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ORIGINAL PAPER

# Achondroplasia in children: correlation of ventriculomegaly, size of foramen magnum and jugular foramina, and emissary vein enlargement

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**Abstract**
*Purpose* Achondroplasia is a skeletal dysplasia with diminished growth of the skull base secondary to defective enchondral bone formation. This leads to narrowing of the foramen magnum and jugular foramina, which further leads to ventricular dilatation and prominence of the emissary veins. The primary goal of our study was to determine a correlation between the degree of ventricular dilatation, jugular foramina and foramen magnum narrowing, as well as emissary vein enlargement.
*Methods* Conventional T2-weighted MR images were evaluated for surface area of the foramen magnum and jugular foramina, ventricular dilatation, and emissary veins enlargement in 16 achondroplasia patients and 16 age-matched controls. Ratios were calculated for the individual parameters using median values from age-matched control groups to avoid age as a confounder.
*Results* Compared to age-matched controls, in children with achondroplasia, the surface area of the foramen magnum (median 0.50 $cm^2$, range 0.23–1.37 $cm^2$ vs. 3.14 $cm^2$, 1.83–6.68 $cm^2$, $p<0.001$) and jugular foramina (median 0.02 $cm^2$, range 0–0.10 $cm^2$ vs. 0.21 $cm^2$, 0.03–0.61 $cm^2$, $p<0.001$) were smaller, whereas ventricular dilatation (0.28, 0.24–0.4 vs. 0.26, 0.21–0.28, $p<0.001$) and enlargement of emissary veins (6, 0–11 vs. 0, $p<0.001$) were higher. Amongst the patients, Spearman correlation and multiple regression analysis did not reveal correlation for severity between the individual parameters.
*Conclusions* Our study suggests that in children with achondroplasia, (1) the variation in ventricular dilatation may be related to an unquantifiable interdependent relationship of emissary vein enlargement, venous channel narrowing, and foramen magnum compression and (2) stable ventricular size facilitated by interdependent factors likely obviates the need for ventricular shunt placement.

**Keywords** Achondroplasia · Children · Magnetic resonance imaging · Ventriculomegaly · Foramen magnum

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## Introduction

Achondroplasia is a skeletal dysplasia caused by gain-of-function mutations in the *FGFR3* gene [1]. The phenotype is characterized by disproportionately short stature with rhizomelic shortening of the extremities and results from defective formation of endochondral bones. The skull base is also affected by the defective enchondral bone growth resulting in a hypoplastic skull base with narrowing of the foramen magnum and jugular foramina.

Macrocephaly is a common phenotypic feature of achondroplasia and is caused by hydrocephalus [1, 2]. In children with achondroplasia, an investigation with magnetic resonance imaging (MRI) of the brain is required when there are concerns for hydrocephalus. Ventriculomegaly and

enlargement of the subarachnoid spaces are typical neuroimaging findings in children with achondroplasia [3, 4]. Ventriculomegaly and enlargement of subarachnoid spaces have been attributed to jugular foramina narrowing, impaired venous outflow, and intracranial dural venous hypertension [3–6]. In addition, we have observed prominent meningeal vessels in the subarachnoid/subdural spaces and emissary veins during routine neuroimaging evaluation of children with achondroplasia.

The goals of this study were to (1) assess the surface area of the foramen magnum and jugular foramina, degree of ventriculomegaly, and prominence of the emissary veins and meningeal vessels in children with achondroplasia and age-matched controls and (2) correlate the severity of aforementioned individual measurements in children with achondroplasia to find a causal relationship. We hypothesized a positive correlation between (1) the degree of ventriculomegaly and (2) the narrowing of the foramen magnum and jugular foramina and prominence of emissary veins.

## Materials and methods

This retrospective study was approved by our institutional review board.

### Study population

The inclusion criteria for this study were (1) confirmed diagnosis of achondroplasia (imaging and/or genetic findings), (2) availability of conventional MRI data without artifacts, (3) no history of prior neurosurgery, and (4) age at MRI 18 years and younger. Data from eligible patients were collected through an electronic search of our pediatric neuroradiology database covering the time period between September 1, 2010, and May 31, 2013.

Controls were selected from our pediatric MR database using the following criteria: (1) normal brain anatomy, (2) absence of neurological disorders, and (3) availability of MRI data during the same time period. Controls were individually matched to patients on age within 0.02 years.

### MRI acquisition

All MRI studies were performed on a 1.5-T scanner (Siemens Avanto, Erlangen, Germany) using our standard departmental protocol including 3D T1- and axial T2-weighted images, an axial fluid attenuation inversion recovery (FLAIR) sequence, and an axial diffusion tensor imaging (DTI) sequence with diffusion gradients along 20 noncollinear directions. For the acquisition of high-resolution axial T2-weighted images, the following parameters were used: repetition time (TR) 4190 ms, echo time (TE) 104 ms, slice thickness 4.0 mm, field-of-view (FOV) 200×200 mm, matrix size 320×320.

### Image analysis

Image analysis was performed on the PACS workstation by a pediatric neuroradiologist (TB), a radiologist (GO) and a medical student (BH) in consensus. Readers were not blinded to the controls or patients. Axial T2-weighted images were used for the evaluation. Ventricular size was measured by dividing the bifrontal width and biparietal diameter at the level of the frontal horns of the lateral ventricles (Fig. 1a). The surface area of the foramen magnum was measured using a region of interest (ROI) surface measurement tool. The ROI was placed to cover the entire surface of the foramen magnum (Fig. 1b). A similar measurement was performed for the bilateral jugular foramina and a mean value was calculated (Fig. 1c). If the jugular foramen was not visible at the skull base, a value of 0 was assigned. Normal appearance or nonvisualization of emissary veins was given a score of 0. Prominence of emissary veins was given a score of 1. The prominence of bilateral occipital (maximum score=2), mastoid (maximum score=2) and condylar emissary veins (maximum score=2), bilateral superior ophthalmic veins (maximum score=2), bilateral meningeal vessels (maximum score=2), and occipital sinus (maximum score=1) were assessed (Fig. 2). Emissary veins are valveless veins which drain from the dural venous sinuses into veins outside the skull. The selection of emissary veins is in accordance with Moritani et al. [7].

### Statistical analysis

Data were summarized and compared using nonparametric methods because of the small sample size and nonnormality of some measures. Wilcoxon signed-rank tests were used to test for differences in individual parameters between patients and pair-matched controls. Spearman correlation of the individual parameters—age, ventricular size, foramen magnum surface area, jugular foramina surface area, and enlargement of emissary veins and meningeal vessels was carried out amongst the patient group to test our hypothesis. In order to remove age as a confounder, median values of surface area of the foramen magnum and jugular foramina as well as ventricular size were obtained from the control group for three age-groups, namely, 0–0.99, 1–2.99, and >3 years. The ratios for foramen magnum surface area, jugular foramina surface area, and ventricular size were calculated for each patient with respect to the median value for age obtained from the control groups. Additionally, multiple regression analysis of ventricular size on age and the other parameters was performed. Analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). All tests were two-sided, and observed

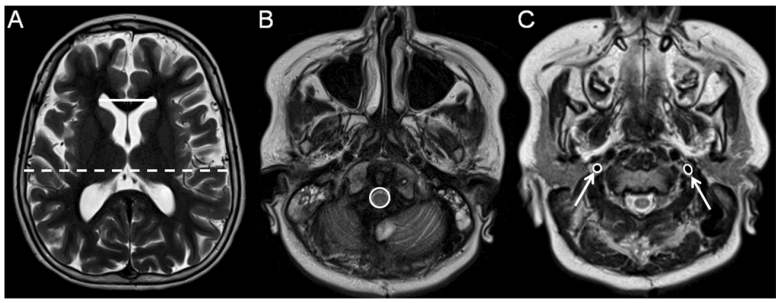


**Fig. 1** Axial T2-weighted images of an 8-year-old boy with achondroplasia showing **a** bifrontal horn width (*white line*) and biparietal diameter (*white dashed line*) measurement; **b** foramen magnum surface area measurement (*circular white outline*); and **c** bilateral foramen magnum measurements (*arrows*) (*oval white outlines*)

differences were considered statistically significant if $p<0.05$. No adjustment was made for multiple comparisons.

## Results

### Characteristics of the study cohort

Between September 1, 2010, and May 31, 2013, in our tertiary pediatric hospital, MR images were acquired in 16 children with achondroplasia. All patients fulfilled the inclusion criteria. The median age at MRI of the 16 patients was 2.2 years (mean 3.5 years, range 18 days to 10.5 years), and 11 (69 %) were males.

The 16 age-matched control children had MR images performed between September 1, 2010 and December 31, 2012. Their median age was 2.2 years (range 18 days to 10.5 years), and 7 (44 %) were male.

### Imaging analysis

Median values and range for all measurements in patients and age-matched controls are shown in Table 1. Patients had a significantly higher ratio between bifrontal width and biparietal diameter compared to controls, representing a higher degree of ventriculomegaly. In addition, the surface of the foramen magnum and jugular foramina was significantly smaller in patients compared to controls. Finally, the degree

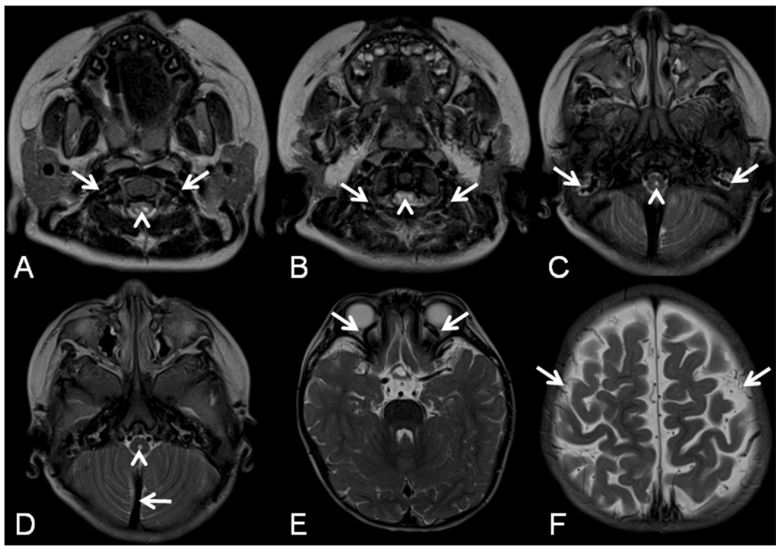


**Fig. 2** Axial T2-weighted images of a 22-month-old girl with achondroplasia showing **a** bilateral condyloid emissary veins (*arrows*) and T2-hyperintense signal in the cervical cord consistent with myelomalacia (*arrowhead*); **b** bilateral occipital emissary veins (*arrows*) and T2-hyperintense signal in the cervical cord consistent with myelomalacia (*arrowhead*); **c** bilateral mastoid emissary veins (*arrows*) and central T2-hyperintense signal in the cervicomedullary junction (arrowhead); **d** prominent occipital sinus (*arrow*) and central T2-hyperintense signal in the cervicomedullary junction (*arrowhead*); **e** bilateral prominent superior ophthalmic veins (*arrows*); and **f** bilateral prominent meningeal vessels (*arrows*) in the prominent subarachnoid spaces overlying the frontal convexities

**Table 1** Measurements in children with achondroplasia and age-matched controls

| | Patients (median, range) | Controls (median, range) | *p* value |
|---|---|---|---|
| Bifrontal width/ biparietal diameter | 0.28 (0.24–0.40) | 0.26 (0.21–0.28) | <0.001 |
| Foramen magnum surface area ($cm^2$) | 0.50 (0.23–1.37) | 3.14 (1.83–6.68) | <0.001 |
| Jugular foramina surface area ($cm^2$) | 0.02 (0.00–0.10) | 0.21 (0.03–0.61) | <0.001 |
| Enlargement of emissary veins and meningeal vessels (grade) | 6 (0–11) | 0 (0–0) | <0.001 |

of enlargement of the emissary veins and meningeal vessels was significantly higher in patients compared to controls.

We then evaluated the individual parameters in patients. Spearman correlation of the individual parameters—age, foramen magnum size, jugular foramina size, ventricular size, and enlargement of emissary veins and meningeal vessels with each other showed no statistically significant correlation. Multiple logistic regression of the ratio between bifrontal width and biparietal diameter on age, foramen magnum size, jugular foramina size, and enlargement of emissary veins and meningeal vessels also resulted in no significant association.

## Discussion

Macrocephaly, hydrocephalus, and cranio-cervical junction (CCJ) compression are the major neurological complications in children with achondroplasia [2, 3]. Routine clinical surveillance for development of these complications is essential in the care of children with achondroplasia [8]. If longitudinal clinical examinations raise concern for complications, neuroimaging studies are indicated.

Some degree of ventriculomegaly is present in almost all children with achondroplasia [3, 9–11]. Neuroimaging studies in children with achondroplasia commonly show increased volume of the ventricles and extra-axial cerebrospinal fluid (CSF) spaces, particularly anteriorly [6]. In our study, we found a statistically significant higher degree of ventriculomegaly in children with achondroplasia compared to age-matched controls. This result is consistent with previous studies.

Hydrocephalus is defined as an active distension of the ventricular system resulting from inadequate passage of CSF from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation [12]. As suggested by this definition, the pathogenesis of hydrocephalus is heterogeneous and complex. In achondroplasia, the etiology of hydrocephalus has been attributed to two broad categories: (1) communicating and (2) noncommunicating hydrocephalus. Communicating hydrocephalus results from impaired venous drainage at the skull base and chronic dural venous hypertension with impaired CSF absorption, causing apparent enlargement of subarachnoid CSF spaces primarily over the sulci [3, 5, 6, 13–15]. Noncommunicating or obstructive hydrocephalus is less common and may be caused by stenosis of the Sylvian aqueduct or obstruction of CSF outflow from the fourth ventricle [3, 16].

Impaired venous drainage in achondroplasia has been shown to be caused by deformation of the skull base, resulting in stenosis of the foramen magnum and jugular foramina [4, 6, 7, 17, 18]. Our study shows a statistically significant smaller surface of the foramen magnum and jugular foramina in children with achondroplasia compared to age-matched controls and are consistent with previous studies. In the literature, there is some debate about the role of stenosis of foramen magnum or jugular foramina as the major cause of hydrocephalus in achondroplasia. Yamada et al. showed that hydrocephalus could be relieved by decompression of the foramen magnum [3]. In addition, Bruhl et al. found a close correlation between degree of ventriculomegaly and foramen magnum stenosis [4]. Other studies however showed that constriction of the jugular foramina may play the major role in reducing the venous drainage and causing hydrocephalus. Lundar et al. reported an improvement of hydrocephalus after osseous decompression of the jugular foramina [15]. In addition, Rollins et al. and Moritani et al. showed a positive correlation between ventricular enlargement and degree of stenosis of the jugular foramina [7, 19]. Our study did not show any correlation between degree of ventriculomegaly and severity of foramen magnum stenosis, stenosis of jugular foramina, and enlargement of emissary veins and meningeal vessels. This is in contrast to the previous literature, but suggests a more complex CSF dynamic process with interplay of several factors and not just one in children with achondroplasia. CSF production, engorgement of emissary veins and meningeal vessels, venous channel narrowing, and narrowing of the foramen magnum appear to be interdependent to create an apparent equilibrium with stable and compensated ventricular dilatation in the majority of achondroplasia patients [16]. In particular, the formation of collateral vessels may play a key role in the absence of progression of ventriculomegaly [18, 19]. Despite stenosis of foramen magnum and jugular foramina, only 10–15 % of children develop progressive hydrocephalus, requiring neurosurgical treatment [8, 20, 21]. The presence of prominent emissary veins and meningeal veins in all but one patient in our study supports the role of collateral vessel formation to compensate for intracranial venous hypertension and increased CSF pressures.

An increase in head circumference measurement across centiles on achondroplasia-specific charts is the best clinical indicator of developing hydrocephalus [8, 22]. When there is concern for developing hydrocephalus requiring surgical management, dedicated neuroimaging studies including CSF flow studies at the level of the CCJ are indicated [4, 19]. Jugular foramen decompression, cranio-cervical decompression, and ventriculo-peritoneal shunt are possible neurosurgical interventions to manage hydrocephalus in achondroplasia [8, 21]. The absence of correlation between degree of ventriculomegaly and severity of foramen magnum or jugular foramina stenosis in our study suggests that the decision for neurosurgical intervention cannot be taken on the basis of individual neuroimaging findings alone.

We are aware of some limitations of our study, including the relatively small number of patients, the retrospective nature of the study, lack of clinical information, and absence of longitudinal postsurgical data.

In conclusion, our study shows a significant narrowing of the foramen magnum and jugular foramina, enlargement of emissary veins and meningeal vessels and increased ventricular size in children with achondroplasia compared to age-matched controls. A correlation between these individual parameters was not found. This suggests a complex CSF dynamic with an unquantifiable interdependent relationship of CSF production, enlargement of emissary veins and meningeal vessels, venous channel narrowing, and narrowing of the foramen magnum to create an apparent equilibrium with stable and compensated ventricular dilatation in the majority of achondroplasia patients.

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**Authors' contributions** TB, TAGMH, and AP conceptualized and designed the study; AP generally supervised the study; TB, GO, BH, and AP participated in the acquisition of data; TB, GO, and BH analyzed conventional neuroimaging data; TB, GO, BH, TAGMH, and AP interpreted the results; KAC performed statistical analysis; TB drafted the manuscript; All the co-authors critically revised the manuscript for intellectual content and read and approved the final manuscript.

**Conflict of interest** All coauthors do not report conflicts of interest.

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