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Characteristics of sleep apnea in infants with Pierre-Robin sequence: Is there improvement with advancing age?

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ABSTRACT

Objectives: To investigate changes in obstructive sleep apnea (OSA) and central sleep apnea (CSA) in infants with Pierre-Robin sequence (PRS) with advancing age and after mandibular distraction osteogenesis (MDO).

Methods: Charts from 141 infants with PRS that presented to our tertiary-care children's hospital between 2005 and 2015 were retrospectively reviewed. Forty-five patients received a polysomnogram (PSG) prior to surgical intervention. Linear regression was utilized to compare age at pre-operative PSG with apnea–hypopnea index (AHI), obstructive apnea–hypopnea index (OAHI), and central apnea index (CAI). We then analyzed a subset of 9 patients who underwent MDO with pre- and post-operative PSGs. Wilcoxon signed-rank test was utilized to examine differences in pre- and post-operative OSA and CSA scores.

Results: Forty-five patients received pre-operative PSGs. Of these, 80.0% demonstrated severe sleep apnea (AHI $\geq$ 10), 68.9% demonstrated severe obstructive sleep apnea (OAHI $\geq$ 10), and 55.6% demonstrated central sleep apnea (CAI $\geq$ 1). There was no significant pattern of decrease in AHI, OAHI, and CAI with increased age up to 1 year. Among the 9 patients who underwent MDO with pre- and post-operative PSGs, significant reductions in AHI, OAHI, CAI, and percentage of total sleep time with arterial oxygen saturation (SaO_2) <90% and significant increases in SaO_2 nadir were identified after MDO.

Conclusions: Contrary to previously examined literature in non-PRS patients, we did not find a decreased severity of central or obstructive sleep apnea with advancing age. Infants with PRS who underwent MDO demonstrated significant decreases in both obstructive and central apnea indices.

1. Introduction

In 1934, a French stomatologist, Pierre Robin, first described a constellation of physical exam findings, which included micrognathia and/or retrognathia, glossoptosis, and possible cleft palate [1]. He also noted problems with upper airway obstruction, feeding, and growth in these children. That sequence now bears his name, and even now, it is a difficult and morbid condition to treat. The incidence of Pierre-Robin sequence (PRS) in the United States (U.S.) is reported to be 1/3120 live births [2]. It has been estimated that approximately 50% of PRS cases are syndromic rather than isolated [3,4]. The most common syndromes are Stickler syndrome, velocardiofacial syndrome, and Treacher-Collins syndrome [3–5].

The overall mortality rate in PRS infants is estimated at 16.6% in the U.S. [6]. The highest mortality rates in this PRS population were found to be in syndromic infants with cardiac anomalies (39%), central nervous system anomalies (33%), and anomalies in two or more distinct organ systems (24%); in contrast, only 1.1% of the deaths were airway obstruction-related [6]. Nevertheless, upper airway obstruction in PRS infants results in high morbidity [7].

Classically, most infants with PRS were thought to develop upper airway obstruction immediately after birth, which was exacerbated during sleep [7]. However, more recent studies have noted a high prevalence of late-onset upper airway obstruction that is missed during the initial neonatal period [8,9]. Up to 70% of PRS infants did not present with upper airway obstructive signs until 24 to 51 days of age in one study, indicating that obstruction

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may insidiously develop over the first two months of life [8]. It is estimated that up to 85–100% of PRS infants have concurrent sleep-disordered breathing, the majority of which is OSA [9,10]. Due to the phenotypic heterogeneity of PRS, there is a need for close prospective monitoring and objective diagnostic techniques, namely PSG, to detect sub-clinical upper airway obstruction [11].

The presence, natural progression, and response to treatment of central sleep apnea (CSA) in the PRS population have not been extensively studied. CSA is a pause in breathing for at least 20 s or the duration of 2 breaths in the absence of inspiratory effort and is associated with an arousal or a greater than 3% oxygen desaturation [12]. This represents a disturbance of the central nervous system's ventilatory control rather than an anatomically obstructive event.

Various invasive and non-invasive treatment modalities exist that treat upper airway obstruction and OSA but not necessarily CSA. Cote et al. reviewed various non-invasive treatment options, including prone or side positioning, nasopharyngeal airway (NPA), and continuous positive airway pressure (CPAP), as well as invasive surgical options, including tracheostomy, tongue–lip adhesion (TLA), subperiosteal release of the floor of the mouth, and mandibular distraction osteogenesis (MDO) [13]. Severe OSA and respiratory distress are likely to be refractory to non-invasive treatment. While NPA placement has been shown to be effective in treating OSA in PRS patients, it is required for a prolonged period of time for therapeutic effect [14]. Persistent airway obstruction despite prone positioning or NPA use is an indication for surgical intervention [13]. Historically, the standard surgical option for patients with severe or refractory OSA was tracheostomy; however, it is costly, has a high morbidity, and can be fatal [15]. Newer surgical options, particularly MDO, offer promise for avoiding tracheostomy or accelerating decannulation in these infants [16,17]. MDO works by slowly advancing the mandible after an initial osteotomy allowing bone and soft tissue growth while advancing the patient's base of tongue [18]. Patients with one level of airway obstruction at the tongue base are ideal candidates for MDO while those with multiple or other sites of airway obstruction are less likely to respond to this treatment [19].

While MDO has been demonstrated to improve OSA, its effect on CSA has not been reported [13,17,19]. The objectives of our study are to analyze the natural progression of OSA and CSA with postnatal age and to determine and quantify both OSA and CSA responses to MDO in PRS infants.

2. Methods

A retrospective review of patients with PRS who presented from 2005 to 2015 to our tertiary care children's hospital was conducted. Institutional review board approval was obtained from the University of Pittsburgh Medical Center prior to initiation of this project. Suitable patients with the clinical diagnosis of PRS were identified from the clinical database of our Cleft-Craniofacial Center, which is maintained by the Division of Pediatric Plastic Surgery. The institution's protocol for newly diagnosed or transferred patients with PRS begins with clinical examination and bedside flexible fiberoptic nasopharyngolarygoscopy to assess airway patency with supine positioning. Those with suspected sleep apnea who can tolerate either supine or lateral positioning for the study are ordered a PSG in order to assess their burden of sleep apnea, both obstructive and central.

Infants who received a PSG before the age of 1 year and before any surgical airway intervention, including tracheostomy, TLA, subperiosteal release of the floor of the mouth, MDO, supraglottoplasty, tonsillectomy, adenoidectomy, palatoplasty, and hyoid suspension, were included in this study. For infants with more than one pre-operative PSG, the earliest PSG was used. Medical information for these patients was identified, reviewed and recorded. All data were entered into a HIPAA-compliant electronic database.

Patient age, sex, gestational age at birth, birth weight, pre-operative airway status, and oxygen requirements were recorded. Pre-operative and post-operative PSG data included apnea–hypopnea index (AHI), obstructive apnea–hypopnea index (OAHI), central apnea index (CAI), percentage of total sleep time (TST) with arterial oxygen saturation (SaO_2) below 90%, SaO_2 nadir, peak carbon dioxide (CO_2) saturation, and the presence of CO_2 retention. History of MDO and age recorded as days-of-life (DOL) at MDO hardware implantation were also documented. All PSG data were defined and scored according to the American Academy of Sleep Medicine (AASM) scoring manual [12]. Sleep apnea, OSA, and CSA were, respectively, defined as AHI, OAHI, and CAI scores greater than 1 with further categorization into mild (1–5), moderate (5–10), and severe (>10). End tidal CO_2 levels were measured transcutaneously, and retention was defined as CO_2 levels higher than 50 mm Hg for at least 25% of TST. All pre- and post-operative PSGs were performed with the Somnostar z4 Sleep System (Carefusion, San Diego, California) at a dedicated pediatric sleep laboratory in our tertiary care hospital in accordance with the AASM 2007 guidelines [12]. All events, including respiratory data, were scored and interpreted using the Somnostar 9.1G diagnostic platform (Carefusion). Physicians board-certified in sleep medicine interpreted all PSGs in this study.

Scatter plots comparing age at pre-operative PSG with AHI, OAHI, and CAI were generated. Since previous literature has noted a spontaneous decrease in CAI and number of apneic episodes with increasing postnatal age before the end of the second month of life [20,21], we performed a sub-analysis of our study population by limiting pre-operative PSGs to those that were conducted before two months of age (DOL 60) and creating scatter plots accordingly. Via Stata 14® (StataCorp, College Station, Texas), simple linear regression was conducted on all scatter plots to calculate the coefficient, R-square (r^2), adjusted r^2, and p-value. A p-value <0.05 was considered significant.

Next, a sub-analysis of patients who did not undergo airway surgical intervention and had multiple PSGs was performed. The same PSG indices as noted above were analyzed. Since these indices of the new study population were not normally distributed, they were presented as medians (range). The difference between the initial and follow-up PSG parameters was calculated, and the Wilcoxon signed-rank test was utilized to assess the significance of the PSG differences for each parameter.

The last part of the study was a separate sub-analysis of our population that only included patients who received MDO and had both pre-operative and post-operative PSGs. The same PSG indices were analyzed and presented as medians (range), and each patient was categorized as having no, mild, moderate, or severe sleep apnea, OSA, and CSA based on the pre-operative and post-operative PSGs. The difference between the pre-operative and post-operative PSG parameters was calculated, and the Wilcoxon signed-rank test was utilized once again to assess the significance of the PSG differences. A one-tailed test was utilized to test if MDO is associated with a reduction in the number of obstructive and central apneic episodes. A p-value <0.05 was considered significant.

3. Results

A total of 141 patients with PRS were investigated in this study; 45 received a pre-operative PSG before the age of 1 year. Of the 45 patients, 62.2% ($N = 28$) were male and 37.8% ($N = 17$) were female, 88.9% ($N = 40$) Caucasian, 6.7% ($N = 3$) African–American and 4.4% ($N = 2$) of unknown race. Median gestation age and mean birth