Autoimmune encephalitis with antibodies against Leucinie-rich Glioma Inactivated 1 and γ-aminobutyric acid-beta-receptor: case report and literature review

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Short report

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Abstract

A 60-year-old man presented with slow response and psychosis. Apart from hyponatremia, serum test also showed positive anti-Leucinie-rich Glioma Inactivated 1 (anti-LGI1) and anti-γ-aminobutyric acid-beta-receptor (anti-$GABA_BR$), and electroencephalogram exhibited moderate diffusion abnormality. The patient responded well to steroid treatment. Here we report the first autoimmune encephalitis(AE) characterized by positive anti-LGI1 and anti-$GABA_BR$, as well as summarizing AE with multiple auto-antibodies reported so far, hopefully to provide experience for clinical practice.

Background

There are basically two kinds of auto-antibodies related to autoimmune encephalitis(AE). One is against neuron surface receptor, among which anti- N-methyl-D-aspartic acid receptor (anti-NMDAR) is the most common, others also including anti-γ-aminobutyric acid-beta-receptor (anti-$GABA_BR$), anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR), anti-Leucinie-rich Glioma Inactivated 1 (anti-LGI1), etc. The other kind is against neuronal intracellular antigen, mainly referring to classic paraneoplastic neurosis antibody, such as anti-Hu, etc[1-2]. Different types of auto-antibodies correspond to specific neurological syndrome, which has strong specificity or directivity for etiological diagnosis. The majority of AE patients have only one of the above auto-antibodies, and very few with multiple auto-antibodies. Herein we report a patient with positive anti-LGI1 and anti-$GABA_BR$ who improved greatly by steroid therapy.

Case Presentation

A 60-year-old Chinese male presented with one-month of slow response and abnormal behavior. He had typhia 40 years ago and left no sequel. Neurological exam revealed poor mental state, slow response and damaged memory, attention, calculation and orientation.

Mini mental state examination score was 15. Cerebrospinal fluid (CSF) electrophoresis IgG index was 0.71 (reference 0.3~0.7). Intracranial pressure was 150mmH_2O. CSF routine biochemistry for protein content and glucose were normal and infectious test for virus, tuberculosis and Cryptococcus were negative. CSF cytology and cytometry were negative for malignant cells. Brain MRI scan with contrast enhancement was normal. Chest enhanced CT scan revealed inflammation in left lower lobe. Serum procalcitonin was 0.048ng/mL (reference<0.046ng/mL), C reaction protein was 8.05mg/L (reference<5mg/L). Serum AE antibody spectrum demonstrated positive anti-LGI1 IgG and anti-$GABA_BR$ IgG, while CSF auto-antibody test was negative. Blood studies revealed sodium was 119mmol/L (reference 135~153mmol/mL) and chlorine was 81mmol/L (reference 90~110mmol/L) at first admission. Electroencephalogram (EEG) indicated moderate diffusion abnormality (Figure 1A and 1B).

For treatment of AE with multiple co-existing antibody, he received 1g and 0.5g intravenous methylprednisolone separately, 3 days for each dosage, and then remained on an oral steroid taper for half year. After intravenous and oral sodium supplement, blood sodium and chlorine gradually increased to normal(Table 1). His mental state improved greatly and EEG recovered to normal.

Table 1. Blood test for sodium and chlorine

Date/time	Blood sodium(mmol/L)	Blood chlorine(mmol/L)
2020-04-21 11:00	119.0	81.0
2020-04-21 20:00	121.9	82.0
2020-04-22	124.0	85.0
2020-04-23	129.0	92.0
2020-04-24	135.0	93.0
2020-04-26	138.0	92.0
2020-04-29	134.0	91.0
2020-04-30	135.0	91.0

Discussion

Co-existence of serum anti-LGI1 and anti-$GABA_BR$ in AE patient has not been previously reported. The 60-year-old patient, with subacute onset, mainly manifested cognitive decline, behavioral abnormality and hyponatremia. The serum anti-LGI1 and anti-$GABA_BR$ were double positive, and

EEG indicated moderate diffusion abnormality. According to the patients' symptoms, AE auto-antibody spectrum test and EEG results, the patient was diagnosed as AE with double auto-antibody positive, ie, anti-LGI1 and anti-$GABA_BR$. The patient responded well to glucocorticoid treatment, and we will continue to follow up the prognosis.

Anti-LGI1 encephalitis, which is mostly found in elderly men with subacute onset, is related to hyponatremia caused by syndrome of inappropriate antidiuretic hormone secretion. Most patients demonstrated cognitive impairment, and about 90% of them have behavioral and/or personality changes. Frequent seizures, especially focal seizure, are seen in the majority of patients, while generalized tonic clonic seizures are not very common. Most patients have no related tumors, only about 10% had thymoma, while other tumors were rare. Up to 75% of cases have normal CSF routine analysis. EEG can show mild diffuse slow wave, and about half may have swelled medial temporal lobe with high T2/flair signal. The good news is the relatively low recurrence rate[3-4]. Anti-$GABA_BR$ encephalitis mostly presents limbic encephalitis symptoms, with temporal lobe epilepsy as the core symptomatology, and most of them are accompanied by cognitive function decline, personality change and mental behavior abnormality. About 50% of patients have small cell lung cancer or neuroendocrine tumor. It is suggested that anti-$GABA_BR$ encephalitis should further take chest CT or PET examination[5].

The overlying of neuronal auto-antibodies may cause the superposition of clinical syndrome, but not a simple complete superposition, which needs to be analyzed according to the specific antibody type and clinical manifestation. According to Professor Guan Hongzhi's newly published review, it is necessary to distinguish whether the antibodies in patients belong to pathogenic markers or concomitant antibodies[6]. The main manifestations of this case are psychobehavioral abnormality and hyponatremia, more similar to clinical manifestations of anti-LGI1 AE.

The co-existence of multiple auto-antibody is rare(summarized in Table 2). Ren Haitao reported 531 cases of AE with auto-antibodies, and only 10 cases detected multiple anti-neuronal antibodies, among whom 5 cases were anti-$GABA_BR$/anti-Hu(+), 1 anti-NMDAR/APQ-4(+), 1 anti-LGI1/anti-CASPR2(+), 1 anti-LGI1/anti-Yo(+), 1 anti-AMPAR/anti-CV2(+) and 1 anti-AMPAR/anti-Hu(+)[6]. In the 20 anti-$GABA_BR$ AE cases reported by Hoftberger, 7 detected multiple auto-antibodies, among whom 3 cases with anti-Sox1, 1 with anti-Ri, 1 with anti-amphiphysin, 1 with anti-GAD65 and 1 with anti-NMDAR[7]. Liu XY recently reported one case characterized by double positive of anti-LGI1 and anti-NMDAR[8]. Boronat reported a case of anti-$GABA_BR$ combined with anti-GAD65, menifestating cerebellar ataxia and thymoid carcinoid[9]. Qi Hengchang reported two cases of AE with multiple auto-antibodies against neuron (one was anti-NMDAR(+), anti-$GABA_BR$(+), and the other anti-LGI1(+), anti CASPR2(+). Both patients were adult women with acute onset. Their first symptom was epilepsy, and the treatment effect was good[10].

The clinical significance of multiple auto-antibody has already raised attention of many neurologists and needs to be interpreted in combination with clinical practice. For example, anti-$GABA_BR$ can be combined with anti-Hu. When anti-$GABA_BR$ is positive, it is recommended to screen anti-Hu and carry out tumor screening at the same time, such as chest CT, tumor markers, etc., excluding the possibility of tumor as much as possible. In this case chest enhanced CT scan didn't find tumor, but the patient was advised to take regular examination during follow-up. At present, many reports of anti-NMDAR combined with anti-MOG suggest that it is necessary to consider the clinical syndrome superposition caused by the antibody superposition, pay attention to the clinical process, and inquire in detail the history and imaging data whether there is a basis for demyelination[11].

Table 2 clinical data of AE cases with multiple auto-antibodies

N.	Sex, age	AE auto-Abs		Other Abs		Clinical menifestation	Brain MRI	tumor	prognosis
		serum	CSF	serum	CSF				
1	M,62	$GABA_BR$	$GABA_BR$	Hu	-	Memory loss, somnolence, conculsion, cough, hoarseness	Normal	Lung cancer	Improve
2	M,61	$GABA_BR$	$GABA_BR$	Hu	-	Epilepsy, somnolence, memory loss	Normal	Lung cancer	Improve
3	M,59	$GABA_BR$	$GABA_BR$	Hu	Hu	Epilepsy, psychosis	Lesions of bilateral hippocampus	Lung cancer	Improve
4	M,58	$GABA_BR$	$GABA_BR$	Hu	Hu	Psychosis, memory loss, numbness of limbs	Lesions of bilateral hippocampus	Lung cancer	Improve
5	M,61	$GABA_BR$	$GABA_BR$ NMDAR	Hu	-	Epilepsy, memory loss, coma	ND	Lung cancer	Improve
6	F,19	-	NMDAR	AQP4	AQP4	Psychosis, memory loss, blepharoptosis	Lesions of bilateral basal ganglia, brainstem	No	Improve
7	F,40	LGI1 CASPR2	LGI1	-	-	Myalgia, fasciculation, epilepsy, insomnia	Normal	No	Improve
8	F,56	LGI1	LGI1	Yo	Yo	Memory loss, conculsion, somnolence, polyphagia	Normal	No	Improve
9	F,50	AMPAR	AMPAR	CV2	CV2	Memory loss, psychosis	Normal	Thymoma	Improve
10	F,51	AMPAR	AMPAR	Hu	-	Psychosis, dysphagia, dysdipsia	Lesions of bilateral cortex	Mediastinal occupying	Dead
11	M,44	ND	$GABA_BR$ NMDAR	-	-	Limbic encephalitis	Not mentioned	No	Complete improve
12	F,63	-	$GABA_BR$		GAD65*	Status epilepticus	Not mentioned	No	Dead
13	M,60	$GABA_BR$	$GABA_BR$		SOX1*	Limbic encephalitis	Not mentioned	SCLC	Partial recovery
14	M,62	$GABA_BR$	$GABA_BR$		Ri*	Limbic encephalitis	Not mentioned	SCLC	-
15	F,68	$GABA_BR$	$GABA_BR$		SOX1*	Limbic encephalitis	Not mentioned	SCLC	Partial recovery
16	M,74	$GABA_BR$	ND	SOX1	ND	Limbic encephalitis	Not mentioned	SCLC	Dead
17	M,77	$GABA_BR$	$GABA_BR$		Amphiphysin*	Limbic encephalitis	Not mentioned	SCLC	Unresponsive
18	F,57	LGI1 NMDAR	-	-	-	Faciobrachial dystonic seizure, hyponatremia, mental disorder	-	No	Improve
19	M,66	$GABA_BR$*		GAD*		Seizures, confusion	Normal	SCLC	Not available

20	M,47	$GABA_BR^*$		SOX1*VGKC		Seizures, behavior change, memory impairment	Bilateral temporal lesions	SCLC	Partial recovery
21	M,70	$GABA_BR^*$		GAD* SOX1		Seizures, memory impairment, confusion	Normal	SCLC	Unresponsive, dead
22	M,58	$GABA_BR^*$		Hu*		Seizures, memory impairment	Bilateral temporal lesions	SCLC	Unresponsive, dead
23	M,61	$GABA_BR^*$		BRSK2*		Memory impairment	Bilateral temporal lesions	SCLC	Unresponsive
24	F,57	$GABA_BR^*$		GAD*		Subacute cerebellar ataxia	Normal	Carcinoid of thymus	Complete recovery
25	F,30	NMDAR $GABA_BR$	NMDAR	-	-	Epilepsy, psychosis, insomnia	Normal	No	Improve
26	F,43	LGI1 CASPR2	CASPR2	-	-	Seizures, weight loss, calculation/ memory/speech disorder	Bilateral hippocampus/ occipital/parietal lesions	No	Improve

Declarations

1. Ethics approval and consent to participate

Protocols were established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics committee of first hospital of Zhengzhou University. Written informed consent was obtained from individual participant.

2. Consent for publication

Written informed consent was obtained from the patient for publication of this case report and companying images.

3. Availability of data and materials

All data generated or analyzed during this study are included in this published article.

4. Competing Interests

The authors declare that they have no competing interests.

5. Funding

This study was funded by the the Joint Construction Project of Henan Province (No. 2018020114 and No. 2018020083) and National Natural Science Foundation of China(81971214).

7. Acknowledgements

Not applicable.

Conclusions

Here we first report a case of AE with co-existing auto-antibodies anti-LGI1 and anti-$GABA_BR$. The clinical characteristics of this case are more inclined to anti-LGI1 encephalitis, showing abnormal mental behavior, hyponatremia, and sensitive to corticosteroid impulse therapy. With the discovery of more multiple auto-antibody positive cases of AE, it will provide evidence for further revealing the clinical characteristics, treatment and prognosis.

Abbreviations

anti-Leucinie-rich Glioma Inactivated 1 anti-LGI1

anti-γ-aminobutyric acid-beta-receptor anti-$GABA_BR$

anti- N-methyl-D-aspartic acid receptor anti-NMDAR

anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor anti-AMPAR

Cerebrospinal fluid CSF

autoimmune encephalitis AE

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6. Authors' contributions

Yi Xie and Jia Wen together collected disease history and radiological data and drafted this manuscript. Zhihua Zhao and Hongbo Liu contributed to the collection and interpretation of the data. Nanchang Xie participated in the design of the article. All authors read and approved the final manuscript.

7. Acknowledgements

Not applicable.

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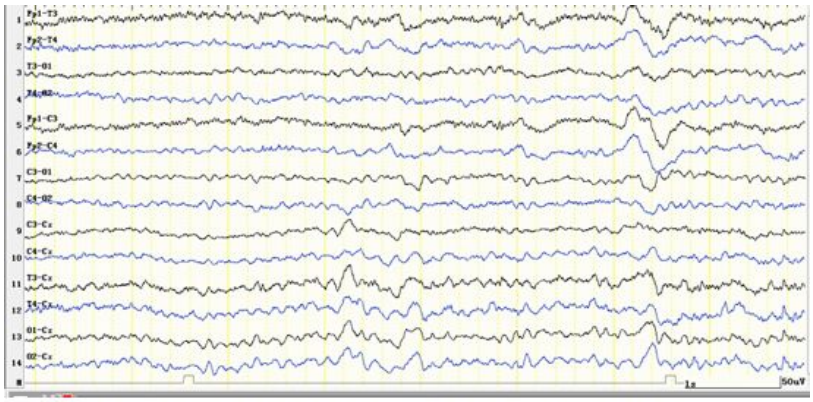
Figures



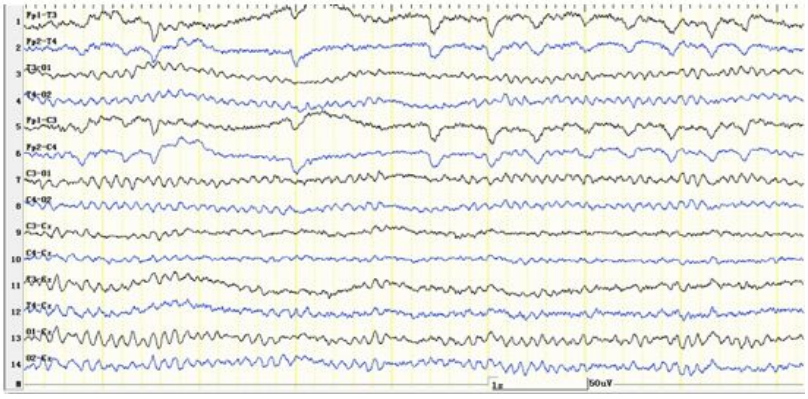


Figure 1

1A. EEG of the patient before treatment(2020-04-21):moderate diffusion abnormality, Wide range of slow waves occur in medium-high waves.
1B. EEG of the patient after treatment(2020-04-29):normal.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- serumantibody.jpg
- csfantibody.jpg