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Sleep disordered breathing in Bardet-Biedl Syndrome

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ABSTRACT

Introduction: Bardet-Biedl Syndrome (BBS) is an autosomal recessive ciliopathy, and obesity is among its defining characteristics. Consequently, the incidence of sleep disordered breathing (SDB) in this population is expected to be high. Due to its relative rarity, the nature of SDB in this population is poorly described. The objective of this study was to review a single institutional experience in the assessment and management of SDB in patients with BBS.

Methods: Retrospective chart review of tertiary care, academic pediatric hospital.

Results: 20 patients with BBS were evaluated over a 25-year period. Median age at initial consultation was 69 months; half of these patients were referred before the diagnosis of BBS was made. Eighteen of twenty patients had symptoms of sleep-disordered breathing. Median follow-up duration was 17.5 months. A wide range of polysomnographic outcomes was observed, including obstructive apnea-hypopnea indexes of 0–195 events/hour. Patients were managed with adenotonsillectomy and/or non-invasive positive pressure ventilation.

Conclusions: SDB is commonly seen in BBS. These patients should be routinely screened for OSA and if present, a polysomnogram should be obtained. Based on patient characteristics, the failure rate of primary surgical intervention, namely adenotonsillectomy, is expected to be high. Further investigation into the role of ancillary diagnostic testing is still needed.

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1. Introduction

Bardet-Biedl Syndrome (BBS) is a rare, autosomal recessive ciliopathic disorder with a host of primary clinical features, including rod-cone dystrophy, polydactyly, obesity, renal anomalies, hypogenitalism, and developmental delay. BBS patients, however, display a wide clinical spectrum that can also include hearing loss, speech delay, dental anomalies, high-arched palate, cardiac anomalies and diabetes mellitus, among others [1]. While the overall incidence of BBS is quite low (approximately 1:100,000), certain populations exhibit higher incidences (up to 1:3750) owing to poorer genetic diversity, namely in the Middle East (Bedouin communities), Denmark (Faroe Islands), and Canada (Newfoundland) [2–4]. The most common presenting symptom that leads to a diagnosis of BBS is rod-cone dystrophy, a progressive loss of retinal rod and cone cells resulting in vision loss. Thus, patients can evade diagnosis depending on the age of onset of visual symptoms.

Clinical diagnostic criteria have been proposed and the diagnosis can be confirmed with genetic testing [1]. Over 20 causal genes have been identified to date [5]. The management of BBS is currently limited to symptom control.

Obesity is a cardinal feature of BBS and affects up to 92% of this patient population [6]. Obesity in BBS is caused by alterations in leptin receptor sensitivity in a mechanism that is distinct from non-BBS obese patients, and research into the molecular genetics is ongoing [7]. BBS patients are distinct in that they have higher adiposity, more visceral abdominal fat, and less lean mass than body mass index-matched controls [8–10]. As the prevalence of sleep disordered breathing (SDB) and obstructive sleep apnea (OSA) increases with increasing BMI, one would suspect OSA to be more prevalent in BBS patients [11]. However, literature search on this association reveals only 3 previously described cases of OSA in BBS patients [12,13]. A better understanding of OSA syndrome in BBS would therefore help to guide the investigation, management and prognosis of these patients. Additionally, understanding OSA in BBS patients is of particular importance because these patients also independently have risk factors for cardiopulmonary dysfunction, including cardiac anomalies, renal disease, and diabetes mellitus.

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The purpose of this study was to review the diagnosis and management of sleep disordered breathing in Bardet-Biedl Syndrome.

2. Materials and methods

A retrospective chart review was carried out at a single tertiary care pediatric hospital. Institutional Research Ethics board approval was obtained (IRB-P00023722). Patients with a diagnosis of BBS were identified using a combination of International Statistical Classification of Disease 10th Revision (ICD-10) codes and Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT). Data on body-mass-index (BMI) was automatically collated for all patients identified via ICD-10 and SNOMED-CT query of the electronic medical record. Regarding comprehensive chart review, only those who had at least one encounter with the Department of Otolaryngology and/or Sleep Medicine were selected for further review. This search query was also cross-referenced with patients who had undergone polysomnographic testing at this institution. No patient with the above ICD-10 or SNOMED-CT codes had undergone a polysomnogram if they had not also seen Otolaryngology and/or Sleep Medicine.

Daytime symptoms (including daytime somnolence, behavioural symptoms, mouth breathing, hyponasal) and nocturnal symptoms (including snoring, apneic pauses, increased work of breathing, night terrors and nocturnal enuresis) were elicited from the consultant's report. Body mass index (BMI) and weight percentile scores were calculated using charts from the World Health Organization and the Center for Disease Control. Polysomnogram (PSG) reports were interpreted using accepted normative values for pediatric patients [14]. Obstructive sleep apnea was defined as an obstructive apnea-hypopnea-index (AHI) of >1 /hour. Data regarding nadir oxyhemoglobin saturation (SpO₂), peak end-tidal CO₂, duration of rapid eye movement (REM) sleep, and periodic limb movement index were also collected.

Descriptive statistics were used for data analysis. Comparisons of independent samples were made using the Mann-Whitney *U* Test and the Kruskal-Wallis Test.

3. Results

Over a 25-year period, 53 patients with an ICD-10 and/or SNOMED-CT code for Bardet-Biedl Syndrome were seen at Boston Children's Hospital. Of these 53, twenty-four patients were seen by Otolaryngology and/or Sleep Medicine specialist at least once. Three patient charts were not available for review, leaving twenty-one patient charts available for review. One patient carried a diagnosis of BBS based on clinical criteria, but was subsequently found to have 16p11.2 microdeletion syndrome and excluded. Twenty patients were, therefore, included in the final analysis. No patient with the above ICD-10 or SNOMED-CT codes had undergone a polysomnogram if they had not also seen Otolaryngology and/or Sleep Medicine.

Fourteen out of twenty patients were male (70%). The median presenting age was 69 months (range 14–331 months). Ten patients presented with a pre-existing diagnosis of BBS; the median age of these patients was 101.5 months (range 45–331). By comparison, the median age in the 11 patients without a known diagnosis was 61.5 months (range 14–108). Among these 11 patients, only 4 were documented to have other comorbidities; these included global developmental delay, facial dysmorphism, hypothyroidism, anterior glottic web, congenital talipes equinovarus, polydactyly, and renal failure. The difference in age at presentation was statistically significant ($p = 0.02852$).

Eighteen of 20 patients (90%) presented with symptoms that were suggestive of sleep disordered breathing. The median weight

at the time of presentation was in the 99th percentile. Eleven (55%) had undergone at least one polysomnogram. Longitudinal BMI data were also available in this group and demonstrated that the majority of these patients remained well above the 95th percentile for their age throughout adolescence (Fig. 1). The mean (SD) BMI in this group was 31.8 (5.2) kg/m². In the patients who did not undergo PSG, the mean (SD) BMI was 30.0 (6.7) kg/m². In the patients who were not seen by Otolaryngology and/or Sleep Medicine, the mean BMI (SD) was 30.9 (7.9) kg/m². The differences in BMI in these groups were not statistically significant ($p = 0.7945$). The remainder of the patient characteristics are presented in Table 1.

3.1. Polysomnogram results

Eleven patients underwent PSG to investigate and diagnose OSA. One patient did not cooperate with application of the leads and as a result, no objective data could be ascertained. The mean age at the time of PSG was 125 months (std. dev. 53). The median BMI of patients at the time of PSG was at the 99.4th percentile. The majority of these patients did not have tonsillar hypertrophy at the time of assessment. Only a small percentage of patients presented with other metabolic comorbidities (namely diabetes mellitus, hypothyroidism, hypertension, non-alcoholic fatty liver disease, or hyperlipidemia). The demographic information of the 10 patients at the time of PSG is summarized in Table 2.

Five patients had PSG-diagnosed OSA at the time of presentation. Their individual obstructive AHIs were 3.5, 13.1 (limited study), 31, 195, and 1–4.2 per hour (range of AHI during continuous positive airway pressure titration of 8–12 cm H₂O). The patient with a limited study was subsequently found to have an obstructive AHI of 67/hour on a later PSG. In the patients with OSA, the AHI increased during REM sleep, from a mean of 41 events/hour overall to a mean 61.5 events/hour during REM sleep. The majority of patients undergoing PSG demonstrated hypoxemia, with 7/10 (70%) exhibiting abnormal SpO₂ nadir ($<90\%$) and 4/10 (40%) with desaturations to less than 90%. Three patients demonstrated hypercapnia, with end-tidal CO₂ in the range between 52 and 60 mmHg. Two patients had abnormal periodic limb movement indexes (defined as >5 movements/hour). The PSG data is summarized in Table 3.

Of the remaining 5 patients, two were found to have few respiratory effort-related arousals, but no true OSA. One patient was found to have mild central sleep apnea and abnormal periodic limb movement (8 events/hour) following adenotonsillectomy. This patient was followed with repeat titration studies for 5 years and his obstructive AHI never increased above 1 event/hour. Unfortunately for this patient, pre-operative PSG data was unavailable. One patient had a normal PSG with no evidence of OSA. One patient had difficulty tolerating the study, and no REM sleep was documented. Though this patient had tonsillar hypertrophy, he was ultimately lost to follow-up. Therefore, of the 10 patients who underwent PSG, 8 demonstrated evidence of SDB.

3.2. Management

Two patients with OSA diagnosed on PSG went on to undergo adenotonsillectomy. Post-operatively, one of these patients demonstrated persistent hypercapnia (end tidal CO₂ >50 mm Hg), and persistence of respiratory event related arousals. The second patient was found to have obstructive apnea events on follow-up PSG (obstructive non-REM AHI was 0.6 events/h). Unfortunately, this post-operative PSG did not capture REM sleep, though one would expect the REM AHI to be higher.

One patient presented after adenotonsillectomy at another institution and had regular follow-up at this institution for 5 years. Throughout this period, this patient had persistent central

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