Title

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CLINICAL VIGNETTE

Acute Encephalopathy due to Voltage-Gated Potassium Channel Antibody (Anti-LGI1 Encephalitis): A Primary Care Perspective

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Introduction

Autoimmune encephalitis refers to a group of disorders characterized by autoantibodies against neuronal antigens. Antigens include receptors such as N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and the B1 subunit of gamma-aminobutyric acid ($GABA_B$).[1] N-methyl-D-aspartate receptors and the voltage-gated potassium complex are the most commonly involved cell-surface antigens.[1] Though it was previously believed that antibodies target the voltage-gated potassium channel, recent literature suggests antibodies target proteins associated within a complex regulating voltage-gated potassium channels, including contactin-associated protein-like 2 (Caspr2) or leucine rich inactivated 1 (LGI1).[1,2] Patients with autoimmune encephalitis typically presents with seizures and neuropsychiatric symptoms including psychosis as well as changes in memory, cognition and behavior.[1]

Case

A 67-year-old male presents to establish care with his new primary care physician. He is accompanied by his wife, who provides most of the history. He has a past medical history significant for voltage-gated potassium channel antibody encephalopathy, coronary artery disease status post stent placement, depression, panic disorder, diabetes, and obstructive sleep apnea. Surgical history is negative and family history is non-contributory. His social history includes remote history of cigarette smoking, no alcohol or recreational drugs.

Three years prior the patient presented to his previous primary care physician with worsening anxiety and depression that did not respond to medication changes. He shortly thereafter presented to the hospital with acute episode of confusion and memory loss while at work. He was diagnosed with encephalitis and was in a vegetative state for 2 weeks. Extensive evaluation led to a diagnosis of voltage-gated potassium channel antibody encephalitis. He received steroids and IVIg. He is currently maintained on mycophenolate mofetil 1000 mg daily. He can easily become manic or depressed despite paroxetine 20 mg daily and risperidone 1.5 mg at bedtime. He has had two relapses since his diagnosis. Clinically, he reports memory loss/amnesia, depressive symptoms, and irritability. He is no longer working. While he is still independent of his basic activities of daily living, he relies on his spouse for assistance with some higher level activities.

Discussion

Immune-mediated encephalitis includes the classic paraneoplastic encephalitis syndromes and the encephalitis syndromes associated with antibodies against neuronal cell surface/ synaptic proteins, often referred to as "autoimmune encephalitis." Voltage-gated potassium channel antibody encephalopathy is a rare type of autoimmune encephalitis. The true antigen associated with this condition has been discovered to be leucine rich glioma inactivated 1 (LGI1), a secreted neuronal protein that functions as a ligand for two epilepsy-related proteins, ADAM22 and ADAM23.[1,2] LGI1 is primarily expressed in the hippocampus and neocortex.[2] While many paraneoplastic encephalitis cases are associated with an underlying malignancy, only 5-10% of autoimmune encephalitis cases are associated with cancer, most commonly thymoma.

Clinically, patients with LGI1 autoimmune encephalitis develop memory disturbances, confusion and seizures. Approximately 80% of patients with LGI1 autoantigens initially present with a variety of focal seizures, half of which are pathognomonic faciobrachial dystonic seizures.[3] FBDS are brief (<3s), stereotyped, posturing movements of the hand and ipsilateral hemi-face with a median frequency of 50/day.[2,3] Most patients have a poor response to antiepileptic drugs and have rapid eye movement (REM) sleep behavior disorder. Labs may demonstrate hyponatremia secondary to the syndrome of inappropriate antidiuretic secretion (SIADH) since LGI1 is also expressed in the hypothalamus and kidney.[1] MRI may show medial temporal lobe hyperintensity and CSF is often normal or only shows oligoclonal bands. Over time, patients often develop hippocampal atrophy, cognitive deficits, and a fixed memory deficit.[3]

Treatment of LGI1 autoimmune encephalitis includes glucocorticoids, IVIg, mycophenolate mofetil, and/or plasma exchange, which results in significant improvement in 70 to 80 percent of patients. Early treatment may prevent development of cognitive impairment and improve long-term outcomes.[4] One small non-randomized study of nine patients who received plasma exchange (50 ml/kg), intravenous immunoglobulin

(2g/kg) and intravenous methylprednisolone (1g×3), followed by maintenance oral prednisolone (1mg/kg/day). Seizures and hyponatremia were treated within one week and cognitive function improved within three months. Only three received mycophenolate mofetil.[5]

Relapses occur in up to one-third of patients, usually in the first 6 months of the disease and are associated with worse clinical outcomes. Despite substantial recovery, cognitive deficits and disability persist in many patients, along with evidence of hippocampal atrophy on MRI. One study reported up to 13% of patients with LGI1 antibodies developing cognitive impairment without criteria of encephalitis. After immunotherapy, only 35% of patients return to their baseline cognitive function.[6] Serum LGI1 antibodies may remain detectable even after full clinical recovery.

In the case of our patient, LGI1 autoimmune encephalitis resulted in long-term memory disturbance and psychiatric symptoms. He had acute confusion and amnesia on initial presentation and was treated with steroids, IVIg, and maintained on mycophenolate mofetil. He requires antidepressant and antipsychotic mediations for management of his psychiatric symptoms. There have been two relapses since diagnosis and he has not returned to his baseline cognitive function. He can no longer work and needs assistance with medication administration, driving, and managing his finances. He is established with a neurologist and is looking into community resources. As primary care physicians, we occassionally encounter very rare diseases. While we usually are not the first to diagnose and treat these rare ailments, we are often at the forefront of long-term management and treatment of such patients. It is important to be aware of such conditions as they impact the long-term health outcomes, cognition, and functional statuses of our patients.

REFERENCES

1. **Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, Cowell JK, Dalmau J**. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol*. 2010 Aug;9(8):776-85. doi: 10.1016/S1474-4422(10)70137-X. Epub 2010 Jun 28. PubMed PMID: 20580615; PubMed Central PMCID: PMC3086669.
2. **Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, Peles E, Buckley C, Lang B, Vincent A**. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain*. 2010 Sep;133(9):2734-48. doi: 10.1093/brain/awq213. Epub 2010 Jul 27. PubMed PMID: 20663977; PubMed Central PMCID: PMC2929337.
3. **Varley J, Taylor J, Irani SR**. Autoantibody-mediated diseases of the CNS: Structure, dysfunction and therapy. *Neuropharmacology*. 2018 Apr;132:71-82. doi: 10.1016/j.neuropharm.2017.04.046. Epub 2017 May 3. Review. PubMed PMID: 28476644.
4. **Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, Clover L, Parkinson A, Bien CG, Omer S, Lang B, Rossor MN, Palace J**. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain*. 2004 Mar;127(Pt 3):701-12. Epub 2004 Feb 11. PubMed PMID: 14960497.
5. **Wong SH, Saunders MD, Larner AJ, Das K, Hart IK**. An effective immunotherapy regimen for VGKC antibody-positive limbic encephalitis. *J Neurol Neurosurg Psychiatry*. 2010 Oct;81(10):1167-9. doi: 10.1136/jnnp.2009.178293. Epub 2010 Jul 26. PubMed PMID: 20660916.
6. **Ariño H, Armangué T, Petit-Pedrol M, Sabater L, Martinez-Hernandez E, Hara M, Lancaster E, Saiz A, Dalmau J, Graus F**. Anti-LGI1-associated cognitive impairment: Presentation and long-term outcome. *Neurology*. 2016 Aug 23;87(8):759-65. doi: 10.1212/WNL.0000000000003009. Epub 2016 Jul 27. PubMed PMID: 27466467; PubMed Central PMCID: PMC4999321.

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