International Journal of Pediatric Otorhinolaryngology 102 (2017) 127–132

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: http://www.ijporlonline.com/

Sleep disordered breathing in Bardet-Biedl Syndrome

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ARTICLE INFO

Article history:
Received 21 June 2017
Received in revised form
1 September 2017
Accepted 2 September 2017
Available online 12 September 2017

Keywords:
Obstructive sleep apnea
Sleep disordered breathing
Bardet-Biedl Syndrome
Obesity
Polysomnography
Apnea-hypopnea index

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.

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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https://doi.org/10.1016/j.ijporl.2017.09.004
0165-5876/

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, hyponasality) 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 (SpO_2), peak end-tidal CO_2, 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/m^2. In the patients who did not undergo PSG, the mean (SD) BMI was 30.0 (6.7) kg/m^2. In the patients who were not seen by Otolaryngology and/or Sleep Medicine, the mean BMI (SD) was 30.9 (7.9) kg/m^2. 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 SpO_2 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.

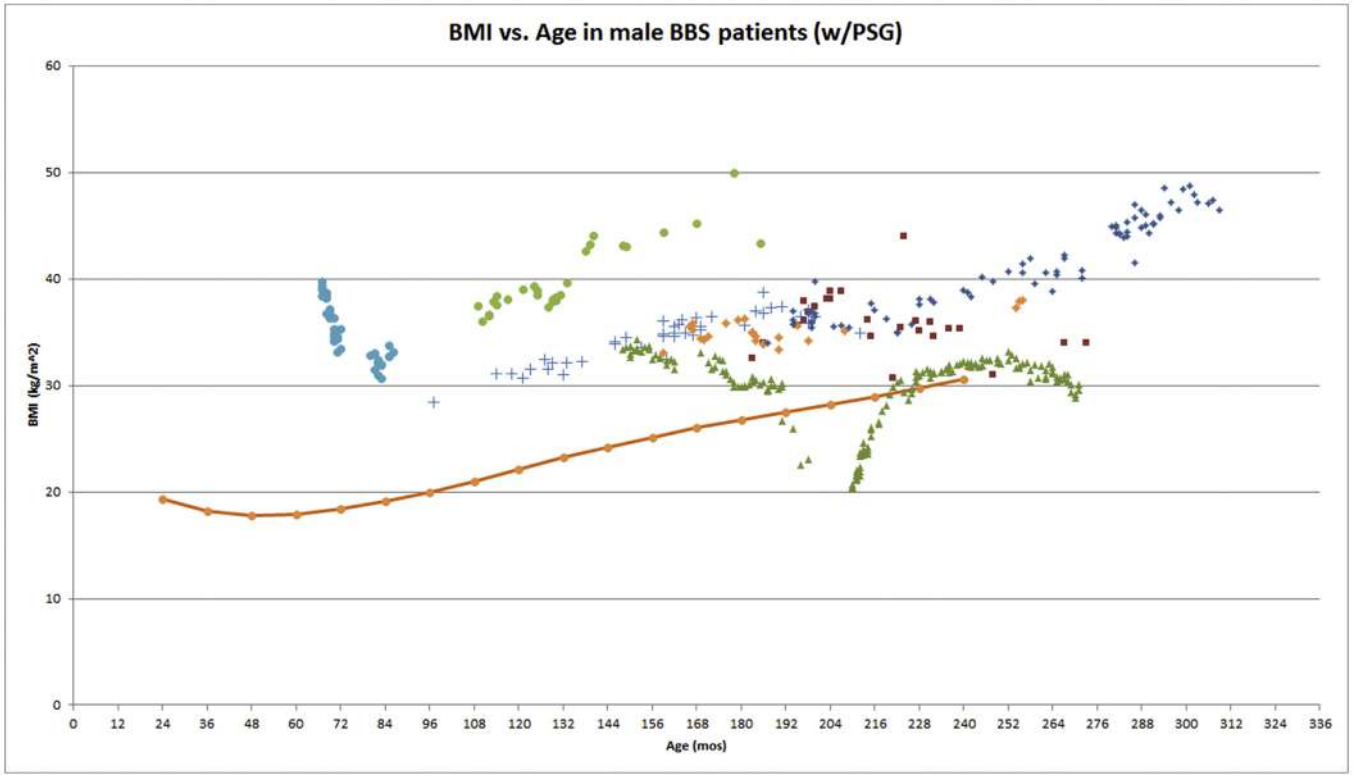
Of the remaining 5 patients, two were found to have few respiratory effort-related arousals, but no true OSA. One patient was found to have mild central sleep apnea and abnormal periodic limb movement (8 events/hour) following adenotonsillectomy. This patient was followed with repeat titration studies 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

a



b

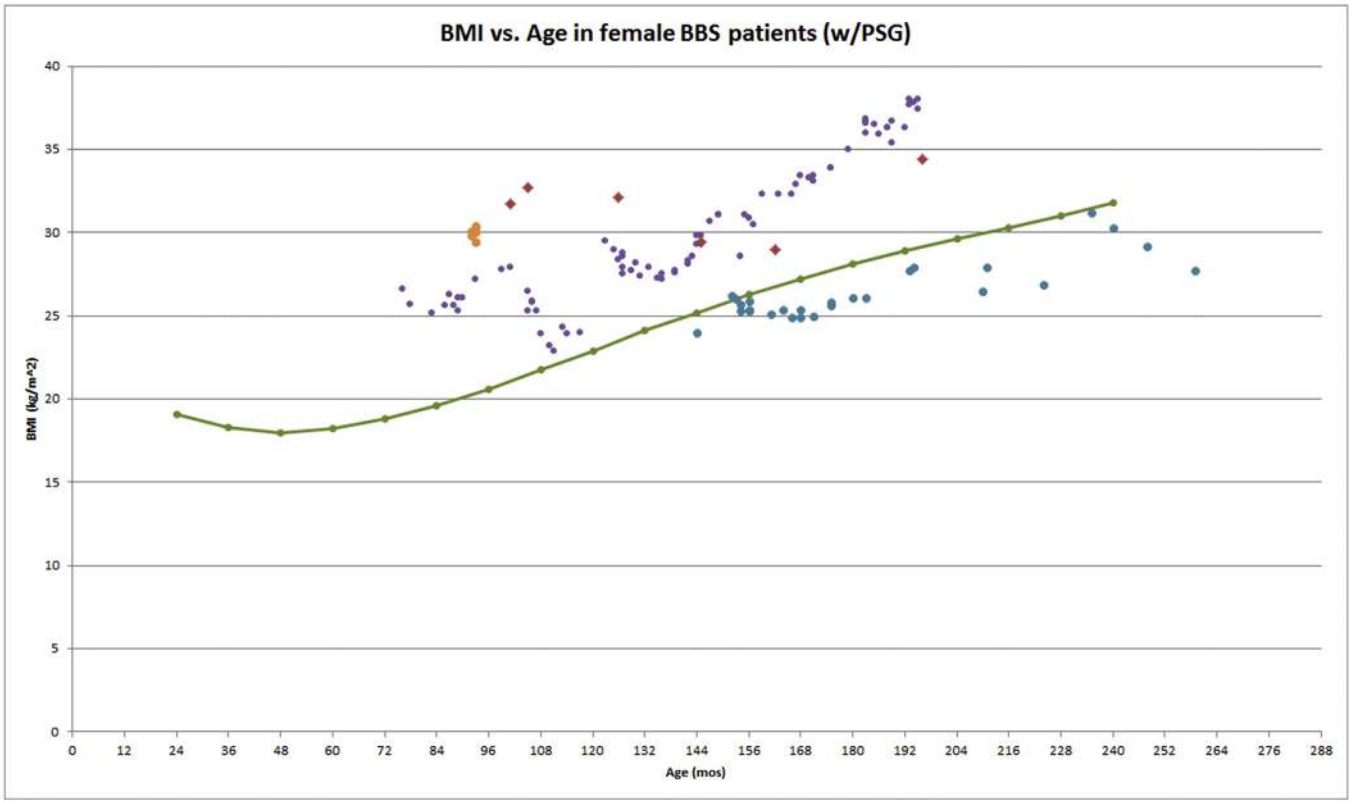


Fig. 1. BMI vs. age for males [A] and females [B]. Each series represents an individual patient. CDC Growth Chart 95th percentile is represented by the dotted line.

Table 1
Baseline patient characteristics.

Total number of patients	20
Age at presentation months – *median (range)*	69 (14–331)
Male - *n (%)*	14 (70%)
BBS was known at initial presentation - *n (%)*	10 (50%)
Reason for referral[a]	
Sleep disordered breathing	11
Recurrent tonsillitis	2
Recurrent otitis media	7
Hoarseness	2
Chronic otorrhea	1
Outpatient vs. inpatient consultation	19:1
History of sleep-disordered breathing symptoms - *n (%)*	18 (90%)
Patients who underwent sleep study - *n*	11
Hearing loss - *n (%)*	8 (38.1%)
Follow-up duration in months – *median (interquartile range)*	17.5 (0.75–91)
Mutation – *n*	
BBS1	7
BBS2	2
BBS9	1
BBS12	2
MKS1	2
Unknown	6

[a] Three patients presented with two chief complaints.

Table 2
Baseline characteristics of BBS patients who underwent PSG.

Total number of patients	10
Gender – M:F	6:4
Age in months – *mean (st. dev)*	125 (53)
BMI (kg/m^2) – *mean (st. dev)*	34 (6.3)
BMI percentile – *median (interquartile range)*	99.5 (97.2–99.9)
Tonsil size[a] - *n*	
Previous tonsillectomy	1
1+	2
2+	4
3+	1
4+	0
Not documented	2
Metabolic comorbidities - *n*	
Diabetes mellitus	0
Hypothyroidism	2
Hypertension	2
Non-alcoholic fatty liver disease	1
Hyperlipidemia	2

[a] Tonsil grading 1–4 as per Brodsky scale [26].

hypoventilation, mild obstructive SDB (respiratory disturbance index of 6/hr), and required non-invasive positive pressure ventilation. One additional patient was referred with a diagnosis of OSA, but PSG data was not available. This patient went on to have an adenotonsillectomy, but post-operative PSG has not yet been performed and has remained on nocturnal continuous positive airway pressure ventilation.

Seven patients presented with symptoms of SDB went on to undergo adenotonsillectomy without a pre-operative polysomnogram. None of these patients were known to have BBS at the time of their consultation or surgery. The follow-up duration of this group of patients was inadequate to ascertain the degree of symptom resolution after surgery. No patient in this group underwent any post-operative testing related to OSA, such as post-operative PSG and/or CPAP titration.

4. Discussion

Bardet-Biedl Syndrome is a rare condition, and evidence-based guidance in managing these patients, particularly from the perspective of the otolaryngologist, is lacking. The otolaryngology literature is limited to case reports describing Laurence-Moon-Bardet-Biedl Syndrome, a phenotypically similar syndrome that is now recognized to be genetically distinct [15–17]; SDB was not noted in these cases. In fact, the presence of OSA in this population has only been reported in three previous cases [12,13]. This is to-date the largest single institution experience reviewing OSA in BBS patients.

As hypothesized, a history suggestive of SDB was elicited in the vast majority of patients presenting to the Otolaryngology and Sleep Medicine services. The majority of PSGs performed demonstrated abnormal findings suggestive of at least upper airway resistance syndrome (multiple respiratory-effort related arousals). With available PSG data in only half the study population, the prevalence of OSA in this series was 5/20 (25%), which is at least consistent with the reported prevalence of OSA in obese children (19–61%) [18]. Though, 25% is likely an underestimation of the true prevalence of OSA in the BBS population. In the patients where longitudinal PSG data was available, it appeared that OSA tended to increase in severity with age, congruent with the tendency for the BMI of these patients to increase with age (Fig. 1). Thus, it is reasonable to expect the incidence of OSA to increase as these patients are followed over time, though the data was insufficient to demonstrate this.

All of the patients requiring treatment were managed with a combination of adenotonsillectomy, continuous positive airway pressure ventilation, and/or referral to a weight management clinic. This data is reflective of current management strategies outlined by the American Academy of Pediatrics, which recommends adenotonsillectomy followed by non-invasive ventilation as first and second line treatment options for OSA [19]. The past 25 years, however, has seen considerable changes to the surgical management strategy of refractory OSA in children [20]. This was due in part to the recognition that patient adenotonsillectomy is not as effective in medically complex children, such as those with obesity [18,21]. In the current study population, the lack of marked tonsillar hypertrophy in the majority of patients, particularly the older ones, is in keeping with this paradigm. In other words, while the primary surgical intervention for OSA is commonly adenotonsillectomy, the

Table 3
Initial PSG parameters.

PSG Parameters‡	n (reported)	Mean	Range	Abnormal Definition	n (abnormal)	Mean*	Range*
Obstructive AHI	10	31.1	0–195	>1/hr	5	41	3.5–195
Central AHI	10	0.43	0–1.1	>1/hr	3	1.03	1–1.1
REM AHI	7	43.7	0–189	>1/hr	5	61.5	1–189
%TST REM sleep+	10	–	–	–	3	–	–
%TST SpO_2<90%	7	5.74	0–40	>10%	4	10.1	0.1–40
SpO_2 nadir	10	82	56–97	<90%	7	76.5	56–87
%TST CO2 >50 mm Hg	5	16.7	0–100	>25%	1	100	–
Peak CO2	7	49	42–60	>50 mmHg	3	56	52–60
Periodic limb movements	9	1.86	0–8	>5/hr	2	7.5	7–8

TST = total sleep time; ‡ Definition of abnormal in parentheses; * mean and range represents abnormal values; + %TST REM sleep were reported as “normal” or “reduced”.

data would suggest that this is unlikely to be successful in correcting OSA in this patient population. Unfortunately, patient compliance with nonsurgical treatments such as weight loss programs and continuous positive airway pressure ventilation is quite poor [22,23]. Data regarding ancillary diagnostic testing, namely cine magnetic resonance imaging and drug induced sleep endoscopy, were not available in this study sample, and reflects the previous lack of institutional availability of these tests. Information regarding the site of upper airway obstruction will be salient in future investigation, as BBS patients may be candidates for site-specific surgical interventions. No patients in the study cohort had undergone any other upper airway surgery for the treatment of OSA.

It is important to note that half the patients who presented to Otolaryngology did so before a diagnosis of BBS was made, and many did so without any other manifestations of the syndrome other than obesity and/or hearing difficulties. Due to delayed and variable onset of visual symptoms, the average age of diagnosis has been estimated to be approximately 9 years [1], which is consistent with the findings of this study. In the United States, the estimated prevalence of obesity ranges from 8.4 to 20.5% depending on age [24]. Thus, it would be challenging to select out undiagnosed BBS patients from nonsyndromic obese patients, despite the tendency for patients without a diagnosis of BBS to present at a younger age (60 months of age vs 101 months in patients with a known diagnosis of BBS). Though it may not always be possible to make a diagnosis of BBS at the time of initial presentation, this series highlights the importance of obtaining a pre-operative PSG in obese patients presenting with sleep disordered breathing, as recommended by the current American Academy of Otolaryngology – Head & Neck Surgery clinical practice guideline [25]. The limited longitudinal data in this study suggests that AHI will worsen with advancing age; hence obtaining baseline polysomnographic data is critical in following these patients over time and assessing treatment response. Moreover, these patients should be followed long-term to monitor weight gain and re-assess of emergence of SDB symptoms.

Notably, 8 of 20 patients were found to have hearing loss, either sensorineural and/or conductive. This rate (40%) is somewhat higher than a previous survey that demonstrated hearing loss prevalence to be 21% in BBS [1], though this may be reflective of selection bias. The majority of the 8 patients in the current study had conductive hearing loss from chronic otitis media, with only two having documented sensorineural hearing loss. These findings highlight the importance of routine hearing screening and otoscopic examination in these patients.

It was interesting that over half (29/53, 55%) of the patients with a ICD-10 and/or SNOMED-CT code for BBS had not been seen in Otolaryngology and/or Sleep Medicine clinic. This study was limited to patients seen by these two services and as such, one of the limitations of this study design is the potential for selection bias. Indeed, the decision to include only patients seen by Otolaryngology and/or Sleep Medicine services restricted the study population. While this increased the risk of selection bias, the study design was justified as patients seen outside the setting of an Otolaryngology/Sleep Medicine clinic (i.e. by Ophthalmology) would not have necessarily been screened for SDB. Thus, the absence of SDB symptoms documented in the chart would not necessarily reflect a true absence of symptoms. This was substantiated by an elicited history of SDB symptoms in 90% (18/20) in the study population, despite only 55% ($n = 11$) being referred for a question of SDB. In fact, what this highlights is that SDB has not generally been a principal consideration in healthcare providers who see these patients. Furthermore, no BBS patient who was not seen by Otolaryngology and/or Sleep Medicine underwent PSG testing at this institution, thereby limiting the amount of objective data that would have been extractable from this population. Finally, an ICD-10 and/or SNOMED-CT code for BBS in the electronic medical record does not represent a true diagnosis of BBS, as evidenced by the patient who was excluded after genetic testing. That said, accounting for all patients identified by the ICD-10/SNOMED-CT query, the most conservative estimate of OSA prevalence in this population would be 9.6% (5/52). Though, with an estimated obesity prevalence of up to 92% [6] and comparable BMIs in the included vs. excluded study population, one would suspect that OSA in many of these BBS patients remains undiagnosed.

The second limitation of this study pertained to PSG data obtained. This data was inconsistently reported, as the earlier studies predated institutional standardization of PSG reporting. This is evident in the data reported in Table 3, namely the percentage total sleep time in REM, hypoxia, and hypercapnia. Finally, there was a lack of longitudinal follow-up in the patient group. This was in part due to the international referral pattern of this hospital, but also highlights a need for ongoing follow-up in complex patients with OSA. Longitudinal data and a larger sample size will help to better elucidate the natural history of sleep disordered breathing as well as the treatment effect in these syndromic obese patients.

5. Conclusion

In summary, sleep disordered breathing is extremely common in BBS and this association is underreported. Consequently, the otolaryngologist plays an integral role in the management of these patients. All BBS patients should be routinely screened for symptoms of OSA. Polysomnography should be considered in all BBS patients with clinical features of OSA, in order to establish baseline disease severity as well as monitor treatment response. In counselling families, adenotonsillectomy as a cure for OSA must be recommended with caution. The long-term outcomes for these patients remain elusive, though the prevalence of obesity places these patients at risk for post-operative adverse outcomes as well as obesity hypoventilation syndrome. Because of this, long-term follow-up and ancillary testing for refractory OSA is of particular importance in this patient population.

Financial disclosure statement

The authors have no financial relationships relevant to this article to disclose.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

Contributors' statement

Drs. Yeung, Katwa, and Lee contributed to the conception and design of the study, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

Acknowledgements

None.

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