Natural History of Weight Gain in Children With Bardet-Biedl Syndrome: Results From the Clinical Registry Investigating Bardet-Biedl Syndrome

Robert Haws,[1] Jeremy Pomeroy,[1] Usha G. Mallya,[2] Brieana C. Buckley,[2] Ryan Kyle,[3] Ariane Faucher,[3] Francis Vekeman,[3] Richard Berg,[1] Jesse Richardson,[1] Sonali Malhotra[2]

[1]Marshfield Clinic Research Institute, Marshfield, WI, USA; [2]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [3]Statlog Econometrics, Montreal, QC, Canada

Presenting Author:
Jeremy Pomeroy
pomeroy.jeremy@marshfieldresearch.org

Summary

- **>80% of children with Bardet-Biedl syndrome (BBS) aged 3 to 17 years enrolled in the international Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) had obesity (ie, body mass index [BMI] ≥95th percentile for age and sex)**
- **Approximately one-third of children had class III obesity (ie, BMI ≥140% of the 95th percentile)**
- **Most children with BBS experienced persistent or worsening obesity over time**

Introduction

- The hypothalamic melanocortin-4 receptor (MC4R) pathway is a key regulator of hunger, satiety, and energy expenditure and influences body weight[1-4]
- BBS is a rare genetic disease characterized by multiorgan pathology, including hyperphagia (pathological, insatiable hunger) and early-onset, severe obesity; impaired MC4R signaling associated with primary cilia dysfunction is hypothesized to be involved in the hyperphagia and obesity associated with BBS[3,5-7]
- Disease characteristics, particularly hyperphagia and obesity, can contribute to high disease burden and impaired quality of life for patients with BBS[6,8-11]
- The natural history of weight gain patterns among individuals with BBS is not clearly understood

Objective

- To investigate the natural history of weight gain in children with BBS enrolled in the international CRIBBS registry

Methods

- CRIBBS is an international registry established in June 2014 by the Marshfield Clinic Research Institute in Wisconsin (NCT02329210) that collects longitudinal data on individuals with BBS
- Data were collected from children with BBS aged 3-17 years with ≥1 BMI assessment enrolled in CRIBBS between 2014 and 2021
  - Children treated with investigational drugs for weight loss were censored at the last assessment before the start of the investigational drug
- BMI and self-reported weight loss interventions were assessed
  - Weight loss interventions included diets (eg, low calorie, low carbohydrate, low sugar, low fat, high protein, and/or established diets for weight loss such as the South Beach Diet or Jenny Craig®), weight loss medications (ie, bupropion, liraglutide, metformin, phendimetrazine, phentermine, semaglutide), and weight loss surgery
- Obesity status was evaluated by the percent of the 95th percentile for BMI and classified on the basis of severity[12]
  - Underweight: BMI <5th percentile for age and sex
  - Normal weight: BMI ≥5th percentile and <85th percentile for age and sex
  - Overweight: BMI ≥85th percentile and <95th percentile for age and sex
  - Class I obesity: BMI corresponding to the 95th percentile for age and sex and <120% BMI corresponding to the 95th percentile
  - Class II obesity: BMI ≥120% and <140% of the 95th percentile
  - Class III obesity: BMI ≥140% of the 95th percentile
- Natural history of weight gain was assessed as change in weight category between the first and last weight assessment among children ages 3 to 17 years with ≥2 BMI measurements that were ≥2 years apart (natural history subset; to capture long-term trends in weight change)

Results

Population

- A total of 331 children with BBS between the ages of 3 and 17 had ≥1 weight measurement and were included in this analysis (Table 1)
  - The median number of follow-up assessments was 3 (range, 1-8)
- At baseline (ie, the first available measurement between ages 3 and 17 years) 81% (n=268) of all children had obesity; the proportions of patients with obesity were generally equally distributed between different obesity classes (Table 2)
  - Class I: 26.0% (n=86)
  - Class II: 24.2% (n=80)
  - Class III: 30.8% (n=102)
- Baseline characteristics were similar between the full sample and the natural history subset

Table 1. Demographics and Baseline Characteristics

	Children with BBS (N=331)	Natural history subset[a] (n=186)
Age, mean (median) [IQR], y	8.7 (9.0) [4.0-13.0]	7.8 (8.0) [4.0-11.0]
Sex, n (%)		
Male	170 (51.4)	99 (53.2)
Female	161 (48.6)	87 (46.8)
Race, n (%)		
White	243 (73.4)	145 (78.0)
Black	11 (3.3)	4 (2.2)
Asian	22 (6.6)	11 (5.9)
Other[b]	53 (16.0)	26 (14.0)
Unknown	2 (0.6)	0
Region, n (%)		
North America	264 (79.8)	154 (82.8)
United States	243 (73.4)	143 (76.9)
Europe	35 (10.6)	18 (9.7)
Australia	18 (5.4)	9 (4.8)
Asia	5 (1.5)	2 (1.1)
Africa	4 (1.2)	2 (1.1)
Oceania	3 (0.9)	1 (0.5)
Unknown	2 (0.6)	0
Type of healthcare insurance, n (% of children in US)		
Public	83 (34.2)	42 (29.4)
Private	119 (49.0)	74 (51.7)
Both public and private	37 (15.2)	23 (16.1)
Unknown coverage	4 (1.6)	4 (2.8)
Obesity status at first weight assessment from age 3-17 years, n (%)		
Underweight	1 (0.3)	0
Normal weight	32 (9.7)	20 (10.8)
Overweight	30 (9.1)	15 (8.1)
Obesity	268 (81.0)	151 (81.2)
Class I obesity	86 (26.0)	48 (25.8)
Class II obesity	80 (24.2)	49 (26.3)
Class III obesity	102 (30.8)	54 (29.0)

[a]Children with ≥2 BMI measurements ≥2 years apart. [b]Middle Eastern, American Indian or Alaska Native, and Pacific Islander.
BBS, Bardet-Biedl syndrome; IQR, interquartile range.

Natural history of weight gain

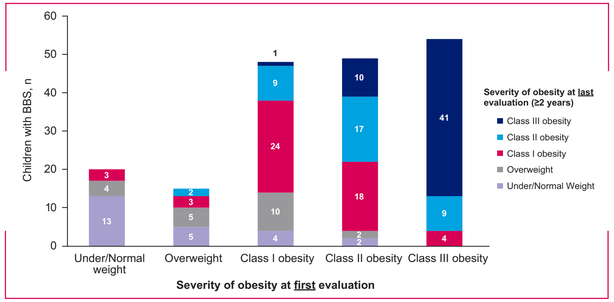
- Among 186 children in the natural history subset (ie, with ≥2 BMI measurements that were ≥2 years apart) evaluated for weight change over time, 81.2% (n=151) had obesity at baseline, including 29.0% (n=54) with class III (severe) obesity (Figure)
- Overall, 67.5% (n=102) of children with obesity at baseline remained in the same or moved to a higher obesity class by the last assessment ≥2 years later (Table 2)
- Across all children in the natural history subset, 17.2% (n=32) moved to a higher weight category by the last assessment (Table 2)
  - Notably, because weight gain was defined as a change in weight category, patients with class III obesity at baseline could not be assessed for weight gain because they could not move to a higher weight category

Table 2. Weight Changes From First to Last Assessment Observed Between Ages 3 and 17 Years, Overall and by Baseline Weight Category

Changes in weight category from first to last assessment, n (%)	Overall (n=186)	Normal weight (n=20)	Overweight (n=15)	Any obesity (n=151)	Class III obesity (n=54)
No improvement	132 (71.0)	20 (100.0)	10 (66.6)	102 (67.5)	41 (75.9)
No change in weight category	100 (53.8)	13 (65.0)	5 (33.3)	82 (54.3)	41 (75.9)
Weight gain[a]	32 (17.2)	7 (35.0)	5 (33.3)	20 (13.2)	NA[b]
Weight loss[c]	54 (29.0)	0 (0.0)	5 (33.3)	49 (32.5)	13 (24.1)

[a]Change from obesity class I to class II/III or from obesity class II to class III was considered weight gain. [b]Given that weight gain was defined as change in weight category, patients with class III obesity at baseline could not move to a higher weight category. [c]Change from obesity class III to class I/II or from obesity class II to obesity class I was considered weight loss. NA, not applicable.

Figure. Change in BMI category from first to last assessment in children with BBS with ≥2 assessments ≥2 years apart (natural history subset).



BBS, Bardet-Biedl syndrome; BMI, body mass index.

Weight loss interventions

- In the full analysis population (N=331) and natural history subset (n=186), 22.7% (n=75) and 32.3% (n=60) of children with obesity reported using weight loss interventions, respectively (Table 3)
  - Baseline class III obesity was overrepresented among children who reported using weight loss interventions (class III obesity, 41.3% [n=31])

Table 3. Weight Loss Interventions

	Children with BBS	
	Full population (N=331)	Natural history subset[a] (n=186)
Children who used a weight loss intervention from CRIBBS enrollment until the last assessment before age 18 years, n (%)	75 (22.7)	60 (32.3)
Types of intervention, n (%)		
Diet only[b]	49 (14.8)	41 (22.0)
Medication only[c]	22 (6.6)	15 (8.1)
Diet + medication	4 (1.2)	4 (2.2)
Surgery ± diet or medication	0	0
Medications used without other interventions, n (%)		
Metformin	24 (7.3)	17 (9.1)
Bupropion	2 (0.6)	2 (1.1)
Liraglutide	0	0
Phendimetrazine	0	0
Semaglutide	0	0

[a]Children with ≥2 BMI measurements ≥2 years apart. [b]Multiple diets possible. [c]Multiple medications possible.
BBS, Bardet-Biedl syndrome.

Strengths and Limitations

- A strength of this analysis is that the CRIBBS database includes the largest sample to date of children with BBS across a range of countries and socioeconomic environments
- Limitations of this study include
  - Anthropomorphic measurements were primarily obtained at healthcare encounters, with some self-reported values, and do not reflect the precision of single-center prospective studies
  - Because weight loss interventions were self-reported, it is possible that routine efforts to manage hunger and overeating were not considered by the patient/caregiver as a weight loss intervention; thus, it is possible the reported weight loss interventions in the current study are undercounted and biased toward high-intensity interventions

Conclusions

- >80% of children enrolled in CRIBBS had class I, II, or III obesity
- Approximately one-third of children with BBS had class III obesity
- Over time, most children with obesity continued to have obesity or experienced additional weight gain despite the use of obesity management strategies, particularly children with class III obesity
- This analysis provides further evidence of the early-onset, severe obesity experienced in BBS and the need for effective interventions

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Disclosures: UGM, BB, and SM are employees of and stockholders in Rhythm Pharmaceuticals, Inc. RH is a stockholder in Rhythm Pharmaceuticals, Inc. **References: 1.** da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **2.** Farooqi, O'Rahilly. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **3.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **4.** Yazdi et al. *PeerJ*. 2015;3:e856. **5.** Seo et al. *Hum Mol Genet*. 2009;18:1323-1331. **6.** Sherafat-Kazemzadeh et al. *Pediatr Obes*. 2013;8:e64-67. **7.** Pomeroy et al. *Pediatr Obes*. 2021;16:e12703. **8.** Forsythe et al. *J Am Soc Nephrol*. 2017;28:963-970. **9.** Heymsfield et al. *Obesity (Silver Spring)*. 2014;22(suppl 1):S1-S17. **10.** Forsythe et al. Poster presented at ObesityWeek®; November 1-5, 2021; Virtual. **11.** Ervin et al. Poster presented at the Pediatric Endocrine Society Annual Meeting; April 28-May 1, 2022; Virtual. **12.** Cuda et al. Pediatric obesity algorithm slides, presented by the Obesity Medicine Association. www.obesitymedicine.org/childhood-obesity. Accessed September 15, 2022.