Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5267-20
Intern Med 60: 1423-1426, 2021
http://internmed.jp

【 CASE REPORT 】

Prader-Willi Syndrome with Slowly Progressive Insulin-dependent Diabetes Mellitus

Yuki Tomoda, Yukiyoshi Okauchi, Arichika Deguchi, Yu Takenoshita, Hiromi Iwahashi and Ikuo Mineo

Abstract:
We report the case of a 52-year-old woman with Prader-Willi syndrome (PWS) and diabetes. Her diabetes was managed with sulfonylurea followed by premixed insulin; however, her glycemic control gradually worsened and became unstable. Her urine and blood C-peptide levels were undetectable. She tested positive for anti-GAD antibodies, and had a high-risk genotype - DRB1*09:01-DQB1*03:03 - for slowly progressive insulin-dependent diabetes mellitus (SPIDDM) in the HLA-DR/DQ region, confirming the diagnosis of SPIDDM. Dysglycemia in PWS is thought to be attributable to hyperphagia and obesity. However, the possibility of SPIDDM might be considered if the insulin secretory capacity is almost lost in patients with PWS.

Key words: Prader-Willi syndrome, slowly progressive insulin-dependent diabetes mellitus, insulin secretion capacity, GAD antibody

(Intern Med 60: 1423-1426, 2021)
(DOI: 10.2169/internalmedicine.5267-20)

Introduction

Prader-Willi Syndrome (PWS) is a genetic disorder with implications on the endocrine and neurologic systems, metabolism, and behavior. PWS results from the lack of the expression of genes on the paternally inherited chromosome 15q11.2-q13 (1, 2). In Japan, the frequency of PWS is estimated to be 1 in 10,000-15,000 live births (3). PWS is characterized by craniofacial anomalies, infantile hypotonia, short stature, hyperphagia, obesity, hypogonadism, and mental retardation (4).

Slowly progressive insulin-dependent diabetes mellitus (SPIDDM), also referred to as latent autoimmune diabetes, generally presents as type 2 diabetes mellitus (T2DM) in adults after previous treatment with oral hypoglycemic agents (5, 6). The diagnostic criteria for SPIDDM were reported by Nishimura et al. (7). SPIDDM patients account for 2.0-10.3% of T2DM patients (8-11). In general, patients test positive for at least one of the islet autoantibodies, including anti-islet cell antibodies (ICA) and/or anti-glutamic acid decarboxylase antibodies (GAD Ab) in the early stage of SPIDDM and then test negative after some years.

Dysglycemia in PWS is thought to be attributable to insulin resistance resulting from hyperphagia and obesity. While a few studies have focused on PWS patients becoming insulin-dependent (12, 13), the merger of PWS and SPIDDM has never been reported.

We herein report a case of PWS associated with SPIDDM. An association with SPIDDM should be considered if a patient with PWS shows a progressive decrease in insulin secretory capacity, leading to insulin dependency.

Case Report

A 52-year-old Japanese woman was referred to our hospital for treatment for diabetes and obesity. Her notable medical history included being unable to consume milk after birth due to muscle weakness. Consequently, she was admitted to hospital for 4 months. Her childhood was characterized by floppy infant syndrome and obesity, thin upper lip, small hands and feet, mental retardation, and hypogonadism. At 23 years of age, she was diagnosed with diabetes mellitus. At 28 years of age, she was admitted to hospital due to a worsening of her glucose tolerance. She was diagnosed with PWS based on typical clinical findings and the exis-

Diabetes Center, Toyonaka Municipal Hospital, Japan
Received: May 6, 2020; Accepted: October 13, 2020; Advance Publication by J-STAGE: November 30, 2020
Correspondence to Dr. Yukiyoshi Okauchi, yokauchi0713@gmail.com

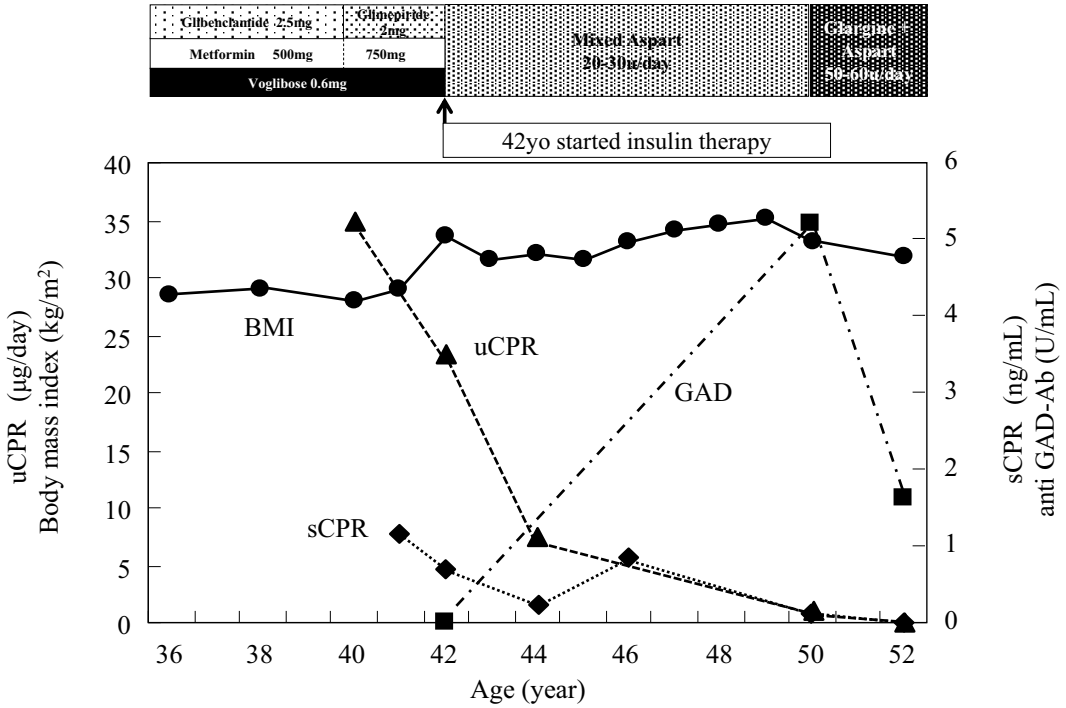

Figure. **The clinical course after 36 years of age, including the patient's body mass index, urinary and serum C-peptide level and anti-GAD antibody level. The duration of the administration of pharmacological agents is represented by the length of each square relative to the years on the x-axis. Changes in the urinary C-peptide level and body mass index are shown by the dashed line and the continuous line plotted against the y-axis, respectively (left). Changes in the serum C-peptide level and the anti-GAD Ab titer are shown by the black dotted line and the long dashed short dashed line plotted against the y-axis, respectively (right). GAD: glutamic acid decarboxylase, CPR: C-peptide immunoreactivity, uCPR: urine CPR, sCPR: serum CPR**

tence of a deletion in chromosome 15 involving bands 15q11.2-q13. Meanwhile, treatment with a sulfonylurea agent was initiated.

Thereafter, treatment with oral hypoglycemic agents was continued; however, her glycemic control gradually worsened, and she was occasionally admitted to hospital. At 42 years of age, when her glycemic control worsened and became unstable, her urine C-peptide immunoreactivity (CPR) level decreased to 23.3 μg/day, and serum CPR level was 0.68 ng/mL. Thus, premixed insulin injection therapy was initiated and the administration of the sulfonylurea agent was stopped. At that time, her GAD Ab level, measured by the radioimmunoassay (RIA) method, was negative (<0.3 U/mL). Two years later, she was readmitted to the hospital and showed a further decrease in endogenous insulin secretion capacity (urine CPR 7.5 μg/day, serum CPR 0.24 ng/mL); thus, intensive insulin therapy with insulin aspart and neutral protamine Hagedorn insulin was initiated (Figure).

At 50 years of age, her urine and serum CPR levels were 1.0 μg/day and 0.1 ng/mL, respectively. Her GAD Ab titer (RIA) was positive [5.2 U/mL (normal range, <1.5 U/mL)] and her basal insulin was changed from neutral protamine Hagedorn insulin to glargine. Two years later, she was referred to our hospital.

A physical examination on admission revealed that her height was 139.5 cm and her body weight was 61.7 kg (body mass index: 31.9 kg/m^2). Her laboratory data are shown in Table. Her plasma glucose and HbA1c levels were 203 mg/dL and 11.2%, respectively. Her GAD Ab titer (RIA) was 1.6 U/mL (normal range, <1.5 U/mL). Her serum levels of fasting CPR and urinary excretion of CPR were as low as <0.1 ng/mL (0.6-1.8 ng/mL) and <0.2 μg/day (20.1-155 μg/day), respectively. We examined her CPR response in a 1-mg glucagon test. ΔCPR, the difference between peak value (<0.1 ng/mL) and the base value (<0.1 ng/mL), was zero. Her human leukocyte antigen (HLA) type was DRB1*09:01-DQB1*03:03, which is a genetic risk marker for Type 1 diabetes (T1DM) or SPIDDM (14). The patient was diagnosed with SPIDDM based on a positive GAD Ab titer and non-insulin requiring period of >3 months.

Discussion

Dysglycemia in PWS is thought to be due to insulin resistance and hyperphagia (15). Currently, reduced insulin secretion has also been claimed as a contributing factor (2). Some reports have indicated that patients with PWS have lower insulin levels and greater insulin sensitivity in comparison to obese controls (16).

Patients with T1DM eventually progress to an insulin-

Table. Laboratory Tests on Admission.

Complete blood count		Reference ranges	Hormone		Reference ranges
WBC (/μL)	9,200	3,500-8,500	ACTH (pg/mL)	12.9	7.2-63.3
RBC (/μL)	491×10^4	430-570	Cortisol (μg/dL)	11.3	4.0-19.3
Hb (g/dL)	14.2	13.5-17.5	TSH (μIU/mL)	3.63	0.35-4.94
Plt (/μL)	22.5×10^4	12.0-38.0	FT4 (ng/dL)	1.14	0.70-1.48
			C-peptide (ng/mL)	<0.1	0.6-1.8
Blood Chemistry		Reference ranges	Renin activity (ng/mL/h)	2.3	0.2-2.3
AST (IU/L)	31	10-37	Aldosteron (pg/mL)	47	30-159
ALT (IU/L)	28	4-40	HbA1c (%)	11.2	4.6-6.2
LDH (IU/L)	229	100-211	Glycoalbumin (%)	32.4	12.3-16.5
γ-GTP (IU/L)	20	8-45	Anti GAD Ab (RIA) (U/mL)	1.6	<1.5
CK (IU/L)	35	60-250	Anti Insulin Ab (nU/mL)	463	<125
TP (g/dL)	7.4	6.7-8.3	TPO-Ab (IU/mL)	7.0	<16
Alb (g/dL)	3.7	3.8-5.1	Urinary C-peptide (μg/day)	<1.1	20.1-155
T-Bil (mg/dL)	0.81	0.20-1.20	Urinary albumin (mg/day)	6.9	≤22.0
BUN (mg/dL)	13	8-20			
Cre (mg/dL)	0.43	0.30-0.90	Urinalysis		
Na (mEq/L)	138	135-147	Protein	(-)	
K (mEq/L)	4.2	3.6-5.0	Glucose	(4+)	
Cl (mEq/L)	99	98-108	Ketone	(-)	
T-Chol (mg/dL)	201	130-219	Occult blood	(-)	
TG (mg/dL)	133	<150			
HDL-C (mg/dL)	47	≥40	Glucagon (1mg) Challenge Test		
Glucose (mg/dL)	206	60-110	0 min C-peptide (ng/mL)	<0.1	
			6 min C-peptide (ng/mL)	<0.1	

WBC: white blood count, RBC: red blood count, Hb: hemoglobin, Plt: platelet count, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: gamma glutamyl transferase, CK: creatine kinase , TP: total protein, Alb: albumin, T-Bil: total bilirubin, BUN:blood urea nitrogen, Cre: creatinine, T-Chol: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, FT4: free thyroxine, HbA1c: hemoglobin A1c, GAD: glutamic acid decarboxylase, TPO: thyroid peroxidase

dependent state, although the speed of progression differs among patients. There have only been a few reports on PWS with T1DM (12, 13). To the best of our knowledge, T1DM-susceptible genes have not been found in the deleted chromosomal region of PWS.

According to the TOKYO Study, there is a possibility that diabetic patients with a high GAD Ab titer (≥10 U/mL) will progress to an insulin-dependent state (17). GAD Ab titers in patients with SPIDDM are considered to be higher in comparison to patients with T1DM; however, course of the decline is similar to that of patients with T1DM. Moreover, cases with low GAD Ab titers (<10 U/mL) also show a lower pancreatic β-cell function and require insulin therapy for good glycemic control in comparison to patients with a negative GAD antibody titer (18).

At 42 years of age, when she required insulin therapy, her insulin secretion capacity was still retained, and her GAD Ab titer was negative. Her GAD Ab titer was 5.2 U/mL at 50 years of age when her insulin secretion capacity was completely lost. Although her GAD Ab titers were not clear between the 42 and 50 years of age, during that period they might have been higher than the values at 50 years of age. Alternatively, her GAD Ab titers might have been as low as approximately 5.2 U/mL during that period, but the β cell function might have been reduced, even when the GAD antibody titer was low, as demonstrated by Umayahara et al. (18). Thus, the pathophysiology of SPIDDM might have developed during that period.

Specific haplotypes on the DRB1 and DQB1 loci are strongly associated with T1DM and SPIDDM. The patient's HLA haplotype, DRB1*09:01-DQB1*03:03, is an HLA haplotype that is associated with an increased risk of developing T1DM and SPIDDM; its frequency in the general Japanese population is approximately 4.5% (14, 19). In addition, the patient's other HLA haplotype, DRB1*13:02-DQB1*06:04, is a neutral type in T1DM. The presence of one susceptible and one neutral haplotype has been reported to be associated with slowly progressive T1DM (14).

When a patient has a risk-associated HLA haplotype and shows a progressive reduction in insulin secretory capacity, an association with SPIDDM should be considered, even in patients with PWS.

In summary, we reported the case of a woman with PWS and SPIDDM. If a patient with PWS shows a progressive reduction in insulin secretory capacity, we should check the patient's GAD Ab, and-when possible-determine the HLA haplotype. If a patient is diagnosed with SPIDDM, even if they have underlying PWS, intensive insulin therapy should be started.

Author's disclosure of potential Conflicts of Interest (COI).
Hiromi Iwahashi: Research funding, Novo Nordisk Pharma, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Taisho Toyama Pharmaceutical, Ono Pharmaceutical and MSD.

Acknowledgments

We thank Dr. Masafumi Koga, Dr. Yuko Nakamura, and Dr. Akinori Kitagawa for the provision of patient's information.

References

1. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med **14**: 10-26, 2012.
2. Heksch R, Kamboj M, Anglin K, Obrynba K. Review of Prader-Willi syndrome: the endocrine approach. Transl Pediatr **6**: 274-285, 2017.
3. Tsuchiya T, Oto Y, Ayabe T, Obata K, Murakami N, Nagai T. Characterization of diabetes mellitus in Japanese Prader-Willi syndrome. Clin Pediatr Endocrinol **20**: 33-38, 2011.
4. Holm VA, Cassidy SB, Butler MG, et al. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics **91**: 398-402, 1993.
5. Kobayashi T. Slowly progressive IDDM. Nippon Rinsho (Jpn J Clin Med) **57**: 607-611, 1999 (in Japanese, Abstract in English).
6. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med **15**: 539-553, 1998.
7. Nishimura A, Matsumura K, Kikuno S, et al. Slowly progressive type 1 diabetes mellitus: current knowledge and future perspectives. Diabetes Metab Syndr Obes **12**: 2461-2477, 2019.
8. Tanaka S, Awata T, Shimada A, et al. Clinical characteristics of slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM): 1st Subcommittee Report on SPIDDM, Committee on type 1 diabetes, Japan Diabetes Society. J Japan Diab Soc **54**: 65-75, 2011 (in Japanese, Abstract in English).
9. Kobayashi T, Nakanishi K, Sugimoto T, et al. Maleness as risk factor for slowly progressive IDDM. Diabetes Care **12**: 7-11, 1989.
10. Yamada K, Yuan X, Inada C, et al. Combined measurements of GAD65 and ICA512 antibodies in acute onset and slowly progressive IDDM. Diabetes Res Clin Pract **35**: 91-98, 1997.
11. Takino H, Yamasaki H, Abiru N, et al. Antibodies to GAD in Japanese patients classified as Type 2 diabetes at diagnosis. High titer of GAD Ab is a predictive marker for early insulin treatment-report of west Japan (Kyushu, Yamaguchi, Osaka) study for GAD Ab (+) diabetes. Diabet Med **19**: 730-734, 2002.
12. Anhalt H, Eckert KH, Hintz RL, Neely EK. Type I diabetes mellitus, ketoacidosis and thromboembolism in an adolescent with Prader-Willi syndrome. Acta Paediatr **85**: 516, 1996.
13. Bassali R, Hoffman WH, Chen H, Tuck-Muller CM. Hyperlipidemia, insulin-dependent diabetes mellitus, and rapidly progressive diabetic retinopathy and nephropathy in Prader-Willi syndrome with del(15)(q11.2q13). Am J Med Genet **71**: 267-270, 1997.
14. Kawabata Y, Ikegami H, Awata T, et al. Differential association of HLA with three subtypes of type 1 diabetes: fulminant, slowly progressive and acute-onset. Diabetologia **52**: 2513-2521, 2009.
15. Nagai T, Mori M. Prader-Willi syndrome, diabetes mellitus and hypogonadism. Biomed Pharmacother **53**: 452-454, 1999.
16. Emerick JE, Vogt KS. Endocrine manifestations and management of Prader-Willi syndrome. Int J Pediatr Endocrinol **2013**: 14, 2013.
17. Maruyama T, Tanaka S, Shimada A, et al. Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus. J Clin Endocrinol Metab **93**: 2115-2121, 2008.
18. Umayahara Y, Ohkusu T, Kubo F, et al. Prevalence and pathophysiological relevance of GAD antibody in Japanese patients with non-insulin-dependent state of diabetes mellitus. J Japan Diab Soc **53**: 341-350, 2010 (in Japanese, Abstract in English).
19. Ikegami H, Noso S, Babaya N, Hiromine Y, Kawabata Y. Genetic basis of Type 1 diabetes: similarities and differences between East and West. Rev Diabet Stud **5**: 64-72, 2008.