Achondroplasia Foramen Magnum Score: screening infants for stenosis

Moira S Cheung ,[1] Melita Irving,[2] Alessandra Cocca ,[1] Rui Santos,[3] Meera Shaunak,[1] Harry Dougherty,[1] Ata Siddiqui,[4] Paul Gringras,[5] Dominic Thompson[6]

[1]Department of Paediatric Endocrinology, Evelina London Children's Hospital, London, UK
[2]Department of Clinical Genetics, Guy's and St Thomas' NHS Foundation Trust, London, UK
[3]Department of Paediatric Radiology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[4]Department of Neuroradiology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[5]Department of Sleep and Neurodisability, Evelina London Children's Hospital, London, UK
[6]Department of Paediatric Neurosurgery, Great Ormond Street Hospital, London, UK

Correspondence to
Dr Moira S Cheung, Department of Paediatric Endocrinology, Evelina London Children's Hospital, London SE1 7EH, UK; Moira.Cheung@gstt.nhs.uk

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ABSTRACT

Background Achondroplasia is associated with foramen magnum stenosis (FMS) and significant risk of morbidity and sudden death in infants. A sensitive and reliable method of detecting infants who require decompressive surgery is required. This study aims to describe the incidence and severity of FMS in an unselected, sequential series of infants using a novel MRI score and retrospectively correlate severity with clinical examination and cardiorespiratory sleep (CRS) studies.

Methods The Achondroplasia Foramen Magnum Score (AFMS) was developed and scores were retrospectively correlated with clinical and CRS data over a 3-year period.

Results Of 36 infants (M:F, 18:18), 2 (5.6%) did not have FMS (AFMS0); 13 (36.1%) had FMS with preservation of the cerebrospinal fluid (CSF) spaces (AFMS1); 3 (8.3%) had FMS with loss of the CSF space but no spinal cord distortion (AFMS2); 13 (36.1%) had FMS with flattening of the cervical cord without signal change (AFMS3); and 5 (13.9%) had FMS resulting in cervical cord signal change (AFMS4). Mean Total Apnea and Hypopnea Index (TAHI) for AFMS0–4 was 3.4, 6.41, 2.97, 10.5 and 25.8, respectively. Severe TAHI had a specificity of 89% but only a 59% sensitivity for AFMS3–4. Neurological examination was normal in 34/36 (94%) patients. Overall, 9/36 (25%) infants required neurosurgery with minimal surgical complications.

Conclusions Clinical examination and CRS have a low sensitivity for predicting the effects of foramen stenosis on the spinal cord. Routine screening with MRI using AFMS can aid in detecting early spinal cord changes and has the potential to reduce infant morbidity and mortality.

What is already known on this topic?

- Foramen magnum stenosis (FMS) is a complication that can cause sudden infant death in infants with achondroplasia.
- Sleep studies are not sensitive for detecting FMS.
- Neurosurgical decompression is an effective treatment for FMS.

What this study adds?

- Achondroplasia Foramen Magnum Score (AFMS) is a novel simple scoring system which categorises the severity of FMS on MRI.
- Half of infants with achondroplasia show spinal cord changes on MRI of whom the majority (94%) will have a normal clinical examination.
- Routine screening with MRI using AFMS can detect early spinal cord changes and has the potential to reduce infant morbidity and mortality.

INTRODUCTION

Achondroplasia is the most common form of non-lethal skeletal dysplasia affecting 1 in 25 000–30 000 births. The phenotype is secondary to unregulated, constitutively activated signal transduction of fibroblast growth factor receptor 3 (FGFR3). Most cases (80%) occur de novo, however some are transmitted in an autosomal dominant manner.[1]

During normal skeletal maturation, *FGFR3* has a negative regulatory effect on bone growth. A recurrent pathogenic variant (c.1138G>A; p.Gly380Arg) in *FGFR3* leads to site-specific abnormalities in endochondral and intramembranous bone growth and development.[2] Pathological foramen magnum stenosis (FMS), as seen in achondroplasia, is postulated to be secondary to hypertrophy of the occipital rim, overgrowth of the opisthion and abnormal position and premature closure of skull base synchondroses.[3] Compression of vital brainstem structures including central respiratory centres, cranial nerve nuclei and cranial nerves can occur resulting in disordered breathing. Centrally mediated apnoea, a recognised complication of FMS, is a likely contributory factor to the increased risk of sudden unexpected death in infancy in this population group, which is reported to be as high as 7.5% in infants.[4 5]

Achondroplasia typically presents in the last trimester or at birth so recognition by neonatal/general paediatricians of early complications is important. There is a lack of consensus surrounding the need for and optimal timing and choice of screening modality for cervicomedullary compression in infants with achondroplasia.[3]

The American Academy of Pediatrics recommends either CT or MRI to evaluate changes at the foramen magnum (FM) in all infants with achondroplasia.[6] However, more recently best practice guidance based on expert consensus recommended that MRI scans should be reserved for those infants with either an abnormal detailed clinical neurological history and examination (performed every 2 months for the first year of life), or polysomnography (PSG) abnormalities suggestive of FMS.[7] Abnormal neurological manifestations of

FMS include hypotonia, motor delay, feeding and sleep disorders,[8] and clinical features of myelopathy such as hyper-reflexia and ankle clonus, when present, strongly predict the need for decompression surgery in the infant population.[9] Neurological sequelae, however, are a late manifestation of high cervical spinal cord compression and considerable experience of what is 'normal' in achondroplasia is required to determine what constitutes clinically significant findings. Furthermore, there are no studies assessing the sensitivity or specificity of abnormal clinical examination findings.

Studies examining the predictive value of PSG or cardiorespiratory sleep (CRS) study parameters in the identification of FMS in children with achondroplasia suggest low screening sensitivity.[10 11]

Neurosurgical opinion regarding the need for surgery in the face of FMS in achondroplasia remains inconsistent and practice varies significantly between different centres,[12] with rates of cervicomedullary decompression ranging from 4.6% to 43%.[13] There are no agreed criteria for grading the radiological changes at the FM in these individuals, or consensus on when it is appropriate to intervene surgically. While the outcome of neurosurgical intervention is generally favourable,[14] severe complications, such as cerebrospinal fluid (CSF) leakage, vascular injury and worsening neurological function, are well recognised, therefore a sensitive and reliable method of selecting infants who require decompression surgery is required.

STUDY AIMS

This study aimed to describe the incidence of FMS in an unselected, sequential series of infants with achondroplasia using MRI and to correlate this with findings from clinical examination and respiratory sleep studies. To achieve this an MRI-based grading system was devised to objectify the effect of FMS on the cervicomedullary junction (figure 1). We also aimed to describe the neurosurgical intervention and associated complication rate.

ACHONDROPLASIA SERVICE

Our tertiary achondroplasia multidisciplinary clinic is the largest service in the UK and provides regular surveillance for over 200 children confirmed by either *FGFR3* analysis or conventional radiographic skeletal survey. Since the screening programme began in 2016 all infants have undergone routine screening MRI of the brain and cervical spine, CRS and careful neurological examination performed by a consultant paediatrician with over 10 years' experience of examining children with rare skeletal disorders. Neurosurgery referral is made based on abnormal neurological examination, severely abnormal CRS or MRI changes within the spinal cord.

PATIENTS AND METHODS

Medical records and imaging of all infants attending the clinic over a 4-year period from January 2016 to January 2019 were retrospectively reviewed. Data extracted included demographic data, the timing and method of diagnosis, clinical history suggestive of apnoea, physical examination findings, MRI images, CRS results, neurosurgical interventions and any related complications.

For infants under 6 months the MRI policy is to use a 'feed and wrap' method. If this is unsuccessful, an MRI under general anaesthesia was then undertaken. The diagnostic MRI was performed using the standard institutional protocol, including sagittal and axial T2 images of the FM, and was reported by a paediatric neuroradiologist and independently scored by a second paediatric radiologist. MRI reports were graded as normal, or, in the presence of craniovertebral junction (CVJ) abnormalities, using the Achondroplasia Foramen Magnum Score (AFMS) as shown in figure 1. AFMS1 is defined as constitutional narrowing of the FM with preservation of CSF evident in either sagittal or axial T2 images. AFMS2 is defined as narrowing of the FM with loss of CSF space surrounding the cord but without cord distortion. AFMS3 is defined as having evidence of cord compression

AFMS0	AFMS1	AFMS2	AFMS3	AFMS4
Normal foramen magnum	Constitutional narrowing of the foramen magnum with preserved CSF (no cord distortion)	Narrowing of the foramen magnum with loss of CSF space surrounding the cord	Loss of the CSF space with cord compression	Cord compression and signal changes (Myelomalacia)

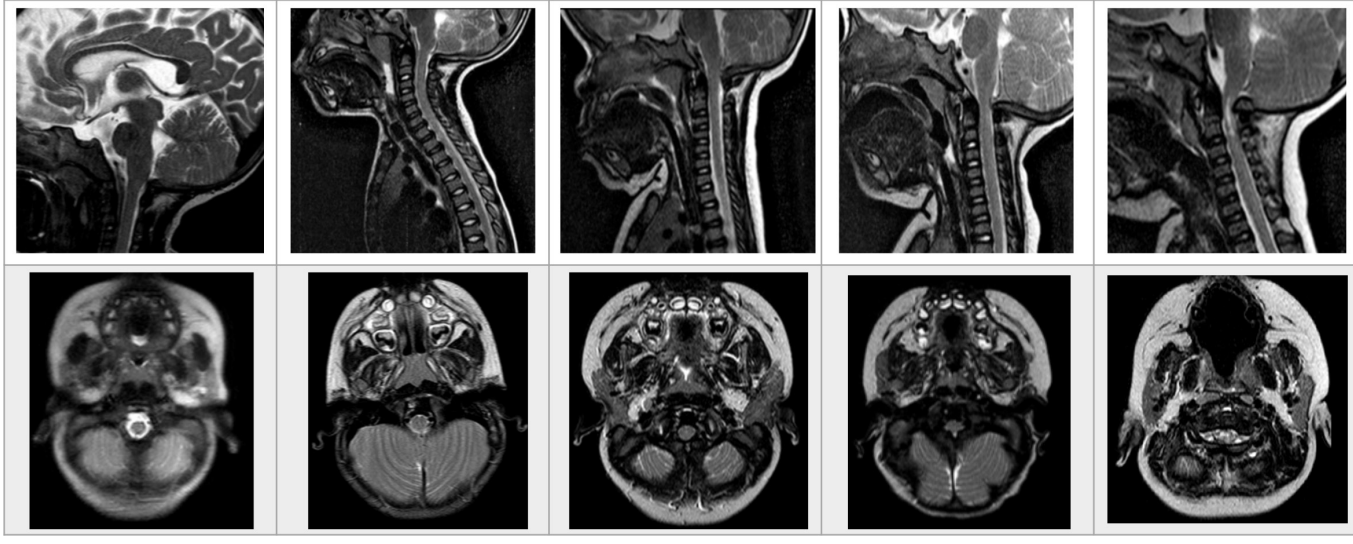

Figure 1 Achondroplasia Foramen Magnum Score (AFMS). CSF, cerebrospinal fluid.

Table 1 Baseline characteristics of patients

Characteristic	Number of infants (n=36)
Gender	
Male	18 (50%)
Female	18 (50%)
Timing of diagnosis	
Antenatal period	23 (64%)
Postnatal period	12 (33%)
Unknown	1 (3%)
Diagnostic investigations	
Genetic testing (*FGFR3*)	33 (92%)
Skeletal survey only	3 (8%)

at FM but without cord signal changes and AFMS4 is the presence of cord compression and cord signal changes in T2 images.

CRS results were reviewed to determine if there was an association between the frequency, type and severity of apnoeic events and FMS (according to AFMS). Using criteria from the American Academy of Sleep Medicine,[15] the Apnea and Hypopnea Index (AHI) was calculated as a function of per hour of sleep and further classified into obstructive and central apnoeic events. Depending on the frequency of obstructive sleep events, this was further subdivided into mild (1 to <5 episodes/hour), moderate (5–10 episodes/hour) or severe (>10 episodes/hour) categories. Subjective parental reports of snoring and apnoeic 'breath-holding' episodes were noted.

The neurosurgical procedure for FMS in achondroplasia consisted of bony decompression at the level of the FM and posterior arch of the atlas. Postoperative CT was performed to confirm the extent of decompression and operative and perioperative morbidity outcomes were collected.

Study subjects with a skeletal dysplasia diagnosis other than achondroplasia and those whose MRI studies were non-diagnostic were excluded.

RESULTS

During the study period, 37 infants with achondroplasia underwent surveillance MRI scans of the brain and cervical spine in their first year of life. One infant was excluded from the study due to poor quality imaging from movement artefact and therefore 36 infants were included. The baseline characteristics of the infants included in this study are reported in table 1. Mean age at first MRI scan was 7 (SD±4) months. At the time of case note review, the age range of the included patients was 1–5 years.

Only 2 (5.6%) infants had no evidence of FM narrowing reported (AFMS0). Constitutional FM narrowing with preservation of the CSF space around the cord (AFM1) was reported in 13 (36.1%). FM narrowing with loss of the CSF spaces but no spinal cord compression (AFMS2) was reported in 3 (8.3%). FM narrowing with flattening/distortion of the cervical cord (AFMS3) was reported in 13 (36.1%). FM narrowing resulting in cervical cord T2 signal change (AFMS4) was reported in 5 (13.9%). Spinal cord changes were present in 50% of all infants (AFMS3–4: n=18, F:M 10:8). According to protocol, all infants with spinal cord signal change had FM decompression. In infants with spinal cord flattening but no signal change, assessment of clinical examination and CRS studies contributed to the decision to either operate or monitor with a repeat MRI in 1 year.

Only patients with AFMS3 or AFMS4 changes underwent FM decompression (n=8). Another infant had only mild changes at the FM (AFMS1), but the additional presence of hydrocephalus necessitated ventriculoperitoneal shunting without FM decompression (n=1). The seven patients with AFMS3 at initial screening who did not undergo decompression at that stage had a repeat MRI after a year. Of these, three had progressed to AFMS4 and then underwent decompression, two remained at AFMS3 while the other two improved to AFMS1 and AFMS2 (figure 2). All patients who underwent decompression with AFMS4 had residual myelomalacia identified on their follow-up MRI a year after surgery (figure 3).

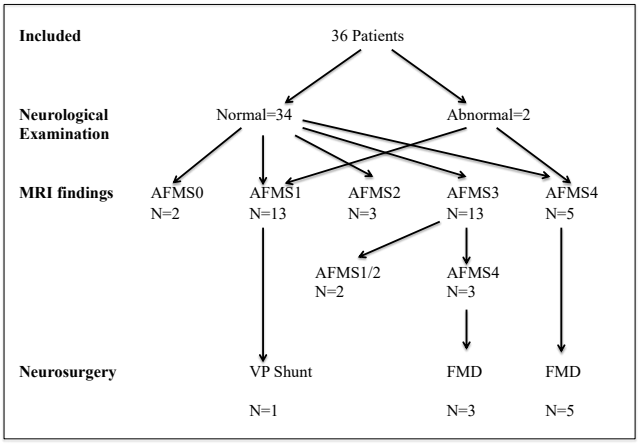

Figure 2 Algorithm showing the neurological examination, as defined by the presence of abnormalities in deep tendon reflexes, sustained clonus, hypotonia/hypertonia, paresis, asymmetry of movement or abnormal plantar responses, MRI changes, need for neurosurgical intervention. AFMS, Achondroplasia Foramen Magnum Score; FMD, foramen magnum decompression; VP, ventriculoperitoneal.

Overall, 25% (9/36) of the total cohort and 44% of AFMS3–4 (8/18) underwent neurosurgery, at a mean age of 15 months (range 9.5–28 months). This comprised eight children who underwent FM decompression, and one child requiring ventriculoperitoneal shunt insertion.

Postoperative complications in these patients included one wound infection, which completely resolved with antibiotics, and one case of restenosis where repeat FM decompression was required 15 weeks after the initial surgery because of new bone formation. There was no reintubation or adverse neurological complications in any surgical cases.

Only two infants (2/36) had abnormal clinical findings on neurological examination. The first had unilateral absence of deep tendon reflexes, dilated scalp veins and pronounced

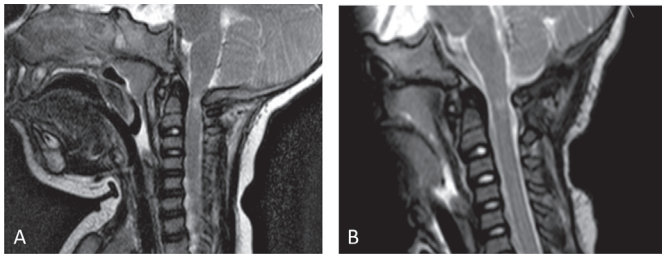

Figure 3 Image (A) demonstrates the MRI finding in an infant with AFMS4 prior to foramen magnum decompression and image (B) is the follow-up scan 1 year after surgery. There is now no compression of the spinal cord, but signal change remains. AFMS, Achondroplasia Foramen Magnum Score.

Table 2 Cardiorespiratory sleep study indices and Achondroplasia Foramen Magnum Score (AFMS)

	AFMS0	AFMS1	AFMS2	AFMS3	AFMS4
Patient, n (%)	2 (5.6)	13 (36.1)	3 (8.3)	13 (36.1)	5 (13.9)
OSA (%)					
Normal	0	3 (23)	0	1 (8)	0
Mild	2 (100)	6 (46)	3 (100)	3 (23)	1 (20)
Moderate	0	2 (15)	0	2 (15)	0
Severe	0	2 (15)	0	6 (46)	4 (80)
Missing data	0	0	0	1 (8%)	0
TAHI					
Mean (SD)	3.4 (0)	6.41 (8.98)	2.97 (1.67)	10.5 (8.86)	25.77 (20.65)
Median	3.40	4.10	2.00	8.50	23.40
OAHI					
Mean (SD)	0.99 (0)	4.1 (7.57)	1.07 (0.12)	4.3 (5.30)	24.88 (20.81)
Median	1.30	1.30	1.00	2.10	23.25
CAHI					
Mean (SD)	0.1 (0)	2.81 (2.77)	0.8 (0.2)	5.34 (8.03)	0.73 (0.8)
Median	0.10	2.40	0.80	3.00	0.40

CAHI, Central Apnea and Hypopnea Index in episodes per hour; OAHI, Obstructive Apnea and Hypopnea Index in episodes per hour; OSA, obstructive sleep apnoea; TAHI, Total Apnea and Hypopnea Index in episodes per hour.

hypotonia. MRI demonstrated ventriculomegaly requiring a ventriculoperitoneal shunt, but only AFMS1. The second infant with increased upper limb reflexes, but normal lower limb reflexes and AFMS4, had FM decompression. Therefore, out of 36 infants, abnormal routine clinical neurological examination (n=2) had a high specificity of 100% for AFMS3/4 or significant ventriculomegaly (n=19), but a low sensitivity of 11% (n=17 of true negatives) in this age group.

Snoring or sleep apnoea was subjectively reported in 22 (61.1%) infants, and 35 infants underwent screening CRS (one was performed in a local hospital and detailed CRS results were not available so excluded from the analysis). Overall, disordered sleep breathing was detected in 88.5% (n=31) of infants. Only 11% (n=4) of patients had normal CRS. Mild obstructive sleep apnoea (OSA) was reported in 15 (42.9%) infants and moderate OSA was noted in 4 (11.4%) infants. Severe OSA was detected in 12 (43.8%) infants (table 2). There was a positive correlation between AFMS and severity of OSA (correlation coefficient 0.42), but the negative predictive value of an infant (n=35) having AFMS0–2 (n=18) with a normal or mild AHI (n=14) is 70.6%. The probability of having AFMS3–4 (n=17) if an infant has moderate to severe AHI (n=16), that is, positive predictive value, is 75.0%. For those with severe AHI (n=12) the specificity is 88.9% and sensitivity is 58.8%.

DISCUSSION

The literature is conflicting regarding the role of surveillance for the widely recognised complication of FMS in infants with achondroplasia. Currently, there are no evidence-based guidelines and the two most commonly cited recommendations are based predominantly on consensus expert opinion.[6 7] Furthermore, there is no objective quantification for the severity of FMS.[12] We have proposed a novel scoring system to clearly define MRI changes as a result of FMS and retrospectively correlated this with clinical examination and CRS data to establish if these can be used in early surveillance for FMS. The study has shown that AFMS3–4 is common (50%) in infancy and that while neither CRS nor clinical examination is sensitive enough to screen for this, screening MRI, using the AFMS, is possible.

The 2015 'best practice' paper reported the conclusions of a Delphi consensus conducted by 11 professional experts in skeletal dysplasia, including one neurosurgeon. The paper acknowledged a paucity of good-quality evidence on which to base guidelines but recommended that MRI studies should be used in presence of abnormalities on screening tests (history, physical and overnight sleep studies) and not in isolation (recommendation 22).[7] This contradicts the guidance from the American Academy of Pediatrics (2005), recommending that evaluation of every infant with achondroplasia should include assessment for craniocervical junction risks, which includes neuroimaging (CT or MRI) and PSG.[6]

Pauli *et al*[9] reported outcomes, over a 12-year period, of 53 infants with achondroplasia, referred for concerns including neurological or respiratory compromise, who underwent prospective MRI screening and 22 infants. Of these, 13.3% (n=10) underwent neurosurgical FM decompression with dramatic improvement in neurological function, although some had a degree of residual neurological deficit. Sanders *et al*[13] analysed data spanning 20 years' experience, describing findings in 49 infants with achondroplasia. Of these, 27/49 (55%) of patients had cord signal changes on MRI, only 3/49 (6%) had abnormal neurological findings and 20/49 (40.8%) of the patients underwent decompression surgery. They also concluded that PSG was a poor predictor of spinal cord changes on MRI.

Sleep disordered breathing is common in achondroplasia and a predominantly obstructive pattern of sleep apnoea was seen. Although anatomical causes in part may be responsible, centrally mediated obstructive causes can be due to compression at the level of the FM compromising bulbar function.[5] Although there is worsening sleep apnoea with increasing severity of FMS, patients with AFMS3–4 can have normal or mild OSA on cardiorespiratory studies as this study has shown. Severe TAHI had a specificity of 89% but only a 59% sensitivity for grade AFMS3–4. Although abnormal neurological examination had a high specificity of 100%, it also had a low sensitivity of only 11.1%. Therefore, both CRS and clinical examination are poor screening tests for severe stenosis and would have missed five (27% of those with AFMS3–4) patients in our cohort with AFMS3/4.

FM dimensions in achondroplasia are reduced compared with other children but enlarge with age.[6] As such it is infants and toddlers who are at particular risk of spinal cord compression, which may lead to oedema, irreversible neuronal loss and myelomalacia, best identified on MRI T2-weighted images. Thus, AFMS4 indicates an advanced stage of spinal cord compression and when established, changes persist and do not fully resolve even into adulthood[16] (figure 3). The precise long-term neurological and functional implications of these findings have not been well documented in achondroplasia although they are considered to have sinister significance in other situations such as in mucopolysaccharidosis disorders.[17] Neurosurgery was performed on 25% of our total cohort with low operative and perioperative morbidity and bone only decompression of the FM was effective in improving the dimensions of the FM. Although our specialist centre has had good neurosurgical outcomes, these operations are not without risks and concerns regarding routine MRI imaging leading to increased or unnecessary neurosurgical intervention, and associated risks, are also acknowledged.

In comparison to previous studies, the strength of our study is the contemporaneous, systematic collection of patient history and examination findings coupled with investigations of CRS

and MRI performed by the same tertiary team over a relatively short time frame in an unselected population.

The strengths of the AFMS are that it can be used on standard MRI sequences, no measurements are required and the score is not age specific. Importantly, the score aims to evaluate not the size of the FM per se, but rather the effect on the underlying neuraxis. In order to allow accurate assessment, good-quality images of the FM are required; based on our experience, we recommend a minimal of sagittal and axial T2 high-resolution sequences to include the CVJ.

There are a number of limitations of this study. Data collection was retrospective. The timing of the MRI within the first year was variable and it is acknowledged that the dimensions of the FM change in the early years,[6] with the potential for improvement in as well as progression of cervicomedullary compromise.

In summary, 50% of achondroplasia infants in this study had MRI evidence of severe FMS (AFMS3–4) and 25% of infants underwent neurosurgery with minor complications. Neurological examination and CRS are poor predictors of severity of FMS. Therefore, we suggest that all infants with achondroplasia should have routine screening with MRI, using high-resolution sagittal and axial T2-weighted image sequences of the brain to include the cervicomedullary junction with the aim being to reduce infant morbidity and mortality from FMS.

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Contributors MSC conceptualised and designed the study, coordinated and supervised the data collection, and drafted the initial manuscript. DT designed the AFMS scoring system. MI provided expertise in achondroplasia. RS provided the images and reviewed the radiology. AS reviewed the radiology. PG provided expertise on the background sleep studies. AC, HD and MS designed the data collection instruments, collected the data and carried out the initial analyses. All authors reviewed and revised the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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ORCID iDs
Moira S Cheung http://orcid.org/0000-0003-0742-7595
Alessandra Cocca http://orcid.org/0000-0003-4312-4591

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