Original Article

Polysomnographic findings in infants with Pierre Robin sequence

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Abstract:

INTRODUCTION: Pierre Robin sequence (PRS) is characterized by the triad of micrognathia, glossoptosis, and upper airway obstruction. It is commonly associated with the secondary cleft palate. Infants with PRS commonly have sleep-disordered breathing (SDB); including obstructive sleep apnea (OSA) as well as central sleep breathing abnormalities that are present from infancy.

AIM OF THE STUDY: Evaluate the prevalence and severity of SDB in infants with PRS using polysomnography (PSG).

SETTINGS AND DESIGN: We retrospectively reviewed the sleep laboratory database at The Hospital for Sick Children, Toronto, during the period of May 2007 to March 2016.

STATISTICAL ANALYSIS: Comparisons of PSG data were made between the OSA and non-OSA group using the Student's t-test for age and body mass index, Wilcoxon signed ranks test for the continuous PSG data and Chi-squared test for the categorical variables.

METHODS: Patients with PRS were identified and their initial PSG was selected for this study. The main indication for referral was ongoing concerns regarding OSA symptoms.

RESULTS: A total of 46 patients (28 females) were included with a mean age (±standard deviation) of 0.8 (±0.3) year. Twenty-two out of 46 (47%) had evidence of OSA of which 10 had mild, 3 had moderate, and 9 had severe OSA. The PRS infants with OSA were younger than the non-OSA group. Significant correlations were found between desaturation and arousal indices with obstructive apnea–hypopnea index.

CONCLUSION: This retrospective chart review confirms a high prevalence of OSA in this population. Prospective longitudinal studies are needed to evaluate the outcomes of OSA in PRS population.

Key words:

Infants, obstructive sleep apnea, sleep-disordered breathing, Pierre Robin sequence

Pierre Robin sequence (PRS) is characterized by the triad of micrognathia, glossoptosis, and upper airway obstruction.[1] It is commonly associated with the secondary cleft palate, but other phenotypes have also been described.[2] This is usually secondary to failure of fusion of palate due to mandibular hypoplasia and glossoptosis during embryogenesis.[3-5] It is estimated that the PRS affects 1 child for every 8500 births.[6] The sequence can be isolated or associated with other syndromes.[4]

Sleep-disordered breathing (SDB) is a spectrum of sleep-related breathing abnormalities that include obstructive sleep apnea (OSA), central sleep apnea (CSA), and nocturnal hypoventilation. The most common sleep disorder seen in children is OSA.[7] CSA and nocturnal hypoventilation are less common than OSA. The prevalence of OSA is around 2%–6% in pediatric age group.[8-10] Children with OSA are at high risk for failure to thrive, poor neurocognitive outcomes, and cardiovascular dysfunction which are secondary to intermittent chronic hypoxia and sleep fragmentation.[11-14] Overnight polysomnography (PSG) is the current gold standard for diagnosis of SDB.[15]

Children with PRS are at risk of SDB that can be present from infancy. The upper airway obstruction caused by different mechanisms including anatomical abnormalities and mechanical collapse of the pharyngeal wall,[3,16] as well as maxillary hypoplasia.[17] Other entity frequently seen in PRS; gastroesophageal reflux disease (GERD) during infancy may also worsen the degree of OSA.[18]

In children with PRS, OSA has been described in several case reports and series. However, most

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of these studies are based on clinical assessment. Few of these studies described the prevalence using PSG[19-25] with only two cross-sectional studies that described the OSA in PRS infants using the American Academy of Sleep Medicine (AASM) scoring criteria.[24,25]

There are many treatment options for these patients including surgical and nonsurgical therapies but to date, there is no consensus in the literature to the best therapeutic approach. However, many institutions have adopted the personalized algorithms to manage their patients with PRS.[26] Treatment options include prone positioning,[27-29] nasopharyngeal tube (NPT) insertion,[30,31] palatal reconstruction,[32] tongue-lip adhesion (TLA),[27,33] and mandibular distraction osteogenesis (MDO)[34,35] which were used to avoid tracheostomy.[36]

In relation to the paucity in the literature in regards to prevalence and predictors of OSA,[37] the aim of this study was to evaluate this in a referred population.

Methods

We retrospectively reviewed the sleep laboratory database at The Hospital for Sick Children, Toronto, during the period of May 2007 to March 2016. The study protocol was reviewed and approved by The Hospital for Sick Children's Research Ethics Board (number: 1000046034). We identified infants <2 years of age with a diagnosis of PRS that underwent baseline overnight PSG. Patients with previous cleft palate repair and previous or current history of tracheostomy were excluded. We also excluded patients with cyanotic congenital heart disease and chronic lung disease managed by oxygen therapy. Demographics, anthropometrics (body mass index [BMI] was calculated as weight [kg]/height [m]^2), and PSG variables were abstracted from the health-care record.

The patients underwent standard overnight PSG using a Natus (Natus Medical Incorporation, San Carlos, CA, USA) system. PSG measurements included electroencephalogram, electro-oculogram, submental electromyogram (EMG), and bilateral anterior tibialis EMG. Respiratory measurements included chest wall and abdominal movement using chest wall and abdominal belts; nasal airflow measurements using nasal air pressure transducer and oronasal thermal sensor, oxygen saturation (SaO_2) (Masimo, Irvine, CA, USA); transcutaneous carbon dioxide and/or end-tidal carbon dioxide.

The PSGs were scored using the AASM acquisition and scoring standards.[38] All PSG studies were interpreted by pediatric sleep physicians at The Hospital for Sick Children. An obstructive apnea event was scored when airflow dropped at least 90% from the baseline with chest and/or abdominal motion throughout the entire event; the duration of which was at least a minimum of two baseline breaths. A hypopnea event was scored when airflow dropped at least 30% from baseline, the duration of which was at least a minimum of two baseline breaths. Central apnea event was defined as the absence of chest and/or abdominal movement associated with a cessation of airflow for more than 20 s or lasting more than 2 baseline respiratory cycles if it was associated with an arousal, an awakening or an oxygen desaturation of at least 3%. The desaturation index was calculated on the basis of the number of oxygen desaturation events ≥3% during sleep divided by the total sleep time. OSA was defined as obstructive apnea–hypopnea index (OAHI) ≥2 events/h of sleep. Mild OSA: OAHI ≥2 and <5 events/h of sleep, moderate OSA: OAHI ≥5 and <10 events/h of sleep, and severe OSA: OAHI ≥10 events/h of sleep. A significant CSA was defined as central apnea index of ≥5 events/h of sleep.[39]

Age and BMI were reported as the mean and standard deviation (SD). PSG data were reported as median with interquartile range for continuous variables and frequencies for categorical variables. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Comparisons of PSG data were made between the OSA and non-OSA group using the Student's *t*-test for age and BMI, and Wilcoxon signed ranks test for the continuous PSG data and Chi-squared test for the categorical variables. Univariate logistic regression analysis was used to determine the effect of the following variables to predict OSA: age, gender, BMI, presence of an underlying genetic defect, previous intervention for OSA, and prone position sleep percentage time. If the effect was significant for any predictor, a multivariable logistic regression for these variables together will be used in one model. Correlations between OSA and arousals and desaturations indices were evaluated using Spearman's correlation coefficient. A $P < 0.05$ was considered significant.

Results

From May 2007 to March 2016, a total number of 46 PRS infants (28 females) were identified for baseline assessment. The mean age (±SD) was 0.8 (±0.3) year. The data for these 46 patients are summarized in Table 1.

Overall 22 out of 46 patients had evidence of OSA. Of those, 10 were mild, 3 moderate, and 9 had severe OSA. There were four children who had an underlying significant CSA all they ranged between 5–10 events/h and no intervention recommended. The most common genetic abnormalities associated with those infants were Stickler syndrome constituting 60% of syndromic patients. Most of these infants had a brain ultrasound to rule out any structural abnormality, and it was abnormal in 10 infants who underwent a brain magnetic resonant imaging. The results were abnormal in eight out of ten infants. One child had Chiari malformation that required surgical decompression. Other findings were posterior fossa abnormalities, small posterior fossa without Chiari malformation, complex right temporal cyst, tiny lesion in the left thalamus, thinned corpus callosum, abnormal signal intensity, and microcephaly. There were 15 infants who had interventions to treat SDB before their first PSG. Those were: NPT ($n = 9$), TLA ($n = 4$), and MDO ($n = 2$). There were 27 infants who had clinical evidence for GERD, and they were initiated on antireflux treatment prior to the PSG.

From a demographic perspective, OSA group was younger than non-OSA group ($P = 0.009$). Comparisons of PSG variables between OSA and no OSA infants are summarized in Table 2. Prone position was associated with less respiratory events ($P = 0.001$). There were statistically significant difference in arousals index ($P = 0.001$), desaturations index ($P = 0.004$), and SaO_2 nadir ($P = 0.003$) between two groups. Other variables showed no significant differences.

By using univariate regression analysis, only the age was significant in OSA prediction ($P = 0.02$); however, there was no significant prediction in the multivariable regression model. The correlation between overnight oximetry and PSG showed that the desaturations index correlated with the OAHI ($r = 0.64$, $P < 0.0001$). There was a significant correlation between the arousal index and the OAHI ($r = 0.64$, $P = 0.004$).

Table 1: Baseline and polysomnography data of Pierre Robin sequence infants

Patient characteristic and PSG variables (*n*=46)*	Baseline PSG
Age (years), mean±SD	0.8±0.3
BMI, (kg/m^2), mean±SD	16.8±2.2
Male:female	18:28
TST (min)	403.7 (351.0-433.5)
Sleep efficiency (%)	83.8 (74.1-91.3)
Sleep latency (min)	7.3 (0.2-23.8)
REM latency (min)	48.0 (27.5-75.4)
Stage 1 TST (%)	2.5 (1.25-6.6)
Stage 2 TST (%)	50.3 (42.8-62.0)
Slow wave sleep TST (%)	23.6 (10.9-32.5)
REM TST (%)	20.4 (13.6-29.9)
Prone (%)	10.7 (0-46.5)
Arousals, (total index)	10.1 (6.7-15.1)
Mean sleep SaO_2 (%)	98 (96-99)
Minimum SaO_2 (%)	82 (77-86)
Peak CO_2, (mmHg)	49 (44-55)
Desaturations index	2.6 (0.9-6.8)
OAHI	1.91 (0.4-5.9)
CAI	1.5 (0.6-3.0)

*Unless otherwise specified all data were reported in median with IQR for continuous variables. IQR = Interquartile range, SD = Standard deviation, BMI = Body mass index, CAI = Central apnea index, OAHI = Obstructive apnea-hypopnea index, PSG = Polysomnography, PRS = Pierre Robin sequence, REM = Rapid eye movements, SaO_2 = Oxygen saturation, TST = Total sleep time

Discussion

To our knowledge, this is the largest review evaluating the prevalence of OSA in PRS infants with formal full PSG using the AASM scoring guidelines. As previously reported, we found that the prevalence of OSA in PRS infants was high (47%). There were several methods to estimate the severity of SDB. Clinical symptoms like snoring do not correlate clinically with the severity of OSA in cleft palate population including PRS.[25] Furthermore, a patient with CSA may be asymptomatic and only detected by formal overnight PSG as shown in our study. Bravo *et al.* have previously proposed that a video-nasopharyngoscopy can be used as an alternative to PSG to assess for the severity of SDB in PRS infants.[22] Other methods such as using overnight oximetry,[40] maxilla-mandibular discrepancy, and jaw index have been used for the assessment of SDB.[41] In our paper, we used the gold standard PSG with AASM scoring criteria to estimate the prevalence of SDB.

The prevalence of SDB in PRS varied in the literature. In two early studies by Freed *et al*.[42] and Bull *et al*.,[19] they did not define the scoring methods. Moreover, old studies used a significant apnea if >15 s and/or heart rate dropped below 80 beats per minute or saturation <85% and OAHI >2/h.[20] A small study showed that only one child of 7 (14%) studied by overnight PSG has the evidence of SDB.[43] Another study using AASM scoring criteria and OSA defined as an apnea–hypopnea index >1 showed a high prevalence of SDB in this population estimated up to 85%.[24] Others reported 39 infants admitted to Neonatal Intensive Care Unit showed that all infants had SDB.[44] In that study, the respiratory event was significant

Table 2: Baseline and polysomnography data of obstructive sleep apnea and nonobstructive sleep apnea infants

Patient characteristic and PSG variables*	OSA (*n*=22)	Non-OSA (*n*=24)	*P*§
Age (years), mean±SD	0.7±0.3	0.9±0.1	0.009
BMI (kg/m^2), mean±SD	16.3±2.2	17.3±2.2	0.21
Male:female	9:13	9:15	0.81
TST (min)	411.7 (359.5-471.0)	391.7 (344.5-415.7)	0.12
Sleep efficiency (%)	86.4 (78.5-92.8)	79.3 (73.7-90.0)	0.25
Sleep latency (min)	4.4 (0.2-12.6)	17.6 (0.35-31.2)	0.23
REM latency (min)	45.6 (27.0-72.5)	66.0 (30.8-115.5)	0.28
Stage 1 TST (%)	2.5 (1.4-8.3)	2.6 (0.9-6.3)	0.79
Stage 2 TST (%)	45.8 (27.0-72.5)	53.1 (45.7-68.4)	0.07
Slow wave sleep TST (%)	27.0 (19.0-42.6)	18.6 (10.6-29.1)	0.06
REM TST (%)	21.3 (15.0-36.6)	19.6 (8.7-25.6)	0.23
Prone of TST (%)	0 (0-30.8)	37.4 (1.1-55.6)	0.02
Arousals (total index)	13.2 (9.6-17.9)	7.8 (4.3-11.2)	0.001
Mean sleep SaO_2 (%)	98 (96-99)	98 (97-99)	0.78
Minimum SaO_2 (%)	78 (72-84)	84 (81-87)	0.003
Peak CO_2, (mmHg)	49 (44-56)	48 (42-52)	0.24
Desaturations index	5.4 (2.0-20.3)	1.7 (0.5-2.9)	0.004
OAHI	6.0 (2.7-25.2)	0.4 (0.1-1.4)	<0.001
CAI	1.7 (0.5-3.1)	1.35 (0.6-3.0)	0.75

*Unless otherwise specified all data were reported in median with interquartile range for continuous variables, §For age and BMI, Student's *t*-test was used and for gender, Chi-square test was used. For PSG data, Wilcoxon rank-sum test was used. BMI = Body mass index, CAI = Central apnea index, OAHI = Obstructive apnea-hypopnea index, OSA = Obstructive sleep apnea, PSG = Polysomnography, REM = Rapid eye movements, SaO_2= Oxygen saturation, TST = Total sleep time, SD = Standard deviation

if lasting >2 respiratory cycle duration and associated with arousal or >3% desaturation; apnea is defined as decrease in airflow to <20% baseline amplitude and hypopnea is decrease in airflow to 20%–50% of baseline amplitude.[44] Maclean *et al*. included eight patients with PRS in their study about cleft palate and all of the participants did have OSA with combined mixed and obstructive apnea index of >3/h.[25] Bravo *et al*. reported that 31 out of 52 (59%) infants had OSA by using respiratory disturbance index >5/h of sleep.[22] The differences in the prevalence are likely related to the variations in the scoring criteria, and respiratory indices cutoff values for OSA definition between these studies. Another important factor should be considered in the prevalence variation between studies was the patient selection criteria. The two studies that used AASM scoring criteria had a very limited number of PRS infants. The first one by Anderson *et al*. had only 13 patients and the other one by Maclean *et al*. had only eight infants with PRS. To our knowledge, our study has the largest number of patients reported in the literature.

We found a strong correlation between the desaturations index and OAHI. Wagener *et al*. reported on the use of overnight oximetry to assess the severity of SDB.[40] Reddy suggested that infants with no significant desaturations events and growing well can be assessed by oximetry alone. On the other hand, those who are stable on prone position but exerting feeding difficulties need to have both oximetry and PSG. For the patients with desaturations while prone, Reddy recommended for NPT insertion prior to the PSG study.[45] The use of oximetry can be useful as a screening tool, but we should consider its limitations that it does not measure arousals as we also found a significant correlation between the arousal index and the severity of the OSA, a finding that has not been described previously. Another concern about oximetry is that it cannot differentiate between central and obstructive events.

There are still no clear guidelines to advice on the best time to perform PSG in PRS infants. The clinical presentation of PRS infants and the timing to perform PSG varied in the literature. Wilson *et al*. have reported a late presentation in infants with PRS as some of them were premature.[46] On the other hand, Benjamin and Walker have noted early symptoms of SDB in the first 12 h of life.[47] Gilhooly *et al*. reported on an infant who had a normal initial PSG but his study at 13 days of age was abnormal.[20] We found that PRS infants with OSA were younger than non-OSA ones however as this was a referred sample likely the OSA group had early presentation than the non-OSA group. From the previous observations, it is difficult to reach to certain consensus and guideline for the timing of the PSG.

The diagnosis and treatment of OSA in the PRS infants is crucial to reduce the long-term complications. These complications include failure to thrive which may worsen the long-term outcome from growth and neurobehavioral function. Growth failure even after the management of SDB may indicate residual SDB events. The importance of detecting SDB is the potential improvement in feeding difficulties, growth and neurological outcome, or other consequences like cardiovascular dysfunction which has been documented in children with SDB.

There were some notable limitations to our study. First, it is a retrospective study. All the patients were referred from plastic surgery clinic, and some of them did not have complete airway assessment, swallowing, and genetic studies. Our sample may not be representative for PRS population, and it only represents specific infants with SDB symptoms who were referred by other facility. Furthermore, we used multivariable analysis models in this work, but this could be affected by the small sample size we had.

Conclusion

This retrospective review confirms a high prevalence of SDB in infants with PRS. Further prospective longitudinal studies are needed to evaluate the cardiopulmonary and neurocognitive function in PRS infants with SDB and also to understand the effect of airway intervention in the long-term outcome.

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Conflicts of interest

There are no conflicts of interest.

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