

Non-inflammation cerebrospinal fluid and normal brain magnetic resonance images of Autoimmune encephalitis

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Research article

Keywords: Autoimmune encephalitis, Magnetic resonance images, Cerebrospinal fluid

Posted Date: May 26th, 2019

DOI: <https://doi.org/10.21203/rs.2.9845/v1>

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Abstract

Background We set out to investigate the characteristics and factors related to non-inflammation cerebrospinal fluid (CSF) and normal brain magnetic resonance images (MRI) of autoimmune encephalitis (AE) in patients. **Methods** The distribution and characteristics of brain MRI and CSF in 124 patients who were living with anti-NMDAR(71), LGI1(26),CASPR2(4),GABAR(23) encephalitis and who had been admitted between October 2016 and May 2018 were analyzed prospectively. **Results** 12 of the 124 patients(1%) had a normal MRI and non-inflammation CSF.Ten of them were LGI1(83%),while the remaining 1 patient was NMDAR(8.3%),1 patient was CASPR2(8.3%).The clinical symptoms including epilepsy, psychosis, cognitive disorders, conscious disorders, headache, faciobrachial dystonic seizure (FBDS), speech disorders and hypoventilation. AE with non-inflammation CSF and normal MRI with good clinical prognosis. The median modified Rankin Scale (mRS) was low, and recurrence rate was also low. **Conclusion** The clinical manifestations of on-inflammation CSF and brain MRI-negative patients with AE are not specific, but suggest a better prognosis and a lower recurrence rates.

Background

AE is considered one of the most common causes of noninfectious acute encephalitis.It is estimated that 20% of all encephalitis cases in northern Europe are immune-mediated [1].AE is typically an acute or subacute onset and that may become chronic later[2].AE has a wide variety of clinical manifestations including behavioral and psychiatric symptoms, autonomic disturbances, movement disorders and seizures[2][3].Suggested mechanisms that may trigger AE include tumors (paraneoplastic), infections (parainfectious),or it may be cryptogenic[3].Immunotherapy and tumor removal lead to substantial improvement in about 80% of the patients, especially when treated at an early disease stage[4].

Methods

Clinical data from 124 patients who were diagnosed with AE in the Department of Neurology of The first affiliated Hospital of Zhengzhou University from October 2016 and May 2018 were collected and analyzed.The diagnosis of AE according with 2016 Lancet Neurol diagnostic criteria [2]. Inclusion criteria were normal brain MRI manifestations, CSF leukocytes were less than 5×10^6 , lymphocyte was less than 70%, electrophoresis ALB quotient was less than 9, oligoclonal band negative. 12 patients met the criteria.We collected detailed demographic and clinical data from a total of 12 patients, including their gender, age, clinical symptoms, MRI(The regular MRI series included axial T2-weighted image (T2WI), T1-weighted image (T1WI), and Fluid-Attenuated Inversion Recovery image (Flair) and MRI enhancement), electroencephalogram (EEG), CSF and tumor correlation. All patients received a full range of laboratory tests, including standard biochemistry, rheumatic indicators,thyroid function,infectious diseases, paraneoplastic markers(Hu/yo/ri/ma), tumor markers, CSF examination(including routine, biochemical, cytological, electrophoresis and auto-immune encephalitis antibodies). CSF was detected using an indirect immunofluorescence staining kit (German EU, Fall2d-6), including NMDAR antibodies, GABABR antibodies, CASPR2 antibodies, AMPAR1,2 antibodies and LGI1 antibodies. In addition, to detect any potential tumors, all the participants underwent chest, abdominal and pelvic Computed Tomography (CT).

Evaluation of prognosis

Clinical outcome were evaluated in each patients, and the modified Rankin Scale (mRS) was obtained at a 6-month follow-up. We also collected the recurrence rate of patients after 1 year of follow-up. Clinical outcome was collected by telephone inter-view and/or follow-up clinic visits. Our study was approved by the First Affiliated Hospital of Zhengzhou University's ethics committee (Keyan-2019-LW-001). Written informed consent from each patient was obtained before enrollment in the study.

Result

Among 124 AE patients, 12 met the criteria, including 7 males and 5 females, aged from 23 to 69 years, with an average age of 48.1 years. The time from onset to diagnosis ranged from 1 day to 120 days, with an average of 35.4 days.The clinical data of all patients are shown in Table 1.

Of 26 cases of anti-LGI1 antibody encephalitis, 10 cases met the criteria (38.5%), 71 cases of anti-NMDAR encephalitis, 1 case met the criteria (1.4%), 4 cases of anti-CASPR2 encephalitis, and 1 case met the criteria (25%).The first and core symptoms in this group of patients were seizures and cognitive disorders. Tonic-clonic seizures were the most common.FBDS occurred in only one patient.Secondly, the main manifestations were cognitive impairment and mental symptoms, including memory decline, slow reaction, decreased level of consciousness, irritability and so on. Other clinical manifestations included sleep disorder, speech disorder, headache, diplopia and blurred vision. Only one patient developed fever in all patients. Table 1.

All patients had no abnormal brain lesions on MRI. The white blood cell count and lymphocyte count in CSF were normal, the ALB quotient was less than 9, and the oligoclonal bands were negative. 12 patients were examined for autoimmune antibodies in CSF. The results showed that one of the antibodies was positive for LGI1, NMDA and CASPR2, while the others were negative. Data are shown in table 2.

8 patients received treatment with oral antiepileptic drugs (AEDs), including oxcarbazepine, topiramate, valproic acid, levetiracetam. 9 patients received methylprednisolone pulse therapy (1000, 500, 250, 120 mg/d for 3 days each). Application of gamma globulin in 2 cases (0.4 g/kg.d for 5 days). 3 patients were given dexamethasone (15 mg/d). 1 patient was given prednisone (1 mg/kg.d). All patients had significantly improved at discharge. All patients continued to take oral prednisone (prednisone tablets from 60 mg/d, gradual decrement), with a follow-up period of 3–17 months. No patients relapsed within 3 months. 1 patient was dead within 9 months. No glucocorticoids were taken orally in 9 patients who were followed up. Oral antiepileptic drugs (valproic acid) for 1 patient. No new tumors. Data are shown in table 3.

Discussion

Recently, AE has been recognized more and more. Compared with paraneoplastic encephalitis, AE has or does not have tumors and has a better response to immunotherapy [5][6]. The clinical manifestations and imaging manifestations of AE were various. Epilepsy seizures and disturbance of consciousness were the most common clinical symptoms. Hippocampal damage was also a common imaging manifestation [2][7].

In this study, 1 anti-NMDAR encephalitis patient presented with onset of headache accompanied by vomiting, irritability, and reduced visual acuity, with no apparent history of infection. Subsequent lumbar puncture showed that CSF pressure was high (240 mm H₂O). The patient was diagnosed early, and admitted on the second day of symptom onset. Studies have found that 80% of anti-NMDAR encephalitis patients have non-specific symptoms accompanied by a preceding infection, such as fever, headaches, or viral-like presentations (gastrointestinal or respiratory symptoms) [8][9]. However, AE can present with core symptoms that are similar to infectious encephalitis, except for fever and elevated polymorphous cells in the cerebrospinal fluid [10][11].

In this patient, no abnormality was observed in brain MRI. There was no parenchymal injury and no evidence of damage to the limbic system. According to the literature, only 35% of anti-NMDAR encephalitis patients have abnormal brain MRI results on disease onset. In fact, only 50% of patients have abnormal MRI results during the entire course of the disease, which mainly present as grey and white matter hyperintensities [4]. When present, MRI abnormalities can involve the limbic system (e.g., medial temporal lobe, cingulate gyrus, etc.) [8][10], which could facilitate the early diagnosis of anti-NMDAR encephalitis.

One clinical study on anti-NMDAR encephalitis found that inflammatory changes were detected in the CSF of only 44.8% of patients. Levels of elevated leukocytes, lymphocytes or proteins in the CSF was associated with the time between symptom onset and diagnosis/treatment [12]. Oligoclonal bands were rarely observed at the early stages of the disease, becoming more evident at later stages [11]. This suggests that CSF can be negative for inflammatory changes and markers of blood brain barrier damage in the early stages of the disease.

In our study, only 1 out of the 71 anti-NMDAR encephalitis patients (1.4%) was negative for both inflammatory changes in the CSF and brain MRI. A confirmed diagnosis was obtained early and immunotherapy was initiated. On follow-up after 9 months, no recurrence was found, and no sequela was observed. This suggests that the early diagnosis of anti-NMDAR encephalitis and the initiation of immunotherapy as soon as possible are key factors for a good prognosis [4].

In addition to commonly observed symptoms of limbic encephalitis (such as cognitive impairment, epilepsy, and mental disorder), anti-LGI1 encephalitis is associated with faciobrachial dystonic seizures (FBDS) and refractory hyponatremia [13]. In contrast to other limbic encephalitis, anti-LGI1 encephalitis is rarely accompanied by tumors [14] and responds well to immunotherapy [15]. In this study, the 8 patients with anti-LGI1 encephalitis had initial clinical presentation of tonic-clonic seizures, with 1 having headaches at disease onset and 1 having memory impairment at disease onset. During the entire course of the disease, only 1 patient showed typical FBDS episodes.

Around 70% of anti-LGI1 encephalitis patients show T2/FLAIR MRI hyperintensities in the hippocampus or temporal lobe (unilateral or bilateral), with some that extended to the amygdala, insula, or striatum [16][17]. MRI is atypical in the early stage of the disease, especially in the FBDS stage, although there are cases of high T2 signal in individual cases [18][19]. During the limbic encephalitis phase, unilateral or bilateral T2/FLAIR hyperintensities can be detected in the medial temporal lobe in most patients, which may be accompanied with basal signal changes [15, 18, 20–21]. These results suggest that the occurrence or disappearance of abnormal MRI is related to the time of onset. Different MRI examination time may lead to the illusion that the imaging results are inconsistent with the clinical symptoms. Therefore, the occurrence time and existence time of T1 and T2 anomalies need to be further studied. In this study, the duration from disease onset to confirmed diagnosis was 20 to 120 days. Only 1 patient with tonic-clonic seizures was absent of clinical presentations of limbic system

damage. The remaining 9 patients all had memory, cognitive, mental, and behavioral abnormalities, all of which were symptoms of damage to the limbic system. No evidence of damage to the basal ganglia and limbic system were observed in our patients. Bilateral striatal hypermetabolism had been observed in FDG-PET in a patient with frequent bilateral FBDS episodes with no cognitive impairment and no MRI basal ganglia abnormalities[22]. This suggests that FDG-PET examinations can be used to identify intracranial metabolic lesions in anti-LGI1 encephalitis patients with normal MRI results. This would also aid in differentiating whether FBDS is epilepsy or dystonia [23], and should be considered in future studies. Our patients did not undergo FDG-PET examination; therefore, we cannot ascertain whether this would prove useful in our study.

Ten patients had intracranial pressure lower than 180 mm H₂O, with no apparent symptoms of meningeal damage and no significant inflammatory changes in the CSF. Recently proposed diagnostic criteria for AE are less restrictive, and do not require evidence of inflammatory response in the central nervous system (CNS) [24]. Our study support that these criteria were suitable. After treatment with first-line immunotherapy for 2 weeks, clinical symptoms were alleviated in all patients. After 3–17 months of follow-up, 70% of patients had a good prognosis, 2 patients were unable to be followed up with, and 1 patient died (due to epileptic seizures). One patient was given oral AEDs and 9 patients were not given oral glucocorticoids. The major legacy symptoms were memory impairment and dizziness. Overall prognosis was good and mRS score was 0–1.

Some patients with anti-CASPR2 encephalitis may progress to Morvan's syndrome or limbic encephalitis[15]. The characteristics of Morvan's syndrome are encephalopathy with prominent mental symptoms, insomnia, dysautonomia, and neuromuscular rigidity, almost always in male patients[25][26]. In this study, 1 young female patient developed anti-CASPR2 encephalitis, accounting for 25% (1/4). The patient sought medical attention on the first day of disease onset, when she experienced fever and apparent mental symptoms accompanied by headaches, but no apparent autonomic nervous system symptoms, muscle tremors, myotonia, or pathological pain. Immunotherapy was given the next day, and symptoms rapidly improved following treatment. During the 14-month follow-up period, the patient only experienced headaches and did not have thymomas or other tumors.

anti-NMDAR and anti-CASPR2 encephalitis acute onset and obtained early diagnosis and immunotherapy. Brain MRI and cerebrospinal fluid tests carried out at the early stages of the disease were negative, suggesting that patients with early AE may not experience inflammation. However, more case studies are required for verification.

In this study, we analyzed the clinical characteristics of AE patients with no inflammatory changes in CSF and normal brain MRI results, and found that most patients had anti-LGI1 encephalitis and very few patients had anti-NMDAR encephalitis. There were no significant differences in the clinical presentations of these patients and those with elevated cell counts in the cerebrospinal fluid and/or MRI abnormalities. Early disease detection and initiation of immunotherapy as soon as possible was significantly associated with improved clinical prognosis.

This study has some limitations. It only included 124 patients with AE, a relatively small sample size. Nonetheless, we found that even if patients have negative MRI results and no inflammatory changes in the cerebrospinal fluid, diagnosis of AE cannot be excluded when clinical presentations such as epileptic seizures, memory impairment, and abnormal mental behavior are present. Further comprehensive testing of the AE antibody in blood and cerebrospinal fluid is needed to prevent misdiagnosis.

Conclusion

The main clinical manifestations of AE are epilepsy, cognitive impairment, memory impairment, mental and behavioral abnormalities, and cerebrospinal fluid and brain MRI can be completely normal.

Early diagnosis of AE and early immunotherapy therapy have better prognosis. The diagnosis of autoimmune encephalitis should not be omitted because of normal cerebrospinal fluid and brain MRI.

Abbreviations

CSF:cerebrospinal fluid;MRI:magnetic resonance images;AE:autoimmune

encephalitis; NMDAR:N-methyl-D-aspartate receptor;LGI1:leucine-rich

glioma-inactivated 1;CASPR2: Contactin-associated protein-like 2;GABAR:

receptor: γ-aminobutyric acid receptor-B; FBDS:faciobrachial dystonic seizure;

mRS: modified Rankin Scale; T2WI:T2-weighted image;T1WI: T1-weighted

image;Flair:Fluid-Attenuated Inversion Recovery image;EEG:electroencephalogram;

AEDs:antiepileptic drugs.

Declarations

Ethics approval and consent to participate

This study was approved by the First Affiliated Hospital of Zhengzhou University's ethics committee. All patients or the patient's next-of-kin provided written informed consent to participate if a patient could not sign due to disability. And this was also approved by the ethics committee. A copy of the written consent is available for review by the Editor of this journal.

Consent for publication

Written informed consent was obtained from the patients for publication of this research and any accompanying images or from the patient's next-of-kin.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interest.

Funding

This study was supported by the National Natural Science Foundation of China (grant number 81771397).

Authors' contributions

YJL studied concept and carried out the treatment. YKZ drafted the manuscript. PZ revised the manuscript. LHL, CZW and QMZ collected the data and participated in the clinical evaluation of the patients. YC performed the data analysis and interpretation. All authors read and approved the final manuscript.

Acknowledgements

We thank all of the subjects and medical staff for their assistance with this study.

References

1. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D et al. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. *Lancet Infect Dis.* 2010;10(12):835-44.
2. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15(4):391-404.
3. Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol.* 2014;13(6):575-86.
4. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Flourance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol.* 2013;12:157–165.
5. Dalmau J, Rosenfeld MR Autoimmune encephalitis update. *Neuro Oncol.* 2014;16:771–778.
6. Irani SR, Gelfand JM, Bettcher BM, Singhal NS, Geschwind MD Effect of rituximab in patients with leucine-rich, glioma-inactivated 1 antibody-associated encephalopathy. *JAMA Neurol.* 2014;71:896–900.

7. Finke C, Bruehl H, Du¨zel E, Heekeren HR, Ploner CJ Neural correlates of short-term memory reorganization in humans with hippocampal damage. *J Neurosci.*2013;33:11061–11069.
8. Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai, M., Dessain, S.K., Rosenfeld, M.R., Balice-Gordon, R., Lynch, D.R.. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* 2008;7:1091–1098.
9. Wang, J. M. Li, F. Y. Hu et al. Anti-NMDA receptor encephalitis: clinical characteristics, predictors of outcome and the knowledge gap in Southwest China. *European Journal of Neurology*, vol. 23, no. 3, pp. 2016. 621–629, 2016.
10. Leypoldt, F., Armangue, T., Dalmau, J.. Autoimmune encephalopathies. *Ann. N. Y. Acad. Sci.* 2015;1338, 94–114.
11. S.Gable, H. Sheriff, J. Dalmau, D. H. Tilley, and C. A. Glaser. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project,” *Clinical Infectious Diseases*, vol. 2012;54(7)899–904.
12. Mariana Espinola-Nadurille Non-inflammatory cerebrospinal fluid delays the diagnosis and start of immunotherapy in anti-NMDAR encephalitis. *Arq Neuropsiquitar.* 2018;76(1):2-5.
13. Irani SR AS, Waters P. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan’s syndrome and acquired neuromyotonia. *Brain.* 2010;133:2734–48.
14. Irani SR, Gelfand JM, Al-Diwani A, Vincent A. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. *Ann Neurol.* 2014;76:168–84.
15. [Asztely F, Kumlien E. The diagnosis and treatment of limbic encephalitis. *Acta Neurol Scand.* 2012;126:365–75.
16. van Sonderen A, Thijs RD. Anti-LGI1 encephalitis: Clinical syndrome and long-term followup. *Neurology.* 2016;87:1449–56.
17. Celicanin M, Blaabjerg M, Maersk-Moller C, Beniczky S, Marner L, Thomsen C, Bach FW, Kondziella D, Andersen H, Somnier F, Illes Z, Pinborg LH. Autoimmune encephalitis associated with voltage-gated potassium channels-complex and leucine-rich glioma-inactivated 1 antibodies a national cohort study. *Eur J Neurol.* 2017;24:999–1005.
18. Irani SR, Stagg CJ, Schott JM, Rosenthal CR, Schneider SA, Pettingill P, Pettingill R, Waters P, Thomas A, Voets NL, Cardoso MJ, Cash DM, Manning EN, Lang B, Smith SJM, Vincent A, Johnson MR. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. *Brain.*2013;136:3151–3162.
19. Plantone D, Renna R, Grossi D, Plantone F, Iorio R. Teaching Neurolmages: basal ganglia involvement in facio-brachial dystonic seizures associated with LGI1 antibodies. *Neurology.* 2013;80:183–184.
20. Lai M, Huijbers MGM, Lancaster E, Graus F, Bataller L, Balicegordon R, Cowell JK, Dalmau J. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels : a case series. *Lancet Neurol.*2010;9:776–785.
21. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, Schott JM, Armstrong RJ, S Zagami A, Bleasel A, et al. Faciobrachial dystonic seizures precede LGI1 antibody limbic encephalitis. *Ann Neurol.* 2011;69:892–900.
22. Fidzinski P, Jarius S, Gaebler C, Boegner F, Nohr R, Ruprecht K. Faciobrachial dystonic seizures and antibodies to Lgi1 in a 92-year-old patient: a case report. *J Neurol Sci.*2014;347:404–405.
23. Striano P, Belcastro V, Striano S, Irani SR, Schott JM, Vincent A, Smith SJM, Andrade D, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? *Neurology.* 2011;77:2140–2143.
24. Weishuai Li, Si Wu, Qingping Meng, Xiaotian Zhang, Yang Guo, Lin Cong, Shuyan Cong and Dongming Zheng. RESEARCH ARTICLE Open Access Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study. *BMC Neurology.*2018;18:96.
25. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. *Neurology.*2011;77:179–189.
26. Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, Zuliani L, Watanabe O, Lang B, Buckley C, Vincent A. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol.*2012;72:241–255.

Tables

Table1 Clinical symptoms

Characteristic	Sex	Age	Onset to visit [days]	Initial symptoms	Other symptoms
Case 1	Male	48	30	Headache	Nausea and weakness, blurred vision(3-4/d); behavioral and psychiatric symptoms, tremble
Case 2	Male	69	90	Tonic-clonic seizures	FBDS(20/d) Memory deficit, Dizzy; Sleep disorder
Case 3	Male	54	30	Memory deficit	psychiatric symptoms,
Case 4	Male	66	20	Tonic-clonic Seizure	Psychiatric symptoms (excitement, confusion) []
Case 5	Male	59	60	Tonic-clonic Seizure	Disturbance of consciousness [] drowsiness []
Case 6	Male	61	61	Tonic_clonic Seizure	Cognitive impairment
Case 7	Female	51	40	Tonic_clonic Seizure	No
Case 8	Male	52	20	Tonic_clonic Seizure	Memory deficit [] Sleep disorders [] Dizzy and vomiting
Case 9	Female	47	120	Tonic_clonic Seizure,	Slow response and memory deficit
Case 10	Female	28	30	Tonic_clonic Seizure	memory deficit
Case 11	Female	25	1	Irritability headache and vomiting	Vomiting [] Visual impairment
Case 12	Female	37	3	fever	behavioral and psychiatric symptoms, headac

Table 2 CSF examination and Brain MRI

Characteristic	AE antibody [] CSF []	White bloodcell(CSF) (normal 0-5×10 ⁶ /L)	Lymphocyte ratio	Monocyte ratio	Protein(CSF) (normal 0.15-0.45g/L)	Glucose(CSF) (normal 2.5-4.5mmol/L)	Chloride	ALB	OB	Brain MRI
Case 1	LGI1 1:32	0	68	30	249	5.42	124.8	6.51	Negative	Normal
Case 2	LGI1 1:3.2	0	68	32	525.3	4.12	120.9	7.85	Negative	Normal
Case 3	LGI1 1:3.2	0	49	45	284.5	3.66	115.9	3.67	Negative	Normal
Case 4	LGI1 1:3.2	2	63	35	398.4	3.51	130	6.29	Negative	Normal
Case 5	LGI1 1:3.2	4	70	30	615.9	4.1	110.9	6.29	Negative	Normal
Case 6	LGI1 1:3.2	2	60	38	489.1	3.65	126.5	6.43	Negative	Normal
Case 7	LGI1 1:3.2	4	68	30	254.5	3.04	129	3.69	Negative	Normal
Case 8	LGI1 1:32	0	68	22	57.6	4.06	126	5.31	Negative	Normal
Case 9	LGI1 1:32	4	57	43	234.9	2.9	99.1	5.76	Negative	Normal
Case 10	LGI1 1:3.2	2	68	32	276.3	2.32	127	6.41	Negative	Normal
Case 11	NMDA 1:3.2	4	70	30	167	4.4	123.7	4.43	Negative	Normal
Case 12	CASPR2 1:32	2	62	36	130.5	3.8	126	3.49	Negative	Normal

Table 3 Treatment and follow-up

Characteristic	AEDs	Immunotherapy	Symptoms at discharge	Length of stay(days)	Follow up time(months)	Relapse	Remaining symptoms	Oral medicine	Cancer	mRS
≥ 1	No	methylprednisolone +Gammaglobulin	Improved	12	17	No	Memory deficit	No	No	1
≥ 2	Topiramate oxcarbazepine	Dexamethasone	Improved	15	14	No	slow response Dizzy and memory deficit	No	No	1
≥ 3	oxcarbazepine	Prednisone	Improved	20	9	No	Dead	No	No	
≥ 4	Sodium valproate	methylprednisolone	Improved	13	15	No	Memory deficit	Sodium valproate	No	1
≥ 5	Magnesium valproate oxcarbazepine	methylprednisolone +Gammaglobulin	Improved	29	15	No	No	No	No	0
≥ 6	No	methylprednisolone	Improved	9	14	No	Memory deficit	No	No	1
≥ 7	oxcarbazepine	methylprednisolone	Improved	15	12	No	No	No	No	0
≥ 8	Magnesium valproate	methylprednisolone	Improved	30				No		
≥ 9	oxcarbazepine	Methylprednisolone	Improved	16				No		
≥ 10	Levetiracetam Magnesium valproate	Dexamethasone	Improved	12	6	No	Memory deficit	No	No	0
≥ 11	No	methylprednisolone	Improved	18	9	No	No	No	No	0
≥ 12	No	methylprednisolone	Improved	14	10	No	No	Dizzy	No	1