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RESEARCH PAPER

Clinical relevance of positive voltage-gated potassium channel (VGKC)-complex antibodies: experience from a tertiary referral centre

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ABSTRACT

Background Voltage-gated potassium channel (VGKC)-complex antibodies can be associated with a range of immunotherapy-responsive clinical presentations including limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. However, there are patients with positive levels in whom the significance is uncertain.

Objective To evaluate the clinical significance associated with positive (>100 pM) VGKC-complex antibodies.

Methods Over a 4-year period, 1053 samples were sent for testing of which 55 were positive. The clinical presentations, final diagnoses and responses to immunotherapies, when given, were assessed retrospectively and the likelihood of autoimmunity was categorised as definite, possible, unlikely or undetermined (modified from Zuliani *et al* 2012).

Results Only 4 of the 32 patients with low-positive (100–400 pM) levels were considered definitely autoimmune, 3 with peripheral nerve hyperexcitability and 1 with a thymoma; 3 were given immunotherapies. Of the remaining 28 with low-positive levels, 13 (3 of whom had tumours) were considered possibly autoimmune, and 15 were unlikely or undetermined; 1 was given immunotherapy unsuccessfully. Of the 23 patients with high-positive (>400 pM) levels, 12 were given immunotherapies, 11 of whom showed a good response. 11 were considered definitely autoimmune, 10 with limbic encephalitis (antibody specificity: 5 LGI1, 1 contactin2, 2 negative, 2 untested) and 1 with a tumour. In the remaining 12, autoimmunity was considered possible (n=9; most had not received immunotherapies), or unlikely (n=3).

Conclusions As antibody testing becomes more widely available, and many samples are referred from patients with less clear-cut diagnoses, it is important to assess the utility of the results. VGKC-complex antibodies in the range of 100–400 pM (0.1–0.4 nM) were considered clinically relevant in rare conditions with peripheral nerve hyperexcitability and appeared to associate with tumours (12.5%). By contrast high-positive (>400 pM; >0.4 nM) levels were considered definitely (38%) or possibly (49%) clinically relevant, but not all patients had a 'classical' limbic encephalitis and some did not receive immunotherapies.

INTRODUCTION

Autoantibodies against the voltage-gated potassium channel (VGKC) complex measured by radioimmuno-precipitation have been reported in a broad

spectrum of immunotherapy-responsive neurological illnesses in children and adults. Initially, low levels (<400 pM) were associated with peripheral nerve hyperexcitability syndromes (mainly acquired neuro-myotonia), but higher levels were subsequently found in Morvan's syndrome, and in patients with reversible limbic encephalitis.^{1–4} In the first case series, 10 patients with limbic encephalitis had VGKC-complex values from 450 to 5128 pM, but some controls were reported to have low positive titres.⁵ Many subsequent reports have confirmed that VGKC-complex antibodies are associated with limbic encephalitis and a broader range of phenotypes, and in some patients, VGKC-complex antibodies <400 pM did appear to be clinically relevant.⁶

Latterly it has become clear that VGKC antibodies are not directed against the VGKC itself, but against other cell surface antigens that form part of the VGKC complex. Antigenic targets include leucine-rich glioma-inactivated protein 1 (LGI1),⁷ typically associated with limbic encephalitis (LE) and a distinctive seizure disorder, faciobrachial dystonic seizures⁸ and contactin-associated protein 2 (CAPSR-2), more frequently associated with peripheral nerve hyperexcitability syndromes including Morvan's syndrome (neuromyotonia, neuropsychiatric features, sleep disturbance, dysautonomia).⁹ Antibodies to Contactin2 are much less frequent with no syndrome-specific phenotype having been identified. However, in a proportion of patients with positive VGKC-complex antibodies, a specific antigenic target has not been defined, suggesting that the antibodies may be directed against other antigens within the complex and raising questions about the antibody specificity and relevance.

To investigate the relevance of VGKC-complex antibodies in routine clinical practice, we performed a retrospective analysis of a large case series of individuals from one institution where antibody testing had been requested as part of the diagnostic work-up. We specifically aimed to address the relevance of low-positive versus high-positive antibody levels, and whether discovery of a positive antibody influenced management.

METHODS

Following an initial brief audit of 44 VGKC-complex antibody-positive subjects, we performed a comprehensive retrospective review of all patients seen at the National Hospital for Neurology and Neurosurgery, Queen Square, who

had VGKC antibodies requested between January 2008 and January 2012. The electronic records of clinic correspondence, neuropsychology, imaging and other blood results were reviewed. Subjects were classified as having 'high positive' (≥ 400 pM) or 'low positive' (100 to 400 pM) VGKC-complex antibodies. Duration of follow-up was defined as the time from the first to the most recent neurological assessment. The treating neurologist's final diagnosis was recorded. The likelihood of each patient having an autoimmune VGKC-complex antibody-related syndrome was retrospectively determined using a modified version of previously published guidelines^{10 11} (tables 1 and 2).

SEROLOGY

Serum VGKC-complex antibodies were tested using a radioimmunoprecipitation assay.³ Cell-based assays for CASPR2, LGI1 and contactin 2 antibodies were performed using human embryonic kidney cells transfected with cDNAs encoding the relevant proteins.⁹

RESULTS

An initial audit of 44 VGKC-complex antibody-positive patients demonstrated that 32 had values < 400 pM, of whom 90% were not considered to be autoimmune, whereas 9 of the 12 with higher levels were considered to have an immunotherapy-responsive autoimmune disease. To study this more formally we collected all results from 2008 to January 2012 inclusive.

During this time, the serum of 1053 subjects was tested for VGKC-complex antibodies of whom 55 subjects (5.5%) had one or more positive levels (> 100 pM). Thirty-two subjects were only ever low positive; and the remaining 23 had high-positive levels at presentation or on subsequent sampling. A summary of clinical presentation, VGKC-complex, LGI1 and CASPR2 antibodies and treatment responses (where available) in the low- and high-positive groups are given in tables 1 and 2, ordered according to the likelihood of an autoimmune condition.

Low-positive patients

Thirty-two subjects, assessed in general neurology, specialist cognitive disorders, neuromuscular and movement disorder services, only ever had low positive levels (100–400 pM; mean age 52 (SD 18.8), male:female ratio 0.9:1). Many of these subjects had symptoms for many months (median 24, range 1–132 months) at the time the antibodies were first measured. They were followed up for a median of 23.5 (0–48) months. Four had more than one VGKC-complex antibody measured, and in three the subsequent samples were within the normal range (< 100 pM).

Only four of these patients (13%) were considered to have a definite or probable autoimmune disease (one with a paraneoplastic cerebellar syndrome, one with acquired neuromyotonia and two with Morvan's syndrome). The latter two patients were given immunotherapies, although only one (a patient with Morvan's and a prior thymoma resection) showed a significant improvement (reduction in modified Rankin score from 5 to 3). The remaining 28 patients had a variety of peripheral (n=3), central (n=17) or psychiatric (n=4) disorders; no definite diagnosis was made in four patients (see table 1). Although 13 individuals were retrospectively categorised on the basis of clinical features and investigations as possibly having an autoimmune disorder, none was given immunotherapy. Antibodies directed against LGI1 or CASPR2 antibodies were present in only 3 of the 32 patients (table 1). Two of these had peripheral nerve hyperexcitability, but they were not given immunotherapy.

Three of the 32 patients had a malignancy first detected around the time the antibodies were tested (endometrial cancer in one, breast cancer in two); a further three subjects were screened for malignancy with whole body fluorodeoxyglucose (FDG) PET scanning which was negative in each case.

High-positive patients

Seventeen patients had high levels of VGKC-complex antibodies (> 400 pM) ranging from 401 to 6846 pM when first tested, and a further six individuals initially had low values which rose to high on subsequent sampling. The clinical features are summarised in table 2.

The mean age was 59 (SD 19.4) with a male:female ratio of 1.3:1, and median time from symptom onset to VGKC-complex measurement of 30 months (range 0.5–206). On the basis of the clinical syndrome and/or response to immunotherapies, 11 (including one individual fulfilling criteria for paraneoplastic disease) were retrospectively classified as having a definite autoimmune condition. Ten individuals had limbic encephalitis, of whom six of eight tested had LGI1 (5) or contactin-2 (1) antibodies. These 10 patients were treated with immunotherapies and showed a good response to treatment. Nine of the remainder were retrospectively assessed as possibly having an autoimmune condition but were not given immunotherapies. Two other individuals had a neurodegenerative condition, and one had hepatic toxicity.

Overall, the suggested autoimmune categories (figure 1) were related to the antibody titre (figure 2A; $p=0.013$, Fisher's exact test). It was noted that the median time from symptom onset to antibody testing was six months (range 0.5–120) in those patients considered to have a definite VGKC-complex-related disease compared with 28 months (range 0.5–206) in those classified as possible or unlikely (figure 2B; $p=0.04$, Kruskal–Wallis test).

DISCUSSION

In this unselected retrospective series of adults seen in a tertiary neurology setting, 5.5% of patients showed a positive VGKC-complex antibody result. While the range of conditions in which antibody testing was requested, was inevitably subject to referral bias and may not be entirely representative of the patients seen in a less specialised setting, when we considered retrospectively the likelihood of an autoimmune basis for the disorders,¹⁰ high positive values were more common in conditions well described in the context of VGKC-complex antibodies, such as limbic encephalitis, whereas low positive values were more likely to have an alternative, non-autoimmune or unclear diagnosis. The results confirm that high titres of VGKC antibodies are very likely to be clinically relevant, particularly when tested within a few months of onset, whereas values < 400 pM should be interpreted with care. Nevertheless, the relatively high number (4/32, 13%) of low-positive cases with tumours suggests that low-positive VGKC-complex antibody levels may be an onconeural marker in some situations.^{11–13}

Many of the 'high-positive' patients had limbic encephalitis or related syndromes (relapsing encephalopathy, seizures), although one subject had an alternative autoantibody (anti-glutamate decarboxylase (GAD)) that was consistent with their neurological presentation of Stiff Person Syndrome. Although the patients with limbic encephalitis were treated with good responses, neurologists had exercised their clinical judgement in not trying immunotherapy for most of the related syndromes, which, therefore, were defined as 'possible' autoimmune. By contrast, the 'low-positive' patients had many more neurodegenerative diagnoses, atypical presentations or uncertain diagnoses,

Table 1 Clinical features in patients with VGKC-complex antibodies <400 pM

Subject	Highest VGKC levels; other specific antibody if found*	Physician's diagnosis/duration of follow-up	CSF (cerebrospinal fluid)	Response to immunotherapies	VGKC-complex related syndrome
M, 57	398	Morvan's syndrome/34 months	2 WC; Pro N	Yes	Definite
M, 72	168	Morvan's syndrome and CIDP/36 months; Thymoma	NT	Yes	Definite
F, 71	124, NT	Autoimmune/paraneoplastic cerebellar syndrome; Endometrial carcinoma	1 WC, Pro 0.64, cytology, culture negative	No	Paraneoplastic
F, 67	301/LGI1	Neuromyotonia/9 months	NT	Not tried	Definite
F, 69	144, NMDAR low, GlyR	Amnesia/23 months	Acellular, Pro N, cytology -ve	Not tried	Possible
F, 64	170	None made/28 months	Acellular, Pro 0.7, OCB +ve serum and CSF	Not tried	Possible
M, 25	173	Brainstem migraine/6 months	<1 WC, 16 RC, Pro 0.43, Culture -ve	Not tried	Possible
F, 22	316	Idiopathic generalised epilepsy/9 months	46 WC, (lymph); 4 RC, Pro 0.46, Culture -ve; OCB +ve CSF only	Not tried	Possible
M, 86	358/LGI1 and CASPR2	Idiopathic Parkinson's disease/3 months	NT	Not tried	Possible
F 40	391	Myoclonic jerks of undetermined aetiology/7 months	NT	Not tried	Possible
M 48	201	Infective encephalopathy improvement with antibiotics/24 months	7 WC (lymph); 0 RC, Pro N, Culture -ve	Not tried	Possible
M, 18	117/LGI1 and CASPR2	Nerve hyperexcitability syndrome/18 months	NT	Not tried	Possible
M, 55	100	Length dependent sensory axonal neuropathy/13 months	NT	Not tried	Possible
F, 38	149	Suspected muscle channel disease/44 months	NT	Not tried	Possible
F, 43	212	Dystonia of undetermined aetiology/40 months, Breast cancer	WC<1, RC 1200, OCB +ve in CSF and serum, Pro 0.7	Not tried	Possible paraneoplastic
F, 42	138	Functional movement disorder/51 months, Breast cancer	Acellular, Pro N, OCB -ve	Not tried	Possible Paraneoplastic
F, 23	186	None made, spontaneous improvement/6 months	Acellular; Pro N; OCB -ve	Not tried	Possible
M, 64	143	Multi-system atrophy/60 months	<1WC, 8 RC, OCB -ve, cytology -ve	IVIG, no improvement	Unlikely
F, 61	183	Alzheimer's disease/34 months	NT	Not tried	Unlikely
F, 75	221	Lewy Body Dementia/8 months	Acellular, Pro N	Not tried	Unlikely
M, 75	130	Embolic stroke secondary to atrial fibrillation/6 months	32 RC, <1 WC, Pro N	Not tried	Unlikely
M, 74	106	Alzheimer's disease/12 months	Acellular, Pro N	Not tried	Unlikely
M, 54	118	Motor Neurone disease/24 months	NT	Not tried	Unlikely
F, 57	119	Lewy Body dementia/vascular dementia/24 months	NT	Not tried	Unlikely
M, 70	162	Depression/12 months	NT	Not tried	Unlikely
F, 18	352	Allgrove syndrome/7 months	Acellular; Pro N	Not tried	Unlikely
M, 62	126	Alcohol withdrawal	NT	Not tried	Unlikely
F, 60	108	Anxiety disorder	NT	Not tried	Undetermined
M, 37	118	Psychological disorder	NT	Not tried	Undetermined
F, 34	119	None made	NT	Not tried	Undetermined
F, 62	124	None made	NT	Not tried	Undetermined
M, 38	103	None made	NT	Not tried	Undetermined

*All available samples were tested for LGI1 and CASPR2; most were not tested for contactin-2. Likelihood of VGKC-complex antibody being related to autoimmunity was determined based on previously published guidelines^{10 11} modified as follows: definite: recognised neurological syndrome and treatment with immunotherapy successful; possible: recognised or possible neurological syndrome and immunotherapy unsuccessful or untried; unlikely: unrelated clinical syndrome and more likely alternative diagnosis; undetermined: unrelated clinical syndrome and no likely relevance. Some samples were not available for retesting (NA).

CIDP, chronic idiopathic demyelinating polyneuropathy; LGI1, leucine-rich glioma-inactivated 1; NMDAR, methyl-D-aspartate; N, normal; NT, not tested; OCB, oligoclonal bands; Lymph, lymphocytes; Pro, protein (normal range < 0.65 g/l); RC, red cells; VGKC, voltage-gated potassium channel; WC, white cells.

and only 12% were considered to have a definite autoimmune condition, and only four were given immunotherapy. Importantly, no patient with a VGKC-complex level <400 pM had limbic encephalitis or epilepsy of unknown aetiology, although such patients have been identified elsewhere,⁶ and low-

positive VGKC levels have been associated with classical autoimmune syndromes in a few children.^{14 15}

As so many of the low-positive cohorts had unrelated or alternative diagnoses, these data provide strong evidence that considerably less weight should be put on a low- rather than a

Table 2 Clinical features in patients with VGKC-complex antibodies >400 pM

Subject	Highest VGKC levels/ specific antibody if found*	Physician's diagnosis/duration of follow-up	CSF	Response to immunotherapies	Autoimmune likelihood
M, 61	453, LGI1	Limbic encephalitis/60 months	NA	Yes	Definite
F, 62	751, LGI1	Limbic encephalitis	Acellular; Pro N; OCB -ve	Yes	Definite
M, 54	1032, LGI1	Limbic encephalitis/24 months	Acellular, Pro N	Yes	Definite
F, 83	1555, LGI1	Limbic encephalitis/31 months	NT	Yes	Definite
M, 70	6846, LGI1	Limbic encephalitis/20 months	NA	Yes	Definite
M, 74	1098, Contactin2	Possible limbic encephalitis/36 months	5 WC (lymph); Pro 0.55 matched OCB	Yes	Definite
M, 68	5067	Limbic encephalitis/38 months	Acellular; Pro N; matched OCB	Yes	Definite
M 56	555	Limbic encephalitis/63 months	WC<1, RC 8, Pro N, matched OCB	Yes	Definite
F, 74	2208, NT	Limbic encephalitis/52 months	NT	Yes	Definite
M, 73	555, NT	Limbic encephalitis/6 months	Acellular; Pro 0.83, OCB -ve	Yes	Definite
M, 72	857	Paraneoplastic syndrome; bladder cancer	Acellular; Pro 1.59; OCB -ve	Not tried	Paraneoplastic
F, 52	454	Neuromyotonia associated with VGKC antibodies/ 38 months	NT	Not tried	Possible
M, 40	552	Stiff person syndrome/30 months, GAD Ab positive	1 WC; 2 RC, Pro N	Yes, partial	Possible
F, 44	1652	Cognitive and cerebellar syndrome/50 months	WC 3; RC 1200; Pro N; OCB +ve CSF and serum	Equivocal	Possible
F, 67	548	Choreiform movement disorder of undetermined aetiology/39 months	WC<1; RC 72; Pro 0.49	Not tried	Possible
M, 38	569	Possible mitochondrial disease, possible acquired neuromyotonia, possible periodic paralysis/ 36 months	NT	Not tried	Possible
F, 25	1084	Intractable childhood onset focal epilepsy of undetermined aetiology/13 months	NT	Not tried	Possible
M, 22	1477	Asperger's syndrome + elevated VGKC of undetermined aetiology/60 months	Acellular; Pro N, OCB -ve.	Not tried	Possible
M, 30	4893	Intractable epilepsy aetiology undetermined/ 6 months	NT	Not tried	Possible
M, 60	448	Possible periodic paralysis	NT	Not tried	Possible
M, 58	987, NT	Hepatic encephalopathy (evidence of liver failure and raised ammonia)/1 month	NT	Not tried	Unlikely
M, 69	868	Frontotemporal lobar degeneration/20 months	Acellular; Pro N; OCB -ve	Not tried	Unlikely
F, 80	969	Lewy body dementia/7 months	Acellular, Pro N, OCB +ve CSF and serum	Not tried	Unlikely

See footnote to table 1.

*120; low-grade peripheral nervous system symptoms for 120 months, with new symptoms developing 6 months before the diagnosis of cancer.
GAD, glutamate decarboxylase; NT, not tested; OCB, oligoclonal bands; RC, red cells; VGKC, voltage-gated potassium channel; WC, white cells.

high-positive antibody level. An exception to this is in the context of peripheral nerve hyperexcitability consistent with neuromyotonia, where VGKC-complex antibodies at low levels are common¹ and do not necessarily show binding to LGI1 or CASPR2 (Vincent, M Kiernan, O Watanabe, unpublished data).

Thus, we suggest that low-positive VGKC-complex antibodies may be secondary to other disease pathologies, and it is possible that they are part of a normal repertoire of autoantibodies found in otherwise healthy individuals, which can, under certain circumstances, rise to detectable levels. It is notable that a significant proportion of the low-positive cohorts was diagnosed with a neurodegenerative disorder and in one case with a genetically defined disease, Allgrove syndrome.¹⁶ In keeping with recent reports that VGKC levels can occasionally be elevated in cases of Creutzfeldt Jacob disease,¹⁷ these cases demonstrate that elevated antibodies can be found in degenerative neurological diseases, when their presence is unlikely to be clinically relevant.

The number of subjects (3/32, 9.4%) who were positive for LGI1 or CASPR2 in the low-positive VGKC cohort was significantly lower than that (6/20, 30%) of the unselected high-positive subjects (χ^2 4.5, $p=0.034$) and that (6/8, 75%) of the limbic encephalitis subjects tested. However, two patients with a definite clinical diagnosis of autoimmune limbic encephalitis were not positive for LGI1 or CASPR2 antibodies, suggesting that there are other antibody targets within the VGKC complex as suggested previously⁹ and by others.¹⁸ Those with high-positive VGKC-complex and LGI1 antibodies all had limbic encephalitis, confirming that LGI1 antibodies are common in this condition.⁷

A relatively high proportion (three cases, 10%) of patients with low-positive antibodies had tumours (three with breast cancer, one with endometrial carcinoma) and one further subject had a thymoma that was resected before he presented. This is significantly higher than the expected incidence within the general

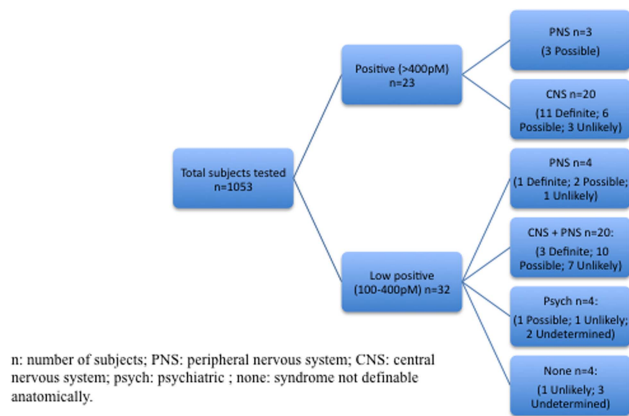


Figure 1 Summary of all patients tested for voltage-gated potassium channel antibodies, their diagnostic classification and autoimmune probability.

population (0.004% per annum age in the 40–59 age range; 0.014% per annum in the 60–74 age range, <http://www.cancerresearchuk.org/cancer-info/cancerstats>) and very similar to another recent study.¹⁸ While the long duration of neurological symptoms without overt evidence of malignancy in a significant proportion of cases is reassuring, and screening for malignancy may well have been prompted by other factors, the prevalence of underlying malignancy in the low-positive group as a whole is unknown and should be the focus of further study.¹³

Recently, Klein *et al*¹⁸ reported the clinical presentations of a larger group of VGKC-complex positive patients showing that a small proportion of low-positive VGKC-complex patients are also positive for LGI1 or CASPR2. Although clinical follow-up of these cases was limited, they suggest that these are more likely to be of clinical relevance. Our findings are broadly compatible with their findings; patients with lower antibody titres were less likely to have a specific antigenic target or to have a probable autoimmune condition, except those with LGI1 or CASPR2 antibodies and/or with hyperexcitability syndromes. However, one patient with idiopathic Parkinson's disease and VGKC antibodies at 358 pM was positive for LGI1 and CASPR2 antibodies but was not considered by the treating neurologist to have a definite autoimmune diagnosis and was not treated as such.

It is not clear why high antibody titres are more associated with central nervous system disorders, often without peripheral dysfunction, while low antibody titres cluster more with peripheral hyperexcitability. Certainly very high VGKC/LGI1 antibodies are associated with limbic encephalitis,^{7 9} as shown here, but lower levels of both can be found in peripheral nerve hyperexcitability. Such examples serve to illustrate that antibody results need always to be interpreted in the clinical context, and that our understanding of the pathophysiological underpinnings of many of these syndromes is still incomplete. Nevertheless, the broad rule of thumb that low-positive titres—particularly without a specific antigenic target—are less likely to be relevant is of potential clinical utility.

In conclusion, in this retrospective series, high-positive VGKC antibodies strongly predicted an autoimmune or possibly autoimmune aetiology, suggesting that the cut-off that we use for a high-positive antibody level (>400 pM) has clinical utility, at least for adults. By contrast, the majority of patients with low-positive VGKC-complex antibodies did not have an identifiable antigenic target, or a syndrome thought to be related to the

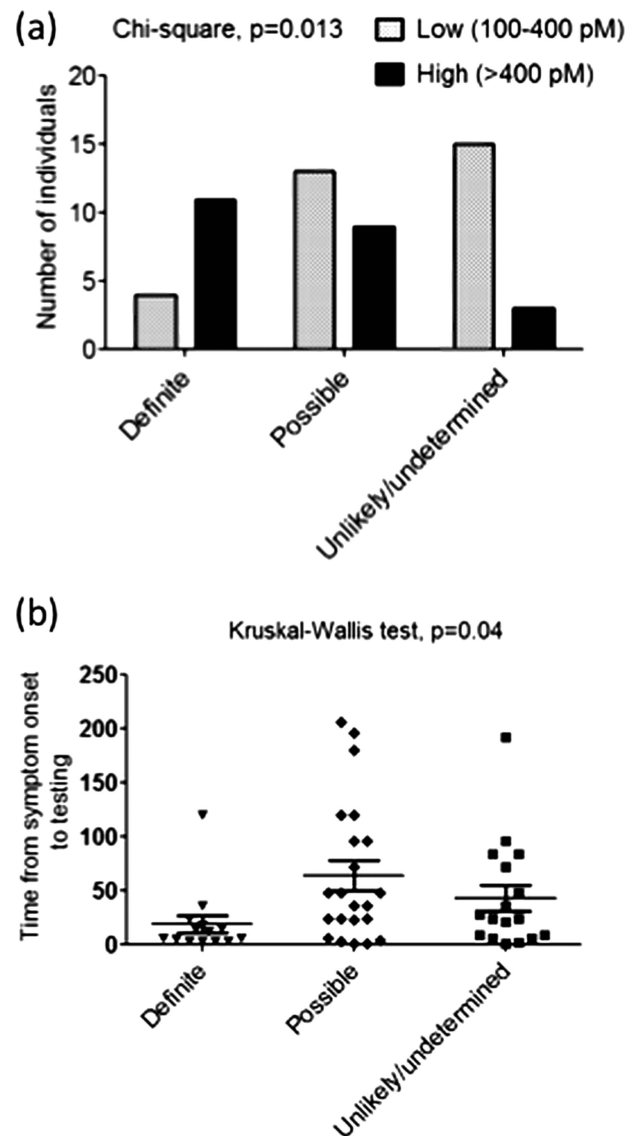


Figure 2 (A) The number of patients in each of the given categories divided between high and low voltage-gated potassium channel-complex antibodies ($p=0.004$, χ^2 , analysed on GraphPad Prism). (B) The duration of symptoms at sampling in patients divided between definite, possible and unlikely or undetermined categories. One-way ANOVA, $p=0.04$.

presence of the antibodies; in many patients, a definite alternative diagnosis was reached, and the result rarely altered management. In some cases, however, low-positive VGKC-complex antibodies may reflect a broader autoimmune tendency. The possibility of an occult—perhaps unrelated—neoplasm should always be considered in individuals with a definite or possible autoimmune syndrome. While our data suggest a possible increased risk of an occult tumour in individuals with isolated low-positive antibodies, irrespective of the clinical syndrome, in most patients, these antibodies are not markers of paraneoplasia and further studies are required to demonstrate whether and which occult tumours should be actively sought. These data suggest that, particularly in the absence of a specific antigenic target or a phenotype associated with VGKC-complex antibodies (eg, limbic encephalitis, faciobrachial dystonic seizures, neuromyotonia), low positive antibodies should be interpreted with care. In case of doubt antibody levels should be rechecked after an interval to ensure they are not rising.

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Contributors The study was initiated by AV with RWP, MSZ and RA. The medical records were searched and data were compiled by RWP, MSZ and RA. JMS and AV reviewed the findings and the data presentation. The final manuscript was written by RWP, AV and JMS.

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Competing interests AV and the University of Oxford hold patents and receive royalties and payments for antibody tests. JMS is a HEFCE Clinical Senior Lecturer and receives funding from Alzheimer's Research UK and the Alzheimer's Society. RWP, MSZ and RA have no competing interests.

Ethics approval AV received approval from Oxfordshire REC A (07/Q1604/28 Immune factors in neurological diseases) for the study of any patients whose samples were referred for testing. This work was submitted to the UCL/UCLH Joint Research Office who confirmed its classification as Service Evaluation rather than research according to NHS Health Research Authority guidance, and accordingly that review by a Research Ethics Committee was not required (<http://www.nres.nhs.uk/applications/is-your-project-research/>).

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