Sleep-Disordered Breathing in the Context of Pulmonary Hypertension in Pediatric Patients with Co-Morbid Conditions: Case Series and Review of the Literature

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Received: 23 Jan, 2018 | Accepted: 12 Apr, 2018 | Published: 18 Apr, 2018

Introduction

Pulmonary Arterial Hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterized by a progressive increase in pulmonary vascular resistance leading to right heart failure and death [1]. The definition for children with Pulmonary Hypertension (PH) is as follows: Mean Pulmonary Artery Pressure (mPAP) ≥ 25 mmHg, normal pulmonary capillary wedge pressure (≤ 15 mmHg) and an increased Pulmonary Vascular Resistance (PVR) [2].

Etiologies of PH are classified according to the latest nice classification system [3]. Sleep-disordered breathing (obstructive sleep apnea, hypoxemia and/or hypoventilation) is part of Group 3 PH, which addresses diseases of the respiratory system. Adult literature has addressed the association between sleep-disordered breathing and PH, and other disorders, which have prompted some to advocate for more aggressive screening with polysomnography and echocardiography [4].

One study treated patients with sleep-disordered breathing diagnosed with PH and receiving PH-specific medications and found improvement in 6 minute walk distances as well as systolic pulmonary artery pressures after treating with positive pressure ventilation or adenotonsillectomy with resolution of their sleep-disordered breathing symptoms [5]. In cases where PH is felt to be secondary to sleep-disordered breathing, previous reports in adults have found that treating sleep-disordered breathing resolves signs of PH [6,7]. Data regarding sleep disordered breathing in the context of pediatric PH is sparse. Recent registries have quoted that OSA is an infrequent cause of PH [8-10]. Data looking into other co-morbidities related to sleep-disordered breathing and PH is sparse as well.

The aim of this study was to help elucidate the prevalence of sleep-disordered breathing among children with PH by retrospectively analyzing all children with evidence of PH.
on echocardiograms at our center over a ten-year period. We also reviewed the literature and suggest a practical approach to evaluating these patients.

Data was retrospectively collected from patients aged 21 years or younger with ICD-9 diagnoses of Primary PH, Secondary PH, and congestive heart failure due to PH. Data was collected from January 2003 to March 2013 from one center, which served as an initial site of diagnosis, a referral site, and a heart and lung transplant center. Patients were diagnosed with PH from either echocardiogram and/or Right Heart Catheterization (RHC) reports confirming pulmonary hypertension (estimated pulmonary artery pressures > 25 mmHg based on indirect measurements on echocardiogram and increased pulmonary vascular resistance > 3 Woods Units on cardiac catheterization) from patient record review. Records of patients with PH were analyzed for evidence of sleep-disordered breathing based on baseline characteristics, echocardiographic data (most notably estimated right ventricular pressure from tricuspid regurgitant jet velocity and right ventricular changes) and data obtained from a polysomnogram (apnea-hypopnea index > five per hour, oxyhemoglobin saturations, end-tidal carbon dioxide, arousal index) if available, as this was retrospective data collection. Patients were included in the analysis if they met criteria for echocardiographic changes consistent with PH and evidence of sleep-disordered breathing on both echocardiogram and polysomnogram before and after an intervention ameliorating symptoms of sleep-disordered breathing as evidence from reported history or post-intervention polysomnogram.

Report of Cases

Three thousand seven hundred fifty-four patient records were reviewed and found to have a diagnosis of PH. After duplicates were removed, 1,613 (One thousand six hundred thirteen remained). Seven hundred thirty-one patients had elevated PAPs from January 1, 2003 to March 22, 2013 as per echocardiography and catheterization data. Twelve patients with PH were documented to have sleep-disordered breathing with an ICD-9 diagnosis and corresponding polysomnogram. Five patients had evidence of sleep-disordered breathing with corresponding echocardiograms evaluating evidence of PH before and after an intervention addressing the sleep-disordered breathing. Characteristics and parameters from polysomnogram and echocardiogram from all five patients are presented in table 1. Seven patients were eliminated due to no results from echocardiograms. One patient had central hypoventilation; three patients had no initial echocardiogram before polysomnogram or interventions and three patients had echocardiograms which did not show indirect evidence of PH.

Patient 1

The first patient with Trisomy 21 initially presented with pneumonia and night time snoring at fifteen years of age. He was then initiated on Continuous Positive Airway Pressure (CPAP) of 6 centimeters of water (cm H2O). An echocardiogram during this admission showed an estimated right ventricular systolic pressure (based on tricuspid regurgitant jet velocity) of 38.5 mmHg (mildly increased [11]). A polysomnogram one month later revealed an Apnea-Hypopnea Index (AHI) of 12.8/hour with an Arousal Index (AIr) of 14.4/hour. Oxyhemoglobin desaturation to 85% was also evident for the initial 2 hours with no support. Because of this, continuous positive airway pressure (CPAP) was titrated to a pressure of 12 cm H2O which resulted in a residual AHI of 0.5/hour with saturations above 90%. One year later, a repeat echocardiogram showed no evidence of PH.

### Table 1: OSA and PH Patients with Polysomnogram and PH on Echocardiography

| Patient | Age (years) | Sex | Comorbidity | BMI (kg/m²) | Total Sleep Time (min) | Sleep Efficiency (%) | Arousal Index (hr) | Stage N1 (%) | Stage N2 (%) | Stage N3 Sleep (%) | REM Sleep (%) | OAIH (#/hour) | AHI (#/hour) | Oxygen nadir (%) | TST saturation<90% | PH grade (all by echocardiogram)* | Intervention | PH at follow up |
|---------|-------------|-----|-------------|-------------|------------------------|----------------------|-------------------|--------------|--------------|------------------|--------------|---------------|--------------|----------------|----------------------|----------------|-----------------|
| Pt 1    | 15          | M   | Trn21       | 26.49       | 423                    | 92.2                 | 14.4              | 0.2          | 0.5          | 20.4             | 16.3         | 7.5            | 12.8          | 85              | 3.5                  | mild          | Normal         |
| Pt 2    | 5           | M   | PWS         | 41.85       | 352                    | 83                   | 9.7               | 0.3          | 0.3          | 25.4             | 16.2         | 3.1            | 29.2          | 62              | 40.2                 | mild          | Normal         |
| Pt 3    | 15          | M   | PWS         | 85.29       | 401.5                  | 91.4                 | 9.7               | 0.3          | 0.3          | 14.4             | 10.3         | 5.2            | 5.4           | 62              | 37.6                 | mild          | BiPAP, AT       |
| Pt 4    | 0.8         | M   | Trn21       | N/A         | 251.5                  | 61.1                 | 8.5               | 2.9          | 0.5          | 27.8             | 2.2          | 2.4            | 16.7          | 87              | 16.6                 | mod           | BiPAP, AT       |
| Pt 5    | 17          | M   | OI          | 37.82       | 251.5                  | 65                   | 2.4               | 4.1          | 7.0          | 17.2             | 10.4         | 2.2            | 22.2          | 60              | 1.6                  | mod           | BiPAP          |

**Abbreviations:** M: Male; OI: Osteogenesis Imperfect; Trn21: Trisomy 21; PWS: Prader-Willi Syndrome; BMI: Body Mass Index; REM: Rapid Eye Movement; OAIH: Obstructive Apnea-Hypopnea Index; N/A: Not performed; AHI: Apnea-Hypopnea Index; PH: Pulmonary Hypertension; mod: moderate; CPAP: Continuous Positive Airway Pressure; BiPAP: Bilevel Positive Airway Pressure; AT: Adenotonsillectomy; f/u: follow up. + split sleep study performed; *mild PH indicates estimated RVSP of 35 mmHg to 45 mmHg and moderate PH indicates estimated RVSP of 45 mmHg to 55 mmHg [11].

**Citation:** Singh A, Ingram D, Muzumdar H (2018) Sleep-Disordered Breathing in the Context of Pulmonary Hypertension in Pediatric Patients with Co-Morbid Conditions: Case Series and Review of the Literature. J Sleep Disord Med Care 1(2): dx.doi.org/10.16966/2577-882X.106
and a repeat polysomnogram showed an AHI of 12.8/hr, with desaturations of 83% with no support, but residual AHI was 0 with the saturation nadir of 94% on a CPAP of 11 cmH₂O. This patient, as per report, remains compliant with CPAP during sleep.

**Patient 2**

This patient was initially seen as an inpatient at four years of age. He had a history of Prader-Willi Syndrome (PWS), sleep-disordered breathing and PH. An echocardiogram during his hospitalization demonstrated indirect findings of PH with Right Ventricle (RV) hypertrophy and dilation, but no tricuspid regurgitant jet velocity to accurately assess right ventricular systolic pressure. A polysomnogram showed that with bi-level positive airway pressure (BiPAP) starting at an inspiratory pressure of eleven and expiratory pressure of five (11/5 with 2 liters per minute of supplemental oxygen via mask), his AHI was 29.2/hr, and ArI was 9.7/hr. Oxyhemoglobin saturations for this portion of the study averaged 89% and was >89% for 58.9% of the time and between 80-89% for 36.5% of sleep time. End-tidal carbon dioxide also remained elevated above 50 Torr for at least twenty percent of the night. BiPAP was then increased to 24/7 with 3 liters per minute of supplemental oxygen. The resulting AHI was 0.5/hr and ArI was 1.5/hr. After an adenotonsillectomy was performed, the patient was discharged home with BiPAP. Echocardiograms two and six years later demonstrated no evidence of PH as the patient was still using BiPAP and supplemental oxygen. The patient also reported losing forty-four pounds, but was then lost to follow up with no repeat polysomnogram performed.

**Patient 3**

Patient three was diagnosed with PWS and initiated on BiPAP at five years of age for evidence of sleep-disordered breathing. Initial documentation was present when he was evaluated by a pulmonologist at eleven years of age with no respiratory symptoms reported. Whether or not he was still in BiPAP was not reported. An echocardiogram showed an estimated right ventricular systolic pressure at thirty-six mmHg; however, the TRJV was not well visualized and was reported to have been underestimated. He began developing symptoms of sleep-disordered breathing so a polysomnogram with BiPAP titration occurred at fourteen years of age. This polysomnogram with BiPAP settings of 26/10 with 2 L/min of supplemental oxygen showed an ArI of 8.7/hr and an AHI of 5.4/hr. Oxyhemoglobin saturation was >89% during 58.3% of sleep time and from 80-89% during 34.2% of sleep time. This patient has not followed up with his PH and his OSA status remains unknown as there have been no follow up testing.

**Patient 4**

A patient with Trisomy 21, infantile spasms, gastro-esophageal reflux and congenital subglottic stenosis had a normal initial polysomnogram which was performed at ten months of age. One year later, a repeat polysomnogram (performed due to increased symptoms of sleep-disordered breathing) revealed an AHI of 16.7/hr with an ArI of 2.4/hour which improved with CPAP of 6 cm H₂O. An adenotonsillectomy was performed six months later and an echocardiogram performed at that time showed increased estimated RVSP as high as forty-seven mmHg, based on tricuspid jet velocity. At a follow up appointment two months later, an echocardiogram was normal and showed no indirect evidence of pulmonary hypertension while a repeat polysomnogram showed a decreased apnea-hypopnea index with no support.

**Patient 5**

Patient five had a history of Osteogenesis Imperfecta (OI) and was admitted for a bone fracture at seventeen years of age. While sleeping during his hospitalization, hypoxemia was noted and an echocardiogram showed mildly elevated RVSP by tricuspid regurgitant jet velocity (thirty-three mmHg), and pulmonary artery acceleration time estimated pulmonary artery pressures to be fifty mmHg. A polysomnogram then showed evidence of sleep-disordered breathing so BiPAP 12/4 was implemented. At a two-year follow up, the patient was tolerating BiPAP with infrequent sleep-disordered breathing symptoms; however no repeat echocardiogram or polysomnogram has been performed to confirm objective improvement in PH or OSA.

**Discussion and Conclusion**

This small case series of patients with concomitant PH and sleep disordered breathing yielded five male patients having indirect evidence of PH on echocardiogram, whether it was before or after a polysomnogram. Two patients were diagnosed with Trisomy 21 and two patients with PWS. After intervention (non-invasive positive pressure ventilation and/or adenotonsillectomy), those who underwent post intervention echocardiogram demonstrated improvement in PH. Patient two had no post-intervention polysomnogram while patients three and five had no post intervention echocardiogram or polysomnogram for objective confirmation or resolution.

The relationship between PH and sleep disordered breathing in children remains not fully understood, perhaps due its infrequency in this population, or lack of awareness. A recent meta-analysis did publish moderate evidence of right heart changes in children with obstructive sleep apnea [12]. Our findings indicate that comorbidities exist in association with sleep-disordered breathing and PH, particularly in syndromes that predispose children to sleep-disordered breathing.

Based on recent publications from registries and databases of children with PH [8-10] the prevalence of sleep-disordered breathing in children with PH is variable, as it is in adults (between 17-70%) [13]. Sleep-disordered breathing also occurs in children with other pulmonary processes that cause PH, such as bronchopulmonary Dysplasia (BPD) [14].

The prevalence of PH in Trisomy 21 patients with Congenital Heart Disease (CHD) has been estimated at thirty to fifty
percent [15]. It is recommended to evaluate children with Trisomy 21 for congenital heart disease or signs of PH with an echocardiogram, even without signs or symptoms [15], and evaluate for pulmonary disease. Numerous factors in children with Trisomy 21 can increase the likelihood of airway disease; hypoplasia of facial and oropharyngeal structures as well as hypotonia increasing the likelihood of upper airway obstruction. One report investigated four infants with Trisomy 21 who developed OSA and cor pulmonale from chronic upper airway obstruction. Relieving the obstruction (three out of the four patients improved after tracheostomy) also relieved cor pulmonale [16].

Children with trisomy 21 may benefit from a multidisciplinary approach with providers in cardiology, otolaryngology, and pulmonology. In one report, children with trisomy 21 and sleep-disordered breathing were evaluated for elevated estimated PAPs on echocardiogram (using tricuspid regurgitant jet velocity) and also underwent electrocardiogram, chest radiography, cardiac catheterization, polysomnography and bronchoscopy (if indicated) to evaluate for upper airway obstruction [15].

In our examples of patients with trisomy 21 and PH, positive pressure ventilation and adenotonsillectomy normalized indirect findings on echocardiogram. These patients did not undergo a cardiac catheterization, as per previously cited recommendations [15]. This raises the issue of whether or not these patients with sleep-disordered breathing and comorbidities need to be evaluated earlier and more thoroughly when evaluating for PH.

There have been no known reports of patients with PWS and sleep-disordered breathing in the context of PH, but rates of sleep-disordered breathing among children with PWS range from 44% to 100%, secondary to several factors including craniofacial structure, obesity, and hypotonia. One review quoted the prevalence of sleep-disordered breathing in PWS children was 79.9%, with 53% having mild OSA and 22% and 25% having moderate and severe OSA, respectively [17]. This review found that 46.7% of patients with PWS and OSA had normalized AHI following surgical intervention (adenotonsillectomy), which suggests that repeat polysomnogram should be performed to assess for residual disease [17]. It is also reasonable that for patients with PWS and OSA with PH, we would recommend a post-intervention echocardiogram and polysomnogram.

In our case series, all patients were male. The review cited above noted that of the nine studies examined (and reported gender), seventy-four patients had symptoms of sleep-disordered breathing and forty-three were male (58%) [17]. Our two male patients with PWS and OSA were four and five years of age at the time of evaluation. The prior review noted no change in OSA prevalence in patients with PWS across four age groups (≤ 2 years (89%), >2 to ≤ 7 years (89%), >7 to ≤ 14 years (86.5%) and >14 to ≤ 18 years (76.2%) [17]. Our two patients with PWS were obese with body mass indices (BMI) of forty-one and eighty-five, respectively which contributed to their sleep-disordered breathing. The impact of weight was also reported in the above analysis where three studies measured BMI and showed an increase in OSA with greater BMI and BMI percentile (normalized for age and gender) [17].

The incidence of OSA in patients with co morbidities such as trisomy 21 and PWS is increased compared to that of the general population due to a variety of factors, including increased prevalence of obesity, craniofacial features, and hypotonia. Our study looked at pediatric patients already diagnosed with PH by indirect evidence on echocardiogram and retrospectively searched for a diagnosis of OSA. In contrast, the review described above began with patients with PWS and sleep-disordered breathing, but did not evaluate for PH.

Several studies have described the relationship between sleep-disordered breathing and increased pulmonary artery pressures. One case series evaluated four patients with adenotonsillar hypertrophy who developed cor pulmonale. These patients underwent non invasive evaluations and underwent adenotonsillectomy, and echocardiograms and radio nucleotide angiography normalized [18]. Another study investigated twenty-six children with sleep disordered breathing presenting with cor pulmonale. Eleven children had OSA and cor pulmonale as seen by right ventricular hypertrophy on echocardiogram and cardiomegaly on chest radiograph. Four patients were treated with adenotonsillectomy and the remainder underwent tracheostomy placement with no further evidence of cor pulmonale [19]. The five patients in our case series improved with adenotonsillectomy and/or noninvasive positive pressure ventilation and did not require tracheostomy placement.

Yilmaz et al. [20] investigated mean Pulmonary Artery Pressures (mPAP) in fifty-two children with adenotonsillar hypertrophy and found a statistically significant increased baseline mPAP when compared to thirty-three control subjects (study group mPAP 23.13 ± 7.68, control group mPAP 16.11 ± 7.24, p<0.05). After patients underwent adenotonsillectomy, there was a significant decrease in mPAP to 17.00 ± 6.99, p<0.05). Of note, the mPAP value of 23.13 does not meet the strictest definition of PH (mPAP of twenty-five mmHg or greater). The authors of this study defined PH as having estimated mPAP (as estimated by Doppler echocardiogram) of twenty mmHg or greater [20].

Other studies have looked at children with sleep-disordered breathing and evidence of PH on echocardiogram and have found improved parameters after addressing OSA [21,22], but questions remained regarding the tools used to assess for OSA and PH.

Our study's retrospective design is inferior to a prospective study for determining accurate prevalence estimates of OSA in children with PH, as our low prevalence contradicts other...
studies and common knowledge regarding the relationship between sleep-disordered breathing and PH. This may have been due to missing data due to the retrospective design of the study. In addition, many children could not be included in analysis due to missing data, including additional parameters to confirm a diagnosis of PH, which may include right and left ventricular dimensions, tricuspid annular systolic excursion/velocity, intraventricular septal flattening. Our sample size is small, which precludes evaluating for additional relationships between comorbidities and sleep-disordered breathing and PH as well as limiting its generalizability. Finally, the true prevalence of OSA among children with PH is underestimated given that not all children had screening polysomnogram performed.

This case series highlights the important interrelationships between PH, sleep-disordered breathing, and underlying medical comorbidities. Our findings suggest that children with PH and either Trisomy 21 or PWS are at increased risk for OSA, which is common medical knowledge. While optimal screening and management algorithms remain to be fully elucidated, screening for sleep-disordered breathing in children with PH and comorbidities such as Trisomy 21 and PWS with overnight polysomnogram and echocardiography may identify and promptly treat an underlying cause of PH while avoiding worsening morbidity and mortality. More rigorous studies looking at various echocardiographic parameters done in conjunction with polysomnography pre and post-intervention with a larger sample size should be performed in order to define ages to begin screening.

References