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Case Report

A case report on leucine rich glioma inactivated 1 antibody encephalitis

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ABSTRACT

Anti-leucine rich glioma inactivated 1 (LGI1) antibody-mediated encephalitis represents an autoantibody mediated variant of limbic encephalitis (LE). We hereby report the case of a 69-year-old female patient experiencing symptoms of giddiness and forgetfulness, which have persisted for the past 90 days. Additionally, she has exhibited behaviours such as irrelevant conversations, confusion, and jerky movements. Upon reviewing her medical history, it was found that she has been diagnosed with hypertension and bronchial asthma, both of which are being managed with ongoing medication. The MRI scan of the brain revealed bilateral, asymmetrical FLAIR hyperintensities within the amygdala and medial temporal lobes (MTL) on both sides, as well as in the left capsuloganglionic region. Further investigations revealed presence of LGI 1 antibodies in both CSF and serum. Subsequently, administration of intravenous immunoglobulin and steroids was initiated, which demonstrated a significant enhancement in her cognitive function. This case study serves to underscore critical elements that ought to prompt the early suspicion of LGI1 encephalitis, such as hyponatremia, autonomic dysfunction, and recurrent refractory seizures. The prompt identification of this condition is correlated with an increased probability of improved clinical results and the maintenance of brain structural integrity, which is intricately connected to the commencement of immunosuppressive treatment.

Keywords: Behavioural changes, Refractory seizure, FBDs, Hyponatremia, Autoimmune encephalitis and LGI 1 antibody autoimmune encephalitis

INTRODUCTION

Anti-leucine-rich-glioma-inactivated 1 (LGI 1) antibody encephalitis represents a rare form of autoimmune encephalitis (AE), specifically associated with antibodies against the voltage-gated potassium channel (VGKC) complex (VGKC), initially described in 2010.[1] LGI 1 encephalitis is probably the second most common type after anti-N-methyl-D-asparate receptor (NMDAR) encephalitis.[2] It typically manifests between the ages of 30 to 80 years, with a higher prevalence observed in males during their sixth to seventh decade of life.[3] In addition to the common symptoms of LE such as cognitive decline and seizures, this disease is associated with faciobrachial dystonic seizures (FBDS) and refractory hyponatremia along with sleep disturbances.[4] Seizures are common in patients with LGI1 and FBDS are very particular for anti-LGI1 encephalitis, despite the fact that, they are presented only in minority of the patients.[5]

LGI 1 antibody encephalitis is a potentially reversible disease affecting the MTL of the central nervous system and is quickly responsive to immunotherapy, yet long-term outcomes are characterized poorly.[6] A multitude of immunotherapeutic approaches for LGI 1 antibody encephalitis have demonstrated potential efficacy, including corticosteroids and intravenous immunoglobulins (IVIg).[7] However, definitive treatment guidelines for optimal management remain elusive and the selection of immunosuppressive medications is typically based on an empirical decision by the treating physician. Herein, we report a case of 69 years old female with LGI 1 antibody encephalitis who presented with its classical symptoms

CASE REPORT

A 69 years old female presented with complaints of giddiness and history of forgetting things for 90 days along with irrelevant talk, confusion and jerky movements of the face and upper limbs with each episode lasting between 2 to 3 seconds. Her prior medical history indicated that she was taking medication for bronchial asthma and hypertension. The patient was admitted in our hospital for further management. Upon neurological examination, patient was disoriented, conscious and followed simple commands.

Physical examination revealed; Temp 36.2°, HR 78 beats/min, BP 137/70 mmHg, RR 24 breaths/ minute, and SpO_2 90% at room air. Mini mental state examination (MMSE) showed

significant recent memory loss with a score of 18/30. Blood investigations revealed serum creatinine 1.30 mg/dL, hyponatremia (sodium-128 mmol/L), magnesium 1.80 mg/dL, vit B12 681 pg/mL whereas RBS, CBC, blood urea were within the normal limits. Thyroid profile was normal and lipid profile showed LDL 40 mg/dL and total cholesterol was 219 mg/dL.

Generalized intermittent slowing was observed on EEG. Brain MRI revealed a FLAIR hyperintense signal indicative of edema in the head of the caudate nucleus and left lentiform nucleus (Figure 1). MRI of brain was suggestive of bilateral, asymmetrical FLAIR hyperintensities suggestive of oedema in amygdala and MTL on both sides (Figure 1) and left capsuloganglionic region suggestive of encephalitis (Figure 2). Further PET-CT of whole body with brain was done, which manifested FDG avidity in bilateral caudate nuclei suspecting the AE.

Later on, the patient underwent a lumbar puncture to collect CSF for analysis. Biochemical analysis of cerebrospinal fluid (CSF) revealed normal cell count and cytology with protein 27 mgs/dL and sugar 116 mgs/dL. The CSF sample was negative when detected with the film array ME panel, Indian-ink and also tested Gram negative.

Moreover, analysis of CSF and serum through AE panel, confirmed the presence of LGI 1 antibodies in both the samples. Whereas, neuronal paraneoplastic panel analysis of CSF and serum were tested negative. The patient was treated with inj. methylprednisolone 1 gm (IV infusion, 5 days) followed by oral prednisolone 50 mg (once daily). Over six months of follow up, the patient showed an improvement in the symptoms by 40-45%.

Film array meningitis panel tested with CSF sample yielded negative result. Smears for India Inc and gram stain, both yielded negative result in the CSF sample.

LGI 1 antibody was detected in AE panel in both CSF and serum samples, whereas neuronal paraneoplastic panel in both CSF and serum were tested negative.

DISCUSSION

LGI 1-antibodies are closely associated with LE, represents a recently identified autoimmune disorder characterized by the presence of antibodies directed against components of the VGKC protein complex. These VGKCs play a crucial role in the regulation of both the central nervous system (CNS) and peripheral nervous system (PNS) excitability.[8] The VGKC protein complex is composed of two distinct types: LGI1 and CASPR2. LGI1, a glycoprotein secreted from the presynaptic terminal and engages with domains 22 and 23 of the presynaptic ADAM (a disintegrin and metalloproteinase). This interaction acts to impede the process of signal transduction across synapses. ADAM metalloproteinase, thereby inhibit the signal transduction across synapses. Antibodies directed against LGI1 interfere with this inhibitory process, thereby promoting neuronal excitability.[9]

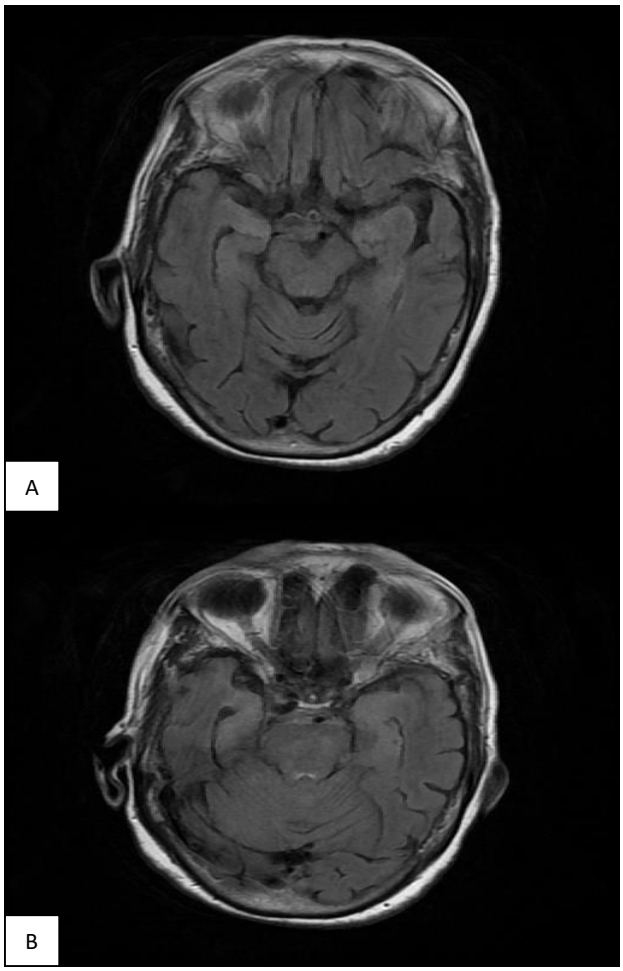

Figure 1 (A and B): MRI images indicative of FLAIR hyperintense signal suggestive of edema in the left lentiform nucleus and head of caudate nucleus.

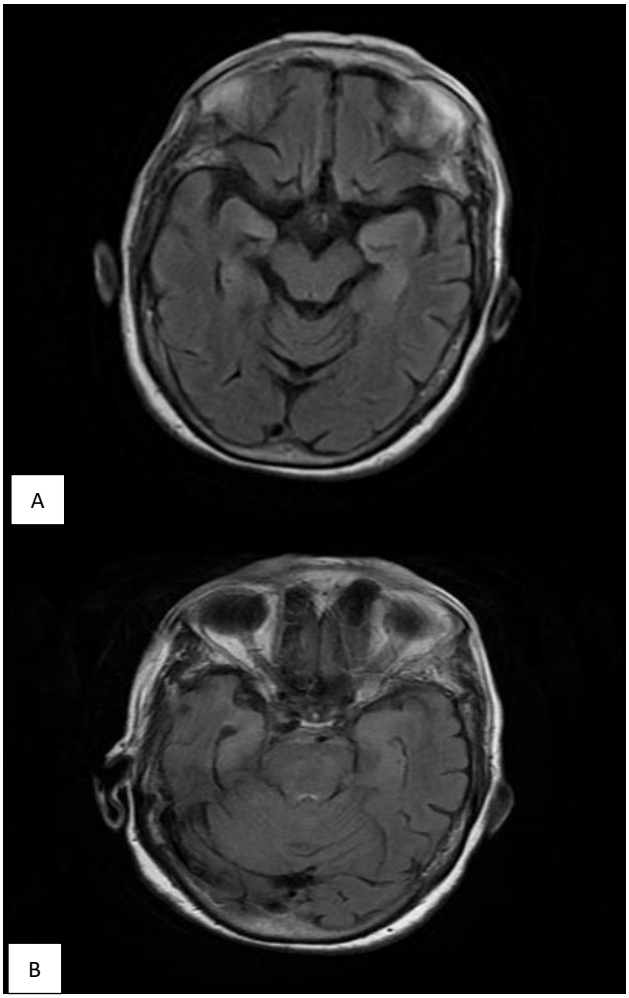

Figure 2 (A and B): Subtle FLAIR hyperintense signal suggestive of edema in bilateral MTL and left gangliocapsular region suggestive of encephalitis.

LGI1 is characterized by its occurrence between the ages of 30 to 80 years with a higher prevalence observed in males, however the reported patient is a 69 years old female. The condition is a subacute disorder characterized by the presence of LE symptoms, including memory impairment, epileptic seizures and behavioural distortions linked to facio-brachial dystonic seizures (FBDS) and hyponatremia.[10] Our patient presented with recent history of memory deterioration, altered behaviour and FBDS. In general, in LGI1, peripheral manifestations such as neuropathy and autonomic dysfunction often coexist but our patient did not show any such manifestations. A study on CSF findings in LGI1 antibody-associated AE typically showed scarce and infrequent CSF inflammation and completely normal CSF was observed in two thirds of patients with LGI 1 encephalitis.[11] In another study by Navarro et al a moderate pleocytosis (8-14 white cells /mm^3) was detected in 10% of patients.[12] CSF analysis in our patient did not show any pleocytosis. The prevalence of LGI 1 antibody detection in CSF is found to be lower in comparison to that observed in serum. LGI 1 antibody was detected in AE panel in both CSF and serum samples of our patient.

More than half of individuals afflicted with LGI 1 antibody encephalitis also present with hyponatremia, with a significant number of these cases being refractory to treatment. The mechanism through which hyponatremia is initiated is likely linked to reduced levels of anti-diuretic hormone (ADH) due to the impact of LGI 1 antibodies on the hypothalamic paraventricular nucleus and the kidneys.[13] Hyponatremia, a finding seen in more than half of cases with anti-LGI 1 encephalitis, is associated with a variety of EEG abnormalities such as slowing of the background activity. We noted the presence of hyponatremia in our patient, characterized by a sodium concentration of 128 mEq/L. A review study on electroencephalographic findings in anti-LGI1 AE shows that, 70% of the cases had hyponatremia.[14] Cognitive impairment could be seen in most of the patients with anti-LGI 1 encephalitis and it is often due to memory deterioration and about 25% of patients have complete recovery of cognitive function, where as in others mild disability may be a persistent sequel of the disease.[15] In the present case, the patient presented with forgetting things for 90 days with MMSE score of 18 and altered behaviour. Following her hospitalization and subsequent treatment, there was a gradual improvement in her cognitive function. Nonetheless, upon her return for a review after 10 days, her memory function was found to be within the normal range.

Epilepsy and cognitive impairment were significant clinical manifestations observed in patients diagnosed with LGI 1 antibody encephalitis. Epilepsy often includes focal seizures, muscle jerks, and full-body convulsions.[16] Among patients with positive LGI antibody nearly 20%-40% have FBDS, which is short, frequent, together with dystonia, simple upper limbs spasm and contraction and ipsilateral face twitch for 3 sec, several times a day. It has been noted that FBDS often manifest prior to the onset of other symptoms in a considerable proportion of patients.[17] Our patient had a history of recurrent episodes characterized by dystonic jerky movements of the face and upper limbs, each episode lasting between 2 to 3 seconds. It is important to note that abnormalities observed in EEGs may be nonspecific, encompassing focal or generalized slowing, as well as epileptiform discharges, in approximately half of the patients diagnosed with anti-LGI 1 encephalitis.[18] Upon admission, an electroencephalogram (EEG) was conducted, revealing intermittent generalized slowing in our patient.

Hyperintensity in bilateral MTL and basal ganglia regions on magnetic resonance imaging (MRI) is a key feature of LGI 1 antibody encephalitis. Memory impairment was found to be associated with the presence of MTL lesions, whereas patients with functional brain dysfunction syndrome (FBDS) were more frequently observed to have brain grey matter (BG) lesions, as

reported by Shao et al.[19] A significant correlation between MTL lesions and memory impairment was demonstrated in the same study, suggesting MTL is responsible for memory deficits. Brain MRI of our patient showed bilateral, asymmetrical FLAIR hyperintensities in amygdala and MTL on both sides and left capsuloganglionic region. This explains the memory deficits seen in our patient.

Anti-LGI1 encephalitis is intricately linked to metabolic abnormalities within the MTL and the basal ganglia, as evidenced by PET-CT imaging studies. A study on the clinical value of F-FDG-PET in AE associated with LGI1 antibody shows a prevalence rate of 82% for metabolic abnormalities in the basal ganglia and 68% in the MTL.[20] Furthermore, a study by Pan et al observed significantly increased PET signals in several brain regions, including the bilateral basal ganglia, bilateral temporal lobe, left praecuneus, left medial part of the superior frontal gyrus, right postcentral gyrus, left calcarine fissure, and surrounding cortex.[21] This suggests that patients with anti-LGI 1 encephalitis exhibit hypermetabolism in these areas. Conversely, a decrease in PET signals was noted in the right supplementary motor area, bilateral calcarine fissure, and surrounding cortex, as well as in the lobule III of the vermis, indicating hypometabolism in these regions. The frontal lobe, parietal lobe, occipital lobe, and cerebellum have not been extensively studied in the context of anti-LGI 1 encephalitis by previous researchers. Our patient PET-CT of whole body with brain had shown FDG avidity in bilateral caudate nuclei suspecting AE.

Patients with FBDS are generally resistant to antiseizure medications but demonstrate a favorable response to immunotherapies, thereby immunotherapy is given priority over antiseizure drugs in patients with FBDS. Our patient received treatment with Methyl Prednisolone and oral Prednisolone tolerating the treatment well and showing improvement.

CONCLUSION

In conclusion, patients harbouring LGI 1 autoantibodies exhibit a remarkable response to immunotherapy, with over 95% of them showing significant improvement. The standard approach to treatment involves the initiation of first-line immunotherapies which include corticosteroids, intravenous immunoglobulin, or plasma exchange. Early combinations of these treatments have been found to enhance efficacy. In certain cases, the addition of second-line immunotherapies, such as cyclophosphamide or rituximab, may be necessary.

Patients with FBDS typically demonstrate resistance to antiseizure medications. However, they show a favourable response to immunotherapies indicating that these medications should be prioritized over antiseizures in their treatment regimen.

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