GAD-65-Associated Limbic Encephalitis – Early Diagnosis and Course of Disease, Treated with IV Methylprednisolone

An 80-year-old male was brought to the emergency room complaining of being confused for a few hours. The patient went to the toilet and came out by himself, although in a confused state and not knowing how to tie his trousers which lasted for 5-6 minutes, following which he fell asleep. On observation at the emergency room patient was fully oriented with the amnesia for the event. There was a history of productive cough and mild fever for 4-5 days. Chest X-ray suggested bilateral pneumonitis, and the event of altered sensorium was at first instance, thought to be the result of hypoxia secondary to pneumonitis. However, the probability of the event being an isolated complex partial seizure was also considered, and the patient was evaluated for the same and was started on anti-seizure medications. Patient's MRI brain was essentially normal [Figure 1a]. Electroencephalogram (EEG) showed bilateral temporal intermittent rhythmic delta (TIRDA) waves, right temporal spike, and sharp wave discharges. Based on the EEG findings possibility of limbic encephalitis was thought of. The patient could not immediately undergo brain Positron emission tomography (PET)-CT in view of the requirement of Intensive care unit (ICU) monitoring and Non Invasive Ventilation (NIV) ventilation for severe pneumonitis and was given pulse IV steroid therapy of 1 gram of methylprednisolone for 5 days. The serum and cerebrospinal fluid (CSF) study showed normal CSF proteins, cells, and positive glutamic acid decarboxylase 65 (GAD 65) antibodies. Fluorodeoxyglucose (FDG)-PET CT brain after 8 days revealed hypermetabolism of bilateral basal ganglia and bilateral medial temporal/hippocampal region with diffuse hypometabolism in bilateral frontal and temporoparietal regions suggestive of limbic encephalitis [Figure 1b and c]. The patient was given oral steroids and mycophenolate mofetil after IV steroids, as the family denied the treatment with IV immunoglobulins or plasmapheresis. A 4-month follow-up of the patient showed no further seizures and reduced aggressiveness, but recent memory impairment persisted.

Autoimmune encephalitis (AE) is caused by the abnormal immune response to neuron antigen. AE can be induced by infection, by malignancy, or it can be idiopathic. AE associated with antibodies against intracellular antigens includes anti-GAD antibodies, anti-Hu antibodies seen in small cell lung cancer, anti-Tr antibodies seen in Hodgkin lymphoma, and anti-Yo antibodies seen in gynecologic tumors.[1] Autoimmune encephalitis associated with antibodies against cell surface proteins includes anti-LGI1 and anti-CASPR2 antibodies in limbic encephalitis.[2] Autoimmune encephalitis associated with antibodies against synaptic receptors includes anti-NMDA receptor antibodies, anti-Gamma- aminobutyric acid A(GABAA) and anti-GABAB receptor antibodies, and anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor antibodies.[3]

GAD 65 antibody-associated encephalitis is a rare type of autoimmune encephalitis, wherein neuronal cytoplasmic antigen GAD65 antibodies are produced, resulting in an autoimmune response. GAD is a pyridoxal 59-phosphate-dependent and rate-limiting enzyme in the synthesis of Gamma- aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. Antibodies against GAD cause an imbalance in neurotransmitters, leading to excessive glutamate and aspartic acid levels and inducing neuronal hyperexcitability.[4] GAD65-associated antibodies act on the terminals of GABAergic interneurons to depress the GABA release on the interneuron. The reduction of spill-over GABA simultaneously attenuates

the inhibition of glutamate release from neighboring excitatory synapses. Such a dual synaptic impairment, the depression at GABA synapses, and the potentiation at glutamate synapses elicit a marked excitation of neurons.[5]

The common clinical manifestations of autoimmune encephalitis are seizures, cognitive impairment, bladder and/or bowel incontinence, movement disorders, sleep disturbances, and behavioral disturbances. Mutism, autonomic disturbances, and visual hallucinations are other symptoms reported.[6] Our patient had one episode of complex partial seizure and recent memory impairment and behavioral changes in the form of occasional aggressiveness and restlessness. Once the methylprednisolone pulse therapy was started with anti-epileptics, there were no further seizures, and follow-up EEG after 5 days showed no epileptiform discharges; TIRDA persisted. Behavioral changes were reduced in the next 2 months on mycophenolate mofetil. Memory impairment persisted, but patient and family members expressed an inability to consent to plasma exchange or intravenous immunoglobulin (IVIG) administration.

MRI in GAD-associated limbic encephalitis shows the hyperintense lesions in medial temporal lobes predominantly but rarely restricted to just temporal lobes on T2 and Fluid-attenuated inversion recovery (FLAIR) images. Up to 25% of cases have normal MRI with a syndrome typical of Limbic encephalitis (LE), and EEG is usually abnormal showing epileptic activity or slowing. There is poor concordance between MRI, CSF, and FDG-PET. FDG-PET commonly shows hypermetabolism, but focal areas of hypometabolism may also be observed. MRI brain did not show any significant finding in our patient, but EEG showed right temporal slowing with TIRDA and intermittent right temporal epileptiform discharges. PET showed hypermetabolism in bilateral basal ganglia, bilateral medial temporal/hippocampal region, and diffuse hypometabolism in bilateral frontal and temporoparietal regions.

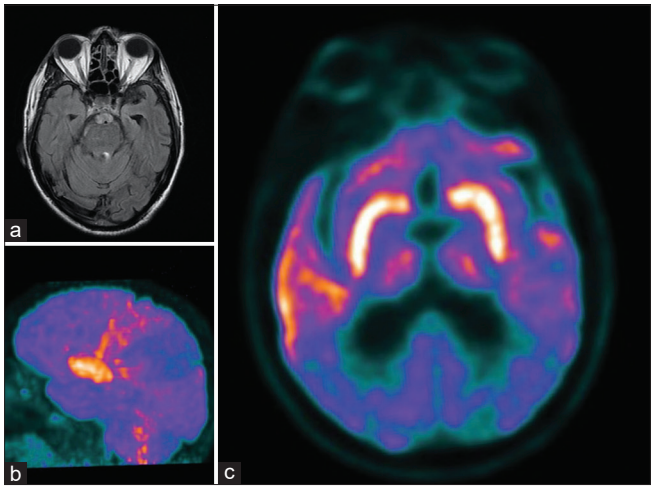

Figure 1: (a) FLAIR axial section MRI showing no limbic hyperintensities. (b and c) FDG-PET sagittal and axial sections showing hypermetabolism in bilateral basal ganglia

While steroids, intravenous pulse therapy, IVIG, and plasma exchange (PLEX) have been used to treat autoimmune encephalitis, comprehensive data regarding the efficacy of various treatment modalities are lacking, making treatment dependent on the clinician's expertise. There are scattered reports of few patients improving with just steroid pulse therapy. Limbic encephalitis with GAD antibodies in patients with associated tumors had poor response even to the combined high steroid and immunotherapy.

Improvement in seizures for only a short duration has been reported with PLEX.[7,8]

Under intensive corticosteroid therapy, only partial response in seizures and cognitive symptoms have been reported in a case series.[9] The benefits of immunotherapies are considered temporary.[10] Hence, the routine use of immunotherapy in these patients is still debatable. Our patient received methylprednisolone pulse therapy for 5 days followed by oral mycophenolate mofetil and did not show any signs of deterioration in a follow-up of 2 months with improvement in behavioral changes and persistence of memory impairment.

Concluding, the treatment therapy and response in GAD 65 patients is still debatable. Our patient, who had no associated malignancy and was diagnosed relatively early, showed a good immediate response in the first 2 months. There were no new symptoms noted in these two months. This might suggest that early diagnosis and initiation of treatment may play a vital role in predicting the prognosis in GAD-related limbic encephalitis patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Monalisa Vegda, Manmohan Mehndiratta

Department of Neurology, BLK-Max Hospital, Delhi, India

Address for correspondence: Dr. Monalisa Vegda, Department of Neurology, BLK-Max Hospital, Delhi, India.
E-mail: monalisavegda@gmail.com

References

1. Gresa-Arribas N, Ariño H, Martínez-Hernández E, Petit-Pedrol M, Sabater L, Saiz A, *et al*. Antibodies to inhibitory synaptic proteins in neurological syndromes associated with glutamic acid decarboxylase autoimmunity. PLoS One 2015;10:e0121364. doi: 10.1371/journal.pone.0121364.
2. Lai M, Huijbers MGM, Lancaster E, Graus F, Bataller L,

Balice-Gordon R, *et al*. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: A case series. Lancet Neurol 2010;9:776-85.
3. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, *et al*. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 2009;65:424-34.
4. Probst C, Saschenbrecker S, Stoecker W, Komorowski L. Anti-neuronal autoantibodies: Current diagnostic challenges. Mult Scler Relat Disord 2014;3:303-20.
5. Mitoma H, Mizusawa H. Autoantibodies to GAD and autoimmune-mediated neurological diseases. Nihon Rinsho 2013;71:921-6.
6. Behar KL. GABA synthesis and metabolism. In: Squire LR, editor. Encyclopedia of Neuroscience. Academic Press; 2009. p. 433-9.
7. Mata S, Muscas GC, Naldi I, Rosati E, Paladini S, Cruciatti B, *et al*. Non-paraneoplastic limbic encephalitis associated with anti-glutamic acid decarboxylase antibodies. J Neuroimmunol 2008;199:155-9.
8. Mazzi G, DeRoia D, Cruciatti B, Mata S, Catapano R. Plasma exchange for anti GAD associated nonparaneoplastic limbic encephalitis. Transfus Apher Sci 2008;39:229-33.
9. Malter MP, Frisch C, Zeitler H, Surges R, Urbach H, Helmstaedter C, *et al*. Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies. Seizure 2015;30:57-63.
10. Pittock SJ, Yoshikawa H, Ahlskog JE, Tisch SH, Benarroch EE, Kryzer TJ, *et al*. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clin Proc 2006;81:1207-14.

Submitted: 21-Jul-2023 **Revised:** 31-Jul-2023 **Accepted:** 08-Aug-2023
Published: 25-Sep-2023

DOI: 10.4103/aian.aian_644_23