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Quantification of the surgical burden associated with achondroplasia: a comprehensive review of the literature

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Background and objectives

- Achondroplasia (ACH) is a rare, genetic condition resulting in disproportionate short stature and numerous multi-systemic comorbidities[1]
- Current management centres around symptom alleviation and surgical interventions of comorbidities[2]
- New drug therapies for ACH may potentially impact comorbidities and the need for surgical interventions[3]
- Understanding rates of these events among untreated individuals ('background rates') can aid evaluation of potential effects of new ACH treatment options
- This review provides a quantification of the prevalence of ACH-related surgeries by age-group for use as reference point for future treatment evaluation

Methods

- Based on PRISMA principles, we conducted a comprehensive review of the peer-review literature of English-language articles published from 1990 onwards
- Using Medline/EMBASE databases, search terms for surgeries were applied by body system:
  - **ENT:** Adenoid-/tonsillectomy, tympanotomy, grommet insertion
  - **Neurological:** Decompression surgery, foraminotomy, shunting or ventriculostomy
  - **Spinal:** Laminectomy, lumber spine decompression
  - **Limb:** Osteotomies, limb lengthening
- Articles reporting results from clinical trials, case studies, or studies evaluating surgical outcomes (e.g. on patients selected based on previous surgery) were excluded
- Prevalence data on surgical interventions were abstracted and grouped by age at surgery:
  - **Infancy (0–2 years); Childhood (3–12 years); Adolescence (12–18 years); Adulthood (>18 years); Range (if ages overlapped defined categories)**
  - Surgery 'history' was reported if age at surgery was not reported
  - Denominator for the prevalence estimates was based on individuals with ACH (articles included in quantitative synthesis); articles reporting prevalence estimates for a group with underlying comorbidity warranting surgery were included in count of eligible studies (qualitative synthesis, not shown)
- An a priori decision was made not to utilize meta-analytic techniques to pool estimates in order to document variability in estimates
- After reviewing individual estimates and calculating 95% confidence intervals (CIs) for each surgical type, we summarise descriptive statistics (minimum, maximum) of prevalence estimates by age-group for surgery categories

Results

Figure 1: PRISMA Flow Diagram

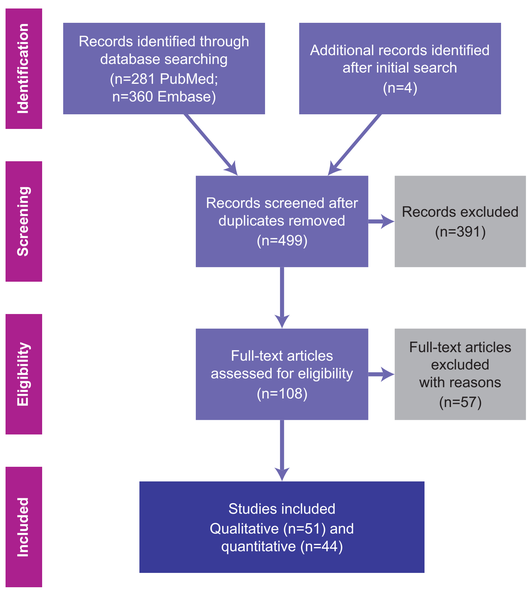

Table 1: Characteristics of 51 Eligible Studies

Region	North America	Europe	Asia-Pacific	International*	Other**
Number of studies	26	11	9	3	3

*Collaboration across continents, **Russia, Brazil, not reported

Setting/ clinic	Tertiary care	Bone/ dysplasia	Pediatrics	Neurology	Orthopedics
Number of studies	15	12	11	7	5

*Setting not reported in 1 study

Design	Chart review	Cohort	Cross-sectional
Number of studies	36	8	7

Size (N of subjects)	N ≤ 30	30<N<100	100<N<300	>400
Number of studies	15	16	12	8

Table 2: Summary of range of prevalence estimates (N=139) by age-groups

Specific surgeries	Distinct age-groups: Infancy 0–2 years %	Childhood 3–12 years %	Adolescence 12–18 years %	Adulthood ≥18 years %	Other reported age range %
At least one surgery (4 estimates from 4 studies): *maximum prevalence **80%***					
At least one surgical procedure		27			22–80
ENT surgery (50 estimates from 19 studies): *maximum prevalence **79%***					
Grommets, tympanostomy tubes, ventilation tubes, myringotomy tubes, pressure equalization tubes	16–57	14–57	13		
Ear ventilation tube history			41	19–44	
ENT, pharyngeal surgery, tracheostomy, turbinectomy, turbinoplasty, upperairway surgery	3–31	6–35			61–65
Adenoidectomy, tonsillectomy, adenotonsillectomy	24–40	7–79	7	2	
Adenoidectomy history			30	16–49	
Neurosurgery (55 estimates from 31 studies): *maximum prevalence **59%***					
Decompression surgery of the brain stem, cervico-medullary or cranio-cervical region, posterior fossa, cervical spine, foramen magnum	1–44	0–59	0–4	5	4–46
FM decompression history			25	15	
Shunt	2–7	0–8	1	0	10
Spinal surgery (14 estimates from 8 studies): *maximum prevalence **34%***					
Laminectomy, spinal stenosis surgery, decompression	0	1–31	3	0–18	10
Spine surgery					13–21
Spine surgery history			4	34	
Limb surgery (15 estimates from 7 studies): *maximum prevalence **59%***					
Osteotomy	0	5–7	10	2	11–21
Humeral, femoral or tibial lengthening history			17–51	18–59	17–22

Number of studies not mutually exclusive across categories.

Summary

- **Overall, the surgical burden was high**
- **Volume of literature was highest for neuro- and lowest for limb surgery**
- **Infancy:** ENT surgery and decompression surgery of the brain and upper spine were the most commonly performed surgeries
- **Childhood:** ENT surgery was most common, followed by decompression surgery of the brain and upper spine as well as lower spine surgery
- **Adolescence:** ENT surgery was highly prevalent as well as orthopaedic limb surgery
- **Adulthood:** Spinal surgery was seen in a fifth of this age-group
- **Range:** Any surgery was recalled by 80%, ENT by 65%, neurosurgery by 26%, spinal surgery by 34% and limb surgery by 59%

Limitations

- Heterogeneity in study design, type of clinical setting, populations and sub-group definitions led to wide variability in estimates
- Prevalence estimates were based on the ACH population, however comorbidity warranting the surgery was not consistently reported
- For estimates based on an age-range or on recalling having a history of surgery, the age at surgery was not discernible
- Revision surgery was not addressed (exclusion criterion)
- Information on multiple surgery types per person or secular trends was too limited to report or draw conclusions

Conclusions

- This review provides a quantification of the surgical burden associated with achondroplasia by age
- Up to 80% of individuals with ACH reported at least one surgery
  - ENT-surgery was most frequent (~80%), neuro- or limb-surgery was found in two-thirds and spinal surgery in one third of individuals
- Surgery was highly prevalent among infants and children, in particular ENT- and neuro-surgeries reflecting the seriousness of the underlying condition at a young age
- The literature reflected medical priorities in management of ACH and focus on pediatric care
  - Neurosurgery was reported in most studies, followed by ENT-surgery; there were fewer studies on spinal and limb surgery (particularly as outcome studies on limb surgeries were excluded)
- ACH is a complex condition carrying a high surgical burden with impact throughout life requiring timely multi-disciplinary care

References

1. Hoover-Fong J et al. Lifetime impact of achondroplasia: Current evidence and perspectives on the natural history. *Bone* 2021; 146:115872. **2.** Savarirayan R et al. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. *Nat Rev Endocrinol.* 2022 Mar;18(3):173-189. **3.** Wrobel W et al. Advantages and disadvantages of different treatment methods in achondroplasia: a review, *Int. J. Mol. Sci.* 22 (2021) 5573.

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