Clinical utility of seropositive voltage-gated potassium channel–complex antibody

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Abstract

Background: Antibodies against voltage-gated potassium channel (VGKC)–complex are implicated in the pathogenesis of acquired neuromyotonia, limbic encephalitis, faciobrachial dystonic seizure, and Morvan syndrome. Outside these entities, the clinical value of VGKC–complex antibodies remains unclear. **Methods:** We conducted a single-center review of patients positive for VGKC–complex antibodies over an 8-year period. **Results:** Among 114 patients positive for VGKC–complex antibody, 11 (9.6%) carrying the diagnosis of limbic encephalitis ($n = 9$) or neuromyotonia ($n = 2$) constituted the classic group, and the remaining 103 cases of various neurologic and non-neurologic disorders comprised the nonclassic group. The median titer for the classic group was higher than the nonclassic group ($p < 0.0001$). A total of 90.9% of the patients in the classic and 21.4% in the nonclassic group possessed high (>0.25 nM) VGKC–complex antibody levels ($p < 0.0001$). A total of 75.0% of the patients in the high-level group had definite or probable autoimmune basis, while non-autoimmune disorders were seen in 75.6% of patients from the low-level group ($p < 0.0001$). A total of 26.3% of patients were found with active or remote solid organ or hematologic malignancy, but no antibody titer difference was observed among subgroups of absent, active, or remote malignancy. Compared to age-matched US national census, rates of active cancer in our cohort were higher in patients older than 45 years. **Conclusions:** High VGKC–complex antibody titers are more likely found in patients with classically associated syndromes and other autoimmune conditions. Low-level VGKC–complex antibodies can be detected in non-specific and mostly nonautoimmune disorders. The presence of VGKC–complex antibody, rather than its level, may serve as a marker of malignancy. *Neurol Clin Pract* 2016;6:409–418

Antibodies against voltage-gated potassium channel (VGKC)–complex were first identified in the peripheral nerve hyperexcitability disorder neuromyotonia, and subsequently in patients with Morvan syndrome, limbic encephalitis (LE), and faciobrachial dystonic seizure.^{1–4} These diagnoses, constituting the classic

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VGKC-complex antibody-mediated neurologic syndromes, were recently shown to be associated with antibodies targeting specific proteins that form complexes with VGKC, primarily leucine-rich glioma inactivated 1 protein (LGI1), contactin-associated protein 2 (CASPR2), and contactin-2.^{4,5} In the last decade, VGKC-complex antibodies have been detected in an expanding spectrum of neurologic disorders, including autonomic dysfunction, chronic epilepsy, peripheral neuropathy, motor neuron disease, dementia, and depression.^{6–10} However, the clinical value of VGKC-complex antibodies in this group of disorders is less clear.

In this study, we sought to analyze the clinical presentation, neurologic diagnoses, and coexisting autoimmune and neoplastic entities in a large cohort of patients positive for VGKC-complex antibody from our center.

METHODS

Standard protocol approvals, registrations, and patient consents

The study was approved by the Cleveland Clinic Institutional Review Board. Requirement for informed consent was waived because of the retrospective design.

Study population

Electronic medical records for over half a million patients evaluated at the Cleveland Clinic Neurologic Institute from 2005 to 2013 were queried to identify patients tested for the presence of serologic antineuronal antibodies using an autoantibody panel commercially performed by Mayo Medical Laboratories (Rochester, MN). Details of included antibodies and detection methods can be found at <http://www.mayomedicallaboratories.com/test-catalog/Performance/83380>. VGKC-complex antibody testing was performed using a radioimmunoassay as previously described.⁸ The upper limit of normal range for the antibody was set at 0.02 nM per the Mayo Medical Laboratory.⁸

Antibody panel ordering was at the discretion of treating neurologists based on patients' clinical features, without predetermined clinical criteria. A comprehensive retrospective review of patients positive for VGKC-complex antibodies was performed. Data extracted included clinical presentation, treatment response, and coexisting malignancy or autoimmune condition.

Determination of autoimmune basis of disease

The probability that a clinical condition was due to an underlying autoimmune process was determined based on previously published criteria.⁹ The designation of definite autoimmunity included patients with a recognized immune-mediated syndrome who underwent successful immunomodulatory treatment. Possible autoimmunity referred to patients who presented with recognized or possible immune-mediated syndrome but immunotherapy was untried or unsuccessful. The unlikely subgroup referred to those with non-immune-mediated syndrome such as degenerative disorders or clearly unrelated alternative diagnoses such as slowly progressive dementia, syncope, or toxic or metabolic neuropathy. The undetermined subgroup included cases whose diagnosis remained unclear despite a thorough or incomplete workup.

Statistical analysis

Data were presented as median and range for continuous variables and percentage for categorical variables. For comparison of categorical variables, χ^2 test or Fisher exact test when the expected count for any contingency table cell fell below 5 were used. For continuous variables, Wilcoxon rank sum test was used for comparison of 2 groups and Kruskal-Wallis test for 3 or more groups. Cancer incidence was compared to data derived from a national age-matched United States census from 2010 using odds ratio (OR) with 95% confidence interval (CI) analyses.^{11,12} Factors associated with a positive response to immunosuppressive treatment were evaluated using univariate logistic regression analysis. All analyses were done with the statistical software package R (<https://www.r-project.org>). A *p* value of 0.05 was established as being significant.

RESULTS

Of 6,032 patients who underwent serum antineuronal antibody evaluation, 114 (1.9%) tested positive for VGKC-complex antibodies. Mean age at symptom onset was 56.5 years, and 61% of the patients were female. Eleven patients were diagnosed with LE ($n = 9$) or neuromyotonia ($n = 2$) and collectively labeled classic VGKC-complex antibody-mediated disease group. Clinical features of LE and neuromyotonia were in keeping with original reports.^{13,14} No cases of faciobrachial dystonic seizure or Morvan syndrome were encountered. The remaining 103 cases were classified as the nonclassic group. Testing for VGKC-complex antibody was performed once in 83 patients and 2–5 times in the remaining 31. For consistency, the highest VGKC-complex antibody titer for each patient was used for analysis. Analysis using the first antibody titer generated similar results (data not shown).

Table 1 shows the distribution of VGKC-complex antibody titers in classic and nonclassic groups, arranged by titer ranges of 0.03–0.09, 0.10–0.19, 0.20–0.24, 0.25–0.29, 0.30–0.39, and ≥ 0.40 nM. Due to the skewed distribution of antibody titers, median instead of mean values were used for group comparisons. The median VGKC-complex antibody titer was 0.74 nM for the classic group and 0.12 nM for the nonclassic group ($p < 0.0001$). Ten of 11 (90.9%) patients in the classic group and 22 of 103 (21.4%) in the nonclassic group possessed VGKC-complex antibody level of ≥ 0.25 nM ($p < 0.0001$). Additionally, 6 of 11 (54.4%) patients in the classic and 15 of 103 (14.5%) in the nonclassic group possessed antibody levels of ≥ 0.4 nM ($p < 0.005$).

The sensitivity and specificity of various VGKC-complex antibody titer cutoffs in diagnosing LE and neuromyotonia were calculated (table 2). A cutoff value of ≥ 0.25 nM maximized the sensitivity (90.9%) while maintaining a reasonably high specificity (78.6%). Raising the cutoff level to 0.3 nM would increase the specificity slightly to 81.6% but reduce the sensitivity to 63.6%. Lowering the cutoff level at 0.2 nM would keep the sensitivity at 90.9% but significantly reduce the specificity to 68.0%.

Table 3 lists the chief neurologic diagnosis or syndrome recorded in the nonclassic group. Various peripheral nervous system (PNS) or CNS disorders were encountered, ranging from peripheral neuropathy, dementia, and amyotrophic lateral sclerosis (ALS) to Creutzfeldt-Jakob disease (CJD). Overall, there were more PNS (55.3%) than CNS disorders (19.4%). In 8 patients with nonspecific symptoms including stuttering speech, nausea/vomiting, or orthostatic lightheadedness, evidence of neurologic disorders was not found after workup was completed.

Table 4 lists cancerous and immunologic disorders observed in the entire cohort. Malignancy workup including CT or whole body fluorodeoxyglucose PET scanning was completed in 81 (71.1%) patients. Thirty (26.3%) patients carried a diagnosis of active ($n = 20$, 17.5%) or remote ($n = 10$, 8.8%) solid organ or hematologic malignancy, with details of cancer types listed in table 4.

Incidences of malignancy for the classic and nonclassic group were 45.4% and 24.3%, respectively ($p = 0.15$). In 28 cases, a cancer diagnosis was already established prior to VGKC-complex antibody testing. Finding of positive VGKC-complex antibodies ultimately led to the discovery of previously unknown cancer in 2 patients (lung cancer; ovarian cancer). In 10 cases of remote cancer, a mean duration of 14.5 years lapsed between cancer diagnosis and antibody detection. The median VGKC-complex antibody titers for the active cancer, remote cancer, and noncancerous subgroups were 0.19 (range 0.06–15.8), 0.22 (range 0.03–7.35), and 0.13 (range 0.03–8.99) nM, respectively ($p = 0.47$).

Compared to an age-matched US national census in 2010, cancer rates in our cohort were higher in individuals aged 45–64 years (OR 26.1, 95% CI 9.0–62.9, $p < 0.001$) and ≥ 65 years (OR 14.8, 95% CI 7.3–28.1, $p < 0.001$). Analysis of the group aged younger than 45 years resulted in an OR of 36.2 for increased cancer incidence with 95% CI 0.89–215.6 (table e-1 at Neurology.org/cp).

Two patients (18.2%) in the classic and 32 patients (31.1%) in the nonclassic group carried coexisting neurologic or systemic autoimmune disorders as listed in table 4 ($p = 0.50$).

Supplemental Data

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Table 1 Difference in antibody titer ranges between the classic voltage-gated potassium channel (VGKC)-complex antibody-mediated disease group and the nonclassic group

	All patients (n = 114)	Classic VGKC-mediated disease group (n = 11)	Nonclassic group (n = 103)
Minimal/maximal range, nM	0.03-15.8	0.09-15.8	0.03-8.99
0.03-0.09	42	1	41
0.10-0.19	29	0	29
0.20-0.29			
0.20-0.24	11	0	11
0.25-0.29	6	3	3
0.30-0.39	5	1	4
≥0.40	21	6	15

The arbitrarily defined range of 0.2-0.29 nM was divided into 2 equal subgroups (0.2-0.24 and 0.25-0.29 nM) as all 3 cases from the classic group within the 0.2-0.29 nM range had titers ≥0.25 nM.

Immunomodulatory treatment was administered in 41 patients. Treatment included corticosteroid, azathioprine, mycophenolate, cyclophosphamide, IV immunoglobulin, or plasmapheresis. Nine of 11 patients (81.8%) in the classic group received immunotherapy and all improved. In comparison, 12 of 32 patients (37.5%) in the nonclassic group improved upon immunomodulatory treatment. In the nonclassic group, none of the following factors were predictive of good response to immunomodulatory treatment: age, sex, disease duration, VGKC antibody titer, presence of autoimmune condition, or cancer status.

Using previously published criteria, the probability of an underlying autoimmunity was determined in each case.⁹ Results were classified according to VGKC-complex antibody levels and are listed in table 5. Most patients (75.0%) with high (≥0.25 nM) VGKC-complex antibody titers had a definite or probable autoimmune basis, while a nonautoimmune mechanism was encountered in 75.6% of patients in the low titer group ($p < 0.0001$).

In 14 patients, one or more positive antineuronal antibodies from the same panel were detected, with 11 cases belonging to the nonclassic group. These included striational smooth muscle antibody (n = 5), voltage-gated calcium channel antibody (n = 4), muscle type acetylcholine receptor antibody (n = 3), ganglionic acetylcholine receptor antibody (n = 2), and glutamic acid decarboxylase antibody (n = 1).

DISCUSSION

Our data provide insight into the clinical significance of VGKC-complex autoantibody positivity: high titers (≥0.25 nM) are more likely associated with classic syndromes such as LE or

Table 2 Sensitivity and specificity of voltage-gated potassium channel (VGKC)-complex antibody detection in diagnosing classic VGKC-complex-mediated syndrome

Ab cutoff, nM	Sensitivity, %	Specificity, %
≥0.1	90.9	39.8
≥0.2	90.9	68.0
≥0.25	90.9	78.6
≥0.3	63.6	81.6
≥0.4	54.5	85.4

Table 3 List of major diagnoses or syndromes in the subgroup of 103 patients with nonclassic voltage-gated potassium channel (VGKC)-complex antibody-associated diseases

Neurologic entity or major symptom	No. (%) of patients	No. of patients with VGKC ≥ 0.25 nM
Peripheral nervous system disorder	57 (55.3)	
Small fiber neuropathy	15	3
Large fiber neuropathy	10	5
Postural orthostatic tachycardia syndrome	10	2
Myopathy/myositis	7	2
Amyotrophic lateral sclerosis	6	1
Mononeuropathy or radiculopathy	6	2
Myasthenia gravis	2	
Autonomic disorder	1	
CNS disorder	20 (19.4)	
Delirium/dementia	8	2
Myelopathy	5	1
Prion disease	3	1
Primary progressive aphasia	2	
Optic neuritis	1	1
Progressive multifocal leukoencephalopathy	1	
Other		
Syncope	5	
Vertigo/ataxia	4	1
Gait abnormality	2	
Somatoform disorder	2	
Involuntary movement	1	
Fibromyalgia	1	
Headache	1	
Incomplete workup	2	
Non-neurologic diagnosis	8	1

neuromyotonia; in patients lacking specific syndromes, the presence of high-level VGKC-complex antibody may indicate an altered autoimmunity status; low-level VGKC-complex antibodies can be seen in a variety of nonspecific conditions, and their clinical relevance appears limited; the presence of VGKC-complex antibody, rather than its level, may serve as a marker of remote or active malignancy; and it is important to assess the utility of a positive VGKC-complex antibody result within the overall clinical context.

Higher VGKC-complex antibody levels associated with classic syndromes

The presence of VGKC-complex antibodies is associated with a group of immunotherapy-responsive clinical presentations including LE, faciobrachial dystonic seizure, Morvan syndrome, and acquired neuromyotonia.^{4,5,15} A previous study analyzed 55 patients possessing VGKC-complex antibodies. Among 23 patients with high VGKC-complex antibody levels

Table 4 Clinical (cancerous and immunologic) association characteristics of the 114 patients

Entity	All patients (n = 114)	Classic group (n = 11)	Nonclassic group (n = 103)
Malignancy workup completed	81	9	72
Malignancy, active ^a	20	3	17
Malignancy, in remission ^b	10	2	8
Coexisting neuroinflammatory disease (e.g., ON, MS, MG, sarcoidosis)	4	1	3
Coexisting systemic inflammatory disease (e.g., SLE, RA, SS, UC)	30	1	29
Cases with coexisting inflammatory disease or malignancy	57	6	51

Abbreviations: MG = myasthenia gravis; MS = multiple sclerosis; ON = optic neuritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SS = Sjögren syndrome; UC = ulcerative colitis.

^aCases of active malignancy were of the following types: lung (n = 4), bladder (n = 3), colon (n = 2), skin (n = 2), prostate (n = 2), thymus (n = 1), adrenal gland (n = 1), cervix (n = 1), breast (n = 1), lymphoma (n = 1), ovary (n = 1), testes (n = 1).

^bCases of malignancy in remission were of the following types: breast (n = 4), prostate (n = 2), uterus (n = 2), ovary (n = 1), colon (n = 1).

(≥ 0.4 nM), 10 patients had LE and 1 neuromyotonia. Among 32 patients with low (< 0.4 nM) levels, only 2 cases of Morvan syndrome and 1 case of neuromyotonia were identified.⁹ Another previous study reported that 10 of 12 patients with VGKC-complex antibody ≥ 0.5 nM had LE, while no autoimmune neurologic disease was encountered in the low-level (< 0.5 nM) group.¹⁶ Our group of patients with classic VGKC-complex antibody-mediated syndromes showed a statistically higher median antibody level than the nonclassic group (0.74 vs 0.12 nM), and a high proportion of patients with high-level (≥ 0.25 nM) antibody (90.9% vs 21.4%). Our results further support higher VGKC-complex antibody titer being more relevant in diagnosing specific syndromes such as LE or acquired neuromyotonia. Based on a post hoc analysis using various cutoff titer levels, we defined a high VGKC-complex antibody level as ≥ 0.25 nM, as this threshold provided the optimal combination of sensitivity (90.9%) and specificity (78.6%). Variances in cutoff levels (e.g., 0.25 nM vs 0.4 nM) between ours and prior reports could be secondary to technical differences in antibody detection methods among laboratories. It is worthwhile pointing out that the diagnosis of LE or neuromyotonia is primarily clinical, and that an elevated VGKC-complex antibody above a certain cutoff level is supportive evidence. The overlap of antibody levels between the classic

Table 5 Likelihood of autoimmunity based on voltage-gated potassium channel-complex antibody titer

Range, nM	All patients ^a	Definite ^a	Possible ^a	Unlikely ^a	Undetermined ^a
0.03-0.09	42	3	8	27	4
0.10-0.24	40	6	3	28	3
0.25-0.39	11	4	4	1	2
≥ 0.40	21	8	8	2	3

^aAutoimmune etiology using criteria from Paterson et al.⁹

The VGKC-complex antibodies are not directed against VGKC itself, but may recognize other cell surface antigens that form the VGKC-complex.

and the nonclassic groups confirms the need for sound clinical judgment in such cases (table 2).

Higher VGKC-complex antibody levels associated with autoimmunity

In our study, high-level VGKC-complex antibodies were identified in some patients in the nonclassic group. A previous study analyzed possible association of high-level VGKC-complex antibodies with nonspecific autoimmune diseases. Among their 23 patients with high (≥ 0.4 nM) levels, definite or possible autoimmune disorders were present in 87.0% of patients. Excluding 10 cases of LE and 1 neuromyotonia, 9 of the remaining 12 patients were diagnosed with possible autoimmune disorder, such as stiff-person syndrome, cerebellar syndrome, or intractable epilepsy.⁹ Our results suggest that the presence of high-level VGKC-complex antibodies can be explained on an autoimmune basis owing to the following observations. First, by usage of a classification scheme similar to a previous report, 76.2% of our patients possessing a VGKC antibody titer of ≥ 0.4 nM had definite or possible clinical autoimmunity, comparable to their result of 87.0%.⁹ Second, 32 patients in the nonclassic group had coexisting neuroinflammatory diseases (optic neuritis, multiple sclerosis, myasthenia gravis, sarcoidosis) or systemic inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, ulcerative colitis) (table 4). Finally, when autoimmune status was classified according to VGKC-complex antibody level (table 5), more patients possessing high-level (≥ 0.25 nM) VGKC-complex antibodies had definite or probable autoimmune basis, while a nonautoimmune condition was seen in the majority of patients in the low-level group (table 5). Our observations suggest that VGKC-complex antibodies, when present at high levels in patients lacking specific syndromes, may serve as a nonspecific marker for the presence of neurologic or non-neurologic autoimmunity. A possible active role of VGKC-complex antibody in the pathogenesis of these known autoimmune neurologic and non-neurologic disorders cannot be excluded.

The VGKC-complex antibodies are not directed against VGKC itself, but may recognize other cell surface antigens that form the VGKC-complex. Identifiable antigenic targets include LGI1, CASPR2, and contactin-2 in a subset of patients, while antigenic targets in the majority of cases remain unidentified.^{5,17,18} The antigenic heterogeneity may at least partially explain the clinical nonspecificity demonstrated by VGKC-complex antibodies. One limitation of our analysis was the lack of data on antibody subtyping and antigen identification.

Low VGKC-complex antibody titer

The 103 cases encountered in the nonclassic group can be generally classified into several categories: well-characterized autoimmune neurologic disorders such as multiple sclerosis or myasthenia gravis; well-established neurodegenerative disorders such as ALS, CJD, or dementia; nonspecific neurologic diagnoses or syndromes such as large fiber neuropathy, small fiber neuropathy, or syncope; and non-neurologic diagnoses. A critical analysis to prove/exclude an association between VGKC-complex antibodies and these diagnoses is difficult, as a non-neurologic autoimmunity may coexist in some cases. Another confounder is the possible presence of low VGKC-complex antibody titer in the healthy population. Our observation that patients with low (< 0.25 nM) VGKC-complex antibody values are more likely to have

In our cohort, only 2 patients were discovered to have malignancy as a result of VGKC-complex antibody positivity.

a nonspecific, nonautoimmune, or unclear diagnosis is similar to results from several previous analyses.^{9,10,16} More PNS than CNS disorders were encountered in the nonclassic group.

The cutoff value of antibody positivity from this particular autoantibody panel was set at 0.02 nM.⁸ A low cutoff level of VGKC-complex antibody increased sensitivity to a broader spectrum of potential autoimmunity. However, it also put the antibody specificity and clinical relevance in question. In our cohort, 55 of 82 (67.1%) patients in the lower titer group (<0.25 nM) were considered unlikely to have an autoimmune condition (table 5). In many cases, the reason for serologic request was often nonspecific or nonclarified. Low-level VGKC-complex antibodies may be representative of secondary immunization following neuronal damage in neurodegenerative diseases, but exerting no effect on the disease course. They could reflect an extension of immune-mediated reaction onto the nervous system in patients with predominantly non-neurologic autoimmunity such as connective tissue disorders, ulcerative colitis, or celiac disease (table 4). It is also possible that low-level VGKC-complex antibodies belong to a normal repertoire of autoantibodies found in healthy individuals, as demonstrated by several studies. For example, a 5% occurrence of low-level VGKC-complex antibodies was noted in 164 healthy elderly participants.¹⁹ In another report, 2% of healthy participants demonstrated elevated VGKC-complex antibody titers.²⁰ Low-level VGKC-complex antibodies recognizing CASPR2 were detected in a small percentage of a healthy population.²¹ Therefore, in the absence of a classically associated syndrome, detection of low level VGKC-complex antibodies should be interpreted with caution. In equivocal cases, antibody levels should be retested to ensure they are not progressively elevating.

Tumor association

Our data suggest that, based on a comparison with an age-matched national census, the oncologic association of VGKC-antibody positivity may be age-dependent. Our cohort's ORs (26.1 for 45–64 years and 14.8 for ≥65 years) for increased cancer risk are similar to an OR of 19.0 reported in another study.¹⁰ The association was not clearly established for those aged younger than 45 years. Our cohort's tumor incidence of 26.3% was also higher than the 14% tumor rate associated with cases positive for ganglionic acetylcholine receptor antibody identified from the same study population.²²

Previous analyses reported varying tumor incidences of 10%–47% in VGKC-complex antibody-positive patients.^{8,9,16,17} One study reported the highest tumor incidence of 47% in their report of 72 patients, and detection of VGKC-complex antibodies expedited tumor diagnosis in 18 patients.⁸ The authors recommended that all VGKC-complex antibody-positive patients undergo comprehensive physical examination, CT of chest, abdomen, and pelvis, mammography (in women), and serum assay of prostate-specific antigen (in men).⁸ Another study reported that malignancy was seen in 7 of 32 patients with positive VGKC-complex antibody, but in 5 cases the cancer diagnosis was established more than 5 years before.¹⁶ In our cohort, only 2 patients were discovered to have malignancy as a result of VGKC-complex antibody positivity. In 93.3% of patients, a diagnosis of malignancy was already established, and in nearly half of the cases, a long duration lapsed between the initial cancer diagnosis and antibody detection. These variations in the rates of cancer diagnosis after antibody detection could be due to inherent differences among patient population, timing of antibody testing, method of cancer screening, and duration of clinical follow-up. The relatively high malignancy rate in our cohort and in previous studies could partly be due to

referral bias as clinicians may have a higher tendency for autoantibody testing in patients who have either remote or active cancer.

No difference in antibody levels between noncancer, active, and remote cancer subgroups was detected in our analysis. No cutoff level of VGKC-complex antibodies could be generated to predict cancer occurrence. These results are similar to those of others in which incidence of malignancy did not defer significantly above or below a 0.4 nM cutoff.¹⁰

Most patients with VGKC-complex antibody positivity (73.7%) do not carry a diagnosis of malignancy. Nevertheless, the relatively high malignancy rate in patients with positive VGKC-complex antibodies suggests that VGKC-complex antibody positivity can serve as an oncologic marker, and that the possibility of an occult neoplasm should be considered.

Limitations

Our retrospective analysis may not be entirely representative of patients seen in less specialized settings due to referral bias. Selection bias was present as well given the lack of predefined clinical criteria prompting antibody testing. Another limitation is the fact that none of our antibody-positive cases underwent antibody subtyping to determine the specific antigenic target of the antibody, such as LGI1, CASPR2, or contactin-2. As more specific antibody testing becomes available, an increase in the specificity is likely to follow. Future research should aim to identify further antigenic targets in association with VGKC-complex antibodies with the ultimate goal of devising practice guidelines to gauge their diagnostic and prognostic value in clinical medicine.

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