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SHORT COMMUNICATION: Hyperphagia among patients with Bardet-Biedl syndrome

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Summary

Background—The importance of hyperphagia as a cause for energy imbalance in humans with Bardet-Biedl syndrome (BBS) has not been established. We therefore compared hyperphagic symptoms in patients with BBS versus controls.

Methods—We studied 13 patients with BBS and 23 nonsyndromic controls with similar age, sex, and BMI z-score. A 13-item hyperphagia questionnaire was completed by patients' parents/guardians.

Results—Total hyperphagia questionnaire score was higher in BBS than controls (27.6±9.0 vs. 19.1±7.9, $p=0.005$). Behavior and drive sub-scales were higher for BBS than controls (12.5±4.1 vs. 7.8±3.2, $p=0.001$, and 11.2±4.1 vs. 8.3±3.8, $p=0.04$, respectively); severity was not significantly different between groups (3.8±1.5 vs. 3.0±1.3, $p=0.072$). After adjustment for demographic variables and BMI-Z score, total and behavior subscale scores remained significantly different between groups, suggesting food-seeking activity, rather than preoccupation with food may be the main hyperphagic feature among patients with BBS.

Conclusion—Appetite dysregulation may contribute to obesity in BBS.

Keywords

hyperphagia; obesity; Bardet-Biedl syndrome; obesity syndromes; polyphagia; energy intake; questionnaire; child; adolescent

Bardet-Biedl syndrome (BBS) is a rare, genetically heterogeneous disorder (1, 2) with retinal dystrophy, post-axial polydactyly, developmental delay, renal abnormalities, and obesity in 70–90% (1, 3, 4). Genes involved in formation, stability, and function of cilia are implicated as causes of BBS (5–7). The high penetrance of the obesity phenotype in patients

suggests that ciliary proteins play an important role in body energy balance and weight regulation. Several mouse models of BBS recapitulate features of the human phenotype and have altered protein/vesicle trafficking in leptin-sensing hypothalamic neurons, possibly inducing leptin resistance and hyperphagia, consistent with the observation that BBS knockout mice consume 20–30% more energy than controls (8, 9). Human studies characterizing the obesity phenotype of patients with BBS are few (10–12) and do not provide definitive data for the contributions of increased energy intake, decreased physical activity or altered metabolism to their obesity. A study of energy homeostasis in 20 BBS overweight or obese subjects and 20 controls reported no differences in energy intake or resting energy expenditure, but found physical activity (by actigraphy) was slightly, but significantly, lower among patients with BBS (10). This study, however, used a self-report 7-day food diary for energy intake assessment that, given the cognitive impairment of patients with BBS, may need to be interpreted cautiously.

There are several syndromes where obesity occurs together with cognitive dysfunction and the obesity is associated with hyperphagic symptoms (13–16). One example is the Prader-Willi syndrome (PWS) (13). Patients with PWS show defects in post-meal satiation and satiety in the laboratory setting (17, 18). They have many hyperphagic characteristics, in addition to overeating, that include preoccupation with food (hyperphagic drive), excessive food seeking such as waking up at night to seek food, foraging through trash, stealing and hiding food (hyperphagic behavior), and significant functional impairment and distress when denied food. To address the challenges of requiring intellectually-impaired participants to report their own behaviors, Dykens et al. (13) developed and validated in patients with PWS, a questionnaire that assesses hyperphagic symptoms by asking caregivers to report their observations. Given the convincing data for hyperphagia found in BBS mouse models (8, 9), we hypothesized that, if increased food intake was a cause of obesity in humans with BBS, the caregivers of patients with BBS would report greater hyperphagic symptoms than would caregivers of equally obese non-syndromic controls.

We recruited a convenient sample of 13 patients diagnosed with BBS using clinical criteria (19) from among participants in an observational study of the genetic and clinical characteristics of patients with BBS (<http://clinicaltrials.gov/ct2/show/NCT00078091>). Healthy control subjects (with no known syndrome associated with obesity or major illness affecting appetite) were selected from among participants in studies of eating behavior and metabolism (<http://clinicaltrials.gov/ct2/show/NCT00758108>, <http://clinicaltrials.gov/ct2/show/NCT00631644>, and <http://clinicaltrials.gov/ct2/show/NCT01237041>). The studies were approved by the NICHD or NHGRI IRBs. Participants provided consent/assent for participation. The Hyperphagia Questionnaire (13) is a 13-item questionnaire with 11 items rated on a 5-point Likert scale (from 1= not a problem at all, to 5= extremely problematic) that produce a total hyperphagic score (range 11–55) and three sub-scales: hyperphagic behavior (range 5–25), hyperphagic drive (range 4–20), and hyperphagic severity (range 2–10) (13). Questions 12 and 13 seek information on the age when a child's interest in food increased and on how much the child's interest in food changes from day to day. The Hyperphagia Questionnaire was completed by the parent/guardian who spent the most time with the participant. Using analyses of covariance (ANCOVA), we compared Hyperphagia Questionnaire scale scores for BBS vs. the control group, adjusting for age, sex, race, and BMI-Z score. Chi-square test was used to compare the two groups for the additional questions; day-to-day variability in behavior is not reported because of many missing responses in the control group.

Characteristics of study subjects are summarized in Table 1. The subjects in the two groups did not differ significantly in sex, age, race, or BMI-Z score, although height was significantly lower among BBS, which might be attributable to slower growth in

adolescence (20). Among patients with BBS, genomic sequencing confirmed 1 case had mutations in BBS6, 1 in BBS7, and 6 in BBS10 (data not shown). In unadjusted comparisons, the total hyperphagia score ($p=0.005$), behavioral subscale ($p=0.001$), and drive subscale scores ($p=0.040$) were significantly greater in patients with BBS than controls (Figure 1). After adjustment for age, sex, race, and BMI-Z score, group differences remained significant for total hyperphagia score ($p=0.032$) and the behavioral subscale ($p=0.003$). Among those whose caregivers reported an age when they first observed increased interest in food, 91% (10/11) of patients with BBS, versus 42% (5/12) of controls reported increased interest in food before age 5 y ($p=0.013$). Each of the subscales and total hyperphagia score were highly correlated across the sample (r 's >0.85 for correlations between scores, all $p<0.001$).

Caregivers reported that patients with BBS displayed hyperphagic behaviors that started in early childhood. Our limited data do not allow us to determine if there are different developmental periods when hyperphagia is more evident, as is found in patients with PWS, whose extreme food seeking behaviors begin after age 2 y but subsequently subside (13, 21). Elevated scores among patients with BBS were comparable to reports from patients with PWS (total: 30.47 ± 5.84 , behavior: 13.57 ± 4.52 , drive: 12.29 ± 3.32 , severity: 4.61 ± 1.63) or WAGR syndrome having BDNF haploinsufficiency (total: 26.37 ± 7.32 , behavior: 10.63 ± 3.22 , drive: 11.53 ± 3.44 , and severity: 4.21 ± 1.70) (13, 14); however, the BBS group analyzed here did not have statistically greater hyperphagic drive or severity sub-scale scores compared to their matched controls. These findings are consistent with the clinical observation that food-seeking activity, rather than preoccupation with food or time spent thinking about food, may be the distinguishing hyperphagic feature in BBS. Patients with BBS typically do not become uncontrollably distressed and/or dysfunctional because of food-related behavior, but may still overeat, more so than individuals with nonsyndromic obesity, when afforded free access to food.

This investigation, the first to document hyperphagic behaviors among patients with BBS, is however limited by its small sample size and the absence of a criterion measure of body composition. Subgroup analyses of a range of age groups, as well as BBS genotypes, ideally in a larger sample, would give additional information, as would detailed studies of energy expenditures. Test meal studies conducted under standard conditions to measure energy intake, satiety, and satiation are warranted to confirm the role of higher intake in energy imbalance among patients with BBS.

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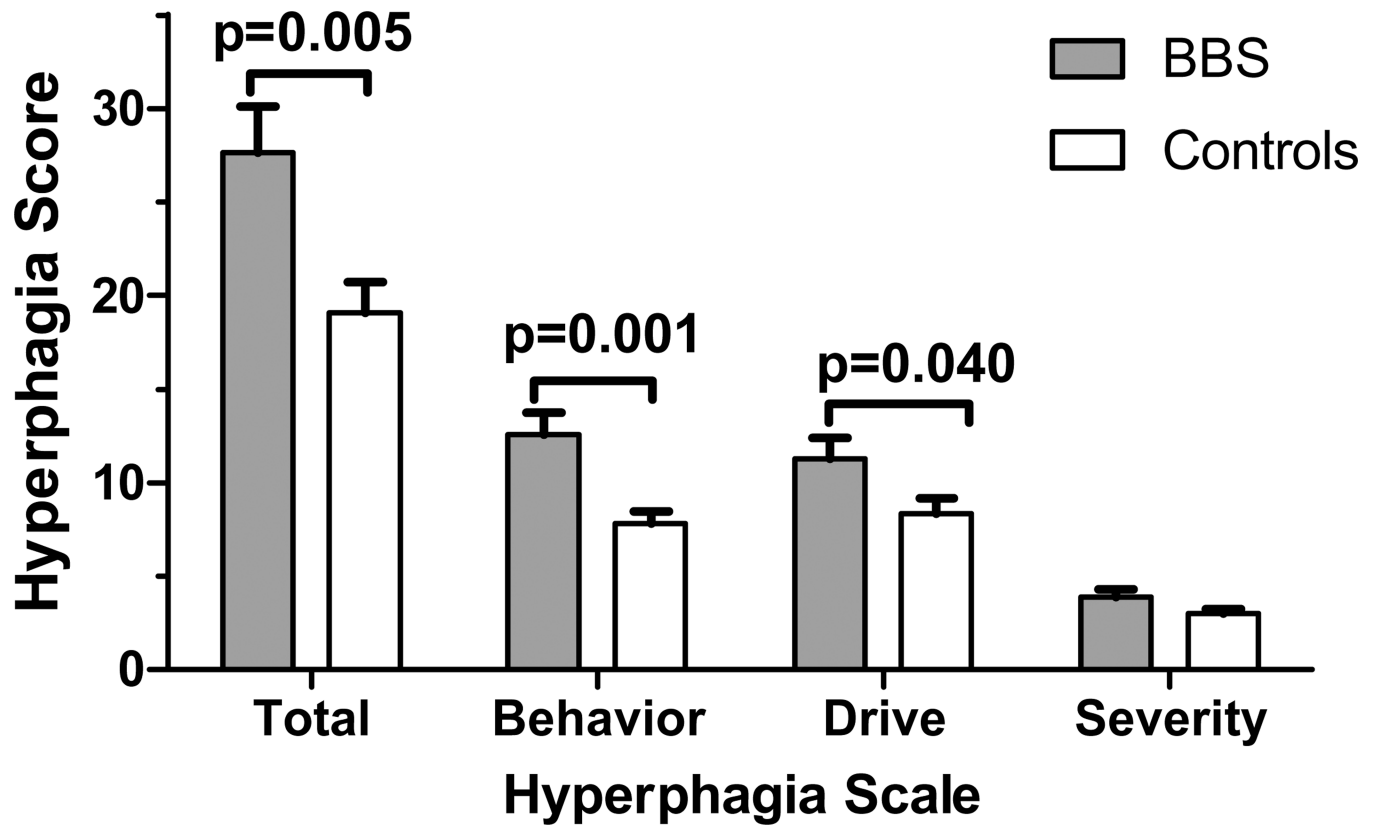


Figure 1. Total hyperphagia score and sub-scale scores assessed with hyperphagia questionnaire. After adjustment for age, sex, race, and BMI-Z score, total score ($p=0.032$) and behavior subscale ($p=0.003$) remained significantly different.

Table 1

Subject characteristics

Characteristic	Patients with BBS (N=13)	Controls (N=23)	<i>p</i> -value [†]
Sex (% female)	54	52	0.923
Race (% Non-Hispanic White)	85	52	0.052
Age (y) [*]	10.3 ± 3.8	12.7 ± 4.2	0.105
Height (cm) [*]	138.1 ± 23.1	154.7 ± 24.2	0.047
Height-Z score [*]	-0.3 ± 1.7	0.6 ± 0.9	0.066
Weight (kg) [*]	65.3 ± 32.9	81.3 ± 32.4	0.172
BMI (kg/m ²) [*]	32.4 ± 12.2	32.5 ± 8.3	0.973
BMI-Z score [*]	2.39 ± 0.58	2.30 ± 0.59	0.673

^{*} Mean ± SD

[†] Chi square for sex and race; t-tests for other characteristics.