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Short Communication

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Genetic Obesity: The Current Treatment Options

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Abstract

A genetic predisposition and environment interact to cause obesity, which results from impaired central control of body weight. The presence of genetic factors is predominant in the development and progression of genetic obesity, including monogenic obesities and syndromic obesity. There is an increased risk of serious and early-onset obesity associated with eating disorders, as well as frequent comorbidities. Genetic diagnosis is not widely available in severely obese children, so their current prevalence estimates of 5 - 10% is probably underestimated. There is evidence that the symptoms are caused by an altered leptin-melanocortin pathway at the hypothalamus. Physical and physical activity have been the primary methods of managing genetic obesity so far. The last few years have brought new therapeutic options to these patients, raising hopes for managing their complex condition and improving their quality of life. To provide individualized care, genetic diagnosis must be implemented in clinical practice. A review of the current clinical management of genetic obesity, as well as the evidence supporting it, is presented in this article. We will also provide some insight into new therapies that are currently being evaluated.

Keywords

Syndromic obesity, Genetic obesity, Children

Introduction

Defining obesity as an excessive accumulation of body fat caused by an inadequate energy balance over the long term, it is a multifactorial and complex disease. Genetic predispositions and environmental factors influence the development of the disorder, which can manifest in early childhood as a lifelong illness [1, 2].

The prevalence of obesity among children has drastically increased in recent decades, and it is one of the major public health challenges of our time. It is estimated that 12% of children aged 7 - 9 in the 33 participating countries of the European Region will be obese by 2020 (Table 1).

People developing severe and early obesity before the age of six years have a high genetic heritability (up to 80%). It is possible to distinguish between frequent polygenic variants that have small effects and rare pathogenic variants that have large effects that cause monogenic and syndromic obesity within this genetic susceptibility. Various genes in the latter group are involved in the leptin-melanocortin pathway, which plays a crucial role in regulating body weight through the central nervous system. As a result of these genetic anomalies, patients with

Table 1: Definitions of pediatric obesity are based on the current clinical practice guidelines on pediatric obesity from the endocrine society [3].

Age (years)	Definition	Source	Diagnosis
< 2	Specific weight for recumbent height ≧ 97.7 percentile	WHO child growth standards	Obesity
> 2	85 - 95 body mass index (BMI) percentile	CDC growth charts	Overweight
> 2	BMI ≧ 120% of the 95th percentile or BMI ≧ 35 kg/m^2		Severe obesity (class 2a)
> 2	BMI ≧140% of the 95th percentile or BMI ≧ 40 kg/m^2		Severe obesity (class 3b)

severe early-onset obesity show impaired satiety and disruptive food-seeking behavior from the first years of life. Additionally, these patients may be suffering from neuropsychiatric, psychiatric, endocrine, and obesity-related comorbidities since childhood. It is therefore complex and challenging to manage these obesities clinically. So far, genetic obesity has been treated with environmental control, starting as early as possible, to avoid obesity progression and help the development of appropriate eating and exercising habits [4]. As new treatment options for genetic obesity have emerged, early diagnosis has become increasingly important for preventing massive weight gain in childhood and the negative effects it has on the health of children.

The purpose of this review is to briefly outline the clinical features of patients with genetic obesity, followed by an outline of the distinct aspects of its current management, with a focus on hyperphagia-targeted therapeutic interventions.

Obesity Genetics and Syndromic Obesity

There is a common link between monogenic obesity and syndromic obesity when it comes to hypothalamic pathologies affecting the satiety signal. Children with BMI higher than 30 kg/m^2 in adulthood before six years of age are considered to have early-onset obesity, as defined by the International Obesity Task Force curve. Often, adiposity rebound occurs very early, before three years of age, or does not occur at all. From the first months of life, eating behavior disorders can be observed. Food restrictions are often intolerable to parents and conflicts are often reported over food restrictions. Foraging strategies may include stealing food and night-time feeding as patients become obsessed with food [5, 6]. It is evident that patients suffering from similar genetic disorders exhibit significant phenotypic variability. Several factors are associated with it, including family and social circumstances, ethnicity, and gender. This article summarizes the most common syndromic and monogenic obesity disorders with associated genetic alterations and specific clinical features. A major factor contributing to these problems is the dysfunction of the leptin-melanocortin pathway, which is regulated by the hypothalamic arcuate and paramedian nuclei. In this pathway, leptin, a hormone synthesized by adipocytes, activates the leptin receptor (LEPR), which in turn stimulates the activity of prohormone subtilisin/kexin 1 convert erase (PCSK1) in anorexigenic neurons, which converts proopiomelanocortin (POMC) into alpha-melanocyte stimulating hormone (α-MSH). Melanocortin receptor type 4 (MC4R) is the natural ligand which triggers the satiety response when activated. As well as MRAP2 encoding the melanocortin receptor accessory protein 2, ADCY3 encodes the adenylate cyclase 3 that transmits the intracellular MC4R activation signal are implicated in the regulation of this pathway. There have been several reports that this signaling is influenced by genes involved in hypothalamus development or MC4R regulation, including semaphorin 3A-G, plexinA1-4 (PLXNA1-4), neuropilin1-2 (NRP1-2), kinase suppressor of Ras 2 (KSR2), and steroid-receptor co-activator 1 (SRC-1). Both monogenic obesity and syndromic obesity are caused by genetic changes in these genes [7].

Monogenic obesity

An obesity caused by monogenic variants on the leptin-melanocortin pathway occurs when there is a pathogenic variant on the gene involved. There is an inconsistency in the association between the mutations in the genes described above (LEP, LEPR, POMC, PCSK1, MC4R mainly) and severe and early obesity with eating disorders [8]. In severe early-onset obesity cohorts, particularly in children, heterozygous variants bearers in the same genes display milder phenotypes with a frequency of 10 - 12% of heterozygous variants. It has been reported that MC4R variants are frequent in the general population, with an incidence of 0.3% in a cohort of newborns screened in the United Kingdom, and more than 5% in children with severe obesity. The other genes cited above are also known to cause obesity in humans in case series or in rodent models, but their frequency in cohorts of overweight and obese patients is not known.

Syndromic obesity

It is distinguished from other types of obesity by the presence of malformations, dysmorphic features, and/or neurodevelopmental disorders such as psychomotor development delay, intellectual disability, and autism spectrum disorders [9-11]. It is estimated that between 80 and 100 syndromes have been identified so far, some of them without an elucidated genetic cause. Several of them are mediated by the leptin-melanocortin pathway.

Approximately one in every fifteen thousand births is affected by Prader-Willi syndrome (PWS). A neonatal diagnosis of this condition is often made when there is severe hypotonia as well as feeding difficulties and dysmorphic characteristics. Hyperphagia is challenged in childhood by an intense impulsivity that leads to morbid obesity early in life. It is even more difficult to manage these symptoms when obesity is combined with interaction and behavioral disorders. With an average life

expectancy of 30 years, this syndrome has a significant impact on quality of life, mortality at all ages, and a major impact on quality of life [12]. In this specific population, severe obesity is most frequently associated with death, highlighting the importance of its control. In rodents with PWS, PCSK1 deficiency and alterations of the orexigenic Agouti-related protein hypothalamic neurons have been described as an inactivation of MAGEL2 and a decrease in MSH neuron density.

About 1/125000 babies are born with Bardet-Biedl syndrome, which is also associated with severe early-onset obesity, polydactyly, renal abnormalities, dysmorphism, and learning disabilities. There are twenty genes implicated in the disease, which is caused by a genetic alteration in the function of the primary cilium [13, 14]. A hypothalamic dysfunction in the leptin-melanocortin pathway may be caused by the impairment of the primary cilium, which contributes to obesity phenotype and severe hyperphagia.

The myelin transcription factor 1-like (MYT1L) variant is another genetic disorder recently described. Hypothalamic development is governed by MYT1L, and heterozygous variants have been associated with severe obesity, intellectual disability, neurobehavioral disorders, and dysmorphic features. In addition, these descriptions illustrate how syndromic and non-syndromic monogenic obesity are similar and how their phenotypes overlap (Figure 1).

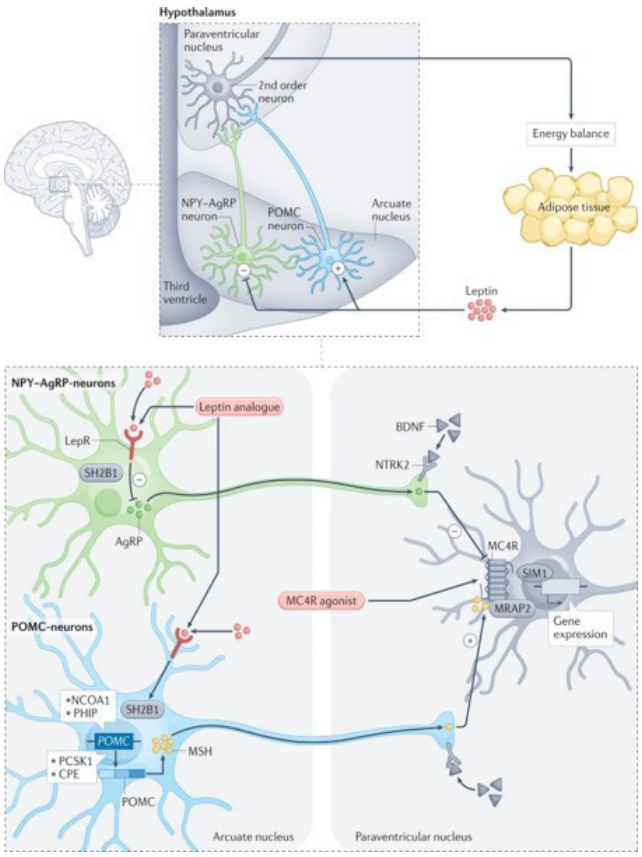


Figure 1: Central nervous system regulation of body weight via the leptin-melanocortin pathway [3].

Treatment of Genetic Obesity with Lifestyle Modification Therapies

A trained health professional's role is to provide nutritional, behavioral, and exercise interventions to patients with common obesity. In cases of early diagnosis, dieticians, psychologists, and teachers of adapted physical activity should intervene with patients with genetic or syndromic obesity or those at risk of severe obesity later in life [15]. To control the environment, caregivers must be instructed. To prevent obesity and eating behavior disorders from developing and aggravating throughout life, these measures should be implemented as early as possible in childhood and maintained throughout life with increased vigilance as we transition from childhood to adulthood [16].

When it comes to diet, the overall goal is to limit uncontrolled intake of food. To limit hyperphagia and disruptive food-seeking behavior, restricting food access, establishing a reassuring eating routine, and ritualizing food intake are helpful. Even if dietary autonomy is rarely possible in genetic obesity with eating disorders, this approach helps patients improve their quality of life and facilitate their social integration by easing their relationship with food [17]. There is tremendous stigma and suffering for patients suffering from monogenic obesity because of the absence of satiety. A slowing of obesity progression has been shown to benefit PWS patients through early restriction of food intake through environment control.

Adapted physical activity is also crucial. Compared to patients with non-syndromic obesity, patients with PWS show a decrease in baseline physical activity. A recent systematic review of exercise in PWS found improvements in physical capacities (maximal oxygen uptake, muscle strength, walking distance), but no weight or fat loss without dietary changes. Nutritional, physical, psychological, and family interventions for obese children with pathogenic MC4R variants resulted in a weight loss of 0.4 BMI-standard deviation score (SDS) compared to obese children without MC4R variation. Unlike their mutation-free counterparts, they were unable to maintain weight loss [18]. The effects of multicomponent lifestyle interventions on health outcomes are therefore positive, but they must be sustained and intensive to be sustained.

Clinical conditions need to be improved holistically and comprehensively and expertise is essential in specialized centers. In addition to managing neuropsychiatric comorbidities, psychological follow-up is crucial for managing the stigma associated with obesity and its repercussions. To guide and improve psychological and educational support, a neuropsychological evaluation can identify cognitive dysfunction or other specific learning disabilities [19]. Comorbidities associated with the genetic defect should also be screened and treated to prevent further complications. It is common for genetic obesity to be accompanied by hormonal deficiency, and treatment can be more effective if it is treated before symptoms develop. The treatment of sleep disorders, digestive disorders, orthopedic deformations, and congenital malformations often requires the assistance of other specialists. Aside from obesity itself, complications may also arise and require additional treatment.

It may also be a critical period in the transition between

pediatric and adult care for such complex patients. PWS patients receiving transitional care had a lower BMI by 10 kg/m^2 and needed fewer antidepressants, according to a retrospective study [20, 21]. As a result, patients' quality of life can be improved, and they can integrate with social structures and build their own lifestyles.

Therapies Based on Pharmacology

Several treatments are now approved to treat common obesity, even though they are not widely practiced and often have modest efficacy. Patients with syndromic or monogenic obesity may be eligible to receive these treatments in the future, but only after careful clinical evaluation. Among these treatments, GLP1 analogs are probably the most promising [22]. A human incretin, GLP-1, stimulates pancreatic β-cell insulin secretion and improves insulin sensitivity when secreted by entero-endocrine cells in response to food intake. By reducing gastric emptying and centrally signaling satiety, it reduces appetite. Improved glucose metabolism and weight loss are possible through these mechanisms. Before being explored as a treatment for obesity, GLP-1 analogs were developed for type 2 diabetes. Injection site pain, dizziness, abdominal pain, and low blood sugar have been reported as side effects [23]. Anaphylactic reactions, pancreatitis, gallbladder and biliary diseases, and acute renal failure have also been reported as serious side effects. It is imperative to pay close attention to the tolerance of these treatments because they are used at 2- to 3-fold higher doses in obesity compared to diabetes. The long-term safety of these treatments is less well understood, and they may need to be prolonged for weight reduction to be significant.

Liraglutide has the most comprehensive scientific support of all GLP-1 analogs. Using liraglutide and lifestyle interventions, 251 adolescents (12 - 17 years) were treated for common obesity with a double-blind, randomized controlled trial (RCT). Compared to placebo, the BMI-SDS decreased by -0.22 after 56 weeks of treatment. 43.3% of people taking liraglutide achieved a reduction in BMI of at least 5%, compared to 18.7% of people taking placebo. Compared to data available for adults with a body weight change of about -5%, these results are consistent. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved liraglutide as a treatment for obesity in adolescents aged 12 - 17 in 2020 at a dose of 3 mg per day subcutaneously. The appropriateness of using this treatment in adolescent obesity remains controversial due to the significant but modest weight loss effects and mode of administration (e.g., daily subcutaneous injection) [2, 24].

In a double-blinded RCT against placebo, exenatide, another GLP-1 analog, showed comparable results. In combination with lifestyle intervention, six months of treatment resulted in a significant but mild reduction in BMI-SDS (-0.09), BMI (-0.8 kg/m^2), and weight (-3 kg). Yet, exenatide has not been approved to treat obesity.

Recent RCTs have shown promising results for semaglutide in treating common obesity in adults and adolescents. In 201 obese adolescents with at least one weight-related comorbidity, a double-blind RCT published in 2022 evaluated semaglutide injections for 68 weeks against placebo [25]. In both groups, lifestyle interventions were proposed. At the end of the study, the treatment resulted in a major mean reduction in BMI of -16.1% (compared to +0.6% with placebo). Further, after 68 weeks on semaglutide, 73% of patients had lost > 5% of weight and 62% had lost >10% of weight, versus 18% and 8% in the placebo group. In the semaglutide group, weight-related quality of life and dyslipidemia significantly improved. The effects of semaglutide on weight loss have been shown to be significantly greater than those of other GLP-1 analogues. In the future, it could pave the way for new therapeutic strategies against obesity [26].

55 adolescents and children with PWS were administered liraglutide daily with diet and exercise intervention for 52 weeks in a multicenter RCT exploring syndromic obesity. The BMI-SDS did not change significantly from baseline, with an estimated difference of -0.1 SDS. Liraglutide significantly reduced hyperphagia scores in adolescents compared to no treatment at week 52, but not in children [27-29]. To date, no RCT has been conducted on PWS or other GLP-1 agonists. So far, GPL-1 agonists have not been tested for their effect on PWS, the only syndromic obesity studied.

In a trial, liraglutide efficacy was compared in 14 carriers of MC4R pathogenic variants against 28 non-mutated patients with monogenic obesity. After 16 weeks of treatment, both groups lost approximately 6% of their body weight, with similar improvements in body fat mass, waist circumference, and glucose tolerance [30]. According to these results, GLP-1 agonists with decreased MC4R signaling are still effective for genetic obesity. GLP-1 agonists have not been studied in other types of monogenic obesity. In view of the substantial expected benefits for these patients, particularly considering its promising results on hypothalamic obesity, further research is required.

Due to its severity and frequency, PWS has received the most intensive therapeutic research among syndromic obesity. Besides causing satiety deficiency, PWS also leads to impaired oxytocin signaling and deficiency of growth hormone [31]. PWS patients should take growth hormone supplements throughout their growth phase from the time of diagnosis. There is evidence that it normalizes height growth in children, increases lean mass, decreases body fat, and improves psychomotor development. Patients may maintain a healthier BMI, body composition, and exercise capacity if they continue to receive treatment during adulthood [32]. Despite mixed results from RCTs on intranasal oxytocin supplementation for PWS patients, it has recently shown promising results, particularly in the youngest patients. A potential therapeutic target is the ghrelin pathway in PWS. An RCT of 40 PWS patients treated with livoletide, a non-acylated ghrelin analog, showed promising results regarding food behavior. For ghrelin to become inactive, it must be converted into its inactive form via an enzyme known as ghrelin O-acyltransferase. PWS is currently being treated with a ghrelin O-acyltransferase inhibitor.

A great step forward in personalized medicine has been made by targeting the leptin-melanocortin pathway. An ex-

ceptionally rare condition caused by homozygous pathogenic variants in the LEP gene has been described. These patients exhibited great weight loss after receiving recombinant leptin (metreleptin), along with normalized metabolic and neuroendocrine functions. A great deal of hope was raised for the treatment of obesity because of this success [33]. Sadly, the treatment of common obesity with leptin monotherapy did not result in sufficient efficacy due to its leptin-resistance. Furthermore, recombinant leptin is not indicated for other types of monogenic obesity, such as LEPR or POMC deficiencies, that interrupt the leptin-melanocortin pathway.

The development of several MC4R agonists has followed intense research efforts since then. There were cardiovascular side-effects associated with the first ones. Recently, setmelanotide (Imcivree, formerly known as RM-493) was discovered as a better tolerated, highly selective MC4R agonist. Since MC4R regulates weight, appetite, and energy expenditure, this G protein-coupled receptor is a key target for increasing energy expenditure and reducing food intake, resulting in negative energy balance [34]. In a trial assessing POMC and LEPR deficient patients with homozygous mutations in POMC and PCSK1 or LEPR, daily subcutaneous injections of setmelanotide for one year resulted in significant appetite control and weight loss. Among the POMC-deficient group (10 patients), the mean weight loss was 25.6%, with 80% losing at least 10% of initial weight and hunger scores decreased by 27%. There was a significant weight loss of 12.6% in the 11 LEPR deficient patients, 45% of whom lost more than 10% of their body weight, and a 44% decrease in hunger score. There were frequent reports of cutaneous hyperpigmentation, but no other serious adverse events. Local cutaneous reactions and transient digestive manifestations were also common after injection. The effects of setmelanotide appear to have been sustained in the two POMC deficient patients treated for more than 7 years. In 2020, the FDA approved setmelanotide for treating obesity in adults and children aged six years and older with confirmed genetic diagnosis of POMC, PCSK1 and LEPR deficiencies, followed by the EMA in 2021 [35-37].

It is more controversial whether setmelanotide works in carriers of the MC4R variant. The MC4R agonist setmelanotide is significantly more potent than the endogenous ligand (α-MSH). Despite defective MC4R mutants, this increased affinity allowed intracellular signaling to be rescued in cell models. In rodent models, MC4R heterozygous mutants responded to setmelanotide in an intermediate manner. The MC4R heterozygous mice injected with saline gained less weight on a high fat diet than the control MC4R heterozygous mice. As compared to wild-type mice, setmelanotide's beneficial effects were less pronounced in MC4R homozygous knockout mice. In phase 1 RCT, 8 patients with MC4R heterozygous pathogenic variants were compared with 49 obese patients who had no mutation to continuously administer setmelanotide subcutaneously for 28 days. In both the MC4R heterozygous and obese control groups, setmelanotide significantly reduced weight loss compared to placebo, with a similar effect of -3.48 kg and -3.07 kg. In MC4R-deficient subjects, further studies are needed to determine whether setmelanotide can effectively induce significant weight loss [2, 38-40].

A 52-week multicenter phase 3 RCT with 32 obese BBS patients over the age of six years studied setmelanotide for its proven impairment of leptin-melanocortin signaling associated with hyperphagia in BBS patients. After 52 weeks of setmelanotide, 32.3% of patients with BBS lost more than 10% of their body weight, resulting in a reduction in hunger scores. A setmelanotide treatment for BBS patients older than six years was approved by the EMA in 2021 and by the FDA in 2022 following results of this study.

It appears that different molecular pathways are affected by different pharmacologic therapies. Genetic and syndromic obesity may also benefit from some studies targeting hypothalamic obesity, since they share some characteristics. Also being evaluated are non-pharmacological interventions, such as deep brain stimulation.

Bariatric Surgery

Currently, sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most performed procedures. In most patients with common obesity, these interventions result in sustainable weight loss and comorbidity remission. Patients with complicated severe obesity who have syndromic or monogenic obesity are regularly treated with bariatric surgery due to their severity. While limited and heterogeneous evidence supports its use in syndromic obesity, its long-term outcomes remain uncertain [41-43].

A monocentric pediatric study of 24 PWS patients with a mean BMI of 46.2 kg/m^2 compared to 72 children with common obesity matched for age, gender, and BMI showed SG to be associated with syndromic obesity. After five years of follow-up, children with PWS began gaining weight, with a BMI loss of 11 kg/m^2 after five years (7 patients' data) significantly lower than the 19 kg/m^2 loss observed in children without PWS. The surgical safety was good, with no major surgical complications reported among PWS patients with obesity comorbidities, primarily obstructive sleep apnea. A systematic review of 202 patients with obesity associated with hyperphagia (114 patients with PWS, 43 patients with MC4R mutations, 38 patients with hypothalamic obesity, and 7 patients with BBS) assessed bariatric surgery outcomes. PWS patients with a median age of 17 years, median weight of 97 kg and median BMI of 49 kg/m^2 were analyzed statistically. Within one year after surgery, these patients lost a median of 24% of their body weight, followed by a significant weight regain. Five of the 104 patients with PWS who died after surgery died within one year of their surgery, making surgical morbidity a concern. A second bariatric surgery was performed on 13 PWS patients. However, there was a trend towards less weight loss and increased surgical reinterventions in other hyperphagic obesities. Surgical complications and weight regain are more likely to occur in PWS patients [44-46]. Bariatric surgery has been reported in isolated cases of patients with other types of syndromic obesity, with varying interventions, follow-up, and outcomes. The study did not assess psychiatric or nutritional complications, which are more frequent in patients with these vulnerabilities. There should be caution when treating patients with syndromic obesity due to behavioral disorders, develop-

mental disorders and compulsive eating behaviors that may interfere with lifestyle changes required after bariatric surgery. Therefore, syndromic obesity does not appear to be an adequate indication for bariatric surgery [47-49].

In terms of retrospective genetic analyses, most of the evidence concerning monogenic non-syndromic obesity relates to long-term outcomes of bariatric surgery. These published studies investigated how heterozygous variants in the leptin-melanocortin pathway impacted long-term outcomes following RYGB in a retrospective case-control study with 50 heterozygous variant carriers and seven genes: LEPR, PCSK1, POMC, SH2B1, SRC1, MC4R, and SIM1, while 100 matched (sex, age, BMI, and time since surgery) controls were analyzed as well. When surgery was performed, the mean age was 51 and the BMI was 46 kg/m^2. Comparing variant carriers with matched controls, they lost -16.6% to -28.7%. In heterozygous patients, the maximum weight loss was 52.7 kg, while in heterozygous patients it was 29.8 kg [50, 51]. In heterozygous variant carriers, RYGB is less effective because there is more weight gain, perhaps due to eating disorders. In 131 obese adults who underwent SG surgery, the 10 patients carrying heterozygous variants in the leptin-melanocortin pathway lost less weight both in the short-term and in the long-term. After a short follow-up of two years, another study of 1014 patients undergoing bariatric surgery involving 30 patients with heterozygous variants in the leptin-melanocortin pathway (12 patients with POMC mutations, 11 patients with MC4R mutations, and 5 patients with PCSK1) found that the weight loss among mutation carriers and controls was similar. Researchers also compared the outcomes of 35 patients with heterozygous likely-pathogenic MC4R variants and 70 mutation-free controls matched for age, sex, BMI, and surgical procedure [52]. After bariatric surgery, the MC4R variant carriers showed a trend to greater weight gain after nadir, which was greater after SG than after RYGB.

There have been eight reports of homozygous variant carriers of POMC, LEPR, or MC4R mutations in the largest case series to date. After an initial median weight loss of 21.5 kg, every patient experienced unsatisfactory long-term outcomes with a median weight regain of 24.1 kg [53].

The melanocortin pathway heterozygous variants are not an absolute contraindication to bariatric surgery unless there is a major eating disorder or neurodevelopmental/psychiatric disorder. Before choosing surgery, caution and multidisciplinary discussion are warranted given the emergence of new effective treatments [54].

Conclusion

Patients with syndromic or monogenic obesity were previously offered only multicomponent lifestyle interventions. Despite the emergence of innovative, targeted treatments in recent years, clinical management of these diseases remains largely traditional, paving the way for personalized medicine in the future. To avoid irreversible anatomical changes and uncertain outcomes, pharmaceutical alternatives to bariatric surgery are now available. There needs to be further research to clarify each treatment's position in these rare and complex clinical conditions. In addition to improving their management, early genetic diagnosis allows access to specialized multidisciplinary care, new molecules, and ongoing clinical trials. Whenever child gains weight rapidly and displays other clinically suggestive characteristics, a genetic analysis should be offered. As a result of their lifelong struggles with obesity and its complications, this population certainly requires special attention. By doing so, patients and their families may be protected from obesity-related complications, conservative treatment approaches will not fail, and stigmatization of patients and their families will be reduced. Outpatient lifestyle interventions, especially if held close to home, may help to improve these features. This hypothesis can currently be explored through specific healthcare pathways in France. If this treatment is implemented, these patients should have a better prognosis in adulthood.

Thankfully, research continues to produce new solutions. Using induced pluripotent stem cell technologies or direct gene repair, patients with monogenic obesity may benefit in the future from CriSPr-mediated gene editing. Physicians and scientists must still work together on improving the conditions and outcomes of these patients, given their clinical severity.

Acknowledgments

None.

Conflict of Interest

None.

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