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Management of obstructive sleep apnea in children with achondroplasia: Outcomes of surgical interventions

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ABSTRACT

Introduction: Children with achondroplasia are predisposed to obstructive sleep apnea (OSA), however little is known regarding surgical interventions and outcomes for this condition. The aim of this study was to evaluate the severity of OSA in children with achondroplasia and report outcomes of surgical interventions using polysomnography (PSG) parameters.

Methods: Retrospective chart review of children with achondroplasia with documented OSA from 2002 to 2018 that had pre- and post-operative PSG results. Additional data extracted included age, gender, and type of surgical interventions. The primary outcome was change in postoperative obstructive apnea hypopnea index (OAHI).

Results: Twenty-two children with achondroplasia were identified that underwent formal PSG before and after confirmed OSA. The median age was 12 months (range 4 days–15.3 years, IQR 2 years) at time of initial PSG evaluation. The majority (72.7%) of patients had severe OSA with a median preoperative OAHI of 14.25 (IQR 9.4). The most common surgical intervention was adenotonsillectomy (n = 15). Multilevel surgical intervention was required in 9 (41.0%) patients. Post-operatively, 16 (72.7%) children experienced a reduction in OAHI, of which four (18.2%) had complete OSA resolution. OAHI scores increased in six (27.3%) children. Patients with the most severe OSA at baseline had greater improvements in post-operative OAHI ($P < 0.01$). Neither type nor number of surgical interventions was associated with improved outcomes ($P = 0.51$, $P = 0.89$ respectively).

Conclusions: Treatment of OSA in children with achondroplasia remains challenging. Although reduction of OAHI is possible, caregivers should be counseled about the likelihood of persistent OSA and the potential for multilevel airway surgery.

1. Introduction

Achondroplasia is the most common type of skeletal dysplasia, estimated to affect more than 250,000 individuals worldwide with an incidence of 1 in 10,000–30,000 births [1]. The phenotype is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*), a transmembrane protein expressed in proliferating chondrocytes responsible for endochondral ossification [2]. Achondroplasia is inherited in an autosomal dominant pattern or can be the result of de novo genetic mutations [3]. In addition to short stature secondary to rhizomelic shortening of the limbs, patients with achondroplasia have distinct facial features characterized by macrocephaly, frontal bossing, midface hypoplasia, and a depressed nasal bridge [4].

Previous research has established that these structural features, in combination with hypotonia of the airway musculature, hypertrophic lymphoid tissue, and restrictive lung disease from thoracic bony deformities, predispose this population to sleep-disordered breathing (SDB) [4,5]. The most common manifestation of SDB is obstructive sleep apnea (OSA), which is estimated to affect approximately 20% of children with achondroplasia [6,7]. Central sleep apnea secondary to brain stem compression from foramen magnum stenosis may further complicate sleeping disorders in this population [8–10].

Despite the complex sleep patterns for children with achondroplasia, management recommendations specific to this population have not been well reported [11]. Previous studies have focused on adenotonsillectomy (AT) alone as treatment for OSA in children with achondroplasia, but few have examined the effectiveness of multilevel surgical interventions [7,8]. Furthermore, studies lack objective measures such as

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obstructive apnea-hypopnea index (OAHI) from formal polysomnography (PSG) to assess unbiased postoperative changes. The present study aims to evaluate the severity of OSA in children with achondroplasia, report our experience and outcomes with multilevel sleep surgeries in cases of persistent OSA, and postoperative changes on PSG following surgery.

2. Materials and methods

2.1. Patient selection

Following Institutional Review Board approval by the University of Utah and the Medical University of South Carolina, a retrospective chart review was conducted on patients under the age of 18 years with *International Classification of Diseases Ninth* (ICD-9) and *Tenth Edition* (ICD-10) diagnosis codes for chondrodystrophy (756.4 and G47.33) from 2002 to 2018. We identified children with a confirmed diagnosis of achondroplasia that were evaluated for SDB. Only children who underwent surgical intervention and had both pre- and post-operative PSG results available were included in the final analyses. Patients that had other forms of chondrodysplasias, children treated solely with positive pressure (either continuous or bi-level), and those without pre- and postoperative sleep studies were excluded.

2.2. Outcomes

Patient charts were reviewed for patient demographics, PSG results, surgical interventions and follow-up duration. The OAHI, defined as the number of obstructive apnea and hypopnea events per hour of sleep, was compared between the first pre-operative PSG obtained before any intervention to the final PSG results following the last surgical intervention. Oxygen saturation nadir (spO2) was defined as the lowest oxygen level reached during the sleep study. PSG were considered normal in the case of a nadir greater than 92% and apnea-hypopnea index of less than 1.5 events per hour (h). Mild obstructive sleep apnea was defined as an OAHI >1.5 and < 5 events/h, moderate sleep apnea as an OAHI ≥ 5 and <10 events/h, and severe sleep apnea as an OAHI ≥ 10 events/h [12]. The primary outcome measure was reduction in OAHI on post-operative PSG, with a $\geq 50\%$ reduction defined as a meaningful improvement in SDB [13–15].

Categorical variables were summarized by frequency and percentage. All continuous variables were assessed for normality using the Shapiro-Wilk test and reported as mean ± standard deviation (SD) or as the median with interquartile range (IQR: 25th and 75th) where appropriate. Comparisons between normally distributed variables were performed using the One Way Analysis of Variance (ANOVA) or the Kruskal-Wallis test for non-parametric data. A P value < 0.05 was considered statistically significant and all statistical analysis was performed using SPSS 24.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Patient population

The combined chart review included 77 patients with achondroplasia, of which 32 had obstructive sleep apnea diagnosed with formal PSG. Five children were managed with positive pressure without surgical intervention and were therefore excluded in the analysis. At the time of this study, we excluded eight children that were awaiting or did not have post-operative PSG performed. One child was lost to follow-up and another underwent cervico-medullary decompression and did not undergo airway intervention. Consequently, a total of 22 children were included in the final analyses (Tables 1 and 2).

There were 13 males (59.1%) with a median age of 12 months (range 4 days–15.3 years, IQR 24) at the time of first PSG. On PSG, three children (13.6%) had mild OSA with a mean OAHI of 2.9 ± 1.4 and three had moderate OSA (13.6%) with a mean OAHI of 8.2 ± 1.6. The majority (72.7%) had severe OSA with a mean OAHI of 25.2 ± 26.2. The overall median preoperative OAHI was 14.0 (IQR 16.4) and mean Sp02 nadir was 75.9% ± 12.1. None of the patients had isolated central sleep apnea, and ten patients (37.0%) had mixed sleep apnea with a component of central apnea with a median preoperative CAHI of 0.77 (IQR 5.23). Four children had foramen magnum stenosis.

Table 1
Patient characteristics and surgical interventions.

	N (%)
Median age at time of PSG, months (range; IQR)	12.5 (0.13–184; 24)
Sex	
Male	13 (59.1)
Female	9 (40.9)
OSA severity	
Mild	3 (13.6)
Moderate	3 (13.6)
Severe	16 (72.7)
Number of surgical interventions	
1	13 (59.1)
2	9 (40.9)
Surgery type	
Adenotonsillectomy only	11
+ Lingual tonsillectomy	1
+ Uvulopalatopharyngoplasty	1
+ Palatopharyngoplasty	1
+ Supraglottoplasty	1
Adenoidectomy only	0
+ Tonsillectomy	3
+ Lingual tonsillectomy	1
Supraglottoplasty only	2
+ Tonsillectomy	1

Abbreviations: PSG, polysomnography; IQR, interquartile range; OSA, obstructive sleep apnea.

Table 2
Individual patient characteristics including surgery type and change in pre- and postoperative polysomnography studies.

Patient	Sex	Age (mo)	Surgery	ΔOAHI	ΔCAHI	ΔSpO2
1	M	137	AT	−6.34	NA	22
2	M	13	AT, DISE	1.35	1.86	6
3	M	63	AT	−4.8	0.12	1
4	F	16	AT, DISE	−8.1	−0.3	22
5	F	17	AT	−2.3	3.1	10.3
6	M	59	AT, DISE	−10.5	−14	1
7	F	34	AT	−11.2	0	7.9
8	F	12	AT, DISE	−15.1	−0.6	1
9	F	0.13	AT	−13.1	2.3	7
10	M	11	AT, DISE	−18.6	−1.6	6
11	M	11	AT, DISE	10.9	0	23
12	M	4	AT, LT, DISE	−0.7	−12.9	30
13	M	184	AT, UPP, DISE	−31.9	−0.6	23
14	M	15	AT, PP	7.02	4.4	−14.3
15	F	3	A, T, DISE	8.7	NA	−11
16	M	6	A, T	3.0	−2.5	0
17	M	7	A, T	−13.7	−0.34	12
18	F	24	A, LT	−8.1	NA	−8
19	M	31	T, SGP, DISE	5.6	0.3	−3.3
20	M	3	SGP, DISE	−31.8	4.4	7.7
21	F	8	SGP	−30.9	−10.5	10
22	F	11	SGP, DISE, AT	−14.5	−4.8	17.5

Abbreviations: **Δ**, change in; OAHI, obstructive apnea-hypopnea index; CAHI, central apnea-hypopnea index; SpO2, oxygen saturation nadir; AT, adenotonsillectomy; A, adenoidectomy; T, tonsillectomy; LT, lingual tonsillectomy; UPP, uvulopalatopharyngoplasty; PP, palatopharyngoplasty; DISE, drug-induced sleep endoscopy; SGP, supraglottoplasty; M, male; F, female; NA, not available; mo, months.

3.2. Interventions

The most common intervention was adenotonsillectomy (AT) in 14 (63.7%) children. Eleven of these children were managed with AT alone, and the remaining three children required a second operation at a later date (one lingual tonsillectomy, one expansion pharyngoplasty, and one uvulopalatopharyngoplasty). Four children (18.2%) initially had an adenoidectomy, all of whom required subsequent surgery (three tonsillectomies and one lingual tonsillectomy). The remaining four children had supraglottoplasty; one after a tonsillectomy and one preceding AT. Twelve patients (54.5%) had drug-induced sleep endoscopy (DISE) performed at the time of their procedure, with nine (40.9%) showing multiple sites of upper airway collapse. A total of 13 children (59.1%) underwent one operation and nine children (40.9%) required more than one operation.

3.3. Outcomes

Median follow-up time was 48.5 months (range, 17 months–11.6 years). A total of 16 (72.7%) children had a reduction in post-operative OAHI (mean percent reduction 66.0% ± 21.2) and six (27.3%) children experienced an OAHI increase, four of which had severe OSA at baseline. Seventeen children (77.3%) also had a post-operative improvement in spO2, with an average improvement of 7.7% ± 11.8. The children who experienced a decrease in spO2 (18%, n = 4) still had moderate to severe OSA on PSG post-operatively. Of patients with a meaningful reduction in OAHI of ≥50%, only female gender (n = 13) was associated with a significant reduction (P = 0.04). Although 62.5% of those with severe OSA experienced a meaningful reduction in OAHI, this was not statistically significant (P = 0.76). Children that underwent adenotonsillectomy or supraglottoplasty had the highest frequency of OAHI reduction, although surgery type was not significantly associated with OAHI reduction (P = 0.51) (Table 3).

Complete resolution of OSA was observed in only four children (18.2%), two with severe OSA and one each with mild and moderate OSA. The number of upper airway surgeries a patient obtained was not associated with a meaningful reduction in OAHI. Patients with a pre-operative OAHI in the first or second quartile (ranges, 2–9 and 10–14) experienced an average increase in the post-operative OAHI of 1.2 ± 6.1 and 0.2 ± 8.9 respectively, while those in the third and fourth quartiles (ranges, 15–24 and 25–118) had an average reduction of 10.7 ± 3.1 and 25.7 ± 8.1 (Fig. 1). The children in the fourth quartile had a significantly greater improvement in post-operative OAHI compared to the rest of the cohort ($p < 0.01$).

Table 3
Patient characteristics based on percentage reduction of OAHI on post-operative polysomnography.[a]

Median age at time of PSG (IQR)	<50% reduction OAHI N = 9	≥50% reduction OAHI N = 13	*P* value
	12 months (79)	13 months (21.5)	0.89
Sex			
Male	8 (61.5)	5 (38.5)	0.04
Female	1 (11.1)	8 (88.9)	
OSA severity			
Mild	2 (66.7)	1 (33.3)	0.76
Moderate	1 (50)	2 (50)	
Severe	6 (37.5)	10 (62.5)	
Number of surgical interventions			
1	3 (23.1)	10 (76.9)	0.09
2	6 (60.7)	3 (33.3)	
Surgery type			
Adenotonsillectomy	6 (40)	9 (60)	0.51
Tonsillectomy	3 (75)	1 (25)	
Adenoidectomy	2 (50)	2 (50)	
Lingual tonsillectomy	1 (50)	1 (50)	
Supraglottoplasty	1 (25)	3 (75)	
UPP	1 (100)	–	
PP	1 (100)	–	

Abbreviations: OAHI, obstructive apnea-hypopnea index; OSA, obstructive sleep apnea; UPP, uvulopalatopharyngoplasty; PP, palatopharyngoplasty.
[a] Data presented as No. (row %) unless otherwise indicated.

4. Discussion

This study investigated the role of upper airway surgery in the treatment of OSA among children with achondroplasia. As demonstrated with other complex medical conditions associated with SDB, such as mucopolysaccharidoses, trisomy 21, and Prader-Willi syndrome, treatment of OSA in children with achondroplasia remains challenging. Several factors may contribute to poor treatment outcomes in this group. Patients with achondroplasia have significant craniofacial and airway abnormalities that are not addressed by common upper airway surgery. Morphological factors such as midface hypoplasia, flattening of the nasal profile, retruded position of the chin and increased mandibular angle can restrict the naso-oropharyngeal cavity and exacerbate OSA [16,17]. Other factors such as hypotonia, pectus excavatum, thoracic kyphosis and lumbar lordosis can also be contributory [18].

Previous studies in this population have demonstrated a predisposition to adenotonsillar hypertrophy and have thus described AT as an effective intervention [4,5]. In a retrospective chart review, Sisk et al. showed that 64% of patients who underwent AT had complete resolution of SDB and did not require further intervention [19]. This rate is lower than what we found in our cohort and other reported studies in children with achondroplasia. In addition, the prior study only contained postoperative polysomnographic data for 6 children while the rest of their analysis relied solely on caregiver-observed symptom improvement. Incomplete resolution of OSA after surgery was also reported by Waters et al. in which 60% of the 10 children who received AT still required CPAP treatment for persistent symptoms [20]. Incomplete resolution of OSA was also reported by Tenconi et al. in which one third of patients with achondroplasia had persistent OSA, although the range of surgeries employed were limited to AT, tonsillectomy, and turbinectomy [21]. Our study demonstrated a high rate of persistent OSA after multilevel surgical intervention, with nearly 25% having increased OAHI scores after surgery. The results show that performing additional sleep surgery did not significantly improve OAHI scores by more than 50% from baseline scores. However, we found a significant reduction in post-operative OAHI for patients in the last quartile with the most severe pre-operative OAHI scores of greater than 25 compared to less severe baseline scores. Taken together, the results suggest that children with very severe OSA are most likely to benefit from surgical intervention

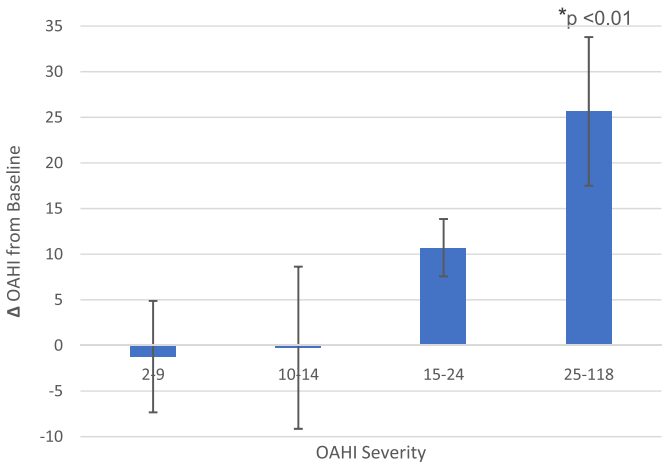

Fig. 1. Changes in postoperative OAHI in children with achondroplasia and obstructive sleep apnea based on pre-operative severity quartile ranges.
Legend: **Δ**, change in; OAHI, obstructive apnea-hypopnea index.

despite the very low likelihood of achieving normal PSG results.

Few studies have reported alternative sleep surgery modalities for children with achondroplasia. In the general pediatric population, supraglottoplasty has been well accepted in the treatment of OSA exacerbated by laryngomalacia [22,23]. The incidence of laryngomalacia has been shown to be greater among children with achondroplasia (5%) compared to the general population (0.5%–1.5%) [22,24]. To date, this is the first study to report outcomes from single-site and multilevel surgical interventions for children with achondroplasia including supraglottoplasty, lingual tonsillectomy, and palatal sleep surgery. It remains unclear which factors may predict improvement and which operations are most appropriate for children with OSA and achondroplasia. Interestingly, all children that underwent adenoidectomy alone required further operations, suggesting that this may be an ineffective first line intervention for this population. Less than 20% of the children in the present study experienced complete resolution of their OSA based on OAHI scores, as compared to the expected 60–80% resolution rate in otherwise healthy children [25,26]. Drug-induced sleep endoscopy (DISE) is a well-accepted and increasingly utilized modality to evaluate areas of collapse in the upper airway to guide surgical decision making for OSA [27]. In the present study, approximately 40% of patients had multilevel collapse and nearly 40% of children required more than one operation. Therefore, DISE may be an appropriate first step to evaluate for multilevel collapse and surgical planning given the craniofacial abnormalities observed with this condition. Due to the persistent nature of the OSA in this population and per current guidelines, postoperative PSG should be pursued following sleep surgery for children with achondroplasia [28]. Caregivers should additionally be counseled about the higher risk of persistent OSA and possible subsequent interventions, as well as the need for long term clinical monitoring.

Limitations of the present study include its small sample size due to the rare disease prevalence of achondroplasia, further narrowed by the inclusion criteria for formal pre- and post-operative PSG data. The results should be interpreted with caution as the study involved patients from two different institutions, introducing variations in surgeon practice and institutional preferences. There was considerable variability in follow-up times, however, the minimum duration was still 1.5 years. Lastly, a consistent definition of appropriate reduction in the OAHI in order to meet criteria of surgical success is not agreed upon in pediatric sleep medicine. OAHI in and of itself as a metric of improved sleep quality is controversial [29]. However, the authors believe that this objective measure is superior to parental reports as it has been shown that parents of children with Down syndrome are unable to predict the presence or severity of OSA by nighttime symptoms [30].

Nonetheless, the present study is still one of the largest representative cohorts to date for objective measures of OSA in children with achondroplasia. Although a prospective study is challenging in identifying OSA in rare disorders such as achondroplasia, a comparison of surgical outcomes in children with isolated AT versus those with preoperative DISE followed by targeted sleep surgery could be explored in future studies. Additionally, questionnaires could also be used to corroborate PSG results and assess for long-term clinical outcomes such as growth, development, and subjective improvement.

5. Conclusion

A unique approach is necessary for the treatment of OSA in children with achondroplasia due to a physiologic predisposition and increased risk of SDB. Our data support previous studies that indicate TA can be an effective treatment in this population and we additionally report our outcomes of multilevel sleep surgery. However, predicting exactly which patient's sleep parameters will improve or worsen after surgical intervention remains unclear. The management of OSA in children with achondroplasia is challenging and monitoring of symptoms should be ongoing, as many are not cured with single-site or multilevel surgery.

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Declaration of competing interest

None declared.

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