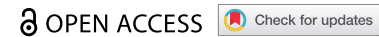




CASE REPORT



Atypical presentation of an elderly male with autoimmune encephalitis: anti-LG1 limbic encephalitis

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ABSTRACT

Introduction: We present a case of an elderly male with anti-LG1 limbic encephalitis involving hypothalamus presenting with acute changes in mental status and persistent hyperthermia.

Case report: A 74-year-old male presented to the hospital with fever and chills. He had also been evaluated by his PCP for changes in his mental status, trouble remembering things, and following directions while driving. A lumbar puncture was performed, and empiric meningitis coverage was initiated. His LP results were not suggestive for any infectious process. An MRI showed bilateral hippocampal edema. As an infectious workup was non-revealing and other causes were ruled out, with the concern for paraneoplastic or autoimmune encephalitis, patient was started on high dose steroids and plasma exchange while results of antibodies for autoimmune and paraneoplastic encephalitis were awaited. After plasmapheresis and a course of steroids, the patient's mental status began to slowly improve. He was discharged from the hospital and on subsequent neurology office visit, his serum autoimmune encephalitis panel returned positive for anti-LGI 1 antibodies. Further management consisted of outpatient rituximab infusion.

Discussion: Diagnosis of limbic encephalitis can be challenging and can present with symptoms of limbic dysfunction. A modest index of suspicion of limbic encephalitis should be kept in adults with altered mental changes. Early recognition and initiation of therapy can be crucial in the management of patients with autoimmune encephalitis and can prevent permanent cognitive impairment and damage.

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1. Introduction

Limbic encephalitis is an inflammatory process in the limbic area of the brain (hippocampus, amygdala, hypothalamus, cingulate gyrus, limbic cortex) which can present with acute or subacute short-term memory loss, cognitive dysfunction, and seizures. Classically, limbic encephalitis is considered a paraneoplastic syndrome with some underlying malignancy [1,2]. There have been few case reports of non-paraneoplastic limbic encephalitis (NPLE) that have not been associated with any underlying malignancy. NPLE has been shown to have a better prognosis than paraneoplastic limbic encephalitis since early diagnosis and treatment with immunotherapy helps achieve a quick return to baseline mental status. We present a case of an elderly male with anti-LG1 limbic encephalitis involving hypothalamus with acute changes in mental status and persistent hyperthermia, who improved with treatment with steroids, plasmapheresis, and rituximab infusion.

2. Case report

A 74-year-old male with a past medical history of stage III CKD and paroxysmal atrial fibrillation was taken to

his primary care physician (PCP) by his wife for changes in his mental status. At baseline, he was independent and able to carry out activities of daily living. With the subacute onset of his symptoms, he had trouble remembering recent things and following directions while driving. He had had no weight loss or appetite changes. During his outpatient workup, an MRI of his head, delayed for 10 days due to insurance issues, showed bilateral hippocampal edema (Figure 1). His memory loss progressed, and he developed fever with chills for which he was referred to the emergency department (ED).

In the ED, his vital signs included: heart rate 95/minute, blood pressure 158/76, respiratory rate 18/minute, and temperature 100.2 F. Physical examination revealed an alert gentleman with impaired short-term memory. His neurological exam did not reveal any cranial nerves or other motor or sensory deficits. A complete blood count, comprehensive metabolic panel were unremarkable. The patient was evaluated by neurology and empiric meningitis coverage was initiated after a lumbar puncture. His cerebrospinal fluid (CSF) analysis revealed 4 nucleated cells, 0 RBCs, protein 44 mg/dl, and glucose 88 mg/dl. HSV 1/2 PCR came back negative and CSF cytology was negative for any malignant cells. Empiric antibiotics and acyclovir were

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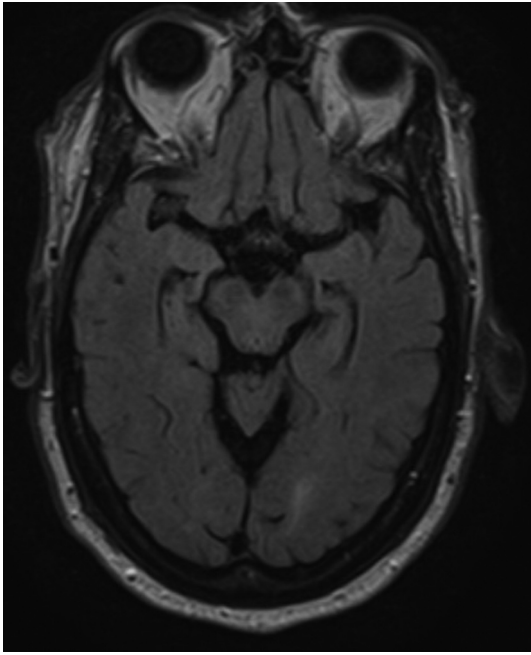


Figure 1. MRI brain showing abnormal signals bilaterally suggestive of hippocampal edema.

discontinued. A routine EEG revealed diffuse slow waves consistent with a mild encephalopathy and a 24-hour EEG did not reveal any subclinical seizures. A CT chest abdomen and pelvis were negative for any mass or lymph nodes concerning for malignancy.

With an infectious workup non-revealing, concern for paraneoplastic or autoimmune encephalitis became high. Antibodies for autoimmune and paraneoplastic encephalitis were sent and while awaiting the results, the patient was started on high dose steroids. He was also started on plasmapheresis on the second day of pulse dose steroids. During the course of his hospital stay, he complained of subjective warmth and chills though there was no documented fever. The patient also had polyuria; the workup for diabetes insipidus was negative. He went into atrial fibrillation with rapid ventricular rhythm which was not controlled with IV diltiazem, metoprolol, and amiodarone. Direct current cardioversion was planned however, after the third course of plasmapheresis, his rhythm converted back to normal sinus rhythm and his heart rate remained controlled. Patient was continued on amiodarone, diltiazem, and apixaban. After plasmapheresis and a course of steroids, the patient's mental status began to slowly improve. He was discharged from the hospital with a plan to follow up with a neurologist. On a subsequent neurology office visit, his serum autoimmune encephalitis panel returned positive for anti-LGI 1 antibodies. A nuclear medicine PET scan of the brain did not show evidence of increased FDG (18-fluoro-2-deoxyglucose) uptake. Further management consisted of outpatient Rituximab infusion.

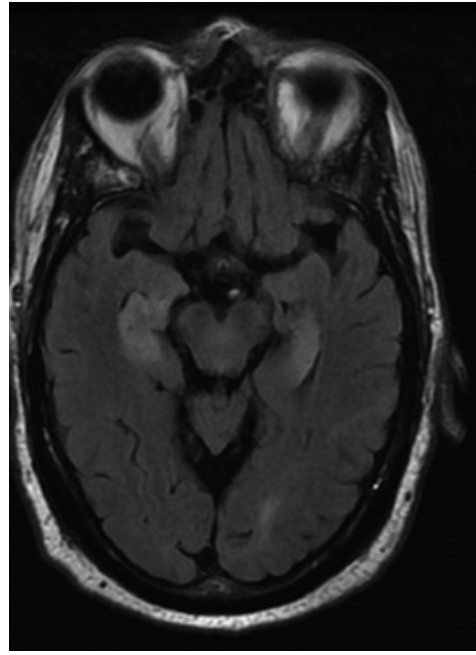


Figure 2. Repeat MRI after 3 months post-treatment showing resolution of hippocampal edema.

A repeat MRI brain done 3 months later showed resolution of hippocampal edema (Figure 2). Patient's mental status returned to his baseline, and he has not had relapse of his symptoms on follow-up.

3. Discussion

Diagnosis of limbic encephalitis can be challenging. It is not a common entity in the elderly, and as in the case of this patient, it may not be considered among the top differential diagnoses. Central nervous system infections including bacterial or viral meningitis and seizure were considered to be likely possibilities during initial evaluation in the ED. Consideration for auto-immune encephalitis was lower given his age, absence of any autoimmune disease, and low concern for malignancy during a thorough workup.

Most cases of autoimmune encephalitis have been reported as a paraneoplastic syndrome as a result of anti-neural autoantibodies directed against intracellular antigens produced by the tumors. Voltage-gated potassium channel complex (VGKC) is one of the common ion channels involved and consists of three different proteins, out of which antibodies against leucine-rich glioma inactivated 1 protein (LGI1) is commonly associated with NPLE [3,4].

Autoimmune encephalitis can have subacute presentation with limbic dysfunction, seizures, and occasional hyponatremia [3,5,6]. Involvement of the hypothalamus can also lead to hyperthermia, somnolence, and endocrine abnormalities. Our patient's sodium level was normal, however they had polyuria which was likely related to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) by the LGI1 expression in the

hypothalamus [4,7]. SIADH is well recognized to occur in association with certain subtypes of limbic encephalitis, especially LGI1 limbic encephalitis [2].

Autoimmune encephalitis, anti-NMDA receptor encephalitis, in particular, have been shown in case reports and series to be associated with rhythm disturbances and atrial fibrillation [8]. Sinus tachycardia and centrally mediated sinus node dysfunction have been reported and loss of central parasympathetic signaling may play a role [9]. Our patient went into atrial fibrillation with rapid ventricular rate and converted into sinus rhythm with plasmapheresis. It is difficult to establish whether his atrial fibrillation is related to the autonomic system activity in the presence of encephalitis or whether it was confounded by low-grade fever in the background of paroxysmal atrial fibrillation.

In Anti-LGI1 LE, cerebrospinal fluid analysis is usually normal. MRI may show signal changes in the medial temporal lobes and basal ganglia. PET scans may show a characteristic increase in the frontal-occipital gradient of cerebral glucose metabolism, which correlates with disease severity. However, a number of patients do not show abnormalities on MRI or PET [10]. MRI for our patient was positive for hippocampal swelling; however, the PET scan did not reveal any increased uptake. One possible explanation for this could be that it was done after he had received a course of steroids and plasmapheresis.

Corticosteroids, intravenous immunoglobulin and plasma exchange can be used for treatment. Other immune-suppressive agents like cyclophosphamide and rituximab can also be used. Some studies have shown that empiric immunotherapy showed a definitive return to baseline with the initiation of rituximab [10]. Saidha et al. also showed that mycophenolate mofetil is an effective agent for improvement in behavior, memory, and seizure in patients with limbic encephalitis [11]. There is no definite guideline on the choice or degree of immunosuppression when there is a high degree of suspicion or after a diagnosis is established.

4. Conclusion

For our patient, considering the MRI findings and subacute changes in mental status, antibodies for autoimmune encephalitis were sent and treatment was started without delay. A modest index of suspicion of limbic encephalitis should be kept in adults with altered mental changes. Early recognition and initiation of therapy can be crucial in the management of patients with autoimmune encephalitis. Especially in NPLE, prompt diagnosis and early treatment might prevent permanent cognitive impairment

and damage. Therapeutic responsiveness of this condition reiterates the importance of diagnosing a reversible neurologic pathology.

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Disclosure statement

The authors report no conflicts of interest.

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