DIAGNOSING BARDET-BIEDL SYNDROME (BBS): TAKE A CLOSER LOOK

Discover more about this clinically and genetically diverse disease and how it may present in your patients[1]

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A CLOSER LOOK AT BBS

BBS is a rare autosomal recessive ciliopathy[1-3]

BBS is a multisystemic disorder caused by ciliary dysfunction that results in highly variable clinical manifestations.

Hyperphagia and obesity are prevalent in BBS and are caused by an impairment in the melanocortin-4 receptor (MC4R) pathway. The MC4R pathway regulates hunger, satiety, and energy expenditure.[4]

The most common clinical features of BBS may include[2,5,6]:


Hyperphagia (insatiable hunger)


Obesity


Visual impairment


Cognitive impairment


Renal anomalies


Postaxial polydactyly


Hypogonadism

Additional clinical features may include[5]:

- Speech delay
- Development delay
- Diabetes mellitus
- Congenital heart disease
- Dental anomalies
- Brachydactyly/syndactyly
- Ataxia/poor coordination
- Anosmia/hyposmia

The presence and severity of clinical features can vary greatly across individuals[1,2]

HOW BBS CAN PRESENT IN YOUR PRACTICE

Determine if your patient may have BBS based on their clinical manifestations

The chart below outlines common clinical features of BBS, how they can present, and tests or labs used to confirm these manifestations.

Most common clinical features	Clinical manifestations		Potential assessments
Hyperphagia[4,7,8] Presents at <5 years of age	• Pathological, insatiable hunger • Long time to satiation • Shorter duration of satiation	• Prolonged feeling of hunger • Severe preoccupation with food and distress if denied food	Utilizing hyperphagia questionnaires, following up with patients/caregivers regarding their behaviors around food
Obesity[5,9-12] Presents at <5 years of age	• Early-onset truncal obesity • Normal birth weight, followed by rapid weight gain		Growth chart, tracking patients' BMI/BMI Z-score over time
Visual impairment[5,13-15] Symptoms usually develop in the first decade of life, and most patients are legally blind by the second/third decade	• Rod-cone dystrophy/retinitis pigmentosa (RP) – Night blindness – Photophobia – Legal blindness – Diminution of color – Overall loss of visual acuity	• Strabismus • Astigmatism • Cataracts • Color blindness • Macular edema and degeneration • Optic atrophy	Electroretinography test (for RP only)

Chart continues on the following pages.

CLINICAL FEATURES AND MANIFESTATIONS OF BBS (cont'd)

Most common clinical features	Clinical manifestations		Potential assessments
Cognitive impairment[15,16] Learning difficulties and developmental delays present in school-aged patients	• Developmental delay (gross motor, fine motor, speech/language) • Mild to moderate learning difficulties • Speech delays, poor articulation, poor language interpretation	• Behavioral problems (immaturity, frustration, obsessive/compulsive nature, poor concentration/ hyperactivity) • Gaze avoidance • Lack of abstract thought	Developmental and/or neurocognitive assessment Routine developmental assessments during early childhood School-aged patients should have annual Individualized Education Programs/504 plans Neuropsychiatric evaluation if signs/symptoms of atypical behaviors or mood disorder
Renal anomalies[5,15,17-20] Renal anomalies can be a major cause of morbidity and mortality in BBS, and chronic kidney disease (CKD) may present in patients <10 years of age	• Cystic tubular disease • Anatomical malformations • Urinary tract abnormalities • Hypertension • Chronic renal failure • Transplantation • Polyuria/polydipsia • Chronic tubulointerstitial nephritis • Glomerular defects • Urinary concentrating defects	• Anatomical malformations at birth, including parenchymal cysts, calyceal cysts, calyceal clubbing and blunting, horseshoe kidney, fetal lobulation, scarring, unilateral renal agenesis, dysplastic kidneys, bladder obstruction, hydronephrosis, ectopic kidney, renal calculi, and vesicoureteral reflux	Regular monitoring/testing of renal function is recommended to diagnose and treat CKD early to prevent morbidity and mortality Ultrasound scan, isotope renography, labs (raised plasma urea and creatinine levels), intravenous pyelogram, renal ultrasonography, renal biopsy
Limb abnormalities[5,21,22] Extra fingers and/or toes can be seen at birth and are typically surgically removed in early childhood (>5 years of age)	• Postaxial polydactyly • Brachydactyly • Syndactyly		Physical examination and discussion about symptoms with patients/caregivers

CLINICAL FEATURES AND MANIFESTATIONS OF BBS (cont'd)

Most common clinical features	Clinical manifestations		Potential assessments
Genitourinary abnormalities[5,13,15,16] May be apparent at puberty	**In males:** • Hypogonadism • Micropenis, small-volume testes, maldescent of testes, cryptorchidism, hypogonadotropic hypogonadism, delayed puberty, infertility	**In females:** • Uterine, fallopian, ovarian, or vaginal hypoplasia or atresia • Low fertility rates	Check follicle-stimulating hormone, luteinizing hormone, estrogen, and testosterone levels if indicated due to delayed puberty Pelvic ultrasound in females to assess for malformations of uterus, fallopian tubes, ovaries, and vagina

Additional clinical features	Clinical manifestations		Potential assessments
Dental anomalies[5,15,23]	• Crowding • Malocclusion/micrognathia • Enamel hypoplasia • Discoloration	• Microdontia • Taurodontism or short roots • High-arched or deep palate • Periodontal disease	Dental exam
Congenital heart disease[5]	• Valvular stenosis • Patent ductus arteriosus • Cardiomyopathy		Echocardiogram, chest x-ray
Speech delay[5,24-26]	• High-pitched nasal speech • Speech delay and deficits • Unintelligible speech		Assessments, such as Ages and Stages Questionnaires, the Language Development Survey, and the MacArthur-Bates Communicative Development Inventories
Neurological deficits[5,15,16]	• Ataxia • Clumsiness • Poor coordination and balance		MRI

BBS HAS A HIGHLY VARIABLE PHENOTYPE WITH COMMON FEATURES THAT EVOLVE OVER TIME[5]

As a result, most patients with BBS are diagnosed in late childhood or early adulthood[5]

	Birth	First years of life (0 to 5 years)	Early childhood (up to 10 years)	Late childhood (>10 years)
Postaxial polydactyly[5,16,21,22,27] (63%-81%)	Extra digits (postaxial)	Typically surgically removed		
Renal anomalies[5,16-18] (53%)	Anatomical malformations	Progressive kidney disease	Polyuria/ Polydipsia	CKD
Hyperphagia and obesity[5,7,28,29] (72%-92%)	Normal birth weight	Rapid weight gain, unusual food seeking	Severe obesity, hyperphagia persists	Truncal obesity
Cognitive impairment[5,15] (>50%)		Developmental delay	Specialized schooling needs	Learning difficulties
Visual impairment[5,30] (93%)			Progressive vision loss, night blindness	Legal blindness
Hypogonadism[5] (59%-98%)			Delayed puberty	

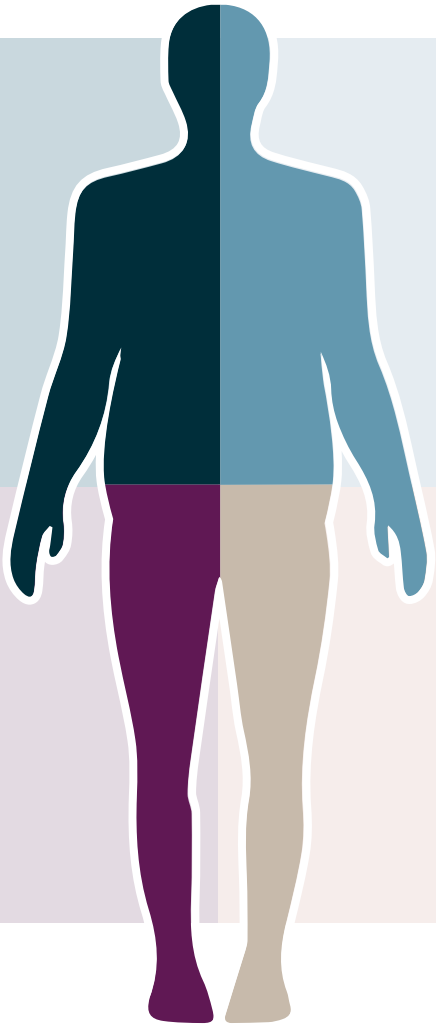
Identifying patients with BBS and treating their hyperphagia and obesity early is critical, as these symptoms can accelerate coexisting health concerns[31]

BBS IS CLINICALLY AND GENETICALLY DIVERSE[1,2]

Factors to consider when diagnosing BBS

Clinical manifestations[1,2,5]

- BBS is a multisystemic disorder with a highly variable phenotype, so clinical features can vary greatly across individuals and evolve over time



Genetics[1]

- Genetic testing can provide additional diagnostic information to help inform your diagnosis. For more information visit **uncoveringrareobesity.com**
- Interpretation of genetic testing results can be limited by the information currently available on the genetics of this disease. Information around the genetics of BBS continues to evolve

Patient history

- Review patients' complete medical history. Some clinical manifestations of BBS may have been previously treated and/or not recognized as a symptom of BBS

Family findings[2,16]

- Family members have an increased risk of inheriting a pathogenic BBS gene, and siblings of those affected are generally diagnosed earlier
- Genetic testing for parents and siblings may provide further diagnostic information. Phenotype can vary between siblings

Consider the complete patient presentation when making a diagnosis

EXPAND YOUR PERSPECTIVE ON BBS

BBS is a rare autosomal recessive ciliopathy[1,2]

- Impairment in the MC4R pathway is a root cause of hyperphagia and obesity, 2 common features of BBS[4]
- Other common features may include visual impairment, cognitive impairment, renal anomalies, postaxial polydactyly, and hypogonadism[2,5,6]

BBS is clinically and genetically diverse, so consider the complete patient presentation[1,2]

- BBS is a multisystemic disorder with a highly variable phenotype that can evolve over time[1,5]
- Clinical manifestations, genetics, patient history, and family findings should all be considered when making a diagnosis

Click here to learn about a treatment for obesity due to BBS

References: 1. Manara E et al. *Ital J Pediatr*. 2019;45(1):72. **2.** Forsythe E et al. *Front Pediatr*. 2018. doi:10.3389/fped.2018.00023. **3.** Vaisse C et al. *Cold Spring Harb Perspect Biol*. 2017;9(7):a028217. **4.** Eneli I et al. *Appl Clin Genet*. 2019;12:87-93. **5.** Forsythe E, Beales PL. *Eur J Hum Genet*. 2013;21(1):8-13. **6.** Pigeyre M et al. *Clin Sci (Lond).* 2016;130(12):943-986. **7.** Sherafat-Kazemzadeh R et al. *Pediatr Obes*. 2013;8(5):e64-e67. **8.** Heymsfield SB et al. *Obesity (Silver Spring).* 2014;22(suppl 1):S1-S17. doi:10.1002/oby.20646. **9.** Hample SE et al. *Pediatrics*. 2023;151(2):e202206064. **10.** Styne DM et al. *J Clin Endocrinol Metab*. 2017;102(3):709-757. **11.** Defining childhood weight status. Centers for Disease Control and Prevention. Accessed January 30, 2023. https://www.cdc.gov/obesity/basics/childhood-defining.html. **12.** Obesity and overweight. World Health Organization. Published June 9, 2021. Accessed January 30, 2023. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. **13.** Florea L et al. *Genes (Basel).* 2021;12(9):1353. doi:10.3390/genes12091353. **14.** Meng X et al. *Front Cell Dev Biol*. 2021;9:635216. doi:10.3389/fcell.2021.635216. **15.** Beales PL et al. *J Med Genet*. 1999;36(6):437-446. **16.** Forsyth R et al. Bardet-Biedl syndrome overview. In: Adam MP et al, eds. *GeneReviews®*. University of Washington; 2003. Updated July 23, 2020. Accessed January 30, 2023. https://www.ncbi.nlm.nih.gov/books/NBK1363. **17.** Forsythe E et al. *J Am Soc Nephrol*. 2017;28(3):963-970. **18.** Putoux A et al. *Pediatr Nephrol*. 2012;27(1):7-15. **19.** Panny A et al. *J Dent Res*. 2017;96(12):1361-1369. doi:10.1177/0022034517716913. **20.** Sandilands EA et al. *Br J Clin Pharmacol*. 2013;76(4):504-515. **21.** Khan OA et al. *Cureus*. 2019;11(2):e4114. **22.** Vlahovic AM, Haxhija EQ. *Pediatric and Adolescent Plastic Surgery for the Clinician*. Springer; 2017:89-105. **23.** Majumdar U et al. *BMJ Case Rep*. 2012;2012:bcr1220115320. **24.** Developmental Screening. Ages & Stages Questionnaire. Accessed January 30, 2023. https://agesandstages.com/about-asq/why-screening-matters/developmental-screening. **25.** The Language Development Survey (LDS). Achenbach System of Empirically Based Assessment. Accessed January 30, 2023. www.aseba.org/research/the-language-development-survey-lds. **26.** The MacArthur-Bates Communicative Development Inventories (MB-CDIs). MacArthur-Bates CDI. Accessed January 30, 2023. www.mb-cdi.stanford.edu. **27.** Agrawal H et al. *Pediatr Rev*. 2018;39(5):e21-e23. **28.** Pomeroy J et al. *Pediatr Obes*. 2021;16(2):e12703. **29.** Katsanis N et al. *Hum Mol Genet*. 2001;10(20):2293-2299. **30.** Weihbrecht K et al. *Med Res Arch*. 2017. doi:10.18103/mra.v5i9.1526. **31.** Kyrou et al. Clinical problems caused by obesity. In: Feingold KR et al, eds. *Endotext*. MDText.com, Inc.; 2018. Updated January 11, 2018. Accessed January 30, 2023. https://www.ncbi.nlm.nih.gov/books/NBK278973/.

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