MECHANISMS IN ENDOCRINOLOGY

Update on treatments for patients with genetic obesity

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Abstract

Obesity, defined by an excess of body fat impacting on health, is a complex disease resulting from the interaction between many genetic/epigenetic factors and environmental triggers. For some clinical situations with severe obesity, it has been possible to classify these obesity forms according to the molecular alterations. These include: (i) syndromic obesity, which associates severe early-onset obesity with neurodevelopmental disorders and/or polymalformative syndrome and (ii) non-syndromic monogenic obesity, due to gene variants most often located in the leptin-melanocortin pathway. In addition to severe obesity, patients affected by these diseases display complex somatic conditions, eventually including obesity comorbidities, neuropsychological and psychiatric disorders. These conditions render the clinical management of these patients particularly challenging. Patients' early diagnosis is critical to allow specialized and multidisciplinary care, with a necessary interaction between the health and social sectors. Up to now, the management of genetic obesity was only based, above all, on controlling the patient's environment, which involves limiting access to food, ensuring a reassuring daily eating environment that limits impulsiveness, and the practice of adapted, supported, and supervised physical activity. Bariatric surgery has also been undertaken in genetic obesity cases with uncertain outcomes. The context is rapidly changing, as new innovative therapies are currently being tested both for syndromic and monogenic forms of obesity. This review focuses on care management and new therapeutic opportunities in genetic obesity, including the use of the melanocortin 4 agonist, setmelanotide. The results from ongoing trials will hopefully pave the way to a future precision medicine approach for genetic obesity.

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Invited Author's profile

Karine Clément (MD, PhD) is a Medical Doctor and Full Professor of Nutrition at Pitié-Salpêtrière hospital and Sorbonne University, Paris. Since 2002, her research unit at INSERM (www.nutriomique.org) works on the pathophysiology of obesity and related disorders. From 2011 to 2016, she created and was the director of the Institute of Cardiometabolism and Nutrition (ICAN). Prof Clément has been primarily involved in genetics of obesity and contributed to the identification of monogenic forms of obesity. Her group is also exploring the link between environmental changes (as changes in lifestyle and nutrition), gut microbiota, immune system and tissue functional modifications (adipose tissue fibrosis and inflammation).

Introduction

Technological advances in recent years, such as candidate gene approaches, next-generation sequencing (NGS), genome-wide association studies (GWAS), and expression studies using microarrays, have led to the discovery of hundreds of genes involved in the development of obesity. There is a proposed continuum between obesity due to polygenic inheritance, the most common form, in which the environment has a critical impact on the phenotypic development, and the rare forms of genetic obesity, which are often severe and show an early onset, with a predominant contribution of genetic factors. These genetic forms are now considered to represent approximately 5–10% of childhood severe obesity (1). As it is described elsewhere (2), we will not describe in detail the clinical progression of obesity from childhood to adulthood that may give rise to the suspicion of genetic obesity and lead to its molecular diagnosis (2). However, it should be noted that early-onset obesity (before 6 years of age) associated with eating disorders, endocrine anomalies (hypogonadism, growth abnormality), and/or signs specific of the syndromic form, such as neurodevelopmental disorders, should alert clinicians and lead to molecular testing. Thus, after summarizing the clinical pictures, we present the latest advances concerning new therapies that have been developed over the past several years that have made it possible to propose effective solutions to patients with genetic obesity.

Clinical subtypes of genetic obesity

Syndromic obesities (ORPHANET code 240371) are defined as obesity starting early in childhood linked to eating behavior disorders and associated with a neurodevelopmental disorder (intellectual impairment, delayed walking, delayed learning, autism spectrum disorders) and/or malformative syndrome. More than 80 syndromes have been described but not all of them have an identified genetic substratum (3). We briefly summarize the main phenotypic traits for the most common syndromes sharing physiopathological characteristics related to hypothalamus impairment.

PWS, of which the frequency is between 1/15 000 to 1/20 000 births, is characterized by severe neonatal hypotonia, eating disorders evolving in several phases (from anorexia with suckling disorders in the first months of life to hyperphagia, with major food impulsivity appearing at approximately 4–8 years of age), abnormal

body composition, with increased fat mass and reduced muscle mass (4), endocrine abnormalities (growth hormone deficiency, hypogonadism), intellectual impairment, and learning difficulties, as well as behavioral disorders, and dysmorphic traits (5). The evolution of PWS from childhood to adulthood is often marked by the development of severe obesity, mostly associated with a switch from difficulties eating to uncontrolled eating behavior. Of note this critical period in the developmental trajectory is markedly influenced by the nature of the patient's environmental care (i.e. provided by caregivers) and implemented specialized care. In other words, early and closely implemented care can limit the severity of uncontrolled eating and the development of obesity (6). PWS is linked to abnormal parental genomic imprinting with the physical or functional absence of chromosomal segment 15q11–q13 of paternal origin. The 15q11.2–q13 region contains a PWS domain with five paternally expressed protein-coding genes including *MRKN3* (makorin 3), *MAGEL2* (MAGE-like 2), *NDN* (necdin), *NPAP1* and *SNURF-SNRPN* (SNRPN upstream reading frame-small nuclear ribonucleoprotein polypeptide N) and *snoRNAs* (7).

The *BBS* phenotype is also heterogeneous with autosomal recessive transmission. In addition to severe early-onset obesity, patients may show retinal dystrophy, polydactyly, kidney abnormalities, hypogonadism, dysmorphia, and learning disabilities. At least 19 genes are involved in BBS, all linked to functioning of the primary cilium (8). Hair cells are critical for properly functioning cellular machinery and are used to transmit signaling messages from the outside to the inside of cells. Hair cells are also involved in mammalian development, contributing, in particular, to right/left symmetry. The precise mechanisms involved in obesity development in BBS are still poorly understood. However, several hypotheses have been put forward (9, 10). One proposes a central origin of obesity due to hypothalamic dysfunction associated with hyperphagia. For example, the loss of BBS proteins leads to synaptic aberrations in principal neurons, especially in structures such as the hippocampus and amygdala (11). Other hypotheses of a peripheral origin involving adipose tissue and adipocyte proliferation or other endocrine tissues (pancreas, stomach, intestine) have also been proposed (10).

The 16p11.2 microdeletion syndrome is a disorder caused by a deletion of a small piece of chromosome 16, detectable by chromosomal microarray analysis. People with 16p11.2 deletion syndrome usually have developmental delay, intellectual disability, and early-onset

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obesity. The prevalence is estimated to be approximately 3 in 10 000. In a large cohort of patients with a 16p11.2 deletion syndrome, satiety was impaired in children before the onset of obesity occurring in adolescence (12). Among genes encompassed by this deletion, the *SH2B1* gene is involved in regulation of leptin signalization in the melanocortin pathway. Patients carrying punctual mutations in this gene present a precocious obesity with hyperphagia, short stature and insulin resistance (13).

Pseudohypoparathyroidism (PHP) is caused by molecular defects that impair hormonal signaling via receptors that are coupled, through the α -subunit of the stimulatory G protein (Gsa), to activation of adenylyl cyclase. PHP describes disorders that share common biochemical features of hypoparathyroidism (i.e. hypocalcemia and hyperphosphatemia) that are the result of resistance of target tissues to the biological actions of parathyroid hormone (PTH). Reports estimated the prevalence to be between 0.34 and 1.1 in 100 000. The most common underlying genetic mechanisms are *de novo* or autosomal dominantly inherited genetic mutations and/or epigenetic, sporadic or genetic-based alterations, within or upstream of *GNAS*. Obesity is very frequent (>90% in children), severe and early-onset (before 2 years of age), with inconstant hyperphagia. Mechanisms of obesity are complex and could be partly due to resistance to MC4R signaling (14). Thus, *GNAS* analysis is important to consider in case of early-onset unexplained obesity.

Non-syndromic monogenic obesities (ORPHANET code 98267) are most often linked to a pathogenic variant of a gene located in the hypothalamic pathway of leptin-melanocortin involved in the regulation of energy balance: leptin (*LEP*), leptin receptor (*LEPR*), proopiomelanocortin (*POMC*), prohormone subtilisin/kexin 1 convertase (*PCSK1*), melanocortin receptor type 3 and 4 (*MC3R* and *MC4R*) (2), MC4R regulatory protein, melanocortin receptor accessory protein 2 (*MRAP2*) (15) and adenylyl cyclase 3 (*ADCY3*) (16). More recently, several reports on genetic screening have found variants in subjects with early and severe obesity involving genes that are probably involved in or regulating this pathway: steroid coreceptor activator-1 (*SRC-1*), semaphorin 3A-G (*SEMA3A-G*), plexinA1-4 (*PLXNA1-4*), neuropilin1-2 (*NRP1-2*), and kinase suppressor of ras 2 (*KSR2*) (17, 18). These monogenic obesities are mainly due autosomal recessive variants in these genes that play a major role in the central control of food intake. Reported subjects with compound heterozygous or homozygous variants have a phenotype that is much more severe than that of heterozygous subjects. In heterozygous subjects, phenotypic expression

may depend in part on the environment and the influence of other genes. These forms of obesity account for at least 5% of the causes of early and severe obesity (19), but this prevalence is probably underestimated and may be higher in certain populations, especially those in which consanguinity is frequently observed (16, 20, 21). Patients with compound heterozygous or homozygous variants for the *LEP*, *LEPR*, *POMC*, *PCSK1*, and *MC4R* genes show early severe obesity accompanied by impaired hunger and satiety signals (22, 23, 24, 25, 26, 27, 28). Weight and BMI curves are characteristic and should draw the immediate attention of clinicians. They most often show a normal birth weight followed by a rapid weight increase and severe obesity that develops from the first 3 years of life. The results of a recent report suggest that variants in the leptin-melanocortin pathway should be sought when BMI exceeds 27 kg/m² at the age of 2 years or 33 kg/m² at the age of 5 years (29). Major hyperphagia and insatiable hunger are suggestive signs. Mutations in melanocortin pathway can be easily distinguished from PWS by the absence of neonatal hypotonia and sucking difficulties.

Along with severe obesity and uncontrolled eating, patients carrying a pathogenic homozygous variant of the *LEP* or *LEPR* genes present pubertal delay and/or a hypogonadotropic hypogonadism and sometimes thyrotropic insufficiency of central origin. Somatotropic insufficiency, leading to growth retardation, can also be observed in carriers of the pathogenic variant of *LEPR* (21, 23).

Subjects with obesity linked to a complete *POMC* deficit (homozygous or compound heterozygous) thus show corticotropic insufficiency and sometimes moderate thyrotropic insufficiency (30, 31). They also display somatotropic and gonadotropic insufficiency and red hair (28, 29). Beyond complete *POMC* deficiency, some heterozygous variants, as well as methylation anomalies, of the *POMC* gene may also be involved in the development of obesity (32, 33). Patients with rare pathogenic variants of the *PCSK1* gene that lead to complete PC1 deficiency (homozygosity or compound heterozygosity) show severe early onset obesity, late postprandial hypoglycemia, and gonadotropic, thyrotropic, and corticotropic insufficiency (25). Löffler et al. described heterozygous variants of *PCSK1* associated with obesity and glucose intolerance in children (34). Based on 845 non-consanguineous European subjects with severe obesity, the prevalence of partial PC1 deficiency (heterozygosity) was estimated to be 0.83% (35). Severe obesity forms linked to heterozygous variants of *LEP*, *LEPR*, *POMC*, and *PCSK1* are more frequent than those related to homozygous or compound heterozygous

variants. For example, in our cohort of 6467 subjects with severe and/or early onset obesity (<6 years old), we found a frequency of 0.8% vs 3.3%, respectively, in carriers of homozygous vs heterozygous variants also showing an attenuated phenotype that could be more dependent on the environment ((21) and C Poitou, unpublished personal data).

Obesity linked to the presence of homozygous or heterozygous compound variants of *MC4R* is rare but severe, close to that of the other forms described for *LEP* and *LEPR* (27, 28). However, there is no associated endocrine deficit (reproductive function and normal fertility, normal corticotrophic function, no somatotrophic deficit). Obesity linked to heterozygous variants of the *MC4R* gene represents approximately 2–3% of severe obesity in children and adults, with more than 166 different functional variants described in various populations (Europeans, Americans, Asians) (36). Children with heterozygous variants have more body fat than non-mutated BMI-matched subjects (37). It was initially reported that they are taller in the first 5 years of life (27) and more hyperphagic, but these characteristics may decrease with age. The association between altered eating behavior and *MC4R* pathogenic variants is variable across studies, depending presumably on the population studied, the functional impact of the *MC4R* variants, and the modalities used to record the altered eating behavior (38, 39).

Overlapping pathophysiology between syndromic and non-syndromic obesity

The distinction between syndromic obesity and non-syndromic monogenic obesity has its limitations, as clinically certain forms of monogenic obesity can be accompanied by neurodevelopmental and/or psychiatric disorders (2). In addition, there is an overlap in their pathophysiology, as most rare forms of obesity involve central anomalies of the regulatory centers of energy homeostasis, in particular the hypothalamus. For example, in PWS, abnormalities of the appetite-suppressing pathways, due to proconvertase 1 (PC1) deficiency and activation of the orexigenic Agouti-related protein (AgRP) neurons, have been described (40, 41). Moreover, inactivation of the *MAGEL2* gene, located in the genomic region classically deleted in PWS (15q11–13), has been shown to be responsible for a decrease in the density of axons of aMSH neurons in a mouse model (42). In BBS, considered to be a ciliopathy, the transport of

LEPR is altered and therefore its localization at the ciliary membrane of POMC neurons is affected (43, 44). Another example is PHP-linked obesity that may be partly due to MC4R resistance (via Gsa). Smith Magenis syndrome, including severe obesity, is linked to the 17p11.2 locus, encompassing the *RAI1* gene. Haploinsufficiency of this gene in murine models leads to a decrease expression of POMC and Brain Derived Neurotrophic Factor (BDNF), probably promoting weight gain (45).

Thus, overlapping pathophysiological aspects suggest that certain pharmacological approaches could be shared between syndromic and monogenic obesity.

Comprehensive and multidisciplinary care

Patients with genetic obesity require comprehensive, specialized, and multidisciplinary approaches to improve their clinical situation. Dietary advice, with the supervision of eating behavior, add combined with other approaches that may include adapted physical activity, psychomotor skills therapy, speech therapy, hormone replacement therapy, etc., should be implemented as early as possible in early childhood, as these measures have been shown to improve the patients' condition (2).

In adulthood, a disorganized transition after pediatric care or the absence of previous care in infancy often leads to a clinical picture dominated by obesity, which is often severe and life-threatening. A study conducted in the United States shows that mortality remains early in PWS, with an average age at death of 29.5 years, with more than 30% due to respiratory causes (46). Early prevention of disease progression is important, including adolescents and young adults with a normal BMI (47). A recent French study evaluating mortality registers for patients with PWS between 2004 and 2014 also found a median age of mortality of 30 years (1 month to 58 years). Mortality from respiratory causes was predominant in children and adults. Here, the causes and age of death were independent of the type of the genetic abnormality (48).

Clinical management should target the specific comorbidities found associated with each syndrome. This includes supplementation of endocrine deficits and treatment of sleep disorders, digestive disorders, orthopedic anomalies, and cardiac and urogenital malformations, among others. It is thus based on detecting and treating complications related to obesity and, because these diseases are complex, multidisciplinary care by a specialized and expert team is essential for patient improvement. From a nutritional point of view, dietary

autonomy is generally unfeasible in genetic obesity with eating disorders. In the context of PWS, the establishment of a strict dietary framework, the limitation of access to food, and the ritualization of food intake are means to prevent obesity, its associated complications, and the resulting excess mortality. This recommendation can also be applicable in the context of syndromic obesity, since uncontrolled eating is a dominant phenotype. The patient's entourage requires education and support, whether it is family or their immediate social network. The establishment of dietary programs closely adapted to each patient is critical, based on measured energy expenditure, when possible in expert clinical centers, as all these rare forms of obesity can be characterized by a deficit in energy expenditure.

Advice and guidance on physical activity is also crucial and should be adapted to the patients' neurodevelopmental disabilities. In PWS, long-term physical exercise leads to a reduction in weight and an improvement in physical performance (49). We recently showed that adult women with PWS have a very high level of physical inactivity in comparison to a group of women sharing the same age and corpulence by measuring physical activity level with an accelerometer. A 16-week program of adapted physical activity at a frequency of 1 h twice per week at home, supervised by an instructor, made it possible to increase their level of physical activity. Acceptability of the program was very satisfactory (50). The use of connected objects, such as a pedometer, can be a useful motivational tool in these situations.

In monogenic obesity, the establishment of a 1-year nutritional and physical exercise program led to weight loss in children with *MC4R* variants equivalent to that of non-carrier children (51). However, *MC4R* variant carriers returned to their baseline weight within 1 year after ending the program, which was not the case for the non-carriers of the variant.

Neuropsychiatric management is also very important for most patients. As such neuro-psychological assessment should be carried out at different stages of life to assess cognitive function and abilities to improve educational and medico-psychological care.

The transition between pediatric and adult care is a critical moment, often associated with breakdowns in both medical and social support, especially if cognitive disorders or intellectual impairment are in the foreground. These aspects are all very demanding and an adult life project, the integration of social structures, and comprehensive and coordinated care should be taken into consideration (52). Caregivers must carefully consider the pediatric-to-

adult transition step, which requires a particular effort for the future of adolescents suffering from genetic obesity, as behavioral problems and obesity frequently worsen in this critical period.

Genetic obesity and bariatric surgery

Current data concerning the effectiveness of bariatric surgery in genetic obesity are based on only a few cases with varying follow-up times (2). More data with long-term patient follow-up are needed. The largest series is based on the analysis of 60 American patients with PWS whose average age was 19.7 ± 6.4 years and the preoperative BMI 51.6 ± 10.1 kg/m². Despite their young age, 31% were diabetic and 15.7% were experiencing heart or respiratory failure. The results were worse for subjects with PWS than for patients with common obesity, with an average weight loss of 2.4% 5 years after a gastric bypass. At the same time, the rate of complications, including death, pulmonary embolism, wall infection, and gastric perforation was higher (53). In another study carried out in Saudi Arabia, a sleeve gastrectomy performed on 24 children and adolescents with PWS (average age 10.7 years) resulted in weight loss of 14.7% at 1 year ($n=22$) and 10.7% ($n=7$) at 5 years, without complications; the results were identical to those of the adolescent control group in this study but the weight loss appeared to be limited relative to that found in common obesity data (54). Conversely, in a Chinese study published in 2012, three patients with PWS underwent bariatric surgery (two sleeve gastrectomy and one mini-gastric by-pass) with good results on weight loss at 2 years (32.5 kg (24.9–38.3 kg)) without any major complication (55). Recently, Sheimann et al. published results of bariatric surgery in 24 children/adolescents PWS compared to 72 non-PWS subjects matched for age, gender, and BMI. All underwent a laparoscopic sleeve-gastrectomy. At 1 year, in the PWS group, the decrease in BMI was 15 kg/m², not different from the non-PWS group ($P=0.3$). Postoperatively, 81.8% of co-morbidities were in complete remission. There were no readmissions or complications after surgery throughout follow-up. At 5 years, the mean BMI loss in PWS was 11 kg/m² but 70% did not have data at that point (56). In 2019, a Chinese study reported the outcome of five patients with PWS following bariatric surgery. At 10 years of follow-up, there was no weight loss and the associated comorbidities were not improved (57). This latter study also reported obesity-related premature death in one patient. In BBS, studies have reported isolated cases with

varying results, depending on the technique, but studies in larger cohorts have not been published. A Belgian team reported the case of a severely obese woman with BBS who underwent a sleeve gastrectomy. This resulted in a 32% total weight loss at 3-year follow-up (58). There were no major complications for these reported cases (59, 60). Of note, no study has precisely reported the nutritional (deficiencies) or psychological complications (possible psychiatric decompensation) that are particularly common in syndromic obesity with physical and mental vulnerability.

In our opinion, surgery should be generally contraindicated in syndromic obesity with eating and neurodevelopmental disorders, apart from exceptional cases, which must be individually discussed with a multidisciplinary expert team. Indeed, the benefit-risk balance is largely unfavorable, given the disappointing results on weight loss outcomes, with frequent weight regain and, most importantly, the risks associated with the physical vulnerability of multi-organ damage linked to the syndrome (digestive, osteopenia, anemia, thromboembolic risk). Moreover, caregivers need to consider the psychological fragility of these patients and, especially for PWS, difficult-to-diagnose postoperative complications (absence of fever, reduction in pain threshold) combined with patient difficulty in manifesting complaints (61).

Concerning monogenic obesity with alterations of the leptin/melanocortin pathway, a few cases of post-surgery outcomes have been reported, again with varying results and duration of follow-up. We reported a patient case with severe obesity due to a homozygous variant of the *LEPR* gene. After gastropasty, the patient initially lost weight (approximately 20 kg), which was maintained for at least 6 years, while remaining obese, at the cost of sustained efforts to fight hyperphagia (62). Two patients from the French Reunion Island, carrying homozygous *LEPR* pathogenic variants underwent bariatric surgery (one gastropasty and one gastric bypass) with, respectively, 44% of weight loss after 9 months and 7% of weight loss after 5 years (21). A Dutch group published the bariatric surgery outcomes of 1014 patients, of whom 30 were diagnosed with monogenic obesity due to heterozygous pathogenic variants, especially in the *POMC* and *PCSK1* genes. Gastric bypass-induced weight loss after 2 years of follow-up of variant carriers was not significantly different from that of patients not carrying a pathogenic variant (63). In a recent Chinese study, with 131 obese subjects in the cohort, 8.4% (11 subjects) carried a heterozygous variant of a gene of the leptin/melanocortin pathway. The

weight loss obtained after 6 years of follow-up for patients carrying variants for the *LEP*, *LEPR*, *SIM1*, and *PCSK1* genes was much lower than that of patients without these variants (64), with also poorer improvement in metabolic comorbidities.

Based on these studies, the presence of homozygous variants of the leptin/melanocortin pathway (i.e. upstream of MC4R), in the absence of psychiatric disorders, major eating disorders, or intellectual impairment, do not appear to represent an absolute contraindication. However, the disappointing results, probably linked to the primary energy balance disorder, and the emergence of new treatments (see below) encourage the utmost caution before deciding on a surgical procedure. The data concerning heterozygous variants of these genes are currently insufficient to provide a basis to make an unequivocal decision.

Concerning MC4R variants, several reports have shown varying outcomes post-bariatric surgery. Aslan et al. reported the case of a patient with a complete MC4R deficiency, leading to insatiable hunger, who underwent gastric banding and vagotomy (65). After initial weight loss in the first four months, the patient regained the lost weight, suggesting this surgery was not adapted for this patient.

The effects of bariatric surgery on weight loss of patients with heterozygous variants of *MC4R* vary between studies and reports, probably linked to the functionality of the variants. They are reviewed in (66). The heterogeneity of the analyzed *MC4R* variants – polymorphisms vs functionality relevant mutations – complicates the interpretation of the published data. Valette et al. reported identical weight loss at 1 year for patients with an *MC4R* variant and those in a control group without the variant, suggesting that a heterozygous variant of *MC4R* does not have a major impact (67). However, a more recent study showed that the presence of a gain of function (GOF) heterozygous variant is associated with an increased risk of binge-eating disorder (BED) before surgery and more reoperations and postoperative complications (39). In a Dutch cohort, 11 patients from nine families with severe early-onset obesity carried heterozygous variants of the *MC4R* gene. Among them, the patients who had a gastric bypass showed weight loss equivalent to that of patients not carrying a mutation. On the other hand, the weight loss was significantly less during the 2 years of follow-up for those who had a sleeve gastrectomy ($n=3$) (63). Based on the published studies, there are currently no arguments against bariatric surgery for patients carrying a heterozygous variant of *MC4R*, apart from

the usual well-known contraindications for common obesity. The strategy to use bariatric surgery in those cases should, however, change in the coming years, due to the development of new treatments.

Toward therapeutic innovations in genetic obesity

The development of new therapeutic strategies is essential because of the marked and early obesity of genetically obese patients. This puts a heavy burden on the quality of life of these patients and on their relatives. Moreover, alternatives to bariatric surgery are necessary for these severe conditions. As these genetic disorders can involve common biological pathways, it is highly possible that a molecule developed for one disorder may be effective for a wider spectrum of genetic abnormalities. Common forms of obesity might also benefit from these developments in the future.

In recent years, a number of innovative therapeutic approaches have been developed, notably for PWS and for patients with alterations of the melanocortin pathway upstream of the MC4R receptor (68, 69). Pharmaceutical interventions reported in NCT clinical trials for weight loss in syndromic and monogenic obesities are described in Table 1, with ongoing and completed studies.

In PWS, abnormalities of the oxytocinergic system have been described. Adults with PWS show a significant reduction in the number of hypothalamic-producing oxytocin neurons and a decrease in circulating oxytocin, whereas elevated levels have been measured in children. A number of clinical features of PWS, such as overeating, obesity, and social interaction disorders, may be linked to alterations in oxytocin regulation. Thus, treatment with oxytocin could plausibly have beneficial effects in PWS, especially in young children (reviewed in (70, 71)). Moreover, oxytocin was shown to improve emotions and autism spectrum disorders, which may be relevant, as some PWS patients display features associated with the autism spectrum. Studies in adults and adolescents with PWS initially showed inconstantly a beneficial effect of the administration of nasal oxytocin on social interaction factors (72, 73). However, two recently published studies have opened up new therapeutic perspectives in PWS. A Dutch, randomized, double-blind study that administered intranasal oxytocin vs placebo for 8 weeks to children aged 6–14 years showed a positive effect on overeating and social behavior in the youngest children (74). At an earlier age, below 6 months, intranasal

administration of oxytocin improved sucking disorders and social interactions in infants (75). These recent promising studies suggest that treatment with oxytocin should probably be administered early in infants and young children to improve eating disorders, because the oxytocinergic system may be more plastic at earlier stages of development. Carbetocin, an oxytocin receptor-selective compound, showed promising results, reducing hyperphagia score after 14 days of treatment (76).

Aside from studies on oxytocin, we have shown that topiramate has a significant effect on the hyperphagia score in adults with PWS in a randomized double-blind study (77). Moreover, a new molecule, AZP-531 (livoletide), a non-acylated ghrelin analog, was also tested in a European multicentric randomized placebo-controlled study. AZP-531 has been shown to inhibit the orexigenic effect of acylated ghrelin in animal models and improve glycemic control and weight loss in humans. The daily injection of a dose of AZP-531 for 14 days in 47 patients with PWS was accompanied by a reduction in the hyperphagia score, without serious adverse effects (78). A phase IIb clinical trial is underway to test the longer-term effectiveness of this molecule (over 12 months), in particular on weight and metabolic improvement, and to ensure safety (NCT03790865). Moreover, GLWL-01, a ghrelin O-acyltransferase inhibitor, showed no significant effect on hyperphagia after 4 weeks of double-blind treatment (NCT03274856). Other therapies are being tested in PWS, such as K⁺-ATP channel agonists (diazoxide choline controlled released), showing a decrease in hyperphagia score in patients with the highest scores at baseline (79). Glucagon-like peptide 1 (GLP-1) receptor agonists, such as liraglutide and exenatide, have been tried out in non-randomized studies or reported in clinical cases (80, 81, 82). For Exenatide, appetite scores decreased after 6 months of treatment but without effect on weight. Clinical trials with GLP-1 agonists are ongoing (Table 1). The association of tesofensine and metoprolol, is being evaluated in PWS. Tesofensine is a triple monoamine (serotonin, noradrenaline, dopamine) reuptake inhibitor with anti-obesity effects, and metoprolol is a β -blocker used to counteract the adverse effects of increased heart rate and blood pressure induced by tesofensine alone; preliminary data show benefits on weight loss but exacerbation of behavioral problems (69). Other innovative therapies are currently being tested, such as the modulation of the gut microbiota by dietary fibers or brain stimulation (Table 1). Beloranib, a methionine aminopeptidase 2 inhibitor, has been tested in PWS with interesting results on weight but was not approved

Table 1 Pharmacological weight loss interventions in syndromic and monogenic non syndromic obesity.

Type of genetic obesity	Pharmaceutical molecule	Mode of administration	Number of cases	Methodology/trial (number, phase, status)	Results	Adverse events	References
Syndromic Prader-Willi	Oxytocin	Intranasal		5 ongoing trials (phases II and III)			NCT03114371, NCT02804373, NCT04283578, NCT03197662, NCT03649477 Tauber <i>et al.</i> (72)
			n = 24 adults PWS 19–67 years	Double-blind RCT, one single dose (oxytocin vs placebo)	Significant increase in trust in others ($P = 0.02$) and decrease in sadness tendencies ($P = 0.02$) with less disruptive behavior ($P = 0.03$) in the 2 days following administration than patients with placebo	No SAE	
			n = 30 PWS aged 12–30 years	Double-blind RCT, cross-over. Eight weeks of oxytocin or placebo followed by a 2-week washout period and then another 8 weeks of oxytocin or placebo	No effect on hyperphagia and behavior except an increase in temper outbursts	No SAE	Einfeld <i>et al.</i> (73)
			n = 25 children PWS 6–14 years	Double-blind RCT, cross-over. Four weeks of oxytocin or placebo directly followed by another 4 weeks of oxytocin or placebo. No washout	No significant effects of oxytocin on social behavior or hyperphagia, but in the 17 children younger than 11 years, significantly less anger ($P = 0.001$), sadness ($P = 0.005$), conflicts ($P = 0.010$) and food-related behavior ($P = 0.011$), and improvement of social behavior ($P = 0.018$) during oxytocin treatment vs placebo	No SAE	Kuppens <i>et al.</i> (74)
			n = 24 children PWS 5–11 years	Double-blind RCT, crossover. Five days of intranasal oxytocin or 5 days of intranasal placebo spray, followed by a 4-week washout period, and then patients returned for 5 days of treatment with the alternate source	Behavioral, socialization, anxiety, and appetite endpoints improved with oxytocin vs placebo but this was not statistically significant (day 6 and 14)	No SAE	Miller <i>et al.</i> (95)

Review		C Poitou and others		Treatments in genetic obesity		183:5	R157
Carbetocin (oxytocin analog)	Intranasal	1 ongoing (phase III)	<i>n</i> = 37 PWS 10–18 years	Double-blind RCT, 14 days carbetocin or placebo	Statistically significant reduction in hyperphagia total score at study end for patients under carbetocin (–15.6) vs patients receiving placebo (–8.9; <i>P</i> = 0.029)	No SAE	NCT03649477 Dykens <i>et al.</i> (76)
	DCCR = diazoxide choline controlled release tablets	Daily oral	2 ongoing (phase III)	10-week open label treatment period, followed by a 4-week double-blind, placebo- controlled treatment period	Decrease of the hyperphagia score (–4.32, <i>n</i> = 11, <i>P</i> = 0.006), especially in patients with moderate to severe baseline hyperphagia and in subjects treated with the highest dose	peripheral edema, transient increases in glucose	NCT03714373, NCT03440814 Kimonis <i>et al.</i> (79)
RM493/ Setmelanotide	Daily s.c.	1 completed (phase II) in PWS adults (16–65 years)	<i>n</i> = 13 PWS 11–21 years	10-week open label treatment period, followed by a 4-week double-blind, placebo- controlled treatment period	Clinically meaningful weight loss despite only modest improvement in hyperphagia (with the highest dose, longest period)	No SAE	NCT02311673
<i>Bifidobacterium animalis</i> spp. Lactis (probiotic)	Oral	1 completed (phase III)	1 ongoing	1 completed (phase III)	No posted results	No SAE	NCT03548480
Fibers (gut microbiota)	Oral	1 ongoing	1 ongoing	1 ongoing	Hyperphagia score reduced significantly with AZP-531. No change in body weight but reduction in waist circumference and fat mass.	No SAE	NCT04150991
AZP-531/Livoteide	Daily s.c.	1 ongoing (phase II)	<i>n</i> = 47 PWS 13–46 years	Double-blind RCT: 14 days of double-blind treatment (AZP-531 or placebo)	Hyperphagia score reduced significantly with AZP-531. No change in body weight but reduction in waist circumference and fat mass.	No SAE	NCT03790865 Allas <i>et al.</i> (78)
GLWL-01, ghrelin O-acyltransferase (GOAT) inhibitor	Oral	Double-blind RCT crossover. Four weeks of double-blind treatment (GLWL-01 vs placebo)	<i>n</i> = 19 PWS mean 22 years	Double-blind RCT crossover. Four weeks of double-blind treatment (GLWL-01 vs placebo)	Hyperphagia score post treatment (0 to 36): 15.9 (1.21) in GLWL-01 subjects vs 14.7 (1.23) in placebo subjects	No SAE	NCT03274856
							(Continued)

Table 1 Continued.

Table 1 Continued.

Review						C Poitou and others	Treatments in genetic obesity	183:5	R158
Type of genetic obesity	Pharmaceutical molecule	Mode of administration	Number of cases	Methodology/trial (number, phase, status)	Results	Adverse events	References		
	Exenatide	Daily s.c.	n = 10 PWS 13–25 years	Open-label, non-randomized, longitudinal study (6 months)	Appetite scores significantly decreased from baseline (32.2 ± 8.7) after 6 months of treatment (25.4 ± 7.2; p = 0.004). HbA1c significantly decreased but not weight	No SAE	Salehi <i>et al.</i> (80)		
	Liraglutide	Daily s.c.	n = 1	1 ongoing (phase III) Case report	Decrease in weight at 1 year of treatment (–5.7 kg)	Unknown	NCT02527200 Senda <i>et al.</i> (81)		
			n = 1	Case report	Decrease in weight at 14 weeks of treatment (–3.2 kg)	Unknown	Cyganek <i>et al.</i> (82)		
	Tesofensine/metoprolol	Oral		1 completed (phase II) in PWS adults 18–30 y	Decrease of weight after 8 weeks (4.8 kg, n = 5), after 13 weeks (7.9 kg, n = 2), vs placebo. Reduction in the total hyperphagia score (from 10 to 1 after 8 weeks and 0 after 13 weeks).	Exacerbation of behavioral problems and CNS disorders.	NCT03149445 Tan <i>et al.</i> (69)		
	Octreotide	Monthly i.m.	n = 9 PWS 10.8–18.9 years	56-week prospective, randomized, cross-over trial	No effect on BMI, on appetite or compulsive behavior toward food	Transient elevation of glucose (2), gallstones (3)	De Waele <i>et al.</i> (96)		
	Topiramate	Oral	n = 62 PWS 12–45 years	RCT study during 8 weeks	Significant improvement in the hyperphagia behavior and severity scores with topiramate vs placebo.	In the topiramate group, 4 cases of sedative effects or psychomotor slowdowns, 4 biological modifications in hepatic function, 4 cases of hyperammonemia, and 2 infectious episodes	Consoli <i>et al.</i> (77)		

Review		C Poitou and others		Treatments in genetic obesity		183:5	R159
Deep brain stimulation	Implantation of electrodes in the lateral hypothalamic area	$n = 4$ PWS 18–28 years	Prospective study, non-randomized: titration (1–2 months), stimulation off (2 months), low-frequency DBS (40 Hz; 1 month), washout (15 days), high-frequency DBS (130 Hz; 1 month), and long-term follow-up (6 months).	Mean 9.6% increase in weight; 5.8% increase in body mass index	2 infections, one associated with skin picking	Franco <i>et al.</i> (97)	
Transcranial direct current stimulation	Transcranial	$n = 32$. 10 adult PWS, 11 adult obese and 11 adult healthy-weight control subjects	Double blind, sham-controlled, multicenter study. PWS and Obese: five consecutive daily sessions. Healthy : a single session.	In PWS, significant change from baseline in TFEQ (Three-Factor Eating Questionnaire) disinhibition ($P < 0.05$, 30 days) and total scores ($P < 0.02$, 30 days), and participant ratings of the DHQ (Dykens Hyperphagia Questionnaire) severity ($P < 0.06$, 5 days) and total scores ($P < 0.05$, 15 days).	No SAE	Bravo <i>et al.</i> (98)	
Cannabidiol	Oral solution	1 (phase II)	1 (phase II)	Terminated because of bankruptcy (phase II)		NCT02844933	
Rimonabant Beloranib (methionine aminopeptidase 2 inhibitor)	Oral Biweekly s.c.	$n = 107$ PWS 12–65 years	1 (phase II) RCT study (1:1:1) to biweekly placebo, 1.8 mg beloranib or 2.4 mg beloranib injection for 26 weeks.	Drug withdrawn Compared with placebo, weight change was greater with 1.8 mg (mean difference -8.2% , 95% CI -10.8 to -5.6 ; $P < 0.0001$) and 2.4 mg beloranib (-9.5% , 95% CI -12.1 to -6.8 ; $P < 0.0001$)	4 venous thrombotic events in the beloranib group (2 fatal events of pulmonary embolism). 1 mental status change, 1 aggression in the beloranib group. Precocious halting of the study.	NCT00603109 Mc Candless <i>et al.</i> (83)	
Bardet-Biedl	Daily s.c.	2 ongoing (phases II and III)	2 ongoing (phases II and III)			NCT03746522, NCT03013543	
Alström	Daily s.c.	2 ongoing (phases II and III)	2 ongoing (phases II and III)			NCT03746522, NCT03013543	
Smith Magenis	Daily s.c.	1 ongoing (phases II and III)	1 ongoing (phases II and III)			NCT03013543	
16p11.2 deletion (including SH2B1 gene)	Daily s.c.	1 ongoing (phases II and III)	1 ongoing (phases II and III)			NCT03013543	

(Continued)

Table 1 Continued.

Type of genetic obesity	Pharmaceutical molecule	Mode of administration	Number of cases	Methodology/trial (number, phase, status)	Results	Adverse events	References
Pseudohypoparathyroidism	Rimonabant	Oral	n = 1	Case report	BMI 40.5 to 33.5 (–16 kg in 6 months). Treatment withdrawn in October 2008.	No SAE	Al Salameh <i>et al.</i> (84)
Monogenic Leptin	Theophylline	Oral		1 not yet recruiting (phase II)			NCT04240821
	Recombinant human leptin	Daily s.c.	n = 1 child (1999) and n = 3 children (2002)	Open-label study, non-randomized.	Loss between 2 and 19 kg of fat mass during 6–48 months of treatment, with reduction in energy intake (45–84%) at 2 months.	Antibodies anti-leptin	Farooqi <i>et al.</i> (99, 100)
	RM493/ setmelanotide	Daily s.c.	3 ongoing, including long term treatment (phases II and III)	3 ongoing, including long term treatment (phases II and III)			NCT03287960, NCT03651765, NCT03013543 Clément <i>et al.</i> (93)
Leptin receptor			n = 3, 14–23 years	Open-label study, non-randomized. Setmelanotide treatment in 3 patients carrying homozygous pathogenic variant in leptin receptor	Loss between 10–25 kg in 13–61 weeks of treatment with a decrease in hunger score	Darkening of skin and a change in hair color	
				3 ongoing, including long term treatment (phases II and III)			NCT03651765, NCT03013543, NCT02896192 Kuhnen <i>et al.</i> (92)
	Propiomelanocortin	Daily s.c.	n = 2 adults 21–26 years	Open-label study, non-randomized. Setmelanotide treatment in 2 patients carrying homozygous/compound heterozygous pathogenic variant in POMC	Patient 1 : loss of 51 kg at 42 weeks, Patient 2 : loss of 20.5 kg at 12 weeks	Darkening of skin and a change in hair color	
PCSK1	Thyroid hormone and ACTH4–10	ACTH: intranasal. Thyroid hormone: oral	n = 2 children	Open-label study, non-randomized. ACTH/thyroid hormone treatment of 2 patients carrying homozygous/compound heterozygous pathogenic variants in POMC	No weight loss with ACTH4–10 after 3 months treatment and with levothyroxin after 1-year treatment	Not reported	Krude <i>et al.</i> (24)
				2 ongoing (phases II and III)			
	RM493/ setmelanotide	Daily s.c.					NCT03651765, NCT02896192

Review		C Poitou and others		Treatments in genetic obesity	183:5	R161
MC4R	RM493/ setmelanotide	Continuous s.c. infusion	<i>n</i> = 8 adults, 22–57 years	Double blind RCT (phase 1b). Patients carrying heterozygous variants in <i>MC4R</i> and healthy obese individuals	Significant weight loss in <i>MC4R</i> variant carriers at Day 29 (–3.48 kg (–4.99, –1.96)), but no significant difference from placebo.	Collet <i>et al.</i> (94)
	Sibutramine	Oral	<i>n</i> = 1 boy, 14 years	Case report. Patient carrying a <i>MC4R</i> homozygous pathogenic variant (complete LOF).	Sibutramine treatment resulted in maintenance of weight and decrease in the hunger score, after 1 year treatment	Hainerová <i>et al.</i> (85)
	Liraglutide	Subcutaneous	<i>n</i> = 42 adults	Prospective case–control study not randomized. 14 obese adults with pathogenic <i>MC4R</i> variants and 28 matched control without <i>MC4R</i> variant	Liraglutide induced an equal, clinically significant weight loss of 6% in both groups (at 16 weeks)	Iepsen <i>et al.</i> (86)

This table summarizes ongoing and completed (with or without published results) pharmaceutical interventions in syndromic and monogenic non syndromic obesity, targeting weight loss or food behavior. Search was performed using PubMed research (keywords: syndrome name AND therapy OR treatment OR clinical trial OR therapeutics) and using ClinicalTrials.gov website. BMI, body mass index; LOF, loss of function; MC4R, melanocortin 4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PWS, Prader–Willi syndrome; RCT, randomized controlled trial; SAE, serious adverse event; CNS, central nervous system; LOF, loss of function.

given serious adverse effects (thrombotic events) (83). Rimonabant, a CB1 cannabinoid antagonist receptor, has been tried in PWS (NCT00603109) and in a patient with pseudohypoparathyroidism (84) with interesting results on weight but this drug was withdrawn in 2008 because of psychiatric side-effects.

Sibutramine was tested in a patient carrying a homozygous pathogenic variant of *MC4R*, without convincing results on weight loss (85). A treatment combining thyroid hormones with intra-nasal ACTH in two patients carrying pathogenic variants of *POMC* had no effect on weight loss (24). More recently, GLP-1 analogs, including liraglutide, have been tested in patients with *MC4R* variants. Weight loss of *MC4R* variant carriers on 3 mg liraglutide/day for 16 weeks was equivalent to that of non-carriers (approximately 6% weight loss), suggesting that the molecule can also be pro-satiatogenic in *MC4R*-linked obesity (86). However, given the importance of leptin/melanocortin pathway alterations in monogenic and syndromic obesity, specifically targeting this pathway should be valuable in treating these severe clinical conditions. Until now, only the rare patients with congenital leptin deficiency were eligible for daily injectable s.c. leptin treatment, resulting in weight loss, mainly linked to a reduction in fat mass, with a significant and rapid effect on the reduction in food intake (87). More recently, the picture has changed, with the development of new pharmacological agonists that act on the MC4R. Of note, new MC4R pharmacological agonists were shown to restore normal activity of some mutated forms of the MC4R in vitro (88). However, there were concerns about the increased risk of elevated blood pressure and heart rate with MC4R stimulation (89). The first development of an MC4R agonist (LY2112688) led to disenchantment because of major adverse effects on heart rate and blood pressure. However, the use of another highly selective agonist of the MC4R (RM-493 or setmelanotide) for 8 weeks in non-human primates led to decreased food intake, increased total energy expenditure, weight loss, and improved insulin sensitivity, with no effect on blood pressure or heart rate (90). Similarly, treatment of humans with RM-493 increases energy expenditure at rest, without cardiovascular side effects, and stimulates fat oxidation (91).

These promising results have paved the way to launching clinical trials with this molecule in patients with genetic alterations in the melanocortin pathway upstream of MC4R (Table 1). The use of this MC4R agonist indeed now makes it possible to replace the lack or inefficiency of the endogenous MC4R ligand (αMSH), in particular in the case of homozygous variants of *POMC* (31) or *LEPR*. In

2016, together with P. Kuhnén (Charité Berlin Hospital, Germany), we showed that the treatment of two patients carrying a homozygous variant of *POMC* with setmelanotide was associated with weight loss (−51.0 and −20.5 kg after 42 and 12 weeks of treatment, respectively, for the two patients) and a rapid and sustained improvement in hyperphagia scores (92). Setmelanotide has also shown its effectiveness in patients with a homozygous pathogenic variant of *LEPR* in terms of weight loss and reduction of overeating over follow-up periods of 45–61 weeks (93). Importantly, no elevation in blood pressure or other serious adverse events have been noted in these patients. Side effects consist mostly of increased pigmentation and irritation at the site of setmelanotide injection. Questions remain concerning the long-term efficiency of setmelanotide and whether other patients, such as those with heterozygous variants in *MC4R*, could benefit from this treatment. In cell models expressing various heterozygous pathogenic variants of *MC4R*, setmelanotide was more efficient than the endogenous ligand, αMSH, in restoring signaling in a subgroup of patients with these variants. Moreover, it appeared that treatment with setmelanotide can induce weight loss in mouse models and in humans, with a varying response, depending on the type of *MC4R* variant involved (94). Currently, clinical trials with setmelanotide are underway in patients with homozygous, heterozygous, or compound heterozygous variants for the *POMC*, *LEPR*, and *PCSK1* genes, as well as in patients with certain heterozygous *MC4R* variants. This molecule is also being tested for other syndromic obesities, such as BBS, Alström syndrome, Smith-Magenis syndrome, and 16p11.2 deletion, because of the links between these syndromes and the impaired function of POMC neurons (Table 1). Potential medium- and long-term side effects will be monitored. Particular attention should probably be given to the chronic stimulation of melanocytes, insofar as setmelanotide also activates the MC1R receptor located on the skin, resulting in generalized hyperpigmentation of these patients.

New developments targeting antibody-type melanocortin pathway activating receptors or restoration of their functionality, in particular *MC4R*, are other potential innovative treatments that could benefit patients with rare genetic forms of obesity in the future.

Conclusion

The early diagnosis and multidisciplinary management of rare genetic obesity should lead to a better prognosis

for these patients in adulthood. However, the transition between pediatric care and adult medicine remains a critical moment, often associated with disruptions of both the medical and social aspects of their care (life plan, integration into medico-social structures, comprehensive and coordinated care). An essential effort for the future of adolescents suffering from genetic obesity must focus on this critical period, when behavioral problems and obesity worsen. New treatments now show promise, particularly for PWS and abnormalities of the leptin/melanocortin pathway, and could change the clinical care and prognosis of patients with genetic obesity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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