Two Clinical Cases of VGKC Antibodies Associated Limbic Encephalitis

A. Straukienė*
Ph. Oppong**
S. Weatherby**
M. Sadler**

**Vilnius University Faculty of Medicine; Vilnius University Hospital Santariškių klinikos; Plymouth Hospitals NHS trust, United Kingdom*

***Plymouth Hospitals NHS trust, United Kingdom*

Summary. Two patients were diagnosed with voltage-gated potassium channel (VGKC) antibody positive limbic encephalitis (LE) at the neurology department, Derriford Hospital, Plymouth, in the United Kingdom. Immunoprecipitation assays for the detection of VGKC antibodies and subunits CASPR2 and LGi1 were performed and the results came back positive. Both patients have received an immunomodulatory regimen and were monitored prospectively. The diagnosed patients had clinical and immunological features of VGKC antibody positive LE. Within 1–2 months after treatment was initiated, VGKC antibody titres reduced considerably. We noticed significant improvement in memory problems and seizure-free activity and this was supported by objective clinical observations and investigations. We believe that our study shows promising results and it proposes a treatment protocol for individual cases of VGKC antibody positive LE.

Keywords: VGKC antibodies- voltage gated potassium channel antibodies, limbic encephalitis.

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INTRODUCTION

The role of autoimmune dysfunction has been investigated since the 1930s [1]. The voltage-gated potassium channel (VGKC) is a group of tetrameric signalling proteins composed of 6- transmembrane- domain subunits, associated with various auxiliary proteins. Leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) are antigenic neuronal targets in the VGKC macromolecular complex [2]. Vincent highlighted, that VGKC antibodies have been reported in association with three main clinical syndromes: neuromyotonia, Morvan's syndrome, and limbic encephalitis [5]. In addition to these syndromes, VGKC-antibodies have also been identified in some patients with idiopathic epilepsy [3]. Tumours appear to be uncommon in typical VGKC-antibody associated limbic encephalitis (LE). However, some other organ-specific autoantibodies and co-existing autoimmune disorders are associated with voltage gated potassium channel (VGKC) autoimmunity. For example, one patient with myasthenia gravis had muscle acetylcholine receptor autoantibodies; one patient with dysphagia, profound weight loss, and generalized weakness had both ANNA-1 and amphiphysin-IgG, and two patients with stiff-man phenomena had GAD65 autoantibodies [4]. Brain MRI usually demonstrates medial temporal lobe hyperintensities, and CSF analysis is normal or reveals lymphocytic pleocytosis [5]. Many patients respond well to treatment which is likely a reflection of the reversible nature of the pathogenic cellular mechanisms. Prompt recognition and diagnosis of VGKC encephalitis is thus essential [6].

Adresas:
Agnė Straukienė
El. paštas: aniukas@gmail.com

METHODS

2 patients were diagnosed with VGKC antibody positive limbic encephalitis and treated at the neurology department, Derriford Hospital, Plymouth, in the United Kingdom. Immunoprecipitation assays for detection of VGKC antibodies and subunits CASPR2 and LGi1 were performed at the John Radcliffe Hospital in Oxford, United Kingdom. The VGKC-antibody titres tend to be higher (4400 pM; normal 5100 pM) in patients with CNS conditions. Addenbrooke's cognitive examination (ACE-R) was used for cognitive function assessment.

PATIENT 1

A 39-year-old female complained of spasmodic twitching in her upper limbs and head. Over the ensuing few months it became more noticeable and she experienced uncontrolled movements of her head and arms lasting up to 5 minutes. There was no alteration in consciousness during these attacks and they apparently did not interfere with her ability to work or carry on with what she is doing at the time. However, she had difficulty with her memory and concentration. Examination confirmed the presence of a fine tremor mainly of her left arm, shoulder, head, and tongue. She had dysdiadochokinesis, very brisk reflexes, present abdominal reflexes, and a flexor plantar response. EEG was unremarkable. Her symptoms worsened. She described variable noises in her head, which when very loud she found difficult to suppress and had an urge to shout them out. She used a variety of words to describe the noise in her head such as "popping", "echoing" and "clanging". Watching television exacerbated the auditory hallucinations. She denied hearing voices talking about her or recognisable voices in her head. These were often grunts or noises but she said that she could come out with "bad words", which she shouted. She had problems with masculine features particularly hirsutism for which she had a range of endocrine investigations. These were all negative. She was taking levothyroxine as replacement therapy following treatment for auto-immune hyperthyroidism. She underwent several investigations including a normal MRI scan of her head and spine. A range of blood tests including full blood count, urea and electrolytes, auto-immune profile associated with paraneoplastic disorders and Stiff Person syndrome and other CNS disorders were all negative. Her lupus screen (ANA, double stranded DNA), immunoglobulins and thyroid function were within normal range and thyroid auto-antibodies were negative. HIV and treponemal pallidum tests were also negative. Huntington's genetic test was negative. Copper was slightly above the normal range. Ca 125R, Ca 19-9 and carcino embryonic antigen were negative. No evidence of malignancy was identified on CT thorax abdomen and pelvis, PET scan or mammography. No neurological cause for her illness was found. Possible explanations for her symptoms included manifestations of a psychiatric disorder or features

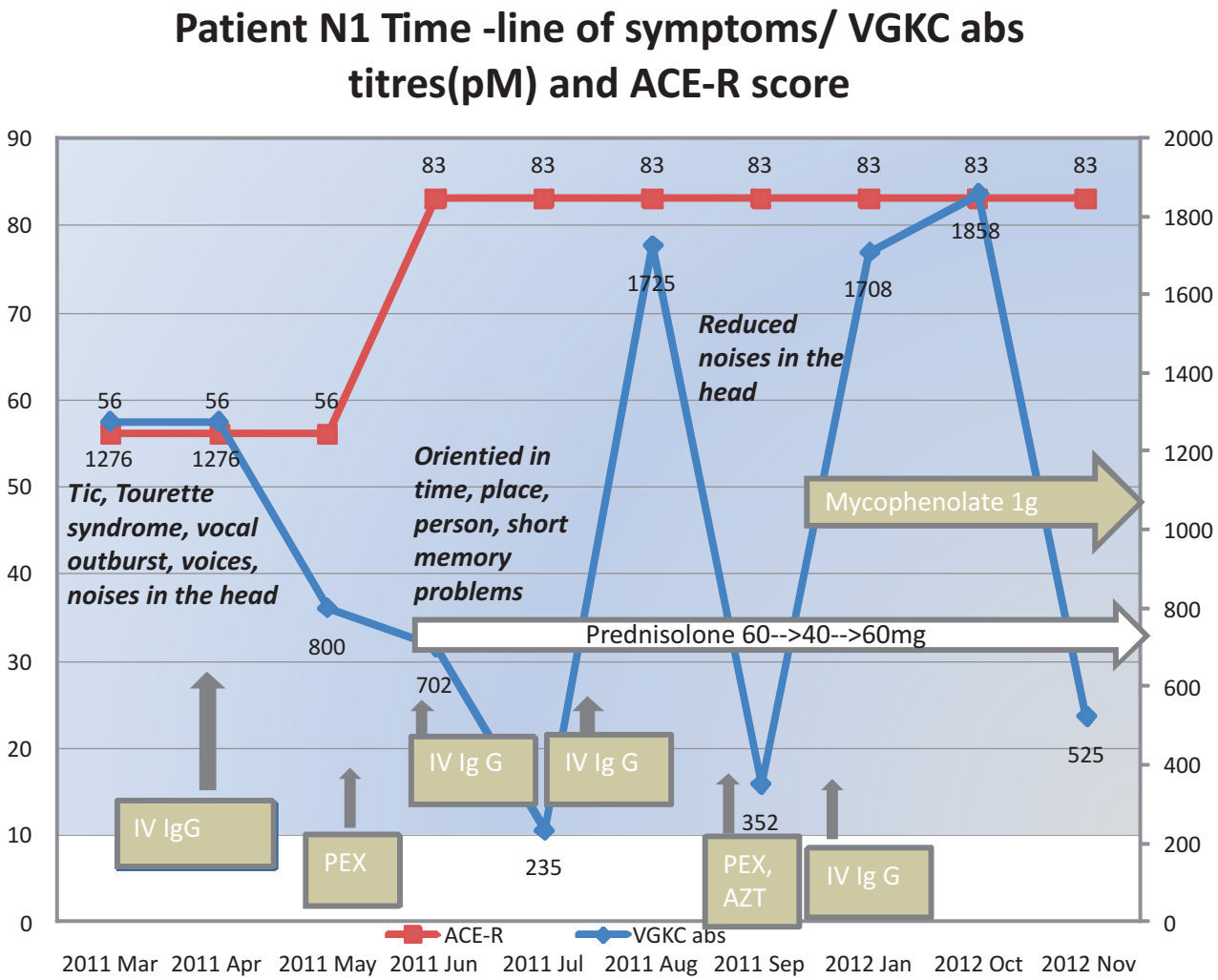

Figure 1. **A voltage-gated potassium channel antibody titre (—◆—) and cognitive function (—■—), and treatment courses over time in months for patient 1.**

related to the CNS autoimmune syndromes. Mental state examination performed by a psychiatrist showed that she was co-operative and rational with no suicidal ideation. There was no evidence of formal thought disorder including thought insertion, withdrawal or thought block. There was no evidence of any command hallucinations. She was aware of the internal voices. She was orientated in time, place and person. She was aware of future events. She had abdominal cramps and was severely constipated for which she required daily enemas. Despite this, her abdomen remained distended. CT scan showed features in keeping with pseudo-obstruction. Colonic transit study did not demonstrate slow-transit. Prucalopride 2 mg per day was introduced with good effect. NMDA was negative. VGKC antibodies were positive with high titres and subtype CASPR2 was positive. Figure 1 shows the fluctuation of VGKC antibody titres in association with treatments given. Diagnosis of auto-immune CASPR2 antibody positive VGKC encephalitis was made. No underlying sinister causes, particularly malignancy, were identified. She underwent various trials of treatment with Azathioprine, plasmapheresis and intravenous immunoglobulin. She had a good clinical response to and tolerance of Mycophenolate 1.5 g b.d. and Prednisolone 50 mg on alternate days. Carbamazepine 200 mg per day and olanzapine 20 mg were used to stabilise her disease symptomatically. We also started levothyroxine, alendronic acid, vitamin D, omeprazole, and domperidone. Her symptoms have not resolved completely, in particular, the noises in her head persist but the voices are much improved. Furthermore, her abdominal distension secondary to gastroparesis which led to splinting of her diaphragm and shortness of breath improved gradually.

PATIENT 2

A 70 year old male presented with involuntary movements. He had involuntary flexion of his arms. Following this he could become quite confused as if he was having visual hallucinations. On other occasions there were brief twitches accompanied by (visual/auditory) hallucinations. EEG showed clear myoclonic jerks with epileptiform discharge on exposure to flickering lights. Later on he developed posturing problems, specifically, turning his head to the left and then more slow and sustained dystonic type movements of his head to the right. His speech became more slurred and he was unsteady on his feet. He had episodes of falling asleep every five minutes, as well as periods of confusion, disorientation, hallucinations, and twitching. He deteriorated over a period of twelve months. He was admitted to the hospital and found to be profoundly hypomagnesaemic, hypocalcaemic, hypophosphotaemic and hyponatraemic. It was thought that the electrolyte derangement was due to primary hypoparathyroidism or vitamin D deficiency. It was also hypothesised that hypomagnesaemia could be attributed to omeprazole therapy. Coeliac disease was considered but was unlikely given the absence of relevant symptoms and a negative tissue transglutaminase antibody test. B12 and folate levels were within the normal range. TSH was borderline elevated with a normal free T4 level. Thyroid peroxydase antibody was positive. pANCA, cANCA, ds DNA, ANA1 and immunoglobulins were within normal ranges. No monoclonal bands were detected on protein eletrophoresis. He had a previous triple coronary artery bypass and had developed congestive cardiac failure and fast atrial fibrillation for which he was started on warfarin. His mobility was re-

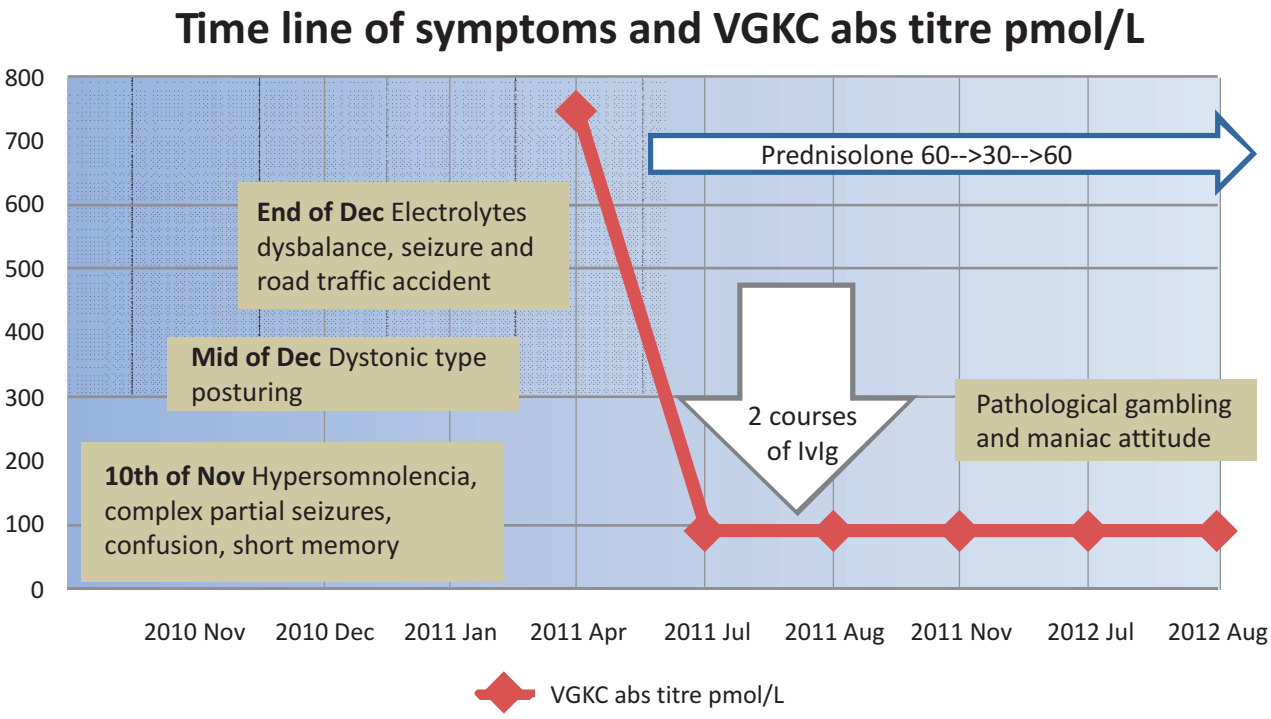

Figure 2. **A voltage-gated potassium channel antibody titre and treatment courses over the time in months for patient 2.**

Table. **A comparison of demographic and clinical features of the two patients**

	Patient 1	**Patient 2**
Age, sex	F, 60	M, 72
Preceding history	Tics, twitches, verbal expletives, possibly auditory hallucinations.	Faciobrachial dystonic seizure
Other manifestations	Noise and voices in her head, vocal utterances, short term memory problems, hirsutism, gastro paresis.	Disorganised character, manic state, short term memory problems, semantic dementia
Lowest serum Sodium recorded (Normal range 133–146 mmol/l)	131	121
Thyroid function	TSH, FT4 derangement	TSH, FT4 derangement
Malignancy	None	None
Neuroimaging CT/MRI	Normal	Normal
EEG	EEG shows an irregular, low amplitude post central rhythm which is slow at 7–8 Hz 20–30 uV. Brief runs of bifrontal theta and slow activity are seen frequently at 2–4 Hz, up to 70 uV. Occasional sharp components are seen mixed with the frontal slow activity.	1st EEG Drowsiness is characterised by rolling eye movements, and most prominently rhythmic theta frequencies 5–6 Hz <40 uV Photic stimulation at 25 and 30 f/sec generalised myoclonic jerks were observed and recorded. 2nd EEG is low amplitude and characterised by intermittent background activity at 9–10 Hz <20 uV symmetrically over posterior regions. An irregular slower activity 2–3 Hz <30 uV is recorded posteriorly. Minimal beta activity <20 Hz Photic stimulation elicits some symmetrical following responses 2–30 f/s.
Pre treatment VGKC abs titres (Normal range less then 100 pM/L)	1276	743
VGKC abs complex protein (CASPR2 and LG1)	CASPR 2 positive, LGi1 negative	Not performed
Coexisting auto antibodies: • ANNA1 • GAD abs • CRMP5 abs • Amphyphisin • AchR abs • VGCaC • NMDA • Adrenal gland abs • TPO	 Negative Negative Negative Negative Negative Negative Negative Negative Negative	 Negative Not performed Not performed Not performed Not performed Negative Negative Negative Positive
Immunosupression treatment	Plamopheresis, IvIg, Prednisolone, Azathioprine, Mycophenolate	IvIg, Prednisolone
Post long term (12 months) treatment VGKC abs titres (Normal range less then 100 pM/L)	525	Normal
Clinical outcome	Continuous noises, but voices are better in her head, bowel motility improved.	Intermitted confusion, disabled.

duced due to heart failure, a left knee replacement and chronic back pain. VGKC antibodies were positive and he was started on high dose prednisolone. This caused steroid induced mania. The amount of money he was spending increased dramatically, he was printing off a multitude of different betting slips and developed features associated with pathological gambling. He continued to receive treatment with steroids for his autoimmune encephalitis throughout the course of the year, and also had courses of intravenous immunoglobulin (see figure 2). His current issues include physical disability; he is wheelchair bound, he is unable to use toilet without assistance, and unable to dress himself. He has poor short term memory, concrete interpretation of proverbs and potential decreased semantic knowledge.

In conclusion this man has developed VGKC positive autoimmune encephalitis characterised by faciobrachial dystonic seizures and cognitive dysfuntion. He was treated with prednisolone, IVIG, quetiapine, warfarin, bisoprolol and sodium valproate 600 mg. He showed good response

to treatment and is seizure free. VGKC antibodies titres reduced dramatically and he has remained stable over the ensuing few months.

DISCUSSION

VGKC positive limbic encephalitis is a relatively rare condition, and current literature includes retrosepective case series of patients treated with different immunomodulatory regimes [7–9]. Both patients in this series received an immunomodulatory regimen and were monitored prospectively. They had clinical, cognitive and immunological features of VGKC positive limbic encephalitis, with one patient having a longer disease course. Within 1–2 months of treatment, VGKC antibody titres reduced considerably. We observed that there was not significant correlation between fluctuation in VGKC antibodies titres and clinical symptoms. The patients and their relatives reported improvement in memory problems and seizure free periods. This was supported by clinical observation and cognitive testing. The benefit of oral steroids in achieving reductions in antibody titre levels and improved cognitive function was suggested by Vincent et al. Our aim was to keep patients on a high dose of steroids to achieve sustained clinical stability. The chosen treatment approach was based in part on prior cases of autoimmune neurological disorder refractory to IVIG alone, and previous experience in this condition [8, 9]. However, risk of adverse events does raise the question of whether plasma exchange is required for rapid reduction of antibodies. VGKC antibodies are not directly responsible for all neurologic manifestation; one of the patients developed severe hyponatraemia that required hospital admission. Correction of electrolyte disturbance did not change clinical manifestation of seizures and confusion. The other studies identified accompanying autoantibodies (e.g., GAD 65 autoantibodies with type 1 diabetes mellitus, ANNA -1 with lung carcinoma). All were negative for our patients apart from TPO antibody which was positive for one patient. However, TPO antibodies are not diagnostic of this disorder and are probably not pathogenic. A diagnosis of Hashimoto encephalopathy is unlikely for this patient because he lacks several clinical characteristics including tremor, myoclonus, and stroke like episodes [10–12]. Cancer must be screened for in all VGKC-autoantibody- positive patients by comprehensive physical examination, CT of the chest, abdomen, and pelvis, mammography (in women), and serum assay for prostatic- specific antigen (in men). In patients with negative CT imaging but with high risk of malignancy due to family history, smoking, or other known carcinogen exposure, whole body PET may be justified. There is a need for pragmatic multicentre randomized controlled trials to determine the optimal treatment regimen for VGKC positive LE using appropriate outcome measures and safety monitoring. We believe that our study shows promising results and proposes treatment protocol for VGKC +LE for individual cases.

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A. Straukienė, Ph. Oppong, S. Weatherby, M. Sadler

LIMBINIS ENCEFALITAS, SUSIJĘS SU ANTIKŪNAIS PRIEŠ ĮTAMPOS VALDOMUS KALIO KANALUS: DU KLINIKINIAI ATVEJAI

Santrauka

Šiame straipsnyje pristatomi du klinikiniai atvejai, kai buvo diagnozuotas ir patvirtintas įtampos valdomų kalio kanalų teigiamų (ĮVKK) antikūnų limbinis encefalitas. Pacientai gydyti Plimuto ligoninėje (Plimutas, Jungtinė Karalystė). Įtampos valdomų kalio kanalų antikūnai ir jų subvienetai CASPR 2 ir LGi1 patvirtinti atlikus imunoprecipitacijos tyrimus John Radcliff ligoninėje Oksforde (Jungtinė Karalystė). Abu pacientai turėjo tipinius klinikinius ir imunologinius požymius, būdingus ĮVKK limbiniam encefalitui. Lentelėse pateikti duomenys apibendrina klinikinę eigą, ir antikūnų svyravimus bei taikytą imunosupresinį gydymą laiko atžvilgiu. Per du mėnesius nuo pradėto gydymo antikūnų titras labai sumažėjo. Gydymo eigoje buvo stebėtas atminties gerėjimas, priepuolių dažnio mažėjimas. Tai nustatyta objektyviais tyrimų duomenimis. Pristatome šiuos klinikinius atvejus manydami, kad tai turės didelės naudos, diagnozuojant šį retą susirgimą ir parenkant atitinkamą imunosupresinio gydymą taktiką.

Raktažodžiai: ĮVKK antikūnai – įtampos valdomi kalio kanalų antikūnai, limbinis encefalitas.