

# Hyponatremia and Voltage Gated Potassium Channel Antibody Associated Limbic Encephalitis

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## Abstract

Limbic encephalitis may occur as an infectious, paraneoplastic, or autoimmune phenomenon. One such cause of limbic encephalitis is voltage gated potassium channel antibodies (VGKC). Hyponatremia with new cognitive decline may be one of the presenting symptoms. The exact mechanism of hyponatremia is unknown though findings consistent with syndrome of inappropriate antidiuretic hormone (SIADH) are observed. We retrospectively reviewed all cases admitted to an academic medical center with a diagnosis of limbic encephalitis (848 adults between 2004 to 2010) and found six cases of VGKC antibody associated limbic encephalitis. Three of the six cases had SIADH that completely or partially resolved with a combination of water restriction and immunotherapy. The reversibility of hyponatremia and limbic encephalitis with immunomodulation suggests an antibody-mediated cause. We further review available literature for association of hyponatremia and VGKC limbic encephalitis and propose mechanisms of for the hyponatremia in autoimmune encephalitis.

**Keywords:** VGKC; Hyponatremia; Limbic encephalitis

## Introduction

Limbic encephalitis (LE) may occur as a paraneoplastic or autoimmune phenomenon and may be associated with syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Ectopic-antibody production can explain SIADH in paraneoplastic cases but the exact mechanism of hyponatremia in antibody-mediated LE, such as voltage gated potassium channel (VGKC), is unknown.

VGKC antibodies have been reported in association with several clinical syndromes involving the central and peripheral nervous systems [1,2]. However, only VGKC-LE has been found associated with hyponatremia with an incidence between 30-100% [3-5]. We present here a retrospective review of our cases of limbic encephalitis with a case series of VGKC-LE and its association of SIADH and review of literature discussing the possible mechanism.

## Methods

We retrospectively reviewed medical charts of 848 adults from 2004-2010 who were clinically diagnosed with LE. Charts were reviewed for paraneoplastic panel, SIADH workup, basic metabolic panels, thyroid function tests, and neuroimaging. We then had a neuroradiologist blinded to the clinical data review the magnetic resonance images (MRI) for hypothalamic hyperintensities. A Pubmed search was performed reviewing the incidence of SIADH in VGKC-LE and other autoimmune syndromes. This study was approved by the institutional IRB.

## Results

Paraneoplastic panel was resulted in 102 of the 848 patients. Six patients were positive for the VGKC antibody (mean age 62.5 years, 3 males). The mean time from clinical onset to diagnosis was 116 days (range 0 to 185 days). No evidence of malignancy on CT chest, abdomen, and pelvis was found in any of the six patients. Cerebrospinal fluid (CSF) results had an average white blood cell count of 4.0 cells/mm<sup>3</sup> (range 1 to 12 cells/mm<sup>3</sup>; normal 0 to 5 cells/mm<sup>3</sup>) and protein of 49.2 mg/dL (range 34 to 69 mg/dL; normal 15 to 60 mg/dL). The clinical features, VGKC titers and monitoring, and provided therapies are found in Table 1.

Average admission sodium was 130.7 mmol/L (range 115 to 141 mmol/L). Three patients had admission sodium levels less than 130 mmol/L with an average of 122.7 mmol/L (range 115 to 128 mmol/L). In these three patients, average urine osmolality was 579.7 mosm/L (range 505 to 677 mosm/L) with urine sodium of 112.3 mmol/L (range 64 to 192 mmol/L). Two of these three patients had hypothalamic involvement with T2/FLAIR hyperintensity seen on MRI brain. Water restriction was instituted during hospitalization for all three hyponatremic patients. Their hyponatremia resolved completely or partially prior to discharge with average serum sodium upon discharge of 133.0 mmol/L (range 126 to 137 mmol/L). Basic metabolic workup and MRI findings can be seen in Table 2.

Serology for other autoimmune antibodies was negative in five of the cases. One case had positive microsomal antibodies (138.6 IU/mL; normal <5 IU/mL) and thyroglobulin antibodies (1209 IU/mL; normal <10 IU/mL) but normal thyroid stimulating hormone (TSH) (4.63 uU/mL; normal 0.4 to 5.5 uU/mL) and free T4 (1.2 ng/dL; normal 0.7 to 1.8 ng/dL). None had diabetes.

## Discussion

We present six cases of LE associated with the VGKC antibody. We found three of the six cases had SIADH consistent with the reported incidence in literature [1,3,5-9]. These cases responded completely or partially to the combination of immunomodulation and water restriction. Two of these three cases had hypothalamic involvement on MRI.

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Patient	Age (yrs); Sex	Clinical Features	Cancer	VGKC Monitoring (days)	VGKC Titer (nmol/L) Normal <0.02nmol/L	CSF Protein Results (mg/dL) Normal 15-60mg/dL	Treatment	AEDS	MRI	Hypothalamic Involvement on MRI
1	93F	Altered mental status	No	Initial	0.13	57	None	None	Global atrophy, laminar necrosis left parietal lobe	No
2	60M	Autonomic seizure	No	Initial	1.58	NA	IVIG	LCM, LTG	Bilateral mesial temporal lobe hyperintensity	Yes
				54	4.22		PLEX			
				161	15.8					
				273	1.94					
3	53F	Altered mental status, depression	No	Initial	0.76	69	IVMP x5 days, IVIG x5 days	LEV, LCM	Bilateral hyperintensity in the restiform bodies	No
4	55M	Altered mental status	No	Initial	3.89	101	IVMP x5 days, PLEX x5 days	ZON, LEV, LCM	Right unilateral mesial temporal lobe hyperintensity	No
5	37F	Complex partial seizure	No	Initial	2.8	47	IVIG x3 days, IVMP x3 days, PLEX x5 days	VPA, LEV, PHT	Bilateral basal ganglia/hippocampus hyperintensity	Yes
				408	0.77					
6	85M	Altered mental status, seizure	No	Initial	0.692	48	IVMP x5 days, PLEX x3 days/week for 2 weeks	VPA, LEV, TPM	Right unilateral mesial temporal lobe hyperintensity	Yes

Abbreviations: M=male, F=female, VGKC=voltage gated potassium channel antibody, CSF=cerebrospinal fluid, IVMP=1 gram of intravenous methylprednisolone, IVIG=0.4g/kg/d of intravenous immunoglobulin, PLEX=plasma exchange

Table 1: Characteristics of patients with serology positive for VGKC antibodies.

Pt	Admission Sodium (nmol/L)	Discharge Sodium (nmol/L)	Urine Osmolality (mOs/kg)	Serum Osmolality (mOs/kg)	Urine Sodium (mmol/L)	Serum BUN (mg/dL)	Serum Creatinine (mg/dL)	Serum Potassium (mmol/L)	TSH (uU/mL)	Water Restriction	Demecocycline	SIADH	Formal endocrinology consult
1	141	137	NA	NA	NA	16	0.84	4.8	5.25	NA	NA	No	No
2	139	137	NA	NA	NA	12	0.74	3.7	1.75	NA	NA	No	No
3	136	141	NA	NA	NA	20	0.73	4	0.46	NA	NA	No	No
4	115	126	677	264	192	6	0.51	3.7	4.63	Yes	Yes	Yes	No
5	126	137	557	256	64	5	0.84	4.1	4.63	Yes	Yes	Yes	Yes
6	128	136	505	276	81	26	0.75	4	1.64	Yes	No	Yes	No

Table 2: Serum and urine laboratory findings.

VGKC proteins constitute a diverse group of tetrameric signaling proteins present on the cell surface different tissue subtypes [1]. These proteins classically have a vital role in cellular action potential and recently have been shown to initiate paraneoplastic autoimmunity as autoantigens [1]. VGKC antibodies are seen in neuromyotonia, Morvan syndrome, epilepsy, and dysautonomic phenomena of hyperhidrosis and gastrointestinal dysmotility [1,2]. Interestingly, hyponatremia is not seen in these disorders [10]. Reports have postulated that the leucine-rich, glioma inactivated 1 (LGI-1) protein may be the target antigen of VGKC mediated LE whereas the contactin-associated protein 2 (CASPR-2) may be the antigen in Isaac's and Morvan's syndrome [9].

The mechanism of SIADH in patients with VGKC-LE is not completely understood. One possible mechanism is inflammation on the hypothalamic-pituitary neuraxis from direct extension. Two of the three hyponatremic patients in our series had hypothalamic hyperintensity on T2/FLAIR MRI. If that's the case, all limbic encephalitis irrespective of the cause may have higher incidences of SIADH. Another possibility is involvement of the hypothalamic osmoreceptors regulating AVP release that are located in the lamina terminalis outside the blood brain barrier [8]. The predominant lack of an inflammatory response in CSF studies makes this mechanism less likely. The fact that most reports of hyponatremia improve with immunotherapy supports an antibody mediated mechanism with the target antigen either at the hypothalamus or perhaps at the Kv1.1 and/

or LGI-1 channels at the renal tubular epithelium, which could explain receptor sensitization and potentiating ADH-induced water transport [7].

Future areas of research should focus on detailed endocrinological evaluation of hyponatremia in patients with autoimmune encephalitis distinguishing SIADH from other causes of hyponatremia, such as cerebral salt wasting. Additionally, the histopathological query of hypothalamic and renal involvement in animal models of autoimmune encephalitis investigating VGKC as well as LGI-1 antibodies in hyponatremic animals would be beneficial to accurately define the causative protein for SIADH in VGKC-LE. The specificity of hyponatremia to VGKC-LE versus other causes of autoimmune encephalitis should also be explored. With the emerging VGKC subtypes and new antigen targets for VGKC antibody associated diseases, it is evident that the associations of LE and secondary features are complex. Our case series emphasizes the association and an early diagnosis of LE given the reversibility with a combination of water restriction and immunomodulation.

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