

## CLINICAL NEUROSCIENCES

# Hidden Fire: Recurrent Neuropsychiatric Manifestations in a Patient with Voltage Gated Potassium Channel Autoimmune Encephalitis

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## ABSTRACT



Recently, voltage gated potassium channel (VGKC) antibodies have been increasingly recognized as an underlying aetiology of cases of autoimmune encephalitis, with diverse clinical presentations that are usually responsive to immunosuppressive therapy. Antibodies against VGKC and its bound protein complexes, including Lgi1 and Caspr2 have been shown to have varied clinical presentations, including psychosis, dementia, memory impairment, multimodal hallucinations, seizures, extrapyramidal features and autonomic dysfunction. It has been recognized that symptomatic profile depends on the antibody profile (Lgi1+, Caspr2+ or VKGC+ with Lg1-/Caspr2-).

Such presenting symptoms might triage patients into the wrong department and delay treatment, which is detrimental since patient's with VGKC encephalitis are unlikely to improve spontaneously nor when optimal treatment such as steroids, plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) is withheld.

Here we present the case of a 16-year-old, previously healthy male that presented with disorganized thinking, persecutory/grandiose delusions and auditory hallucinations. Workup was originally negative, but with his atypical presentation and elevated leukocytes in his cerebrospinal fluid, a diagnosis of autoimmune encephalitis was entertained. Once infectious aetiology was ruled out, patient was started on IVIG therapy with subsequent symptom resolution. VGKC antibody was eventually found to be positive.

While chronic immunosuppressive therapy was considered, patient presented with 2 subsequent similar episodes that were equally responsive to IVIG. Our case calls for a higher index of suspicion of VGKC encephalitis in working up patients with psychiatric symptoms and atypical presentations since patients otherwise managed with anti-psychotics only will have recurrence of symptoms and ultimately might require re-hospitalizations.

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## INTRODUCTION

Due to the expanding availability of serological testing, voltage-gated potassium channel (VGKC) antibodies have been increasingly recognized as the underlying aetiology of cases of autoimmune encephalitis (AE) and peripheral nervous system pathology (Newey *et al.* 2016). VGKC autoimmunity represents diverse clinical presentations that are usually responsive to immune therapy, so these antibodies have now been considered particularly relevant as part of the workup of unexplained cases of subacute onset of epilepsy, nerve hyperexcitability, myopathy, features of psychosis, dementia, memory impairment, multimodal hallucinations, seizures, extrapyramidal features, and autonomic dysfunction (Varley *et al.* 2015; Molloy *et al.* 2011; Bakpa *et al.* 2016), while it remains unclear exactly how these antibodies can cause such varied clinical manifestations (Irani *et al.* 2010).

The VGKC is a complex of Kv1 subunits, with tightly bound protein compounds that is highly expressed within the nervous system, including central synapses, juxtaparanodes of nodes of Ranvier, peripheral motor nerves, and perhaps sensory terminals. They modulate neural activity by regulating the repolarization of the neural membrane (Gastaldi *et al.* 2016). Antibodies against this complex, more specifically, against its tightly bound protein complexes, including: leucine-rich glioma inactivated protein 1 (Lgi1) and the contactin-associated protein 2 (Caspr2) Lgi1 and Caspr2 (Irani *et al.* 2010), have been shown to have diverse clinical presentations. Particularly, it has been shown that anti Lgi1 classically presents with seizures, electrolyte derangements, limbic encephalitis with cognitive disturbances whereas anti Caspr2 traditionally presents as Morvan's syndrome (a condition associated with neuromyotonia, cognitive symptoms and autonomic dysfunction), limbic encephalitis and occasional cerebellar symptoms (Irani *et al.* 2010). Although the incidence of subtypes like anti Lgi1 and anti Caspr2 remains low, it is difficult to ascertain since these entities may go undetected (Ganesan *et al.* 2013).

The importance of maintaining a high index of suspicion for VGKC AE cannot be overstated. Depending on the type of VGKC antibody, presenting symptoms such as agitation and confusion may triage patients into the wrong department and delay treatment (Lai *et al.* 2010; Dalmau and Rosenfeld 2014). Aside from antibody testing, imaging modalities such as magnetic resonance imaging (MRI) may have a lag time, if at all positive, that could prolong early intervention. Patients with VGKC are unlikely to improve spontaneously nor when optimal treatment such as steroids, plasma exchange (PLEX), or intravenous immunoglobulin (IVIG) is withheld (Gastaldi *et al.* 2016). Here, we report the case of a young patient with VGKC antibody related encephalitis who was initially managed for psychosis secondary to substance use and whose symptoms remained uncontrolled until his treatment for AE.

## CASE REPORT

A previously healthy 16-year-old male was admitted to the paediatric ward for a three-day history of unresponsive staring spells followed by periods of incoherent speech with intermittent foul language, with no signs of aphasia. Parents also described two episodes of him running out of the house unexpectedly and found patient standing on the roof of the family vehicle the night before admission. The patient denied awareness of staring spells and had limited awareness during periods of rambling speech.

The initial evaluation found the patient to be alert and oriented to person, place, and time; however, the patient exhibited disorganized thinking, persecutory and grandiose delusions, and described periods of “dreaming” where he saw strange figures in his room at night that were hurting each other. The patient denied suicidal or homicidal ideation at time of admission. Patient endorsed tobacco and alcohol use in the previous six months, although he was unable to quantify amount and frequency. He also admitted to illegal drug use including marijuana, “acid”, and “pills” with last use reported 4 months prior to admission. Father of the patient stated that these staring spells began after his son’s last marijuana use three days prior to admission.

Psychiatry found the patient to be dysphoric, paranoid, and hyper-religious at times during the interview. Patient endorsed auditory hallucinations of a female voice telling the patient he was crazy. The patient had a normal physical exam on admission including no focal neurologic deficits. He denied visual hallucinations at that time. Initial full blood count, metabolic panel, C-reactive protein, erythrocyte sedimentation rate, prolactin, ammonia, thyroid stimulating hormone, arsenic, lead, and mercury levels returned within normal limits. Urine drug screen returned positive for cannabinoids.

Computed tomography of the head was normal. MRI of the brain with and without contrast was ordered and found no intracranial pathology or abnormal enhancement. Based on this history and presentation, psychiatry strongly considered psychotic behaviour consistent with possible substance induced. Psychiatry team also noted that the patient’s clinical picture was not congruent with schizophrenia break. The patient was started on Olanzapine 10mg twice per day for psychosis and 1:1 care started for elopement risk.

Over next two days, the patient found to be sleeping more with regular Olanzapine dosing, but still exhibiting periods of incoherent speech, agitation, and refusing to take oral medications. Neurology was originally consulted to evaluate for a possible seizure disorder.

Emergency detention was put in place on hospital day three due to the increasing agitation, auditory hallucinations, and aggressive behaviour toward hospital staff. An electroencephalogram (EEG) was attempted several times, but patient forcefully removed electrodes and refused exam. The patient was later put under general anaesthesia for lumbar puncture and EEG. EEG had diffuse irregular delta activity with superimposed diffuse beta runs. There were no epileptiform discharges or seizures. Cerebrospinal fluid (CSF) glucose and protein were within normal limits, but the cell count was found to be elevated (nucleated cells 31cells/ $\mu$ l: granulocytes 1%, lymphocytes 80%, monocytes 19%). CSF NMDA receptor antibody and CSF viral panel were negative. Due to his acute presentation and elevated white cell count on CSF analysis, encephalitis was suspected. IVIG therapy at 2g/kg was initiated once an infectious aetiology was ruled out.

Physical restraints were needed to give IVIG therapy as patient remained agitated and attempted to remove intravenous access and run away from staff. Because of the persistent agitation and lack of quality sleep, medications were updated to include Quetiapine 50 mg PO as needed for agitation and Valproic acid 750 mg orally daily for mood stabilization. The day after first IVIG dose, the patient found to have improvement of mental status and was more cooperative with staff. Physical restraints were removed, and patient agreed to take oral medications. The patient remained medically stable and demonstrated a return to baseline. Due to patient’s marked improvement, the patient was discharged after a total of nine days in the hospital. Discharge recommendations included tapering off antipsychotic medications and following up with Psychiatry, Neurology and Immunology to consider chronic immunosuppressive therapy.

Less than two weeks later, the patient returned the hospital with a similar presentation and severe agitation upon admission to the paediatric service. Work-up returned comparable results including repeat NMDA antibodies within normal limits and a positive urine drug screen for cannabinoids. VGKC antibody was ordered. Based on patient’s documented hospital course and positive response to IVIG on prior admission, the patient received IVIG at 2mg/kg soon after admission. The patient required vest restraints for treatment.

The patient elected to receive IVIG at 1g/kg/day x 3 days for a full course. During IVIG course patient had continued improvement of mental status. He was discharged once he was back to baseline. VGKC antibody was eventually found to be positive. Neurology clinic follow-up found the patient to remain at baseline and considered monthly IVIG infusions to prevent recurrence of encephalitis but decided to continue observation at that moment since his acute episode was just resolving. The patient was continued on Valproic acid for a long-term mood stabilization.

Less than two weeks after this clinic visit, the patient was hospitalized a third time with similar symptoms that again resolved with IVIG therapy at 2g/kg total dose. Follow up with Neurology and Immunology was recommended to discuss prophylactic management of encephalitis. The patient had one documented follow up with Neurology and was then lost to follow up for over three years before a third presentation to the hospital with a relapse of psychiatric symptoms secondary to encephalitis. The patient once again exhibited a positive response to IVIG therapy and demonstrated a return to his baseline.

## DISCUSSION

Since the discovery of the voltage-gated potassium channels' ability to cause pathogenicity in 2001, research into their ability to cause neuropsychiatric disorders has increased substantially with many new and recent discoveries, especially within the last 5 years. It is now known that oftentimes VGKC antibodies are not actually antibodies against the VGKC subunit itself, but against proteins within the potassium channel, the most commonly studied being Lgi1 and Caspr2 (Prüss and Lennox 2016). However, about half of VGKC antibody positive patients lack antibodies towards both Lgi1 and Caspr2 (Van Sonderen *et al.* 2016). Today's standard commercial assays can detect both Lgi1 and Caspr2 antibodies with good reliability, lending credibility to our belief that testing the presence of such antibodies should be a consideration of physicians treating neuropsychiatric disorders (Yeo *et al.* 2017).

Of consideration, it is recognized that there are three main VGKC positive subgroups: positive for Lgi1 antibodies, positive for Caspr2 antibodies, and VGKC positive while negative for Lgi1 and Caspr2 antibodies (double negatives) (Van Sonderen *et al.* 2016). Due to chronological limitations of our case, we were unable to quantify the exact subtype of our patient. However, consideration should be provided to the nature of these antibodies as vastly different symptoms exist for each subtype and the specificity of symptoms differs by receptor positivity.

Case reports and literature reviews of Lgi1 positive limbic encephalitis indicate a male predominance and an age of onset of approximately 60 (Van Sonderen *et al.* 2016; Shin *et al.* 2013). The presence of seizures appears to be a common presentation in many patients. Highly specific for Lgi1 positive limbic encephalitis are faciobrachial dystonic seizures (FBDS) which are frequently described as upper extremity contractions which are brief and occur multiple times daily (Andrade *et al.* 2011). However, FBDS does occasionally occur in the absence of Lgi1 negativity (such as insular originating seizures) and thus the presence of these seizures is only suggestive of Lgi1 positivity and must be weighed against a full review of the patient's symptoms (Patira *et al.* 2016). Of particular concern for Lgi1 positive limbic encephalitis patients, is the presence of hyponatremia which was reported in 60% of Lgi1 antibody positive patients (Van Sonderen *et al.* 2016). Due to the additional risk of seizures in patients with severe hyponatremia, electrolyte monitoring is vital in patients with this diagnosis. Our patient's hospital course was negative for seizures or seizure-like activity and his electrolytes appeared within normal limits. However, due to the lack of a standardized constellation of symptoms associated with Lgi1 positive limbic encephalitis,

Lgi1 positive encephalitis is still a probable diagnosis for our patient.

Caspr2 antibody positive encephalitis appears to show a significant male predominance as well as cognitive deficits, seizures and occasional cerebellar symptoms (Irani *et al.* 2010). Caspr2 antibody positive encephalitis doesn't appear to have the predominance of hyponatremia as associated with Lgi1 antibody positive encephalitis. There is some indication that neoplasms, with the most common being thymomas, are associated with Caspr2 positivity (Irani *et al.* 2012). Of particular concern is the association of Caspr2 antibody positive encephalitis with Morvan's syndrome, which incidentally shares an association with thymomas (Galié *et al.* 2016). Morvan's Syndrome is a constellation of symptoms which include: neuropsychiatric deficits, muscle cramps and fasciculations (neuromyotonia), peripheral muscular hyperexcitability, poor sleep and occasional autonomic dysfunction (Irani *et al.* 2012). There is also an association between Morvan's and Lgi1 antibodies, although the association with Caspr2 appears much more established by our literature search (Zhang *et al.* 2016). Caspr2 antibody positive encephalitis does occasionally include a relapsing course, although this is largely in line with other forms of autoimmune encephalitis and autoimmune conditions in general.

The prospect of VGKC positivity without positivity of either Lgi1 or Caspr2 antibodies (double negatives) also needs to be considered since a substantial part of VGKC positive patients lack both antibodies. In a recent study (Van Sonderen *et al.* 2016), this phenotype was associated with the presence of limbic encephalitis and encephalomyelitis, although the authors found that when Lgi1 or Caspr2 antibodies were lacking, there were no differences in VGKC positive patients vs VGKC negative patients, so the positivity of VGKC in double negative patients doesn't appear to be a reliable marker of neurological inflammation and its standalone use appears limited at this time

The treatment modalities available for VGKC encephalitis include steroids, PLEX and IVIG. A systematic review of previous studies appears to show that the best clinical outcomes are correlated with the largest decreases of VGKC related antibody titers (Radja and Cavanna 2013). No randomized trials currently exist to test the effectiveness of the various treatment modalities, however, the research available appears to demonstrate that treatment with steroids is associated with the most significant reduction in VGKC antibody levels (Radja and Cavanna 2013). Plausibly, this decrease in antibody levels translates to symptomatic reductions as well.

Consideration should be provided for neuroimaging modalities to assess the resolution of neurological inflammation associated with limbic encephalitis. Presumably fluorodesoxyglucose positron emission tomography (FDG-PET) scans may be used to monitor a patient's progress throughout the patient's treatment course. The regions of the brain most affected in limbic encephalitis are the medial temporal as well as the limbic regions such as the hippocampus and attention should be paid to these areas on neuroimaging scans. There is an observed improvement in glucose hypermetabolism as demonstrated by FDG-PET after treatment,

which correlates with improved clinical results (Fauser *et al.* 2005).

Our patient's MRI scan was largely within appropriate limits, although the scan took place early in the patient's hospital course and additionally MRI's are likely potentially inferior to FDG-PET scans in the diagnosis of VGKC limbic encephalitis.

## CONCLUSIONS

This case demonstrates the need to consider VGKC encephalitis in the setting of altered mental status and psychosis that remains refractory to psychiatric treatment. Our case calls for a higher index of suspicion in working patients up for neuropsychiatric symptoms within the given context.

Ordering CSF antibodies and MRI allows further workup and appropriate treatment. Patients otherwise managed with antipsychotics will have a recurrence of symptoms and ultimately require rehospitalization, as our patient did.

By identifying more patients with VGKC autoimmunity, we can learn more about the optimal immunosuppressive treatment. Due to the relatively recent discovery of VGKC, our knowledge of this condition remains relatively limited. However, we hope that future clinicians will not only develop an index of suspicion for this condition but also develop a greater knowledge of VGKC subtype stratification, treatment monitoring and the most medically and cost-effective treatments for this potentially devastating and oftentimes treatment-resistant condition.

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