Clinical Pediatric Endocrinology

Vol.29 / No.2
April 2020
pp 81–84

Case Report

Efficacy of sodium-glucose cotransporter 2 inhibitor with glucagon-like peptide-1 receptor agonist for the glycemic control of a patient with Prader-Willi syndrome: a case report

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Abstract. Prader-Willi syndrome (PWS) is often related to severe obesity and diabetes mellitus (DM). Clinical findings suggesting the benefits of glucagon-like peptide-1 (GLP-1) receptor agonists for glycemic control of DM in PWS have been recently increasing. However, there are only a few reports describing the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors for PWS. We present a diabetic female with PWS, whose glycemic control was deteriorated at the age of 19 but improved to a certain extent by introducing the GLP-1 analog liraglutide. At the age of 20, the SGLT2 inhibitor empagliflozin was administered. Subsequently, her HbA1c level and body weight markedly decreased. Improvement in both insulin resistance and secretion was observed during the subsequent six months. In addition to GLP-1 receptor agonists, SGLT2 inhibitors may be a potential approach for the management of DM in PWS, especially in young patients whose pancreatic insulin secretion capabilities are still preserved.

Key words: Prader-Willi syndrome, diabetes mellitus, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors

Introduction

Prader-Willi syndrome (PWS), a complex multisystem disorder, occurs due to the lack of expression of the paternally active genes in the critical region on chromosome 15 (15q11.2-q13). Its clinical manifestations include infantile hypotonia, characteristic facial appearance, short stature, hyperphagia, early onset of obesity, hypogonadism, mental retardation, and behavior disturbance (1). The prevalence of diabetes mellitus (DM) in PWS ranges between 7 and 40% (2). In Japan, the frequency of DM has been reported to be 26.2%, whereas the median age of onset is 15 yr (3). Although the majority of patients with DM in PWS present characteristics similar to those with type 2 DM (T2DM), the precise mechanism underlying DM in PWS has not yet been elucidated. Consequently, no definite pharmacological treatment strategy has been established for the management of DM in PWS.

Glucagon-like peptide-1 (GLP-1) analogs or receptor agonists increase insulin secretion and suppress glucagon levels in a glucose-dependent manner. They also delay gastric emptying and increase satiety. The beneficial effect of the GLP-1 receptor agonists for the management of DM in PWS has been recently reported (4–7). Sodium-glucose cotransporter 2 (SGLT2) inhibitors, belonging to a novel class of antidiabetic drugs, reduce plasma glucose concentrations and body weight by inhibiting glucose transportation in the kidney. In 2018, Horikawa *et al*. (8) were the first to report that using the SGLT2 inhibitor as an add-on drug to the GLP-1 receptor agonists could be markedly effective for the glycemic control of an adult patient with PWS. Here, we report a 20-yr-old patient with PWS whose glycemic control was significantly improved following the combination therapy with the SGLT2 inhibitor and GLP-1 analog.

Case Report

The present case study comprised a Japanese female who was born by normal vaginal delivery at the gestational age of 35 wk. Her weight and height

Received: December 10, 2019 Accepted: February 14, 2020
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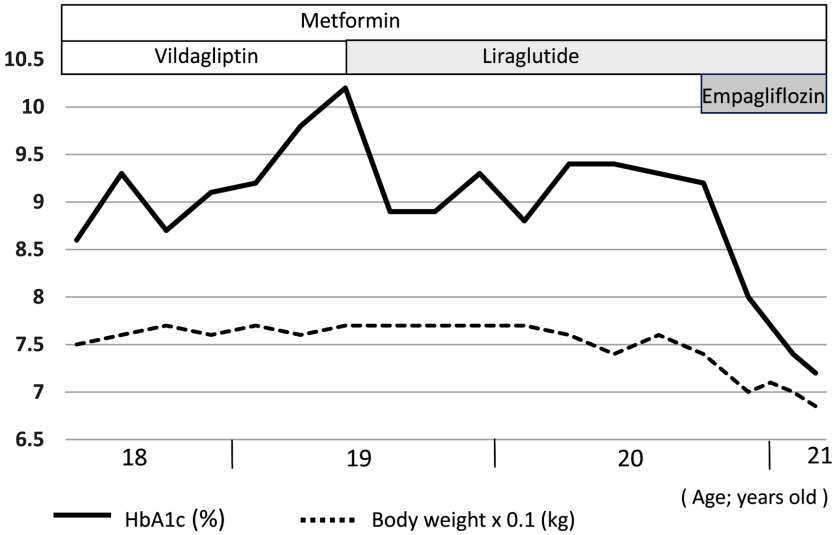

Fig. 1. Clinical course during the recent three years. The solid and dotted lines represent HbA1c (%) and body weight × 0.1 (kg), respectively. Prescribed medications are shown on the top.

at birth were 2,260 g and 44.5 cm, respectively. She was not diagnosed with neonatal asphyxia; however owing to hypotonia, feeding her with a nasogastric tube was necessary for adequate weight gain. The patient was clinically diagnosed with typical features of PWS at the age of one mo, which was later confirmed by genetic testing, revealing abnormal DNA methylation at chromosome 15. During the age of 7–8, noninvasive positive pressure ventilation was required to manage her obstructive sleep apnea and infection-related acute respiratory failure; she was also diagnosed with mental retardation. Her degree of obesity markedly increased from +7% to +161% between the ages 3 and 7, and continued to be approximately +100% till she was 10 yr old, despite administering a trial treatment consisting of diet control and various pharmacological agents, such as mazindol (1 mg/d), herbal medicine (bofutsushosan; 5 g/d), topiramate (100 mg/d) or clonazepam (0.5 mg/d). She was diagnosed as a diabetic at the age of 14 yr. At that time, her body height and weight were 138.1 cm (–3.65 SD) and 79.4 kg (+3.81 SD), respectively, indicating a +94% degree of obesity. Her HbA1c level was 7.1%, and the anti-glutamic acid decarboxylase antibody was negative. The serum C peptide immunoreactivity (CPR) and immunoreactive insulin were 8.9 ng/ml and 52.9 μU/ml, respectively, while her plasma glucose concentration was 170 mg/dl. Diet therapy of 1,400 kcal per day was recommended but was not followed. Metformin (500 mg/d, later up to 1,750 mg/d) was then introduced and dipeptidyl peptidase (DPP)-4 inhibitor (sitagliptin at 50 mg/d, later switched to vildagliptin at 100 mg/d) was administered at the age of 15 yr. Her level of HbA1c had been maintained at approximately 7% but gradually increased after she graduated from the special education school where diet and physical exercise had been regularly monitored. Miglitol (100 mg/d) was administered but not highly effective. At the age of 19 yr and 5 mo, her degree of obesity remained unchanged; however, her HbA1c level deteriorated to 10.2% (**Fig. 1**). The urine CPR remained above 100 μg per day and the serum Δ CPR induced by glucagon administration was 2.3 ng/ml. The homeostasis model assessment (HOMA)-insulin resistance (IR) level was 10.5 and the HOMA-β cell function (HOMA-β) was 44.5 (**Table 1**). These data suggested increased insulin resistance but not insulin deficiency. Vildagliptin was then switched to the GLP-1 analog liraglutide. Although liraglutide treatment (0.9 mg/d) did not significantly decrease her body weight, her HbA1c level improved to 8.8% after 4 mo. However, further improvement was not achieved, and thus, SGLT2 inhibitor, empagliflozin (10 mg/d), was administered at the age of 20 yr and 9 mo. Immediately after, her body weight and HbA1c level markedly decreased. A weight loss of approximately 5.5 kg (7.4%) was achieved during the subsequent 5 mo without altering dietary intake; furthermore, her HbA1c level notably improved from 9.2 to 7.2%. The HOMA-IR level reduced to 6.2, while HOMA-β increased to 85.0. Her elevated liver enzymes and dyslipidemia tended to improve. In addition, the serum β-hydroxybutyrate level was found to be 0.1 mmol/l, and ketonuria was not observed. Noticeably, she showed no sign of diabetic retinopathy, microalbuminuria, or hypertension.

Discussion

PWS is the most common genetic cause of obesity. Dietary restriction, physical activity, and behavior management are fundamental in the prevention and management of obesity in PWS. Although some tips on suitable eating behavior for patients with PWS have been proposed (9), successful weight loss and maintenance are rarely accomplished because of food-seeking behavior and lack of appetite control.

doi: 10.1297/cpe.29.81

Table 1. Physical and laboratory findings

Age	19 yr 5 mon*	20 yr 9 mon**	21 yr 3 mon
Body weight (kg)	76.6	74.0	68.5
BMI (kg/m^2)	40.2	38.9	36.0
FPG (mg/dl)	220	149	139
HbA1c (%)	10.2	9.2	7.2
AST (IU/l)	59	34	34
ALT (IU/l)	70	52	43
TC (mg/dl)	179	162	167
TG (mg/dl)	138	142	98
HDL-C (mg/dl)	28	28	30
HOMA-IR	10.5	–	6.2
HOMA-β	44.5	–	85.0

*, at the time of introducing liraglutide; **, at the time of adding empagliflozin. BMI, body mass index; FPG, fasting plasma glucose concentration; HbA1c, glycated hemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; HOMA-β, homeostasis model assessment β cell function.

In the present case, the patient did not receive GH treatment, as she was already obese when GH therapy was initially approved in Japan for patients with PWS. GH may decrease insulin sensitivity, whereas the improvement of body composition by GH treatment may lower the risk of DM. Tsuchiya *et al*. (3) reported that the frequency of DM in PWS was 9.7% among the patients treated with GH, while 41.2% in the patient who did not receive GH treatment developed to DM. Among the Korean patients with PWS, 72.4% in the DM group and 90.9% in the non-DM group had a history of GH treatment (10). These results may suggest that GH therapy is not a risk factor for DM in patients with PWS.

Although morbid obesity is a strong factor for developing DM in PWS, the relationship between obesity and DM is more complex and appears to differ among PWS and non-PWS individuals. Irizarry *et al*. (11) reviewed recent findings indicating that lower fasting insulin and HOMA-IR levels are observed in adults and adolescents with PWS compared with BMI-matched controls, and additionally, increased insulin sensitivity and elevated levels of adiponectin are recognized in PWS patients. Although the role of β-cell dysfunction in PWS has been considered, it remains to be elucidated. These results suggest that the optimal pharmacological treatment for DM in PWS may not be completely consistent with that for T2DM in non-PWS individuals.

In a previous study published in 2011 (3), α-glucosidase inhibitors and metformin were frequently used and 64.7% of the diabetic patients with PWS had been treated with insulin. Several recent studies reported the effectiveness of GLP-1 preparations for glycemic control in PWS (4–7). Although the role of GLP-1 has not been completely elucidated, GLP-1 receptor agonists seem to be a promising therapy for PWS. However, patients with significant hyperphagia should be properly focused, since these drugs delay gastric emptying. There are several case reports on binge eating-induced idiopathic gastric necrosis and fatal rupture in patients with PWS (12).

SGLT2 inhibitors reduce plasma glucose concentration and body weight by inhibiting glucose absorption in the kidney. They also exert preventive effects on major adverse cardiovascular events, heart failure hospitalization, and progression of renal impairment (13). In contrast, several risks of using SGLT2 inhibitors have been reported, and the latest edition of "recommendations" updated in July 2019 declares safety concerns, such as diabetic ketoacidosis, especially when used in type 1 diabetic patients; hypoglycemia, when used with sulfonylurea or insulin; volume depletion; skin lesion; and urogenital infections. Severe ketoacidosis induced by a combination of a strict low-carbohydrate diet and SGLT2 inhibition was reported in a diabetic patient with PWS (14). This case report cautioned about the consumption of low-carbohydrate diet during the administration of SGLT2 inhibitors and did not demonstrate PWS as a risk factor for SGLT2 inhibitor-related ketoacidosis. We believe that empagliflozin may be significantly effective for glycemic control in the present case, but careful observation and a daily diet schedule is necessary for her insulin secretion capability to avoid the development of severe ketoacidosis.

The combined administration of GLP-1 preparations and SGLT2 inhibitors has been recognized to be effective for overweight patients with T2DM, since these drugs possess several complementary features (15). For example, the appetite of these patients may be stimulated by SGLT2 inhibitors but suppressed by GLP-1 receptor agonists. Although insulin secretion is known to be induced by GLP-1 receptor agonists, it may be enhanced by SGLT2 inhibitors, possibly through different mechanisms, including the attenuation of glucotoxicity and improvement of insulin resistance. It has been reported that a SGLT2 inhibitor, tofogliflozin,

doi: 10.1297/cpe.29.81

increases insulin secretion especially in patients with high insulin levels at the baseline, suggesting that SGLT2 inhibitors may facilitate the recovery of β-cell dysfunction when the insulin secretion capacity is preserved to a certain extent (16). Consistently, both insulin resistance and secretion were improved in our patient.

Although liraglutide seemed to be effective for glycemic control to a certain extent in the present case, the effect of add-on therapy of empagliflozin was evident. We were unable to determine whether the favorable outcome was due to empagliflozin alone or the combined administration of empagliflozin and liraglutide.

SGLT-2 inhibitors with or without GLP-1 receptor agonists may be a suitable approach for treating diabetic patients with PWS, especially young patients whose pancreatic insulin secretion capabilities are still relatively strong. Further case studies are required to elucidate the benefits and risks of the administration of these drugs for the management of DM in PWS.

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