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Case Report

Spotting LGI1 Antibody Encephalitis Early Before Disease Progression

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Abstract

Anti-leucine-rich glioma inactivated protein 1 (LGI1) associated encephalitis is a type of limbic encephalitis first described in 2010. We present the case of a 68-year-old male who was admitted to our hospital with faciobrachial dystonic seizures (FBDS), which are brief dystonic contractions of the ipsilateral face and arm, as well as memory and cognitive complaints. This patient's FBDS was first recognized in the outpatient Neurology clinic 1.5 years prior to his hospitalization, and was treated with levetiracetam. Unfortunately, the patient's levetiracetam was stopped after a few months of treatment due to neuropsychiatric side effects, and another antiepileptic medication was never started. The patient was lost to follow up with the Neurology clinic for one year, and no follow up was arranged by his primary care team to determine the etiology of his FBDS. Once in the hospital, his FBDS symptoms were recognized, and believed to be secondary to LGI1 associated encephalitis. The patient was treated with 5-days of pulse dose steroids, and started on Lacosamide for seizure prevention. He was discharged on a 3-month oral prednisone taper, but experienced psychosis during the taper and required further steroid dose reduction. This case highlights the need to meticulously taper immunotherapy to maintain adequate treatment and avoid disease relapse, while monitoring for steroid-induced adverse effects. The pertinent "take away" point is that the presentation of FBDS should be a red flag feature recognized by both primary care and Neurology providers in the outpatient setting. This should be followed with workup to confirm or exclude LGI1 encephalitis.

Introduction

Limbic encephalitis with antibodies against leucine-rich glioma-inactivated 1 (LGI1) was first reported in 2010.[1] It manifests with symptoms such as memory deficit, cognitive impairment, behavioral changes, brief but frequent faciobrachial dystonic seizures (FBDS) that are often refractory to antiseizure medications, hyponatremia, autonomic symptoms, and sleep disturbances [1]. The estimated annual incidence is 0.83 per million persons [2]. Anti-LGI1 encephalitis usually presents between 30-80 years [3] and is more common in males in their 60s [1]. Beyond the typical manifestations of LGI1 encephalitis, there are a variety of prodromal symptoms such as paroxysmal limb weakness, dizzy spells, and hyperhidrosis [4]. Early recognition of FBDS is crucial because these unique seizures are highly characteristic of LGI1 encephalitis and often predate the onset of cognitive decline. However, FBDS may be initially misdiagnosed as panic attacks, cramps, or other benign conditions, especially in a primary care setting (REF: Confusion, Faciobrachial Dystonic Seizures, and Critical Hyponatremia in a Patient with Voltage-Gated Potassium Channel Encephalitis). This case report highlights the importance of recognizing FBDS as an early warning sign of LGI1 encephalitis for generalist clinicians and cautious tapering of immunotherapy which is needed to balance recurrence of LGI1 encephalitis and steroid-induced adverse effects.

Case Description

A 68-year-old white, non-Hispanic male with a history of anxiety, hypertension, and hyperlipidemia presented to our emergency department (ED) after a new onset focal to bilateral tonic-clonic (GTC) seizure episode, with dysarthria, 5-10 minutes of convulsing, drooling, and urinary incontinence. For 1.5 years prior to presentation, the patient experienced brief (~30 seconds) spells multiple times a day. These episodes were initially considered to be "panic attacks." Episodes were described as a "rush sensation, like a low-grade electrical impulse" felt in his upper torso, during which he became hoarse, had facial grimacing (frowning), and made a clicking noise. There was no loss of consciousness or confusion during the events. Levetiracetam had been started for concern of focal seizures; however, this medication was stopped 14 months prior to presentation in the ED due to neuropsychiatric side effects. No alternative antiseizure therapy was initiated. Brain imaging and electroencephalogram (EEG) done a year prior to admission were reportedly unremarkable, and the patient was lost to follow-up until he presented to the ED.

The patient had no family history of seizures. Social history includes being a former smoker (quit 50 years ago) and consuming 4 drinks of alcohol per week. Physical exam revealed bilateral lower extremity edema, and venous stasis dermatitis. A superficial laceration on the right anterolateral aspect of tongue consistent with a bite

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during recent seizure was noted. Head computed tomography (CT) imaging without contrast and electrocardiogram at admission were unremarkable. Chest x-ray revealed an enlarged cardiac silhouette and an incompletely healed fracture of the mid left clavicle. Pertinent laboratory findings were hyponatremia (124 mg/dL), elevated C-Reactive Protein and Creatine Kinase, routine EEG showed diffuse slowing in the theta-delta range and a single seizure. Oral Lacosamide 100 mg twice daily was started.

Long-term Video Monitoring (LTVM) EEG in the hospital revealed subclinical focal onset bilateral independent temporal lobe seizures. He remained confused and agitated. Lacosamide was titrated up, and seizures abated with improvement in his mental state. An MRI Brain with and without contrast showed increased T2 FLAIR signal around the temporal poles and hippocampus. Patient was later discharged home on Lacosamide 150 mg twice daily. Paraneoplastic and encephalitis antibody laboratory panels were sent. During outpatient follow-up he reported no further seizures.

The patient returned to the ED a month after discharge with more seizure like episodes. Lacosamide was increased to 200 mg twice daily, and immunosuppressive therapy was initiated with 1 gram of IV methylprednisolone each day for five days as his previously sent laboratory tests resulted positive for anti-LGI1 antibody (no titer level reported), Myelin antibody (titer 1:160, normal <1:40), and VGKC antibody (90 pmol/L, normal <80pmol/L). Thyroid ultrasound and CT with contrast of chest, abdomen, and pelvis were negative for malignancy. A lumbar puncture was performed, and CSF was noninfectious with WBC 0 /mm^3, RBC 31 /mm^3, Glucose 65 mg/dL, and Protein 26 mg/dL. LTVM EEG throughout this admission was without any new focal sensory seizures. He was discharged on a 3-month oral prednisone taper starting at 60 mg a day and continuing Lacosamide 150 mg twice daily. At this time a paraneoplastic antibody expanded panel was collected and repeat antibody tesing was negative.

During subsequent outpatient follow-up a month after his second hospitalization, the patient reported being seizure free since discharge and being compliant with anti-epileptic medication. However, the patient reported dizziness and poor balance, which was thought to be secondary to Lacosamide, so his Lacosamide dose was reduced to 100 mg in the morning and 150 mg at night. Additionally, the patient's wife reported that he was having personality changes (anger, more emotional), paranoia, irritability, confusion, hallucinations, hyperactivity, insomnia, and new onset bilateral pitting edema in lower extremities since discharge. The pitting edema, psychosis, confusion, and insomnia were believed to be secondary to high-dose prednisone, therefore the dose of the prednisone was reduced to 30 mg a day. On follow up another month later, the previously reported symptoms had resolved, with the patient on 10 mg daily oral prednisone, and Lacosamide 100 mg in the morning and 150 mg at night. The patient remained stable and asymptomatic for over a year since diagnosis of LGI1 encephalitis with no recurrence of seizures or evidence of cognitive impairment. He continues to take prednisone 10 mg daily and lacosamide for prevention of seizures more than one year since his last seizure.

Discussion

LGI1 encephalitis is a highly treatable form of autoimmune encephalitis, but it requires prompt recognition to prevent progression to generalized tonic clonic seizures. LGI1 is a secretory synaptic glycoprotein that is a functional domain of the voltage-gated potassium channel complex (VGKC), and is primarily expressed in the temporal cortex and hippocampus 3 [5], a hippocampal region involved in memory encoding [6]. The known symptom of hyponatremia in anti-LGI1 encephalitis could be attributed to a syndrome of inappropriate antidiuretic hormone secretion [7]. Hyponatremia can itself cause altered mental status [18], which can contribute to neuropsychiatric presentation of LGI1 encephalitis. Changes on Brain MRI are found in LGI1 encephalitis, with the mesial temporal lobe and basal ganglia most commonly affected [8,9]. Particularly, hippocampal atrophy and hyperintense signal alterations in the medial temporal lobes [8,9]. These structural changes correlate with verbal and visuospatial memory deficits that are present after disease remission [8,9].

This case report is limited by the lack of formal neurocognitive and neuropsychiatric testing. Anti-LGI1 encephalitis has been associated with other concurrent antibodies such as anti-thyroglobulin antibodies [7]. In our case, the VGKC antibody and Myelin antibody were both positive, but the Myelin Associated Glycoprotein antibody was negative. In a prior study it was demonstrated that a positive VGKC antibody test without antibodies to LGI1 and contactin-associated protein-like 2 was not indicative of autoimmune inflammation.[1] Implication of myelin antibody in anti-LGI1 encephalitis is not clear and warrants further exploration.

Delays in diagnosing anti-LGI1 encephalitis remain a concern, particularly in general practice. Early symptoms can be subtle or attributed to more common conditions. Delayed diagnosis of anti-LGI1 encephalitis in some patients can be attributed to initial presentation with only psychiatric symptoms [10-12] and occurrence of psychiatric symptoms also present in more common geriatric conditions [11]. Others, especially older adults, may have nonspecific cognitive changes that are mistakenly attributed to age-related issues or dementia. Our patient experienced episodes of FBDS for 1.5 years, and was off of antiseizure medication for >1 year, prior to his generalized tonic clonic seizures and presentation in the ED. 10-100 FBDS episodes typically occur daily in patients with anti-LGI1 encephalitis [19], representing a recurring symptom that should be recognized by a primary care provider leading to subsequent neurology workup. A meta-analysis reported that the mean number of days from LGI1 encephalitis symptom onset to immunotherapy for 206 patients was 100.3 (range: 5–330) [17]. In this context, our patient had a drastically delayed diagnosis of LGI1 encephalitis. The clinical significance of this delayed presentation is heightened by the fact that delayed diagnosis of anti-LGI1 encephalitis can lead to irreversible limbic damage and cortical atrophy [11]. With this understanding, primary care providers should immediately setup a neurology consultation thereby limiting patients being lost to follow-up.

The use of diagnostic scoring tools such as: the Antibody Prevalence in Epilepsy and Encephalopathy, and the Response to Immunotherapy in Epilepsy and Encephalopathy will help to facilitate diagnosis and expedite treatment [13]. These clinical tools can be of particular benefit to primary care providers to facilitate diagnosis of adult-onset seizures, thereby mitigating delay in working up patients with LGI1 encephalitis.

This case supports using current standard of care recommendations for anti-LGI1 encephalitis treatment. Prior reports indicate anti-LGI1 encephalitis is responsive to antiepileptic drugs, particularly sodium channel blockers (e.g., carbamazepine and lacosamide), and using steroids for immunosuppressive therapy [14]. Anti-LGI1 encephalitis has traditionally been thought of as a monophasic disease, however relapse has been reported in about 30% of cases, and is associated with early tapering of steroids [15]. In this case, a 5-day high dose steroid pulse therapy was used, while other published cases used a similar duration of the steroid pulse dosing (e.g., 3-6 days) [9]. The clinical utility of steroids is likely due to the LGI1 antibodies being IgG4, and responsive to steroids [8]. The patient in this case experienced psychosis during his steroid taper, which may have been caused by the LGI1 antibody or the steroids. First-line immunotherapies for autoimmune encephalitis include corticosteroids, intravenous immunoglobulin, and plasma exchange, and second-line agents include rituximab, cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate [16]. It can be debated whether or not the patient should have been started on additional immunotherapy, as there is limited data on the optimal combination and sequencing of first-line immunotherapy regimens for anti-LGI1 encephalitis [17]. Our case reinforces the need for further research on how to add on immunotherapy to treat relapse of LGI1 encephalitis.

Conclusion

This case highlights the importance of early recognition of FBDS by primary care providers, and the need to rapidly workup and closely follow patients to exclude LGI1 encephalitis and mitigate disease progression. Furthermore, it underscores the need to meticulously taper immunotherapy while balancing steroid dose to mitigate disease relapse and steroid-induced adverse effects.

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