Achondroplasia Natural History Study (CLARITY): 60-year experience in cervicomedullary decompression in achondroplasia from four skeletal dysplasia centers

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OBJECTIVE The authors sought to determine the overall incidence of cervicomedullary decompression (CMD) in patients with achondroplasia and the characteristics associated with those surgeries across multiple institutions with experience caring for individuals with skeletal dysplasias.

METHODS Data from CLARITY (Achondroplasia Natural History Study) for 1374 patients with achondroplasia from four skeletal dysplasia centers (A. I. duPont Hospital for Children, Johns Hopkins University, University of Texas Health, and University of Wisconsin School of Medicine and Public Health) followed from 1957 to 2017 were recorded in a Research Electronic Data Capture (REDCap) database. Data collected and analyzed included surgeries, indications, complications, ages at time of procedures, screening procedures, and medical diagnoses.

RESULTS There were 314 CMD procedures in 281 patients (20.5% of the entire cohort). The median age of first CMD was 1.3 years in males and 1.1 years in females. Over time, there was a decrease in the median age of patients at first CMD. All patients born before 1980 who underwent CMD had the procedure after 5 years of age, whereas 98% of patients born after 2010 underwent CMD before 5 years of age. In addition, a greater proportion of patients born in more recent decades had documented neuroimaging and polysomnography (PSG) prior to CMD. Ventriculoperitoneal shunts (VPSs) were placed more frequently in patients undergoing CMD (23%) than in the entire cohort (8%). Patients who required either CMD or VPS were 7 times more likely to require both surgeries than patients who required neither surgery (OR 7.0, 95% CI 4.66–10.53; p < 0.0001). Overall, 10.3% of patients who underwent CMD required a subsequent CMD.

CONCLUSIONS The prevalence of CMD in this large achondroplasia cohort was 20%, with more recently treated patients undergoing first CMD at younger ages than earlier patients. The use of neuroimaging and PSG screening modalities increased over time, suggesting that increased and better surveillance contributed to earlier identification and intervention in patients with cervicomedullary stenosis and its complications.

KEYWORDS achondroplasia; foramen magnum stenosis; cervicomedullary decompression; pediatrics; database; spine

ACHONDROPLASIA is the most common short-statured skeletal dysplasia, with an estimated birth prevalence of 1 per 20,000–30,000 live births.1 Achondroplasia is caused by a mutation in the fibroblast growth factor receptor 3 gene (FGFR3),2 with one mutation (G1138A) responsible for over 98% of all cases.3 This mutation results in constitutive inhibition of endochondral growth.1 The recognizable clinical characteristics include disproportionate short stature with rhizomesomelia of the limbs and macrocephaly with frontal bossing. In addition,
there are distinct, recognizable, but highly variable skeletal manifestations of achondroplasia, including cervicomedullary compression.1 Because of premature closure of cranial base synchondroses, the foramen magnum is smaller in both the transverse and sagittal dimensions in individuals with achondroplasia compared to those with average stature.4

Stenosis of the foramen magnum and subsequent compression of neurotissues requiring cervicomedullary decompression (CMD) is estimated to occur in 5%–41% of children with achondroplasia.5,6,8 The wide variability reflects the various methods of ascertainment used to obtain this information. Signs and symptoms of compression include abnormal neurological examination, and long-track signs (e.g., clonus and hyperreflexia), gross motor developmental delay, central apnea, signal changes in the spinal cord as seen on MRI, and even sudden infant death.5 Life-threatening respiratory difficulties and myelopathy can be cured by CMD.6–12 Increased awareness and improved management of critical foramen magnum stenosis began in the early 1980s.11,12 Untreated foramen magnum stenosis and subsequent upper cervical and medullary compression have been definitively related to the increased rates of sudden unexpected death in infants with achondroplasia.5,13–15

Infant mortality in achondroplasia has decreased in the last few decades, and a recent study by Hashmi et al.,16 using the national death index to assess the vital status of patients with achondroplasia seen in clinics since 1986, identified only 1 infant death in 855 patients. It is generally considered that improved surveillance and intervention for cervicomedullary compression help explain this finding. Data on CMD were analyzed from a large cohort of patients with achondroplasia over more than 4 decades cared for in four different skeletal dysplasia centers (CLARITY [Achondroplasia Natural History Study]). Here, we present CLARITY data related to the rate of CMD and characteristics associated with those surgeries across a multi-institutional cohort of individuals with achondroplasia.

Methods

CLARITY was approved by the Institutional Review Boards of Johns Hopkins University (JHU), A. I. du Pont Hospital for Children (AIDHC), McGovern Medical School at University of Texas Health (UTH), and University of Wisconsin School of Medicine and Public Health (UW). The CLARITY investigation and overall study design were described previously and included both a retrospective and prospective section.17 In this paper, we focus on data collected during the retrospective portion of CLARITY. In brief, all available medical records pertaining to anthropometry, surgical burden, sleep disordered breathing, and radiographic imaging from 1374 patients with achondroplasia evaluated from 1957 through 2017 at the four institutions were entered into a Research Electronic Data Capture (REDCap) database.17 The total achondroplasia cohort is referred to as the Primary Achondroplasia Cohort (PAC). The analyses presented herein focus on CMD, the date and patient age CMD was performed, indications, and outcomes. For these analyses, CMD was defined as surgical enlargement of the foramen magnum alone or enlargement of the foramen magnum plus C1 or C1 and C2 laminectomy.

Surgical indications were categorized as follows: acute life-threatening event, central apnea by polysomnography (PSG), abnormal MRI findings, persistent and severe hypotonia, significant gross motor developmental delay, hyperreflexia, asymmetrical reflexes, abnormal Babinski response, and high cervical myelopathy (weakness/paralysis, clonus, foramen magnum stenosis, cervical stenosis, and abnormal neurological signs). MRI diagnostic findings included T2-signal abnormality, syrinx, cord indentation, and obliteration of subarachnoid fluid layer/flow. Outcomes were assessed and categorized as follows: good outcome, no improvement, rehospitalization, repeat procedure, anesthetic complication, bleeding, poor wound healing, pseudarthrosis, paresthesia, dislocation, pulmonary complication, infection, worsened medical condition, unknown, and other. VPS procedures were noted in the brain surgery category. There was no limitation as to number of responses within a category.

Descriptive statistics (SAS) were reported as frequencies (percent) for categorical variables. Mean values (with standard deviations [SDs]) were calculated for normally distributed continuous variables, and median values (with interquartile ranges [IQRs]) were reported for nonnormally distributed continuous variables. Medians were reported instead of means to decrease the effect of outliers. PROC LIFETEST, the nonparametric procedure, was used to create the curves and calculate the probability of being free from surgery at each time interval. The “failure” time or the time-to-event was calculated based on the age at first CMD, and the “censor” time was calculated based on the age at the last known medical contact for people who did not have the surgery.

The odds ratio (OR) and 95% confidence interval (CI) were calculated to determine the likelihood of spine and lower-extremity surgery occurring after CMD and shunting, as well as other risk factors in this achondroplasia cohort. The OR and 95% CI were calculated for 2 × 2 contingency tables. The Cochran-Mantel-Haenszel test was used to compare the ORs of various 2 × 2 tables; p < 0.05 was considered significant.

Results

In CLARITY, the PAC consisted of 1374 patients, of whom 281 (20.5%) underwent 314 CMD procedures. Of the 281 patients who underwent CMD, 133 (47.3%) were male and 148 (52.7%) were female, with 22% and 19% of all female and male patients, respectively, undergoing CMD. The median age at first CMD was 1.3 years in male and 1.1 years in female patients. As shown in Table 1, there was no statistically significant difference in the need for decompression (p = 0.28) or in the mean or median ages of first decompression in male versus female patients. The percentages of patients undergoing CMD at each study center were as follows: 83/299 (28%) at JHU, 73/384 (19%) at AIDHC, 39/218 (18%) at UTH, and 86/475 (18%) at UW. Three centers had a similar median age for un-
undergoing first CMD—JHU (1.1 years), AIDHC (1.5 years), and UW (1.1 years)—but the median age was considerably older at UTH (4.1 years). Examining the characteristics of first CMD by birth decade revealed notable differences: the median age at the time of surgery was 19.8 years for patients born before 1980, whereas much earlier ages were reported for patients born in later decades (1.3 years for those born in the 1980s and 1990s, 1.2 years for those born in the 2000s, and 0.9 years for those born in the 2010s).

All of the patients born before 1980 underwent initial decompression after 5 years of age. For patients born in the 1980s, 64% (30/47) who underwent CMD had the procedure by age 2 years and 91% (43/47) had the procedure by age 5 years. In contrast, in the most recent birth cohort, 91% (50/55) of all first CMD surgeries were completed by 2 years of age and 98% (54/55) by 5 years of age (Fig. 1). The greatest increase in proportion of a birth cohort undergoing CMD was between patients born before 1980 and those born in the 1980s (9.0% vs 20.3%, an increase of 11%). Over the subsequent 3 decades, there was little change in the percentage of patients undergoing CMD (24.8%, 22.5%, and 23% in the 1990s, 2000s, and 2010s, respectively).

Kaplan-Meier survival analysis shows that the probability of having CMD increases rapidly to 14.5% during the first 2 years of life, after which it gradually increases before plateauing at 27% by age 40 years (Fig. 2). When the analysis was performed with only patients born after 1980, a similar increase to 14.4% was observed by age 2 years, but the plateau was reached much earlier at age 10 years, when 19.7% of the PAC born in 1980–2017 had undergone CMD. Interestingly, only 9 patients born after 1980 underwent initial CMD after 10 years of age, with the last CMD in this group of patients performed at age 16.6 years.

The overall first CMD rate ranged from 8.5% to 25.2% by birth decade (Table 1) and 17.9% to 27.8% by treatment center (Table 2). Analysis of CMD rate by center and birth decade yielded 20 unique treatment center–birth decade cohorts with CMD rates of 0%–40%. The highest rates were 40.0% in the 2000 birth decade at UT and 37.7% in the 1990 birth decade at JHU.
Of the 281 patients who underwent CMD, 257 (91%) had at least one indication for CMD documented in the medical record, of whom 217 had imaging indications documented, 90 had clinical motor indications documented, and 59 had respiratory indications documented (Table 3). Although many patients had indications in multiple domains, the largest indication category was imaging abnormalities (Fig. 3). In contrast, in the birth cohort born before 1980, motor indications (n = 10) were the predominant indication for the 20 patients with a documented indication, followed by imaging (n = 9) and respiratory concerns (n = 2). When different combinations of two indication categories were examined, motor and imaging findings were the most common combination of indications in cohorts born before 1980 and after 1980.

The median (range) follow-up time for patients with a CMD was 10.7 years (range 1.2–64.6 years). The median follow-up time for patients without a CMD was 11.7 years (range 0.03–70.2 years), with person-years measured as the age at the last known contact. Most patients (78%) had positive and uncomplicated outcomes; 11 (3.9%) did not improve, 3 (1.0%) had worsened medical status, and 13 (4.6%) had no outcome recorded. Eight patients (2.8%) required readmission within 1 month, and 4 (1.4%) required a repeat procedure within 1 year. Eighteen percent of patients had at least one complication, with 4 patients (1.4%) developing an infection, 3 (1.0%) bleeding, 3 (1.0%) paresthesia, 2 (0.7%) poor wound healing, and 2 patients (0.7%) developing pulmonary complication. There were no CMD-related deaths.

Overall, 10.3% (29/281) of patients undergoing CMD required a subsequent CMD, most commonly due to persistent stenosis demonstrated by imaging or recurrence of motor symptoms. Two patients (1.1%) had three CMDs and 1 patient (0.4%) had four CMDs. Of repeat CMD procedures, 41% (12/29) occurred in patients born in the 1990s (Table 4). The median time between repeat procedures ranged from 2.2 to 3.0 years, and the median (range) patient age for the second CMD was 6.1 years (range 0.8–37.7 years) (Table 4). No correlation was found between patient age at first CMD and the need for a second CMD (the median age for first CMD in those requiring subsequent CMD was 1.2 years, with a range of 0.7–36.7 years).

JHU had the highest prevalence of subsequent CMD, with 14/83 (17%) patients requiring this procedure, followed by AIDHC (7/73; 9.5%), UW (7/86; 8%), and UTH (1/39; 2.6%).

Screening procedures to detect critical cervicomedullary compression included PSG and imaging of the cranio cervical junction with MRI or CT scan. Over the entire study period, 63.6% of patients undergoing CMD had either PSG or MRI/CT within 4 months prior to undergoing CMD, with 27.8% having both PSG and imaging screening (Table 5). Prior to the year 2000, 50% of patients had one of the two screening tests, compared with 70% and 92.8% of patients in the 2000 and 2010 birth cohorts, respectively.

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**TABLE 2. Distribution of first CMD surgeries in PAC by birth decade and center**

<table>
<thead>
<tr>
<th>Birth Decade</th>
<th>AIDHC</th>
<th>JHU</th>
<th>UTH</th>
<th>UW</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010s</td>
<td>16</td>
<td>15</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>2000s</td>
<td>23</td>
<td>21</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>1990s</td>
<td>22</td>
<td>29</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>1980s</td>
<td>12</td>
<td>14</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>&lt;1980</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>83</td>
<td>39</td>
<td>86</td>
</tr>
</tbody>
</table>

**TABLE 3. Indication categories for CMD**

<table>
<thead>
<tr>
<th>Neurological/Motor Indications</th>
<th>Respiratory Indications</th>
<th>Imaging Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive hypotonia</td>
<td>Central apnea</td>
<td>Syrinx</td>
</tr>
<tr>
<td>Excessively delayed gross motor development</td>
<td>Severe obstructive apnea</td>
<td>Cord indentation or obliteration of subarachnoid fluid later</td>
</tr>
<tr>
<td>Signs of myelopathy such as abnormal reflexes or clonus</td>
<td>Apparent life-threatening event</td>
<td>T2-signal abnormality in upper cervical cord near foramen magnum</td>
</tr>
</tbody>
</table>

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**FIG. 3.** Venn diagram of indications for all first CMDs. Imaging (n = 217) was the most common single indication, and neurological/motor and imaging findings (n = 195) were the most common combined indications.
A substantial number of patients who underwent CMD also underwent ventriculoperitoneal shunt (VPS) placement, with an almost equal number having VPS before and after the CMD. Of the 281 patients who underwent CMD, 65 (23%; 34 males, 31 females) had VPS placement, with 26 patients having VPS placement before CMD, 25 after CMD, and 14 concurrently with CMD. Of the 1374 PAC patients, 110 patients (64 males, 46 females) had a total of 141 VPS surgeries. While 8% (110/1374) of the entire cohort required VPS, 23% of patients who required CMD also underwent VPS. The overall OR of a patient requiring both a CMD and VPS after needing either surgery was 7.0 (95% CI 4.66–10.53; p < 0.0001). VPS placement was less common in the 2010–2017 cohort and peaked in the 1990s’ cohort when some surgeons placed a VPS in conjunction with the CMD procedure to prevent a postoperative CSF fistula. Interestingly, patients who had CMD were 1.9 times (95% CI 1.30–2.63) more likely to have distal spine surgery later in their lives than patients who did not undergo CMD.

### Discussion

**CLARITY**, the large, multicenter, historical cohort study spanning more than 60 years, showed that 20.5% of the PAC underwent CMD. This rate falls well within published CMD rates of 5%–41% in achondroplasia cohorts and is similar to the 18% CMD rate reported in a recent 15-year review of achondroplasia outcomes in France. The similarity of the results of these studies provides important guidance information for healthcare providers and families.

In the oldest birth cohort (those born before 1980), the overall CMD rate (9%) was lower and CMDs were performed at a much older patient age (median age 19.9 years) than later cohorts with a median age at first CMD of 1.3 years. This outcome is not surprising, as foramen magnum compression and sudden death were not recognized and reported until the 1980s. Increased surveillance following these reports led to better recognition of this severe and life-threatening problem and more CMDs, as reflected at these four skeletal dysplasia centers. The reasons for higher rates of CMD in certain birth cohorts at certain centers are not clear, and factors such as smaller sample size, selection bias, and surgeon-specific indications may play a role.

Screening for cervical compression has increased over the years and is correlated with a continuous decrease in the median age of patients undergoing CMD (Tables 1 and 5). This is unlikely to be only a result of increased awareness, since each of the study centers had played a pivotal role in recognizing the issues related to the craniocervical junction in achondroplasia. It is possible that earlier referrals spurred by earlier (prenatal and neonatal) diagnosis trends and better evaluation tools led to this phenomenon.

Indications for CMD dramatically changed over the more than 40 years for which there is information in the PAC. For patients evaluated after the year 2000, more than 88% had an imaging finding indication for CMD, and only one-third had neurological signs reported in the medical record. In contrast, 50% of patients in the oldest cohort had neurological signs/symptoms as an indication for CMD. This change is likely related to increased recognition of foramen magnum compression and intervention prior to neurological damage. Similarly, indications for CMD related to respiratory issues have increased as PSG screening has increased and also likely reflect better assessment and documentation.

The outcomes from initial CMD were positive overall. Serious complications were infrequent and, remarkably, there were no deaths attributed to CMD surgery. These findings complement the study results of Ho et al., who found that quality of life was not diminished in patients who underwent CMD compared with individuals with achondroplasia who did not require CMD surgery. However, 10% of patients undergoing CMD required a second CMD, indicating that at least in this large cohort, 1/50 (2%) individuals with achondroplasia require more than one CMD surgery.

A substantially larger proportion of individuals undergoing CMD also had a VPS (23% compared to 8% in the PAC). This large percentage may reflect surgical care in earlier decades when some surgeons elected to place a VPS concurrent with CMD surgery. Alternatively, since individuals with severe foramen magnum constrictions usually have severe narrowing of the jugular foramina (due to the same biological phenomenon), there may be an increased occurrence of hydrocephalus secondary to

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**TABLE 4. Description of 281 patients undergoing CMD**

<table>
<thead>
<tr>
<th>Overall no. of pts</th>
<th>29</th>
<th>3</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between repeat CMDs, yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.4</td>
<td>2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.3 ± 4.1</td>
<td>6.1 ± 6.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Birth decade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010s</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2000s</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1990s</td>
<td>12</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1980s</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;1980</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

**TABLE 5. Distribution of evaluations within 4 months of first CMD**

<table>
<thead>
<tr>
<th>Evaluations for CMD, %</th>
<th>PSG Only</th>
<th>MRI/CT Only</th>
<th>PSG &amp; MRI/CT</th>
<th>PSG or MRI/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.7</td>
<td>30.1</td>
<td>27.8</td>
<td>63.6</td>
</tr>
<tr>
<td>Birth decade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010s</td>
<td>5.5</td>
<td>30.9</td>
<td>56.4</td>
<td>92.8</td>
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<tr>
<td>2000s</td>
<td>5.0</td>
<td>38.8</td>
<td>26.3</td>
<td>70.1</td>
</tr>
<tr>
<td>1990s</td>
<td>5.1</td>
<td>27.8</td>
<td>15.2</td>
<td>48.1</td>
</tr>
<tr>
<td>1980s</td>
<td>8.5</td>
<td>21.3</td>
<td>23.4</td>
<td>53.2</td>
</tr>
<tr>
<td>&lt;1980</td>
<td>5.0</td>
<td>35.0</td>
<td>15.0</td>
<td>55.0</td>
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intracranial venous hypertension requiring VPS. Further study is needed in this area.

There are limitations to this study. Medical records were up to 63 years old and varied in their accessibility and completeness such that details regarding surgery indications and outcomes may have been missing. Differences in outcomes by birth cohort are likely influenced by changes in training and surgical methods as well as advances in diagnostic technologies over the long study period. MRI and CT scan data could not be separated. We acknowledge the lack of data regarding MRI indications for CMD. We plan to analyze the MRI scans we have cataloged and present these findings in a future paper. The CMD procedure itself has changed, which may affect CMD and VPS data. Only prospective investigations will allow for more detailed analyses to address the questions raised in this retrospective study.

Conclusions

In summary, CLARITY provides a rich resource for expanding and validating the natural history of achondroplasia. While cervical medullary compression is a well-documented complication in achondroplasia, our study results demonstrate that only 20% of individuals required CMD. This rate was consistent across study centers, virtually constant during the more recent birth decades, and similar to the findings of a recent study in France. The present study also indicates that CMD is relatively safe and resolves neurological and life-threatening complications. Future prospective studies will focus on collecting more details regarding the signs, symptoms, indications, and optimal timing of surgical intervention to better improve quality of life in achondroplasia.

Acknowledgments

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References


Disclosures

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Author Contributions
Conception and design: Pauli, Alade, Hecht, Hoover-Fong, Bober. Acquisition of data: Legare, Pauli, Alade, Hashmi, Smid, Modaff, Little, Rodriguez-Buritica, Serna. Analysis and interpretation of data: Legare, Hashmi, Campbell, Rodriguez-Buritica, Hecht, Hoover-Fong, Bober. Drafting the article: Legare, Bober. Critically revising the article: Legare, Pauli, Campbell, Rodriguez-Buritica, Hecht, Hoover-Fong, Bober. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Legare. Statistical analysis: Legare, Liu. Administrative/technical/material support: Modaff. Study supervision: Legare, Pauli, Alade, Hecht, Hoover-Fong, Bober.

Supplemental Information
Previous Presentations
Some of these data were presented as a platform presentation at the International Skeletal Dysplasia Society meeting in Oslo, Norway, September 11, 2019.

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