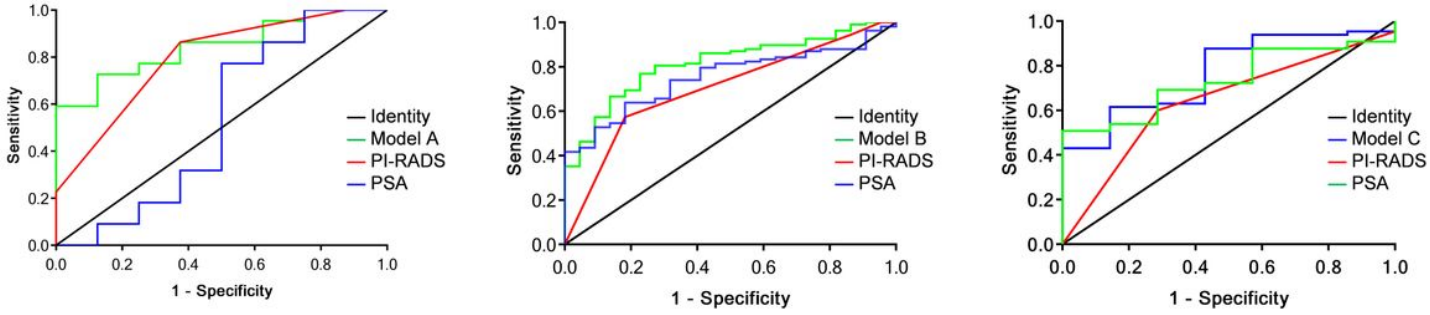

Figure 1

Serial magnetic resonance imaging of the patient with teratoma at different disease stages. A-D were taken 1 month after the onset of cognitive impairment. Bilateral hippocampal hyperintensity is seen on T2 (A) and T2-FLAIR (B), without restricted diffusion (C) and enhancement (D). E and F are repeat studies 3 months after the onset of cognitive impairment,showing slight improvement. G-J were taken 5 months after the onset of cognitive impairment. T2 (G) and T2-FLAIR (axial (H) and coronal (I)) showed only minimal right hippocampal hyperintensity, and no progressive cerebral atrophy. Arterial spin labeling (I) showed slightly decreased blood flow within the left temporal lobe.

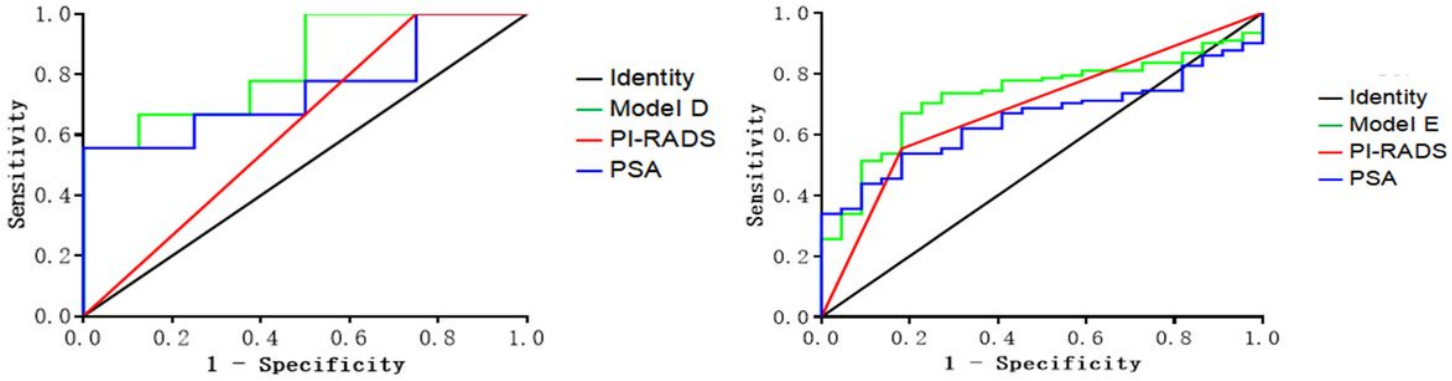

Figure 2

Immunohistochemistry staining of LGI1 in teratoma tissue from our patient with LGI1 encephalitis and teratoma. A (×100) and B (×200) shows abundant thyroid gland structures in teratoma tissue; thyroid cells were positively stained. C (×40) and D (×200) shows widespread staining of teratoma tissue.