Annals of Case Reports and Clinical Studies
Case Report (ISSN: 2834-5673)

Efficacy of Liraglutide in the Management of Hyperphagia, Severe Obesity, and Liver Steatosis/Fibrosis Indices in Prader Willi Syndrome: A Case Report

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Citation: *Zumbolo F, Pugliese G, de Alteriis G, Muscogiuri G, Barrea L, Aprano S, et al. Efficacy of Liraglutide in the Management of Hyperphagia, Severe Obesity, and Liver Steatosis/Fibrosis Indices in Prader Willi Syndrome: A Case Report. Ann Case Rep Clin Stud. 2024;3(3):1-2.*

Received Date: 28 May, 2024; **Accepted Date:** 03 June, 2024; **Published Date:** 06 June, 2024

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ABSTRACT

Objectives: Hyperphagia and severe obesity resistant to dietary interventions represent common clinical features of Prader Willi Syndrome (PWS). Currently, there are no drugs approved for the treatment of obesity in PWS patients. Liraglutide, a long-acting human Glucagon Like Peptide-1 (GLP-1) analogue, is an effective drug for the treatment of non-syndromic obesity. Here we describe a case of a young female patient with PWS affected by persistent hyperphagia and severe obesity resistant to previous weight loss attempts that was successfully treated with liraglutide.

Methods: Liraglutide was administered subcutaneously at a starting dosage of 0.6 mg/day, in weekly intervals until the dosage of 3 mg/day for 6 months in addition to a mild hypocaloric diet. Hyperphagia, assessed by Hyperphagia Questionnaire (HQ), Quality of Life (QoL), assessed by The Short Form-36 (SF-36), anthropometric measurements, metabolic profile, and liver steatosis/fibrosis indices, were evaluated at baseline and at 6 months.

Results: The score of hyperphagia dropped from 16 to 6. Percent Weight Loss (%WL) percent excess weight loss (%EWL) were 12% and 26%, respectively, and associated with improvements in insulin resistance, liver steatosis/fibrosis indices, resulting in the transition from advanced to mild fibrosis.

Conclusions: In our case report, treatment with liraglutide in addition to a mild hypocaloric diet resulted in improvements in hyperphagia, excess body weight, insulin resistance, and liver steatosis/fibrosis indices, which were not previously achieved after diet alone. Liraglutide could represent a valid therapeutic strategy for the management of hyperphagia and weight loss in patients with PWS.

Keywords: Glucagon Like Peptide-1 analogue; Prader Willi Syndrome; liraglutide, hyperphagia, syndromic obesity

INTRODUCTION

Prader Willi syndrome (PWS) is a rare genetic disease, caused by the loss of expression of the paternal genes of chromosome 15q11- q13, determined by paternal deletion (65% - 70%), maternal uniparental disomy (20% - 30%), or imprinting defects (1% - 3%). PWS is characterized by impaired hypothalamic neurodevelopment, severe hypotonia and feeding disorders in the neonatal period, followed by developmental delay and/or intellectual disability, persistent hyperphagia, and endocrine dysfunctions that lead to progressive, severe obesity throughout adult life. Severe obesity is associated with cardiometabolic risk factors, such as hypertension, dyslipidemia, type 2 diabetes and MAFLD (liver disease associated with metabolic dysfunction) that have a significant impact on the overall mortality of the population affected by PWS [1]. Subjects with PWS have low compliance to follow food restrictions due to their increased food-seeking behavior, with inability to comply with the proposed dietary program [1]. Liraglutide is a Glucagon Like Peptide-1 (GLP- 1) receptor analog that controls appetite by increasing satiety, decreases body weight, and improves glycemic control [2]. Currently, there are no drugs approved for the treatment of hyperphagia in patient with PWS [3]. A double-blind multicenter study lasting 52 weeks compared a long-acting GLP-1 analogue with placebo in a group of PWS patients aged 6 to 17 years, obtaining no significant changes in Body Mass Index (BMI), despite an improvement in hyperphagia [4]. Two other case reports in PWS patients on treatment with liraglutide showed a significant weight loss after treatment [5,6]. However, very recently, GLP-1 receptor agonists have been indicated as potentially effective for managing hypothalamic obesity throughout pathways independent of the hypothalamus [7].

CASE DESCRIPTION

Here we report a young female patient with PWS, whose hyperphagia, severe obesity, metabolic profile, and liver steatosis/fibrosis indices improved after 6 months of treatment with liraglutide in addition to a mild hypocaloric diet.

A 28-year-old PWS female patient, diagnosed at birth by genetic testing that identified the deletion of the region located at the proximal part of chromosome 15, was admitted in July 2023 to the obesity outpatient clinic of the Unit of Endocrinology, Federico II University Hospital for severe obesity (BMI 44 kg/m 2), complicated by insulin resistance, MAFLD, and Obstructive Sleep Apnoea Syndrome (OSAS). The patient presented primary amenorrhea, but hormone replacement was discontinued within a few years of starting because of a deep vein thrombosis event. The patient was on therapy with calcium carbonate + vitamin D3 (1g/880 IU) 1 tablet/day; perphenazine 4 mg 2 tablets/day.

MATERIALS AND METHODS

The patient was unable to comply with the prescription of a mild hypocaloric diet (1400 kcal/day, 55% carbohydrate, 30% fat, and 15% protein). Liraglutide 3.0 mg injected once per day was started, without incorporating further diet or lifestyle modifications, for 6 months. After obtaining the written informed consent from the care- giver, liraglutide was initially given at a dose of 0.6 mg/day, and slowly increased over 4 weeks until the final dose of 3.0 mg/day. For safety monitoring, fasting plasma glucose, amylase and lipase were measured to monitor the possible onset of adverse events.

Hyperphagia, assessed by a validate questionnaire (the 11-item version of the Hyperphagia Questionnaire), with a response format on a 5-point scale (scored 1–5), and administered to the patient's usual caregiver [8].

Body composition was assessed by Bioelectrical Impedance Analysis (BIA). Normal values of fat mass and fat free mass in young female were 16% to 20% and 78% to 80%, respectively. Homeostatic Model Assessment-Insulin Resistance (HoMA-IR), the Fatty Liver Index (FLI), the Fibrosis 4 (FIB-4) index, NAFLD Fibrosis Score were calculated, as previously reported [9]. Diagnosis of liver steatosis and fibrosis were obtained by transient elastography (TE-Fibroscan®), as previously reported [9]. In details, controlled attenuation parameter (CAP) was S1 (11% to 33% of liver affected by fatty change): 238 to 260 dB/m; S2 (34% to 66% of liver affected by fatty change): 260 to 290 dB/m; S3 (>67% of liver affected by fatty change): 290 to 400 dB/m. Stiffness threshold values were F1 (little or no scarring in liver) ≤ 7.5 kPa; F2 (moderate scarring in liver) 7.5 to 10 kPa; F3 (severe scarring in liver) 10 to 14 kPa; F4 (very severe scarring in liver) ≥ 14 kPa.

RESULTS

No relevant side effects were observed during treatment. As reported in Table 1, after 6 months of therapy, the score of hyperphagia dropped from 16 to 6, with significant reduction in food seeking (Table 1). Patient obtained a weight loss of 10.5 kg, percent Weight Loss (%WL) and percent Excess Weight Loss (%EWL) were 12% and 26%, respectively. We also observed a reduction in waist circumference of 10 cm and in fat mass (51.2 *vs* 47.9%), and improvement in the percentage of lean mass from 48.8% to 51.4% (Table 2). Weight loss was associated with the improvement in insulin resistance, assessed by HoMA-IR, despite comparable fasting plasma glucose levels (Table 3). In table 4 we reported liver steatosis/fibrosis indices. In particular, we observed a relevant reduction in liver fibrosis, resulting in the transition from severe (F3) to moderate fibrosis (F2), in association with improvements in FLI and NAFLD fibrosis score (Table 4). In addition, there was an increase in QoL, assessed by Short Form-36 (SF-36), with an improvement in role limitations due to physical health and to emotional problems. The patient was motivated to start a program of structured physical activity.

Table 1: 11-items Hyperphagia Questionnaire (HQ) administered to the patient's usual caregiver at baseline and a after 6-month treatment with liraglutide [8].

	Base line	Post Treatment
During the past 2 weeks, how upset did the person generally become when denied a desired food?	2	1
During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?	1	1
During the past 2 weeks, once your child thinks about food, is it easy for you or for other people to divert his attention away from food to other things?	2	1
During the past 2 weeks, how often did the person forage through trash for food?	0	0
During the past 2 weeks, how often did the person get up at night to food seek?	0	0
During the past 2 weeks, how persistent was the person in asking or looking for food after being told "no" or "no more"?	2	0
During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food?	3	3
During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?	2	1
During the past 2 weeks, when others tried to stop the person from asking about food, how	1	0

distressed did he or she generally appear?		
During the past 2 weeks, to what extent can your child be shrewd or quick in getting food?	1	1
During the past 2 weeks, how often did food-related behavior interfere with the person's normal daily activities, such as self-care, recreation, school, or work?	2	1
TOTAL	16	6

Table 2: Anthropometric characteristics and body composition at baseline and a after 6-month treatment with liraglutide.

	Baseline	Post Treatment	Δ
HEIGHT (cm)	146	146	-
WEIGHT (kg)	93.7	83.2	10.5
BMI (kg/m2)	44	39	5
WAIST CIRCUMFERENCE (cm)	109	99	10
FAT MASS (Kg)	47.9	40.5	7.4
FAT MASS (%)	51.2	47.9	3.3
LEAN BODY MASS (Kg)	45.8	42.7	3.1
LEAN BODY MASS (%)	48.8	51.4	2.6

Body composition was evaluated by Bioelectrical Impedance Analysis (BIA). Normal values of fat mass and fat free mass in young female were 16% to 20% and 78% to 80%, respectively.

Table 3: Metabolic profile at baseline and a after 6-month treatment with liraglutide.

	Baseline	Post Treatment	Normal values
Fasting glucose (mg/dL)	75	67	70-110
Fasting insulin	33.7	16	04-24
HbA1c (%)	5.9	5.4	4.0-6.0
(mmol/mol)	41	36	21-42
HoMA-IR	6.2	3.2	<2.5
Total cholesterol (mg/dL)	152	155	<190
HDL-cholesterol (mg/dL)	37	44	>50
LDL-cholesterol (mg/dL)	100	96.2	<115
Triglycerides (mg/dL)	75	74	<150
AST (mU/ml)	26	18	10-50
ALT (mU/ml)	26	20	10-50
Amilase	53	67	28-100 U/l
Lipase	55	71	13-60 U.I./l

HbA1c: Glycated Hemoglobin; HoMA-IR: Homeostatic Model Assessment Insulin Resistance; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

Table 4: Liver steatosis/fibrosis and liver indices at baseline and a after 6-month treatment with liraglutide.

	BASELINE	POST TREATMENT	Normal values
Stiffenss (kPa)	13 (F3)	8 (F2)	2–4 kPa
CAP (dB/m)	360 (S3)	301 (S3)	<237 dB/m
Steatosis	S3	S3	
Fatty liver index	92	84	<60
Fibrosis-4 index	0.41	0.4	< 3.25
NAFLD Fibrosis score	-0.68 (Significant fibrosis)	-1.44 (No significant fibrosis)	< -1.455

CAP: Controlled Attenuation Parameters. Stiffness and CAP were evaluated by transient elastography.

DISCUSSION AND CONCLUSION

We reported that the 6-month administration of liraglutide, in addition to a mild hypocaloric diet, induced meaningful reductions in the score of hyperphagia and body weight in a young female with PWS, in association with improvements in insulin sensitivity and liver steatosis/fibrosis indices.

These results let us to speculate that the reduction in hyperphagia could be attributed either to the well-known effects of GLP-1 on the regulation hunger/satiety circuit and insulin sensitivity. In our case report, the sustained weight loss and the reduced insulin resistance induced by liraglutide contributed to reduce liver damage, favoring a reduction in the liver steatosis/fibrosis indices, albeit liraglutide direct effects in reducing the risk of MAFLD progression cannot be excluded [10].

These novel findings expand the knowledge on further targets of treatment with GLP-1 receptor agonists in PWS patients, commonly unable to comply with the nutrition programs, and shed new light on the management of life-threatening complications in PWS.

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