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Natural history of spinal cord compression stage AFMS3 in infants with achondroplasia: Retrospective cohort study.

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Abstract:

Background and Objective: Foramen magnum stenosis (FMS) is a common, serious complication of achondroplasia in infancy and associated with sudden infant death. The Achondroplasia Foramen Magnum Score (AFMS; 0-4) is used to classify the severity of stenosis to inform appropriate neurosurgical management. Infants with AFMS4 are referred

for neurosurgery, whilst well children with AFMS3 undergo repeat MRI routinely after 12 months.

As the natural history of children with AFMS3 is currently unclear, the objective was to review follow-up magnetic resonance imaging (MRI) scans of infants initially classified as AFMS3 to define more clearly the evolution of this degree of stenosis.

Design: This retrospective cohort study, from two tertiary centres, included infants with a confirmed diagnosis of achondroplasia and AFMS3 on initial MRI who subsequently underwent repeat MRI or proceeded straight to neurosurgery.

Results: Twenty-two cases satisfied the inclusion criteria. Mean age in months was 6.23 (SD±3.82) and 17.95 (SD±7.68) at baseline and follow-up scans, respectively. Follow-up MRI showed no change in 23% (N=5), improvement in 36% (N=8) to either AFMS1 (N=5) or AFMS2 (N=3). There was progression in 41% to AFMS4 (N=8). One case had neurosurgey without follow-up MRI (N=1).

Conclusions: These results support MRI screening for FMS in infants with achondroplasia. Furthermore, infants with AFMS3 should undergo follow-up MRI as over 40% progress prompting neurosurgical intervention. There is currently no consensus on frequency or timing of screening for AFMS3 in achondroplasia; however, we suggest that guidance for follow-up imaging is modified to six months to detect progression earlier in this at-risk cohort.

What is already known on this topic: Foramen magnum stenosis (FMS) is a severe, lifethreatening complication of achondroplasia. The Achondroplasia Foramen Magnum Score (AFMS) 0-4 is widely used and grades the severity of stenosis. FMS can improve or worsen but the natural history is not understood.

What this study adds: AFMS3 (Evidence of cord compression at the FM without cord signal changes on MRI) improves or remains stable in 59% of infants but progresses, thus neurosurgery is indicated, in 41% of infants.

How this study might affect research practice or policy: Previously repeat MRI was performed after 12 months, however as a result of this study we have modified the time interval to 6 months to try to earlier identify infants who have progressed and are at greater risk from severe FMS.

Introduction

Achondroplasia is the most common form of non-lethal skeletal dysplasia, affecting 1 in 25,000-30,000 births. It is an autosomal dominant condition with approximately 80% of cases occurring *de novo* [1]. The phenotype results from a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene, in which unregulated, constitutively activated signal transduction of FGFR3 occurs. 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 specific abnormalities in endochondral and intramembranous bone growth and development [2].

Clinically, achondroplasia presents with a wide range of skeletal abnormalities, classically a disproportionately short stature with rhizomelic shortening of the limbs [3]. The skull (macrocephaly and frontal bossing) and spinal column (spinal stenosis, thoracolumbar kyphosis and lumbar lordosis) are also typically affected[4]. Functionally, there is limited rotation and extension of the elbows and hips, with laxity of the hip and hypermobile joints [1].

Clinically significant FMS needing neurosurgical intervention is estimated to occur in approximately 4.6-43% of infants and young children with Achondroplasia [5]. Untreated, FMS is associated with acute or chronic neurological complications which result in significant morbidity and a sudden unexpected mortality rate of up to 7.5% in infants with achondroplasia [6]. The abnormal size and shape of the foramen magnum (FM) is thought to result from hypertrophy of the occipital rim, thickened opisthion spurs and premature closure of the skull base synchondroses [7]. Neurosurgical decompression is an effective treatment for FMS and has been shown to have a low rate of complications [8,9].

A thorough understanding of the natural history of achondroplasia is critical to inform screening strategies, ensure optimal patient care and to evaluate the efficacy of emerging achondroplasia specific therapies in clinical trials [10].

The Achondroplasia Foramen Magnum Score (AFMS; 0-4, Table 1) was developed to facilitate early detection of stenosis and categorise the severity of FMS on magnetic resonance imaging (MRI) [11,12]. The AFMS has been shown to have good observer reliability [13] and informs appropriate neurosurgical referral [12]. Local practice is that children with AFMS4 or symptomatic children with AFMS3 are referred for neurosurgery, whilst asymptomatic children with AFMS3 undergo repeat MRI after 12 months. Clinical screening for at risk children is challenging as neurological examination does not correlate well with cervicomedulary compression. Symptoms and signs can be a late manifestation and are often difficult to elicit due the young age [14].

It has been well documented that FMS can both progress or improve [11,15]. Achondroplasia is a rare disorder and routine screening for FMS was only recently more widely adopted, therefore there is little natural history data on the likelihood of children switching between grades as they grow. By definition, children with AFMS4 have evidence of spinal cord damage and therefore knowledge of the natural history of AFMS3 might offer an opportunity to instigate earlier treatment and prevent spinal cord injury. In addition to informing neurosurgical management decisions natural history information is of particular relevance to potential clinical trials investigating disease modifying medical therapies.

Objective

This retrospective study aims to describe the natural history of FMS defined by AFMS on repeat MRI imaging of infants who were given an AFMS grading of 3 on their baseline scan.

Design, Setting and Patients

Infants with a confirmed diagnosis of achondroplasia and AFMS3 on initial MRI who subsequently underwent repeat MRI, at two tertiary Children's Hospitals were identified. The MRIs were performed between 2013 and 2023.

The medical and imaging records of these infants were retrospectively reviewed. Data extracted included timing and method of diagnosis, sex, family history, non-achondroplasia co-morbidities, neurological examination findings, sleep study results, AFMS grading, neurosurgical interventions and postoperative complications.

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. For infants under six months the 'feed and wrap' method was used in accordance with MRI policy; if unsuccessful, MRI was performed under general anaesthesia.

All MRI images were re-evaluated by a site-specific radiologist to identify and grade CVJ changes using the AFMS as an objective assessment of FMS (Table 1).

Infants who did not undergo follow-up MRI were excluded unless they progressed straight to surgery due to symptoms. Infants who had been recruited into clinical trials were also excluded as this may have impacted the natural history of FMS.

Foramen magnum decompression. For those children who require surgery this is carried out in the prone position, under total intravenous anaesthesia to facilitate the use of intraoperative neurophysiological monitoring of somatosensory and motor evoked potentials. A portion of the occipital bone, down to, and including the foramen magnum is then removed using high speed drill under magnification (Fig 1). The width of the decompression is calculated from the preoperative imaging. An extradural, transverse ligamentous band is typically encountered at the level of the foramen magnum; this is excised in order to

complete the decompression. The dura is not opened and it is rarely necessary to remove the posterior arch of the atlas.

Results:

Twenty-two infants with achondroplasia, graded as AFMS3 on initial MRI, satisfied the inclusion criteria. The baseline characteristics of the infants included in this study are reported in Table 2. Mean age in months was 6.23 (SD±3.82) and 17.95 (SD±7.68) at baseline and follow-up scans, respectively. Follow-up MRI showed improvement in 36.2% (n=8) to either AFMS1 or AFMS2.There was no change in AFMS classification in 22.7% (n=5) of cases, which remained AFMS3 and progression in 40.9% (n=9) of cases to AFMS4 (Figure 2).

The mean interval time between scans in this study was 11.57 (SD±6.06) months. The time interval of rescanning of those who progressed (1-13mo) was shorter (P=0.02) than those who did not progress (4-26mo).

The clinical neurological examination of 21 (95%) infants was documented as normal at baseline with one (5%) demonstrating an abnormal neurological examination (increased reflexes and clonus).

There was no statistically significant difference in the apnoea hypoxic indices (see Table 2), of those who did and did not progress to AFM4. The median (IQR) apnoea hypoxic indices were 7.4 (7.7) and 4.7 (12.0) events per hour respectively.

One child had a concurrent respiratory infection and was admitted to intensive care with a bulging fontanelle. The MRI performed showed AFMS3. As the infant was symptomatic, and felt to be at high risk of progression he did not have a repeat MRI but underwent decompression after which made a good recovery. Of those who had repeat MRIs and deteriorated to AFMS4, 8/8 went on to have neurosurgical intervention; seven had foramen

magnum decompression and of these one had decompression followed by shunt placement for a pseudomeningocele two weeks after initial decompression. All these children are clinically doing well currently. The final child who progressed to AFMS4 had a shunt placement without decompression at the age of 4 months but went on to have meningitis and needed multiple shunt revisions. The patient had severe developmental delay, did not walk and died at the age of 4 years suddenly at home– the cause of death was not recorded in the hospital records. Postoperative complications in this cohort included development of a pseudomeningocele (warrenting the shunt insertion post FMD), one wound infection which was resolved with antibiotics, one case of foramen magnum re-stenosis which required repeat decompression fifteen weeks after the initial surgery due to new bone formation and the child who developed meningitis and needed multiple shunt revisions.

Discussion

We have previously demonstrated that in infants with achondroplasia, FMS with subsequent cervicomedullary compression is a dynamic situation that can either improve or worsen over time [11]. Our study shows that more than 40% of patients with AFMS3 progress to AFMS4 with associated oedema, irreversible neuronal loss and myelomalacia at the cervicomeduallry junction. These infants are at high risk of acute life-threatening events and many have moderate to severe sleep apnoea. There is no current consensus on timing or frequency of monitoring for FMS or when scans should be repeated.

The locally determined timing of the repeat MRI scan at 12 months is arbitrary so, with the aim to instigate earlier treatment, we suggest that infants with AFMS3 should be rescanned at 6-month intervals until the age of 2 years; an operation is needed or there is demonstrable improvement of AFMS. The choice of screening at 6 months was made weighing up the risks of a general anaesthetic verses the benefits of earlier neurosurgical intervention. This time frame should be reassessed at a later date when more data is available. The youngest infant with AFM3 was one month of age at baseline scan. This infant went on to have a

second scan at 9 months of age which confirmed progression to AFMS4 and an abnormal neurological examination with significant clonus and surgical decompression was performed. This highlights that infants can develop significant FMS at a very early age and so MRI screening as an adjunct to careful monitoring of clinical symptoms and sleep studies should not be delayed in this at-risk group. Although FMS does not correlate well with sleep studies and not helpful in predicting severity, as this study confers, FMS is well documented to be associated with both central and obstructive apnoeas.

Whilst it may be appear preferable to operate on children before they develop spinal cord changes, currently there are no factors that allow prediction of which AFMS3 patients will improve and which will deteriorate. Of particular note the median Apnoea Hypoxia Index in those who deteriorated was not significantly different from those who improved (Table 2) demonstrating that sleep studies cannot differentiate the severity of FMS. Therefore, it would seem pragmatic to offer surgery to AFMS3 patients only when accompanied by clinical symptoms or signs.

As can be seen in the results, neurosurgical outcomes reported by these specialist centres, were by in large minor, but even so some serious complications did occur. Neurosurgical procedures, especially in small infants, carry significant risks and so procedures should ideally be performed by experienced specialists in achondroplasia and decisions made by the multidisciplinary team after reviewing all the information.

There are a number of limitations to this study. Data collection was retrospective and the number of patients with AFMS3 is small. Data was collected from two specialist centres over a number of years and during this time, the monitoring and neurosurgical management may have evolved. Infants who entered a clinical trial were excluded from this data, and although small numbers, this may have affected the distribution of data. The timing of the initial and the follow-up MRI scans had high variability.

Conclusion

The natural history of FMS in Achondroplasia infants initially diagnosed with AFMS3 is unpredictable. Whilst just over 1/3 of patients will improve their grade on subsequent imaging, a similar proportion will progress and require neurosurgical intervention. Clinical assessment and sleep studies correlates poorly with radiological progression, and although repeat MRI scans are likely be performed under general anaesthesia which also carries a small but significant risk, this study confirms that AFMS3 patients are an at-risk group and therefore warrant follow-up imaging. The optimal interval before repeat scan is unclearbut until further data is available a six-month follow-up scan is recommended.

Contributors: M.S.C. conceptualised and designed the study, coordinated and supervised the data collection and drafted the initial manuscript. C.H., C.B. were involved with initial manuscript writing, D.T. conceptualised study and reviewed progress. F.A. provided the images and reviewed the radiology. A.C.O. reviewed the radiology. A.C., C.H., C.B., N.J., S.B., A.C.O. and M.S. designed the data collection instruments, collected the data and carried out the initial analyses. All authors reviewed, revised and approved the final manuscript. M.S.C. is responsible for the overall content as a guarantor.

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STROBE: this cohort study was checked in accordance with the STROBE checklist

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AFMS0	Normal foramen magnum.
AFMS1	Constitutional narrowing of the FM with preservation of CSF, evident in either sagittal or axial T2 images
AFMS2	Narrowing of the FM with loss of CSF space surrounding the cord but without cord distortion.
AFMS3	Evidence of cord compression at the FM without cord signal changes
AFMS4	Presence of cord compression and cord signal changes in T2 images

Table 1 Scoring for achondroplasia foramen magnum score (AFMS).

Figure Legends

Figure 1. Intraoperative image of foramen magnum decompression

before (1a) and after (1b) bone removal

Fig 2 Flow-diagram summarising outcomes in infants with an achondroplasia foramen magnum score (AFMS) 3 on initial magnetic resonance images (MRI). Sagittal T2 midline spine echo – spin echo (SE)) (**a**–**c**) and gradient echo gradient-recalled echo (GRE) (**d**) MRI of the skull base in a 6 month old girl (**a**), a 18 month-old boy (**b**), a 14month-old boy (**c**) and a 19 month-old girl (**d**) with achondroplasia. Note the high signal within the cord in AFMS4 (*arrow* in **d**) note that both SE and GRE T2 WI should be used in order to better demonstrate subtle cord signal abnormalities. Definitions of each grade are given in Table 1

	Number of infants (%)
Gender	Female N=12 (54.5%), Male N=10 (45.5%)
Genetic confirmation of achondroplasia	N=22 (100%)
Family history of achondroplasia	N=1 (4.5%)
Timing of diagnosis	N=17 antenally (77%), N=5 (23%) postnatally
Co-morbidities	N=3, Cleft palet, dunchennes muscular dystrophy, acute viral chest infection
Neurological signs	N=2 (9%)
Mean (SD) age of initial MRI (months)	6.2 (3.8)
Mean (SD) age at follow up MRI	18.0 (7.7)
Median (IQR) baseline AHI of all infants	6.15 (11.2)
Median (IQR) baseline AHI of infants that deteriorated	6.3 (11.1)
Median (IQR) baseline AHI of infants that improved or remained stable	6.0 (12.8)
Neurosurgical intervention (FMD/Shunt)	N= 9/22 (41%) FMD N=7, FMD and Shunt N=1, Shunt only N=1

Table 2

Baseline characteristics of the infants, their investigations and outcomes, FMD foramen magnum decompression, IQR Interquartile range, AHI Apnoea Hypoxia Index.