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Review Article

Unusual clinical manifestation of Anti-GAD65 encephalitis in a patient with a background of epilepsy presented with seizure and altered mental status: A case report and literature review

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Abstract

Background: A 67-year-old male with epilepsy and alcohol abuse disorder presented with neurologic impairment, severely altered mental status and on-off focal seizures. There was no response to the initial anti-epileptic treatment, infectious aetiologies were ruled out, and magnetic resonance imaging revealed unilateral signal changes. The patient was successfully treated clinically with intravenous immunoglobulin and high-dose methylprednisolone. Anti-GAD65 antibodies were found in the autoimmune encephalitis panel after discharge. This case demonstrates the importance of including autoimmune encephalitis in the differential diagnosis of a patient with altered sensorium after ruling out more common aetiologies in order to avoid treatment delays and improve prognosis.

Keywords: autoimmune encephalitis; herpes encephalitis; anti-GAD; seizure; epilepsy; alcohol use disorder

INTRODUCTION

Encephalitis is a type of brain inflammation that can occur as a result of a variety of causes. Encephalitis ranked as fifth contributor to disability-adjusted life years in south Asia and 14th in Australasia, Western Europe, and high-income North America.[1] Encephalitis can be caused by infectious agents, including viruses, bacteria, parasites, and fungi.[1,2] Furthermore, non-infectious processes can contribute to encephalitis, with the aetiology remaining unknown in approximately 20% or more of cases.[3]Autoimmune encephalitis (AE) is a subtype of encephalitis triggered by various aetiologies, such as viral infections, paraneoplastic syndromes, or autoimmune disorders. AE is characterized by an antibody response against brain parenchymal antigens.[4]

The diagnosis of AE has improved due to advancements in identifying new neural autoantibody biomarkers and enhanced clinician awareness. However, the diagnosis of autoimmune encephalitis remains relatively rare in the overall population.[5] It is important to note that numerous conditions can mimic the symptoms of autoimmune encephalitis, making accurate diagnosis challenging. These diagnostic mimics are more prevalent than actual AE cases and encompass many conditions, including toxic/metabolic encephalopathies, functional neurological disorders, primary psychiatric diseases, neurodegenerative disorders, neoplasms, and epilepsy.[6] Additionally, AE is usually tricky to diagnose because it presents with a nonspecific clinical presentation with multiple neuropsychiatric manifestations, such as psychosis, behavioural abnormalities, seizures, and coma.[7]

Specific criteria were set to assist clinicians in accurately classify AE cases as definite or possible (Figure 1).

delays in establishing a diagnosis and initiating treatment has been linked to worse prognosis and higher relapse rate.[8] The presence of characteristic clinical features, such as the subacute onset of neurological or psychiatric symptoms, as well as the detection of autoantibodies associated with AE in the patient's serum or cerebrospinal fluid and electroencephalogram evaluations are typically required for a definitive diagnosis.[9] Whereas a diagnosis of possible autoimmune encephalitis may be made when the clinical presentation strongly suggests AE, but autoantibody testing results are unavailable, inconclusive, or pending. It should be noted that these diagnostic criteria are

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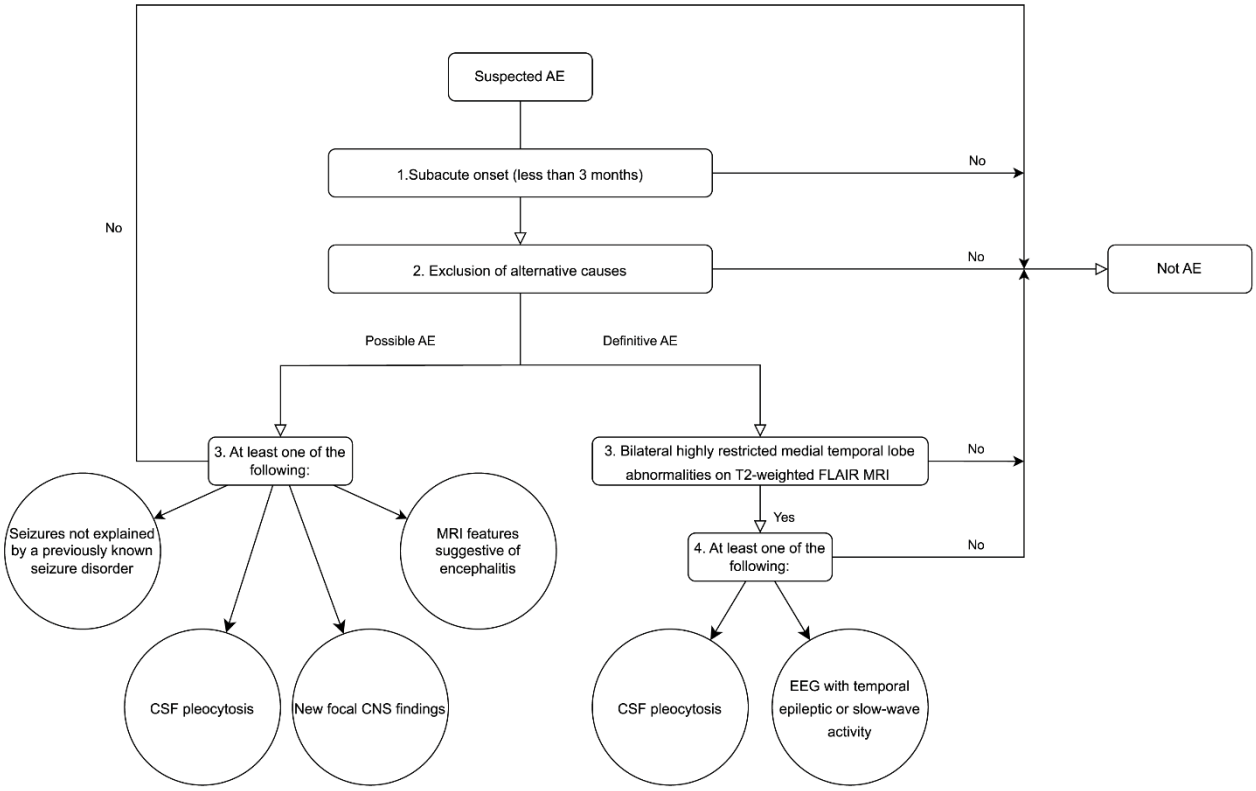

Figure 1. Algorithm of the diagnostic criteria of possible and definite autoimmune encephalitis

only guidelines and may differ depending on specific guidelines and expert consensus. Furthermore, reasonable efforts should be made to rule out other possible causes of the observed symptoms, such as infectious or metabolic aetiologies.[10]

Frequently AE is associated with multiple antibodies, including anti-NMDA and anti-GABAB receptors, among others. Additionally, glutamic acid decarboxylase antibodies (anti-GAD) have been implicated in various neurological disorders such as stiff-person syndrome, seizures, cerebellar ataxia, and encephalitis. However, they are considered a rare cause of AE, often leading to higher misdiagnosis rates and delays in treatment initiation due to the absence of typical symptoms.[11] In general, most AE syndromes, particularly non-paraneoplastic AE, are considered responsive to treatment since the associated antibodies can reversibly impact the target antigens.

CASE PRESENTATION

A 67-year-old Yemeni male was brought to the Emergency Department by his family after being found unresponsive on the bed with dry blood in his mouth and urine on the bed sheets. His medical history was notable for epilepsy on Levetiracetam 500 mg twice daily and alcoholism. He was recently admitted to the hospital for a tonic-clonic seizure that necessitated Intensive Care Unit (ICU) admission and intubation. The family noticed a change in his personality and behaviour after he was discharged. His daughter stated that he was well before going to bed, and his last alcoholic drink was one day ago. Furthermore, his post-ictal confusion status usually lasts thirty minutes before he returns to his baseline.

Upon presenting, the patient's vitals were as follows: temperature 37°C, heart rate 78 beats per minute, respiratory rate 20 breaths per minute, blood pressure 93/51 mmHg, and pulse oximeter 96%. On assessment, the patient appeared confused, disoriented, and dishevelled, he was not following commands, moved all four limbs, was nonverbal, and could only moan. The Glasgow Coma Score was 11/15. Initial tests revealed leucocytosis with predominant neutrophilia (WBC 20.2 x109/L), microcytic anaemia (Hg 95 g/L), low ethanol level (2.2 mmol/L), mild respiratory acidosis, unremarkable metabolic panel, normal lactate, glucose, CRP (C-reactive Protein), renal function, urine analysis, and liver function test. A plane head CT (Computed Tomography) scan revealed no abnormal findings. The patient was admitted for a breakthrough seizure with a prolonged aphasic post-ictal state.

Magnetic resonance imaging (MRI) of the brain was performed to rule out stroke, which revealed a left mesial temporal lobe hippocampal formation T2 hyperintense signal with no significant expansion and amygdala involvement, as shown in Figure 2.

Based on the MRI, the differential diagnosis included a secondary signal change to seizure, limbic encephalitis, and possibly herpes encephalitis. Acyclovir, ceftriaxone, ampicillin, and vancomycin were given to the patient empirically. CSF (cerebrospinal fluid) analysis showed predominately neutrophilic pleocytosis (nucleated cells of 122 x10^6/L with 87% neutrophils), normal protein 0.32 g/L (0.15-0.45 g/L),

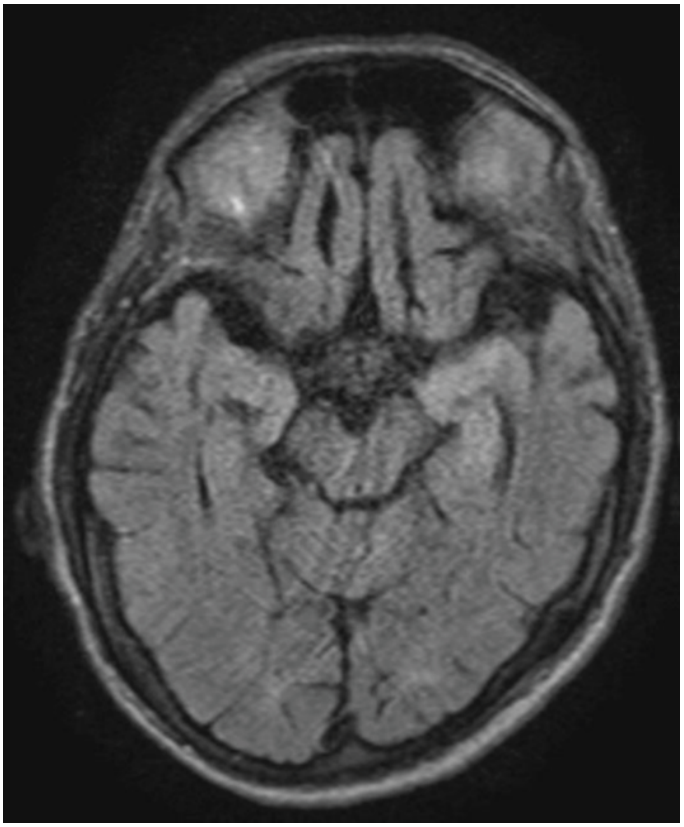

Figure 2. *FLIAR T2* Brain MRI showing left mesial temporal lobe hippocampal formation T2 hyperintense signal without significant expansion and with involvement of the amygdala.

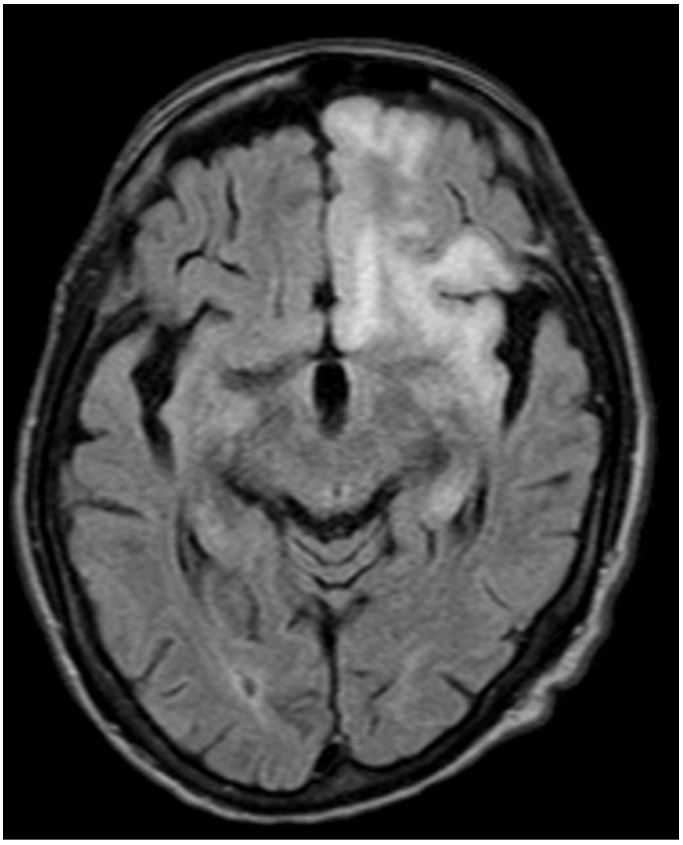

Figure 3. *FLIAR T2* T2 Brain MRI showing significant progression with left frontal, mesial temporal, insular cortical and subcortical signal changes.

normal glucose 4.5 mmol/L, normal IgG (Immunoglobulin G) 27 mg/L (15-30 mg/L), and elevated LDH (lactate dehydrogenase) 43 IU/L (< 25 IU/L). Biofire and culture tests on CSF PCR (Polymerase Chain Reaction) were negative. Antibiotics were discontinued, and the patient was continued on acyclovir. The electroencephalogram (EEG) revealed epileptiform discharges from the left hemisphere. His anti-epileptic medication was supplemented with locusomide.

Five days later, the patient was steadily deteriorating and experiencing on-and-off focal seizures with impaired consciousness. A panel of serum autoimmune encephalitis antibodies and a panel of paraneoplastic antibodies were sent. A second CSF analysis revealed no WBCs. A repeat brain MRI revealed significant progression with changes in the left frontal, mesial temporal, and insular cortical and subcortical signals, as shown in Figure 3.

The patient was given IVIG (Intravenous Immunoglobulin) for five days, and the locusomide was changed to valproic acid.

After five days of IVIG, a reassessment revealed partial resolution of symptoms with residual confusion, so the patient was started on intravenous methylprednisolone 1000 mg daily for another five days. A follow-up MRI revealed a stable left frontal temporal cortical and subcortical signal abnormality, as shown in Figure 4.

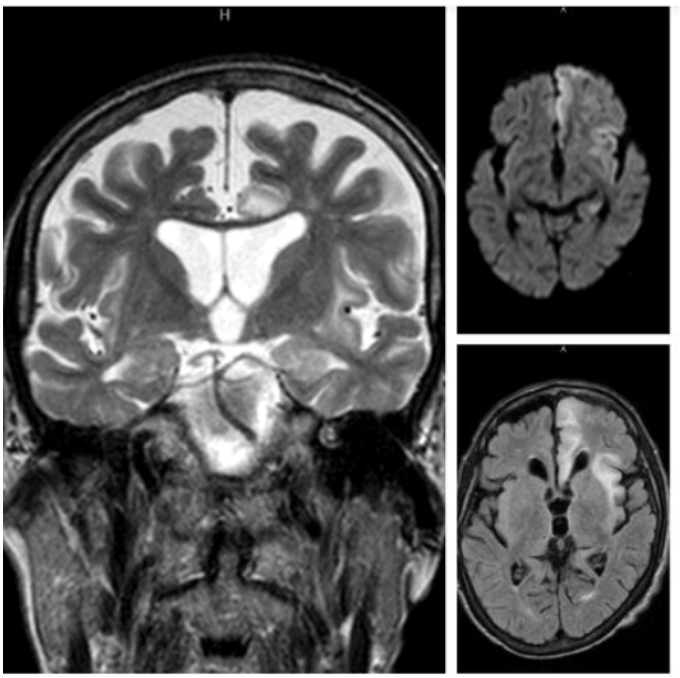

Figure 4. Follow up MRI showing stable left frontal temporal cortical and subcortical signal abnormality.

MR spectroscopy also reveals a hypermetabolic profile, but the short time course of changes clearly favours an inflammatory rather than a neoplastic process. A CT chest/abdomen/pelvis scan was also performed to rule out potential hidden malignancies.

The patient was discharged three days later, and an outpatient follow-up was scheduled. Seven days later, the patient returned to the clinic fully recovered. His autoimmune encephalitis antibodies panel was positive for anti-GAD65 0.03 nmol/L (reference value 0.02 nmol/L).

DISCUSSION

AE is a syndrome characterized by the presence of autoantibodies against various self-antigens in the central nervous system, resulting in a constellation of clinical features such as epilepsy, psychiatric, motor, and cognitive manifestations.[4,8] Antibodies directed against the limbic system, which includes the cingulate cortex, frontonasal cortex, hippocampus, and medial temporal lobe, cause limbic encephalitis.[4]

Antibodies to GAD65, an enzyme that converts glutamate to GABA, are linked to AE.[12] Seizures were the most common manifestation in one study of GAD-related AE, occurring in 97% of patients.[13] This is followed by cognitive impairment, most notably short-term memory issues, and psychiatric manifestations, most notably depression and personality changes.[13] All these characteristics were demonstrated by our patient, supporting the diagnosis. However, the majority of the patients reported are young adults, but cases of older adults up to 70 years old have also been reported.[13] According to the same study, up to 24% of patients experience seizures.[13] It is unclear whether this patient's recent episode of status epilepticus is related to his primary seizure disorder or AE, but the deterioration in the function that followed the episode points to AE as the likely cause.

As the MRI findings were unilateral, this case meets the criteria for possible AE. However, the differential diagnosis was difficult in this case because the patient had a known history of seizure disorder and alcohol abuse disorder, which could explain the initial presentation. One study of seizure disorders in patients over 50 discovered that patients with seizures caused by AE had a higher prevalence of neuropsychiatric deficits and CSF pleocytosis.[14] Although alcoholism was proposed as the cause of one case's reported patient presentation, the lack of improvement with abstinence and the disease's progressive nature pointed toward AE.[15]

Infection, particularly herpes encephalitis, was the most important differential in this patient as he had high WBC on presentation, and the initial CSF was neutrophilic predominant, indicating infection. One study examining the difference between status epilepticus caused by infection and AE discovered that younger females with psychotic features were more likely to have AE as the cause.[16] This made the diagnosis more difficult because the patient did not fit the standard epidemiological picture. However, according to the same study, neutrophils predominated in up to 15.4% of AE patients.[16] The negative CSF supports the diagnosis of AE over infection. Negative Biofire, typical MRI features [cortical and subcortical involvement.[17] (Figure 3)] and CSF normalization.[18] are suggestive of GAD-related AE.

Although the patient had a low GAD-65 titre, which argues against the diagnosis, the patient's presentation, which meets the criteria for AE, the progression of the disease with characteristic features on MRI, and the excellent response to treatment (as discussed below) all point to the diagnosis, especially since the antibody titre may be low at initial analysis.[8] One study found that approximately half of AE patients have negative antibody titres, with no significant differences in terms of presentation and respond to treatment compared to patients with positive titres.[19]

The mainstay of AE treatment is immunotherapy; first-line therapy includes intravenous steroids combined with either IVIG or plasmapheresis and other second-line agents in the event of a lack of response.[8,12] However, the difficulty in distinguishing AE from infection in the early stages of the disease makes steroid use problematic.[8,12] In this case, starting with IVIG may be a safer option, but the efficacy of IVIG as monotherapy has not been thoroughly studied.[12] According to one study, 12 of 18 patients who received IVIG required additional immunotherapy,[20] as did our patient. Furthermore, early tumour screening is critical, and because neurological symptoms may precede tumour detection, repeat follow-up is essential.[8] Our patient's prognosis of non-paraneoplastic AE and AE with isolated GAD-65 antibodies is favourable with complete resolution of symptoms.[13,14]

CONCLUSION

This case report emphasizes the importance of including autoimmune encephalitis in the differential diagnosis of a patient with seizures and mental status changes after infection, and other more common aetiologies have been ruled out. The treatment is time-sensitive and primarily consists of immunotherapy. More research and systematic reviews are needed to understand better the various manifestations of anti-GAD65 antibody encephalitis, which can aid in establishing a prompt diagnosis, allow for early treatment to improve outcomes, and reduce relapses.

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CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

References

1. Collaborators GBDN. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):459-80. https://doi.org/10.1016/s1474-4422(18)30499-x
2. Ellul M, Solomon T. Acute encephalitis - diagnosis and management. Clin Med (Lond). 2018;18(2):155-9. https://doi.org/10.7861/clinmedicine.18-2-155
3. Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ, et al. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012;64(4):347-73. https://doi.org/10.1016/j.jinf.2011.11.014
4. Ding JB, Dongas J, Hu K, Ding M. Autoimmune Limbic Encephalitis: A Review of Clinicoradiological Features and the Challenges of Diagnosis. Cureus. 2021;13(8):e17529. https://doi.org/10.7759/cureus.17529
5. Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol. 2018;83(1):166-77. https://doi.org/10.1002/ana.25131
6. Abboud H, Probasco JC, Irani S, Ances B, Benavides DR, Bradshaw M, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry. 2021;92(7):757-68. https://doi.org/10.1136/jnnp-2020-325300
7. Diaz-Arias LA, Pardo CA, Probasco JC. Autoimmune Encephalitis in the Intensive Care Unit. https://doi.org/10.1007/s12028-016-0370-7
8. Hermetter C, Fazekas F, Hochmeister S. Systematic Review: Syndromes, Early Diagnosis, and Treatment in Autoimmune Encephalitis. Front Neurol. 2018;9:706. https://doi.org/10.3389/fneur.2018.00706
9. Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157-65. https://doi.org/10.1016/s1474-4422(12)70310-1
10. 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. https://doi.org/10.1016/s1474-4422(15)00401-9
11. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338(1):94-114. https://doi.org/10.1097/01.nrl.0000259483.70041.55
12. Shin YW, Lee ST, Park KI, Jung KH, Jung KY, Lee SK, et al. Treatment strategies for autoimmune encephalitis. Ther Adv Neurol Disord. 2018;11:1756285617722347. https://doi.org/10.1177/1756285617722347
13. Gagnon MM, Savard M. Limbic Encephalitis Associated With GAD65 Antibodies: Brief Review of the Relevant literature. Can J Neurol Sci. 2016;43(4):486-93. https://doi.org/10.1017/cjn.2016.13
14. Süße M, Zank M, von Podewils V, von Podewils F. Autoimmune Encephalitis in Late-Onset Seizures: When to Suspect and How to Treat. 2021;12:633999. https://doi.org/10.3389/fneur.2021.633999
15. Li Y, Wang Q, Liu C, Wu Y. Anti-N-Methyl-d-Aspartate Receptor Encephalitis in a Patient with Alcoholism: A Rare Case Report. Front Psychiatry. 2017;8:141. https://doi.org/10.3389/fpsyt.2017.00141
16. Lin C-H, Lu Y-T, Ho C-J, Shih F-Y, Tsai M-H. The Different Clinical Features Between Autoimmune and Infectious Status Epilepticus. 2019;10:25. https://doi.org/10.3389/fneur.2019.00025
17. Fredriksen JR, Carr CM, Koeller KK, Verdoorn JT, Gadoth A, Pittock SJ, et al. MRI findings in glutamic acid decarboxylase associated autoimmune epilepsy. Neuroradiology. 2018;60(3):239-45. https://doi.org/10.1007/s00234-018-1976-6
18. Zrzavy T, Höftberger R, Wimmer I, Berger T, Rommer P, Macher S. Longitudinal CSF Findings in Autoimmune Encephalitis-A Monocentric Cohort Study.Front Immunol. 2021;12:646940 https://doi.org/10.3389/fimmu.2021.646940
19. Pradhan S, Das A, Das A, Mulmuley M. Antibody Negative Autoimmune Encephalitis- Does it Differ from Definite One? Ann Indian Acad Neurol. 2019;22(4):401-8. https://doi.org/10.4103/aian.aian_206_19
20. Lee ST, Lee HS, Lee WJ, Cha HA, Kim SH, Shin SY, et al. The safety and efficacy of intravenous immunoglobulin in autoimmune encephalitis. Ann Clin Transl Neurol. 2022;9(5):610-21. https://doi.org/10.1002/acn3.51540