Treatment Options for Children with Monogenic Forms of Obesity

I. Aldhoon Hainerová a · J. Lebl b

a Department of Pediatrics and Center for Research of Diabetes, Metabolism and Nutrition, Third Faculty of Medicine and b Department of Pediatrics, Second Faculty of Medicine, Charles University, Prague, Czech Republic

Abstract
Mutations in genes involved in energy balance regulation within the central nervous system lead to monogenic forms of obesity. Individuals with these mutations are characterized by early-onset obesity and in some cases by endocrine abnormalities. Carriers of leptin gene mutations are able to normalize their body weight after daily subcutaneous leptin administration. Pharmacotherapy targeting the specific-gene deficiencies has not clinically been tested in other monogenic obesities. Mutations in the melanocortin 4 receptor gene (MC4R) represent the most common monogenic cause of human obesity. Several treatment options have been investigated in subjects with MC4R mutations. Few studies showed that an intensive lifestyle intervention induces similar weight reduction in MC4R mutation carriers in comparison to MC4R mutation noncarriers. However, long-term body weight maintenance is hardly ever achieved in MC4R mutation carriers. Sibutramine, serotonin and noradrenalin reuptake inhibitor, in MC4R mutation carriers induced weight reduction and improved cardiometabolic health risks. This result was also found in our homozygous MC4R mutation carrier. In vitro studies of melanocortin agonists efficiently activate mutated MC4R with impaired endogenous agonist functional response and thus, further research in the development of drugs for MC4R mutations is needed. An administration of intranasal adrenocorticotropic hormone was not shown to be effective in subjects with pro-opiomelanocortin gene mutations. Bariatric surgery has also been performed in few of MC4R mutation carriers. After gastric banding, lower body weight reduction and worse improvement of metabolic complications was found in MC4R mutation carriers versus noncarriers. However, preliminary results suggest that diversionary operations as gastric bypass represent a suitable method also for MC4R mutation carriers. In conclusion, the management of monogenic obesities still remains a challenge.

Obesity is a complex disorder that is caused by several genetic and non-genetic risk factors. From the genetic point of view, obesity can be classified either as syndromic or monogenic or polygenic. Syndromic obesity is apart from obesity additionally distinguished by mental retardation, dysmorphic features, and organ-specific developmental abnormalities. Monogenic obesity is obesity associated with a single gene...
mutation, which is sufficient by itself to cause weight gain in a food abundant context. Obesity due to single gene mutation is usually severe and characterized by an early-onset. Common obesities are usually determined by multiple gene polymorphisms and such a genetic make-up may predispose to energy storage [1]. This is considered as polygenic obesity.

Several milestones in genetics of obesity have been achieved. Among those are the twin and adoption studies with a discovery that genetic factors play a considerable role in body weight regulation [2, 3]. In 1994, cloning of the leptin gene was reported [4]. Later, rodent models and family studies in particular those on consanguineous pedigrees led to an identification of the leptin-melanocortin pathway.

The leptin-melanocortin pathway is the predominant regulatory system governing appetite and satiety. Leptin crosses the blood-brain barrier and activates its receptor located within the hypothalamus. This action leads to activation of anorexigenic neuropeptides (pro-opiomelanocortin (POMC), cocaine-amphetamine related transcript) and inhibition of orexigenic neuropeptides (neuropeptide Y, agouti-related peptide). POMC is processed by enzymes prohormone convertase 1 (PC1) and 2. One of its derived peptides is α-melanocyte-stimulating hormone (α-MSH) that activates melanocortin type 3 and 4 receptors (MC3R and MC4R) (fig. 1). MC4R is crucial for body weight regulation as it inhibits orexigenic effectors and stimulates anorexigenic effectors downstream. The importance of this signaling system in energy balance is well illustrated by cases of gene mutation within this pathway [5].

The aims of obesity treatment are to lose weight, maintain the weight loss on the long term, and improve obesity-related comorbidities. There is evidence that genetic factors not only predispose to weight gain and development of obesity but also modulate the response to therapeutic intervention in terms of weight loss [6]. In relation to lifestyle modifications, it is known that weight-loss maintenance in the long term is very difficult to achieve. It is assumed that less than 5% of the obese people who follow these recommendations effectively lose weight and maintain that weight loss [7, 8]. To date, pharmacotherapy of obese children and adolescents is very limited. It is well recognized that in adults bariatric surgery represents the most effective therapy [9]. However, bariatric procedures favorably affect not only insulin secretion and sensitivity, but also secretion of gastrointestinal hormones (e.g. glucagon-like peptide

Fig. 1. Leptin-melanocortin pathway. Most monogenic obesities are frequently due to gene mutations within the leptin-melanocortin pathway (for description, see text).
1, peptide YY, gastric inhibitory polypeptide, ghrelin) that regulate energy balance. Bariatric surgery may also be a way of the treatment for morbid obesity in children but the relevance of an invasive surgery procedure in childhood or adolescence is still under debate [10]. There is no wonder that in 2003, the American Academy of Pediatrics proclaimed prevention as the first line of treatment [11].

To date, eight monogenic genes (leptin [LEP], leptin receptor [LEPR], PC1, POMC, MC4R, single-minded homolog 1 [SIM1], brain-derived neurotrophic factor [BDNF], neurotrophic tyrosine kinase receptor type 2 [NTRK2]) that are either involved in the neuronal differentiation of the paraventricular nucleus or in the leptin-melanocortin pathway could explain up to 10% of cases with early-onset extreme obesity and hyperphagia [5]. Mutation carriers apart from severe early-onset obesity manifest with additional specific features which may help in genetic diagnosis of morbid obesity in an individual [modified according to Choquet H et al. [30]. LEP = leptin; LEPR = leptin receptor; PC1 = prohormone convertase 1; POMC = pro-opiomelanocortin; MC4R = melanocortin type 4 receptor; SIM1 = single-minded homolog 1; BDNF = brain-derived neurotrophic factor; NTRK2 = neurotrophic tyrosine kinase receptor type 2.

Table 1. General and specific features of single gene mutations

<table>
<thead>
<tr>
<th>General features</th>
<th>Specific features</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset obesity and hyperphagia</td>
<td>Low levels of circulating leptin</td>
<td>LEP</td>
</tr>
<tr>
<td></td>
<td>Impaired immunity (high rate of childhood infections)</td>
<td>LEPR</td>
</tr>
<tr>
<td></td>
<td>Hypogonadism</td>
<td>LEPR, PC1</td>
</tr>
<tr>
<td></td>
<td>Adrenal insufficiency (e.g. hypoglycemia, convulsion, pale skin, red hair, jaundice)</td>
<td>POMC</td>
</tr>
<tr>
<td></td>
<td>Malabsorption (intestinal dysfunction), glucose homeostasis disturbances, low levels of insulin</td>
<td>PC1</td>
</tr>
<tr>
<td></td>
<td>Variable effect on body weight in heterozygous mutation carriers</td>
<td>MC4R</td>
</tr>
<tr>
<td>Developmental delays</td>
<td>Variable effect on body weight in heterozygous mutation carriers</td>
<td>SIM1, BDNF, NTRK2</td>
</tr>
</tbody>
</table>

Obesity due to a single gene mutation is usually severe and characterized by early-onset accompanied by hyperphagia. Mutation carriers manifest with additional specific features which may help in genetic diagnosis of morbid obesity in an individual [modified according to Choquet H et al. [30]. LEP = leptin; LEPR = leptin receptor; PC1 = prohormone convertase 1; POMC = pro-opiomelanocortin; MC4R = melanocortin type 4 receptor; SIM1 = single-minded homolog 1; BDNF = brain-derived neurotrophic factor; NTRK2 = neurotrophic tyrosine kinase receptor type 2.
Mutations of *LEP* are of autosomal recessive inheritance and are extremely rare. To date, 20 patients have been reported mostly of non-Caucasian origin (e.g. Pakistani and Turkish). Severe hyperphagia and impaired satiety lead to early-onset extreme obesity. Further, hypogonadism, impaired T cell-mediated immunity, extremely low levels of leptin, higher levels of insulin and in some cases type 2 diabetes and dyslipidemia can be found in these mutation carriers [14]. However, daily subcutaneous injection of recombinant methionyl human leptin in the evening at a dose of 0.02–0.04 mg/kg reverses all aspects of the phenotype. A decrease of body weight and fat mass content is achieved without any instruction on dietary changes or on an increase in physical activity. This is probably due to spontaneous decrease of energy intake by almost 50% and changes in macronutrient content. Leptin replacement led to increased physical activity level without the reduction in metabolic rate that is usually associated with weight loss [15]. Positive effect on lipid profile and insulin sensitivity was also demonstrated [16]. In addition, development of secondary sexual characteristics and normal sexual function was observed. Ovulation and menstrual periods became regular [17]. Leptin withdrawal for 6 weeks resulted in substantial weight gain.

Mutations of *LEPR* were mainly described in specific ethnic groups (e.g. Algerian, Turkmen and Egyptian), in which consanguinity is common. Such a mutation should be considered in subjects with hyperphagia and severe obesity in the absence of developmental delay or dysmorphism. To date, there are nine families reported and only homozygous or compound heterozygous carriers are affected due to impaired receptor signaling. Heterozygous carriers have similar body weight to a wild type. Mutation carriers express hyperphagia from the first months of life leading to severe obesity and increase in body fat. Further, hypogonadotrophic hypogonadism, reduced adult final height due to the lack of the pubertal spurt and severe infections due to impaired T cell immunity are characteristic for the mutation carriers. Serum leptin levels are increased but within the range predicted by the elevated fat mass. Until now, no therapy has been suggested.

Due to the fact that POMC-derived peptides activate melanocortin receptors that are implicated in energy balance, adrenal steroidogenesis and pigmentation, adrenal insufficiency, severe obesity with hyperphagia and red hair pigmentation and fair skin are typically found in *POMC* mutation carriers. However, a lack of typical pigment phenotype and the presence of multiple pituitary hormone abnormalities have also been described. Heterozygous carriers have normal or mildly elevated body weight. Despite the fact that the management of obesity in POMC deficiency remains a challenge, several attempts for reversing severe obesity have been tried. A hypocaloric balanced diet applied for 12 months in 3 children with a variant associated with early-onset obesity in heterozygous form normalized their weight as well as fat mass and insulin resistance [18]. An administration of adrenocorticotropic hormone (ACTH$_{4-10}$), which resembles α-melanocyte-stimulating hormone (α-MSH), was shown to be effective in reducing body weight in normal weight individuals. Even the maximum dose (5 mg/day) of intranasally administered ACTH$_{4-10}$ in two
POMC-deficient patients had no effect on weight, body composition or metabolic rate. This can probably be explained by lower affinity of ACTH4-10 to MC4R [19]. A 1-year treatment with thyroid hormone of these patients with mild central hypothyroidism also did not result in a significant reduction of body weight [19].

Mutation carriers of the POMC-PC1 exhibit early-onset obesity in spite of malabsorption, glucose homeostasis disturbance and hypogonadism [5]. Few cases have been detected so far and no treatment has been proposed.

Mutations of MC4R represent the most common monogenic form of obesity. The prevalence of these mutations are 2–6% in extremely obese children and adolescents, 1–2% among obese adults and up to 0.5% of the normal weight population. Two polymorphisms of MC4R have been found to have small protective effect for the development of obesity [20]. Currently, over 130 functionally relevant mutations, mostly leading to intracellular retention, have been identified. The effect size of MC4R mutations is lower than those of the LEP and LEPR mutations.

A variety of experimental studies on the management of MC4R disruption have been conducted. Studies with melanocortin agonists showed that mutated human MC4R with impaired endogenous agonist functional response can be activated by some of these agonists and might represent valuable therapeutic target [21]. Further, pharmacological chaperones that recover cell surface expression may represent a candidate for the development of a targeted therapy suitable for a large subset of patients with MC4R-deficient obesity [22].

Effect of lifestyle intervention in MC4R mutation carriers has been evaluated in two studies. Similar weight loss during 6 weeks of the inpatient management program was achieved in mutation carriers in comparison to noncarriers [23]. In a 1-year outpatient lifestyle intervention, children with MC4R mutations with reduced gene function reached a similar degree of weight reduction as mutation noncarriers. However, the maintenance of the weight loss in MC4R mutation carriers failed in contrast to noncarriers [24].

The effect of sibutramine, a reuptake inhibitor of serotonin, norepinephrine and dopamine, in children with hypothalamic obesity including those with MC4R mutations and syndromic obesity such as Prader-Willi syndrome was also investigated. Results showed that the weight loss in response to sibutramine treatment was achieved in both groups, but to a lesser extent in cases of hypothalamic obesity [25]. One of our MC4R mutation patients, a homozygous MC4R mutation carrier Gly181Asp (age 18 years, body weight 174.4 kg, BMI 55 kg/m²) underwent a 1-year therapy with sibutramine (fig. 2). After 1 year, minor weight gain (1.4 kg) was demonstrated (fig. 2). Further, there was an improvement of dyslipidemia, insulin sensitivity and a decrease of liver enzymes, uric acid, hunger and Beck depression score. Sibutramine was well tolerated by this patient. A year after cessation of the antiobesity drug, the patient’s body weight increased by 10.8 kg [26].

Bariatric procedures were performed in a few cases of MC4R mutation carriers. Laparoscopic gastric banding in MC4R variant carriers led to less weight reduction,
showed less improvement in metabolic syndrome and had more postoperative complications than in noncarriers [27]. After roux-en-Y gastric bypass, four functionally relevant heterozygous MC4R mutation carriers achieved similar rates of weight loss after 1 year of follow-up compared to 8 patients without MC4R mutations [28]. A recent report demonstrated a poor weight loss in an adolescent with complete MC4R deficiency undergoing laparoscopic adjustable gastric banding and truncal vagotomy [29].

In conclusion, LEP mutation is the first and until now the only genetic form of human obesity that is successfully pharmacologically treated. Individuals with MC4R monogenic conditions respond well to multidisciplinary interventions as do non-monogenic obese subjects. However, MC4R mutation carriers have difficulties to maintain their weight loss. It seems that only long-term, intensive and well-controlled lifestyle interventions are efficient for these subjects. Chemical chaperones and pharmacological agonists efficiently restore cell surface expression and endogenous agonist response of mutated MC4R. Their beneficial effects in MC4R deficient monogenic patients remain to be demonstrated. Preliminary results suggest that diversionary

Fig. 2. MC4R homozygous mutation carrier (Gly181Asp) at the age of 18 years (weight 174.4 kg, height 178 cm, BMI 55.0 kg/m²) and the weight development since his birth including body weight maintenance on a year of sibutramine treatment at the age of 18 years.
operations, which are more invasive, efficiently improve the neurohormonal control of satiety better than gastric banding procedures, and could therefore be indicated in monogenic hyperphagic subjects. The most important preventive strategy for all monogenic mutation carriers may be restriction of food access which requires training and active participation of the parents. In the future, new drug agents involved in the central nervous system regulation probably will also be tried in these cases of severe obesity based on single gene mutations. The use of novel combination drugs (phentermine/topiramate; bupropion/naltrexone) and gastrointestinal hormone analogues (liraglutide; exenatide) in the treatment of monogenic obesities should be further investigated. Finally, these cases may also be subjected to potential gene engineering.

Acknowledgements

Supported by the Czech research project of MSM VZ No. 0021620814 and the Czech Ministry of Health IGA grant NT 12342–5.

References