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Pharmacological Treatment of a Patient with Life-long Obesity and Heterozygous Complete loss-of-function Melanocortin 4 Receptor Mutation

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Abstract

The heterozygous melanocortin 4 receptor (MC4R) mutation is considered a primary factor in 2% to 4% of patients with obesity. Pharmacological treatment, including long-term, is emerging as a new standard for obese patients; however, there are no published reports on treatment outcomes in obese patients with documented MC4R mutations. Weight loss occurs with diet restriction or bariatric surgery and is often followed by a weight regain phase in patients with or without the MC4R mutation, indicating the need for an alternative approach to weight loss such as pharmacological treatment.

This case study describes a 48-year-old woman who experienced lifelong obesity and a history of dieting that started in childhood with episodes of weight loss followed by weight gain. Her highest weight was 320 pounds in 2007. Her family's medical history included diabetes, prediabetes, and obesity. She presented to the clinic in January 2013 weighing 286.2 pounds with at-risk cardiovascular and cardiometabolic profiles. Treatment was initiated to control insulin resistance and metabolic syndrome, lower cholesterol and triglycerides, and manage hypothyroidism. Weight-loss treatment also began with a combination of bupropion and naltrexone or carbonic anhydrase inhibitors and naltrexone. Her on-treatment nutrition included eating from all food groups without counting calories or excessive exercise. In late 2014, she tested positive for a heterozygous complete loss-of-function MC4R gene mutation and weighed 213 pounds. The patient's lowest weight while on treatment was 166 pounds in August 2015. By November 2016, after experiencing partial weight regain, her weight had been stable for 6 months at approximately 198 pounds,a 30% reduction in weight from 2013.

Pharmacological treatment is emerging as a recommended approach to weight loss. This case is an example of how, despite partial weight regain after weight loss, targeted pharmacological treatment can improve long-term outcomes including in patients with the MC4R complete loss-of-function mutation.

Keywords: Obesity: Melanocortin type-4 receptor; MC4R; Pharmacological agent; Diet; Bariatric surgery; Weight loss

Abbreviations: HDL: High Density Lipoprotein; LDL P: Low Density Lipoprotein Particle; LOF: Loss of Function; MC4R: Melanocortin Type-4 Receptor; WHO: World Health Organization

Introduction

According to the World Health Organization (WHO), the worldwide prevalence of obesity more than doubled between 1980 and 2014 [1]. In the United States, the Centers for Disease Control and Prevention reported the prevalence of obesity from 2011 to2014 was 36.5% among adults and 17% among youth (2 years to 19 years) [2]. The WHO attributes the fundamental cause of overweight and obesity to the long-held notion of an energy imbalance between calories consumed and calories expended [1].

While overfeeding may be the cause of weight gain in some cases, scientists recognized as early as the first part of the 20th century that some people with weight problems could not be cured by radical diet restriction and that a faulty metabolism driven by hormones contributed to weight problems [3,4].

Furthermore, in the 21st century, the traditional treatment of diet and exercise for many overweight patients was considered to be effective only for a short time with many patients regaining the weight they lost or weighing more than their pre-diet weight [5-8].

A significant genetic component is associated with obesity, and mutations in melanocortin type-4 receptor (MC4R) are the most common genetic cause of obesity [9,10]. Since the MC4R regulates metabolic functions including energy expenditure, appetite, and insulin regulation, the impact of MC4R malfunction contributes to the pathophysiology of obesity in affected patients. Some of these mutations reduce gene function; others eliminate function altogether. Patients with the loss-of-function (LOF) MC4R mutation experience an increased appetite or hyperphagia, which may start in childhood. These mutations are considered to limit the extent to which weight loss or the maintenance of weight loss occurs with different weight reduction methods such as lifestyle intervention in children [11] and bariatric surgery for adolescent and adult patients [12-14].

Recognizing that most overweight or obese patients, including those with loss of MC4R function, may not have the long-term weight loss outcomes desired with traditional weight loss methods, I have implemented targeted treatment for patients using pharmacological agents to correct the underlying metabolic malfunction associated with excess weight and other medical conditions such as type 2 diabetes, hypertension, and hyperlipidemia. This treatment approach to obesity is consistent with the new guidelines from the Endocrine Society which include the use of appropriately prescribed medications to promote weight loss or minimize weight gain by targeting the metabolic system [15]. This case study describes the pharmacological treatment of a female patient with obesity who was found to have a heterozygous, complete LOF MC4R gene mutation. To the best of my knowledge, this is the first published report that describes the successful long-term treatment of obesity with the complete LOF MC4R mutation using a pharmacological approach that over time is adjusted to meet the metabolic needs of the patient.

Case Description or Summary

A 48-year-old Caucasian female was seen in the clinic in January 2013. Her weight was 286.2 pounds; height, 5 feet 5 inches; BMI, 47.6; and body fat composition, 53.2%. The patient experienced lifelong obesity with failed weight regulation. There is a history of diabetes and pre-diabetes throughout the family. The patient's mother had childhood onset obesity and the father had adult onset obesity. Both parents had hypertension and hyperlipidemia. The patient's sibling, a brother, has class II, adult onset obesity. The patient's mother, maternal grandmother, and maternal great grandmother had breast cancer.

The patient recalled dieting early in life starting at 7-years-old. At age 12 years, the patient gained 80 pounds and grew 1 inch in height, reaching a weight of 210 pounds by 13 years old. She continued to diet throughout high school with temporary weight loss to 190 pounds. In college, her weight increased to 240 pounds. After college, from 1999 through 2007, the patient continued to diet with three episodes of weight loss and regain. Her highest weight was 320 pounds in 2007, which decreased to 210 pounds in 2008, then increased to and held steady at 286 pounds until 2013.

At her first visit to the clinic in 2013, the patient weighed 286.2 pounds, had pre-hypertension, mild hypothyroidism, hyperlipidemia with elevated triglycerides, elevated low density lipoprotein (LDL), and elevated LDL particle (LDL P) counts (Table 1). She had insulin resistance with fasting insulin elevation. Mixed-meal tolerance testing showed a markedly elevated first phase insulin response at the 30-minute post-prandial time point. Computed tomography cardiac-calcium score indicated minimal identifiable calcified coronary plaque.

Table 1: Summary of Weight, Blood Pressure and Laboratory Test Results Over Time.

Fasting Laboratory Values												
Date	Weight (lbs)	Blood Pressure Systolic	Diastolic (mmHg)	Insulin (mU/mL)	Glucose (mg/dL)	HbA1c	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	LDL P	Small LDL P
1/30/2013	286.2	143	85	33.4	90	5.6	269	154	175	63	2435	805
2/27/2013	280.6	131	84	-	-	-	-	-	-	-	-	-
4/23/2013	264.2	141	82	11.6	92	5.5	146	117	64	59	1090	594
7/24/2013	242.2	105	72	16.6	86	5.5	-	-	-	-	-	-
11/8/2013	225.6	121	83	6.3	85	5.8	283	150	191	62	2116	627
1/21/2014	212.8	138	86	6.7	80	5.4	168	109	79	67	1213	502
4/1/2014	196	121	84	13.9	95	-	-	-	-	-	-	-
7/9/2014	190	109	72	13.4	87	5.9	147	94	65	63	860	417
10/28/2014	169	119	78	21.1	88	5.3	159	81	75	68	863	0
5/5/2015	173.8	127	85	5.7	83	5.5	170	101	78	72	851	452

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8/3/2015	166.2	134	84	15	87	5.4	268	100	173	75	1671	395
10/14/2015	177	127	83	14.9	88	5.3	167	59	73	82	747	0
12/21/2015	176.4	136	89	26.9	86	5.5	278	80	177	85	1501	175
2/4/2016	180.2	133	88	7.7	84	5.4	204	77	109	80	1105	358
4/19/2016	186	106	72	7.1	78	5.3	262	132	166	70	1386	166
5/26/2016	191.8	108	70	-	-	-	-	-	-	-	-	-
6/27/2016	198	108	72	-	-	-	-	-	-	-	-	-
7/27/2016	203.2	120	80	10.2	90	5.4	310	104	209	80	1638	325
9/15/2016	205.6	113	77	9	85	5.3	242	85	150	75	1512	544
11/10/2016	198	-	-	-	-	-	-	-	-	-	-	-
12/7/2016	200	-	-	-	-	-	-	-	-	-	-	-

LDL P: Low Density Lipoprotein Particles; HDL: High Density Lipoprotein

The initial treatment for the patient was directed at regulating her insulin resistance and metabolic syndrome. That treatment included metformin 1000 mg twice a day, liraglutide 1.2 mg once a day, acarbose 50 mg three times a day (before meals) to regulate the exaggerated first phase post-prandial insulin response. Additionally, rosuvastatin 20 mg once a day and levothyroxine 25 mcg once a day were prescribed. She continued on these medications with varying doses of alpha glucosidase inhibitors, GLP1 mimetics, and metformin as the primary treatment. To achieve and maintain weight loss, a combination of bupropion and naltrexone or carbonic anhydrase inhibitors and naltrexone were also prescribed during the treatment process.

Lifestyle recommendations included eating from all food groups throughout the day and alternating meals and snacks every few hours. There were no calorie limitations or carbohydrate or dietary fat restrictions. No formal exercise was recommended other than for the patient to continue with her usual activity consisting of walking 60 to 100 minutes per week.

In January 2014, after the first year of treatment, the patient's weight was 213 pounds and body fat composition was 41%. In late 2014, a buccal swab was positive for a heterozygous, LOF MC4R gene mutation.

Figure 1: Change in patient weight from 2013 to 2015 with pharmacological treatment.

In January 2015, after two years of treatment, the patient's weight was 169 pounds (Figure 1). Her cardiovascular and cardiometabolic profiles had improved significantly. After a three-month period of weight maintenance, her body weight began to increase and then stabilized at about 198 pounds over a six-month period in 2016.

This case demonstrated that pharmacological treatment resulted in fairly prompt weight loss; however, weight-loss maintenance has been difficult to achieve. Although the patient regained some of the lost weight, her weight thus far (November 2016), with ongoing pharmacological treatment, is stable at 30% less than her initial body weight in January 2013.

Discussion

This case report is the first to discuss the pharmacological treatment, weight loss and weight-loss maintenance of a patient with complete LOF MC4R mutation and who ate a normal diet, did not count calories, and did not participate in an unusual level of exercise. This treatment has provided the longest period of time in the patient's life during which she achieved and maintained weight loss and a time during which she achieved her lowest adult weight. In this case, the weight loss was dramatic sustaining at least a 30% reduction and remarkable considering that the patient had complete LOF of MC4R gene mutation. The importance and significance of this patient's weight loss can be illustrated by reviewing the weight loss outcomes in patients with MC4R mutations who have resorted to the mainstay of diet and exercise or to the increasingly popular weight loss technique of bariatric surgery.

The one-year lifestyle intervention (exercise, behavior, and nutrition therapy) among children (5 years to 16 years) with and without MC4R mutations led to weight loss in both groups of patients [11]. However, the maintenance of weight loss among children with MC4R mutations and reduced receptor function failed in contrast to children without such mutations ($P < 0.001$ adjusted for BMI-standard deviation score at baseline, age, and gender in an intention-to-treat analysis) providing additional evidence of the influence of these mutations on weight status.

In a study by Valette, et al. the impact of MC4R mutations on weight loss in obese patients one year after bariatric surgery showed that weight loss was achievable; the authors

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concluded that functional MC4R mutations and genetic variants did not influence weight loss and body composition after bariatric surgery [13]. The interpretation of the study results is limited; however, since the study did not assess weight loss maintenance in patients with the MC4R mutations compared with those without the mutations, only a few patients (n=9) were heterozygous for functional MC4R mutations, and the follow-up period after surgery was short.

Bariatric surgery for obese children with and without MC4R mutations led to weight loss among both groups of patients, but there was less weight reduction for the patients with the MC4R mutations [12]. In contrast, morbidly obese adolescent patients with heterozygous MC4R mutations experienced weight loss after restrictive bariatric surgery procedures that was no less than the weight lost by controls without the MC4R mutations [14]. No weight-loss maintenance occurred other than post-operative care instructions advising patients to follow a standard restrictive dietary protocol of initially a diet that was pureed, then one that was blended followed by a soft diet, and beyond that, a well-balanced low-fat diet. The study was limited by the small number of patients with the MC4R mutation (n=4) and postoperative follow-up visits that were less frequent than planned. Although the difference in weight loss between the two groups did not reach statistical significance, the authors concluded that the favorable effect of the bariatric surgery on weight loss was not mediated by MC4R mutations.

Targeted pharmacological treatment with a mix of pharmacological agents will continue for the patient described in this case study with a goal of further reduction in cardiometabolic risk and maintenance of the most normal body weight possible.

Conclusion

Appropriate use of pharmacological agents may be effective for weight loss in patients with life-long weight problems, including those with complete LOF MC4R mutations, and as a long-term weight-loss maintenance strategy.

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