A Case Report on Obstructive Sleep Apnea in a Pediatric Patient with Achondroplasia

Eljohn C. Yee, MD and Agnes T. Remulla, MD

Department of Otolaryngology – Head and Neck Surgery, College of Medicine and Philippine General Hospital, University of the Philippines Manila

ABSTRACT

A 22-month-old male diagnosed with achondroplasia was referred for difficulty in sleeping and was diagnosed to have severe obstructive sleep apnea (OSA) on polysomnography (PSG) (AHI 50.1). This patient had macrocephaly, midface hypoplasia, flat nasal bridge, relative macroglossia and enlarged palatine and adenoid tonsils. The patient underwent bilateral tonsillectomy with adenoidectomy without complication. Six months post-op, repeat polysomnography revealed a still severe (AHI 15.7) OSA with preferential recovery of REM and N3 sleep. Further outpatient follow-up and management is warranted. OSA despite being common in this subset of patients remains overlooked and not prioritized because of the multitude of coexisting concerns. Management of OSA in children with achondroplasia shows improved sleep structure and is helpful for further growth and development.

Keywords: achondroplasia, OSA, pediatric sleep apnea, tonsillectomy

INTRODUCTION

Patients with achondroplasia, especially children, are vulnerable to sleep-related disorders. Patients with achondroplasia – the most common genetic form of dwarfism – are recognized by their characteristic phenotypic presentation of disproportionate short stature, craniofacial and skeletal abnormalities, and motor developmental delays due to errors in endochondral ossification.[1] Given these characteristics, these patients commonly have respiratory problems and disturbed sleep.

At present, there is no fixed criteria established for the diagnosis of achondroplasia. Genetic testing is the confirmatory test; however, clinical features often suffice to diagnose Achondroplasia. According to the study of Silao, Asper, Abaya Chiong and David-Padilla in 2008, the majority of, if not all, achondroplasia cases in Filipinos, can be attributed to G380R amino acid substitutions in the FGFR3 gene.[2]

This mutation in the FGFR3 on chromosome 4 leads to the failure of endochondral ossification. Fibroblast growth factors (FGFs) are structural proteins associated with cell growth, migration, wound healing, and angiogenesis. Their function is mediated in the cellular level by the FGF receptor (a tyrosine kinase receptor). The metabolic function of the FGFR3 gene is to limit osteogenesis; mutations in this gene enhance the limiting of endochondral ossification, causing a decrease in the rate of growth of the proliferative zone of the physis, a decrease in thickness of the hypertrophic cell zone, and eventually a diminution in the endochondral bone growth.[1]

Achondroplasia has an average incidence between 1:7,500 and 1:70,000 live births.[2,3] More notable features in

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Corresponding author: Eljohn C. Yee, MD
Department of Otolaryngology – Head and Neck Surgery
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Manila 1000, Philippines
Email: eljohnyee@gmail.com
ORCiD: https://orcid.org/0000-0002-5396-2153

their physical attributes include macrocephaly, exaggerated lumbar lordosis, short proximal limb segments (rhizomelia), and bowing of the mesial segments of the legs.[4] However, patients with achondroplasia, especially children, consult for the management of major respiratory problems including obstructive sleep apnea, waking cyanotic episodes, and chronic respiratory insufficiency and failure.[5] Specific developmental abnormalities in achondroplasia – such as mid-facial hypoplasia, generalized hypotonia, upper airway obstruction, dysplasia of the basiocciput, and craniovertebral junction with foramen magnum stenosis and even possible thoracic cage restriction – often predispose these children to life-threatening situations.[5]

Obstructive sleep apnea (OSA) is the most common respiratory complication in children with achondroplasia; about two-thirds of patients with achondroplasia present with OSA.[6] OSA from the American Thoracic Society, "is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleeping patterns."[7] The current gold standard for the diagnosis of OSA is a nocturnal, in-lab polysomnography (PSG) study; where most clinicians agree that an apnea hypopnea index (AHI) >5/hour in children requires treatment.[8] Untreated or mismanaged OSA leads to several complications due to intermittent-chronic hypoxemia. These complications include pulmonary hypertension, right ventricular dysfunction, and cor pulmonale. In children, persistent OSA has caused failure to thrive and growth retardation; and has been increasingly linked to attention deficit hyperactivity disorder.[9] These complications may be difficult to recognize and much more, to manage in children with achondroplasia. Thus, it is important to document the approach and treatment of OSA in this subset of patients, especially those deemed for operative management. To date, there is no available literature that documents the management of OSA in children with achondroplasia in the Philippines.

CASE PRESENTATION

This is a case of a male toddler who was referred in March 2019 for snoring and noisy breathing during sleep with instances of night awakenings. Assent for case reporting was obtained from the patient's mother. The patient is a known case of achondroplasia; genetically confirmed to have a c.1138 Glycine-to-Arginine mutation in the FGFR3 gene.

The patient was born preterm (33 weeks AOG) with dysmorphic features to a then 41-year-old G_1P_1 (1001) at a hospital in Australia via emergency Low Transverse Cesarean Section secondary to preterm premature rupture of membranes and polyhydramnios, assisted by a physician. The patient's parents have no family history of achondroplasia, dwarfism or associated genetic disorders. The patient was born with dysmorphic features. Skeletal survey done showed craniofacial discordance with a larger head circumference. The patient was noted to have subtle broadening of the metaphyses of the ends of the long bones with no significant bowing with mild exaggeration of the normal lumbar lordosis.

During admission, the patient developed a high grade fever and further assessment showed neonatal sepsis and *E. coli* meningitis. The patient was admitted at the Neonatal Intensive Care Unit, managed with antibiotics for 1 month with improvement of status. The patient was sent home well; and was on close follow-up with his pediatrician.

At the time of consult, the patient was 22 months old and was noted to have difficulty in sleeping, often with episodes of awakening and changing in position.

Upon physical examination, the patient was noted to weigh 10.2 kg; to have macrocephaly (head circumference of 51 cm Z score >3); short stature (body length of 71 cm Z score <-3); frontal bossing and a depressed nasal bridge (Figure 1). Based on the achondroplasia growth chart however, the weight of the patient was in the >75th percentile; the head circumference was within the mean; and the body length was in the 50th percentile.[4,10] On follow-up with Pediatrics, the patient was noted to still have a patent anterior fontanelle. The patient had a cranial ultrasound and was diagnosed to have communicating hydrocephalus. The patient was referred to Neurosurgery for monitoring.

On examination of the oral cavity, the patient had bilaterally enlarged tonsils, Brodsky grade III, bifid uvula (Figure 2) and "relative" macroglossia.[11] On nasopharyngoscopy, the patient was noted to have enlarged adenoids and an unremarkable epiglottis (Figure 3).

The patient underwent diagnostic polysomnography at 1 year of age; and was diagnosed to have severe OSA with an apnea/hypopnea index (AHI) of 50.1; mean oxygenation of 90% and lowest oxygen saturation of 60%. The patient was then recommended for tonsillectomy.

In addition, the patient also had mild to moderate pulmonary arterial hypertension on 2D echocardiography (Estimated Pulmonary Arterial Pressure 40-50 mmHg); the patient also underwent auditory brainstem response of both ears which showed within normal hearing thresholds.

Prior to surgery, the patient was seen by the Anesthesiology and Neurosurgery departments for assessment and clearance of the communicating hydrocephalus and foramen magnum narrowing as it was a concern for positioning. Upon assessment, hydrocephalus was deemed stable and non-progressing. The patient was eventually cleared by the co-managing services for surgery.

On March 23, 2019, the patient underwent bilateral tonsillectomy with adenoidectomy. The right tonsil measured 2.3 x 1.5 x 1.0 cm; left tonsil measured 2.0 x 1.5 x 1.0 cm (Figure 4); adenoidal tissue aggregated diameter measured 1.3 cm. Histopathologic analysis revealed chronic follicular tonsillitis for all samples.

The patient was monitored in an intensive care unit for pulmonary complications. Post-operatively, the patient was noted to have improvement in night awakenings; however,

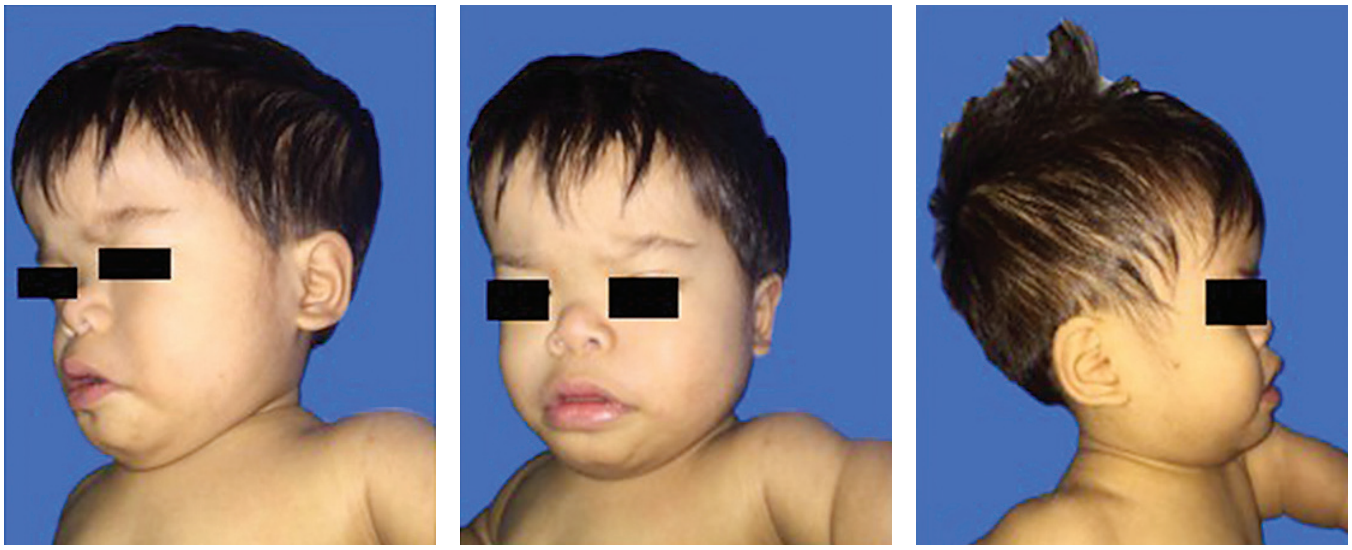

Figure 1. Patient profile shows frontal bossing and a depressed nasal bridge.

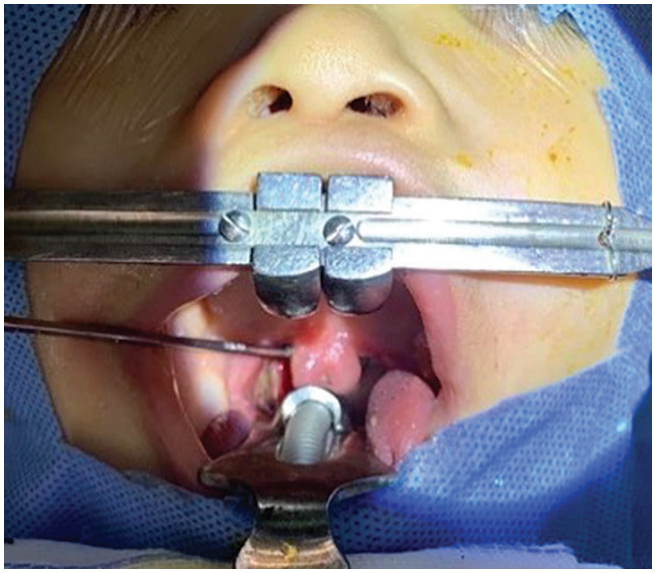

Figure 2. Bifid uvula.

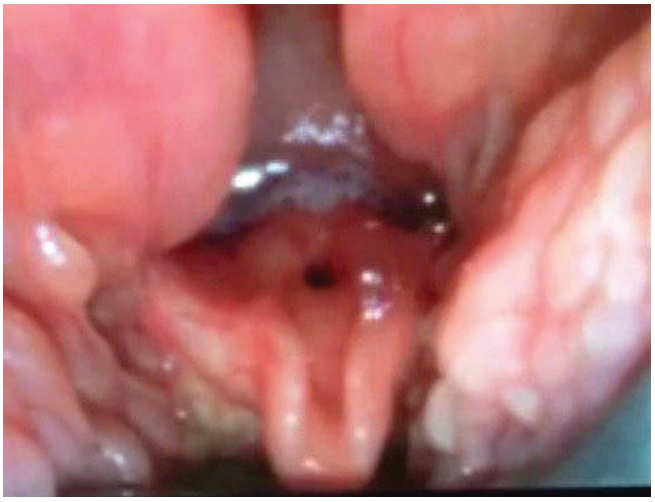

Figure 3. Tail of the tonsil, epiglottis, base of tongue on nasopharyngoscopy.

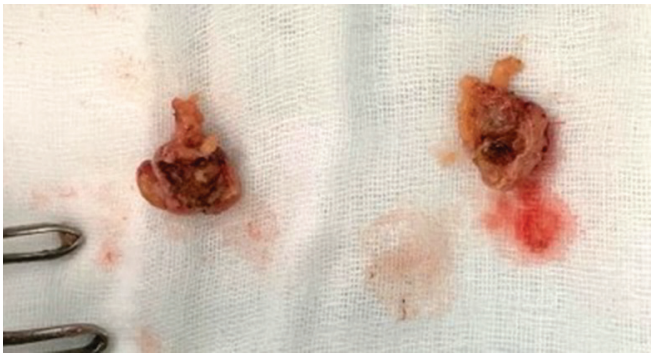

Figure 4. Right and left tonsils.

he still experienced snoring, but to a lesser extent. No post-operative bleeding or pulmonary complications were noted. The patient was sent home two days post-op.

In the interim, the patient was on follow up with Neurosurgery for monitoring of the hydrocephalus. A cranial CT scan with contrast was done and it was noted to have moderate dilatation of the bilateral lateral, third, and fourth ventricles, signifying a communicating type of hydrocephalus; elevated brainstem associated with a large suprasellar cistern and vertically oriented straight sinus and a narrowed foramen magnum. However, these findings were deemed stable and did not need immediate surgical intervention. (Figures 5 and 6).

Cephalometric studies on the skull were also done noting an enlarged skull vault and a small skull base. The skull was

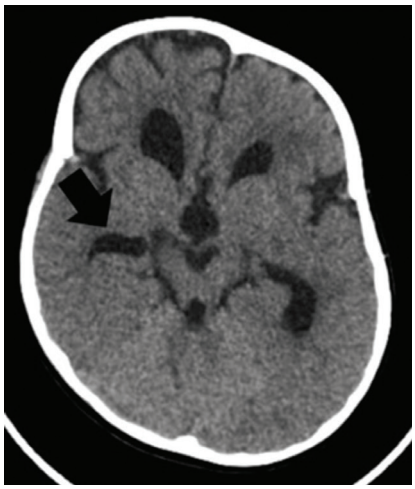

Figure 5. Hydrocephalus: dilated temporal horns of the lateral ventricle *(black arrow)*.

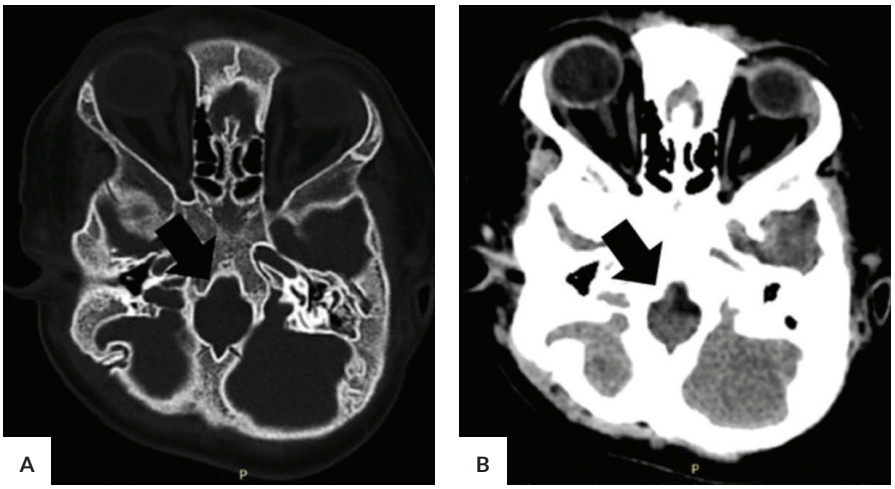

Figure 6. (A) Narrowed foramen magnum in bone window *(black arrow)*. **(B)** Narrowed foramen magnum in brain window *(black arrow)*.

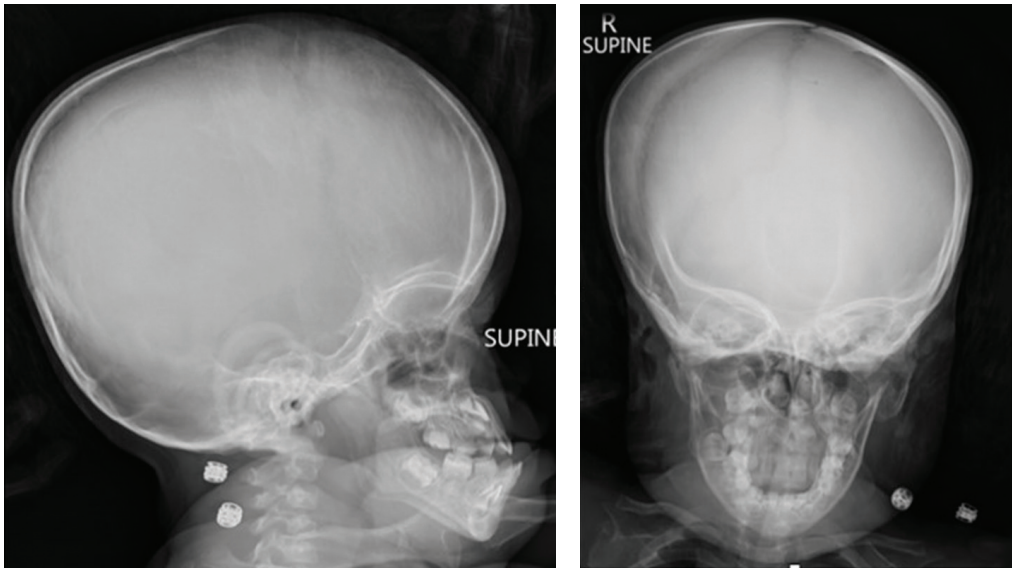

Figure 7. Cephalometric studies (Lateral and AP views) show mesocephalic, macrocephalic skull.

noted to be mesocephalic (measures related to the shape of the skull anterior-posterior diameter; more on the norm in the shape)[12] with a cephalic index of 86.7 (N 71.7-90.4) and macrocephalic (larger in size)[12] with a modulus of 16.9 (N 14.5 to 16.8); also with a flattened midface and nasal bridge (Figure 7).

Six months after surgery, there was noted improvement in the sleep quality of the patient. The patient has been reported to be less irritable; more active during the day, with significant improvement in the loudness of snoring. A repeat diagnostic polysomnography in the same institution however showed the patient to still have severe OSA; with an AHI of 15.7 mean oxygenation of 97% and lowest oxygen saturation of 83%.

One year after surgery, the patient still had noisy breathing while awake and snoring, albeit with significant improvement. The patient was noted to be less irritable; more active during the day, with improvement in the loudness of snoring. Patient is for enrollment to an outpatient program on continuous positive airway pressure (CPAP) therapy; and is on close follow up. Table 1 presents a summary of patient characteristics, work up and management.

DISCUSSION

OSA remains to be a common sleep-related disorder due to an anatomic or functional narrowing of the airways. Treatment particularly revolves around the relief of obstruction

and eventual reversal of some of its complications. For the case presented, preoperative and postoperative polysomnography were done to document the outcome of tonsillectomy and adenoidectomy on the patient (Table 2).

Repeat polysomnogram 6 months post-surgery showed improvement in the AHI and REM sleep. When sleep is disturbed for long periods, sleep architecture shifts to favor shallow sleep stages; with fragmentation and loss of REM and N3 sleep. Preferential recovery of REM sleep and N3 usually occurs after improvement of sleep. For this patient, there is significant improvement in the length of REM sleep from 1.4% to 14.6% and increase of N3 from 70% to 82%. OSA has improved but still remains severe post-surgery (with a pre-operative AHI of 50.1 to 15.7 respiratory events per hour of sleep post-surgery) with concomitant improvement in lowest oxygen saturation and mean oxygen saturation.

Given the patient's profile, the patient is predisposed to be at risk of several possible sleep and respiratory events. Children with achondroplasia, due to errors in endochondral ossification present with several anatomic abnormalities that further complicate the management of OSA. Because of this, residual OSA after tonsillectomy and adenoidectomy is likely. This should be further managed through possible surgical and non-surgical approaches.

Table 1. Patient Summary

Patient	Characteristics	
History	Nighttime awakenings, noisy breathing, snoring	
Physical Exam	Short stature, frontal bossing, depressed nasal bridge, bilaterally enlarged tonsils and adenoids, bifid uvula, relative macroglossia	
Diagnostics	Genetic Testing	c.1138 Glycine-to-Arginine mutation in the FGFR3 gene
	Skeletal Survey	craniofacial discordance, larger head circumference, subtle broadening of the metaphyses of the ends of the long bones
	Cranial UTZ and CT scan	Communicating hydrocephalus
	Cephalometry	Mesocephalic shape, macrocephalic size, flattened midface and nasal bridge
	2D Echo	Pulmonary Arterial Hypertension
PSG	Preop AHI: 50.1	6 months post-op AHI: 15.7
Management	Tonsillectomy, adenoidectomy, Out-patient CPAP therapy	

Genetics

The disease is autosomal dominant, but 80% come from new mutations.[13] The patient has no known family history of achondroplasia, however the genetic testing confirmed that the patient was heterozygous for the trait. The development of this condition for the patient has likely been from a new mutation.

Obstructive Sleep Apnea

Most of the respiratory complications of children with achondroplasia come from the anatomic features of the disease. This patient had enlarged tonsils, a flattened midface and nasal bridge, and relative macroglossia. Sleep-disordered breathing is the most common in this subset of patients and is often obstructive but may also be central in nature.[14,15]

The combination of midface hypoplasia, micrognathia, and depressed nasal bridge causing narrow nasal passages or choanal stenosis, relative adenoid and tonsillar hyper-trophy, relative macroglossia, a high palate and decreased temporo-mandibular joint mobility and airway muscle hypotonia predisposes these patients to upper airway obstruction and OSA. Cervical cord compression at the cervical medullary junction may cause central sleep apneas (CSA) and may require surgical decompression in infancy or early childhood.[14]

In the management of OSA in these patients, literature has reported that cure rates after adenotonsillectomy have been reported in 46.9% after initial surgery. However, ongoing treatment intervention was required in 5.3–12.3% of patients.[16]

For this case, the primary problem was OSA due to anatomic features attributable to achondroplasia. Although there was stenosis of the foramen magnum, no significant CSA was detected. The patient will continue to be monitored by his pediatricians and neurosurgeon.

Table 2. Preoperative and Post-operative Diagnostic Polysomnograph

Parameter	Pre-operative	Post-operative	Normal Value (Children to adults)[6]
Sleep time	416 min	368 min	-
NREM 1	15.5 min (3.7%)	1.5 min (0.4%)	2-5%
NREM 2	104 min (25%)	7.5 min (2%)	35-45%
NREM 3	291.4 min (70%)	305 min (82%)	13-23%
REM	6 min (1.4%)	54 min (14.6%)	30 %
Apnea/Hypopnea Index	50.1	15.7	Mild <5; moderate 5-10; >10 severe
Wake after sleep onset	19	19	
Arousal Index	11.1	11.1	
Lowest Oxygen Saturation	60	83	
Mean Saturation	90	97	

Table 3. Outcomes of Children with Achondroplasia with OSA undergoing surgery

	Sisk et al. 1999[17]	Booth et al. 2020[18]
Patient Population	34	22
Study Type	Retrospective cohort	Retrospective cohort
Intervention	Adenotonsillectomy in 22; adenoidectomy 10 alone; 2 tonsillectomy alone	Adenotonsillectomy only in 11; Supraglottoplasty only in 2; 9 multilevel airway surgeries
Further Intervention	Post adenotonsillectomy: 64%: complete resolution 4.5%: prone positioning in sleep 4.5%: nocturnal CPAP 4.5%: persistent central apnea 9%: mild snoring no further intervention done 13.5%: required additional surgery: uvulectomy, revision adenoidectomy, uvulopalatopharyngoplasty, ± CPAP	Post adenotonsillectomy: 36.4%: required additional surgery: lingual tonsillectomy, Uvulopharyngoplasty, palatopharyngoplasty, supraglottoplasty 4 (out of 22) 18.2% patients had adenoidectomy and eventual tonsillectomy and lingual tonsillectomy
Outcomes	100% improvement in awake respiratory distress, 88% improvement in compensatory sighs, 67% improvement in glottal stops and daytime symptoms	72.7% reduction in post-operative AHI (mean percent reduction 66% ± 21.2); 27.3% worsening AHI. 77.3% improvement in SpO_2%, 18% worse SpO_2%.

Further management and future directions

Residual OSA in patients with achondroplasia following surgical treatment has been described by other studies. In a study by Sisk et al., out of 22 patients who underwent adenotonsillectomy as the first-line surgical therapy, 3 required further surgery to correct their obstruction (Table 3).[17] Surgical outcomes in a study by Booth et al. in 2020 also showcase majority of patients with achondroplasia improving with just adenotonsillectomy, but with a significant subset requiring multilevel airway surgery (Table 3).[18] In another study by Waters et al. in 1996, almost sixty percent of the subset of patients who underwent tonsillectomy and adenoidectomy required further treatment for OSA, primarily involving CPAP.[19] Midface hypoplasia and a depressed nasal bridge may have significant residual OSA following surgery.[1] Hence, tonsillectomy and adenoidectomy alone may not suffice in the treatment of OSA in achondroplasia.

Patients with residual OSA after surgery can opt for positive pressure ventilation (PPV). CPAP is often implemented in infancy and provides effective long term treatment of persisting OSA.[20] For this case, the patient is to be referred for outpatient CPAP use and for re-evaluation if any surgical management is again warranted.

Initiating out-patient CPAP on this subset of patients may be faced with several issues. A study by Amaddeo et al. in 2018 on outpatient initiation of long-term CPAP therapy in children, the subset of children who presented with several developmental delays and behavioral problems never accepted CPAP therapy despite repeated training and visits.[21]

In addition, problems with mask fitting in the use of CPAP may be encountered due to significant midface hypoplasia and the possibility of aggravating this deficiency due to the pressure over the hypoplastic midface.

Further studies suggest that integrated age-adapted education program on CPAP use and a strict follow-up are essential in maintaining compliance.[21] In a case report by Ottonello in 2007, treatment of achondroplasia hypoventilation syndrome and OSA, soft masks individually fitted with silicon cushions were used in assisted controlled pressure ventilation. Although major difficulties in the use of CPAP were encountered initially, these resolved after a few days with the efficacious collaboration of the patient's parents and allied health care personnel.[5] This patient has been on follow up for out-patient CPAP therapy with notable improvement in sleep and night awakenings; with persistent therapy and monitoring, outcomes are expected to improve however, it is important to reiterate that complete resolution may be difficult.

CONCLUSION

OSA remains a common problem faced by children with achondroplasia. Unfortunately, it is frequently overlooked or not prioritized because of the multitude of coexisting concerns. Management of OSA in patients with achondroplasia remains complex. Tonsillectomy with adenoidectomy is a suitable first line surgical treatment for achondroplastic children with OSA associated with adenotonsillar hypertrophy. Complete resolution from this single modality is unlikely. Therefore, close follow-up is needed to monitor persistent airway obstruction and provide additional treatments – such as positive pressure ventilation coupled with an integrated out-patient education program on CPAP. In children with Achondroplasia, management of OSA is accompanied by improvement in sleep structure and is helpful for further growth and development.

Statement of Authorship

Both authors contributed to the conceptualization of work, acquisition and analysis of data, drafting and revising, and approval of the final version submitted.

Author Disclosure

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