Sleep disordered breathing in children with achondroplasia

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Background: **Children with achondroplasia often have breathing problems, especially during sleep. The most important treatments are adenotonsillectomy (for treating upper obstruction) and/or neurosurgery (for resolving cervicomedullar junction stenosis).**

Data sources: **We reviewed the scientific literature on polysomnographic investigations which assessed the severity of respiratory disorders during sleep.**

Results: **Recent findings have highlighted the importance of clinical investigations in patients with achondroplasia, differentiating between those that look for neurological patterns and those that look for respiratory problems during sleep. In particular, magnetic resonance imaging (MRI) and somatosensory evoked potentials are the main tools to evaluate necessary neurosurgery and over myelopathy, respectively.**

Conclusions: **The use of polysomnography enables clinicians to identify children with upper airway obstruction and to quantify disease severity; it is not suitable for MRI and/or neurosurgery considerations.**

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Key words: **achondroplasia;**
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Introduction

Achondroplasia is the most common skeletal dysplasia, recognizable at birth, with an estimated prevalence of 0.36-0.60 per 10,000 births in the United States.[1] Achondroplasia is caused by a heterozygous mutation of fibroblast growth factor receptor 3 gene (*FGFR3*), located on the short arm of chromosome 4 (4p16.3).[2] Life expectancy is long; therefore, the severity of the medical complications associated with achondroplasia varies greatly.[3] In addition to their short stature, patients have macrocephaly and facial hypoplasia, especially with jawbone and abnormal musculoskeletal growth leading to neurological and cardiorespiratory complications.[4]

Children with achondroplasia often have breathing problems, especially during sleep. Sleep disordered breathing (SDB) is well documented in the scientific literature.[5-7] The reported prevalence of SDB varies between 22% and 93%.[4,6,8-10] Snoring, breathing through the mouth and orthodontic problems are frequently involved, particularly in preschoolers with obstructive sleep apnea syndrome (OSAS).[10] OSAS can increase the risk of sudden death in childhood[11-13] and the emergence/persistence of neurocognitive disability in adulthood.[14] The guidelines of the American Academy of Pediatrics (AAP) recommend clinical supervision and early detection of sleep disorders in children at high risk, such as those affected by achondroplasia.[15] Several causes are responsible for OSAS in children with achondroplasia.

The aim of the present paper focuses on the factors predisposing OSAS in achondroplasia and the role of both radiology and polysomnography in the light of new research papers on the topic. Moreover, we discuss whether radiology and polysomnography are interchangeable or complementary in the best clinical practice of these patients.

A literature search for studies published in English in Web of Science, MEDLINE and Scopus databases was conducted using the following keywords: "achondroplasia, children, polysomnography" or "achondroplasia, children, sleep study" or "achondroplasia, children, sleep disordered breathing". A total of 45 published papers were found. Single case reports, retrospective series and case series were included due

to the limited literature available. Three were reviews (one of which was excluded because it did not concern the topic). Moreover, studies which did not perform or declare a polysomnographic or sleep study investigation for the diagnosis of OSAS were excluded.

Pathophysiologies of sleep disordered breathing

Factors predisposing SDB in children with achondroplasia are hypoplasia of the middle portion of the facial bones, dysplasia of the skull base and cervical stenosis responsible for compression of the spinal cord.[16] Children with achondroplasia have a smaller diameter of the foramen magnum that persists for life. This problem is present in 28% of the patients with OSAS, suggesting a link between hydrocephalus and breathing problems during sleep. In the most severe cases, this complication can lead to hydrocephalus.[17] Myelopathy, a result of pressure on the cervical spinal cord, leads to central apneas (CA) and causes an increased risk of sudden death.[18,19]

Craniofacial and airway morphology are important factors that contribute to the obstruction of the upper airways in these children.[20] Mid-face hypoplasia and flattening of the nasal profile, which causing a small naso-oropharyngeal cavity, contribute to OSAS (Fig. 1). In particular, the craniofacial/airway morphology of children with achondroplasia is characterized by upper airway stenosis, a retruded position of the chin, an increased mandibular angle due to partial early ossification of cranial bones, and an increased lower facial height due to the increased mandibular angle, which lead to snoring and apnea during sleep.[20]

Other causes of difficult breathing in children with achondroplasia are hypotonia, pectus excavatum, reduced anteroposterior diameter, thoracic kyphosis and lumbar lordosis.[10]

Hypoxemia without apnea was found in 44% of children under 14 years of age. Some of them had both hypoxemia and hypercarbia, which suggested the presence of a reduced pulmonary reserve. This condition can be generated from restrictive lung diseases secondary to hypotonia, kyphosis at the thoracolumbar and short chest cavity.[8] Hypotonia is responsible for the delay in motor skills. The thoracolumbar hump develops secondary to axial hypotonia that resolves spontaneously with age; with the acquisition of a standing position, it evolves to hyperlordosis.

The high incidence of SDB in children with achondroplasia maybe due to other medical conditions such as adenotonsillar hypertrophy and recurrent infections of the upper respiratory tract. Enlarged tonsils and adenoids may worsen the obstruction and predispose to recurrent infections of the upper respiratory tract, particularly in childhood. However, because not all children with adenotonsillar hypertrophy have OSAS,[21] other clinical conditions such as peculiar craniofacial morphology, may have a role in causing SDB. Indeed, a close relationship has been found between abnormal bone growth, reduced base of the cranium and hypoplasia of the middle third of the face, and obstruction of the upper airways. These factors help to explain the persistence of significant OSAS even after an adenotonsillectomy.[6] Moreover, in one study, an endoscopic evaluation of children with achondroplasia who had OSAS under polysomnography revealed that 5.5% (aged between 1 and 20 months) showed airway malacia that required more invasive airway treatments.[22]

Clinical and instrumental investigations are important to assess the conditions predisposing to SDB in these children so that optimal management of the condition can be planned.

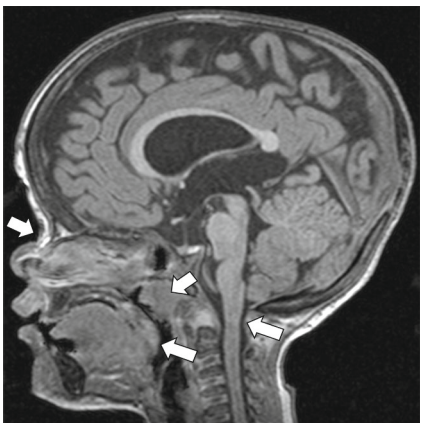

Fig. 1. Magnetic resonance imaging of the skull of a 2-year-old boy with achondroplasia showing the craniofacial and airway morphology.

Magnetic resonance imaging and somatosensory evoked potentials

Both magnetic resonance imaging (MRI) and somatosensory evoked potentials (SEPs) are able to explore the anatomical structures involved in cervical spinal cord stenosis.[12] SEPs and MRI (or cranial computed tomography) may be carried out in patients with neurological symptoms suggesting hydrocephalus or foramen magnum stenosis.[16] Many babies between 6 and 12 months were asymptomatic despite the compression of the spinal cord.[23] In a study of nine patients who underwent neurosurgery, each had abnormal SEPs and abnormal plain CT, but only four had obvious sleep apneas prior to surgery.[24] Overnight sleep studies performed on 20 subjects did not show any correlation between abnormal SEPs and

apnea index during sleep, either qualitatively or quantitatively.[25] Conversely, conventional SEPs are confirmed to be highly specific in the most severely affected patients, like symptomatic patients with myelomalacia, for instance.[26] In particular, the median nerve (MN)-SEPs, notably the subcortical tracings, are accurate for the detection of cervical myelopathy. On the contrary, the posterior tibial nerve (PTN)-SEPs are less sensitive.[27] In a case report regarding progressively worsening hypotonic quadriparesis, a severe cervicomedullary compression was confirmed by MRI. SEPs revealed bilaterally prolonged interpeak Erb-N13 latencies, slowing of central conduction time N13-N20 from right MN stimulation, and block from the left median nerve. In spite of suboccipital craniectomy and cervical-C1 laminectomy, both the neurologic and respiratory problems (rapid, shallow and almost abdominal breathing) remained unchanged and the patient died 4 1/2 months later.[13] In a retrospective study, 10 neurologically compromised infants (4 to 23 months) were assessed prior to surgery with MRI. After cervicomedullary decompression, 70% of the children showed an improved neurological condition (and sleep respiratory pattern), but one displayed neurological deterioration.[28] Recently, MRI was not recommended to be used alone to assess significant foramen magnum stenosis in infants with achondroplasia, nor in isolation to dictate surgical interventions. MRI findings must be viewed in concert with a physical exam, history and sleep study.[29] Radiology is a static evaluation that is not able to demonstrate the respiratory pattern of children with achondroplasia.

Polysomnography

A summary of the medical literature concerning SDB in achondroplasia patients in which overnight PSN was included in the clinical evaluation is shown in Supplementary Table.[6,8,9,11,14,22,24,25,28-48]

With PSN, authors showed that the frequency of SDB in patients with achondroplasia was high, ranging from 42% to 82%.[9,17,24,25,39,44,46,49] Airway malacia was frequently observed in these children (5.5%) and associated with increased occurrence of OSAS.[22] One study that took a questionnaire survey among Australian families revealed that PSN studies for SDB in children with achondroplasia (0-5 years) were done in only 38% in the first 12 months and only one-third of children by age 5 had undergone a formal PSN study.[47] An assessment of these investigations has been proven to be quite difficult mainly because of geographic or service capacity reasons.

In two studies, CA and more often central hypopnea, were demonstrated through overnight PSN to investigate for neurological involvements.[45,50] In another study, hydrocephalus was a condition linked to the findings of CA at PSN. Authors suggested that high-risk infants can be identified through a comprehensive evaluation that included neurological and general examinations, computed tomography for foramen magnum stenosis, and PSN evaluation.[16] Abnormal PSN was associated with reduced mental capacity at psychometric testing and with a history of respiratory dysfunction.[41] Other studies suggested that PSN was not able to assess neurosurgery indications if based only on a CA assessment,[45,49,51] although it was able to recognize clinical improvement after decompressive neurosurgery[28,40,45,48] or upper airway surgery.[8,21,41,44]

In another review study, there was no correlation reported between OSAS severity assessed by PSN and abnormalities on SEPs evaluation at the first evaluation in 30 initial studies; but repeat SEPs studies in 10 subjects, after clinically effective treatment for OSAS, showed modestly improved SEPs scores in five out of seven cases (71%) that initially had abnormal values.[14] From another study, SEPs was not effective to screen for respiratory abnormalities.[25]

Two studies used polygraphy. One study used it together with other clinical investigations to assess the severity of SDB and its classification;[16] another for the follow-up of children who had undergone interventions for SDB, where it confirmed an improvement in SDB after upper airway surgery and/or noninvasive positive-pressure ventilation (NPPV).[6]

In summary, SDB was more frequent in younger achondroplasia patients (≤3 years) and symptoms were underreported by parents;[38] decompressive surgery[33-35,44,45] or midface distraction osteogenesis[32] gained improvement of SDB signs and symptoms. A 2-year-old girl with achondroplasia female was reported with repeated episodes of respiratory pauses during sleep and recurrent sighs; brief CA not associated with desaturations and/or electroencephalogram (EEG) arousal suggested a subclinical respiratory dysfunction.[37] Another case concerned a neurologically asymptomatic 3-month-old female child with snoring; she had mild SDB with CA and obstructive apneas (OA) that spontaneously resolved without intervention three months later, which were linked to immaturity of the brainstem.[36] Minor findings regarded unconfirmed alteration of growth hormone (GH) excretion during sleep.[30,31,42]

A summary of the medical literature concerning SDB in achondroplasia patients in which overnight PSN was included in the clinical evaluation is shown in Supplementary Table. Review articles (Table) reported that respiratory disorders in these children are complex[52]

Table. Summary of the review that included an evaluation of sleep disordered breathing in children affected by achondroplasia

Author[ref.]	Target of review	Sleep disordered breathing	Conclusions
Lyford-Pike S, 2012[52]	Otolaryngology evaluation (in skeletal dysplasias); middle ear disease and hearing loss involvement	Causes are complex	ATE is first-line treatment
Afsharpaiman S, 2013[7]	Respiratory dysfunctions and their sequelae in achondroplasia	Common respiratory disorder is OA; 95% of preschool children snore, 45% had witnessed apnea	ATE led to an Apnea Index improvement

ATE: adenotonsillectomy; OA: obstructive apnea.

and very common[7] and that adenotonsillectomy is the first line measure and leads to great improvement of symptoms.

Overnight polysomnography

Polysomnography (PSN), at a minimum, must include an overnight sleep study with EEG to investigate for CA and OA, hypoxia and hypercapnia.[29] A higher index of SDB was demonstrated with PSN in very young children with achondroplasia compared to normal controls. The former have a lower index of spontaneous awakening and breathing. This finding suggested a higher risk of sudden death.[9] Furthermore, it has been observed that PSN is important in children under 2 years old who are at the greatest risk of developing OSAS.[17]

Our recent study[38] on 9 children with achondroplasia compared the characteristics of sleep reported by parents and the sleep structure breathing pattern from an overnight polysomnographic test. Of all the children, SDB was more severe in the youngest (age under 3 years). Enlarged tonsils and adenoids were not always correlated with respiratory problems in sleep. In addition, respiratory symptoms reported by parents were not always consistent with the results shown by PSN. This reflects the objective difficulty that parents encounter in assessing the quality of sleep of their children.

Some studies showed that both CA and the apnea-hypopnea index (AHI), assessed by overnight PSN, did not correlate with the stenosis of the foramen magnum,[17,51] contrary to what other studies have reported.[16,49] In one study, PSN was suggested as a post-surgery follow-up. When done after decompression surgery, the cervical spinal cord showed full resolution of CA in symptomatic patients with achondroplasia.[48] Unfortunately, some difficulties have been reported concerning the application of this technique. In particular, the experience of the polysomnographer/respiratory physician must be reliable, and the number of certified pediatric sleep medicine centers is generally small.[29]

Polygraphic sleep study

Many cardiorespiratory sleep studies in unaffected children were done with thorax and abdomen effort bands, airflow measures, ECG, pulse oximetry (SpO_2) monitoring,[53] snoring by laryngeal microphone and position analysis. Zucconi et al[43] evaluated an at-home portable system in a sleep laboratory comprising measurements of airflow (thermistry), snoring, chest and abdominal wall movements, ECG, position, and oximetry with good sensitivity. Rosen et al showed an a sensitivity of 88% and specificity of 98% in diagnosing a laboratory PSN based AHI >5/hour. This was proposed as a technically adequate method to detect apnea and to quantify the degree of hypoxia,[54] reporting excellent data in 61% of cases and good in 36%.[55] Such devices seem to be technically feasible also in school-aged children[56] if analyses are performed in accordance with the technical and digital specifications of the American Academy of Sleep Medicine (AASM) rules.[57]

In children with achondroplasia, an overnight polygraphic sleep study that records nasal flow, respiratory movements (bands), tracheal sounds, body position, ECG, heart rate, transcutaneous oxygen, and carbon dioxide pressure was done in room air to score for OA and CA.[6]

Recently, home respiratory polygraphy in children with a clinical suspicion of OSAS emerged as a potentially useful and reliable approach for the diagnosis with a sensitivity of 91% and a specificity of 94%.[58] Accordingly, in our children, we did an assessment of continuous monitoring of nasal airflow, chest and abdominal respiratory movements (thoracic and abdominal belts), arterial oxygen saturation (SaO_2; digital pulse oxymetry), heart rate (finger probe), ECG, body position (mercury sensor) and tracheal sounds (microphone). Estimated total sleep time (eTST), movement periods,[59] respiratory events,[57,60] and phase angle as an index of inspiratory effort[61] were evaluated according to published criteria. Overnight polygraphy is able to detect OA (Fig. 2) and CA (Fig. 3) and to score respiratory patterns during sleep.

Conclusions

Children with achondroplasia often have breathing problems, especially during sleep. Recent findings have highlighted the importance of instrumental investigations in patients with achondroplasia, differentiating between those that investigate neurological patterns (MRI and SEPs) and those looking at sleep respiratory aspects (PSN). In particular, MRI and SEPs are the main tools to

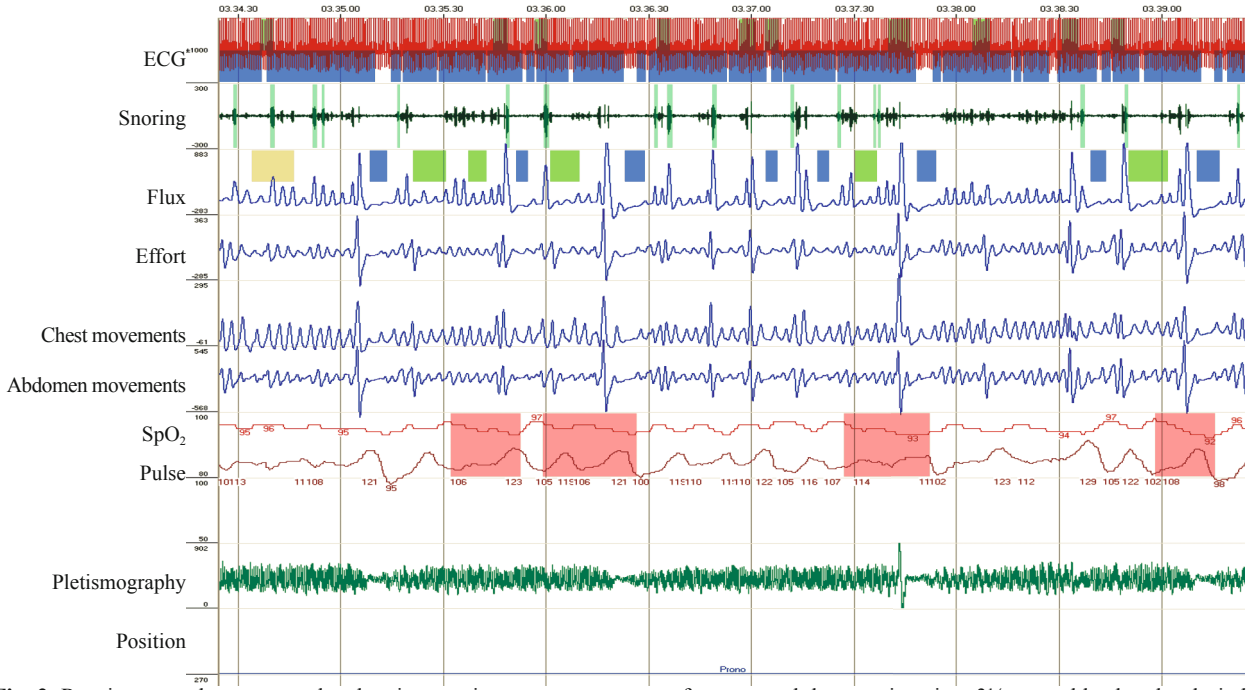

Fig. 2. Respiratory polysomnography showing snoring, recurrent events of apneas and desaturations in a 3½-year-old achondroplasia boy with severe OSAS. Both MRI and SEPs results were normal. ECG: electrocardiogram; MRI: magnetic resonance imaging; OSAS: obstructive sleep apnea syndrome; SEPs: somatosensory evoked potentials; SpO_2: blood oxygen saturation level.

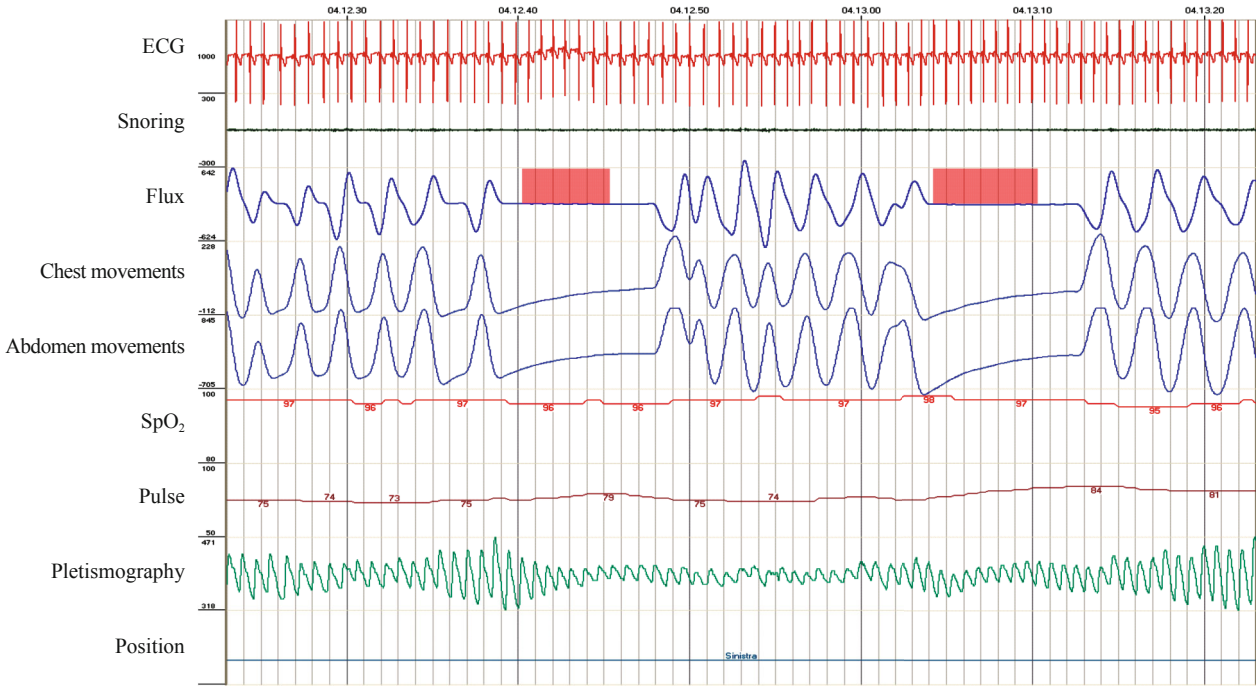

Fig. 3. Respiratory polysomnography showing central apneas in a 12-year-old achondroplasia girl with mild OSAS, with no desaturation or changes in HR. ECG: electrocardiogram; HR: hearth rate; OSAS: obstructive sleep apnea syndrome; SpO_2: blood oxygen saturation level.

evaluate the need for neurosurgery and over myelopathy, respectively, but not to assess OSAS severity. The study of sleep by PSN enables the clinician to identify children who have OSAS and to classify its severity; it is not suitable for MRI and/or neurosurgery considerations. Unfortunately, research studies regarding respiratory polygraphy in these children are limited today. There are many difficulties in referring patients to a certified pediatric sleep center. Further studies are necessary to confirm the suitability of polygraphic studies, with

appropriate channels, in patients with achondroplasia to investigate obstructive events and oxygen desaturations during sleep in view of possible upper-airway surgery (adenotonsillectomy) and follow-up.

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