Bone 127 (2019) 499–502

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Meeting report from the achondroplasia foramen magnum workshop, Salzburg, Austria 22nd June 2019

Moira S. Cheung[a,*], Inês Alves[b], Lars Hagenäs[c], Klaus Mohnike[d]

[a] Evelina London Children's Hospital, Guys and St Thomas' NHS Foundation Trust, London, UK
[b] BOND ePAG, EUPATI Portugal, Evora, Portugal
[c] Karolinska Institute, Stockholm, Sweden
[d] University of Magdeburg, Magdeburg, Germany

ARTICLE INFO

Keywords:
Achondroplasia
Children
Foramen magnum stenosis
Neurosurgery
Pathogenesis
Screening

ABSTRACT

A pre-meeting workshop on foramen magnum stenosis in children with achondroplasia was held in Salzburg, Austria at the 9th International Conference on Children's Bone Health (ICCBH) 22–25 June 2019. The screening, monitoring and surgical approach to foramen magnum stenosis still remains controversial with conflicting guidance in the literature. The structure of the workshop consisted of lectures, a debate, expert and delegate discussion and concluded with a research proposal and further next steps. In total, representation by 40 institutions from 22 different countries that care for approximately 1375 children with achondroplasia, were in attendance.

1. Introduction

When working with rare diseases, it is important for centres internationally, to work collaboratively to develop best practise and together push the field forward scientifically. This was exemplified by the level of interest in the achondroplasia foramen magnum workshop held in Salzburg, Austria at the 9th International Conference on Children's Bone Heath (ICCBH), 22–25 June 2019. Foramen magnum stenosis (FMS) in achondroplasia is a recognised cause of child morbidity and mortality. The screening, monitoring and surgical approach to FMS still remains controversial.

This workshop was co-organised under the European Reference Network on Rare Bone Diseases (ERN BOND WG4) program and invited clinical leads, associated specialists, patient and pharmaceutical companies' representatives. In total, delegates from 40 different institutions representing 22 countries attended this workshop. These clinicians collectively looked after approximately 1375 children with achondroplasia. The structure of the workshop consisted of opening lectures, a debate and then a discussion by experts and delegates. The workshop was concluded with a proposal for a natural history study of FMS and summary of key steps forward.

2. Lectures

2.1. Pathophysiology of foramen magnum stenosis in achondroplasia and other skeletal dysplasias

2.1.1. Prof Jürgen Spranger (Baden Baden, Germany)

The basic defect in all members of the achondroplasia family is an altered Fibroblast Growth Factor Receptor caused by *FGFR3* mutations. The altered FGFR3 is constitutively activated, signal transduction unregulated, and this results in reduced endochondral growth. Insufficient amounts of bone are formed adjacent to the growth plates explaining the deficient tubular bone growth and short limb dwarfism characterizing achondroplasia. Growth plates are special forms of synchondroses uniting bone ends. Premature fusion of occipital synchondroses has been found in young children with achondroplasia [1]. However, this does not explain neonatal FMS. As in tubular bones, reduced chondrocyte proliferation seems to be its cause before and during the first months of life, when the synchondroses of the basicranium are still open. Defective chondrocyte proliferation and differentiation may predispose to premature early fusion. Curiously this phenomenon is not present in tubular bones: Bone age is not constitutively advanced in children with achondroplasia. Premature osseous fusion occurs in craniosynostosis syndromes leading to smaller than normal and deformed foramen magnum [2].

* Corresponding author.
E-mail addresses: moira.cheung@gstt.nhs.uk (M.S. Cheung), inesp.alves@gmail.com (I. Alves), lars.hagenas@ki.se (L. Hagenäs), Klaus.mohnike@med.ovgu.de (K. Mohnike).

https://doi.org/10.1016/j.bone.2019.07.020
Received 9 July 2019; Accepted 16 July 2019
Available online 17 July 2019

2.2. Radiology of foramen magnum disorders in achondroplasia

2.2.1. Dr. Amaka Offiah (Sheffield, UK)

Synchondroses are the gaps between the various bones of the occiput (basiocciput, exo-occiput and supraocciput). They are cartilaginous structures that can be identified on imaging. They allow growth but (unlike the physeal plate) do not contribute directly to growth between the different bones. They fuse at different ages (posterior intraoccipital 2–7 y, anterior intraoccipital 3–9 y, spheno-occipital 9–15 y, occipitomastoidal and petro-occipital 20–50 y). Calandrelli [1] showed that in achondroplasia there is premature fusion of the synchondroses which can be seen on T1 weighted images. This group postulated that this premature fusion causes reduced FM area and medullary compression in some cases.

The FM is small antenatally secondary to the abnormal shape of the skull. Skull shape abnormalities are caused by hypertrophy of the occipital rim, overgrowth of the opisthion, abnormal position of the synochondroses and premature fusion of the synchondroses. The sequelae are: an obstruction to the flow of CSF, causing emissary vein enlargement; narrowing of venous channels and FM stenosis. These may lead to the cord abnormalities — cervical myelopathy and syrinx formation.

Helpful modalities to evaluate FMS and cord abnormalities include:

Radiographs: These can be useful in screening for C1/2 instability but not in evaluating FMS.

Ultrasound: This is easily accessible and there is no radiation but is operator dependent and relies on an open fontanelle. This modality is particularly useful antenatally and there are normative curves for the FM. Visualization of the upper spinal cord is limited.

CT: Imaging is very rapid and gives excellent visualization of bone. It is not user dependant but there is a radiation dose penalty — however this is very small to the fetus (3.5 mGy, which is well below the actionable level of 50 mGy). Nevertheless, CT cannot reliably be used before 30 weeks gestation due to artefact caused by fetal movement. CT is relatively poor for looking at the spinal cord. Overgrowth of the opisthion (which may be asymmetrical) is readily demonstrated on CT.

MRI: Like CT, this provides multiplanar views, infants can be fed and wrapped but older children will need to be sedated or anaesthetised. Antenatal MRI can detect FMS although there is limited data on this. MRI is useful for looking at emissary vein enlargement and dynamic MRI flexion and extension improves the identification of effacement of the CSF. Furthermore, MRI allows CSF flow rates to be measured (although the interpretation is not clear). Ventricular index can be measured for hydrocephalus and cerebral atrophy can be identified.

Brouwer [3] looked at MRIs in adults aged 13–64 y with achondroplasia who were asymptomatic. In this study, 6/7 cases with high cord signal also had thinning of the cord. It is important to note that these changes are different to the cervical myelopathy that is seen with younger patients who have narrowing of the FMS, CSF effacement and kinking of the cord.

A UK group [4] presented the achondroplasia foramen magnum severity score (AFMSS) in children, a four point scoring system which is simple to use, no normative data is needed and is not age dependent. The changes in cord signal that are presented in this scoring system are not the same as the high signal that is present in adults which is likely to represent a different pathological entity, suggesting that some modification of the AFMSS is needed.

Children with FMS also get spinal stenosis and therefore they should all have their spine imaged. There is narrowing of the interpedicular distances of the lumbar spine in achondroplasia, which worsens with age but is not usually present at birth. The shape of the spinal canal is different and the spinal canal and transverse processes in achondroplasia are typically narrow.

Dr. Offiah's recommendations:

1) Image the whole spine with MRI (including flow rate)
2) Use AFMSS in infants and a modified version in older children.

2.3. Mechanisms for respiratory dysregulation secondary to craniocervical compression in achondroplasia and related disorders

2.3.1. Dr. Christina Lampe (Giessen, Germany)

In achondroplasia (n = 30) abnormal subcortical somatosensory evoked potentials indicated high cervical myelopathy [5] with sensitivities of the SEPs were 0.89 for cervical cord compression, 0.92 for myelomalacia and 1.0 for the clinically symptomatic patients. This was confirmed by Fornarino S. et al., recently [6]. Similarly, craniocervical cord compression is a frequent finding and life threatening complication in mucopolysaccharidosis VI, due to a progressive GAG accumulation in the soft tissues. In our experience a combined score including neurological examination, somato-sensoric nerve evoked potentials, SEP and MRI was a good predictor for cervical cord compression. Decompression surgery was performed in 14/ 31 MPS VI patients with a combined score significant different from non-operated children ($p < 0.001$): 62% of patients improved in total CCJ score, 46% in neurological examination, 39% in SEP and 27% in MRI. The most sensitive parameter was the SEP with score 1: prolongation of at least one of the following interpeak latencies: N9/P13; N9/N13b; N13a/N20. Score 2: loss of P13 and/or N13b (brainstem). Score 3: loss of N20 (cortical).

A worldwide registry of MPS VI [7] recommended regular follow-up assessments with a standardized procedure of clinical neurological, electrophysiological and imaging.

2.4. Sleep apnoea and the challenges of respiratory management in infants with achondroplasia

2.4.1. Dr. Josef Milerad (Stockholm, Sweden)

Ventilatory impairment, as evident by decreased oxygenation or elevated carbon dioxide levels (but not necessarily total cessation of breathing movements “apnoea”) is, in our experience, common in children with achondroplasia. Our data suggest that these breathing problems ranging from mild to severe may be present in up to 70% of ACH children. Increased inspiratory resistance possibly due to small upper airway or asynchrony between inspiratory effort and upper airway tone was a common cause in our group of patients. Polysomnography if performed early could offer valuable information [8,9].

3. Debate: Should all babies with achondroplasia have MRI screening for FMS?

3.1. Dominic Thompson (Paediatric Neurosurgeon, London, UK)

3.1.1. For the motion ‘All babies with achondroplasia should have MRI screening for FMS’

Normative data is available that describes the growth of the foramen in infants and young children with Achondroplasia. The growth trajectory is not linear, there is a period until 3–5 years when the foramen is particularly small during which the contents of the foramen magnum are vulnerable to compression.

Stenosis of the foramen magnum can result in effacement of the CSF spaces, distortion of the spinal cord and ultimately damage to the parenchyma of the spinal cord. When compression of the cervicomedullary junction occurs this results in spinal cord oedema and ultimately myelomalacia due to axonal loss. Spinal cord oedema can be detected on T2 weighted MRI sequences.

Studies of adults with Achondroplasia have shown a high prevalence of MRI T2 signal change, typically without coexisting stenosis. It is hypothesised that this represents the legacy of an earlier period of FMS. The clinical significance of this finding is not currently well described and is an area for urgent evaluation.

Sudden infant death is well recognised in infants with Achondroplasia; this is likely related to acute respiratory compromise. Whether or not such acute respiratory events are the direct result of compression at the foramen magnum remains unproven, however in a recent consensus statement all experts agreed that FMS contributes to mortality in infants with achondroplasia [10].

Published clinical experience indicates that many (the majority) of infants and young children, with MRI proven compression and spinal cord signal change do not have overt symptoms or clinical signs of foramen magnum compression (myelopathy, motor regression, bulbar dysfunction). Furthermore, the results of respiratory sleep studies, whilst commonly abnormal in this population, have poor correlation with the degree of foramen magnum stenosis. Electrophysiological studies too, have been shown to lack the sensitivity to predict critical foramen magnum stenosis in this high-risk group of young achondroplasia patients.

In all other examples of skeletal dysplasia the presence of signal change with in the spinal cord is considered a serious finding, mandating at least neurosurgical review and consideration for treatment. Indeed the consensus view of Achondroplasia experts is that foramen magnum decompression is appropriate in the presence of spinal cord signal changes [10].

Notwithstanding the need for careful patient selection and counselling, the safety of foramen magnum decompression has been confirmed in a large number of surgical series.

To justify a screening policy, the disease entity needs to be sufficiently prevalent in the target population, there needs to be a sensitive and specific test to detect the disease process, and an appropriate treatment that can benefit natural history needs to be available. These criteria are satisfied in young patients with Achondroplasia.

In the light of the above, it would seem prudent to offer MRI screening for children with achondroplasia who are within the at risk group (< 4 years) for foramen magnum stenosis. A simple MRI grading is proposed that allows severity of foramen magnum stenosis and its effect on the neuraxis to be evaluated. Patients found to be at risk can then be referred for neurosurgical assessment and treatment.

It is acknowledged that a number of questions remain unanswered. What is the precise natural history of T2 signal change in Achondroplasia? What are the late implications of this finding? Should we re-evaluate the prognostic significance of respiratory sleep studies in detecting critical FMS? These studies have hitherto been used as a means of identifying *central* respiratory disturbance in this population; it is now acknowledged that potentially serious *obstructive* patterns of breathing may also have a central aetiology.

It is proposed that MRI Screening in Achondroplasia will not only benefit individuals, potentially avoiding sudden infant death and chronic myelopathy, but also provide greater understanding on which future evidence-based policy can be founded.

3.2. Klane K White (Paediatric Orthopaedic Surgeon, Seattle, USA)

3.2.1. Against the motion 'All babies with achondroplasia should have MRI screening for FMS'

Infant mortality is higher in children with achondroplasia compared to the general population. This increased mortality has been historically attributed to foramen magnum stenosis and resultant cervicomedullary spinal cord compression and central sleep apnea. As such universal MRI screening for foramen magnum stenosis has been advocated. Critical review of the literature would suggest that a causative relationship between foramen magnum stenosis and increased infant mortality is weak, and may be more attributable to obstructive apnea. Furthermore, there are inherent risks associated with the general anesthesia required to obtain the MRI and there is concern for overtreatment with foramen magnum decompression and its inherent risks. Foramen magnum stenosis and cervicomedullary compression represent a real health issue for children with achondroplasia, and when symptomatic, should be addressed. Given the risk-benefit profile and the unclear relationship between cervicomedullary compression and the increased rate of infant mortality, however, universal screening is not necessary and may in fact increase morbidity in this population. As such, polysomnography and careful clinical monitoring are recommended, with selective use of MRI screening in infants for foramen magnum stenosis and cervicomeduallry compression.

4. Expert opinion and general discussion

4.1. Expert panel: Ms Inês Alves (Évora, Portugal), Dr Genevève Baujat (Paris, France), Dr Philip Kunkel (Hamburg, Germany), Prof Geert Mortier (Antwerp, Belgium), Dr Louise Tofts (Sydney, Australia), Dr Michael Wright (Newcastle upon Tyne, UK)

Dr. Tofts pointed out that screening by neurological examination looks for signs of spinal cord injury and not the FMS. In an abnormal examination there is already a cord injury so is a late sign of cord damage. In the Paris group, there is a holistic, multidisciplinary approach using clinical examination, polysomnography and MRI to assess these children as it is felt that there is no one clinical test which is sufficient. They have had cases where there has been severe FMS (AFMSS 3–4) with normal polysomnography and examination.

Another expert expressed that there is no evidence currently that clinicians are missing a treatable problem in asymptomatic children without screening. There is no natural history evidence that there is an adverse outcome in the asymptomatic patients who may have had spinal cord signal changes.

Delegates pointed out that there is a need for a unified approach to measurements and imaging. This should include head positioning and the type of MRI images that should be obtained. It was also pointed out that any consensus statements that include all specialties that are involved in the pathway and for this topic especially the neurosurgeons.

Ms. Alves (patient representative, ERN BOND ePAG) emphasised that clinicians should not only be focussing on death as an outcome but should be looking for optimal health. As the natural history of FMS is still not fully understood, clinicians and researchers should work together to come to a consensus of best practise as soon as possible. It is very distressing and confusing for families that experts have differing opinions.

Dr. Wright pointed out that in 1997, during the second International Skeletal Dysplasia Society meeting, the same issues were still being discussed and there is still no agreed consensus over 20 years later, it is important for the sake of the families that find some answers. In an attempt to move forward, it may be that those who do not screen should start screening with the view that over 5 years we look at the data and come up with a definitive conclusion.

4.2. Vote results

For the motion: Before 30 and After 30.
Against the motion: Before 13 and After 10.
(Some abstinences both before and after).

4.3. Research study proposal

4.3.1. Prof Klaus Mohnike (Magdeburg, Germany)

Craniocervical cord compression is a frequent finding and life threatening complication in achondroplasia. BOND-ERN will introduce a database to capture the natural history, neurological examination, functional investigations (SEP, sleep lab) and MRI-DICOM studies. All participants will include all new acho-patients based on the European RD Registry Infrastructure (ERDRI), at the EU-JRC (Joint Research Centre). Participants will use open source software (RedCap, OSSE, etc.) with standardized agreed parameters; meaning data elements of the registries are defined in the ERDRI.MDR (Metadata Repository).

Each centre will document regular follow-up assessments with a standardized procedure of clinical neurological, electrophysiological and imaging on their own centre-based protected server. i.e. each registry knows what item the other one collected, whereas the data-owner will keep data sovereignty. For shared analysis, each centre can deliver de-identified patient's data to BOND-ERN or for collective publication. Using this standardized documentation will also help for uploading data on CPMS.

4.4. Final remarks on the workshop: handling of foramen magnum stenosis in achondroplasia

4.4.1. Dr. Lars Hagenäs (Stockholm, Sweden)

Collectively, the participants have together experience of taking care of > 1000 children with achondroplasia. This creates an ideal situation for a possible randomized controlled study (RCT) that evaluates different attitudes toward investigation and handling of foramen magnum stenosis (FMS) potentially affecting medullar integrity. Questions at hand for such a study include the correlation between degree of stenosis and respiratory problems as well as deviant neurology or accelerating head circumference. Also the long-term consequences of a kinked medulla or absence of liquor pulsation at foramen magnum level with regard to gliosis or syrinx need to be investigated. The possible correlation between head circumference development and jugular foramina congestion of venous outlet from the skull is also of interest.

Yet it could be hard to get unbiased acceptance for an RCT due to possible increased risks at sedation of the infant and young child having decreased ability to compensate for insufficient respiration due to diminished upper airways and muscular hypotonia and also safety issues at manipulating head position when there is no muscle control. Further, randomized decisions regarding neurosurgical procedures at similar degrees of stenosis may need long time postsurgical observations before evidence based decisions could be made.

Systematic information on spontaneous development of foramen magnum size and medullar affection when significant stenosis is detected early in infancy is lacking and needs to be investigated.

Despite the large number of individuals and a relatively homogeneous phenotype reported experience in handling the principally constant FMS in achondroplasia is very restricted and probably limited to severe cases. Neuroradiological evaluation, a prerequisite for decisions seems to be largely absent.

Contributing to the difficulty of recognizing pathological neurology is that the majority of infants and young children with achondroplasia have significant muscular hypotonia with decreased deep tendon reflexes.

A majority of infants with achondroplasia have disordered breathing with desaturations, hypopnea and apnea, with no clear association to medullar compression or T2 MR signal changes.

A generally accepted scoring system for degree of medullary impingement in FMS is a necessary prerequisite for comparing clinical routines and studies in achondroplasia. Similarly needed is a generally accepted scoring system for respiration pathology.

Lastly, exploring the neurological and respiratory situation together with neuroradiological status in a large cohort of unselected adult individuals with achondroplasia might give some answers regarding handling of infants and children with achondroplasia.

5. Conclusions

It is clear that the effect of the genetic mutation in FGFR3 is responsible for significant morbidity that results in narrowing of the spinal canal both the base of the skull and the spine. There was wide agreement that when this results in symptomatic spinal cord compression at the foramen magnum, neurosurgical management with decompression is indicated.

Screening methods to prevent of this complication however remained controversial and underpinned by the lack of natural history data in asymptomatic patients with spinal cord changes. In the best interests of patients and to minimise harm, arguments both for and against screening all babies with MRI were eloquently proposed.

Positive outcomes of the workshop included increased awareness and understanding of FMS in achondroplasia, a high level of global engagement and going forward, a willingness to participate in studies to address some of the deficits in knowledge. There was wide agreement for a unified MRI scanning guideline so that we can share similar data.

A newer development in our role of working with rare bone disease has included advising pharmaceutical companies of important clinical outcomes. Whilst an accessible and measurable outcome is growth, morbidities in achondroplasia such as spinal cord compression, may have far greater implications for development, mobility and quality of life than short stature in itself. International, cross specialty, collaborative working is essential to improve the care of patients in rare disease. This current time is especially important, as there are rapid advances in pharmacological interventions for children with achondroplasia.

We are very grateful for the generous sponsorship of the pharmaceutical companies, Ascendis, BioMarin and QED Therapeutics and to the ICCBH Steering Group for facilitating the organisation and enabling this workshop to take place.

References

[1] R. Calandrelli, M. Panfili, G. D'Apolito, G. Zampino, A. Pedicelli, F. Pilato, C. Colosimo, Quantitative approach to the posterior cranial fossa and craniocervical junction in asymptomatic children with achondroplasia, Neuroradiology 59 (2017) 1031–1041, https://doi.org/10.1007/s00234-017-1887-y.

[2] B.F.M. Rijken, M.H. Lequin, F. van der Lijn, M.-L.C. van Veelen-Vincent, J. de Rooi, Y.Y. Hoogendam, W.J. Niessen, I.M.J. Mathijssen, The role of the posterior fossa in developing Chiari I malformation in children with craniosynostosis syndromes, J. Craniomaxillofac. Surg. 43 (2015) 813–819, https://doi.org/10.1016/j.jcms.2015.04.001.

[3] P.A. Brouwer, C.M. Lubout, J.M. van Dijk, C.L. Vleggeert-Lankamp, Cervical high-intensity intramedullary lesions in achondroplasia: aetiology, prevalence and clinical relevance, Eur. Radiol. 22 (2012) 2264–2272, https://doi.org/10.1007/s00330-012-2488-0.

[4] H. Dougherty, M. Shaunak, M. Irving, D. Thompson, M. Cheung S., Identification of Characteristic Neurological Complications in Infants with Achondroplasia by Routine MRI Screening, Horm. Res. Paediatr. 82 (2018).

[5] R. Boor, G. Fricke, K. Brühl, J. Spranger, Abnormal subcortical somatosensory evoked potentials indicate high cervical myelopathy in achondroplasia, Eur. J. Pediatr. 158 (1999) 662–667 http://www.ncbi.nlm.nih.gov/pubmed/10445347 (accessed July 3, 2019).

[6] S. Fornarino, D.P. Rossi, M. Severino, A. Pistorio, A.E.M. Allegri, S. Martelli, L. Doria Lamba, P. Lanteri, Early impairment of somatosensory evoked potentials in very young children with achondroplasia with foramen magnum stenosis, Dev. Med. Child Neurol. 59 (2017) 192–198, https://doi.org/10.1111/dmcn.13243.

[7] G.A. Solanki, P.P. Sun, K.W. Martin, C.J. Hendriksz, C. Lampe, N. Guffon, A. Hung, Z. Sisic, R. Shediac, P.R. Harmatz, CSP Study Group, Cervical cord compression in mucopolysaccharidosis VI (MPS VI): findings from the MPS VI Clinical Surveillance Program (CSP), Mol. Genet. Metab. 118 (2016) 310–318, https://doi.org/10.1016/j.ymgme.2016.06.001.

[8] E. Horemuzova, M. Katz-Salamon, J. Milerad, Breathing patterns, oxygen and carbon dioxide levels in sleeping healthy infants during the first nine months after birth, Acta Paediatr. 89 (2000) 1284–1289.

[9] J. Milerad, O. Larson, C. Hagberg, M. Ideberg, Associated malformations in infants with cleft lip and palate: a prospective, population-based study, Pediatrics 100 (1997) 180–186, https://doi.org/10.1542/peds.100.2.180.

[10] K.K. White, V. Bompadre, M.J. Goldberg, M.B. Bober, J.W. Campbell, T.J. Cho, J. Hoover-Fong, W. Mackenzie, S.E. Parnell, C. Raggio, D.M. Rapoport, S.A. Spencer, R. Savarirayan, Best practices in the evaluation and treatment of foramen magnum stenosis in achondroplasia during infancy, Am. J. Med. Genet. A 170 (2016) 42–51, https://doi.org/10.1002/ajmg.a.37394.