Case Report

Conjoint glutamic acid decarboxylase 65 and P/Q voltage gated calcium channel antibodies in autoimmune epilepsy: A case report

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A B S T R A C T

Numerous autoantibodies are implicated in the pathogenesis of autoimmune epilepsy. In the past decade, many case series reported the association of glutamic acid decarboxylase 65 (GAD 65) antibodies with epilepsy. Conjoint presence of GAD 65 antibodies with antinuclear, anti-thyroid, and anti-parietal cell antibodies has often been demonstrated. However, concomitant elevated levels of GAD 65 and P/Q voltage gated calcium channel (VGCC) antibodies is rare. We report a case of autoimmune epilepsy with conjoint GAD 65 and P/Q VGCC antibodies in the absence of malignancy. This report highlights a possible role of P/Q VGCC antibodies in the pathogenesis of autoimmune epilepsy.

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1. Introduction

Autoimmune epilepsy has become a fact in modern medicine. The new ILAE classification of the epilepsies recently added immune epilepsy as one of the etiological groups [1]. Accumulating data support the presence an immune-mediated pathogenesis in drug-resistant epilepsy even in the absence of limbic encephalitis or malignancy. Examples of antibodies implicated in this disorder include N-methyl-D-aspartate receptor (NMDA) antibodies, voltage gated potassium channel complex (VGKC) antibodies, collapsin response mediator protein 5 (CRMP-5) antibodies, ganglionic acetylcholine receptor antibodies, and GAD 65 antibodies [2]. Voltage gated calcium channel antibodies, on the other hand, have not yet been linked to autoimmune epilepsy.

2. Case

A 26-year-old right handed non-smoker female with history of type 1 diabetes mellitus (DM), hypothyroidism, hyperlipidemia, and asthma was referred to our clinic with a two year history of new onset recurrent seizures. She had no history of head trauma nor did she have a previous personal history of seizures. Moreover, there was no history of maternal illness during pregnancy. The patient was a product of spontaneous vaginal delivery and she cried immediately after birth. Her growth and development were normal. The patient describes two types of seizures. The first type started two years prior to her presentation, when she developed focal aware seizures in the form of a de ja vu which usually lasted for 10 to 15 s. The frequency of these seizures was twice every month, and they were not followed by convulsions. The patient visited a psychiatrist who diagnosed her with panic attacks and started her on escitalopram. Despite treatment with escitalopram, the patient continued to have recurrent focal aware seizures and developed a second type described as generalized tonic-clonic (GTC) convulsion without a preceding aura. Her diagnosis was revisited thereafter and she was started on levetiracetam which did not control her symptoms.

By the time she was referred to our clinic, the patient was already on levetiracetam 500 mg twice a day and lamotrigine 50 mg twice a day. Her cognitive (déjà vu) seizure frequency was once to twice per month, and she has already had multiple GTCs with a frequency of one every three months. The patient’s examination was unremarkable upon presentation. EEG and MRI were ordered for further evaluation and her levetiracetam dose was increased. Her first EEG showed bilateral fronto-temporal intermittent slow activity with no epileptiform discharges. Her brain MRI was normal.

Three months later, the patient came for a follow-up evaluation and reported that her seizures did not respond well to the levetiracetam dose increment, so her anti-seizure medications were further increased. A repeat EEG and a brain PET CT were ordered. Her second EEG demonstrated bilateral fronto-temporal epileptiform discharges in addition to intermittent slow activity in the bilateral fronto-temporal regions. The PET scan was reported normal.

After coming for the third follow-up evaluation, the patient complained of experiencing a single episode of incomplete retrograde amnesia which lasted for one day. Her seizure frequency decreased this time. Her mental status and neurological exam were completely normal upon this visit. Anti-thyroid-peroxidase and anti-thyroglobulin antibodies were ordered and came back negative. A paraneoplastic panel was also ordered and showed elevated P/Q VGCC antibody levels.

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of 0.05 nmol/L (normal: ≤ 0.02 nmol/L). Three months later, the same investigation was ordered and showed marginally elevated P/Q VGCC antibodies at a level of 0.05. To rule out malignancy, a CT of the chest, abdomen, and pelvis was done and reported normal.

At the next visit, the patient described suboptimal seizure control again; having 1-2 focal aware seizures per month and GTCs every three months despite reaching maximum doses of levetiracetam and lamotrigine. An epilepsy panel was ordered and the results showed elevated serum P/Q VGCC antibodies at a level of 0.06 nmol/L in addition to high GAD 65 antibody levels of 22.2 (normal: ≤ 0.02 nmol/L). Other antibodies including NMDA, VGKCc, and N-type VGCC were all negative. A lumbar puncture was performed to measure autoantibody levels in the CSF. White cell count, biochemistry, and cultures of CSF came out normal. Cerebrospinal fluid autoantibodies showed elevated GAD 65 antibody levels of 0.27 nmol/L (normal: ≤ 0.02 nmol/L). Note that serum and CSF antibody levels were tested by Mayo Clinic laboratories in Mayo Clinic (Rochester, Minnesota).

Given the absence of structural, infectious, and metabolic causes; in addition to the borderline positivity of antineuronal antibodies, the patient’s diagnosis was presumed to be autoimmune epilepsy. She was given 1 g of intravenous methylprednisolone (IVMP) for 3 days followed by oral prednisone at a dose of 10 mg daily. Her anti-seizure drugs (ASDs) were kept at 1500 mg twice daily of levetiracetam and lamotrigine 150 mg twice daily. Her seizure frequency decreased to focal aware seizures (déjà vu) once every 3 months and had no further GTCs. Attempts of tapering oral prednisone and introducing azathioprine failed due to development of Azathioprine allergy and increased frequency of seizures on smaller doses of prednisone. A repeat MRI and EEG one year after starting steroid therapy was normal for both studies. This patient continues to be followed in the neurology and immunology clinics and was finally placed on mycophenolate mofetil 1 g BID in addition to her preexisting treatment regimen of prednisone and anti-seizure medications. By the time this report was written, the patient has completed 1 year of immunotherapy and steroids. Since then, she had only 4 focal aware seizures and no GTCs.

3. Discussion

Glutamic acid decarboxylase (GAD) is the major enzyme that catalyzes the conversion of glutamic acid to gamma aminobutyric acid (GABA). Two major types of GAD exist: GAD 65 and GAD67. GAD 65 is present in nerve terminals while GAD 67 is found all over the nerve cell. Antibodies directed against the GAD enzyme block the conversion of glutamic acid to GABA, therefore reducing GABA levels. Low levels of GABA, which is an inhibitory neurotransmitter, can cause seizures.

Several neurological syndromes have been associated with anti-GAD antibodies including stiff person syndrome, cerebellar ataxia, epilepsy, limbic encephalitis, dancing eye syndrome, and Miller Fischer syndrome [3]. Aside from their well-known association with autoimmune disorders such as type 1 diabetes mellitus, presence of anti-GAD antibodies has been often found to be concomitant with other antibodies such as antithyroid, antinuclear, and antiparietal cell antibodies [4-5]. However, conjoint presence of both anti-GAD 65 and anti-P/Q VGCC antibodies is very rare. As far as we know, this is the first reported case of autoimmune epilepsy with GAD 65 and P/Q VGCC antibodies.

The classical teaching about VGCC antibody positivity is its occurrence in Lambert Eaton myasthenic syndrome (LEMS) and lung cancer. Yet, its presence in many other neurological and oncological conditions has become recently known. Zalewski et al. reported positivity of VGCC antibodies in patients with variable neurological diagnoses such as autoimmune encephalopathy, degenerative dementia, cerebellar ataxia without demyelination or stroke, multiple sclerosis, parkinsonism, and amyotrophic lateral sclerosis. Out of the 236 cases he included in his study, 24 had coexisting anti-VGCC (P/Q or N-type or both) and anti-GAD 65 antibodies. Nevertheless, the author did not elaborate on their presentations. Only 10 out of the 236 anti-VGCC antibody positive patients had seizures, 2 out of whom were attributed to autoimmune epilepsy. Interesting enough, 7 out of the 10 patients with seizures had low P/Q VGCC titers (0.03–0.09 nmol/L), 3 had moderate titers (0.1–0.99 nmol/L), and none had high titers [6].

Titers of GAD 65 antibodies are usually 100–1000 times higher in neurological disorders than they are in patients with DM [7]. Titers that are ≤ 0.02 nmol/L are considered negative. 80% of patients with type 1 DM have mildly elevated titers (0.03–19.9 nmol/L). This is also true for 25% of patients with LEMS, myasthenia gravis, and other rarer autoimmune disorders [8–9]. When GAD 65 antibody titers exceed 20 nmol/L and patients have neurological symptoms, an autoimmune etiology of the symptoms should highly be suspected. Neurological manifestations associated with such values include cerebellar ataxia, seizures with or without encephalitis, stiff man phenomena, and brainstem involvement (nystagmus, ophthalmoplegia, dysphagia, and vertigo) [10].

The association of GAD 65 antibodies with immune mediated temporal lobe epilepsy has become an established finding in literature. Errichello et al. reported 4 anti-GAD 65 positive TLE cases, M. Falip reported 5 cases, while Malter et al. looked at the treatment outcomes of 13 cases with the same condition [11–13]. Our case consolidates the current evidence about the association of GAD antibodies and temporal lobe epilepsy. It also raises a question about a possible role for anti P/Q VGCC antibodies in autoimmune temporal lobe epilepsy.

Many controversies arise around the management of autoimmune epilepsy. Lack of response to pulse steroids has been considered a major feature in anti-GAD antibody positive encephalitis according to some literature [14]. On the contrary, a cohort of 13 patients with anti-GAD antibody positive TLE compared the following therapies with each other: corticosteroids, IVIG, plasmapheresis, and rituximab. Seizure frequency reduction was achieved during a 3 month follow-up period with the author suggesting that rituximab is a safe and efficacious treatment option in autoimmune limbic epilepsy [15]. The second case had positive voltage gated potassium channel complex (VGKcc) and P/Q VGCC antibodies in a patient with autoimmune encephalopathy and refractory seizures. Significant improvement was seen during a 1 month follow-up after treatment with IVMP and IVIG [16].

In our case, the possibility of immune-mediated epilepsy was only entertained after ruling out other causes. Although antineuronal antibodies were borderline positive, their clinical significance should not be ruled out. False positive results are also a possibility, however, GAD 65 antibodies were measured in serum and then measured in CSF three months later. Equally important, P/Q VGCC antibody levels were measured in serum at 3 separate clinic visits which were 3 months apart. Levels of GAD 65 antibodies in our patient were higher than what would be expected in type 1 DM. P/Q VGCC antibody levels, on the other hand, were mildly elevated similar to most cases with seizures reported by Zalewski et al. [6].

4. Conclusion

We report a case of autoimmune epilepsy with conjoint GAD 65 and P/Q VGCC antibodies in the absence of malignancy. This report emphasizes the role of GAD 65 antibodies in the pathogenesis of autoimmune disease.
epilepsy. It also raises a question about the possible role of P/Q VGCC antibodies in the pathogenesis of this disease. Whether the presence of conjoint autoantibodies alters the pathogenesis and response to treatment in autoimmune epilepsy or not is difficult to determine from a single case. However, accumulating further cases in the future will help in answering this question. Given the increased coincidental presence of anti-VGCC antibodies with other antibodies that are well known to be associated with autoimmune epilepsy, we recommend further screening of this antibody in suspected cases of autoimmune epilepsy.

**Financial disclosure**

None.

**Conflict of interest**

There is no conflict of interest.

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