Medical complications in children with achondroplasia: learnings from PROPEL – a prospective clinical assessment study

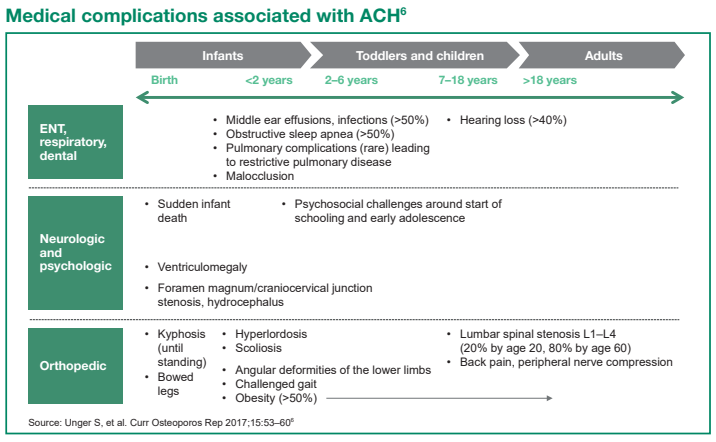
Ravi Savarirayan,[1] Josep Maria De Bergua,[2] Paul Arundel,[3] Jean Pierre Salles,[4] Antonio Leiva-Gea,[5] Vrinda Saraff,[6] Helen McDevitt,[7] Maria Salcedo Montejo,[8] Marc Nicolino,[9] Valerie Cormier-Daire,[10] Peter Kannu,[11] Mars Skae,[12] Michael B. Bober,[13] John Phillips III,[14] Toby Candler,[15] Paul Harmatz,[16] Howard Saal,[17] Julie Hoover-Fong,[18] Richard Weng,[19] Elena Muslimova,[19] Terry Cho,[19] Daniela Rogoff,[19] Melita Irving[20]

[1]Murdoch Children's Research Institute, Melbourne, Australia; [2]Hospital Vithas San José, Vitoria-Gasteiz, Spain; [3]Sheffield Children's NHS Foundation Trust, Sheffield, UK; [4]Hôpital des Enfants – Toulouse, Toulouse, France; [5]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [6]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; [7]NHS Greater Glasgow and Clyde, Glasgow, UK; [8]Hospital Universitario La Paz, Madrid, Spain; [9]Hôpital Femme Mère Enfant, Bron, France; [10]Hôpital Necker-Enfants Malades, Paris, France; [11]University of Alberta – Stollery Children's Hospital, Edmonton, Canada; [12]Manchester University NHS Foundation Trust, Manchester, UK; [13]Nemours/Alfred I. duPont Hospital for Children, Wilmington, USA; [14]Vanderbilt University Medical Center Nashville, USA; [15]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK; [16]Benioff Children's Hospital Oakland, Oakland, USA; [17]Cincinnati Children's Hospital Medical Center, Cincinnati, USA; [18]Johns Hopkins University, Baltimore, USA; [19]QED Therapeutics, San Francisco, USA; [20]Guy's and St Thomas' NHS Foundation Trust, London, UK

Background

- Achondroplasia (ACH) is the most common short-limbed skeletal dysplasia, affecting between 1 in 15,000 and 1 in 30,000 live births, with an estimated global prevalence of 250,000.[1,2]
- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor-3 gene (*FGFR3*),[3,4] which is a negative regulator of endochondral bone formation.
- Characteristic clinical features include disproportionate short stature, smaller than average chest, macrocephaly with frontal bossing, midface hypoplasia, curvature of the spine, hypermobile joints, leg bowing, and shortening of the fingers and toes.[5]
- Individuals with ACH experience a variety of physical, functional, and psychosocial complications and challenges throughout their lifetime.[6,7]

Medical complications associated with ACH[6]



Source: Unger S, et al. Curr Osteoporos Rep 2017;15:53–60[6]

PROPEL study

- PROPEL (NCT04035811) is an ongoing, prospective, non-interventional clinical assessment study designed to collect baseline growth data and to characterize the natural history of ACH in children being considered for future enrollment in interventional studies with infigratinib, an oral FGFR1–3 tyrosine kinase inhibitor, sponsored by QED Therapeutics.
- Children with ACH aged between 2.5 and <17 years are eligible for enrollment in PROPEL and are evaluated at screening/baseline, month 3, month 6, and every 6 months thereafter.
- The maximum duration of participation in PROPEL is 2 years.

PROPEL study key inclusion/exclusion criteria

Key inclusion criteria
• Signed informed consent by study participant or parent(s) or legally authorized representative and signed informed assent by the study participant (when applicable)
• Age 2.5 to 17 years at study entry
• Diagnosis of ACH (as confirmed by the Principal Investigator, Co-principal Investigator, or other qualified clinical geneticist)
• Ambulatory and able to stand without assistance
Key exclusion criteria
• Hypochondroplasia or short stature condition other than ACH
• Females who have had their menarche
• Annualized height velocity ≤1.5 cm/year over a period ≥6 months prior to screening
• Concurrent disease or condition that, in the view of the investigator and/or study sponsor, may impact growth or where the treatment is known to impact growth
• Significant abnormality in screening laboratory results
• Treatment with growth hormone, insulin-like growth factor-1, or anabolic steroids in the previous 6 months
• Regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable)
• Previous guided growth surgery or limb-lengthening surgery within 12 months prior to screening

Objectives

- Here we describe the medical complications reported as medical history and occurring during PROPEL.
- Medical history collected at screening/baseline is summarized using system organ class (SOC) and preferred terms:
  - Individual subjects are counted once within an SOC, even if they presented more than one event within that SOC.
  - Individual subjects are counted once if they presented more than one event with the same preferred term but are counted more than once if they presented events in more than one preferred term/lower-level term.

Results

- To date, a total of 97 children with ACH have been enrolled at 19 sites in Europe, Australia, and North America. The PROPEL study is ongoing.
- Baseline characteristics of enrolled children are shown in the table below.
- The most common procedures and/or medical disorders reported as medical history were in the following categories:
  - Surgical and medical procedures (68.0%).
  - Respiratory, thoracic and mediastinal disorders (53.6%).
  - Infections and infestations (51.5%).
  - Musculoskeletal and connective tissue disorders (38.1%).
  - Congenital, familial and genetic disorders (31.9%).
  - Nervous system disorders (18.6%).
  - Ear and labyrinth disorders (17.5%).

Baseline characteristics

Characteristic	Total (n=97)
Age, years	
Mean (SD)	6.3 (2.5)
Median (range)	6.5 (2.5–10.8)
Age group, n (%)	
<3 years	12 (12.4)
3 to <5 years	24 (24.7)
5 to <8 years	29 (29.9)
≥8 years	32 (33.0)
Sex, n (%)	
Male	41 (42.3)
Female	56 (57.8)
Race, n (%)	
White	63 (65.0)
Asian	9 (9.3)
Black or African American	5 (5.1)
Other	8 (8.2)
Not reported	12 (12.4)

Medical history

Surgical and medical procedures occurring in ≥1 subject

- A total of 66 children (68.0%) had undergone surgical or medical procedures, with a mean of 3.1 procedures per child (1–15 surgeries per subject).
- The most common types of surgery or procedure were pressure-equalizing ear tube insertion (36.1%), adenoidectomy (26.8%) and tonsillectomy (19.6%).
- Twenty-one (21.6%) children had undergone at least 1 surgery (1–6 surgeries/child) for spine or cranial decompression.

Term	No. of subjects (%)*
Ear procedures and operations	
Ear tube insertion	35 (36.1)
Myringotomy	5 (5.2)
Adenoid/tonsil procedures and operations	
Adenoidectomy	26 (26.8)
Tonsillectomy	19 (19.6)
Adenotonsillectomy	15 (15.5)
Spinal and cranial surgeries	
Decompressive craniectomy	14 (14.4)
Spinal decompression	6 (6.2)
Spinal laminectomy	3 (3.1)
Palatal implant	3 (3.1)
Device therapy	3 (3.1)
Ventriculo-peritoneal shunt	2 (2.1)
Mechanical ventilation	2 (2.1)
Turbinectomy	2 (2.1)

*Children could be counted more than once if they underwent ≥1 type of procedure

Respiratory, thoracic and mediastinal disorders

- A history of respiratory disorders was reported in 52 children (53.6%).
- The most common respiratory, thoracic, and mediastinal disorder was sleep apnea syndrome (45.4%).

Respiratory disorders occurring in ≥1 subject	No. of subjects (%)*
Sleep apnea syndrome	44 (45.4)
Adenoidal hypertrophy	8 (8.2)
Nasal congestion	4 (4.1)
Snoring	3 (3.1)
Tonsillar hypertrophy	2 (2.1)

*Children could be counted more than once if they had ≥1 type of event

Infections and infestations

- A history of infections and infestations was reported in 50 children (51.5%).
- The most common of these were ear infections (49.5%).

Ear infections	No. of subjects (%)*
Otitis media (serous)	15 (15.5)
Otitis media	13 (13.4)
Otitis media (recurrent)	9 (9.3)
Otitis media (chronic)	6 (6.2)
Glue ear	5 (5.2)

*Children could be counted more than once if they had ≥1 type of event

Musculoskeletal and connective tissue disorders in ≥1 subject

- A total of 37 children (38.1%) had a history of musculoskeletal disorders, the most common of which were kyphosis (18.6%) and knee deformity (13.4%).
- Spinal stenosis was reported in 5 children (5.2%).

Musculoskeletal disorders occurring in ≥1 subject	No. of subjects (%)*
Kyphosis	18 (18.6)
Knee deformity	13 (13.4)
Lordosis	7 (7.2)
Spinal stenosis	5 (5.2)
Arthropathy	3 (3.1)
Arthralgia	2 (2.1)
Blount's disease	2 (2.1)
Cervical spinal stenosis	2 (2.1)
Lumbar spinal stenosis	2 (2.1)

*Children could be counted more than once if they had ≥1 type of event

Other conditions/events reported in ≥1 subject

- Congenital disorders reported in ≥1 subject were: foramen magnum stenosis (n=22; 22.7%); atrial septal defect (n=2; 2.1%); and patent ductus arteriosus (n=2; 2.1%).
- Disorders in the central nervous system were reported in 18 (18.6%) children, the most common being cerebral ventricle dilatation (5.2%).
- Ear and labyrinth disorders were found in 17 (17.5%) children, all of whom presented hearing impairment.

CNS disorders	No. of subjects (%)*
Cerebral ventricle dilatation	5 (5.2)
Speech disorder developmental	3 (3.1)
Spinal cord compression	3 (3.1)
Gross motor delay	2 (2.1)
Hydrocephalus	2 (2.1)

Ear and labyrinth disorders	No. of subjects (%)*
Deafness	7 (7.2)
Conductive deafness	6 (6.2)
Eustachian tube dysfunction	5 (5.2)
Hypoacusis	4 (4.1)

*Children could be counted more than once if they had ≥1 type of event

Events occurring during PROPEL

- While participating in the PROPEL study, 20 children (20.6%) underwent at least 1 surgical procedure, the most common being ear tube insertion (n=7). The same number of children (n=20, 20.6%) underwent investigations, the most common being imaging tests.
- Infections and infestations occurred in 37 children (38.1%), ear infections being the most commonly occurring (n=20; 1–3 episodes/subject).

Surgical/medical procedures and investigations

Surgical and medical procedures	No. of subjects (%)*
Ear tube insertion	7 (7.2)
Tooth extraction	2 (2.1)
Adenoidectomy	1 (1.0)
Adenotonsillectomy	1 (1.0)
Bladder catheterisation	1 (1.0)
CSF shunt removal	1 (1.0)
Decompressive craniectomy	1 (1.0)
Epiphysiodesis	1 (1.0)
Patent ductus arteriosus repair	1 (1.0)
Spinal laminectomy	1 (1.0)
Suture insertion	1 (1.0)
Tonsillectomy	1 (1.0)
Tooth repair	1 (1.0)
Tracheostomy closure	1 (1.0)
Tracheostomy tube removal	1 (1.0)
Tympanoplasty	1 (1.0)
Ventriculo-peritoneal shunt	1 (1.0)

Investigations	No. of subjects (%)*
X-ray (spinal; limb)	10 (10.3)
Magnetic resonance imaging	7 (7.2)
SARS-CoV-1 test	5 (5.2)
Sleep study	4 (4.1)
Acoustic stimulation tests	2 (2.1)
Audiogram	2 (2.1)
Angiogram	1 (1.0)
Blood test	1 (1.0)
Computerised tomogram	1 (1.0)
Computerised tomogram head	1 (1.0)
Oesophagogastroduodenoscopy	1 (1.0)
Ophthalmological examination	1 (1.0)
Tympanometry	1 (1.0)

*Children could be counted more than once if they had ≥1 type of event

Disorders

Description	No. of subjects (%)*
Infections and infestations	
Ear infections	20 (20.6)
Nasopharyngitis	11 (11.3)
COVID-19	5 (5.2)
Respiratory, thoracic and mediastinal disorders	
Sleep apnea	5 (5.2)
Cough	5 (5.2)
Rhinorrea/nasal congestion	2 (2.1)
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	8 (8.2)
Arthralgia	3 (3.1)
Knee deformity	3 (3.1)
Injury, poisoning and procedural complications	
Head injury	4 (4.1)
Fall	3 (3.1)
Skin laceration	2 (2.1)
Gastrointestinal disorders	
Vomiting	2 (2.1)
Constipation	2 (2.1)
Dental caries	2 (2.1)
General disorders and administration site	
Pyrexia	3 (3.1)
Eye disorders	
Myopia	2 (2.1)
Skin and subcutaneous tissue disorders	
Dermatitis/eczema	3 (3.1)
Psychiatric disorders	
ADHD	2 (2.1)
Ear and labyrinth disorders	
Conductive deadness/ear pain	2 (2.1)
Immune system disorders	
Seasonal allergy	2 (2.1)

*Children could be counted more than once if they had ≥1 type of event

Current status

- The PROPEL study is ongoing and enrolling participants as of March 2023. The study has a planned total enrollment of more than 200 children.
- The PROPEL study is expected to contribute to the characterization of the natural history of ACH and lead to sufficient enrollment into interventional trials of infigratinib in children with ACH, including the Phase 2 PROPEL 2 study and the upcoming Phase 3 study.

Conclusions

- These medical history data from the PROPEL study highlight the significant complications and high number of interventions experienced by children with ACH throughout infancy and childhood.
- These data underline the importance of expert management of this complex condition.

Acknowledgments

- The authors would like to acknowledge all study participants, parent(s) or legally authorized representatives, together with participating sites, investigators, and study staff involved in PROPEL.
- Editorial/writing support for this poster was provided by Miller Medical Communications Ltd. This work was funded by the study sponsor (QED Therapeutics Inc., an affiliate of BridgeBio Pharma).

References

1. Horton WA, et al. Lancet 2007;370:162–72.
2. Waller DK, et al. Am J Med Genet A 2008;146A:2385–9.
3. Shiang R, et al. Cell 1994;78:333–42.
4. Bellus GA, et al. Am J Hum Genet 1995;56:368–73.
5. Hoover-Fong J, et al. Am J Med Genet A 2017;173:1226–30.
6. Unger S, et al. Curr Osteoporos Rep 2017;15:53–60.
7. Savarirayan R, et al. Nat Rev Endocrin 2022;18:173–89.

Presented at IMPE 2023, Buenos Aires, Argentina, March 4–7, 2023

bridgebio | QED therapeutics a bridgebio company

QR CODE SCAN ME