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# Bardet-Biedl syndrome: A clinical overview focusing on diagnosis, outcomes and best-practice management

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## Abstract

Bardet-Biedl syndrome (BBS) is a genetic disorder characterized by early-onset obesity, polydactyly, genital and kidney anomalies, developmental delay and vision loss due to rod-cone dystrophy. BBS is an autosomal recessive disorder with >20 implicated genes. The genotype–phenotype relationship in BBS is not clear, and there may be additional modifying factors. The underlying mechanism is dysfunction of primary cilia. In BBS, receptor trafficking in and out of the cilia is compromised, affecting multiple organ systems. Along with early-onset obesity, hyperphagia is a prominent symptom and contributes significantly to clinical morbidity and caregiver burden. While there is no cure for BBS, setmelanotide is a new pharmacotherapy approved for treatment of obesity in BBS. The differential diagnosis for BBS includes other ciliopathies, such as Alstrom syndrome, and other genetic obesity syndromes, such as Prader-Willi syndrome. Careful clinical history and genetic testing can help determine the diagnosis and a multidisciplinary team is necessary to guide clinical management.

**KEYWORDS**
appetite control, body composition, clinical physiology, energy regulation

## 1 | CASE VIGNETTE

A 3-year-old male was referred for evaluation of developmental delays and early-onset obesity. He was born at full term with birth weight 4.2 kg and length 53.5 cm, appropriate for gestational age. Bilateral hydronephrosis was noted prenatally and confirmed on postnatal ultrasonography. There was no vesicoureteral reflux. Additional anomalies were noted at birth including a sacral dimple and right postaxial polydactyly.

In the first year of life, the infant had several viral respiratory illnesses but did not require hospitalization. Current medications included albuterol as needed, but no oral or inhaled steroid use in the past year. Developmental history was significant for delays in gross motor skills and speech. He sat at 8 months, walked at 18 months, at 3 years old had 100 words and was receiving physical and speech therapy.

Parental history was significant for adult-onset obesity in the mother and father. The child's older sibling was of normal weight.

At 3 years old, the weight was 34 kg (>99th percentile, z-score 5.9) and height 102 cm (95th percentile) and body mass index (BMI) 32.5 kg/m$^2$ (>99th percentile, z-score 7.87). Examination showed no dysmorphic features. Stretched penis length was 2 cm with bilateral descended testes.

Due to the presence of early-onset obesity, developmental delays, kidney anomalies and postaxial polydactyly, Bardet-Biedl syndrome (BBS) was suspected. A BBS genetic panel was sent and was positive for two different heterozygous pathogenic nonsense variants in *BBS9*. Additional evaluation included an echocardiogram (normal) and ophthalmology dilated examination (normal). Due to the borderline micropenis on examination and a high risk of hypogonadism, the boy was seen by endocrinology and treated with a 3-month course of testosterone 50 mg intramuscularly. He required glasses for myopia at

5 years old. Due to rod cone dystrophy, his vision began to decrease around 8 years old, and he moved to a school for the blind at 10 years old. His renal function was followed with yearly creatinine levels and remained normal.

The boy continued to struggle with obesity throughout childhood. Linear growth was normal, and he reached a final height of 174 cm at 14 years old. At 5 years old his BMI was >200% of the 95th percentile and remained in that range throughout childhood. His parents reported that he always wanted to eat and would become upset if he saw someone else eating. He would manipulate adults to obtain extra meals (e.g., eating lunch with both mum and dad, or at home and at school). At 10 years old the family added alarms on the refrigerator and pantry, but they felt helpless and unable to control his weight gain and appetite. The patient preferred video games and sedentary activities and did not meet recommended daily physical activity metrics.

### 1.1 | Diagnosis of BBS

Bardet-Biedl syndrome is an autosomal recessive disorder with over 20 implicated genes. There are no sex differences in prevalence or phenotype. While there are several communities with high prevalence of BBS (1:13500 in Kuwait, 1:17500 in Newfoundland), the overall prevalence is estimated at 1:160000 people.[1,2] Despite our growing understanding of the underlying genetics, BBS remains a clinical diagnosis. The diagnosis can be made if the patient has four of six major features: rod cone dystrophy, obesity, genital anomalies, renal anomalies, postaxial polydactyly and cognitive impairment. Alternate diagnostic criteria can be met with three major features and two minor features (Table 1). Genetic testing is recommended to help confirm the diagnosis, and 80% of patients will have a known genetic aetiology for BBS. The genotype–phenotype relationship in BBS is still being explored. In general, complete loss-of-function variants seem to lead to a more severe phenotype than partial loss-of-function variants.[3,4]

Prior to the more widespread use of genetic testing for patients with developmental delays and early-onset obesity, the average age of diagnosis for BBS was 9 years.[5] This correlates with the average age of onset for visual disturbances, which often led to the diagnosis.[5] In a more recent analysis of the Clinical Registry Investigating BBS (CRIBBS) database, the median age of diagnosis had improved to 5.8 years.[4] In our clinical practice, over the past decade patients were all diagnosed by the age of 6 years and prior to the onset of vision loss. The most common reason for suspicion of BBS was early-onset obesity. Other presenting concerns included micropenis, developmental delays and renal anomalies. Early diagnosis allows for anticipatory guidance and can be particularly helpful in slowing or preventing the onset of obesity. Whole-exome sequencing is now a first-line diagnostic test for patients with multiple congenital anomalies, rather than targeted sequencing. Genetic testing is recommended for children with onset of obesity prior to 5 years old, particularly if there are signs of syndromic obesity, hyperphagia, or a family history of severe obesity.[6] If insurance coverage is an issue, there is currently a free Genetic Obesity panel available through www.uncoveringrareobesity.com.

**TABLE 1** Major and minor clinical criteria for Bardet-Biedl syndrome.

| Major criteria | Incidence | Average age onset |
|---|---|---|
| Rod cone dystrophy | 90%–100% | 8 years |
| Obesity | 80% | 2–5 years |
| Postaxial polydactyly | 69% | Perinatal |
| Hypogonadism | 97% males | 13% undescended testes, remaining diagnosed in adolescence |
| Renal anomalies or renal dysfunction | 52% or 42% | Perinatal or childhood |
| Cognitive impairment | 50% | Infancy |
| Minor criteria | | |
| Speech delay | Diabetes | Developmental delay |
| Dental anomalies | Ataxia | Congenital heart disease |
| Brachydactyly | Syndactyly | Anosmia/hyposmia |
| Genitourinary anomalies | | |

*Note*: Diagnosis can be made if a patient has four major OR three major plus two minor criteria.[5]

## 2 | DIFFERENTIAL DIAGNOSIS

Bardet-Biedl syndrome has significant overlap with other ciliopathies, both in phenotype and genotype. Meckel syndrome can be thought of as the most severe end of the ciliopathy spectrum. It is an autosomal recessive disorder associated with multiple genes, including *BBS13/MSK1* and *BBS14/CEP290*. Truncating mutations in CEP290 can cause Meckel syndrome, while hypomorphic mutations are more likely to cause BBS.[7] Meckel syndrome is often fatal in utero due severe organ malformation. Characteristic features include occipital meningoencephalocele, renal dysplasia, lung hypoplasia, situs inversus and polydactyly.[8] At the mildest end of the spectrum, a single loss-of-function variant in CEP290 can cause adult-onset nephronophthisis. Nephronophthisis is a common cause of end-stage renal disease, characterized by cysts in the corticomedullary junction.[8] Joubert syndrome (cerebellar malformations), Leber congenital amaurosis (severe retinal dystrophy) and Senior-Loken syndrome (retinal degeneration and nephronophthisis) are also associated with *BBS14/CEP290* variants.[9,10] More than 100 distinct pathogenic variants have been identified in *CEP290*. The wide phenotypic spread is thought to be due to both severity of the variant, multiple allelism and second

site modifiers.[8,9] Unsurprisingly, the genotype–phenotype relationship in ciliopathies is not clear.[9]

Alstrom syndrome is another ciliopathy that clinically resembles BBS. It is an autosomal recessive disorder due to variants in *ALMS1*. *ALMS1* encodes a ciliary basal body protein and, over time, lack of *ALMS1* leads to loss of cilia, particularly in kidney proximal tubules.[11] This contrasts with BBS where cilia formation is minimally affected but function is abnormal. *ALMS1* is less prevalent, affecting fewer than 1:1000000 people.[12] Similarly to BBS, patients with Alstrom syndrome may have rod cone dystrophy, early-onset obesity, hypogonadism and renal dysfunction, but patients with Alstrom syndrome also have neurosensory hearing loss, short stature, dilated cardiomyopathy and a higher risk of type 2 diabetes. Patients with Alstrom syndrome do not have polydactyly or cognitive impairment (Table 2).

In patients without renal disease, the main early childhood features of BBS are developmental delays and early-onset obesity, as seen in the case vignette. A history of polydactyly can help guide the physician towards a diagnosis of BBS, but after infancy, few families offer this information if not specifically asked. Prader-Willi syndrome (PWS) is often considered in patients with a presentation of developmental delays and obesity, as this is the most common form of syndromic obesity with a prevalence of approximately 1 in 15 000.[13] PWS, however, has a very different clinical history (Table 2). Unlike BBS and most obesity syndromes, PWS has distinct nutritional phases, beginning with notable hypotonia and poor feeding. Most patients are diagnosed during the first year of life due to the neonatal hypotonia. The onset of obesity is not until later in childhood, with a decrease in metabolic rate beginning in the toddler years but the onset of hyperphagia typically does not develop until school age (median 8 years old).[14] PWS is also associated with a behavioural phenotype characterized by rigidity, anxiety, outbursts, and a higher risk of psychosis.[13] PWS is caused by lack of expression of genes encoded in the paternal copy of the 15q11-q13 region, most commonly due to paternal allele deletions or maternal uniparental disomy.[13] Growth hormone is indicated for the treatment of PWS beginning in infancy for treatment of short stature, improvement of body composition, cognition, and adaptive functioning.[15]

Non-syndromic obesity is caused by genetic variants that increase risk of early-onset obesity without significant congenital anomalies or developmental delays. Most of these variants are autosomal recessive, with the notable exception of the melanocortin-4 receptor gene (*MC4R*) which has co-dominant inheritance. In *MC4R* deficiency, heterozygous variants are enough to cause non-syndromic obesity but biallelic variants cause a more severe phenotype.[16] *MC4R* deficiency is the most common genetic cause of obesity with a prevalence of 1 in 1000 people and accounting for up to 6% of severe, early-onset obesity.[17,18] Patients with *MC4R* deficiency have normal cognition and no associated congenital anomalies, which makes diagnosis challenging. Table 2 provides an overview of the hallmark characteristics of representative syndromic and nonsyndromic forms of genetic obesity.

## 3 | BEST PRACTICE GUIDELINES

Bardet-Biedl syndrome affects multiple organ systems (Figure 1) and patients benefit from a multidisciplinary team approach. This team is most commonly led by nephrology, genetics or endocrinology as these teams are typically involved in the initial management and diagnosis of BBS. Paediatric patients often have easier access to such teams as paediatric subspecialists are typically located at large, tertiary medical centres. In adult medicine, concerted efforts may be needed to coordinate care across medical practices. If a multidisciplinary clinic is not available, a primary care physician or subspecialty physician needs to assume a coordinating role. Most patients will require care and assessment from developmental paediatrics, ophthalmology, endocrinology and nephrology. Weight management services should be utilized if available.

### 3.1 | Vision loss

Along with obesity, vision loss is the most visible and life-altering feature of BBS. Vision loss is attributable to rod cone dystrophy. Progressive rod cone dystrophies are rare and highly associated with genetic syndromes and should prompt referral to a geneticist for further evaluation. Electroretinography can be used to see early changes, before onset of symptoms, in patients with suspected BBS.[19] Electroretinography has been used in very young children but is often deferred to 4 years or older due to patient cooperation and lack of detectable change. The first vision symptom reported is typically night blindness due to loss of rod cells in the retina.[5] Additional symptoms can include decreased visual acuity photophobia, and loss of colour perception. The vision loss rapidly progresses over an average of 7 years, with complete vision loss reported at around 15 years old (range 8–43 years).[5] Unfortunately, early diagnosis of BBS does not change ophthalmological management as there are no available treatments for progressive rod cone dystrophy. The eye is a promising target for gene therapy due to accessibility of the retinal tissue, immune-privileged status and tight blood-ocular barrier which protect from off target effects.[20] Subretinal gene therapy has been shown to slow vision loss in the BBS mouse model and future research in human subjects is expected.[21,22]

### 3.2 | Cognitive impairment

Most children with BBS have cognitive impairment and developmental delays. Genetic testing is now recommended for all children with global developmental delay.[23] Whole-exome sequencing is increasingly preferred over chromosomal microarray and can detect syndromes such as Bardet-Biedl. Early intervention services, such as physical, occupational and speech therapy, should be mobilized immediately. The cognitive impairment in BBS is mild to moderate.[24] Mild hypotonia, ataxia and decreased coordination may contribute to gross motor skill delays.[5] Due to the concomitant visual impairment, it is

**TABLE 2** Overview of selected syndromic and non-syndromic causes of early-onset obesity.

| | Inheritance | Genetic cause | Early-onset obesity | Hyperphagia | Develop-mental delays | Hypo-gonadism | Physical anomalies | Other |
|---|---|---|---|---|---|---|---|---|
| Bardet-Biedl syndrome | AR | 20+ causative genes | X | X | X | X | • Renal<br>• Genital<br>• Polydactyly | • Rod cone dystrophy |
| Alstrom syndrome | AR | *ALMS1* | X | X | | | • Renal<br>• Genital<br>• Cardiac<br>• Short Stature | • Rod cone dystrophy |
| Prader-Willi syndrome | AD, Paternal inheritance | Deletion or uniparental disomy 15q11.2-q13 | FTT, then obesity | Onset ~8 years | X | X | • Short Stature | • Hypotonia<br>• Hormone deficiencies<br>• Psychiatric |
| Pseudo-hypopara-thyroidism type 1A | AD, Maternal inheritance | *GNAS* | X | Variable | X | X | • Brachydactyly<br>• Short stature | • Resistance to multiple hormones<br>• Subcut-aneos ossifications |
| Leptin deficiency | AR | *LEP* | X | X | | X | | • Immuno-deficiency |
| Leptin receptor deficiency | AR | *LEPR* | X | X | | X | | • Immuno-deficiency |
| Proopio-melano-cortin deficiency | AR | *POMC* | X | X | | | | • Congenital adrenal insufficiency<br>• Decreased skin/hair pigment |
| Pro-hormone convertase 1 deficiency | AR | *PCSK1* | FTT, then obesity | X | | X | • Short stature | • Diarrhoea<br>• Polyuria<br>• Polydipsia<br>• Hormone deficiencies |
| Melano-cortin 4 receptor deficiency | Co-dominant | *MC4R* | X | X | | | | |

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; FTT, failure to thrive; MC4R, melanocortin-4 receptor.

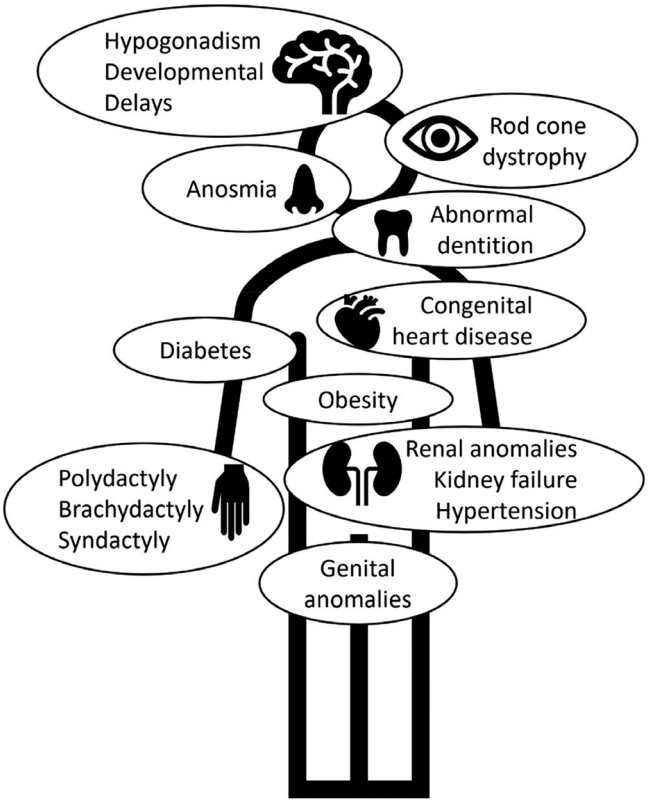


**FIGURE 1** A visual representation of the multiple organ systems affected in Bardet-Biedl syndrome.

difficult to assess what educational resources are due to cognitive impairment versus vision loss. One study reported that half of children attended a special school with 32% receiving additional classroom help prior to onset of vision loss.[5] Assessment by a developmental paediatrician can help determine what educational resources are appropriate.

### 3.3 | Renal Anomalies

Renal anomalies, along with polydactyly, can sometimes be identified on prenatal ultrasonography. The renal anomalies can be impressive with large, hyperechogenic kidneys.[25] In rare cases, this can lead to in utero demise from Potter's sequence oligohydramnios. The differential diagnosis of hyperechogenic kidneys includes polycystic kidney disease, and prenatal genetic testing can be offered through amniocentesis. Structural renal and genital anomalies are found in approximately 50% of patients, and renal/pelvic ultrasonography is recommended at the time of diagnosis.[26] Kidney function laboratories should be followed yearly as chronic renal failure can be seen in childhood and is the major cause of early mortality in BBS.[5,27] In a UK cohort, 31% of children and 42% of adults had some degree of chronic kidney disease.[26] Data from the CRIBBS registry showed that 10% of children had end-stage renal disease at a median age of 8.4 years with cystic renal dysplasia as the most implicated renal anomaly.[27] Overall, 18 of 206 patients in the CRIBBS registry underwent renal transplantation. Patient survival was good, with 94.4% alive at 1 year post-transplant and 79.3% at 25 years post-transplant.

### 3.4 | Hypertension

Even in patients without renal dysfunction, hypertension is more prevalent in BBS than in the general population.[28] Patients with BBS are eight times more likely to develop hypertension than their unaffected family members.[29] There are conflicting data on whether the underlying BBS gene affects the prevalence of hypertension. The mouse model of central nervous system *Bbs1* deficiency developed hypertension associated with increased sympathetic activity.[30] The change in sympathetic tone is thought to be mediated by leptin receptor neurons. Blood pressure should be measured at each visit.

### 3.5 | Hypogonadism

Primary cilia are important for genitourinary development, hypothalamic function, sperm flagellum and the first zygotic mitosis. Genitourinary anomalies are a criterion for BBS diagnosis and are seen in both males and females.[5] Approximately 16% of patients with BBS have one or more lower urinary tract anomaly.[31] A wide variety of anomalies have been reported, including vaginal atresia, urogenital sinus, uterine hypoplasia, uterine duplex and septate vagina in females.[32] In males, reported anomalies include cysts of the epididymis and prostate, unilateral agenesis of seminal vesicles, chordee and hypospadias.[24,31]

Hypogonadism in BBS was traditionally thought to effect only males. Cryptorchidism is common, along with micropenis.[24] Male hypogonadism is mild and can be due to hypogonadotropism or abnormal testicular function.[24,33–36] In one cohort of 11 adult males, spontaneous puberty and normal testicle volume was reported.[24] Laboratory values were significant for normal follicle-stimulating hormone and luteinizing hormone, while testosterone levels were low or low normal. Another study reported that >30% of males had hypogonadism.[37] Males are often infertile, but successful pregnancies have been reported.[1,5] Sperm analysis showed decreased volume and motility, along with severe morphological alterations.[24] Careful evaluation of female patients reveals that they also are at risk for hypogonadotropic hypogonadism and primary ovarian failure.[36] Patients and families should be counselled on the risk of infertility and hypogonadism and yearly monitoring is recommended into adulthood, even in patients who demonstrate spontaneous puberty.

## 4 | BBS AND OBESITY

Bardet-Biedl syndrome is an obesity syndrome with a variable phenotype. The underlying mechanism is dysfunction of primary cilia. While cilia formation is not severely impaired in BBS, the cilia do not

function normally, primarily due to abnormal function of the BBSome. The BBSome is a highly conserved, octameric protein complex that moves proteins, including G-protein coupled receptors, in and out of the cilia.[38,39]

The leptin-melanocortin receptor pathway has been implicated in the pathophysiology of obesity of BBS. Leptin is an adipocyte-derived hormone that provides information to the hypothalamus on energy stores.[40] Leptin receptors are found on neurons in the arcuate nucleus of the hypothalamus, an important region for control of energy homeostasis through the MC4R pathway. In the arcuate nucleus, proopiomelanocortin neurons (anorexigenic) are activated by leptin and neuropeptide Y (NPY)/agouti-related protein (AgRP) neurons (orexiogenic) are inhibited by leptin.[40] Several knockout mouse models (*Bbs2*$^{-/-}$, *Bbs4*$^{-/-}$, *Bbs6*$^{-/-}$) have been shown to be resistant to the anorexigenic effects of leptin, even when food is restricted to prevent obesity-associated leptin resistance.[41] This decrease in leptin receptor signalling was associated with decreased *Pomc* expression but not *Agrp or Npy*. One BBSome protein, BBS1, physically interacts with the leptin receptor and loss of that protein prevents normal receptor trafficking in cilia.[41] Importantly, leptin receptor function is not completely lost due to abnormal trafficking, only decreased.[41,42] Selective deletion of *Bbs1* or *Lztfl1* (BBS17) in the nervous system, but not adipocytes, leads to obesity with increased food intake.[43,44] As expected with hypothalamic resistance to leptin, patients with BBS do have hyperleptinaemia.[37,45] In contrast, patients with BBS have normal levels of other neuroendocrine factors including ghrelin, adiponectin and obestatin.[45]

Other possible mechanisms of obesity in BBS include abnormal trafficking of NPY receptors and insulin resistance. In a *Bbs1* deletion mouse model, NPY2 receptors fail to localize to cilia in the hypothalamus and response to the endogenous ligand (PYY3-36) is reduced.[46] BBS mutations also impair insulin signalling.[47,48] Without normal BBS1 protein function, insulin receptor localization to the cell membrane is reduced.[48] Insulin resistance is common in patients with BBS, out of proportion with their degree of obesity. While both *BBS1* and *BBS10* variants affect insulin receptors in the mouse model, in humans *BBS10* variants were associated with greater insulin resistance than *BBS1* variants.[37]

Obesity is a common feature of BBS, affecting more than 70% of patients.[1,4] Pomeroy et al. utilized the CRIBBS database to determine longitudinal growth patterns utilizing data from more than 500 participants.[4] Infants with BBS typically had a normal birth weight. Obesity increased in prevalence as childhood progressed, peaking in the 6–11-year-old age group at >80% of children and persisting into adulthood. As expected in children with early-onset obesity, height z-scores were above average during childhood, but final adult height was not increased. There is not a clear genotype–phenotype relationship for obesity in BBS, but patients with more severe loss-of-function variants (nonsense, frameshift, etc.) did have a higher BMI than patients with missense variants.[3,4] Variants in *BBS1* may cause later onset of obesity than variants in *BBS10*, but the difference disappears by adolescence.[4,37]

It is not clear how much obesity in BBS is driven by increase in food intake as opposed to decreases in energy expenditure. At least one mouse model of BBS had both reduction in energy expenditure and increase in food intake.[43] Reduction in resting energy expenditure has not been shown in humans with BBS.[49,50] One study found a lower level of physical activity in patients with BBS compared with controls.[50] The significant vision loss associated with BBS may play a role in limited physical activity.

## 4.1 | Management of obesity

The hyperphagia associated with BBS has a significant impact on quality of life for patients and caregivers. A large, multi-country study of 242 caregivers found that hyperphagia had a negative impact on caregiver sleep, mood, work, leisure, and relationships.[51] Over half of caregivers reported that caring for a child with BBS resulted in a reduction in work hours (20%), temporary leave from work (19%) or permanent retirement (15%).[51] Stigma surrounding childhood obesity contributes to additional caregiver stress, particularly in the healthcare domain where caregivers report feeling devalued and inadequate.[52] Caregivers desire support and treatment options beyond referral to a nutritionist.[51,52]

It is important to assess hyperphagic symptoms at all clinic visits. Hyperphagia typically presents in early childhood, before the age of 5 years.[53] Caregivers and patients are unlikely to use the word 'hyperphagia', even when discussing symptoms of uncontrollable hunger.[54] There are no well accepted clinical assessments of hyperphagia, but research methods include Likert scales for hunger/satiety and a hyperphagia questionnaire developed for assessment in PWS.[55] Caregivers of patients with PWS report that BBS causes similar hyperphagic symptoms to those of PWS, as assessed by the hyperphagia questionnaire.[53] In place of a formal questionnaire, clinicians can assess hyperphagia in a qualitative manner using questions such as:

> 'How often do you feel hungry?'
> 'What behaviours do you see when your child is hungry?'
> 'Does hunger or food interfere with daily activities? For example, do you avoid certain social situations like eating out or attending birthday parties?'

Environmental modifications are commonly used to assist with reduction in food intake. This includes food security strategies such as locks, alarms, and motion detectors. Caregivers report using an average of eight strategies to manage hyperphagia.[51] Strategies typically include environmental modifications, keeping food out of sight, scheduled and pre-portioned meals, direct supervision, and avoiding social activities such as parties or restaurants. Planning ahead is critical when travelling or deviating from the usual family routine. Families should be aware of food on television and aromas of food as these can trigger distress. While we usually recommend a modified Atkins diet in an attempt to minimize hyperinsulinism and hunger in other obesity syndromes, high-protein diets should be avoided in BBS due to concomitant renal disease.[56]

Routine assessment of hyperphagic symptoms is particularly important before and after trials of anti-obesity medications, such as

setmelanotide. Setmelanotide was studied in 32 patients with BBS.[57] The cohort had a mean age of 20.2 years old and BMI of 41.6 kg/m$^2$. Adults with BBS ($n = 15$) had a mean BMI reduction of 4.2 kg/m$^2$, which was 9.1% from baseline. Most patients (60%) achieved ≥5% reduction in body weight. In children, 71.4% had a 0.3-point reduction in BMI z-score, which is considered clinically meaningful. The most common adverse events were skin hyperpigmentation, injection site reactions and nausea/vomiting.

Based on results from the above Phase 3 clinical trial, setmelanotide was approved by the US Food and Drug Administration in 2022 for treatment of obesity in patients aged 6 years and older with BBS. Setmelanotide therapy is considered effective if patients lose at least 5% of baseline body weight, or 5% of baseline BMI in the case of paediatric patients, after 1 year of therapy. Setmelanotide is not approved for treatment of hyperphagia, but a study of eight patients and 11 caregivers showed that most patients experienced improvement in food-seeking behaviours, concentration, and social dynamics.[54] While patients and caregivers found decrease in body weight to be the most important effect of setmelanotide treatments, a decrease in hyperphagia was the second most important effect. These patients were interviewed after approximately 2 years of treatment and onset of effect was reported within the first 2 months of treatment. All patients and caregivers reported improved ability to focus, attributed to reduction in hyperphagia. Other improvements included improvement in energy levels, enabling age-appropriate participation in sports and activities.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective anti-obesity medications in the general population. They have not been extensively studied in BBS, but there are concerns that GLP-1RAs may not be as effective in disorders affecting hypothalamic function. Weight loss with GLP-1RAs is limited in other obesity disorders such as hypothalamic obesity and PWS[58,59] An open-label clinical trial in Alstrom syndrome found 5.4% mean weight loss with GLP-1RA treatment, either semaglutide (21 patients) or exenatide (nine patients).[60] In contrast, adults with general obesity had a mean weight loss of 14.9% with semaglutide.[61] There is one case report of successful weight loss with GLP-1RA therapy in a 28-year-old female with BBS and type 2 diabetes.[62] In our clinical experience, GLP-1RAs are not effective at appetite suppression in this population.

It is not clear if bariatric surgery is effective in BBS as data are limited. In the mouse model, at least partial MC4R function is required for response to Roux-en-Y gastric bypass.[63] Since the BBS deficits occur upstream of the MC4R neurons, it is possible that patients with BBS will be less responsive to bariatric surgery. One study looked at response to bariatric surgery in patients with and without a deleterious variant in genes linked to obesity.[64] Patients with the deleterious variants had less weight loss than controls 12 months after bariatric surgery and the many of the identified variants were in BBS-related genes. There are several case reports that show some degree of response to bariatric surgery. A 16-year-old male had successful body weight loss of 33% at 3 years after Roux-en-Y gastric bypass.[65] One case report describes 32% body weight loss 3 years after sleeve gastrectomy in an adult woman with BBS and type 2 diabetes.[49] The patient also reported improvement in symptoms of hyperphagia. Lastly, a 35-year-old male with BBS and type 2 diabetes had 9% weight loss 2 years after gastric banding.[66] Neither patient had resolution of their diabetes post-bariatric surgery.[49,66]

### 4.2 | Obesity comorbidities

Visceral adiposity is greater in patients with BBS compared with controls (26.9% vs. 19.7%; $p < 0.001$) which increases risk of metabolic syndrome.[37] Insulin and leptin resistance is prominent in patients with BBS.[28,37] In one cohort, nine of 20 adult patients with BBS also had a diagnosis of type 2 diabetes.[36] In a study of 47 patients with an average age of 14.8 years, 10% of patients had impaired glucose tolerance.[37] It is reasonable to screen for type 2 diabetes beginning at the onset of puberty or at 10 years old, as per the American Diabetes Association guidelines for patients with overweight or obesity and additional risk factors for diabetes.[67] Hypertriglyceridaemia is also common.[37]

## 5 | CONCLUSIONS

Bardet-Biedl syndrome is a complex syndrome with incompletely understood genetic causes. Patients with BBS benefit from early diagnosis, which is facilitated by the early use of genetic testing in infants with congenital anomalies and/or developmental delays. Early diagnosis may help prevent the development of obesity through environmental controls and the use of new medications, such as setmelanotide. Early diagnosis also allows patients and caregivers to prepare for expected vision loss in later childhood. Due to the multiple comorbidities and organ systems involved with BBS, multiple specialties are often required for appropriate medical management, such as genetics, nephrology, endocrinology, and ophthalmology. Continued research is needed to better understand the underlying mechanisms of BBS as well as the genotype–phenotype relationship.

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Dr. Shoemaker has served on advisory boards for Rhythm Pharmaceuticals.

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