Prevalence and Risk Factors for Central Sleep Apnea in Infants with Laryngomalacia

Archwin Tanphaichitr, MD1,2,3, Pattraporn Tanphaichitr, MD1, Polporn Apiwattanasawee, MD1, Justin Brockbank, MD1, Michael J. Rutter, FRACS2, and Narong Simakajornboon, MD1

No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. To identify the prevalence of and risk factors for central sleep apnea (CSA) in infants who are diagnosed with laryngomalacia.

Study Design. Case series with chart review.

Setting. Quaternary care pediatric hospital.

Subjects and Methods. We performed a chart review in infants with laryngomalacia. All infants had diagnostic polysomnography (PSG) performed from 2003 to 2012. Infants who underwent supraglottoplasty or other upper airway surgery prior to PSG were excluded. CSA was defined as central apnea index ≥ 5. Demographic data, underlying diseases, and PSG data were reviewed and analyzed.

Results. Fifty-four patients met the inclusion criteria. The mean age at the date PSG was performed was 3.4 ± 2.7 months. The prevalence of CSA in infants with laryngomalacia was 46.3%. Odds ratio (OR) of CSA was above 2.0 in patients with the following risk factors: underlying neurologic disease, hypotonia, or syndrome (OR = 2.5, P = .13), history of apparent life-threatening events (OR = 2.7, P = .19), premature infants (OR = 2.2, P = .33), and age less than 3 months (OR = 2.3, P = .15). However, none of the risk factors were statistically significant. Analysis of sleep architecture revealed a decrease in total sleep time (345.4 ± 70.6 minutes vs 393.5 ± 68.3 minutes, P = .02) and sleep efficiency (67.7 ± 8.9% vs 75.2 ± 9.3%, P = .004) in the CSA group.

Conclusion. CSA is relatively common in infants with laryngomalacia. There seems to be a higher prevalence of CSA in infants with certain risk factors, but none of the risk factors are statistically significant. The presence of CSA can lead to alteration in sleep architecture. In addition to clinical evaluation, polysomnography may be warranted for the evaluation of infants with laryngomalacia and associated complex medical conditions.

Keywords

laryngomalacia, central sleep apnea, polysomnography

Received September 24, 2013; revised December 3, 2013; accepted January 7, 2014.

Introduction

Laryngomalacia is the most common congenital laryngeal anomaly and the most common cause of stridor in infants and children.1 The term laryngomalacia was originated in 1942 by Jackson and Jackson to describe the inward collapse of supraglottic structures during inspiration.2 Laryngomalacia is a condition where laryngeal tone is weak and results in dynamic prolapse of supraglottic structures into the airway, causing inspiratory stridor and airway obstruction. Symptoms usually appear within the first 2 weeks of life1; however, it may be delayed by several months after birth.3 Symptoms usually are worst at 6 to 8 months of age and then resolve gradually.1,4 Laryngomalacia can be categorized as mild (inspiratory stridor without other symptoms), moderate (coughing, choking, regurgitation, and feeding difficulty), and severe (apnea, cyanosis, failure to thrive, pectus excavatum, pulmonary hypertension, or cor-pulmonale).5 Despite that laryngomalacia is a self-limited disease in most patients, it can be severe and may need treatment.

1Sleep Disorders Center, Cincinnati Children’s Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA
2Division of Pediatric Otolaryngology–Head and Neck Surgery, Cincinnati Children’s Hospital Medical Center; University of Cincinnati College of Medicine, Cincinnati, Ohio, USA
3Department of Otorhinolaryngology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

This article was presented at the 2013 AAO-HNSF Annual Meeting & OTO EXPO; September 29-October 3, 2013; Vancouver, British Columbia, Canada.

Corresponding Author:
Narong Simakajornboon, MD, Sleep Disorders Center, Division of Pulmonary Medicine, Sleep Disorders Center, Cincinnati Children’s Hospital Medical Center, University of Cincinnati, 3333 Burnet Ave, MLC-2021, Cincinnati, Ohio 45229, USA.
Email: Narong.Simakajornboon@cchmc.org
surgical intervention. It is well accepted that supraglottoplasty is warranted in patients with severe laryngomalacia. The indication for surgery is failure to thrive or severe apnea causing cyanosis or life-threatening levels of hypoxia. Conservative treatment is considered optimal for mild laryngomalacia. In patients with moderate laryngomalacia, polysomnography (PSG) should be considered in the initial evaluation to evaluate the severity of obstructive sleep apnea (OSA) and to assess the outcome after supraglottoplasty. OSA is very common in patients with moderate to severe laryngomalacia with reported incidence of 90-100%. Previous studies showed a significant improvement in PSG outcome after supraglottoplasty in all infants who had moderate laryngomalacia and OSA.

There are multiple etiologic theories of laryngomalacia. Proposed etiologies include the anatomic theory, the cartilaginous theory, the neurologic theory, or a combination of them. Recently, abnormal sensorimotor integrative function of the larynx in congenital laryngomalacia has been proposed by Thompson. Abnormal function of the pathway at the brain stem nuclei can cause weak laryngeal tone, apnea, and swallowing problems. In addition, an abnormality in brain stem neuronal networks responsible for respiratory rhythmodogenesis has been proposed. The nucleus tractus solitarius in the brain stem acts as a relay station for afferent influences that modulate respiration. The nucleus tractus solitarius modulates the output to the phrenic motoneuron pools in the spinal cord that control diaphragm activity. Immaturity of the brain stem in premature animal models demonstrates the absence of diaphragmatic activity, which plays a role in the pathophysiology of central apnea. The nucleus tractus solitarius also sends axonal projections to cell bodies of the recurrent laryngeal nerve (RLN) in the nucleus ambiguous, which is responsible for laryngeal tone, and this function is reduced in patients with laryngomalacia.

According to these proposed theories, central sleep apnea (CSA) should be associated with laryngomalacia because the brain stem nucleus is responsible for both respiration and laryngeal tone. However, there is limited information on CSA in infants with laryngomalacia. Most studies regarding PSG data in patients with laryngomalacia did not focus on central respiratory events.

The purpose of this study is to describe the prevalence and risk factors for CSA in patients with laryngomalacia.

Methods

The case series with chart review was conducted at Cincinnati Children’s Hospital Medical Center (CHMC), a quaternary care pediatric hospital in Cincinnati, Ohio. The study was approved by the institutional review board at CHMC. Overnight polysomnographic studies and medical records were reviewed for cases of laryngomalacia. Only infants with laryngomalacia who had full-night PSG performed from January 2003 to June 2012 were included. Infants who underwent supraglottoplasty or other upper airway surgery prior to PSG were excluded. Infants with split night studies (oxygen titration studies) or inadequate sleep time (<180 minutes) were also excluded. In addition to PSG, demographics, medical comorbidities, symptom severity, and secondary airway lesion data were collected from medical records.

The PSGs were performed in accordance with the American Academy of Sleep Medicine guidelines and were scored by board certified pediatric sleep specialists. The standard infant montage was used, and these variables were recorded simultaneously: body position, left and right electrocorticogram (ROC/A1, LOC/A2), 4-channel electroencephalogram (O1A2,O2A1, C4A1,C3A2), chin electromyogram, electrocardiogram, pulse oximetry and pulse waveform, thoracic and abdominal inductance plethysmography, nasal thermistor, end-tidal pCO2 monitoring (BCI Capnochecks), and transcutaneous pO2 and pCO2 (Tina TCM4/40; Radiometer, Copenhagen, Denmark). Sleep scoring was performed with standard criteria for infants. The scoring was analyzed in 30-second epochs and assigned as awake, REM sleep, and NREM sleep. Sleep efficiency was defined by the percentage of total sleep time divided by the time in bed.

Apnea was defined as cessation of airflow for at least 2 respiratory cycles. Obstructive apnea was defined as cessation of airflow in the presence of continued or increased respiratory effort. Central apnea was defined as an absence of both airflow and movements of the chest wall and abdomen. Hypopnea was defined as a 50% or greater reduction in airflow associated with reduced respiratory effort, and accompanied by oxygen desaturation of at least 3% or arousal or both. Respiratory disturbance index was expressed as the number of apneic and hypopneic events per hour. The obstructive index (OI) was defined as the number of obstructive apnea and hypopnea per hour. The central apnea index (CAI) was defined as the number of central respiratory events per hour. OSA was diagnosed if OI was equal to or more than 1. CSA was diagnosed if CAI was equal to or more than 5. Arousal was defined as a shift in the EEG pattern to frequencies of 8-13 Hz or above 16 Hz for a minimum of 3 seconds. Arousals in REM sleep must be accompanied by a concurrent increase in submental EMG amplitude. Arousal index was expressed as the number of arousals per hour of sleep.

Data were stored in an Excel spreadsheet (Microsoft, Redmond, Washington). The SPSS 19.0 (SPSS Inc, Chicago, Illinois) program was used for statistical analysis. Demographic data and comorbidities were expressed as number (percentage). PSG data were calculated and presented as mean ± SD. The chi-square for trend was used to determine whether there was a statistically significant trend with symptom severity (mild, moderate, severe) and CSA. The Fisher Exact test for univariate analysis and odds ratio were calculated to identify the risk factors for CSA in infants with laryngomalacia. A P value of less than .05 was considered statistically significant.

Results

There were 81 infants diagnosed with laryngomalacia who underwent PSG from January 2003 to June 2012. These infants were referred to sleep laboratory to obtain baseline
TABLE 1. Demographic, Disease, and Baseline Patient Characteristics.

<table>
<thead>
<tr>
<th>Demographic and Baseline Characteristics</th>
<th>Included Patients (n = 54)</th>
<th>Excluded Patients (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age, months</td>
<td>3.4 ± 2.7</td>
<td>6.6 ± 3.8</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>30 (55.6)</td>
<td>21 (77.8)</td>
<td>.056</td>
</tr>
<tr>
<td>Underlying neurologic disease, hypotonia, or syndrome, n (%)(a)</td>
<td>18 (33.3)</td>
<td>12 (44.4)</td>
<td>.342</td>
</tr>
<tr>
<td>Neurologic disease, n (%)</td>
<td>15 (27.8)</td>
<td>10 (37.0)</td>
<td>.449</td>
</tr>
<tr>
<td>Hypotonia, n (%)</td>
<td>12 (22.2)</td>
<td>4 (14.8)</td>
<td>.559</td>
</tr>
<tr>
<td>Congenital syndrome, n (%)</td>
<td>10 (18.5)</td>
<td>4 (14.8)</td>
<td>.765</td>
</tr>
<tr>
<td>Preterm (≤37 weeks), n (%)</td>
<td>8 (14.8)</td>
<td>6 (22.2)</td>
<td>.534</td>
</tr>
<tr>
<td>GERD, n (%)</td>
<td>29 (53.7)</td>
<td>11 (40.7)(b)</td>
<td>.804</td>
</tr>
<tr>
<td>Pulmonary disease, n (%)</td>
<td>14 (25.9)</td>
<td>8 (29.6)</td>
<td>.793</td>
</tr>
<tr>
<td>Secondary airway lesion, n (%)</td>
<td>23 (42.6)</td>
<td>14 (51.9)</td>
<td>.483</td>
</tr>
</tbody>
</table>

Abbreviation: GERD, gastroesophageal reflux disease.
\(a\) Each patient may have more than 1 condition.
\(b\) No data for 4 patients.

Data before surgical intervention especially infants with underlying complex medical conditions. Infants with split night studies or inadequate sleep studies and infants who underwent supraglottoplasty or upper airway surgery prior to PSG were excluded. A total of 54 infants were enrolled and analyzed in this study. The demographics of included and excluded patients are shown in Table 1. Except the age, there was no significant difference in other demographic or baseline characteristics. For included patients, 30 patients (55.6%) were male. The mean age at the time of PSG was 3.4 ± 2.7 months, and age ranged from 0.3 to 11.5 months. Of these 54 infants, 18 infants (33.3%) had underlying neurologic disease, hypotonia, or congenital syndrome. Neurologic disease was found in 15 of 54 patients (27.8%). Seizure was the most common neurologic condition (4 of 15, 26.7%). Other neurologic conditions included Arnold-Chiari malformation, congenital cytomegalovirus infection, macrocephaly, and muscular incoordination. Hypotonia was found in 12 of 54 patients (22.2%). Congenital syndrome was found in 10 of 54 patients (18.5%). Down syndrome was the most common syndrome found in this group (3 of 10, 30%), followed by Pierre Robin Sequence (2 of 10, 20%). Other congenital syndromes included Hurler syndrome, Prader–Willi syndrome, Ehler–Danlos syndrome, Chromosome 1P36 deletion, and mitochondrial complex 1 deficiency. There were 14 of 54 patients (25.9%) who had concomitant pulmonary diseases, including reactive airway disease in 9 patients (9 of 14, 64.3%), recurrent pneumonia in 2 patients (2 of 14, 14.3%), chronic respiratory failure in 2 patients (2 of 14, 14.3%), and bronchiectasis in 1 patient (1 of 14, 7.1%). There were 23 patients (42.6%) who had secondary airway lesions. Mild subglottic stenosis (8 of 23 patients, 34.8%) and tracheomalacia (7 of 23 patients, 30.4%) were the most common secondary airway lesions. Other secondary airway lesions were glossoptosis (3 of 23 patients, 13%), pharyngomalacia (2 of 23 patients, 8.7%), micrognathia (2 of 23 patients, 8.7%), adenotonsillar hypertrophy (1 of 23 patients, 4.3%), tonsillar hypertrophy (1 of 23 patients, 4.3%), and adenoid hypertrophy (1 of 23 patients, 4.3%). There were 8 of 54 patients (14.8%) who had history of prematurity and 29 of 54 patients (53.7%) who had gastroesophageal reflux disease (GERD).

The most common presenting symptoms in these patients was feeding difficulty (37 patients, 68.5%), followed by apnea (32 patients, 59.3%), poor weight gain (18 patients, 33.3%), cyanosis (15 patients, 27.8%), and history of apparent life-threatening events (ALTE) (9 patients, 16.7%), respectively. Of these 54 patients, 11 patients (20.4%) had mild symptoms, 17 patients (31.5%) had moderate symptoms, and 26 patients (48.1%) had severe symptoms. Regarding symptom severity, there was no significant association between symptom severity and the prevalence of CSA ($\chi^2$ for trend = 0.80, $P = .37$).

In terms of respiratory events, OSA was identified in 50 of 54 patients (92.6%) and CSA was identified in 25 of 54 patients (46.3%). Of these 54 patients, 14 patients (25.9%) had mild OSA (OI ≤4.9), 21 patients (38.9%) had moderate OSA (OI 5-14.9), and 15 patients (27.8%) had severe OSA (OI ≥15). The mean OI was 15.6 ± 20.7 per hour (ranged from 0.2 to 104.1). The mean CAI was 6.6 ± 8.7 (ranged from 0 to 56.1). The mean minimal oxygen saturation was 81.8 ± 7.6% (ranged from 63.0 to 95.7).

Potential risk factors for CSA were analyzed using univariate analysis. The results are shown in Table 2. Odds ratio (OR) of CSA was above 2.0 in patients with the following conditions: underlying neurologic disease, hypotonia, or syndrome (OR = 2.5, 95% CI = 0.8-7.9), history of ALTE (OR = 2.7, 95% CI = 0.6-12.4), premature infants (OR = 2.2, 95% CI = 0.5-10.2), and age less than 3 months (OR = 2.3, 95% CI = 0.8-6.9). However, none of the risk factors were statistically significant ($P > .05$) (Table 2). As shown in Table 2, a significant proportion of patients without significant risk factors had CSA (38.9%) in patients without underlying neurologic disease/hypotonia/syndrome, 42.2% in patients without ALTE, 43.5% in patients without prematurity, 34.8% in patients ≥3 months).
Sleep architecture in patients with CSA and without CSA was also compared (Table 3). There was a significant decrease in total sleep time and sleep efficiency in infants with CSA (P = .02 and .004, respectively). However, we did not find a significant difference in arousal index and percentage of REM (active) sleep (P = .89 and .23, respectively). For management of CSA, 19 of 25 patients had available information regarding treatment patterns; 8 patients were treated with low flow supplemental oxygen after oxygen titration study, 2 patients were treated with respiratory stimulant (caffeine), and 9 patients were not treated because CSA was considered mild.

Discussion

Our study has shown that CSA is common in infants with laryngomalacia who were referred to sleep laboratory. Further analysis of conditions associated with CSA in patients with laryngomalacia has indicated that infants with underlying neurologic disease, hypotonia, congenital syndrome, prematurity, history of ALTE, and age less than 3 months are at increased risk. Patients with these risk factors had odds ratio more than 2.0. However, none of the risk factors are statistically significant due to small sample size. Finally, CSA can lead to alteration in sleep architecture.

Etiologic theories of laryngomalacia remain unclear. Neurologic theory has been proposed. Neurologic conditions are the second most commonly reported medical comorbidity of laryngomalacia in the literatures, with an incidence of 8% to 50%. Our study demonstrated that neurologic disease and hypotonia were found in 27.8% and 22.2%, respectively. The relatively high incidence of these underlying diseases in our patients could also support the neurologic theory as an important etiology for laryngomalacia.

There were 18.5% of the patients diagnosed with congenital syndrome. Down syndrome was the most common syndrome found in our study. The previous publications reported that the incidence of congenital anomalies and genetic disorders in laryngomalacia was 8% to 20%. Down syndrome is the most commonly reported associated genetic disorder with laryngomalacia; up to 50% of Down syndrome is associated with laryngomalacia. The other congenital syndromes were less commonly reported.
syndrome patients who have respiratory symptoms also have laryngomalacia. In our study, Down syndrome is a risk factor for CSA in infants with laryngomalacia. A previous study has shown that patients with Down syndrome have increased central respiratory events, which may be related to a dysfunction of the central respiratory control at the brain stem level.32

There are reported studies regarding secondary airway lesions associated with laryngomalacia. The prevalence was 7.5% to 64%.33-37 In this study, secondary airway lesions were found in 42.6%. Subglottic stenosis and tracheomalacia were the 2 most common secondary airway lesions found in our study, which is consistent with previous publications.34,35

Feeding difficulty and apnea were the most common presenting symptoms in this study. This might be explained by abnormal sensorimotor integrative function of the larynx by Thompson.4 Laryngeal tone and sensorimotor integrative function of the larynx are altered in infants with laryngomalacia. Abnormal function of the pathway at the brain stem nuclei can cause weak laryngeal tone, apnea, and create swallowing problems.4 From this theory, laryngomalacia infants with CSA are likely to have swallowing dysfunction and feeding difficulty.

There are several publications regarding PSG findings in patients with laryngomalacia.6,8,38,39 However, most of these studies did not mention CSA in patients with laryngomalacia. These studies concluded that PSG is useful in patients with laryngomalacia to identify OSA and/or to objectively measure outcomes after supraglottoplasty. Supraglottoplasty can improve obstructive sleep parameters in patients with laryngomalacia.6,8,38,39 Because these studies focused on OSA, they may overlook the presence of central respiratory events. There is only 1 previous study by a research group from Brazil in 2006 that concluded the majority of patients with laryngomalacia showed a central-type apnea, while patients with various laryngeal diseases did not present a predominant type of apnea.40 Their research was done in 29 children. Of those 29 children, 18 children were diagnosed with laryngomalacia and 11 children were diagnosed with other laryngeal alterations. All of the 18 children with laryngomalacia had central-type respiratory events while 4 of 11 children with other laryngeal alterations had central-type breathing events. If CSA was defined as CAl equal to or more than 5 (same as our study), the true incidence of CSA in patients with laryngomalacia in that study would be 5 of 18 (27.8%). The prevalence of CSA in our study was higher (46.3%), which could reflect a different population type, as our patients had more complex underlying medical conditions.

We are not aware of any previous publications assessing the risk factors of CSA in patients with laryngomalacia. There seems to be a higher prevalence of CSA in infants with certain risk factors, including underlying neurologic disease, hypotonia, congenital syndrome, history of ALTE, premature infants, and age less than 3 months. Patients with these conditions are at increased risk for CSA as the odds ratio is above 2, but none of the risk factors are statistically significant due to small sample size. The increased risk of CSA in prematurity and young age (less than 3 months) could be explained by the fact that the brain stem and respiratory pattern of the premature and young infants are still in the developmental period. There was an increased risk of CSA in patients with underlying neurologic disease, hypotonia, and congenital syndrome. Therefore, CSA should be suspected in infants with laryngomalacia who have these complex medical conditions. Increased risk of CSA was also noted in infants with laryngomalacia who had history of ALTE. CSA in these infants may contribute to worsening of apnea and could potentially result in ALTE. However, there was no increased risk of CSA in patients with underlying pulmonary disease and history of GERD. Despite that GERD was commonly found in laryngomalacia infants with neurologic disease,4 we failed to identify GERD as a significant risk factor for CSA. The association between GERD and infant apnea is somewhat controversial. While some studies showed correlation between GERD and apnea, other studies demonstrated weak association between them.41,42

In terms of sleep architecture, CSA had a negative impact on sleep quality of the patients. Total sleep time and sleep efficiency were significantly decreased. This can be explained by the fact that central apneic events cause arousals, awakenings, and desaturations in these infants.21

There are limitations in our study. First, this is a retrospective study and some clinical information might be incomplete. Second, PSG is not routinely performed in patients with laryngomalacia. Patients referred to sleep laboratory are likely to have underlying complex medical conditions. The prevalence of CSA in our patients might not represent the otherwise normal infants with laryngomalacia. Third, this study demonstrates increased odds ratio of CSA in infants with certain risk factors, although none of the risk factors are statistically significant due to small sample size. It is important to point out that a significant proportion of patients without risk factors have CSA. Fourth, there is no data on CSA after supraglottoplasty. It remains unknown whether CSA would improve after surgical intervention.

The results of polysomnographic studies in patients with laryngomalacia may help in understanding the pathophysiology of laryngomalacia. If laryngomalacia is associated with CSA, this would be important in terms of evaluation and management. In fact, the presence of CSA in our patients with laryngomalacia influenced the clinicians’ treatment decision as some patients were treated with low flow supplemental oxygen or respiratory stimulant. Physicians need to pay attention to CSA while assessing infants with laryngomalacia, especially at-risk infants, as the CSA component may still persist after supraglottoplasty. This could mean that both preoperative and postoperative PSGs may be warranted. Infants with CSA may require additional management beyond surgery such as respiratory stimulants or supplemental oxygen. Further research is needed to assess the effect of CSA on clinical outcome and to evaluate the outcome of supraglottoplasty on CSA in infants with laryngomalacia.
Conclusion

CSA is relatively common in infants with laryngomalacia. There seems to be a higher prevalence of CSA in infants with certain risk factors, including underlying neurologic disease, hypotonia, congenital syndrome, history of ALTE, premature infants, and age less than 3 months, although none of the risk factors are statistically significant. The presence of CSA can lead to alteration in sleep architecture. In addition to clinical evaluation, PSG may be warranted for the evaluation of infants with laryngomalacia, especially infants with associated complex medical conditions.

Author Contributions

Archwin Tanphaichitr, study design, data acquisition, analysis and interpretation of data, drafting the manuscript, critical review of manuscript, final approval; Pattraporn Tanphaichitr, data acquisition, critical review of the manuscript, final approval; Polporn Apiwattanasawee, data acquisition, critical review of the manuscript, final approval; Justin Brockbank, data acquisition, critical review of the manuscript, final approval; Michael J. Rutter, study design, critical review of manuscript, final approval; Narong Simakajornboon, study design, analysis and interpretation of data, drafting the manuscript, critical review of manuscript, final approval.

Disclosures

Competing interests: None.
Sponsorships: None.
Funding source: None.

References


