CASE REPORT

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Liraglutide Treatment in a Morbidly Obese Adolescent with a *MC4R* Gene Variant: Side Effects Reduce Success

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What is already known on this topic?

Melanocortin-4 receptor gene (*MC4R*) defects cause monogenic obesity. In this situation, management of obesity is challenging because of excessive appetite and standard methods are unlikely to achieve weight loss over the long term. Recently, liraglutide treatment has been reported to provide weight loss in these patients with only gastrointestinal side effects.

What this study adds?

We present a long (43 weeks) experience of liraglutide treatment in an adolescent patient carrying a *MC4R* variant. Unfortunately, the drug could not be tolerated for a longer period due to gastrointestinal side effects, and discontinuation of treatment led to rapid weight gain.

Abstract

Variants of the melanocortin-4 receptor (*MC4R*) gene are the most common cause of monogenic obesity. It has been shown that, while obesity cannot be controlled with diet and exercise, glucagon-like-peptide-1 receptor agonists (GLP-1 RA) provide weight loss in the short term. In this paper, our experience with liraglutide treatment in an adolescent patient carrying a *MC4R* gene variant is presented. A female patient was admitted first at the age of 12.5 years with a complaint of progressive weight gain. She had marked excess of appetite since infancy. On physical examination of the pubertal female patient with a body mass index (BMI) of 36.1 kg/m^2 (3.48 standard deviation score), there was no pathological finding except diffuse acanthosis nigricans. Laboratory examinations revealed only insulin resistance. Weight loss was not achieved with lifestyle changes, metformin and orlistat treatments. On genetic examination, a sporadic heterozygous c.206T > G(p.I69R) variant that had been reported previously, was found in *MC4R* gene. Treatment with the GLP-1 RA, liraglutide, was initiated and a 19.2% reduction was achieved in the body weight and BMI at the end of 32 weeks. However, the patient, whose treatment compliance was disrupted due to significant gastrointestinal complaints, returned to her former weight within a few months (13 weeks) after treatment was stopped. In this case with a known pathogenic variant in *MC4R* gene, decrease of appetite and weight loss were achieved with liraglutide treatment, but side-effects of this treatment led to discontinuation of therapy. In such cases, there is need for effective and tolerable treatment options.

Keywords: Melanocortin-4 receptor defect, obesity, treatment, liraglutide, side effect

Introduction

Variants of the melanocortin-4 receptor (*MC4R*) gene are the most common cause of non-syndromic monogenic obesity (1). The interaction of MC4R with alpha-melanin stimulating hormone causes a decrease in appetite and food intake. Pathogenic variants of the *MC4R* gene located on chromosome 18q21.32 cause early onset, severe obesity. Dominant inherited obesity due to variants of the *MC4R* gene in humans was first described in 1998 (2). Today, more than 300 variants in the gene are known (3). The frequency of variants in the *MC4R* gene in individuals

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with early onset and severe obesity has been reported to be 5.7-8.6% (1,4,5). Early-onset severe obesity, tall stature, hyperphagia, increased lean body mass, normal pubertal age, and normal fertility have been reported in these individuals (1,4). Hyperinsulinemia is a common finding of the disease, and no pathology has been found in other hormones. Farooqi et al. (1) reported that 23 of 29 cases, in whom they detected variants in the *MC4R* gene, carried heterozygous variants, while six carried homozygous variants, and the phenotype was more severe in cases carrying homozygous variants. Currently, there are no specific treatment method recommended for the management of obesity due to *MC4R* variants. Long-term success is unlikely with lifestyle changes (diet, exercise, behavioral therapy) alone (6,7). A study has been published showing that subcutaneous use of the glucagon-like-peptide-1 receptor agonist (GLP-1 RA) liraglutide 3 mg/day for 16 weeks reduced appetite in these cases and provided associated weight loss compared to obese controls (8). This study also reported gastrointestinal side effects (nausea, vomiting, abdominal pain, diarrhea, constipation, reflux) which were generally mild and transient. Subcutaneous liraglutide was generally well tolerated in clinical trials among obese and overweight adults. Most of the side effects reported during treatment were gastrointestinal complaints. The most common causes of discontinuation of treatment were nausea, vomiting and diarrhea (9). In an another study, conducted on a small number of patients with heterozygous *MC4R* variants, weight loss, which was not different from placebo, was found after four weeks of treatment with the MC4R agonist Setmelanotide (Phase 1b study) (3). However, these two drugs have not yet been used in larger patient groups with *MC4R* variants, especially in the long-term. In studies evaluating the efficacy of bariatric surgery in this patient group, the most frequently used method was gastric bypass and in most of these studies, similar weight loss was obtained compared to obese patients without *MC4R* variants (10). However, long-term results are contradictory and there was lower success in some variants compared to others. In this report, we present our experience with liraglutide treatment in a morbidly obese, adolescent girl with a variant in the *MC4R* gene.

Case Report

The female patient was first admitted at the age of 12.5-years with a complaint of excess weight. She was born at 3000 g at term, and fed with breast milk until the age of three, supplementary food was added after six months of age, her motor-mental development was normal and she was obese since infancy. She was followed up for cyclical neutropenia and recurrent urinary tract infection, and had tonsillectomy and appendectomy operations. There was no history of serious obesity in the family. On admission, her body weight (BW) was 89 kg (> 97th percentile), height was 157 cm (50-75 percentile), and BMI was 36.1 kg/m^2 [+3.48 standard deviation score (SDS)]. On physical examination, there was no goiter and the pubertal stage was Tanner 3. Cervical and axillary acanthosis nigricans was present. She looked obese with a diffuse body fat distribution. Her mental status was normal. There was no dysmorphism. Laboratory examinations revealed leukopenia and high fasting insulin level (Table 1). Hepatosteatosis was not detected on abdominal ultrasonography. The patient, who was recommended dietary, exercise, and metformin 2x500 mg (oral) treatments, could not adapt to diet and exercise, and did not use metformin regularly. In the oral glucose tolerance test, performed at the age of 13.9 years, serum glucose and insulin levels at the 120th minute were 163 mg/dL and 244 mcIU/mL, respectively. Glycohemoglobin was 5.5% (normal range 4.5-6.5). When she was 17.2 years old, her BMI was 48 kg/m^2 (+4.5 SDS). She had excessive appetite, could not stay on diet and did not use metformin treatment regularly because of nausea and dizziness. She was recommended orlistat 2x120 mg orally in addition to diet, exercise, and metformin treatment. Since the patient had early onset severe obesity and hyperphagia, a gene panel targeted for genetic obesity was performed. The patient was heterozygous for the c.206T>G(p.I69R) (NM_005912.3) variant in the *MC4R* gene, which had been previously described (10,11). Since this variant was not detected in the parents, it was considered *de novo*. When the patient was 17.9 years old, her BMI was 52.87 kg/m^2 (+4.89 SDS), and upon obtaining the consent of the family, liraglutide treatment was initiated (8). In the first week of treatment, a dose of 0.6 mg/day was administered subcutaneously, then the dose was increased by 0.6 mg once a week, and increased to the full dose (3 mg/day) in the fifth week. Her appetite reduced with treatment. Weight loss achieved after five weeks of treatment was 4.8%. However, nausea, bloating, belching, intermittent abdominal pain, and gas-related pain became more pronounced with the increase to the full dose. Since gastrointestinal side effects associated with liraglutide therapy have been described (8,9), the dose was reduced to 1.8 mg/day, which the patient reported she could tolerate. During the treatment process, the menstrual cycle delayed once. When the dose of liraglutide was increased to 2.4 mg/day, due to slowing of the weight reduction rate, the gastrointestinal complaints recurred and the dose was reduced again to 1.8 mg/day. At the end of 32 weeks of regular use of the drug, a 19.2% reduction was achieved in her BW and BMI (Table 2). Since gastrointestinal

complaints started with the initiation of the drug and became more pronounced with increasing the dose, and were relieved with dose reduction, these gastrointestinal symptoms were thought very likely to be drug side effects. The patient, who could not tolerate the gastrointestinal side effects, was observed to gain weight when she stopped taking the drug for two weeks. After starting the drug at a dose of 1.8 mg/day, the weight gain stopped, but the patient decided to discontinue the drug and did not come to the follow up visits after 43 weeks of treatment initiation. When the patient was contacted by phone, it was learned that she returned to her pre-treatment weight (145 kg) a few months after she discontinued the drug.

Table 1. Results of laboratory analysis of the patient on first admission

Test	Results	Reference range
White blood cell count (10^3/mL)	2.5	4.3-10.3
Hemoglobin (g/dL)	12.6	13.6-17.2
Mean corpuscular volume (fL)	80.7	80.7-95.5
Platelet count (10^3/mL)	242.000	150-400
Alanine aminotransferase (IU/L)	15	0-55
Aspartate aminotransferase (IU/L)	19	5-34
Uric acid (mg/dL)	5.4	2-5.5
Total cholesterol (mg/dL)	151	< 170
Low density lipoprotein (mg/dL)	98	< 130
High density lipoprotein (mg/dL)	44	40-60
Triglyceride (mg/dL)	45	< 150
Free thyroxine (ng/dL)	0.89	0.65-2.3
Thyroid stimulating hormone (µIU/mL)	3.5	0.33-6.0
Cortisol µg/dL (nmol/L)	9.67 (266.8)	5-23 (138-635)
ACTH pg/mL (pmol/L)	23.6 (5.20)	7.2-63.3 (1.6-13.9)
Cortisol after 1 mg dexamethasone µg/dL (nmol/L)	1.0 (27.6)	< 1.8 (49.7)
Luteinising hormone (IU/L)	0.77	0.1-12 Tanner 3
Follicle stimulating hormone (IU/L)	5.7	1.5-12.8 Tanner 3
Estradiol (pg/mL)	80.2	7-60 Tanner 3
Fasting glucose mg/dL (mmol/L)	97 (5.4)	60-100 (3.3-5.6)
Fasting insulin µIU/mL (pmol/L)	50.8 (352.8)	6-27 (41.7-187.5)
Glucohemoglobin (%)	6	4-6
Oral glucose tolerance test 120' glucose mg/dL (mmol/L) 120' insulin mg/dL (mmol/L)	 112 (6.2) 41.5 (288.2)	 < 140 (< 7.8) < 75 (< 520.8)

ACTH: adrenocorticotropic hormone

Table 2. Changes in body weight and body mass index during liraglutide treatment in the follow-up period

Week	Dosage mg/day s.c	Weight kg	Loss of weight kg (%)	BMI kg/m²	Loss of BMI kg/m² (%)
0	0.6	144.8	-	52.87	-
5	3*	137.9	6.9 (4.8)	50.32	2.55 (4.8)
8	1.8	134	10.8 (7.5)	48.90	3.97 (7.5)
19	2.4	130.8	14.0 (9.7)	47.75	5.12 (9.7)
26	2.4*	124	20.8 (14.4)	45.27	7.6 (14.4)
32	1.8*	117	27.8 (19.2)	42.72	10.15 (19.2)
36	After two weeks of treatment cessation	124	20.8 (14.4)	45.27	7.6 (14.4)
38	1.8	124	20.8 (14.4)	45.27	7.6 (14.4)
43	1.8	126	18.8 (13.0)	46.00	6.87 (13.0)
56	0 (13 weeks after treatment cessation)	145**			

*Significant gastrointestinal side effects. s.c: subcutaneus. **Weight measurement at home was learned over the phone.
BMI: body mass index

Genetic Methods

DNA obtained from the patient's peripheral blood sample for genetic analysis was subjected to fragmentation, barcoding, library creation, target enrichment and amplification, and loaded into the next generation sequencing device according to the protocol suggested by the manufacturer (MiSeq, Illumina, San Diego, California). A custom panel containing 41 obesity-related genes (*DYRK1B, LEP, LEPR, MC4R, NR0B2, POMC, UCP3, ADRB2, ADRB3, AGRP, MC3R, NTRK2, PCSK1, SIM1, CARTPT, ENPP1, PPARB, PPARGC SDC3, UCP1, ADIPOQ, NAMPT, CFD, RETN, PPARGC1A, CCK, NPY, SLC2A4, ADD1, SREBF1, PTPN1, IRS-1, GHRL, BDNF, NEGR1, SH2B1, GIPR, TMEM18, FTO, SLC22*) was used for sequencing. Bioinformatics analyzes were performed using Qiagen Bioinformatics solutions (Quiagen, Hilden, Germany) software (QCI Analyze Universal 1.5.0 and Qiagen Clinical Insight Interpret) (4). The c.206T>G, p.I69R variant in *MC4R* gene detected and was also analyzed and confirmed by Sanger sequencing. The amplicon was analyzed by direct sequencing with ABI 3500 (Life Technologies, Waltham, MA, USA). Analysis of the sequence result was performed by Variant Surveyor Programme (SoftGenetics, USA).

Discussion

In this study, an adolescent obese girl with a heterozygous variant in *MC4R* gene who was treated with liraglutide was presented. She achieved weight loss with liraglutide treatment, but could not continue therapy due to gastrointestinal side effects and regained weight after discontinuing the drug. MCR4 defects are characterized by early onset severe obesity, hyperphagia (more prominent especially in younger ages), increased linear growth, and insulin resistance (1). Our patient had excessive appetite and hyperphagia from infancy, and her obesity was worsening. After considering that her obesity may have a genetic cause, gene panel testing was performed and a heterozygous, sporadic variant, c.206T>G, p.I69R, was detected in the *MC4R* gene This variant was previously reported in two morbidly obese children of Iraqi origin (11,12). In keeping with this previous report, the pubertal development of the presented case case was normal and menarche age was 13.5 years. In addition to clinical and laboratory findings of insulin resistance, she also had cyclical neutropenia and recurrent urinary tract infection. It was thought that these findings, which were not described in the previous report, may be incidental.

A standard method for obesity management has not been defined in obese patients with *MC4R* variants. In some of the studies investigating the effect of lifestyle change on weight loss in these patients, it was reported that patients with variants achieved weight loss similar to controls, but this could not be sustained in the long term (6,13). Trier et al. (7) reported that BMI SDS could be reduced in the control group after an average of 1 year of lifestyle change but not in cases with *MC4R* variants. Initially, lifestyle changes and oral metformin were recommended to our patient for obesity management. However, she could not limit food intake, continued to binge, and BMI, and BMI SDS increased at each visit. The addition of orlistat, which is an Food and Drug Administration (FDA) approved drug in the treatment of obesity in children, was also not effective. It has been reported that patients with heterozygous variants in the *MC4R* gene experienced a similar weight loss (6%) compared to the control group after 16 weeks of treatment with GLP-1A liraglutide (3 mg/d, subcutaneous) (8). There were no studies reporting long term data and evaluation after the discontinuation of the treatment. Bariatric surgery, especially with gastric bypass, has been reported to have similar results in terms of weight loss for 1-3 years, in patients with *MC4R* defect compared to control obese patients. In some studies it has been shown that the long-term effects continued for 5-7 years and in others it was reported that the patients regained weight at the end of 5 years; notably, some studies have not elucidated the mechanisms of pathogenicity of the variants (10).

Liraglutide was approved by the FDA in 2014 for the treatment of obesity in adults. Later, in April 2020, the FDA approved the use of the drug in adolescents who met the criteria of age ≥12 years, BMI ≥30 kg/m^2 and BW >60 kg). In the presented patient, liraglutide treatment was started on 20th June 2019, only 1-2 months before she was 18 years of age. In our patient, after 32 weeks of treatment with liraglutide, a 19.2% reduction was achieved in BW and BMI. However, the treatment could not be continued due to intolerable gastrointestinal complaints, especially at doses above 1.8 mg/day. It was learned that the patient returned to her initial weight within months after stopping the treatment. Gastrointestinal complaints were the most commonly reported side-effects during liraglutide therapy. In clinical studies of adult obese patients, it was reported that these side effects were usually well tolerated but also that they led to discontinuation of treatment in a small proportion of patients (1.4-2.9%) (9).

Since appetite control is poor due to genetic pathology in this group of patients, it seems that it is more difficult to maintain long-term effectiveness of the treatment. Therefore, in order to increase success in obesity management and to maintain it for a longer period, the side effects of existing treatment options should be decreased or surgical and medical

treatments should be combined or new treatment options should be investigated.

Conclusion

Monogenic obesity should be considered in patients with early onset obesity and in whom appetite control cannot be achieved. In this case with a known *MC4R* variant, liraglutide treatment provided a decrease in appetite and 19.2% reduction in BW and BMI after 32 weeks of treatment. However, the treatment could not be continued due to side effects and she returned to her previous weight after a period of a few months after the discontinuation of the drug. In such cases, there is a need for effective treatment options with tolerable side effects for effective long-term management.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Emine Çamtosun, Ayşehan Akıncı, Leman Kayaş, Nurdan Çiftci, Concept: Emine Çamtosun, Ayşehan Akıncı, Design: Emine Çamtosun, Ayşehan Akıncı, Data Collection or Processing: Emine Çamtosun, Analysis or Interpretation: Emine Çamtosun, Ayşehan Akıncı, İbrahim Tekedereli, Literature Search: Emine Çamtosun, Writing: Emine Çamtosun, Ayşehan Akıncı, İbrahim Tekedereli.

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