

A case of autoimmune polyendocrine syndrome type I with strong positive GAD antibody titer, followed up with glucose tolerance measured by oral glucose tolerance test

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Submitted: 2016-09-10 Accepted: 2016-11-03 Published online: 2017-01-15

Key words: **autoimmune polyendocrine syndrome type I; glutamic acid decarboxylase; oral glucose tolerance test; impaired glucose tolerance; autoimmune disease**

Neuroendocrinol Lett 2016;37(8):540-542 PMID: 28326749 NEL370816C02 ©2016 Neuroendocrinology Letters • www.nel.edu

Abstract

A 26-year-old Japanese woman presented with adrenal insufficiency, and treatment was started with cortisone and fludrocortisone in 1975. A few years later, she presented with hypoparathyroidism and was diagnosed with autoimmune polyendocrine syndrome type I (APS I), and treatment with calcium and alfacalcidol was started. She was found to have subacute thyroiditis and relative adrenal failure in 2006. Her condition remained stable under treatment with cortisone, fludrocortisone, levothyroxine, calcium lactate, precipitated calcium carbonate and alfacalcidol. While antibodies against pancreatic glutamic acid decarboxylase (GAD) were strongly positive (7,690 U/ml), fasting glucose level was 4.9 mmol/L and HbA1c was 6.3% on admission. As GAD antibody showed a high-titer of >10,000 U/ml and fasting plasma glucose level showed a rising trend, we performed 75-g oral glucose tolerance test (OGTT) 6 years after discharge. Whereas OGTT in 2012 showed impaired glucose tolerance, glucose tolerance had reverted to normal in 2014. A patient with a high-titer GAD antibody does not always have progressive glucose intolerance. GAD antibody positivity is common in not only type 1 diabetes, but also APS I and stiff-person syndrome (SPS). There are differences in recognized epitopes among the three disorders. Epitopes for GAD65 antibody associated with type 1 diabetes are located in the middle region and the COOH-terminal of the GAD65 protein, whereas epitopes associated with SPS reside in the NH2-terminal in addition to the middle region and COOH-terminal. The present case suggests that these differences in epitopes may be related to various pathogenic mechanisms including glucose intolerance.

Abbreviations:

GAD - glutamic acid decarboxylase
IA2 - insulinoma-associated protein 2
IAA - insulin autoantibodies
ZnT8A - zinc transporter 8
LADA - latent autoimmune diabetes in adults

APS I - autoimmune polyendocrine syndrome type I
TSH - thyroid-stimulating hormone
TPO - thyroid peroxidase
OGTT - oral glucose tolerance test
IDDM - insulin-dependent diabetes mellitus
SPS - stiff-person syndrome

INTRODUCTION

The incidence of type 1 diabetes has been increasing worldwide for several decades (Dabelea, 2009). For diagnosis of type 1 diabetes, elevated concentrations of autoantibodies against pancreatic β cells are valuable. The antigens for these autoantibodies are glutamic acid decarboxylase (GAD), insulinoma-associated protein 2 (IA2), insulin autoantibodies (IAA) and zinc transporter 8 (ZnT8A) (Knip *et al.* 2016). Especially, the concentrations of antibodies against GAD are widely used as diagnostic tool and predictive marker of progression for type 1 diabetes. It is also suggested that the autoimmune responses in latent autoimmune diabetes in adults (LADA) and type 1 diabetic patients show different GAD-specific immune responses, particularly in the samples with strong GAD antibody titers (Maruyama *et al.* 2008).

Here we report the first case of autoimmune polyendocrine syndrome type I (APS I) with strong positive GAD antibody titer, followed up with glucose tolerance measured by oral glucose tolerance test.

CASE REPORT

A 26-year-old Japanese woman presented with adrenal insufficiency, and treatment was started with cortisone 75 mg/d and fludrocortisone 0.05 mg/d in 1975. A few years later, she presented with hypoparathyroidism and was diagnosed with APS I, and treatment with calcium 3 g/d and alfacalcidol 2 μ g/d was started. Her parents did not have any autoimmune disorders.

She presented with flu-like symptoms and migratory pain in the neck at the end of July 2006 (at 57 years old). Laboratory tests showed low thyroid-stimulating hormone (TSH) (0.01 μ IU/mL), high free T4 (>100.4 pmol/L) and high C-reactive protein (91.0 mg/L) levels. Anti-TSH receptor antibody and thyroid peroxidase (TPO) autoantibody were negative. The next day she developed fever and disturbance of consciousness, and was admitted to our hospital. She was found to have subacute thyroiditis and relative adrenal failure and was treated with steroids. Her consciousness improved gradually and became clear at 8 days after admission. After discharge, her condition remained stable under treatment with cortisone 50 mg/d, fludro-

cortisone 0.1 mg/d, levothyroxine 75 μ g/d, calcium lactate 6 g/d, precipitated calcium carbonate 1.5 g/d and alfacalcidol 0.75 μ g/d.

While antibodies against pancreatic GAD were strongly positive (7,690 U/ml), fasting glucose level was 4.9 mmol/L and glycohemoglobin (HbA1c) was 6.3% on admission. As GAD antibody showed a high titer of >10,000 U/ml and HbA1c level showed a rising trend, we performed 75-g oral glucose tolerance test (OGTT) 6 years after discharge (at 63 years old). Because OGTT in 2012 showed impaired glucose tolerance (glucose level: before 5.8 mmol/L, 120 min 9.3 mmol/L), she received instructions for diet and physical activity level. Consequently, her glucose tolerance had reverted to normal in 2014 (Table.1). HLA-haplotype in the present case was DRB1*08:03:02-DQB1*05:03:01, which is not susceptible for type 1 diabetes in Japanese patients (Maruyama *et al.* 2007).

DISCUSSION

A patient with a high-titer GAD antibody does not always have progressive glucose intolerance, as this case. APS I is a rare disease, whose prevalence is estimated to be one case per 25,000. 65 kDa glutamic acid decarboxylase (GAD65) is the main antigen of the GAD antibody in patients with type 1 diabetes, and 60 to 80% of patients with type 1 diabetes are GAD65 antibody positive. GAD65 antibody positivity is also found at high frequency (70%) in patients with APS I (Soderbergh *et al.* 2004). Tuomi *et al.* (1996) reported that 17% of patients with APS I (8 of 47) presented with insulin-dependent diabetes mellitus (IDDM); however, there was no association between GAD65 antibody positivity and IDDM among APS I patients.

GAD antibody positivity is common in not only type 1 diabetes, but also APS I and stiff-person syndrome (SPS). There are differences in recognized epitopes among the three disorders (Bjork *et al.* 1994). Epitopes for GAD65 antibody associated with type 1 diabetes are located in the middle region (between amino acids 240 and 435) and the COOH-terminal (between amino acids 451 and 570) of the GAD65 protein, whereas epitopes associated with SPS reside in the NH₂-terminal in addition to the middle region and COOH-terminal (Kim *et al.* 1994).

Tab. 1. Plasma glucose levels and IRI responses to 75-g OGTT.

October, 2012		0 min	30 min	60 min	120 min	180 min	Body weight
glucose	(mmol/L)	5.8	9.6	7.9	9.3	8.1	59.2 (kg)
IRI	(pmol/L)	86	2,160	799	2,938	518	
September, 2014		0 min	30 min	60 min	120 min	180 min	Body weight
glucose	(mmol/L)	5.2	6.7	6.3	7.1	6.1	57.8 (kg)
IRI	(pmol/L)	65	2,592	482	576	576	

OGTT, oral glucose tolerance test; IRI, immunoreactive insulin.

The present case suggests that these differences in epitopes may be related to various pathogenic mechanisms including glucose intolerance.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number 26350905. We thank Dr. Wendy Gray for editing the manuscript.

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