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ORIGINAL COMMUNICATION

Low specificity of voltage-gated calcium channel antibodies in Lambert–Eaton myasthenic syndrome: a call for caution

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Abstract
As testing for neuronal antibodies become more readily available, the spectrum of conditions potentially associated with these autoantibodies has been widening. Voltage-gated calcium channel antibodies (VGCC-Ab) are no exception to this trend. The significance of an elevated VGCC-Ab titer beyond its original clinicopathological correlate, Lambert–Eaton myasthenic syndrome (LEMS) remains undetermined. We sought to determine the diagnostic significance of an elevated serum VGCC-Ab titer in a large single-center cohort of 100 patients. The majority of patients (58%) with elevated VGCC-Ab levels lacked an inflammatory or autoimmune etiology of their neurologic diagnosis. Only six cases (6%) of LEMS and two cases (2%) of SCLC (without LEMS) were identified. No significant differences in antibody titers were seen between the autoimmune and non-autoimmune groups. These findings support the notions that: (a) elevated VGCC-Ab titers without clinical correlation must be interpreted with caution, and (b) the clinical and electrodiagnostic criteria for LEMS should remain the mainstay in the diagnosis of LEMS.

Keywords Neurological paraneoplastic syndrome · Voltage-gated calcium channel antibody · Lambert–Eaton myasthenic syndrome · Autoimmune encephalitis

Introduction

Voltage-gated calcium channels (VGCCs) are multi-subunit, cytoplasmic membrane-spanning channels that allow the trans-membrane influx of calcium in response to an action potential. Given their vital physiological role, it is no surprise that these channels are expressed in numerous organ systems, including the cardiovascular, endocrine, musculoskeletal, nervous and pulmonary systems, and lung tumors [1].

Several VGCC subtypes have been recognized based on their physiological and pharmacological properties [2]. Only two of these subtypes, the P/Q- and N-types, are of interest in clinical practice. At the neuromuscular junction, the P/Q-VGCC subtype, concentrated at the presynaptic nerve terminal, plays a critical role in the initial cascade of events that lead to the release of acetylcholine into the synaptic cleft. Antibodies against P/Q-type VGCC have been found to be the cause of Lambert–Eaton myasthenic syndrome (LEMS), a neuromuscular junction disorder that is frequently associated with small cell lung carcinoma (SCLC) [1–3]. Antibodies directed against the N-type VGCC are also associated with LEMS, but are less frequently implicated than those directed against the P/Q-type [1, 2].

VGCC antibodies (VGCC-Ab) have been reported to be highly sensitive (91%) and specific (100%) for the diagnosis of LEMS and only 1–4% of patients with SCLC without neurological dysfunction harbor these antibodies [2, 4]. In this retrospective analysis, we evaluated the clinical

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significance of elevated VGCC-Ab levels found in a group of 100 patients treated at our institution.

Materials and methods

Study population

The Cleveland Clinic Health System electronic medical records were queried for paraneoplastic antibody panels from 2005 to 2013. Serum paraneoplastic antibody panels were ordered on 6032 patients who were evaluated at the Cleveland Clinic neurology department. Serological antibody tests were ordered at the discretion of patients' neurologists on the basis of history, neurological examination, and other test results. Antibody testing was performed by a reference laboratory, Mayo Medical Laboratories (Rochester, MN, USA). The Institutional Review Board of the Cleveland Clinic approved this study.

The diagnosis of LEMS was based on clinical signs and symptoms as well as electrodiagnostic studies according to the published criteria [4].

Voltage-gated calcium channel antibody testing

Titers of P/Q-type and N-type VGCC-Ab were obtained as part of the serum paraneoplastic antibody panels described above. Specifically, titers of VGCC-Ab were measured using radioimmunoprecipitation assay. The established normal reference range for both P/Q-type and N-type VGCC-Ab is 0.00–0.02 nmol/L [1].

Determination of neurological autoimmunity

Medical records of patients with elevated VGCC-Ab titers (titers > 0.02 nmol/L) were systematically reviewed.

Patients with elevated VGCC-Ab titers were subdivided into two groups. The first group, labeled the "inflammatory group", comprised patients with a suspected autoimmune neurological condition, such as LEMS, paraneoplastic cerebellar degeneration, encephalitis, dysautonomia, or inflammatory neuropathy. These conditions have been reported to be associated with elevated VGCC-Ab levels. In addition, we included patients with neurological autoimmune disorders such as multiple sclerosis or optic neuritis. The second or "non-inflammatory group" consisted of patients with neurological disorders without established autoimmune or inflammatory etiology, e.g., neurodegenerative disorders.

Statistics

Statistical tests, including descriptive statistics, Mann–Whitney *U* test, and Fisher's exact test were performed using SPSS version 21 (IBM, Armonk, NY, USA). *P* values less than 0.05 were considered statistically significant.

Results

Patient characteristics

Of 6032 patients tested, 100 patients (1.65%) were found to have elevated VGCC-Ab titers. Fifty (50%) patients were female and the median age was 56 years. Sixty-five patients had elevated P/Q-type VGCC-Ab, 45 had elevated N-type VGCC-Ab, and 10 patients had elevation of both. In addition to elevated VGCC-Ab, 21 patients were found to have other antibodies associated with neurological disorders such as antibodies to ganglionic nicotinic acetylcholine receptor (gAChR), voltage-gated potassium channel (VGKC), or glutamic acid decarboxylase.

Forty-two patients fell into the inflammatory group (group 1), and the remaining 58 patients into the non-inflammatory group (group 2). Neither the antibody titers nor the proportion of patients positive for either VGCC-Ab subtype differed between the inflammatory and non-inflammatory groups. Patient characteristics and antibody titers of both groups are shown in Table 1.

Neurological conditions associated with elevated VGCC-Ab levels

Table 2 lists the neurological diagnoses found in patients with elevated VGCC-Ab levels.

VGCC-Ab titers in patients with LEMS

There were six cases of clinically and electrodiagnostically confirmed LEMS, per definition all in the inflammatory group. Five of these patients had elevated P/Q-type VGCC-Ab titers (0.20, 0.23, 3.62, 5.01 and 11.4 nmol/L; median 3.62 nmol/L), two had elevated N-type-VGCC Ab titers (0.14 and 0.32 nmol/L, median 0.23 nmol/L), and onepatient had elevated titers of both VGCC-Ab subtypes.

An attempt was made to determine a cutoff value for P/Q-type and N-type VGCC-Ab titers that maximizes both sensitivity and specificity. Due to the low number of LEMS cases and the scattered antibody distribution, we were not able to establish a reasonable cutoff value to differentiate LEMS from non-LEMS cases.

One (16.7%) patient with LEMS had lung cancer with a P/Q-type VGCC-Ab titer of 3.62 nmol/L while N-type VGCC-Ab was undetected. The other five (83.3%) patients with LEMS had no malignancy detected during a mean follow-up period of 37 months.

Table 1 Patient characteristics, VGCC-Ab titers, and diagnoses

	Group 1: inflammatory disorders ($n=42$)	Group 2: non-inflammatory disorders ($n=58$)	*P* value
Female, *n* (%)	27 (64.3%)	23 (39.7%)	
Age (years), median (range)	54 (20–87)	56 (43–71)	
Cancer (active or historical), *n* (%)	10 (23.8%)	16 (27.6%)	0.82
Lung cancer, *n* (%)	3 (2.4%)	1 (1.7%)	0.31
Elevated[a] P/Q-type VGCC-Ab, *n* (%)	29 (69.0%)	36 (62.1%)	0.53
Elevated[a] N-type VGCC-Ab, *n* (%)	20 (47.6%)	25 (43.1%)	0.69
Both VGCC-Ab elevated, *n* (%)	7 (16.7%)	3 (5.2%)	0.09
P/Q type VGCC-Ab titer (nmol/L), median (IQR)	0.15 (0.095–0.335)	0.10 (0.055–0.165)	0.16
N-type VGCC-Ab titer (nmol/L), median (IQR)	0.08 (0.06–0.145)	0.06 (0.05–0.1)	0.07
Other antibodies, *n* (%)	14 (33.3%)	7 (12.1%)	0.01
gAchR-Ab, *n*	3	4	
VGKC-Ab, *n*	4	0	
GAD-Ab, *n*	2	1	
Other Ab, *n*	5	2	

n number of patients, *IQR* interquartile percentage, *gAchR* ganglionic nicotinic acetylcholine receptor, *VGKC* voltage-gated potassium channel, *GAD* glutamic acid decarboxylase

[a]Reference range for P/Q- and N-type VGCC-Ab: 0.00–0.02 nmol/L

VGCC-Ab titers in patients with malignancies

A total of 26 (26.0%) patients carried a diagnosis of a solid organ or hematological malignancy prior to obtaining VGCC-Ab titers, 16 patients with active cancer and 10 patients with remote cancer or cancer in remission. There was no difference in antibody titers between patients with current or prior cancer vs. those without: median P/Q-type and N-type VGCC titers were the same in cancer and non-cancer patients (median P/Q-type VGCC-Ab titer: 0.07 nmol/L, median N-type VGCC-Ab titer: 0.13 nmol/L).

Four patients had a diagnosis of lung cancer: SCLC (3 patients) and adenocarcinoma (1 patient). One of three patients with SCLC had LEMS. VGCC-Ab titer elevation in the two SCLC patients without LEMS was instead associated with paraneoplastic encephalopathy and limbic encephalitis, respectively. The lone patient with lung adenocarcinoma had elevated VGCC-Ab in the setting of multifactorial metabolic encephalopathy.

Imaging surveillance in patients without active malignancy

Of the 84 patients with elevated VGCC-Ab and without active malignancy 57 (67.9%) had imaging to assess for malignancy as part of their follow-up. Thirty-nine (46.4%) patients had computer tomography (CT) of the chest, 42 (50.0%) had CT of the abdomen and pelvis, 14 (16.7%) had whole body positron emission tomography (PET), and 26 (31.0%) had mammography or ultrasound (US) of an organ or body region.

Surveillance imaging led to the detection of malignancy in 7 (8.3%) patients with a median latency of 46 (range 1–76) months between the finding of elevated VGCC-Ab and diagnosis of malignancy. Of the seven patients, one had renal cell carcinoma, one urethral carcinoma, one squamous cell carcinoma of the skin, one tonsillar squamous cell carcinoma, one squamous cell carcinoma of the lung, and two EBV-associated diffuse large B-cell lymphomas. One additional patient was found to have a kidney mass but did not have a tissue diagnosis.

We performed a separate medical records search for patients diagnosed with LEMS at our institution during the study period. A total of nine cases of LEMS including the six aforementioned cases were identified. Eight of nine (88.9%) patients had elevated P/Q-type VGCC-Ab titers (range 0.04–11.4 nmol/L), and three of nine (33.3%) had elevated N-type VGCC-Ab titers (range 0.05–0.32 nmol/L).

Discussion

Specificity of VGCC antibodies in the diagnosis of LEMS

Lambert–Eaton myasthenic syndrome is a rare autoimmune disorder affecting the presynaptic release of acetylcholine at the neuromuscular junction. Its main clinical manifestations include generalized weakness, hyporeflexia, and autonomic dysfunction. The electrodiagnostic hallmark of LEMS is the presence of a presynaptic neuromuscular junction conduction defect that can be detected by repetitive

Table 2 Neurological diagnoses in patients with elevated VGCC-Ab titers

Diagnosis	Number of patients
Inflammatory group ($n=42$)	
Central nervous system disorders	16
Rapidly progressive dementia (not otherwise specified)	3
Paraneoplastic encephalopathy	2
Encephalomyelitis	2
Cerebellar ataxia	1
Longitudinally extensive myelopathy	1
Hashimoto's encephalopathy	1
Multiple sclerosis	1
Limbic encephalitis	1
HIV-encephalopathy	1
Lupus cerebritis	1
Optic neuropathy	1
Opsoclonus–myoclonus (HIV-related)	1
Peripheral nervous system disorders	26
Lambert–Eaton myasthenic syndrome	6
Polyneuropathy	5
Autoimmune autonomic ganglionopathy	5
Inflammatory myopathy	2
Cranial neuritis	2
Systemic autoimmune disease[1]	6
Non-inflammatory group ($n=58$)	
Central neurodegenerative	22
ALS	7
Parkinsonism[2]	7
NPH	3
Dementia	3
Cerebellar ataxia[3]	2
Ischemic/anoxic[4]	7
Toxic–metabolic encephalopathy[5]	5
Peripheral neuropathy[6]	8
Miscellaneous[7]	16

Number of patients per disease entity listed in brackets

ALS amyotrophic lateral sclerosis, *NPH* normal pressure hydrocephalus

[1]Polymyalgia rheumatica (2), vasculitis (2), Sjögren's syndrome (1), mixed-connective tissue disease (1)

[2]Parkinson's disease (3), multiple system atrophy—cerebellar type (3), dementia with Lewy bodies (1)

[3]Spinocerebellar ataxia type 2 (1), hereditary cerebellar ataxia (genetic testing refused) (1), unknown etiology (1)

[4]Ischemic stroke (4), cardiac arrest-induced anoxic brain injury (1)

[5]Toxic metabolic encephalopathies due to: heroin (1), hepatic (1), multifactorial (1), B1 deficiency/Wernicke's (1) and HIV (1)

[6]Peripheral neuropathy due to pyridoxine deficiency (1), leflunomide-induced small fiber neuropathy (1), hereditary (1), critical illness (1), idiopathic small fiber neuropathy (2), idiopathic (2)

[7]Includes fibromyalgia, headache, degenerative disc disease, dizziness, myalgia, diplopia, psychiatric conditions

nerve stimulation (RNS) or isometric exercise. Treatment of LEMS consists of symptomatic treatment with pyridostigmine, guanidine, immunotherapy, and supportive care [4].

3.4-Diaminopyridine (DAP) has long been used for the treatment of LEMS through compassionate use programs after several randomized trials demonstrated its efficacy in the treatment of LEMS [5–8]. In 2009, 3.4-DAP was designated as an orphan drug by the United States Food and Drug Administration (US FDA) and has been available through special compounding pharmacies. More recently, two US pharmaceutical companies conducted clinical trials assessing the efficacy of their 3.4-DAP formulations and demonstrated safety and efficacy in LEMS [9, 10]. Concern was raised that based on these trials, either pharmaceutical company may get US FDA approval and gain market exclusivity of 3.4-DAP for 7 years under the US Orphan Drug Act [11]. A publicly traded company holding exclusive rights may be inclined to raise the drug price to increase its stockholder share prize which may lead to an artificial price hike.

The role of VGCC-Ab in the pathogenesis of LEMS was initially demonstrated in passive transfer experiments using plasma or immunoglobulin G from patients with LEMS [12]. This finding was supported by the fact that removing antibodies using therapeutic plasma exchange and immunosuppressant agents lead to symptom improvement. The expression of functional VGCCs on the surface membrane of small cell lung cancer (SCLC) cells may explain VGCC-Ab positivity in a subgroup of these patients, regardless whether they have paraneoplastic LEMS [1].

Early studies reported a high sensitivity (85–95%) and specificity (98–100%) of elevated serum VGCC-Ab levels for the diagnosis of LEMS [1, 13, 14]. Recently, however, the specificity of VGCC-Ab for diagnosing LEMS has been questioned. Elevated VGCC-Ab levels were found not only in healthy controls [1, 15], but also in patients with autoimmune diseases such as myasthenia gravis, non-autoimmune conditions including amyotrophic lateral sclerosis, neurologic paraneoplastic syndromes such as paraneoplastic cerebellar degeneration, and patients with various cancers without neurologic signs or symptoms.

Two recent retrospective studies looked at the sensitivity and clinical relevance of positive neuronal antibodies for diagnosing paraneoplastic disorders [16, 17]. Abboud et al. reviewed the charts of 401 patients who had serum paraneoplastic panels done as part of evaluation of neurological complaints [16]. Eleven (2.7% of the tested population) patients had elevated P/Q-type VGCC-Ab titers (≥ 0.02 nmol/L) of which seven (63.6%) were deemed to be "clinically irrelevant". Seven (1.7%) patients had elevated N-type VGCC-Ab levels (≥ 0.03 nmol/L) of which four (57.1%) felt to be "clinically irrelevant". Albadareen et al. retrospectively assessed 321 patients with paraneoplastic panels [17]. They calculated a sensitivity of 34.4%

and specificity of 85.8% with a positive predictive value of 21.6% and negative predictive value of 92% for the entire panel. Eleven patients had elevated P/Q-type VGCC-Ab levels of which two (18.2%) were true positive; nine patients had elevated N-type VGCC-Ab with four (44.4%) true positive cases. Authors of both papers concluded that positive or elevated neuronal antibody titers by themselves had a low sensitivity in detecting paraneoplastic syndromes, and rather than being diagnostic presented a helpful confirmatory test in cases with a strong clinical suspicion.

To our knowledge, there is only one retrospective study that looked at the sensitivity and specificity of VGCC-Ab for LEMS specifically [15]. Zalewski et al. performed a review of patients found to have elevated VGCC-Ab. Elevated VGCC-Abs were seen in 1.7% of healthy controls, 3.4% of patients with various neurological disorders, and 4% of neurologically asymptomatic lung cancer patients. A neuromuscular junction disorder was documented in 10 of 236 (4.2%) seropositive patients. LEMS was confirmed by electrodiagnostic studies in six (2.5%) seropositive patients, with a median P/Q-type VGCC-Ab value of 0.49 nmol/L (range 0.17–1.84 nmol/L). Among the ten patients with a neuromuscular junction disorder, two (20%) patients had a high P/Q-type VGCC-Ab titer (≥ 1.00 nmol/L), five (50%) patients had a medium titer (0.10–0.99 nmol/L), and three (30%) patients a low titer (0.03–0.10 nmol/L). Similar to our observation in patients with confirmed LEMS, there was a wide range of antibody elevation among these patients. These findings suggest that the P/Q-Ab titer does not correlate with the likelihood of an autoimmune diagnosis such as LEMS. Despite these data, there continues to be need for clarification regarding the specificity of VGCC-Ab in the diagnosis of LEMS as evidenced by a review published less than a year following Zalewski et al.'s study that reported P/Q-type VGCC-Ab to be a highly specific diagnostic test in LEMS [18].

Among the study population of 100 patients with elevated VGCC-Ab levels, six patients had clinically and electrodiagnostically established LEMS while there were a total of nine patients with proven LEMS during the study period (three of the nine patients were not part of the study population and were identified separately). Based on these numbers, the P/Q-type VGCC-Ab had a diagnostic sensitivity of 88.89% (95% CI 51.75–99.72%) and specificity of 36.17% (95% CI 26.51–46.73%) and the N-type VGCC-Ab had a sensitivity and specificity of 33.33% (95% CI 7.49–7.07%) and 65.96% (95% CI 55.46–75.42%), respectively. Our findings confirm the exceedingly low specificity of both VGCC-Ab subtypes in the diagnosis of LEMS as previously noted by Zalewski et al. [15]. No cutoff value could be generated to differentiate LEMS from other neurological and non-neurological diagnoses. Thus, while the value of the VGCC-Ab test is confirmatory in patients diagnosed with LEMS by clinical and electrodiagnostic criteria, the antibody test alone is not diagnostic in the majority of patients who otherwise lack the typical clinical or electrodiagnostic features.

VGCC antibody as a marker of autoimmunity

The majority of cases in our cohort (58%) lacked an inflammatory etiology of their neurological symptoms which were attributed to diagnoses including neurodegenerative conditions (such as ALS, dementia, Parkinson's disease), genetic diseases, and stroke (Table 2). VGCC-Ab positivity in these conditions is postulated to be a downstream effect of a non-specific immune system activation following neuronal injury from the primary underlying disease process as has been shown to be the case with other neuronal autoantibodies such as VGKC and the ganglionic acetylcholine receptor antibody [19, 20].

The lack of a statistically significant difference in VGCC-Ab titer for either inflammatory or non-inflammatory groups further highlights the considerable limitations of VGCC-Ab titer testing in the diagnosis of a neurological autoimmune disease.

Our study has several limitations. Given its retrospective nature, referral for VGCC and neuronal autoantibody evaluation was performed solely at the discretion of the clinician and was not based on a set of predefined clinical criteria. The low number of LEMS cases ($n = 6$) in our cohort likely decreased the accuracy of sensitivity and specificity of both VGCC-Ab types in the diagnosis of LEMS.

In summary, our study revealed that the majority of patients (58 out of a 100) with positive VGCC-Ab titers did not have an autoimmune or inflammatory cause of their neurological condition. Our findings suggest that the specificity of an elevated VGCC-Ab titer for the diagnosis of LEMS is low (36.17% for P/Q-type VGCC-Ab and 65.96% for N-type VGCC-Ab).

We therefore recommend that neurologists and neuromuscular physicians be cautioned against making a diagnosis of LEMS simply based on positive VGCC-Ab titers. A careful clinical and electrodiagnostic evaluation is needed before making the diagnosis of LEMS due to the possible psychological and financial implications to the patient and the healthcare system.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard Ethical standards concerning safeguarging patients' protected health information, in addition to compliance with the Institutional Review Board were strictly adhered to.

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