Intractable Seizures and Limbic Encephalitis, Unaccounted Complications of Type 1 Diabetes Autoimmunity

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Abstract

Glutamic acid decarboxylase 65kD autoantibody (GAD65Ab) is frequently detected in patients with refractory epilepsy and stiff person syndrome. In contrast to T1D, the pathological role of GAD65Ab in neurological disorders is still debatable. As a result, the implementation of possible immunotherapy is usually delayed. This report presents 2 cases of GAD65Ab-associated brain autoimmunity and their different management. We present clinical data and discuss management based on available evidence in the reviewed literature. Both cases presented with acute on chronic neurological symptoms and were GAD65Ab positive. Case 1, a 30-year-old man with a history of early-onset type 1 diabetes mellitus at 14 months, followed by cryptogenic temporal epilepsy at 11 years of age, presented with intractable seizures. Case 2, a 48-year-old woman, presented with a history of recurrent severe headaches, cognitive impairment, decreased memory, and behavioral symptoms. GAD65Ab was detected in both patients’ sera. Cerebrospinal fluid GAD65Ab was only checked and positive in case 1. Case 2 was diagnosed with limbic encephalitis, treated with immunotherapy, and showed a remarkable clinical improvement. Case 1 with refractory epilepsy failed multiple antiepileptic drugs and responsive-stimulator system treatments. He was finally diagnosed with autoimmune epilepsy. The delay in diagnosis resulted in a lost opportunity for early immunotherapy. In conclusion, autoantibody screening and early initiation of immunotherapy should be considered to manage GAD65Ab-associated neurological disorders.

Key Words: type 1 diabetes mellitus, T1D, autoimmune epilepsy, GAD65Ab, responsive-stimulator system, RNS, limbic encephalitis, stiff person syndrome, SPS

Glutamic acid decarboxylase, 65kD isoform (GAD65), is an enzyme that catalyzes the conversion of glutamate to gamma-aminobutyric acid (GABA), the key inhibitory neurotransmitter of the central nervous system. It is primarily targeted by autoantibodies (GAD65Ab) that are found in the majority (~80%) of patients with type 1 diabetes mellitus (T1D) as well as some individuals with sole neurological disorders [1].

Compared to general populations, patients with T1D are found to have a 2.8- to 5-fold increase in the risk of epilepsy [2,3]. Moreover, patients with epilepsy have been shown to have a 4-fold increase in the odds ratio of T1D [4]. In contrast to T1D, the autoimmune role of GAD65Ab in the pathogenesis of neurological disorders has, to some extent, been controversial. Several other neuronal autoantibodies have been identified in subgroups of patients with epilepsy and other neurological disorders. However, Daif et al found that among patients with refractory epilepsy, anti-GAD65 Ab was the most frequently detected autoantibody [5]. Due to the infrequency of coexisting T1D autoimmunity and neurological disorders, thorough scientific research is still lacking to determine the pathogenic, prognostic, and therapeutic implications of such association.

Here, we present a case of a patient with GAD65Ab-associated limbic encephalitis (LE) who had a remarkable improvement in symptoms after early initiation of immunotherapy. On the other hand, we also present a case of a patient with long-standing T1D coexisting with refractory epilepsy who failed multiple antiepileptic drugs (AEDs) and brain-responsive neurostimulation system (RNS) treatments, because the etiology remained obscure up until levels of GAD65Ab in cerebrospinal fluid (CSF) and serum were finally measured.

Methods

We present clinical data of 2 cases differently treated for their GAD65Ab-associated brain autoimmunity and discuss the pitfalls of management considering the available scientific evidence.

Results

Case 1

A 30-year-old right-handed Caucasian male with a long-standing history of T1D diagnosed at the age of 14 months and a history of refractory epilepsy, reported to the emergency department with continuous seizure activity. In the emergency department, the patient developed hypoxia; as a result, he was intubated, administered Keppra 1500 mg,
and versed 2 mg followed by propofol infusion. Accordingly, the patient was admitted to the intensive care unit.

The patient was diagnosed with cryptogenic bitemporal lobe epilepsy at the age of 11 years and suffered 2 types of seizures (absence seizure and generalized tonic-clonic) 3 to 4 times per week. On presentation, the first hospital seizure was generalized-convulsive, lasted for 5 minutes, and was followed by a confusional state. In addition, during hospitalization, it was documented that he had multiple episodes of loss of awareness and daydreaming, which are characteristic manifestations of LE. In the past, the patient failed to respond to multiple AEDs, including lamotrigine, levetiracetam, phenytoin, pregabalin, topiramate, and valproic acid. Hence, he was a candidate for enrollment in a clinical trial for an RNS at the age of 18 years. However, even though RNS and 4 other AEDs (zonisamide, clobazam, lacosamide, and oxcarbazepine) were simultaneously administered, only a decrease of 50% in seizure frequency was achieved. Neither treatment changed the severity nor the minimum seizure-free period of 3 months.

The patient’s diabetes has been well controlled on home regimen of insulin glargine 34 units twice a day and Humalog 3 units for each 15 g of carbohydrate with meals in addition to Humalog correctional dose (2 units for each 50 mg/dL above 150 mg/dL up to 10 units). On this insulin regimen, his hemoglobin A1c (HbA1c) remained <7% since the onset of seizure, except for an increase of 9% prior to RNS implantation. His HbA1c was 6.8% at current presentation.

On admission, patient’s initial lab results showed pH of 7.10, pCO2 76.9, HCO3 17.0, pO2 262.0, lactate 11.5 mmol/L [reference range: 0.4-2.0], beta hydroxybutyrate 0.59 mmol/L [reference range: 0.02-0.27], anion gap of 20 mmol/L, serum glucose of 229 mg/dL, and HbA1c of 6.8%. His creatinine was slightly elevated at 1.52 mg/dL [reference range: 0.70-1.20] but with normal blood urea nitrogen of 14 mg/dL. Other electrolytes were in the normal range except for elevated magnesium of 3.0 mg/dL [reference range: 1.8-2.6]. His complete blood count resulted in a white blood count of 14.3, hemoglobin of 17.3, hematocrit of 53.9, and normal platelet count. Computed tomography brain scan showed the absence of brain stimulator electrodes (RNS) from the occipital approach extending to the skull base; there was no radiological evidence for intracranial hemorrhage or infarction. Chest X-ray demonstrated bibasilar opacities. The patient’s AED levels showed a low level of zonisamide at < 2.6; lacosamide levels were within normal limits.

The patient was started on intravenous (IV) insulin infusion as management of hyperglycemia and IV antibiotics for presumed aspiration pneumonia. Two days postadmission, our endocrinology team was sought out for further diabetes treatment. The patient’s diabetes has been well controlled on home regimen of insulin glargine 34 units twice a day and Humalog 3 units for each 15 g of carbohydrate with meals in addition to Humalog correctional dose as needed. Following the extubation, the patient was extremely violent and agitated. Thus, he has treated with Seroquel 12.5 mg, increased to 25 mg at bedtime.

The regimen of AEDs was adjusted by the neurology team. A new regimen including an increased dose of clobazam from 15/15 to 20/20, zonisamide, and lacosamide was continued while oxcarbazepine was discontinued during the hospital stay. Following this medication regimen, the patient remained seizure-free throughout his 7-day hospital stay. Finally, he was discharged with an outpatient follow-up appointment with his neurologist to address new findings of GAD65 antibodies in CSF. A trial of IV immunoglobulins (IVIG) was planned; however, the patient lost the follow-up in our clinic.

Case 2

A 48-year-old right-handed Caucasian female presented with a 2-month history of recurrent severe headaches associated with cognitive impairment, decreased memory, and behavioral symptoms in the form of agitation, hallucinations, and paranoia with episodes of disorientation, confusion, and visual blurring. She complained of stiffness and rigidity involving neck and back muscles with spams and difficulty ambulating and frequent falls. The patient complained of fatigue and generalized muscular weakness but had no other symptoms suggestive of hypothyroidism (ie, weight gain, fluid retention, slowed movement or speech, and no history of constipation or menorrhagia). The patient’s family history is positive for T1DM in her son, but no other history of autoimmune disorders including Hashimoto’s thyroiditis or Graves’ disease. Motor system examination revealed generalized rigidity, muscle strength was 5/5 in all 4 limbs, deep tendon reflexes were normal, and down-going plantar bilaterally. Sensory examination was normal with intact cerebellar signs.

Neuropsychological testing showed a cognitive decline in the form of impairment of short-term memory. Magnetic resonance imaging of the brain with contrast did not show any significant abnormality. Lumbar puncture and CSF analysis revealed lymphocytic pleocytosis, with elevated total white cell count. Electroencephalography monitoring showed background slowing. Given the patient’s clinical presentation and investigational workup, a diagnosis of LE was considered. The patient received treatment with IVIG 60 gm × 1 infusion and unexpectedly improved her muscle stiffness, which raised suspicion for stiff person syndrome (SPS). Because of possibility of SPS, GAD65Ab was initially checked and came back at 6.7 IU/ml (0-5 IU/mL), and 2 months later, it was at 148 IU/ml (0-5 IU/mL). HbA1c was normal, however, at 5.3% without evidence for diabetes.

Because of a possible association with other common autoimmune conditions, thyroid function tests were assessed and showed that thyroid-stimulating hormone was 0.98 micro IU/ml (0.1-5 micro IU/ml), but free thyroxine (T4) was low at 0.66 ng/dL (0.71-1.85 ng/dL). Due to lack of feasibility, neither total T4 nor direct dialysis assay of free T4 were done for this patient. Nevertheless, thyroid peroxidase antibodies were checked and found to be elevated at 45 IU/ml (0-35 IU/ml). Thyroglobulin antibodies were also positive at 42.4 IU/ml (0-40 IU/ml). She was therefore diagnosed with Hashimoto’s thyroiditis and started on the full weight-based replacement dose of levothyroxine (LT4) 125 mcg/day for her autoimmune hypothyroidism.

At the outpatient follow-up, she reported significant improvement of muscle stiffness/spasms and cognitive and be-
havioral symptoms. Additionally, she reports an improvement in her energy level with no symptoms suggestive of hyperthyroidism on the current 125-mcg dose of LT4. The patient was instructed to repeat thyroid function tests 4 weeks after the initiation of LT4; however, she lost the follow-up in our clinic.

Discussion

Autoantibody-associated neurological disorders are well-described phenomena in scientific literature. The pathological role of those autoantibodies is, however, contentious. Anti-GAD65Ab is a hallmark for the diagnosis of T1D. However, unlike T1D, patients with suspected GAD65-related neurological autoimmunity tend to have a higher titer of GAD65 autoantibody [1].

Budhram et al defined the high-titer GAD65Ab as more than 20 nmol/L (>2000 IU/mL) in patients with SPS, cerebellar ataxia, refractory epilepsy, LE, and overlapping neurological syndromes [6]. Despite this high titer of GAD65Ab, its level does not correlate with the clinical severity of those disorders [1].

Baekkeskov et al described the difference in immunoreactivity of GAD65Abs with brain GAD65 in GABAergic neurons in patients with SPS, cerebellar ataxia, refractory epilepsy, LE, and overlapping neurological syndromes [6]. In a similar manner, Limatainen et al confirmed the existence of distinctive epitope recognition patterns of GAD65Ab among patients with T1D, epilepsy, or SPS. They noted, however, that 6 out of 10 patients with both T1D and epilepsy had serum GAD65Abs that shared GAD65 epitopes. Additionally, of those 10 patients, 2 CSF samples collected from 2 patients reflected a perfectly matching epitope recognition pattern [8].

Based on these findings, the presence of GAD65Ab in CSF samples should, to some extent, confirm the diagnosis of autoimmune-mediated neurological disorders. While the presence in serum GAD65Ab alone cannot confirm them, epitope specificity might help explain the presence of these conditions isolated or combined.

Immunotherapy (ie, IVIG and potentially other immunosuppressive agents) is considered helpful for patients with SPS and autoimmune epilepsy. The time from onset of symptoms to initiation of immunotherapy seems to be an essential determinant for favorable outcomes. Quek et al indicated that early initiation of immunotherapy from the onset of epilepsy is associated with better outcomes regarding frequency and severity of seizures. The median time from seizure onset to the initiation of immunotherapy was 4 months and 2 years for both responders and nonresponders, respectively [9]. On the other hand, Joubert et al found that the median time of 13 months for the initiation of immunotherapy was associated with inadequate responses among patients with either LE or temporal lobe epilepsy [10].

Moreover, Budhram et al found that the late initiation of immunotherapy in patients with epilepsy (median time of 50 months from symptoms onset to first immunotherapy) was associated with worse outcomes than other individuals where earlier implementation was pursued (median time from onset to initiation of immunotherapy ranges from 5-30 months) [6].

The progressive nature of destructive autoimmune disorders and the lack of neuronal regenerative capacity could result in irreversible brain damage if the autoimmune process is not aborted or ameliorated by immunotherapy at the early clinical stage of the disease.

For instance, in a case series study, Mäkelä et al compared the response to multiple immunotherapies among 6 patients with GAD65-associated epilepsy, in whom the treatment was initiated at different time intervals from the onset of seizures. Their observation suggested 3 progressive clinical stages of GAD65 autoimmune epilepsy starting by acute reversible immunoreaction that could progress to irreversible brain damage leading to hippocampal sclerosis or atrophy, as shown in the magnetic resonance imaging findings of 2 patients who did not respond to late immunotherapy, surgery, or AED. On the other hand, they reported a complete response to early immunotherapy (ie, 3 months after the onset of seizure) in 1 case with an associated Hashimoto’s thyroiditis after 1 year of treatment with IVIG and single AED [11].

Those studies showed an improvement of neurological symptoms post IVIG therapy. However, the IVIG therapy was not effective in the management of patients with isolated autoimmune diabetes [12]. In a prospective study, the rule of IVIG therapy in diabetes control was unviable among 16 patients with coexisting T1D and the immune-mediated chronic inflammatory demyelinating polyneuropathy (CIDP) [13]. In contrast, T1D went into remission post IVIG therapy for a preexisting CIDP in a single case report with coexisting disorders (ie, T1D and CIDP) [14].

Multiple case series and retrospective studies reported the initial trial IVIG therapy in patients with GAD65Ab-associated neurological disorders. Alternative immunotherapies, including methylprednisolone, prednisolone, mycophenolate, rituximab, and immunoadaption, were utilized in nonresponders to IVIG therapy and showed variable outcomes.

A trial of RNS in GAD65Ab-associated refractory epilepsy among 4 patients who failed multiple AEDs and immunotherapy treatment showed that RNS was associated with remarkable improvement in seizure outcome among all participants [15]. However, that was not the approach for the first presented case. Our first patient did not receive a trial of immunotherapy and RNS did not help. On the other hand, the initiation of IVIG at the time of diagnosis for the case 2 patient was associated with encouraging outcomes.

GAD65-associated neurological disorders frequently coexist with autoimmune endocrinopathies. Therefore, the awareness of endocrinologists regarding this association could facilitate the early diagnosis of GAD65-associated neuropathy and aid—through a multidisciplinary approach—the early initiation of immunotherapy.

Conclusion

Considering the role of GAD65Ab-associated brain autoimmunity among patients with T1D or other autoimmune endocrinopathies could promote early initiation of immunotherapy. Clinicians should be aware of the higher risk of autoimmune epilepsy among these patients.
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All authors have no conflict of interest to disclose.

Data Availability
Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Previous Presentation
One of the 2 cases was previously presented: Khan M, Hao J, Chaudhry F, Tiwari A, Sharma H, Jaume J. Response to IVIG leads to diagnosis of stiff person syndrome in a patient with limbic encephalitis and GAD65 autoantibodies (Ab) without diabetes. Poster presented at: ENDO2017; April 2017, Orlando, FL. Retrieved June 29, 2021. https://endo.confex.com/endo/2017endo/meetingapp.cgi/Paper/30219

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