

Monogenic and Syndromic Obesity: Therapeutic Implications

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About the Author



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Introduction

Obesity is a complex, progressive and relapsing neuroendocrine condition, characterized by disordered communication between the gastrointestinal tract, adipocytes and the hypothalamus.¹ It is a heterogeneous condition with unique etiologies, broadly classified as: polygenic obesity, monogenic obesity, syndromic obesity and secondary obesity.² The most common form of obesity is polygenic, a highly heritable condition that involves the clustering of genes that increase the risk for obesity. This inherited genetic risk is exploited by socio-biologic exposures.¹ Monogenic and syndromic obesity result from rare genetic mutations and are characterized by early onset severe obesity and hyperphagia.³ Secondary obesity may occur as a result of medication exposures, hypothalamic damage or primary endocrine disorders.⁴ Accurate classification of obesity is critical to inform surveillance and management strategies, decrease health risk and improve quality of life through newly available targeted therapies.⁴

Recognizing Monogenic and Syndromic Obesity

Monogenic and syndromic forms of obesity are caused by mutations in genes involved in the neuroendocrine control of body weight. They result in early onset and severe obesity (BMI Class II, III) with rapid weight gain typically within the first 2 years of life and Class II, III obesity by age 5. They have associated hyperphagia and impaired satiety. They may have neurodevelopmental differences, unique physical features and/or associated endocrinopathies. Although syndromic obesity is more often associated with developmental delay, dysmorphic features and multisystem involvement than monogenic obesity, this is not exclusive. While these conditions are rare, there is concern that they are under-recognized since consideration of genetic testing in those living with severe obesity remains low.⁵ Monogenic and syndromic forms of obesity are typically resistant to weight management strategies including low responsiveness to traditional anti-obesity medications and metabolic bariatric surgery. While the onset of symptoms begins early in life, adults living with these rare forms of obesity may have

never been assessed or investigated, leading to missed therapeutic opportunities that could be life changing.⁶ Hyperphagia in these conditions is a result of genetic mutations that lead to heightened and unrelenting feelings of hunger. It takes a longer time and larger volumes of food to sense satiety and feelings of satiety are short lived. Thoughts of food are often intrusive and all-encompassing, leading to food seeking, food foraging, night time eating, and high distress if food is unavailable or restricted. High food pre-occupation can interfere with focus, concentration, task completion, education, and employment attainment. Hyperphagia can have a negative impact on quality of life for both the person living with the condition and their caregivers, and can interfere with peer and family relationships.⁷

The risk for weight-related health complications among people living with monogenic and syndromic obesity is high, given the early onset and severity of the obesity with which they live. This includes cardiometabolic health risk, biomechanical health complications and psychosocial challenges.⁸ Co-existing neurodevelopmental challenges can also present as barriers to accessing and engaging weight management support.⁹ The consequences of severe obesity are often the primary cause of shortened life expectancy in these forms of obesity.¹⁰

Disorders of leptin and melanocortin 4 Receptor (MC4R) signalling are responsible for many of these conditions. The availability of the MC4R agonist setmelanotide has allowed people living with a subset of these rare forms of obesity much-needed support in the management of their associated hyperphagia and body weight.

The Role of Leptin and MC4R Signalling in Body Weight Regulation

Leptin is secreted by adipocytes and acts as our main signal of nutritional status (**Table 1**).¹¹ Leptin signalling promotes satiety and energy expenditure. Leptin binds to the leptin receptor at the level of the ventromedial hypothalamus to stimulate production of proopiomelanocortin (POMC), which is subsequently cleaved by the enzyme PCSK1 to ACTH and alpha MSH. Alpha MSH binds to MC4R to transmit the signal of satiety or fullness and impact energy expenditure. Leptin signalling is enhanced by SH2B1, an adaptor signalling protein, which is also involved in peripheral insulin signalling. Rare genetic mutations within this pathway including genes encoding MC4R, POMC, PCSK1, leptin receptor, leptin, and SH2B1, as

well as those associated with Bardet Biedl Syndrome (BBS), Alstrom Syndrome, Albright osteodystrophy, and Prader Willi Syndrome have been identified. Disruption of signalling through this pathway leads to hyperphagia and early onset severe obesity.¹²

Disorders of leptin signalling can also lead to short stature, delayed puberty, hypothyroidism, emotional lability, behavioural difficulties, intellectual disabilities, and altered immune function.¹²

Clinical Characteristics of Monogenic and Syndromic Forms of Obesity

Syndromic obesity is associated with early onset obesity and other clinical manifestations that involve multiple systems, including neurodevelopment, physical features, congenital malformations, and other organ involvement. The most common obesity syndromes, including Prader Willi Syndrome, Bardet Biedl Syndrome, Alstrom Syndrome, and Albright osteodystrophy have co-occurring hypothalamic dysfunction.

Monogenic forms of obesity present with very early onset and rapid weight gain, most often within the first 2 years of life. Cognitive development is often normal, although not exclusively. Some monogenic forms of obesity are associated with endocrinopathies, most commonly hypogonadism, but may also include thyroid dysfunction, adrenal insufficiency, hyperinsulinemia, and tall or short stature. These individuals may have unique physical features (pale skin, red hair), higher risk for infection, transient neonatal malabsorptive diarrhea and/or cholestasis.

Assessment and Management

Clinical practice guidelines recommend assessment for possible monogenic or syndromic forms of obesity in children with severe obesity (BMI Class II, >120% of the 95th percentile OR >35 kg/m²) before age 5 years, with hyperphagia and/or a family history of severe obesity.⁴ Diagnostic gene panels or exome-based sequencing are recommended. If there are coexisting features of syndromic causes such as developmental delay, unique physical features, vision loss or renal impairment, genetic tests targeting the suspected syndromic form of obesity should be considered.

Management should include an interdisciplinary team with expertise in weight management, neurodevelopment and behaviour. Behavioural approaches to hyperphagia are very challenging and may include securing the home food environment

Condition/Gene	Hyperphagia	Clinical features	Endocrinopathies	Targeted therapy
Monogenic Obesity				
Leptin Deficiency	+++	Onset of obesity within the first few months of life; increased risk for infection	Hypogonadism Hypothyroidism Short stature	Metreleptin
Leptin Receptor Deficiency	+++	As above; less frequent recurrent infections	Hypogonadism	MC4R agonist: Setmelanotide
SH2B1 deficiency (mediates leptin signaling centrally and insulin signaling peripherally)	+++	Leptin and insulin resistance; language delays; behavioural difficulties	Insulin resistance Type 2 Diabetes Short stature	MC4R agonist: Setmelanotide
POMC deficiency	+++	Pale skin; red hair; cholestatic jaundice in infancy	ACTH deficiency	MC4R agonist: setmelanotide
PCSK1 deficiency	+++	Neonatal malabsorptive diarrhea	Adrenal insufficiency Postprandial hypoglycemia; hypogonadism Diabetes Insipidus Hypothyroidism	MC4R agonist: setmelanotide
MC4R deficiency * (most common monogenic form of obesity)	+++	n/a	Tall stature; accelerated linear growth; hyperinsulinemia; increased lean muscle and body fat mass	n/a
Obesity Syndromes				
Bardet Biedl Syndrome (ciliopathy; disordered leptin signalling)	++	Polydactyly Visual impairment Structural and/or functional renal abnormalities Intellectual disability	Hypogonadism Truncal obesity	MC4R agonist: setmelanotide
Alstrom Syndrome (Ciliopathy)	++	Progressive visual, hearing and renal impairment Cardiomyopathy	Insulin resistance Truncal obesity; early adrenarche; advanced bone age	n/a
Albright Hereditary Osteodystrophy (GNAS mutation; impaired MC4R signalling)	++	Round faces Short 4th and 5th metacarpal and metatarsal bones; subcutaneous ossifications	PTH; TSH; LH/FSH resistance Short stature	n/a
Prader Willi Syndrome (increased ghrelin; PCSK1 impairment)	++ (onset age 2 y)	Neonatal hypotonia; global developmental delay	Hypothalamic dysfunction; growth hormone deficiency; hypogonadism; high ghrelin; decreased resting energy expenditure	n/a

Table 1. Genetic and clinical characteristics for monogenic and syndromic forms of obesity; courtesy of Stasia Hadjiyannakis, MD.

(locks on the refrigerator and pantry) along with constant supervision and limited independence in food preparation, portioning, access, and consumption.²

Targeted pharmacotherapy is available for some conditions. Metreleptin, a synthetic analog of leptin, is approved for use in individuals with congenital leptin deficiency. It is administered subcutaneously and can reverse most of the features of this condition.^{13,14} Setmelanotide (MC4R agonist) is effective for conditions where MC4R activation is impaired (POMC, PCSK1, SH2B, leptin receptor deficiency, and BBS). In Phase 3 trials 8 of 10 (80%) of those with POMC deficiency, 5 of 11 (45%) of those with LEPR deficiency and 32.2% of those with BBS lost 10% or more of their body weight from baseline.¹⁵⁻¹⁷ Setmelanotide binds to and activates melanocortin receptors and thus helps to decrease symptoms of hyperphagia and increase energy expenditure. It is administered by subcutaneous injection. The most common side effects are hypersensitivity at the injection site and hyperpigmentation of the skin.

The effectiveness of GLP-1 agonists in these conditions is mixed and evidence is limited to case series, reports and open label studies. In individuals with MC4R variants, liraglutide was found to result in 6% weight loss after 16 weeks.¹⁸ In children with Prader Willi Syndrome, there were reported decreases in hyperphagia symptoms but no clinically significant decreases in body weight or BMI.^{19,20} Larger randomized control trials are needed to determine whether or not GLP-1 agonists are effective and safe in this patient population. The role of metabolic bariatric surgery is unclear and is most often associated with weight regain over the long term in individuals with monogenic and syndromic forms of obesity (case series).²¹⁻²⁴

Conclusion

Early recognition, diagnosis and timely intervention for individuals living with monogenic and syndromic forms of obesity can be life changing. It can lead to targeted treatment and surveillance for obesity- and non-obesity-related sequelae and give context to the challenges faced when applying more traditional approaches to weight management. Targeted therapies can also provide some relief from the unrelenting and distressing hyperphagia many of these individuals face. Much of what we learn in the discovery and management of monogenic and syndromic obesity can also inform the understanding and support provided for individuals living with polygenic obesity.

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