Exponential increase of glutamic acid decarboxylase (GAD) antibody titer after initiating and stopping insulin in a patient with slowly progressive type 1 diabetes

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Abstract. Few articles have described fluctuations in glutamic acid decarboxylase antibody (GADAb) levels after a diagnosis of slowly progressive type 1 diabetes (SPIDDM). Here, we present a case in which GADAb levels exponentially increased after initiating and stopping insulin. A 64-year-old female patient newly diagnosed with SPIDDM was admitted and started multiple daily insulin injections. The patient’s GADAb titer was 6.9 U/ml (normal: <1.4 U/ml) and the patient had a type 1 diabetes susceptible HLA class II haplotype known in the Japanese population as: DRB1*04:05-DQB1*04:01. When the patient’s “honeymoon period” set in, hypoglycemia was observed and the dose of insulin was reduced. Two months after the diagnosis, 1 unit of insulin glargine/day was being injected and the patient demonstrated good glycemic control. Subsequently, the patient’s home doctor recommended that insulin injections be stopped. Three months after the diagnosis, the patient’s GADAb titer suddenly increased to 1600 U/mL. The patient’s GADAb titer decreased but was still positive (40 U/mL) 36 months after diagnosis. HbA1c levels were maintained below 7%, and oral glucose tolerance tests at 10, 26, and 36 months after diagnosis suggested that the patient had preserved insulin secretion. To the best of our knowledge, this is the first report that describes exponential increases in GADAb after initiating and stopping insulin in a patient with SPIDDM.

Key words: Slowly progressive type 1 diabetes (SPIDDM), Latent autoimmune diabetes in adults (LADA), Glutamic acid decarboxylase (GAD) antibody, Insulin therapy

Type 1 diabetes is characterized by the destruction of pancreatic beta cells; several autoantibodies such as glutamic acid decarboxylase (GAD) antibody, islet cell antibody (ICA), and IA-2 antibody are considered specific to type 1 diabetes [1-4]. In particular, the GAD antibody is the single most sensitive antigen-defined autoantibody marker of type 1 diabetes [5] and is characteristically high in older adults with slowly progressive type 1 diabetes (SPIDDM).

The GAD antibody persists or gradually diminishes after disease onset, [6] and few articles have described a case in which the GAD antibody levels increase after diagnosis. In this report, we describe a case with SPIDDM whose GAD antibody exponentially increased after initiating and stopping insulin therapy. We believe that this case is worth discussing to help clarify the role of the GAD antibody in SPIDDM.

Case Report

A 64-year-old Japanese woman was admitted to our hospital with a diagnosis of SPIDDM. Two months before admission, she lost 3 kg weight but didn’t feel any hyperglycemic symptoms. One week before admission, when she was seen in the clinic for a health check, her fasting glucose and hemoglobin A1c levels were 259 mg/dL and 8.9%, respectively; thus she was referred to our hospital. Her GAD antibody level, which was determined with a commercially available radioimmunoassay kit (Cosmic, Tokyo, Japan) was positive (6.9 U/ml). Therefore she was diagnosed with SPIDDM and admitted to our hospital to initiate insulin therapy.

Her medical history was significant for gastric pol-
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of insulin aspart and glargine (12 units/day), which was gradually increased to 32 units/day at day 8 after admission. When her "honeymoon period" set in, she experienced hypoglycemia, and her insulin dosage was reduced to 28 units/day on discharge. Nevertheless she had frequent hypoglycemia, and her insulin dosage was continually reduced. One month after diagnosis, her insulin dosage was reduced to 1 unit/day (insulin glargine 1 unit/day) but her fasting glucose level was still around 80 to 100 mg/dL and postprandial glucose level was around 160 to 190 mg/dL. When she visited her home doctor 2 months after diagnosis, the doctor stopped insulin glargine and prescribed voglibose 0.9 mg/day. Three months after diagnosis, her GAD antibody titer suddenly increased to 1600 U/mL and thereafter gradually decreased. Results of her self-monitoring glucose levels were 65 to 120 mg/dL after fasting and 120 to 280 mg/dL for postprandial tests, and her HbA1c levels remained under 7%. Up to 3 months after diagnosis, there was no increase in ICA or IA-2 antibody levels, pancreatic enzymes, thyroid dysfunction, or thyroid antibody changes. In addition, interferon was not prescribed for this patient. There was no history of viral infection before the rise of GAD antibody.

Ten months after diagnosis, insulin glargine 1 unit/day/}

yps, which were resected endoscopically when she was 45 years old, and dyslipidemia treated with diet therapy, although follow up data were not available. Neither perinatal glycosuria nor gestational diabetes had been detected during her pregnancies. She drank about 540 mL of wine or Japanese Sake three times a week and had smoked until age 60. Her brother had type 2 diabetes and her father had a history of stroke.

On examination, her weight was 53.5 kg, her height was 160 cm, and her body mass index was 21 kg/m². Vital signs and the remainder of the examination, including deep tendon reflex and vibration sensation, were normal.

Laboratory test results on admission are shown in Table 1. She had type 1 diabetes susceptible HLA class II haplotype, referred to in Japanese as follows: DRB1*04:05-DQB1*04:01

<table>
<thead>
<tr>
<th>Table 1 Laboratory data on admission</th>
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<tbody>
<tr>
<td>WBC (μl) 4500</td>
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<tr>
<td>RBC (10⁶/μl) 449</td>
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<tr>
<td>Hb (g/dl) 14.0</td>
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<tr>
<td>Ht (%) 42.4</td>
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<tr>
<td>Plt (10⁵/μl) 20.2</td>
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<tr>
<td>TP (g/dl) 7.1</td>
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<tr>
<td>CK (IU/l) 231</td>
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<tr>
<td>AST (IU/l) 16</td>
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<tr>
<td>ALT (IU/l) 17</td>
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<tr>
<td>LDH (IU/l) 155</td>
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<tr>
<td>ALP (IU/l) 260</td>
</tr>
<tr>
<td>γGTP (IU/l) 17</td>
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<tr>
<td>BUN (mg/dl) 13</td>
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<tr>
<td>Cr (mg/dl) 0.5</td>
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<tr>
<td>UA (mg/dl) 3.4</td>
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<tr>
<td>T-Bil (mg/dl) 1.0</td>
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<tr>
<td>CRP (mg/dl) 0.0</td>
</tr>
</tbody>
</table>

TPoAb, thyroid peroxidase antibody (ECLIA); TGAAb, Thyroglobulin antibody (ECLIA); TRAb, TSH receptor antibody; HbA1c, hemoglobin A1c; GA, glycated albumin; FBG, fasting blood glucose; sCPR, serum C-peptide; uCPR, urine C-peptide; uACR, urine albumin to creatinine ratio; GAD Ab, glutamic acid decarboxylase antibody; ICA, islet cell antibody; IA-2, insulinoma-associated protein 2; IAb, insulin antibody; ANA, antinuclear antibodies; RF, rheumatoid factor.

She had mild diabetic autonomic neuropathy and simple diabetic retinopathy but showed no evidence of nephropathy or macroangiopathy. Abdominal ultrasound examination and magnetic resonance imaging showed neither pancreatic tumor nor pancreatic swelling. Thyroid ultrasound examination showed no abnormalities.

Initial treatment consisted of subcutaneous injection of insulin aspart and glargine (12 units/day), which was gradually increased to 32 units/day at day 8 after admission. When her “honeymoon period” set in, she experienced hypoglycemia, and her insulin dosage was reduced to 28 units/day on discharge. Nevertheless she had frequent hypoglycemia, and her insulin dosage was continually reduced. One month after diagnosis, her insulin dosage was reduced to 1 unit/day (insulin glargine 1 unit/day) but her fasting glucose level was still around 80 to 100 mg/dL and postprandial glucose level was around 160 to 190 mg/dL. When she visited her home doctor 2 months after diagnosis, the doctor stopped insulin glargine and prescribed voglibose 0.9 mg/day.

Three months after diagnosis, her GAD antibody titer suddenly increased to 1600 U/mL and thereafter gradually decreased. Results of her self-monitoring glucose levels were 65 to 120 mg/dL after fasting and 120 to 280 mg/dL for postprandial tests, and her HbA1c levels remained under 7%. Up to 3 months after diagnosis, there was no increase in ICA or IA-2 antibody levels, pancreatic enzymes, thyroid dysfunction, or thyroid antibody changes. In addition, interferon was not prescribed for this patient. There was no history of viral infection before the rise of GAD antibody.

Ten months after diagnosis, insulin glargine 1 unit/
GADAb increase after stopping insulin

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the first report that describes an exponential increase of GAD antibody after initiating and stopping insulin in a patient with SPIDDM.

In this case, the GAD antibody titer increased from 6.9 U/mL to 1600 U/mL. It has been reported that GAD antibodies are demonstrable both before and at the onset of SPIDDM, persist for 10-20 years, but show some decline over time [7-10]. However, an exponential increase of GAD antibody titers after diagnosis is rare. Only a few articles have reported a case with increased GAD antibody titers after diagnosis. It is known that patients with autoimmune thyroid disease (AITD) have a higher prevalence of having GAD antibody and have higher levels of GAD antibody than patients without AITD [11, 12]. Irie et al. reported a case of a 62-year-old woman with SPIDDM whose GAD antibody titer increased from 1.9 to 126000 U/ml after emerging Grave’s disease [13]. This case is similar to our case in that the GAD antibody titer increased suddenly and extremely, but our case was not positive for thyroid autoantibodies and showed no abnormalities in an ultrasound examination of the thyroid, suggesting she did not have AITD. It has been reported that GAD antibody titers increase after emerging acute pancreatitis [14] or interferon use [15], but neither serum pancreatic enzyme, abdominal ultrasound examination, nor pancreatic magnetic resonance imaging showed any abnormalities, and interferon was not prescribed in our case.

The exponential increase of the GAD antibody titers occurred shortly after initiating and stopping insulin in this patient. Only four cases have been reported in terms of turning out to be positive for GAD antibodies after insulin administration. Nakamura et al. reported one case with a transient increase of GAD antibody titers with insulin allergy after initiating insulin, [16] and the same authors recently reported two additional cases of insulin-triggered type 1 diabetes [17]. However, their case developed insulin-deficient diabetes after initiating insulin, while our case did not develop insulin-deficient diabetes. Furthermore, our case had neither insulin autoantibodies nor allergic skin lesions. Ito et al. reported a case whose GAD antibody level changed to positive (1.8 U/ml) 5 years after initiating insulin, following an increase to 36.2 U/ml 10 years after insulin initiation [18]. However, this time period was too long and degree of increase in GAD antibody levels too small compared with our case. Therefore, different mechanisms are likely involved.

Discussion

We encountered a case whose GAD antibody increased from 6.9 U/mL to 1600 U/mL. This sudden increase occurred shortly after initiating and stopping insulin therapy. To the best of our knowledge, this is
The actual cause of the sudden increase of GAD antibody and the underlying mechanism in this patient are unclear, but initiating and stopping insulin were the only changes before the GAD antibody increase, and we suppose this might be the reason. However, because this case started and stopped insulin within a few months before the rise of GAD antibody, it is difficult to specify which (or both) affected the rise of GAD antibody. One possibility of the sudden increase of GAD antibody titers is that insulin injections triggered some immune response, following GAD antibody titers increase. It has been reported that proinsulin/insulin may be the target antigen in non-obese diabetes mice and in humans [19, 20]. Thus, starting and stopping external insulin injections might cause exponential increases of GAD antibodies. Nishida et al. suggested that insulin injections induced GAD-reactive and insulin peptide-reactive Th1 cells, resulting in beta cell destruction [17]. They also suggested that type 1 diabetes mellitus (T1DM)-susceptible HLA haplotype and the insulin gene variable number of tandem repeats (VNTR) may play an essential role in insulin-triggered T1DM. Although our case had T1DM-susceptible HLA haplotype, we could not study the insulin gene VNTR. Another possibility is that the profile of GAD antibody changed after the introduction and cessation of insulin injections. It has been demonstrated that GAD antibody titers in stiff-man-syndrome, autoimmune polyendocrine syndrome, and T1DM are different [21-23]. Furthermore, the binding epitope of GAD antibody in patients with SPIDDM and patients with acute insulin dependent diabetes are different [24]. Unfortunately, we could not study the binding region of GAD antibody in the sera before and after introduction and cessation of insulin injections, as changes in the binding epitope of GAD antibodies might have affected the exponential increase in GAD antibodies.

This case had preserved insulin secretion for more than 36 months after insulin administration and an exponential increase in GAD antibody titers. On the other hand, the cases of Nishida et al. became insulin-deficient diabetes several months after insulin administration and an increase in GAD antibody titers (mean duration, 7.7±6.1 months) [17]. These differences suggest that the mechanisms underlying our case and their case might be different. However, it is known that high
GAD antibodies titers are associated with low fasting C-peptide values as a marker of reduced pancreatic beta-cell function [25, 26] and predict insulin requirements [27]. Long-term patient follow up is needed to confirm these findings. In conclusion, we described a case in which GAD antibody titers exponentially increased after initiating and stopping insulin therapy. This case is worth discussing to help clarify the role of the GAD antibodies in SPIDDM.

**Disclosure**

The authors state that they have no Conflict of Interest (COI).

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**References**


