A Case of Episodic Generalized Ataxia and Tonic-Clonic Seizure Associated with Anti-Voltage Gated Potassium Channel Antibody Syndrome

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Patient Presentation

A 62-year-old man with PMH of dyslipidemia presents to our hospital ER with a chief complaint of gait instability. He states that this morning while shopping he began feeling unsteady while walking around. This did not alleviate within the next hour, prompting him to visit ED for evaluation. He reports adding 2-lb ankle weights when going on a 3-mile walk this morning. Patient endorses an upper respiratory infection one week ago. He denies any weakness, numbness, tingling, upper extremity changes, loss of consciousness, or trauma.

Past surgical history: none
Social history: occasional alcohol use, daily tobacco abuse, no other drug use
Family history: no pertinent history
ROS: positive for bilateral gait instability. Negative for numbness, tingling, weakness.
Vitals: BP 139/74mmHg. Pulse 81bpm. Temp 97.6F. Respiratory rate 18. SpO2 97%
Physical exam: bilateral lower extremity ataxia. NIH SS 2 (ataxia in 2 limbs).

Differential diagnoses included ICH, ischemic stroke, encephalopathy. Workup in ER included stat CT and CTA that were negative for acute changes. Per standard of care for presumed ischemic stroke, patient received TNK injection. Further workup with MRI brain was normal. Bilateral lower extremity ataxia resolved within 24 hours and patient was discharged on day 2 of hospitalization.

Patient returned to ER two weeks later with new onset witnessed generalized tonic-clonic seizure with encephalopathy. During the hospitalization, he had recurrent episodes of right lower extremity rhythmic twitching. EEG showed left temporal focal seizure with secondary generalization. He was started on Trileptal 600mg BID. Repeat brain MRI was negative. Workup for new onset focal epilepsy with negative MRI included anti-voltage gated potassium channel (anti-VGKC) antibody. Two days later he continued to complain of right lower extremity rhythmic twitching. Repeat EEG showed continued interictal epileptiform discharge in the left temporal region. He was loaded with Keppra 1000mg and continued on 500mg BID. The following day his sodium was 129. The subsequent day his sodium dropped to 128. As a result, his Trileptal was decreased from 600mg BID to 300mg BID and his Keppra increased from 500mg BID to 1000mg BID. His sodium stabilized the next day and he was discharged.

1 week later, results of anti-VGKC antibody returned and were elevated at 183. He was instructed to return to hospital for 5-day course of IVIG and steroid treatment, which he completed, resulting in significant clinical improvement. He also underwent CT chest, abdomen, and pelvis which were negative.

Introduction

Anti-voltage gated potassium channel-complex encephalitis (anti-VGKC-complex encephalitis) is caused by antibodies against voltage gated potassium channel complex thought to contribute to conditions such as epilepsy, neuromyotonia. Believed to be autoimmune in etiology, research into this condition has been rapidly progressing with further advancements in medicine.

Anti-VGKC antibodies are thought to be directed towards associated/complexed proteins. Primary ones focused on in this condition are Leucine-rich, glioma inactivated (LGI1) and Contactin-associated protein 2 (CASPR2). Cause is unknown, however intestinal permeability is thought to be a large factor as a leading hypothesis. HLA-DQ2 and HLA-DQ8 gene-carriers are more prone to this disease. Thymomas when diagnosed are also thought to possibly be contributory to etiology.

Anti-VGKC-complex encephalitis was first reported in neuromyotonia (peripheral nerve hyperexcitability that causes seizure-like activity). Common signs and symptoms in anti-LGI1 encephalitis include seizures (84%), amnesia/confusion (100%), hyponatremia (60%), movement disorders, sleep disorders, and ataxia. Tonic seizures that do not respond to typical anti-epileptics may precede the disorders diagnosis. Testing should be for anti-LGI1-antibodies. Common presentation in anti-CASPR2 encephalitis is peripheral nerve hyperexcitability, which is usually seen in Morvan's syndrome, a disease notably associated with neuromyotonia and limbic encephalitis. Symptoms include agitation, tremor, muscle rigidity, and GI symptoms.

Lab Results

Voltage Gated Potassium Channel Antibody, serum (Now)

Status: Final result Visible to patient: Yes (seen)

0 Result Notes

Component Ref Range & Units	2 mo ago
Voltage Gated Potassium Channel Antibody, Serum 0 - 31 pmol/L	183 ^

Comment: (NOTE)
Repeated and verified
INTERPRETIVE INFORMATION: Voltage-Gated Potassium Channel (VGKC) Antibody, Serum

Negative ..... 31 pmol/L or less
Indeterminate... 32 - 87 pmol/L
Positive ..... 88 pmol/L or greater

Voltage-Gated Potassium Channel (VGKC) antibodies are associated with neuromuscular weakness as found in neuromyotonia (also known as Issacs syndrome) and Morvan syndrome. VGKC antibodies are also associated with paraneoplastic neurological syndromes and limbic encephalitis however, VGKC antibody-associated limbic encephalitis may be associated with antibodies to leucine-rich, glioma-inactivated 1 protein (LGI1) or contactin-associated protein-2 (CASPR2) instead of potassium channel antigens. A substantial number of VGKC-antibody positive cases are negative for LGI1 and CASPR2 IgG autoantibodies, not all VGKC complex antigens are known. The clinical significance of this test can only be determined in conjunction with the patient's clinical history and related laboratory testing.

2024 1/9/24 05:00	1/25/24 16:47	1/29/24 02:44	1/30/24 02:40	1/31/24 04:09	2/6/24 17:23	2/8/24 15:15	2/9/24 16:04	2/10/24 06:10	Time Mark
137	135	134	129	128	134	133	136	136	ROUTINE CHEMISTRY Sodium

Trend of patient's sodium levels throughout his hospital course.

Figure 1: Illustration of the VGKC Complexes

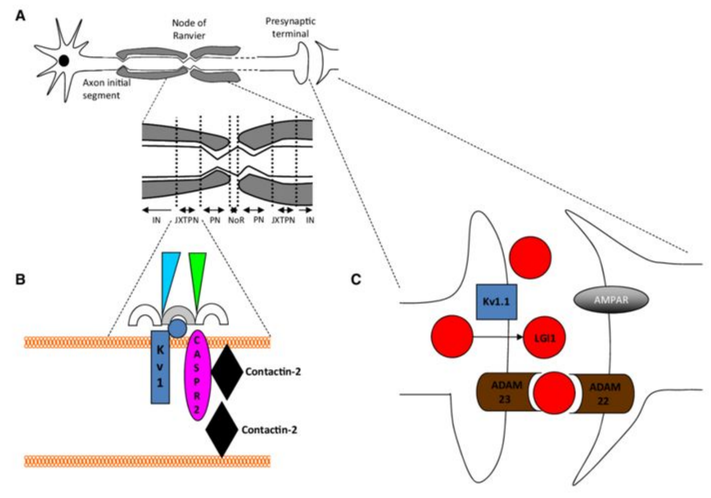

Fig. 1 Illustration of the VGKC Complexes shows the association of Kv1s, CASPR2 (contactin-associated protein), LG1 (leucine-rich glioma inactivated), and other components of the complexes. **A** shows neuronal subcellular domains. **B** shows JXPTN (juxtaparanode), Kv1 channels (*blue*, alpha subunit = rectangle, beta subunit = circle), CASPR2 (*pink oval*), contactin-2 (*black diamond*), MAGUKs (membrane-associated-guanylate kinase) (*semicircles*), protein 4.1B/spectrin/ankyrins (*blue/green triangles*). **C** shows synaptic Kv1 organization with Kv1 (*blue*, such as Kv1.1), LGI1 (*red*), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) and ADAM22/23 (a disintegrin and metalloproteinase 22/23) (*brown*) anchored at post-synaptic membranes.

Discussion/Conclusion

Classic symptoms of anti-VGKC encephalitis include behavioral and mood changes, memory impairment, and temporal lobe seizures. This patient initially presented with bilateral lower extremity ataxia that resolved within 24 hours after receiving TNK. His witnessed generalized tonic-clonic seizure, encephalopathy, evidence of left temporal lobe focal seizure with secondary generalization on EEG, and the presence of serum anti-VGKC antibody points towards the diagnosis of anti-VGKC antibody encephalitis.

Prior studies have demonstrated a lack of correlation between MRI abnormalities and clinical presentation in anti-VGKC encephalitis. This patient had no MRI changes during his hospitalizations. Anti-VGKC antibody encephalitis is common in paraneoplastic syndrome, and most patients with anti-VGKC-antibody-positivity have small cell lung cancer. CT chest, abdomen, and pelvis imaging of this patient was negative.

In our patient, anticonvulsant therapy with immunomodulation using IVIG and corticosteroids showed significant clinical improvement.

Anti-VGKC encephalitis can be challenging to diagnose due to its variable clinical presentation. This case emphasizes the need for further research regarding the pathophysiology of this condition and early-intervention strategies for vulnerable patients.

Ultimately, this patient was continued on Trileptal 300 mg BID and Keppra 1000 mg BID. He will continue high dose steroids with monthly IVIG for 6 months, at which time reevaluation is warranted to discuss continued need for antiepileptics. Normal seizure precautions were discussed.

Long term prognosis is unclear at this time; however, given symptomatic relief with known regimen for antiepileptics, patients should not see worsening symptoms. Should there be worsening symptoms, general causes should be further explored. This is similar to the case of worsening hyponatremia noted with initial medication regimen. Patients may require re-initiation of medications after discontinuation should symptoms persist; however, close neurological follow up and evaluation is highly recommended.

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