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SHORT COMMUNICATION

Melanocortin-4 receptor signaling is not required for short-term weight loss after sleeve gastrectomy in pediatric patients

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Homozygous or compound heterozygous melanocortin-4 receptor (MC4R) mutations are rare with fewer than 10 patients described in current literature. Here we report the short- and long-term outcomes for four children ages 4.5–14 who are homozygous for loss-of-function mutations in the MC4R and underwent laparoscopic sleeve gastrectomy. All four patients experienced significant weight loss and improvement in, or resolution of, their comorbidities in the short term. One patient, however, has had significant weight regain in the long term. We conclude that MC4R signaling is not required for short-term weight loss after laparoscopic sleeve gastrectomy in children. Behavior modification may be more important for long-term weight maintenance, but patients with homozygous MC4R deficiency should not be excluded from consideration for sleeve gastrectomy. However, as at least one copy of functional MC4R is necessary and sufficient to induce long-term postoperative weight loss benefits, patients with complete loss of MC4R functionality might be less likely to exhibit the same benefits resulting from bariatric surgery.

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INTRODUCTION

Obesity is a common and highly morbid disease. Recent large population studies in the United States have revealed an overall obesity rate of 32% and a severe obesity (body mass index >50) rate of 5%.[1] Nearly 10% of all US healthcare costs can be attributed to obesity, amounting to $>$\$168 billion dollars.[2] In particular, childhood obesity is on the rise and $>4\%$ of adolescents meet criteria for morbid obesity.[3] Several recent reports have demonstrated the efficacy of bariatric surgery in this population.[4,5] Moreover, the preponderance of data now suggests the superiority of bariatric surgery to medical therapies for sustained weight loss and relief from obesity-related metabolic conditions in adults and children.[6–11]

Vertical sleeve gastrectomy (VSG) is a type of restrictive bariatric surgery that permanently reduces the size of the stomach by ~80%.[12] It causes weight loss by inducing early satiety and mechanically limiting gastric volume. VSG has been advocated in the pediatric population because of its demonstrated efficacy in the short term, its low operative morbidity and its ability to be easily converted to a Roux-en-Y gastric bypass.[13] Long-term data are not yet available.

Some authors have proposed that certain forms of obesity are refractory to surgical therapy.[3,14] One such form of obesity is associated with deficits in the MC4R signaling pathway. MC4R is transmembrane receptor that is expressed in hypothalamic neurons. Activation of this receptor by melanocortins leads to decreased food intake and increased energy expenditure.[15] Defects in MC4R signaling have been implicated in ~5% of adolescents with obesity[3] and MC4R deficiency is the most common form of monogenetic obesity.[16] Data from MC4R null mice suggest that complete abrogation of the MC4R signaling pathway results in obesity that does not respond to gastric bypass.[17] Furthermore, Aslan *et al* described the failure of gastric banding with truncal vagotomy in an adolescent who had complete functional loss of MC4R. These findings are contradicted by a study in MC4R null rats in whom VSG was shown to be effective.[18] In addition, human studies have shown that bariatric surgery is effective in MC4R heterozygotes.[3] In light of these data, we evaluated VSG in four children who were homozygous for loss-of-function mutations in MC4R, and describe their short- and long-term results in this report.

CASES

Patient 1 is an 8.5-year-old Kuwaiti girl who weighed 159 kg with a body mass index (BMI) of 71.2 kg m^{-2}. She was diagnosed with homozygous MC4R deficiency at the age of 2 and both her parents were found to be heterozygotes. Specifically, she was found to be homozygous for the missense mutation T162I by single-gene sequencing (Athena Diagnostic, Worchester MA, USA).[19] She was originally referred to our institution at the age of 6, when she weighed 124 kg and her BMI was 60 kg m^{-2}. Her comorbidities at that time were obstructive sleep apnea, hypertension, asthma, nocturia, gastroesophageal reflux disease and Blount's disease. VSG was not offered because it was felt that her young age precluded understanding the behavioral changes required for long-term success. After 2 years of unsuccessful medical management with diet and exercise, and an increase of 11 in her BMI, the decision was made to proceed with surgery. Her obesity-related comorbidities had all worsened. In addition, she was unable to perform activities of daily living without help from her parents due to her obesity. Her preoperative vital signs were normal except for mild hypertension. Her physical exam was notable for morbid obesity and bilateral lower extremity edema. Her laboratory studies demonstrated normal liver and renal function, but did indicate a mild anemia. She underwent an

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uncomplicated laparoscopic VSG and was discharged 4 days after the operation on a liquid diet. Four months after surgery, she had lost 26 kg corresponding to a drop in BMI to 59.5 kg m^{-2}. At 6 and 12 months after surgery, her weight loss had plateaued (Figure 1). There has been substantial improvement in her symptoms including complete resolution of her nocturia. She is now able to care for herself and perform all activities of daily livings independently. Laboratory values 1 year after surgery reveal a stable Hemoglobin A1C (HgbA1c) (Figure 2), and no abnormalities in her nutritional panel including calcium (data not shown). Her height has increased from 149.5 to 151 cm over the 12 months since her operation, and 151 cm places her in the 98 percentile for her age and gender.

Patient 2 is a 12-year-old Emirati boy who weighed 143 kg with a BMI of 52 kg m^{-2}. He was treated with metformin for Type 2 diabetes at the Imperial College of London Diabetes Center (ICLDC) in Abu Dhabi, but was referred for surgical evaluation at another institution. On examination the child was noted to have morbid obesity, hyperphagia and acanthosis nigricans. No dysmorphic features were observed. Aside from a mild elevation in blood pressure, all vital signs were normal. Laboratory studies indicated normal renal, liver and thyroid function with a HgbA1c of 8.1. The child underwent an uneventful laparoscopic sleeve gastrectomy at the outside center, unbeknownst initially to the ICLDC. Six months post surgery the patient had lost 18 kg (BMI 45 kg m^{-2}) and was off metformin. HgbA1c was 6.1. Genetic testing after surgery indicated that the child did not carry a functional copy of the MCR4 allele. His mutation was in fact identical to that of patient 1, T162I; both parents are heterozygotes for this mutation. Unfortunately, starting approximately a year after surgery, this patient started to regain his lost weight. He is now 5 years from surgery and has regained all of his weight, and is nearly 20 kg heavier than his pre-surgical weight (Figure 1). In contrast, his HgbA1c (Figure 2) decreased after surgery and is now 6.3 while back on metformin. There are no other laboratory values available for this patient. His height increased from 166 to 171cm over the 5 years since his operation.

Patient 3 is the 14-year-old sister of patient 2 and was also referred for surgical evaluation after initial evaluation at the ICLDC. Her weight was 150 kg and her BMI was 60 kg m^{-2} at the time of surgery, and she required insulin for her diabetes. Like her brother she had acanthosis nigricans, normal laboratory values and a mild elevation in her blood pressure. She underwent laparoscopic sleeve gastrectomy. Six months post surgery she had lost 22 kg (BMI 53 kg m^{-2}) (Figure 1) and was on metformin monotherapy without any need for insulin. Her HgbA1c decreased from 9.7 to 7.2 postoperatively (Figure 2). Like her brother, postoperative genetic testing revealed a MCR4 $-/-$ genotype with the same missense mutation T162I. Unlike her brother, however, she has been able to maintain her weight loss in the long term. Nearly 5 years have elapsed since her surgery and she has been able to maintain her weight near or below 130 kg (BMI $<$ 50 kg m^{-2}). Surprisingly, her HgbA1C levels have fluctuated overtime and have not responded in parallel with her weight loss, and she is currently on Victoza with a level of 8.2 (Figure 2). Her calcium and other nutritional laboratory values have remained in the normal range 5 years after surgery (data not shown). Her height has grown from 156 to 160 cm in the 5 years after surgery.

Patient 4 is a 4-year-old Emirati girl who weighed 67.8 kg with a BMI of 44 kg m^{-2}. She was initially referred for surgical evaluation due to a high suspicion for a monogenetic form of obesity. Genetic testing revealed that she was homozygous for the same mutation as the previous three patients. During her preoperative evaluation, she was found to have acanthosis nigricans, hypertension, obstructive sleep apnea and mild insulin resistance. Her review of systems was notable for urinary incontinence. She underwent an uncomplicated laparoscopic VSG. She was discharged on the second postoperative day on a liquid diet. At 2 months of follow-up, she has lost 10 kg and her BMI has dropped to 38.8 kg m^{-2} (Figure 1). After 4 months, she had lost a total of 12 kg and her BMI decreased to 36 as she has also grown 3 cm over the time period. Her insulin resistance has already improved as evidence by improvement in her acanthosis nigricans but her HgbA1C is unchanged (Figure 2).

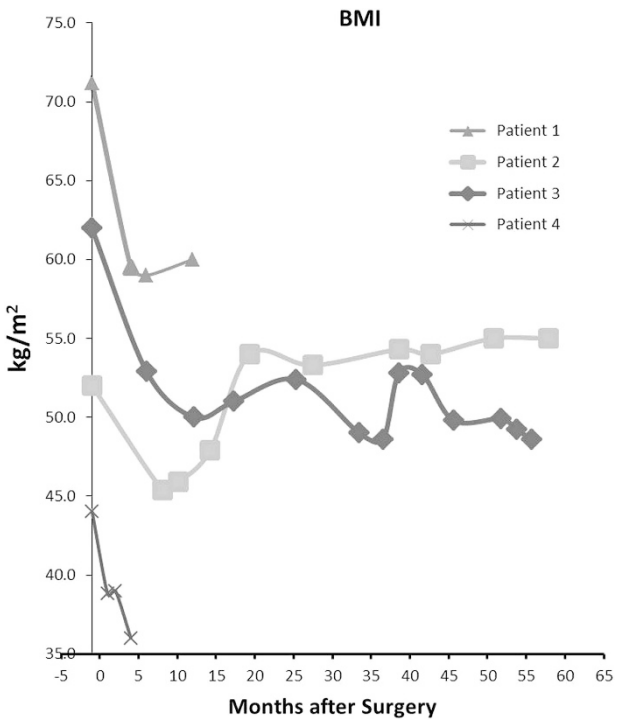

Figure 1. BMI curves for patients starting 1 month before surgery.

DISCUSSION

Previous studies have demonstrated the efficacy of restrictive bariatric surgery in adolescents with one functional copy of MC4R.[3] Studies in rodents have demonstrated mixed results with complete MC4R loss of function.[17,18] Some investigators have hypothesized that loss of MC4R function eliminates the necessary

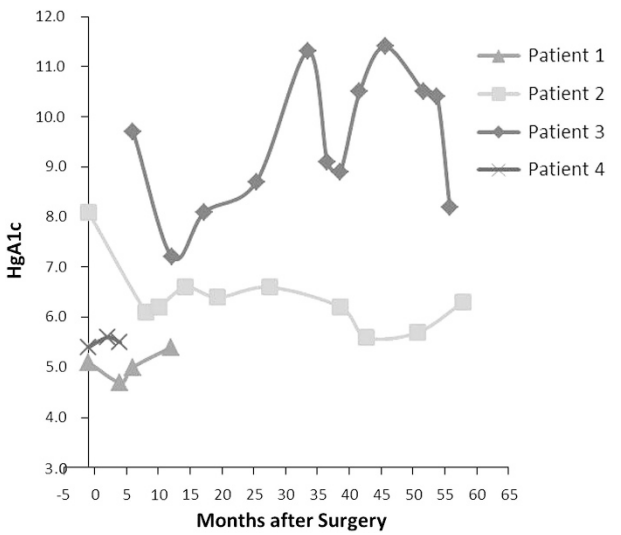

Figure 2. HbA1c curves for patients starting 1 month before surgery.

signaling to decrease appetite and food intake that is often seen after bariatric surgery.[14] MC4R defects lead to obesity, hyperphagia, decreased energy expenditure and insulin resistance.[15,20] It is proposed that the mechanism of weight loss in restrictive bariatric surgery, early satiety, is completely dependent on melanocortin signaling.[3,14] However, we hypothesized that alternative signaling mechanisms are sufficient to mediate weight loss after VSG in the MC4R−/− background due to the rat data regarding VSG and the data from human MC4R heterozygotes.

To our knowledge, this report describes the first use of laparoscopic VSG to treat MC4R null patients. This series of patients is of particular interest because they all carry the identical T162I mutation. This is likely a reflection of all four patient's common Arab ancestry. Early postoperative data demonstrated dramatic weight loss in three patients at 12 months of follow-up and at 4 months in patient 4, suggesting that the mechanisms by which VSG works in the short term are, at least, partially independent of MC4R functioning. It may be simply that the physical restriction of the VSG causes early satiety that is transmitted to the brain via pathways that are not reliant on MC4R signaling. Alternatively, changes in the gut hormonal milieu may be responsible. The decrement in leptin and ghrelin, seen in both animals and humans, after VSG may in part mediate MC4R-independent weight loss.[21] Also glucagon-like peptide-1 (GLP-1), a known incretin and inhibitor of anabolism has been shown to be significantly increased in animals and humans after VSG and could be responsible for the short-term weight loss seen in our patients.[22] GLP-1 decreases appetite and food consumption,[23] and Kelly *et al.* demonstrated that GLP-1 receptor agonist treatment reduces BMI and body weight in adolescents with severe obesity.[24]

Despite the short-term weight loss results in our study, it is important to note that our patients are still obese after surgery. Adjunct medical therapies may be of particular use to this population of patients whose obesity has unique challenges. GLP-1 agonists have been shown to cause weight loss with a relatively benign side-effect profile.[25] Although, we have not yet attempted adjuvant medical therapy in these patients, plateauing or regaining of weight (as was seen in patient 2) may provide rationale to do so. The use of pharmacotherapy in any morbidly obese patient who remains obese after surgery may be reasonable, however, available pharmacotherapy for patients in the UAE is limited to or list at (and even its use is severely restricted) and there are no weight loss medications that are approved for use in children in the US. The absence of pharmacological options was indeed part of the rationale to offer surgery to patient 4 at such a young age. Our aim was to address her weight before her BMI reaching the higher values of the other three patients, and thus leaving her closer to a normal weight BMI after surgery.

The short-term weight loss seen in our study was associated with improved glycemic control in the two patients with preoperative diabetes from the UAE. Unfortunately, patient 3's HbA1c has increased overtime and is well above its preoperative level despite her weight loss. Paradoxically patient 2, patient 3's brother has not been able to maintain his short-term weight loss but has a markedly improved HbA1c albeit both patients are now on medications to improve their insulin sensitivity. Patient 1 continues to on her metformin for now despite normal HbA1c values.

It is interesting to note that patient 2 has regained all of the weight he initially lost, but his sister and patient 1 who have the same MC4R genotype have been able to maintain their weight loss. This finding suggests that long-term weight maintenance may be related more to the patient's ability to make lifestyle and behavioral changes on the backdrop of a MC4R null genotype. These lifestyle changes may need to be more drastic in this patient population, but certainly the success of patient 3 in keeping her weight under control for 4 years suggests that it is possible to make said changes. Patient 1 will require close long-term follow-up to ensure that she follows the path of patient 3, and not patient 2, at least in terms of weight loss.

Although surgical intervention is the most effective treatment for obesity, the potential of targeted treatment using pharmacological chaperons should not be ignored. The specific T162 mutation identified in the patients in this study has been previously characterized *in vitro*. Cells with this mutation were unable to transport the MC4R to the plasma membrane.[16] However, small molecules have been shown to reverse this phenotype by chaperoning MC4R to the plasma membrane.[26] More recently a novel human MC4R antagonist, Ipsen 17 has been identified as the most universal chaperone, successfully rescuing 11 of 12 reported *MC4R* null mutations.[27] Although these therapies may not be widely available at present, they certainly could be alternatives or adjuncts VSG in the future.

This study preliminarily suggests that MC4R function is not required for short-term weight loss after VSG. Follow-up with these patients is ongoing and longer term data will assess the durability of these results. Our initial findings, however, suggest that MC4R null patients may be offered VSG as part of a clinical trial or research study as short-term weight loss was achieved in all four of our patients. Furthermore, our results suggest that redundant pathways are likely involved in early satiety following VSG. The limitations of this study are its small size and relatively short follow-up. There are few patients with MC4R−/−, but these results should prompt the possibility of surgical therapy for these patients once they are identified. In turn, this will lead to more data regarding the efficacy of surgery for patients homozygous for MC4R mutations, which hopefully can enlighten the field overtime.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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