What's different about teratoma-associated anti-LGI1 encephalitis? A long-term clinical and neuroimaging case series

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March 10, 2021

Abstract

Background Anti-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. Methods Clinical data for 10 people with anti-LGI1 encephalitis and 3 people with anti-N-Methyl-D-aspartate receptor (NMDAR) encephalitis with teratoma were collected. Microscopic pathological examination and immunohistochemical (IHC) assay of the LGI1 antibody were performed on teratoma tissue obtained by laparoscopic oophorocystectomy. Results In our teratoma associated anti-LGI1 encephalitis case, teratoma pathology was characterized by mostly thyroid tissue and IHC assay confirmed partial or focal positive nuclear staining of LGI1 in some tumor cells. The case was similar to the non-teratoma (NT) group in many ways: age at onset; percent presenting with rapidly progressive dementia (RPD) and psychiatric symptoms; hyponatremia; normal cerebrospinal fluid (CSF) results except for positive LGI1 antibody; bilateral hippocampal hyperintensity on magnetic resonance imaging (MRI); diffuse slow waves on electroencephalogram (EEG); good response to immunotherapy and mild residual cognitive deficit. Her chronic anxiety and status epilepticus (SE) were the biggest differences compared with NT group. Interestingly, the case presented many differences compared with anti-NMDAR encephalitis with teratoma: older onset age, prominent anxiety, SE, hyponatremia, normal CSF cell count, hippocampal hyperintensity on MRI and slowly recovered and residual short-term memory impairment. Conclusion In our series, anti-LGI1 encephalitis included common clinical features: RPD, faciobrachial dystonic seizures, behavioral disorders, hyponatremia, T2-MRI hyperintensity of hippocampus and residual cognitive deficit, but a larger accumulation of cases is needed to improve our knowledge base.

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Running title: Anti-LGI1 encephalitis case serials

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Acknowledgments: This work was supported by the National Natural Science Foundation of China (81974279), China association against epilepsy fund for epilepsy research-UCB fund (2020020A) and Grants for returned overseas doctors of Tongji Hospital. The authors would like to thank the patients and their family for the participation, all referring physicians and Prof. Changshu Ke for his interpretation of the pathalogical sections.

Abstract

BackgroundAnti-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.**Methods** Clinical data for 10 people with anti-LGI1 encephalitis and 3 people with anti-N-Methyl-D-aspartate receptor (NMDAR) encephalitis with teratoma were collected. Microscopic pathological examination and immunohistochemical (IHC) assay of the LGI1 antibody were performed on teratoma tissue obtained by laparoscopic oophorocystectomy.**Results** In our teratoma associated anti-LGI1 encephalitis case, teratoma pathology was characterized by mostly thyroid tissue and IHC assay confirmed partial or focal positive nuclear staining of LGI1 in some tumor cells. The case was similar to the non-teratoma (NT) group in many ways: age at onset; percent presenting with rapidly progressive dementia (RPD) and psychiatric symptoms; hyponatremia; normal cerebrospinal fluid (CSF) results except for positive LGI1 antibody; bilateral hippocampal hyperintensity on magnetic resonance imaging (MRI); diffuse slow waves on electroencephalogram (EEG); good response to immunotherapy and mild residual cognitive deficit. Her chronic anxiety and status epilepticus (SE) were the biggest differences compared with NT group. Interestingly, the case presented many differences compared with anti-NMDAR encephalitis with teratoma: older onset age, prominent anxiety, SE, hyponatremia, normal CSF cell count, hippocampal hyperintensity on MRI and slowly recovered and residual short-term memory impairment.**Conclusion** In our series, anti-LGI1 encephalitis included common clinical features: RPD, faciobrachial dystonic seizures, behavioral disorders, hyponatremia, T2-MRI hyperintensity of hippocampus and residual cognitive deficit, but a larger accumulation of cases is needed to improve our knowledge base.

Key words: Anti-leucine-rich glioma-inactivated 1 encephalitis, anti-N-methyl-d-aspartate receptor encephalitis, rapidly progressive dementia, faciobrachial dystonic seizures, teratoma

Introduction

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, anti-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 anti-NMDAR encephalitis and ovarian teratoma[9]. In a descriptive clinical report including 81 patients with anti-NMDAR 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 anti-LGI1 encephalitis [12]. In one study, less than 10% anti-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 anti-LGI1 encephalitis comorbid with ovarian teratoma; pathological association was indicated by immunohistochemistry showing partial or focal positive nuclear staining of LGI1 was appreciated in some tumor cells. 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 anti-LGI1 encephalitis cases without ovarian teratoma were also summarized and compared with this rare case to explore the possible diagnostic clues to anti-LGI1 encephalitis with and without teratoma.

Materials and Methods

Clinical data

Ten patients were diagnosed with anti-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$\pm$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, 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 neuropsychological assessment, we used the following evaluation scales: 1) MMSE: cognitive impairment was determined when the score was under 26; 2) MoCA: cognitive impairment was considered if the score was under 24; 3) HAMA and HAMD: anxiety or depression was considered while the score was equal or over 7 and further divided to: mild (7-14), moderate (14-21) and severe ($>$21); 4) BI: we define the patients with daily dysfunction while the score was under 80.

All assessments was conducted by two experienced neuropsychologists and the results showed later was the average results.

For the CSF results, we defined normal as cell count < 8 cells/mL, protein level [?]0.30g/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 FLAIR (TR/TE/TI 2991/24/868ms, matrix size 320x320, FOV 24x24cm^2, slice thickness 5mm, gap 1.5mm), T2-weighted FSE (TR/TE 4579/102ms, matrix size 320x224, FOV 24x24cm^2, echo train length 20, slice thickness 5mm, gap 1.5mm), T2-FLAIR (TR/TE/TI 8000/160/2100ms, matrix size 256x256, FOV 24x24cm^2, slice thickness 5mm, gap 1.5mm), diffusion-weighted imaging (DWI), 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 4788/14.7ms, post label delay (PLD) 1525ms, slice thickness 4mm, NEX=3, time duration 4min38s).

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 anti-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 deterioration. 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 firstly with increased glucose level of 15.79 mmol/L (normal range 3.9-6.1 mmol/L), hemoglobin A1c (HbA1c) 10.90% (normal range 4.27%-6.07%), urine sugar 4+ (normal range none). 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 Table1) and she could not complete the MoCA because of irritability. Laboratory data confirmed slightly decreased sodium level of 135.4 mmol/L (normal range 136-145 mmol/L), potassium 2.87mmol/L (normal range 3.5-5.1 mmol/L), thyroid stimulating hormone 0.324 uIU/ml (normal range 0.35-4.94 uIU/ml), free triiodothyronine (FT(3)) 1.03 pg/ml (normal range 1.71-3.71 pg/ml) and free thyronine (FT(4)) 0.65 ng/dl (normal range 0.70-1.48ng/ml), increased glucose level of 12.48 mmol/L (normal range 3.9-6.1 mmol/L), but normal complete blood counts, urinalysis, liver and renal function, myocardial infarction markers, coagulation functions and rheumatic antibody detection results (antinuclear antibodies, anti-dsDNA antibodies, antinuclear chromatin antibodies, anti-RNP A antibodies, anti-RNP B antibodies, anti-Sm/nRNP antibodies, anti-Sm antibodies, anti-SS-A antibodies, anti-Ro-52 antibodies, anti-SS-B antibodies, anti-Scl-70 antibodies, anti-Jo-1 antibodies, Anti-centromeric B antibody, and anti-ribosomal P protein antibodies) and immunity results (IgG, IgA, IgM, C3 and C4). 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). 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 (200mg/d, I.V.) and 2.5mg olanzapine were given immediately with the diagnosis of possible AE.

On day 8, she was transferred to intensive care unit (ICU) because of convulsive status epilepticus (SE) for 20 minutes unresponsive to diazepam (10mg I.V.) twice and phenobarbital (200mg 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 anti-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 200mg/d with combined intravenous immunoglobulin (IVIG) ((0.4mg/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 CT indicated a possible teratoma in this region. Gynecologic oncologists recommended elective surgery after the anti-LGI1 encephalitis was stable. One week later, neuropsychological assessment was performed with MMSE of 19 and MOCA of 20 (details in Table1). She was discharged with continued oral prednisone acetate (10mg/d), LEV (1500mg/d) and olanzapine (1.66mg/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 anti-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, meanwhile also with a few components from multiple embryonal layers and was consistent with mature teratoma. And immunohistochemistry showed partial or focal positive nuclear staining of LGI1 was appreciated in some tumor cells.

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 Table1) and a mild mood problem with HAMA (Hamilton Anxiety Scale) 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 Table1).

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 Table1), 8 for 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 FLAIR were now gone on the left hippocampus though still present on the right side without volume 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 anti-LGI1 encephalitis cases with and without teratoma

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

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 for nine 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 SE 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.

Clinical manifestations in teratoma-associated anti-LGI1 encephalitis and anti-NMDAR encephalitis cases

The clinical features of this case of teratoma-associated anti-LGI1 encephalitis and the three cases of anti-NMDAR encephalitis with teratoma were summarized in Table 2.

There are many different points between the two subgroups: 1) age at onset of anti-LGI1 encephalitis with teratoma was older than that of anti-NMDAR encephalitis (average age 27.7); 2) our teratoma-associated anti-LGI1 encephalitis case presented with chronic anxiety as a prominent symptom at onset, compared to acute onset and no mood changes during the disease course in the anti-NMDAR encephalitis with teratoma; 3) the anti-LGI1 encephalitis case developed convulsive SE during disease course, but never had single generalized tonic-clonic seizure (GTCS), which was seen in 67% of anti-NMDAR encephalitis cases; 4) fever, headache and sleep disorder has been seen in anti-NMDAR encephalitis was absent in the anti-LGI1 encephalitis case; 5) the anti-LGI1 case presented hyponatremia, was not seen in any of the anti-NMDAR encephalitis cases; 6) normal CSF cell count presented in the anti-LGI1 encephalitis case was elevated in 67% of anti-NMDAR encephalitis; 7) typical hippocampal hyperintensity on T2/FLAIR MRI in anti-LGI encephalitis was seen in only 33% of anti-NMDAR encephalitis. Additionally, lesion on MRI without enhancement in anti-LGI1 encephalitis was characteristic compared to meningeal enhancement in 33% of anti-NMDAR encephalitis. 8) residual short-term memory impairment in the anti-LGI1 encephalitis was recovered fully in 67% of anti-NMDAR encephalitis.

Also several similarities they shared, including 1) cognitive impairment, as seen in 67% of the anti-NMDAR encephalitis; 2) behavioral disorders and sleep disorders, as seen in 100% of the anti-NMDAR encephalitis; 3) the anti-LGI1 case and two of three anti-NMDAR encephalitis patients were all transferred to ICU because of respiratory disorders; 4) diffused slow wave in EEG, as seen in 67% of the anti-NMDAR encephalitis.

Follow-up and prognosis of the anti-LGI1 encephalitis with and without teratoma and anti-NMDAR encephalitis with teratoma

We followed the anti-LGI1 encephalitis 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; and the three anti-NMDAR encephalitis patients for average 27.0±17.8 months. Teratoma was all asymptomatic in the four AE cases, which was diagnosed through routine gynecologic examination before admission in one patient and diagnosed because of aetiological screening for AE in the other three. After immunotherapy and removal of the teratoma, the teratoma associated anti-LGI1 and anti-NMDAR encephalitis patients recovered, becoming seizure-free and living independently, especially 67% of anti-NMDAR encephalitis recovered fully (mRS=0) without symptom. Similarly, immune therapy (MPT, IVIG, plasma exchange and/or immunosuppressant) 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 MPT followed by oral azathioprine. None of the patients relapsed within the follow-up period.

Discussion

Unlike anti-NMDAR encephalitis, anti-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 anti-LGI1 encephalitis with teratoma. By comparing this case with other cases of anti-LGl1 encephalitis without teratoma in our center, we have derived several possible diagnostic biomarkers of anti-LGI1 encephalitis in hopes of promoting its early diagnosis.

The mechanism of anti-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 anti-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 anti-LGI1 encephalitis was associated with the teratoma in our case for several reasons: 1) IHC staining confirmed that partial or focal positive nuclear staining of LGI1 was appreciated in some tumor cells. Although by Karen Head et al's work, LGI1 did not express in normal mice thyroid[17], we think the positive expression of LGI1 in the tumor cells of teratoma in our case is still reasonable, based on reasons below: a) considering the nature of benign germ cell tumor of struma-ovarii in this case, the neoplastic thyroidal follicular cells were different from cells in normal thyroid and may acquire the abnormal expression of LGI1 protein during the development of teratoma; b) based on the reported immunohistochemical images from the article by Karen Head et al[17], Fig3 B showed positive staining of LGI1 within the ovarian follicle-like structure, suggesting its possible expression in the germ cells. Although normal thyroid tissue derived from the endodermal layer typically showed negative LGI1 expression, the possibility of positive expression of LGI1 in some neoplastic thyroidal follicular cells within the struma-ovarii cannot be totally excluded. 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[18] (additionally, thyroid cancer can be comorbid with anti-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 anti-LGI1 encephalitis today[19-25].

The most representative and high-incidence subtype of AE associated with teratoma was anti-NMDAR encephalitis; NMDA receptor-expressing neurons have been described in the neural tissue within teratoma, which was pathogenetic of anti-NMDAR encephalitis [26]. Unlike NMDA receptors, which are the extracel-

lular domain of the GluN1 subunit[27], 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 anti-LGI1 encephalitis compared with anti-NMDAR encephalitis. Nevertheless, LGI1 forms a trans-synaptic complex with presynaptic proteins and is involved in synaptic transmission of neuronal excitability[28], so anti-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 anti-LGI1 encephalitis, including, 1) acute or sub-acute onset of RPD in relatively older aged population[3, 29, 30], 2) FBDS[3, 29, 31], 3) hyponatremia[3, 30] and 4) hyperintensity of bilateral hippocampus on T2 and T2-FLAIR MRI[3, 29].

More importantly, our anti-LGI1 encephalitis case with teratoma presented several specific features that might differentiate it from other subtypes of AE, but perhaps even other cases of anti-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 anti-NMDAR encephalitis, 86% of 100 cases presented headache, fever of a non-specific viral-like illness as prodromal symptom in one case series report[32], and in another study anti-NMDAR encephalitis patients developed psychiatric symptom and short term memory loss in less than two weeks[33]. 77% of 22 anti-$GABA_BR$ encephalitis patients presented isolated recurrent seizure at onset[34]. 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[35].

Secondly, seizure is one of the most common symptoms of AE, but the clinical manifestation varies among different subtypes. The incidence of seizure in anti-NMDAR encephalitis and anti-$GABA_BR$ encephalitis is the highest, followed by anti-LGI1 and anti-AMPA encephalitis. Whereas the most typical seizure type with diagnostic specificity is FBDS in anti-LGI1 encephalitis, seen in almost half of 39 confirmed cases, FBDS were not seen in our case with teratoma[3]. Anti-NMDAR encephalitis has more seizure types at onset; a study of seven cases found that 43% had GTCS, 43% had focal seizures and 14% had both simultaneously [36]. Seizure was relatively uncommon in anti-AMPA encephalitis (20% of patients), typically GTCS[37]. SE is seen more often in anti-GABA encephalitis, based on the limited literature: seen in 58% of one series of 12 anti-$GABA_AR$ encephalitis cases[38] and 27% in another series of 11 confirmed $GABA_BR$ encephalitis subjects[39], compared with only 6% of 100 anti-NMDAR encephalitis patients[40] and 5% of 19 anti-LGI1 encephalitis patients[41]). Interestingly, our case with teratoma developed SE on her 8^{th} day of admission. We think there are two interpretations, 1) SE may be more typical in anti-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 until 5 months following the acute disease stage in our patient was highly consistent with reported anti-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[35]. Recovery from cognitive and neuropsychological symptoms is quicker and more complete in other forms of AE. 75% of 100 confirmed patients with ani-NMDAR encephalitis 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[32]. This is consistent with our three anti-NMDAR encephalitis, which presented fully recovery in 67% of cases. Serial observation of patients with anti-$GABA_BR$ encephalitis indicated that 35% recovered fully and 40% improved markedly, except for recurrent seizures in 50% of 20 cases comorbid with SCLC[42]. Our case suggested that the cognitive deficits in anti-LGI1 encephalitis might need longer time to recover than those in anti-NMDAR or $GABA_BR$ encephalitis.

Overall, given our experience with our small anti-LGI1 encephalitis cohort, we suggest that physicians should consider the diagnosis of anti-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 anti-LGI1 encephalitis and if instituted early might avoid

deterioration and need for ICU management. Further illumination of specific clinical biomarkers of anti-LGI1 encephalitis with teratoma will require collection of more cases.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81974279), China association against epilepsy fund for epilepsy research-UCB fund (2020020A) and Grants for returned overseas doctors of Tongji Hospital. The authors would like to thank the patients and their family for the participation, all referring physicians and Prof. Changshu Ke for his interpretation of the pathological sections.

Author 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.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethics approval

The study was approved by the HUST Ethics Committee on Human Research.

Consent to participate

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.

Code availability

Not applicable

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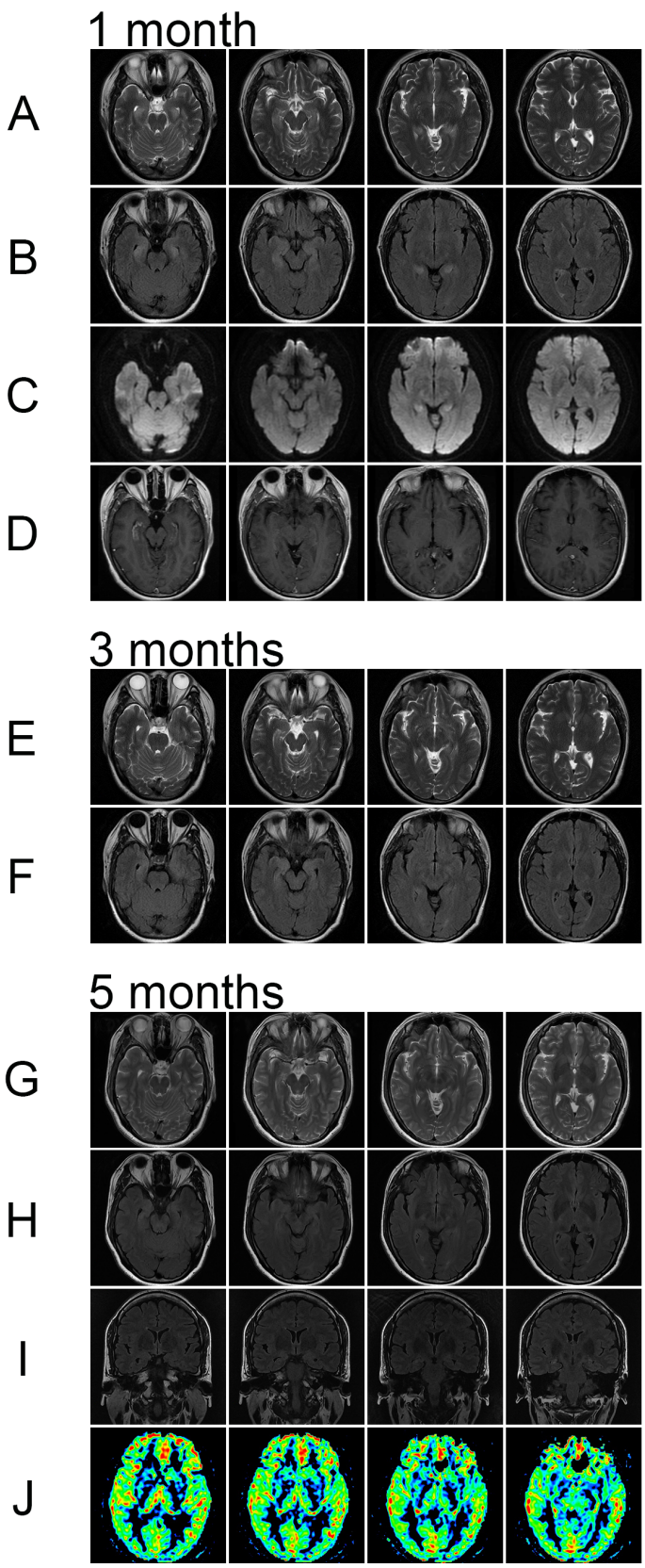

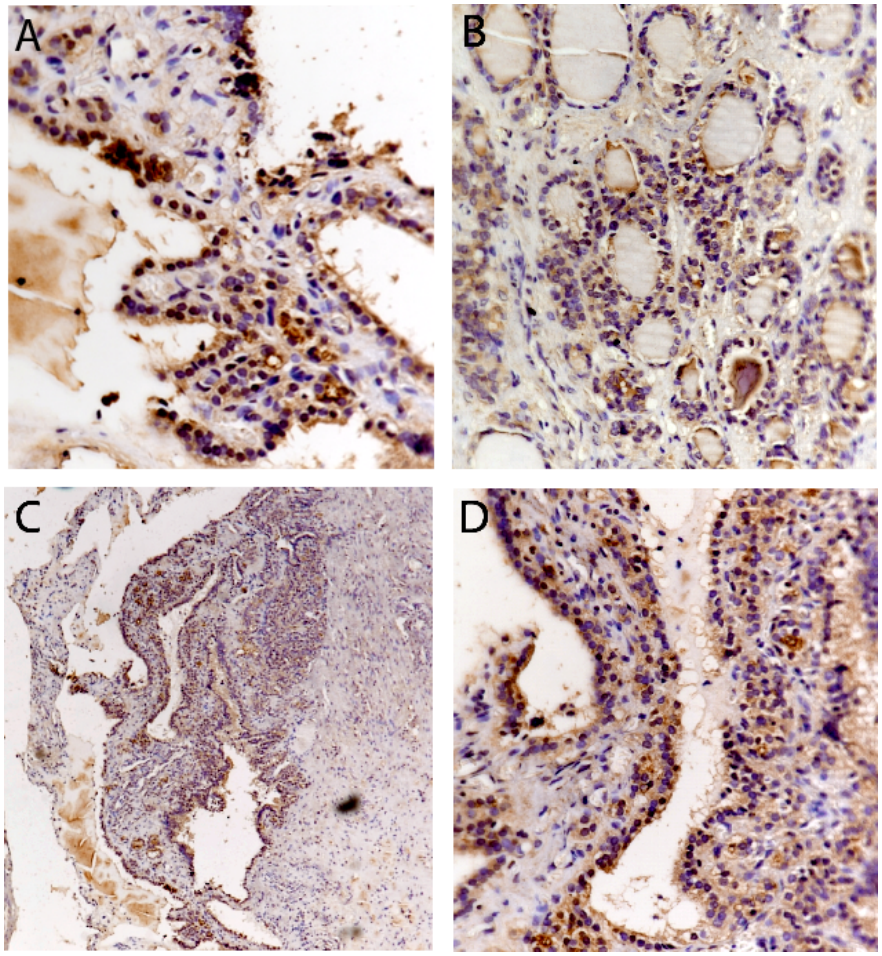

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