Case Report
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LIRAGLUTIDE TREATMENT IN A PATIENT WITH DIABETES MELLITUS IN PRADER-WILLI SYNDROME

Y. Uzuki[1], K. Uetake[1], T. Toshihiro[2, *]

[1]Department of Pediatrics, Obihiro Kousei Hospital, Obihiro-City, Hokkaido, Japan
[2] Department of Pediatrics, Hokkaido University School of Medicine, Sapporo, Hokkaido, Japan

Abstract

Introduction. Prader-Willi syndrome (PWS) is one of the most common known genetic causes of morbidly obese, resulting in diabetes mellitus (DM) and the management of DM in PWS is difficult. Recently, glucagon-like peptide 1 (GLP-1) receptor agonists have been introduced for the treatment of type 2 DM. Here, we report the use of liraglutide, a GLP-1 receptor agonist, in a patient with DM in PWS.

Case report. A Japanese male patient was diagnosed as having PWS at the age of 1 year. He was mentally retarted and developed morbid obesity. When he was 18 years old, his weight was 79 kg and height was 152 cm (BMI 34.1 kg/m^2). His HbA1c level was 6.2 % and thus DM was diagnosed. Despite several medications, the control of DM worsened and thus at the age of 22 years his body weight and HbA1c further increased (83 kg and 10.8%, respectively). At this time, liraglutide was initiated. His weight and BMI did not change, however his HbA1c level decreased to 7.4 % after one year treatment. He did not have any side effects of liraglutide. This case indicates that GLP-1 receptor agonists may be useful for the treatment of DM with PWS.

Key words: Prader-Willi syndrome, diabetes mellitus, glucagon-like-peptide 1 (GLP-1).

INTRODUCTION

Prader-Willi syndrome (PWS) is one of the most common known genetic causes of obesity with a prevalence of 1:10,000-1:25, 0000 (1, 2). PWS is characterized by severe hyperphagia, mental retardation, short stature, and hypogonadism. As a result of their hyperphagia, PWS patients often become morbidly obese, resulting in diabetes mellitus (DM). The mechanism of uncontrolled food intake is likely to be related to the elevated plasma ghrelin levels, however this is still debatable (1, 3, 4). The management of DM in PWS is difficult, entailing a combination of dietary control, weight reduction, oral hypoglycemic agents and insulin.

Recently, glucagon-like peptide 1 (GLP-1) receptor agonists have been

*Correspondence to: Toshihiro Tajima M.D., Ph.D, Department of Pediatrics, Hokkaido University School of Medicine, N15, W7, Sapporo, Japan, 060-8638, Tel: +81-11-706-5954, Fax: +81-11-706-7898, E-mail: tajeari@med.hokudai.ac.jp

introduced for the treatment of type 2 DM (5, 6). These agonists have been used with promising results in non-diabetic obese patients (7). A novel treatment modality for hyperphagia and DM in PWS may therefore involve GLP-1 receptor agonists. Here, we report the use of liraglutide, a GLP-1 receptor agonist, in a patient with DM in PWS.

CASE REPORT

The patient is now a 23 years-old male. After birth, the patient, who had typical features of PWS such as failure to thrive, hypotonia, developmental delay and characteristic dysmorophic features, was diagnosed as having PWS at the age of 1 year. Fluorescent *in situ* hybridization (FISH) analysis could not detect paternal 15q11-13 deletion, which was responsible genetic region for PWS. DNA methylation analysis with parent-specific primers at the PWS critical region (SNRPN locus) showed only maternal pattern, confirming the diagnosis of PWS (8). He and his family were provided with psychological support together with dietary advice; however, the results were poor, as at the age of 9 years, his weight was 47 kg and he was 132.4 cm in height (BMI 26.9 kg/m^2). He did not undergo growth hormone therapy, because health insurance had not approve growth hormone therapy for PWS during his childhood.

When he was 18 years old, his body weight increased to 75 kg and he reached adult height (152 cm, BMI 32.4 kg/m^2). His genitalia was Tanner stage II, and both of his testicular volume were 6 mL. He did not show polydipsia and polyuria; however, his HbA1c levels had increased to 6.2%. Elevated fasting and postprandial glucose levels were noticed (120 mg/dL and 178 mg/dL after 2 hours, respectively). Thus, his DM was diagnosed.

Further endocrinological examination demonstrated low serum LH (0.14 mIU/mL, normal range 2.03~11.8 mIU/mL), low serum FSH (1.56 mIU/mL, normal range 5.69~16.6 mIU/mL), and low serum testosterone (124 ng/dL, normal range 300~1017 ng/dL).

These findings suggested hypo-gonadotropic hypogonadism. His thyroid hormone status was within normal range (TSH, 0.58 mU/mL, free T4 1.14 ng/dL, and free T3, 2.72 pg/mL, respectively). Regarding hypogonadism, parents did not want further examination and sex hormone replacement.

Hypoglycemia treatment of metformin (750 mg/day) and voglibose (600 mg/day) was initiated. Control of his DM and hyperphagia was difficult, and glimepiride (4 mg/day) was added to his medication. At the age of 21 years, he was hypertensive, and thus angiotensin converting enzyme inhibitor (cilazapril, 1mg) was started. At the age of 22 years, his HbA1c further increased (10.8%). At this time his weight was 83 kg and his height was 152 cm (BMI 35.9 kg/m^2). Laboratory analyses showed that the fasting plasma glucose was 185 mg/dL and urine ketone bodies were negative. Fasting blood C-peptide and insulin levels were 2.4 ng/ml and 10.5 mU/ml, respectively. Urinary C-peptide concentrations measured were 55.0 mg/day (normal range 20.1~155 mg/day). These findings indicated that he was still

Table 1. Weight, BMI, fasting levels of c-peptide, HbA1c before, at 6 and 12 months after the initiation of liraglutide

Time course	Weight (kg)	BMI (kg/m^2)	C-peptide (ng/mL)	HbA1c (%)
Before	83	35.9	2.4	10.8
After 6 months	82.5	35.7	1.8	7.2
After 12 months	83	35.9	2.0	7.4

considered to be insulin resistant, and thus we decided to use liraglutide (0.9 mg/day) together with glimepiride. His body weight, fasting c-peptide, and HbA1C levels were summarized in Table 1. At follow-up 8 weeks later, his HbA1c level had dropped to 7.1%. The treatment was well tolerated and he did not complain of side effects such as bloating, nausea and vomiting. His weight did not decrease, and based on an interview with his mother, his appetite and satiety did not change. After 48 weeks, his weight did not reduce. His fasting C-peptide and insulin were 2.0 ng/mL and 8.2 mU/mL, respectively and HbA1c slightly increased up to 7.4 %. In total therefore, over the entire period of 48 weeks of liraglutide therapy, a reduction of HbA1c levels by 3.4 % was achieved.

DISCUSSION

To our knowledge, the use of GLP-1 agonists in the treatment of DM of PWS has been reported only twice previously (9, 10). Cyganek *et al.* (9) described the use of liraglutide in an 18-years old female. According to their study, over the 14 weeks of therapy, her HbA1c was reduced by 1.9 % and her body weight decreased by 2 kg, and the patient had satiety. Seetho *et al.* (10) have also reported the use of GLP-1 in the treatment of a 19-year old female patient with PWS. They used exenatide, another GLP-1 agonist available for treatment of DM. During the first 6 months of treatment, the patient responded and her HbA1c and body weight were both reduced (11.4% to 9.1%, and 127.8 kg to 92.5 kg, respectively). Furthermore, she showed no side effects. Her glycemic control worsened over the next 6 months (HbA1c rose to 11.8%) and her weight plateaued. It was described, however, that the patient`s satiety remained, and the treatment therefore appeared to be effective.

Recently, the effects of a single dose of exenatide were studied in eight PWS patients, four of which had DM (11). This pilot study demonstrated that exenatide was safe and effective in increasing satiety and lowering glucose in PWS patients. The endogenous appetite peptide ghrelin increases food intake in humans and elevated ghrelin levels may contribute to the pathogenesis of obesity in PWS (3, 4). In the pilot study referred to above, fasting ghrelin levels increased in PWS patients, but exenatide administration did not reduce ghrelin levels. This result suggests that satiety after exenatide

administration may have a direct central role rather than an effect through the ghrelin pathway, a possibility that warrants further study.

In our study, the plasma ghrelin and gut peptides were not measured and his satiety was just evaluated by the interview of his mother. In the literature reported by Cyganek *et al.* (9), their dose of liraglutide was 1.8 mg/day, which is double the dose in the current study. Furthermore, it has been reported the dose of liraglutide ranged from 1.2 to 3.0 mg was more effective for weight loss compared to 0.9 mg of dose (7). Because his body weight did not reduce in our study, the dose of liraglutide may be not enough to suppress the appetite. As the health insurance in Japan just approved the dose of 0.9 mg of liraglutide, we could not increase the dose of liraglutide. Thus, glucose-dependent insulinotropic action and/or suppression of glucagon secretion of liraglutide seem to be effective for reducing his HbA1c level in our patient (5, 6, 11). As long term result of liraglutide for DM in PWS patients has not been determined yet, careful follow-up of this patient is required.

In conclusion, this case including two previous studies indicates that GLP-1 receptor agonists may be useful for the management of DM in PWS patients.

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Conflict of interest.

The authors declare that there is no conflict of interest.

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