Clinical Investigation

Characterization of Diabetes Mellitus in Japanese Prader-Willi Syndrome

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Abstract. Prader-Willi syndrome (PWS) is frequently associated with marked obesity and diabetes mellitus (DM). Although the overall frequency of DM in PWS ranges from 7–20%, there is only limited data available on Japanese patients. This study evaluated five factors associated with DM in PWS: 1) frequency, 2) age of onset, 3) risk factors, 4) long-term complications and 5) treatment. Sixty-five patients, ranging in age from 10 to 53 yr, were studied retrospectively. The frequency of DM in patients over 10 yr of age was 26.2% (17/65 patients). The age of DM onset ranged from 10 to 29 yr with a median age of 15 yr. The body mass index (BMI) was significantly higher in the DM group in comparison with the non-DM group. The number of patients using growth hormone (GH) in the DM group was significantly lower than the number that did not. Proteinuria (urinary excretion of albumin/ creatinine at spot collection: U-Alb/Cr $\geq$300 mg/gCr) was observed in 1/17 patients (5.9%), microalbuminuria (U-Alb/Cr 30–300 mg/gCr) was observed in 4/17 patients (23.5%) and nonproliferative retinopathy was observed in 2/17 patients (11.8%). Among oral hypoglycemic agents, alpha-glucosidase inhibitors (α-GI) were most often used in our patients (10/17, 58.8%). Eleven out of 17 patients (64.7%) had been treated with insulin.

Key words: Prader-Willi syndrome, diabetes mellitus

Introduction

Prader-Willi syndrome (PWS) is characterized by craniofacial anomalies, infantile hypotonia, short stature, hyperphagia, early onset of obesity, hypogonadism, and mental retardation (1). Approximately 70% of cases with PWS are due to a paternal deletion on chromosome

15 (15q11-q13); 25% of cases have maternal uniparental disomy (UPD) of chromosome 15; and the remaining cases result from genetic imprinting mutations and balanced translocation (2). The frequency of PWS is estimated to be one in 10,000–15,000 live births in Japan (3). PWS is associated with marked obesity and a tendency to show an increased risk for the development of diabetes mellitus (DM). Patients with PWS tend to die suddenly and unexpectedly. Leg cellulites and pulmonary embolism secondary to massive obesity and DM are often seen in adult patients (4). The overall frequency of DM in PWS ranges between 7–20 percent (5). Butler reported the prevalence for DM to be 25% in

adult patients (6). However, there are only a few reports concerning the frequency of DM in Japanese PWS patients. This study investigated the frequency, age of onset, risk factors, long-term complications and treatment of DM in patients with PWS.

Subjects and Methods

A total of 153 Japanese PWS patients (96 males and 57 females) ranging in age from 10 mo to 53 yr were enrolled as subjects at Dokkyo Medical University Koshigaya Hospital. Among them 65 patients ≥10 yr of age were selected for the study. Patients above 10 yr of age were selected as the subjects because the youngest patient with DM was 10 yr old. All PWS subjects showed abnormal methylation testing with a polymerase chain reaction (PCR) analysis consistent with the diagnosis of PWS (1, 7). The presence of the 15q11-q13 deletion was identified by fluorescence *in situ* hybridization (FISH) using 15q11-q13 probes. The presence of UPD was determined by PCR using established methods with polymorphic DNA microsatellites from the chromosome 15q11-q13 region. The diagnosis of DM was based on the criteria established by the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus on 1999. Briefly, a diagnosis of DM was made if any of the following criteria were met: 1) fasting plasma glucose (FPG) ≥ 126 mg/dl and/or 2-h oral glucose tolerance test (with 75 g glucose) plasma glucose (2hPG) ≥ 200 mg/dl and/or casual plasma glucose (CPG) ≥ 200 mg/dl are met on two or more occasions; 2) FPG ≥ 126 mg/dl and/or 2hPG ≥ 200 mg/dl and/or CPG ≥ 200 mg/dl are met on at least one occasion accompanied by typical diabetic symptoms and/or HbA1c ≥ 6.5% and/or diabetic retinopathy (8). Detailed medical data including gestational age, birth weight, body mass index (BMI), gender, genotype, growth hormone (GH) use and treatment were obtained from all patients. All medications for DM were chosen

at the clinicians' discretion. The urinary excretion of albumin/creatinine at spot collection (U-Alb/Cr; normal value <30 mg/gCr) was used to evaluate diabetic nephropathy. Proteinuria and microalbuminuria were confirmed by obtaining at least two urine samples over a 3–6 mo period (9). All diabetic patients were examined regularly by an ophthalmologist. The Student's *t*-test, Welch's *t*-test and χ^2 test were used to compare differences between sample groups. A p value of <0.05 was considered to be statistically significant.

Results

The samples (Table 1)

The 65 individuals with PWS included 43 males and 22 females. Their ages ranged from 10 to 53 yr, with a median age of 19 yr. Genetic laboratory tests revealed that 52 patients had a 15q11-q13 deletion and 13 had maternal UPD for chromosome 15.

Frequency of DM (Table 1)

Seventeen out of the 65 patients (26.2%) had developed DM.

Onset of DM (Fig.1)

The age of DM onset ranged from 10 to 29 yr with a median age of 15 yr.

Risk factors (Tables 2 and 3)

There were no significant differences in gestational age and birth weight between the DM and non-DM group. The BMI was significantly

Table 1 Background of PWS subjects (n=65) and frequency of DM

Age (yr)	median	19
	range	10–53
Male / Female		43/22
Deletion / UPD		52/13
Diabetes mellitus		17 (26.2%)

UPD: uniparental disomy.
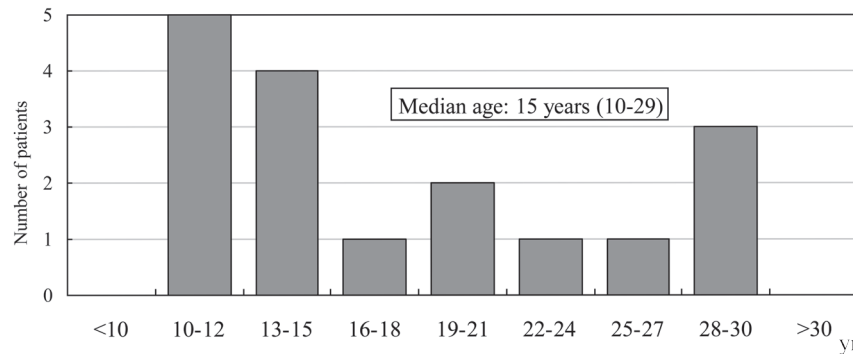
Fig. 1 Onset of DM (n=17).

Table 2 Risk factors 1 (Comparison between the DM and Non-DM group)

	DM	Non-DM	p
n	17	48	
Gestational age (wk)	39.4 ± 2.5	39.3 ± 2.2	NS
Birth weight (g)	$2,670 \pm 368$	$2,620 \pm 423$	NS
BMI (kg/m^2)	43.3 ± 12.7	25.5 ± 8.6	<0.01

NS: not significant.

higher in the DM group in comparison with the non-DM group (p<0.01, Table 2). While gender and genotype made no significant differences, GH use was significantly lower in the DM group (p<0.05, Table 3).

Long-term complications and treatment of DM (Table 4)

Proteinuria (U-Alb/Cr $\geq$300 mg/gCr), microalbuminuria (U-Alb/Cr 30–300 mg/gCr) and nonproliferative retinopathy were observed in 1 (5.9%, case 4), 4 (23.5%, case 2, 3, 7 and 10) and 2 DM patients (11.8%, cases 1 and 10), respectively. All patients were treated with insulin injection or oral hypoglycemic agents. Alpha-glucosidase inhibitors (α-GI) were the most frequently used oral hypoglycemic agents in the DM patients (10/17, 58.8%). Eleven patients (11/17, 64.7%) had been treated with insulin.

Table 3 Risk factors 2 (Comparison of gender, genotype and GH use of DM patients)

Male	Female	p
12 / 43 (27.9%)	5 / 22 (22.7%)	NS

Deletion	UPD	p
13 / 52 (25.0%)	4 / 13 (30.8%)	NS

GH use (+)	GH use (–)	p
3 / 31 (9.7%)	14 / 34 (41.2%)	<0.05

NS: not significant. UPD: uniparental disomy.

Discussion

Obesity is a major health problem in PWS with increased risk for DM and other complications (3). DM in PWS is classified as a "Various genetic syndromes often associated with diabetes" on the etiological classification of DM and related

Table 4 Long-term complications and treatment of DM patients (n=17)

Case	Gender	Genotype	Age of onset (yr)	Diabetes duration (yr)	BMI (kg/m^2)*	GH use	HbA$_{1C}$ (%)#	DN	DR	Treatment
1	M	D	29	9	?	–	7.3	–	NR	S → T
2	M	D	29	3	33.6	–	6.3	Mi	–	α → 30R/30R, A
3	M	D	24	8	45.7	–	9.4	Mi	–	Me, S, α → Q/Q/Q/B, A
4	M	D	12	18	?	–	5.9	P	–	Me, S, T → 30R/30R, Me, A
5	F	U	10	20	?	–	?	?	?	RN/R/RN
6	M	D	29	0	65.7	–	7.0	–	–	α
7	M	D	26	2	68.2	–	5.3	Mi	–	Q/Q/Q/B → Me, α
8	M	D	17	8	35.0	–	9.1	–	–	S, T → Me, S, α,
9	M	D	19	5	35.8	–	7.0	–	–	30R/30R
10	F	D	11	12	42.2	+	6.2	Mi	NR	R/R/R/N, A
11	F	D	12	8	36.4	+	5.8	–	–	Insulin → S, α, Me → none
12	F	D	19	0	50.7	–	6.6	–	–	Me, α
13	M	D	14	5	56.8	–	5.0	–	–	α
14	M	D	15	3	31.7	–	5.8	–	–	30R/30R → Me, α
15	M	U	13	4	42.6	–	5.1	–	–	T, α
16	F	U	12	2	27.6	+	6.1	–	–	30R/30R
17	M	U	13	0	33.5	–	9.5	–	–	30R/30R

M: male. F: female. D: deletion. U: uniparental disomy. DN: diabetic nephropathy. Mi: microalbuminuria (U-Alb/Cr 30–300 mg/gCr). P: proteinuria (U-Alb/Cr ≥300 mg/gCr). DR: diabetic retinopathy. NR: nonproliferative retinopathy. S: sulfonylureas. T: thiazolidinediones. α: alpha-glucosidase inhibitors. A: angiotensin receptor blockers. Me: metformin. 30R: premixed insulin. Q: quick-acting insulin analogue. B: Basal long-acting analogue. R: regular insulin. N: NPH insulin. *: at diagnosis of DM. #: at last follow-up.

disorders of glucose tolerance by the Japan Diabetes Society (8), but the glucose tolerance of these patients is usually similar to that of patients with type 2 DM (T2DM), which is most commonly seen in overweight patients without PWS (5). Even though PWS patients become overweight in early childhood due to an insatiable appetite, onset of DM is generally during adolescence at the earliest (6). Therefore, there are very few clinical reports of DM in children younger than 10 yr of age (10). The frequency of DM in this hospital was 26.2%. The results for the Japanese patients were similar to those for Caucasians, suggesting the absence of racial differences. Although the overall prevalence was similar to that in previous reports, the onset of DM was earlier than that in previous reports (6). This may be due to the higher rate of T2DM in Asian diabetic children than in Caucasians

(11).

Small for gestational age (SGA) is a risk factor for obesity and T2DM in adulthood. Unfavorable influences in the fetal environment may program metabolic homeostasis in later life and affect glucose tolerance (12). This study identified no statistical differences in gestational age and birth weight between the DM and non-DM groups. Only a higher BMI was associated with DM. There is limited information on the risk factors of DM in patients with PWS. However, most studies report that obesity is a major problem for these patients (13). The current results may suggest that the incidence of DM in PWS is strongly correlated with dietary habits after birth.

The potential influence of GH treatment on the risk of DM in PWS is twofold; GH treatment may decrease insulin sensitivity and further

increase the risk of DM in PWS (14), whereas the improvement of body composition in children with PWS on growth hormone therapy may lower the risk of obesity-related diseases, such as DM, high blood pressure and cardiovascular disease (15). In our study, there were significantly fewer patients with DM in the GH use group (9.7% vs. 41.2%, p<0.05). The difference in the ages and BMIs of the subjects in the with and without GH use groups may be a confounding factor in our study. The median age and BMI in the group with GH use were 20 yr (range: 14–23 yr) and 36.4 kg/m^2 (range: 27.6–42.2 kg/m^2), respectively. Meanwhile, the median age and BMI in the group without GH use tended to be higher with 26.5 yr (range: 13–38 yr) and 42.6 kg/m^2 (31.7–68.2 kg/m^2), respectively (data not shown). The indication for GH administration in PWS patients in Japan is limited to children with a short stature. Therefore, patients who had reached adulthood before the approval of GH use in Japan were less likely to be candidates for GH administration. Moreover, GH is not usually indicated for patients who are already obese, and it is likely that the patients treated with GH had been under stricter dietary control since such patients tended to be younger than those without GH treatment. These factors might have resulted in the outcome of the group without GH being less favorable. Despite these limitations, our study showed that previous GH use is not a risk factor for DM in PWS patients. Further study, including a randomized control trial, is therefore warranted to identify the role of GH use in DM with PWS.

There have so far been few reports of diabetes-related complications in PWS (16). The current results showed that there were no progressive complications, such as renal failure and proliferative retinopathy. These findings may be related to the short period of duration of DM. Otherwise, PWS may not be susceptible to diabetic complications. A long period of observation might reveal more accurate data on the frequency and severity of complications.

Due to the fact that the exact mechanism of DM in PWS remains to be elucidated, no definitive treatment strategy for DM with PWS has yet been established. We adopted diet and exercise as the first-line treatment approach in all patients. Indeed, one patient in the current series showed remarkable weight loss (Table 4, Case 11, BMI 36.4 to 17.9 kg/m^2). He was free of insulin and other medicines at the last follow-up. The optimal pharmacological treatment for PWS with DM remains controversial. Generally, metformin is recommended as a first-line pharmacological treatment for T2DM in children and adolescents (17). Since increased insulin resistance is observed in some PWS patients with DM (18), some experts advocate the use of metformin for these patients (19). However, decreased secretion of insulin is also reported in other patients having DM with PWS (5). Administration of thiazolidinediones as well as sulfonylureas tends to cause an increase of body fat (17), and it may not be appropriate for DM with PWS. In the present retrospective study, all drug therapies were selected at the discretion of individual clinicians at multiple facilities. Further study will be needed to establish better management strategies for such patients. Insulin is necessary in cases where there is evidence of insulin deficiency and where the patient's condition is not controlled by other types of management, but it is not recommended in all other cases because it is also associated with increased weight (20). In addition, patients who are on insulin are at risk for hypoglycemia. The patients in this study accepted self-monitoring of blood glucose and insulin injection. PWS is often associated with stubbornness, persistence and obsessive-compulsive symptoms. Such attitudes may be suitable for self-management of insulin therapy. In addition, insulin therapy may be warranted depending on the situation.

In conclusion, the frequency of DM in Japanese PWS patients was 26.2%. The onset of DM was relatively early, between 10 to 15 yr of age. The only risk factor was obesity. GH use

did not increase the risk of DM. Long-term complications of DM were milder than generally expected. Over 60% of the patients had been treated with insulin.

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