Impact of Sleep and Breathing in Infancy on Outcomes at Three Years of Age for Children with Cleft Lip and/or Palate

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Study Objectives: To evaluate the relationship between sleep disordered breathing (SDB) in early infancy and outcomes at 3 years of age in children with cleft lip and/or palate (CL/P).

Design: Observational follow-up study.

Setting: Multidisciplinary CL/P clinic, tertiary centre.

Participants: Children with CL/P who participated in a study of sleep and breathing in infancy.

Measurements and Results: The families of 52 children were approached for this follow-up study. The children underwent neurocognitive (Bayley Scales of Infant and Toddler Development, Third Edition; BSID-III), quality of life (Infant/Toddler Quality of Life Questionnaire; ITQOL), and growth assessments at 3 years. The families of 33 children (66%) completed follow-up at 36.7 ± 1.4 months. The apnea-hypopnea index (AHI) in infancy was 23.9 ± 18.0 events/h. Mean group BSID-III scores fell within the standardized normal range (10 ± 3) for all domains; however, language scores were lower than control children. Quality of life scores and growth parameter z-scores were similar to published control data. PSG variables in infancy showed significant relationships with outcomes at 3 years of age: lower percentage of AS/REM sleep was associated with lower cognition score; more obstructive events were associated with lower global behavior ITQOL score; and higher number of respiratory events in infancy was associated with lower weight z-score.

Conclusion: Neurocognition, quality of life, and growth measures from children with CL/P fall within a normal range; however, scores in the language domain are lower than controls. Sleep and respiratory elements of SDB in infancy appear to modify these outcomes at 3 years of age.

Keywords: cleft lip and/or palate, longitudinal, Bayley Scales of Infant and Toddler Development, Infant/Toddler Quality of Life Questionnaire

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INTRODUCTION

Structural and functional changes present in the upper airway of infants with cleft lip and/or palate (CL/P) confer an increased risk of sleep disordered breathing (SDB).1 The changes in facial structures include decreased length and height of the maxilla, basal maxillary retrognathia, decreased length of the mandible, and mandibular retrognathia, which all result in a reduced size of the upper airway.2 Disturbance of the structure of the palate and altered insertions of the palatal muscles lead to dis-coordination of palatal movement with laryngeal muscles and also predisposes to airway obstruction.3,4 In both animal models and studies of newborn infants, these structural and functional changes are associated with a spectrum of airway compromise from life threatening airway obstruction to the intermittent airway obstruction during sleep of obstructive sleep apnea (OSA).5,8 In a study of 52 infants with CL/P who underwent PSG at a mean age of 2.7 ± 2.3 months, we demonstrated that 40% of infants had more than 10 obstructive respiratory events/h of sleep, while 14% had more than 20 central events/h of sleep with a mean apnea-hypopnea index (AHI) of 22.8 ± 18.4 events/h.9

SDB in childhood is associated with a range of health consequences including poor growth, neurocognitive compromise, and lower quality of life. There is, however, less information on the effects of OSA in early infancy. Animal models of OSA in early infancy, using exposure to intermittent hypoxia, have demonstrated increased baseline ventilation and decreased response to acute hypoxia—effects which persist after return to normoxia and into adulthood—as well as cognitive impairment.10,11 These effects are seen even with relatively brief exposure to intermittent hypoxia.12 Studies in infants with SDB show lower amounts of REM sleep, poor growth, delayed development, and a higher risk of sudden infant death syndrome (SIDS).13,15 While studies of SDB in childhood show reversal of some of the effects of SDB with treatment,16,17 there is limited information available on the long-term outcomes of SDB in infancy. Treatment studies of infants with CL/P demonstrate that a range of modalities can relieve airway obstruction,18-24 improve feeding skills,24 and improve growth velocity,19,21 but few studies examine treatment outcomes, and none have included long-term follow-up. One study of children age 4-11 years demonstrated significant differences in cognitive and psychosocial development between healthy controls and children with a history of Pierre Robin Sequence, a select group of infants with cleft palate at high risk of OSA.25

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SDB is recognized as an important comorbidity in infants with CL/P; however, the long-term sequelae of SDB in this group are currently unknown. The aim of this study was to investigate the relationship between SDB during early infancy and neurocognitive, quality of life, and growth outcomes at 3 years of age in a group of infants with CL/P. The results from this study will provide clinicians and families with information about the consequences of SDB in infants with CL/P.

METHODS

All families of newborn infants referred to the cleft team were approached for participation in a longitudinal prospective study of sleep and breathing in infants with CL/P. Following their first contact with the cleft team, families were consented for participation and the infant was scheduled for initial polysomnography (PSG). Infants were excluded if a cleft was not confirmed, if they were medically unstable, or if they required medical interventions that precluded the performance of a diagnostic PSG prior to palate surgery. The study protocol was approved by the institution’s research ethics committee.

All treatment decisions were the responsibility of the multidisciplinary cleft team. Standard protocols for cleft care included repair of cleft lips at approximately 3 months and primary palate closure between 9 and 12 months. Surgical procedures for primary palate closure included Langenbeck’s bipedical flaps, Veau-Wardill-Kilner V-Y pushback, Furlow double-reversing Z-palatoplasty, and intervelar veloplasty. No children underwent procedures intended to leave a residual cleft. Decisions with regard to treatment for sleep disordered breathing (SDB) were the responsibility of the Sleep Medicine physicians.

The study consisted of data collection in infancy and follow-up at 3 years of age. A total of 52 infants were enrolled in infancy with the protocol and results of infant PSG previously reported. All infants underwent a diagnostic PSG as soon as possible after identification of their CL/P. At the time of the PSG, demographic information was collected from the medical chart, a parent or guardian completed a sleep and breathing research questionnaire and facial and growth measurements were collected. Families were then invited for follow-up by the research team just before their child’s third birthday.

The main outcome measure collected at 3 years of age was a neurocognitive assessment using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Testing was completed predominantly by 2 nurses, with occupational therapists completing testing when needed. All assessors had completed the Bayley course and were experienced in administering the assessment. The BSID-III consists of 5 subscales including cognitive, receptive language, expressive language, fine motor, and gross motor. Scores which fall outside ± 1 standard deviation (SD) are considered abnormal. BSID-III scores were compared to locally collected data from term born healthy control children participating in a follow-up study of infants who underwent general surgery or cardiac surgery in infancy. Additional outcome measures included the Infant/Toddler Quality of Life Questionnaire (ITQOL; 97 items) and growth parameters. The ITQOL measures quality of life across 9 multi-item scales for infants and toddlers 2 months to 5 years of age (healthactchq.com). ITQOL scores were compared to previously published data collected from control samples, where possible scores range from 0 to 100 and higher scores indicate better quality of life. Z-scores for growth parameters were calculated using the CDC 2000 Growth Reference for children 2-19 years old (www.cdc.gov/growthcharts).

PSGs in infancy and at 3 years of age were completed using standard clinical laboratory procedures. This included determination of sleep state using an electroencephalography, electrooculogram, and submental electromyogram. Channels to evaluate respiratory status included pulse oximetry, nasal/oral air flow by thermistor, nasal pressure, chest and abdominal wall movement using respiratory inductance plethysmography, and diaphragm and abdominal muscle activity by trans-diaphragmatic electromyogram. Carbon dioxide (CO2) was monitored using transcutaneous CO2 (TcCO2). Cardiac monitoring included the pulse signal from the oximeter and electrocardiogram.

Analysis of PSG data was completed by a single experienced scorer using the criteria of the American Academy of Sleep Medicine (AASM). Sleep staging for infants < 6 months of age was completed using the criteria outline by Anders, with AASM criteria applied for those ≥ 6 months. Obstructive apnea was defined as the cessation of airflow (< 10% of baseline level) for a minimum duration of 2 missed breaths with evidence of ongoing respiratory efforts. Central apnea was defined as the cessation of airflow (< 10% of baseline level) for a minimum of 2 missed breaths if followed by an arousal, awakening, or ≥ 3% oxygen desaturation, or for ≥ 20 sec in the absence of any associated events. Mixed apneas included central and obstructive components in the same event. Hypopneas were defined based on a decrease in airflow of 10% to 50% of baseline associated with an arousal, awakening, or ≥ 3% oxygen desaturation. Apnea-hypopnea index (AHI) was calculated based on the number of apneas and hypopneas during sleep divided by the total sleep time. The obstructive-mixed AHI (OMAHI) excluded central respiratory events. Oxygen desaturation index (ODI) was calculated based on the number of oxygen desaturation events ≥ 3% during sleep divided by the total sleep time.

Oxygen saturation nadir represents the lowest oxygen saturation recorded during sleep. There is no accepted AHI cut-point to define an abnormal or pathological AHI in infancy; therefore, the median AHI of 15 events/h from the original study group (i.e., data from 50 infants previously reported) was used to define low (AHI < 15) and high (AHI ≥ 15) within this group.

Data were entered in a database (Microsoft Office Access 2003, Microsoft Corporation). Statistical analysis was performed using IBM SPSS 21.0.0.0 (IBM Corp, 1989, 2012). A p-value ≤ 0.05 was considered to indicate statistical significance. Descriptive analyses were used to examine demographic information, PSG parameters, and neurocognitive results. Logarithmic transformation to normalize distributions was applied to PSG variables including AHI, OMAHI, and ODI. Comparisons for continuous variables between groups were made with Student t-test, paired t-test, and ANOVA. A modified Bonferroni correction was made for multiple comparisons.

RESULTS

A full description of the infant characteristics of the original cohort is available elsewhere. Thirty-four children returned for follow-up at 3 years of age (68% response rate). Neurocognitive
testing was unsuccessful for one child who was not willing to complete any of the tasks for the assessors. Therefore, results for 33 children are available for analysis across the spectrum of CL/P (Table 1). Compared to the original cohort, males were overrepresented in the follow-up cohort (45% vs 57%, P < 0.05), as were infants who were referred for clinical sleep medicine consultation prior to PSG (41% vs 51%, P < 0.05). There were no differences between the original and follow-up cohorts with respect to cleft classification, syndrome status, or infant PSG variables (data not shown).

PSG in infancy was completed at 2.7 ± 2.1 months with an AHI of 24.3 ± 18.0 events/h (Table 2). All infants had an AHI > 1 event/h; all but 1 had an OMAHI > 1 event/h; and 75% had an OMAHI > 3 events/h. Infants with PRS had more severe SDB than infants with isolated cleft, but similar SDB severity compared to infants with syndromes (data not shown). Sleep medicine physicians determined that 30% of infants had normal PSG results. For the remaining infants, 33% were recommended for clinical follow-up without intervention, 6% side lying or prone positioning for sleep, 3% oxygen during sleep, and 27% non-invasive ventilation (NIV) therapy. For 3 infants recommended NIV, families declined starting the therapy.

Among 19 children (57%) who completed PSG at follow-up, PSG parameters in infancy were not different from those children who declined follow-up PSG (data not shown). Comparison of paired infant and follow-up PSG results showed expected changes in sleep architecture, sleep efficiency, and arousal index between infancy and follow-up (Table 2). There was a significant decrease in all respiratory events but no change in minimum oxygen saturation. AHI decreased from infancy to follow-up for all children; however, 72% had AHI > 2 event/h at follow-up. Both OMAHI and central index was < 5 events/h for all children, consistent with mild SDB, at most, in those with residual respiratory events. Between the infant and follow-up assessments, 2 children were diagnosed with epilepsy (6%), and seizures were controlled with anti-epileptic medication. One child was diagnosed with global developmental delay. Four children (12%) were identified as having hearing deficits.

A summary of the outcome measures at 3 years of age is presented in Table 3. Mean BSID-III scaled scores at follow-up were lower than at infancy (Table 3). For example, mean BMI z-score at follow-up was -0.14 ± 2.3 vs -0.55 ± 1.40 at infancy. Mean gross motor z-score was 10.7 ± 2.8 vs 8.77 ± 2.5, and mean expressive language z-score was 10.7 ± 2.8 vs 8.6 ± 3.1. Results are expressed as mean ± standard deviation.
were within the normal range for all domains (Figure 1). Children with a history of CL/P had lower scores than control children on the receptive and expressive language domains (Table 4). BSID-III scaled scores also differed by syndrome status; children with isolated cleft and PRS had higher scores than children with syndromes (Table 5). ITQOL scores were within the range reported in previously published control samples, with syndromes (Table 5). ITQOL scores were within the range reported in previously published control samples; both feeding and growth concerns may have been motivated to participate in follow-up. Syndromes 24,32 Both feeding and growth concerns may have been motivated to participate in follow-up. The percentage for AS/REM sleep in infancy showed a positive correlation with the cognitive domain on the BSID-III (Pearson 0.35, P < 0.05). No other PSG variables in infancy— including sleep efficiency, arousal index, AHI, and ODI—showed relationships with neurocognition at 3 years of age. The 3 children who were recommended for treatment for SDB by their families declined treatment had lower scores on the cognitive domain than the rest of the group (6.33 ± 3.06 vs 9.87 ± 2.2, P < 0.05); one of these children had PRS and one had a syndrome. OMAHI in infancy showed a negative relationship with ITQOL Global Behaviour domain (Pearson -0.43, P < 0.05). There were no significant correlations between PSG variables and growth parameters at 3 years of age. Children with low AHI (< 15) in infancy did not differ from those with high AHI on any outcome variable except for weight, where children with high AHI in infancy had a lower weight z-score at 3 years than children with a low AHI in infancy (-0.54 vs 0.40, P < 0.05).

**DISCUSSION**

This is the first study to report on long-term outcomes of SDB in infants with CL/P. The results demonstrate that, as a group, children with a history of CL/P are doing well at 3 years of age with respect to neurocognition, quality of life, and growth, despite high AHI in infancy. Sleep and breathing differences in infancy, as measured by PSG prior to intervention, demonstrate significant relationships with outcomes at 3 years of age including; (1) higher percentage of AS/REM sleep in infancy correlating with higher cognitive score on the BSID-III; (2) higher OMAHI correlating with lower global behaviour score on the ITQOL; and (3) high AHI in infancy associated with lower weight z-scores at 3 years of age. Children with CL/P do show important deficits in receptive and expressive language compared to control children. Syndrome status influences neurocognitive but not quality of life and growth outcomes.

Limitations of the study must be acknowledged. Follow-up was completed for 66% of the original cohort raising the possibility of selection bias. Males and children referred for sleep medicine consultation prior to initial PSG were overrepresented in the follow-up cohort. The potential effect of more males on outcomes is difficult to anticipate. The higher rate of children referred in the follow-up cohort could bias towards worse outcomes, as these infants may have been identified as at risk for reason other than sleep related symptoms. The original and follow-up cohorts did not differ, however, by syndrome status or infant PSG variables. Families who had concerns about how their children were doing may have been motivated to participate in follow-up.

Common comorbidities associated with CL/P, in addition to airway obstruction, include feeding difficulties, growth failure, speech abnormalities, and developmental delay. Feeding difficulties and failure to thrive are more common in newborns with palatal clefts and those with CL/P in the context of syndromes. Both feeding and growth concerns may lead to delays in the acquisition of fine and gross motor skills, which can be exacerbated by sleep disordered breathing. AHI in infancy showed a positive relationship with outcomes at 3 years of age compared to control children. Syndrome status influences neurocognitive but not quality of life and growth outcomes.

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**Table 4**—Comparison of neurocognitive outcomes between children with a history of CL/P and control children.

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 156)</th>
<th>Cleft (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>39.5 ± 1.1</td>
<td>38.6 ± 1.9</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3553 ± 500</td>
<td>3365 ± 606</td>
</tr>
<tr>
<td>Age at assessment (months)</td>
<td>37.2 ± 1.0</td>
<td>37.7 ± 1.5</td>
</tr>
<tr>
<td>Cognitive</td>
<td>10.3 ± 1.9</td>
<td>9.5 ± 2.5</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>11.4 ± 2.1</td>
<td>10.0 ± 2.5</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>11.0 ± 2.6</td>
<td>8.6 ± 3.0</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>11.4 ± 2.1</td>
<td>10.7 ± 2.8</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>9.9 ± 1.8</td>
<td>8.8 ± 2.5</td>
</tr>
</tbody>
</table>

* Post hoc: control vs cleft, P < 0.05. ** Post hoc: control vs cleft, P < 0.01. † Post hoc: control vs cleft, P < 0.001.

**Table 5**—Neurocognition as measured by Bayley Scales of Infant and Toddler Development III (BSID-III; scaled scores) by syndrome status

<table>
<thead>
<tr>
<th>BSID-III (scaled scores)</th>
<th>Isolated (n = 23)</th>
<th>PRS (n = 7)</th>
<th>Syndrome (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>9.7 ± 2.2</td>
<td>10.3 ± 2.4</td>
<td>6.7 ± 3.2</td>
</tr>
<tr>
<td>Receptive Language</td>
<td>9.9 ± 2.5</td>
<td>10.7 ± 2.1</td>
<td>9.0 ± 3.5</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>8.2 ± 3.0</td>
<td>10.9 ± 1.6</td>
<td>6.3 ± 3.8</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>11.0 ± 2.7</td>
<td>11.6 ± 1.4</td>
<td>6.7 ± 3.2</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>8.7 ± 2.7</td>
<td>9.7 ± 1.1</td>
<td>6.0 ± 2.8</td>
</tr>
</tbody>
</table>

* P = 0.05; post hoc: PRS vs Syndrome, P = 0.087. ** P < 0.05; post hoc: Isolated vs Syndrome and PRS vs Syndrome, P < 0.05.
The results from this study cannot be used to determine which infants with SDB will benefit from treatment and may not generalize to infants with CL/P receiving care in a different context. There are no accepted criteria for defining SDB in infancy. Previous studies in infants have chosen different cut-offs for defining abnormality including: a respiratory disturbance index (RDI) > 5 events/h of sleep; mixed plus obstructive apnea index > 2 events/h of sleep; and AHI > 2 events/h unless > 25% of events were central. In the current study, SDB was identified by experienced pediatric sleep physicians rather than by defined PSG or clinical criteria. It would be unethical to withhold treatment from infants with SDB given the data supporting a negative impact of SDB on neurobehavioral function and quality of life in children. In addition, several studies have demonstrated important comorbidities in infants with SDB, including growth and feeding problems, neurological and behavioral abnormalities and evidence that treatment of SDB improves short-term outcomes. Given this context, the current study demonstrates that infants with CL/P receiving clinical care for SDB by pediatric sleep physicians through a multidisciplinary cleft clinic have normal overall neurocognitive function, quality of life, and growth at 3 years of age compared to reference standards but with some impairment compared to control children. Further work is needed to develop criteria to aid in defining clinically significant abnormalities in infants with SDB and determining whether earlier intervention can improve long-term outcomes.

In summary, the results from the present study support an association between SDB in early infancy and neurocognitive, quality of life, and growth outcomes at 3 years of age. This information supports the need for greater attention to sleep and breathing abnormalities in infants with CL/P. In addition, there is a need for further work examining SDB across infancy to better understand the implications for treatment choices with respect to long-term outcomes.

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**REFERENCES**


