

Beyond height: key outcomes in achondroplasia management

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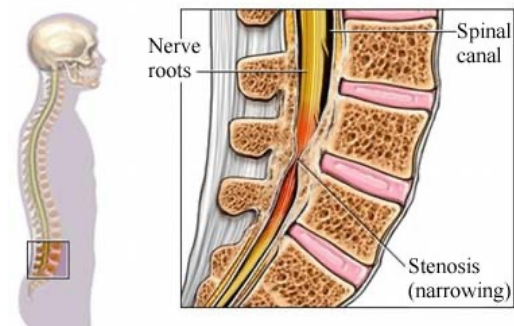
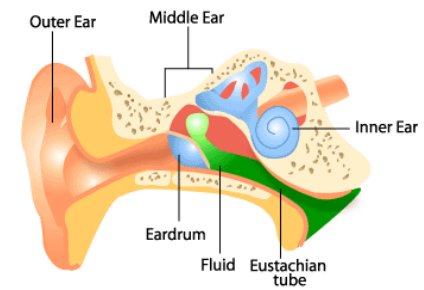
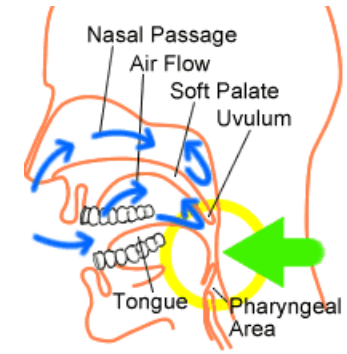
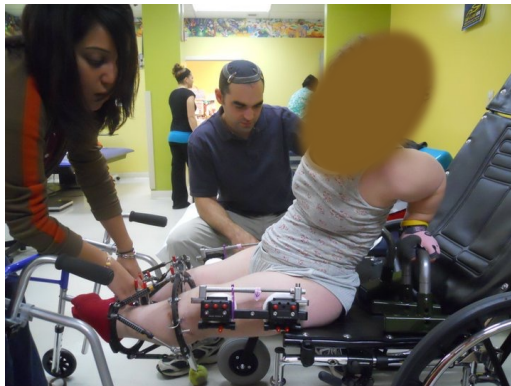
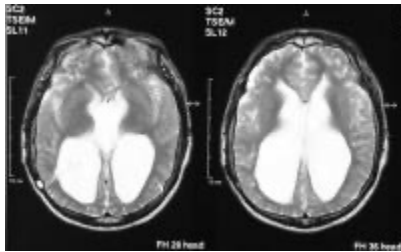


Disclosures

- Receives honoraria from BioMarin, QED, Ascendis, Novo Nordisk, Sanofi



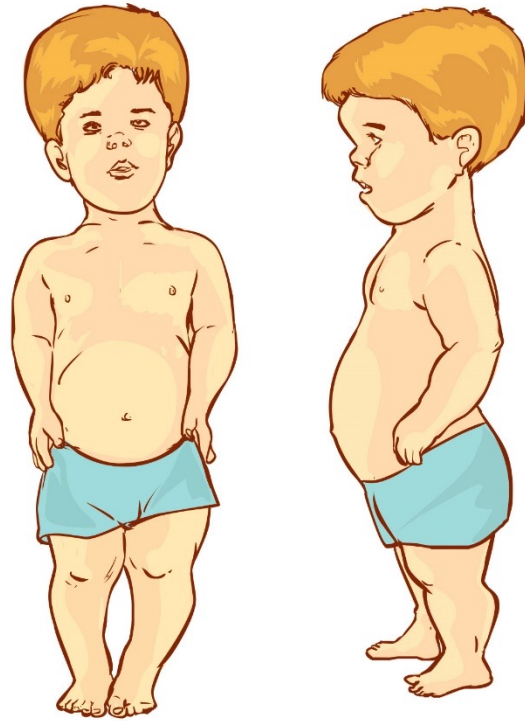
Complications as a consequence of the secondary abnormal bone formation requiring multidisciplinary care



Box 2 Complications of achondroplasia (%) in childhood

- ▶ Neurological
 - ▶ Foramen magnum compression (5–10%)
 - ▶ Craniocervical instability (very rare)
 - ▶ Symptomatic hydrocephalus (6%)
- ▶ Orthopaedic
 - ▶ Progressive, unresolving thoracolumbar kyphosis
 - ▶ Decreased range of movement, elbows and hips
 - ▶ Tibial bowing (10%)
 - ▶ Symptomatic lumbar spinal stenosis (20%)
- ▶ ENT
 - ▶ Recurrent otitis media (89%)
 - ▶ Adenotonsillar hypertrophy (25%)
- ▶ Dental
 - ▶ Dental overcrowding (>50%)
- ▶ Respiratory
 - ▶ Sleep apnoea (75%)
- ▶ Growth
 - ▶ Short stature
 - ▶ Increased body mass index
- ▶ Development
 - ▶ Comparative motor delay
 - ▶ Speech delay (25%)
 - ▶ Conductive hearing loss (40%)
- ▶ Activities of daily living
 - ▶ Restricted through short stature, rhizomelic shortening of upper limbs
- ▶ Psychosocial impact for child and family

Medical and surgical burden of Ach: natural history studies



PROPEL Study - QED

Results

- A total of 86 children with ACH enrolled as of January 2022 at 19 sites in Europe, Australia and North America have been included.
- Of the 86 subjects enrolled, 73 (84.9%) had molecular confirmation of their diagnosis.
- Overall, 79.1% of cases (n=68) were sporadic, whereas 11.6% (n=10) had another family member with diagnosis of ACH. Baseline characteristics are summarized in Table 2.
- The most common conditions reported in the medical histories of subjects are summarized in Table 3.

Table 2. Baseline patient characteristics

| Characteristic | Total (n=86) |
|---------------------------|----------------|
| Age, years | |
| Mean (SD) | 6.1 (2.5) |
| Median (range) | 6.2 (2.5–10.8) |
| Age group, n (%) | |
| <3 years | 12 (14.0) |
| 3 to <5 years | 22 (25.6) |
| 5 to <8 years | 26 (30.2) |
| ≥8 years | 26 (30.2) |
| Sex, n (%) | |
| Male | 34 (39.5) |
| Female | 52 (60.5) |
| Race, n (%) | |
| White | 54 (62.8) |
| Asian | 8 (9.3) |
| Black or African American | 4 (4.7) |
| Other | 7 (8.1) |
| Not reported | 13 (15.1) |

| Characteristic | Number of subjects (%) |
|--|------------------------|
| Surgical and medical procedures | 58 (67.4) |
| Infections and infestations | 46 (53.5) |
| Respiratory, thoracic, and mediastinal disorders | 40 (46.5) |
| Musculoskeletal and connective tissue disorders | 33 (38.4) |
| Congenital, familial, and genetic disorders | 31 (36.0) |
| Nervous system disorders | 16 (18.6) |
| Ear and labyrinth disorder | 15 (17.4) |

Table 4. Surgical and medical procedures occurring in ≥ 1 subject

| Characteristic | Number of subjects (%)* |
|---|-------------------------|
| Adenoidectomy/adenotonsillectomy/tonsillectomy | 34 (39.5) |
| Spinal and cranial surgeries | 21 (24.4) |
| Decompressive craniectomy | 14 (16.3) |
| Spinal decompression | 5 (5.8) |
| Spinal laminectomy | 3 (3.5) |
| Foraminotomy | 1 (1.2) |
| Spinal fusion surgery | 1 (1.2) |
| Spinal operation | 1 (1.2) |
| Ear procedures and operations | 32 (37.2) |
| Ear tube insertion | 32 (37.2) |
| Myringotomy | 3 (3.5) |
| Middle ear operation | 1 (1.2) |
| Ear tube removal | 1 (1.2) |
| Orthopedic procedures | 6 (7.0) |
| Device therapy | 3 (3.5) |
| Meniscus operation | 1 (1.2) |
| Orthopedic procedure | 1 (1.2) |
| Osteotomy | 1 (1.2) |
| Rhizolysis | 1 (1.2) |
| Ventriculo-peritoneal shunt | 2 (2.3) |
| Mechanical ventilation | 2 (2.3) |
| Palatal implant | 2 (2.3) |
| Turbinectomy | 2 (2.3) |

*Subjects could be counted more than once if they underwent ≥ 1 procedure

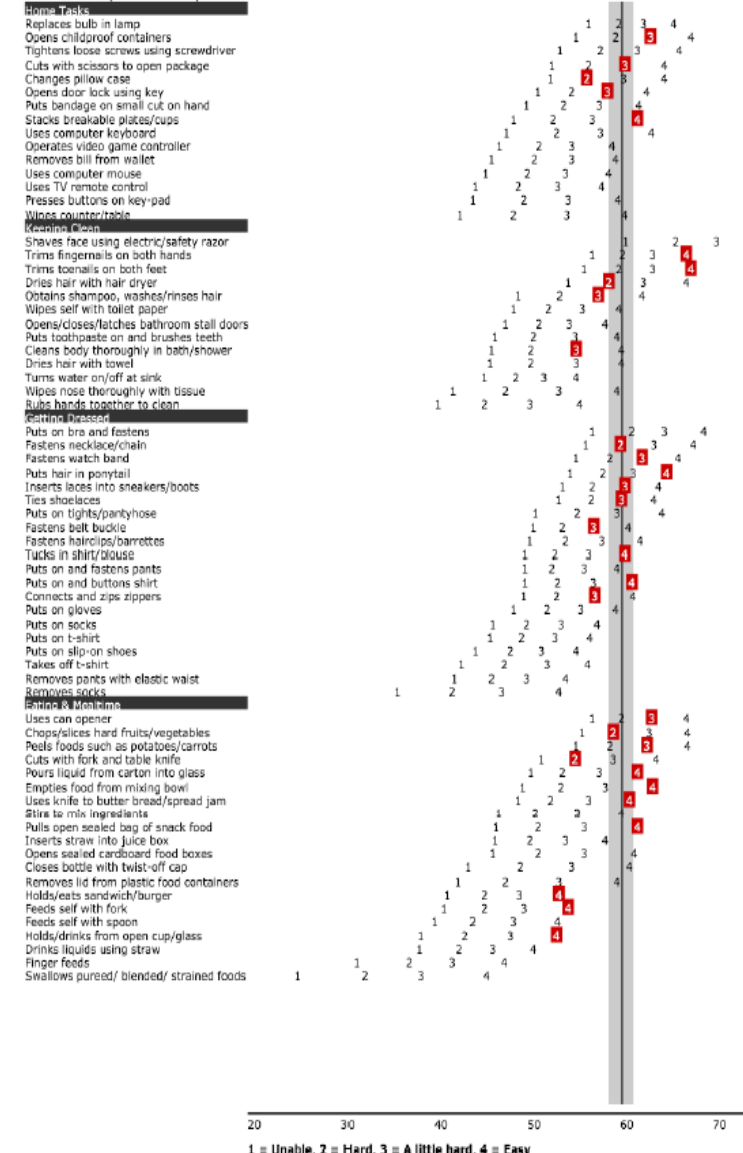
Functionality, independence skills, day-to-day living and health-related quality of life:



Assessment of daily functionality: PEDICAT (n=29, 3-17yo)

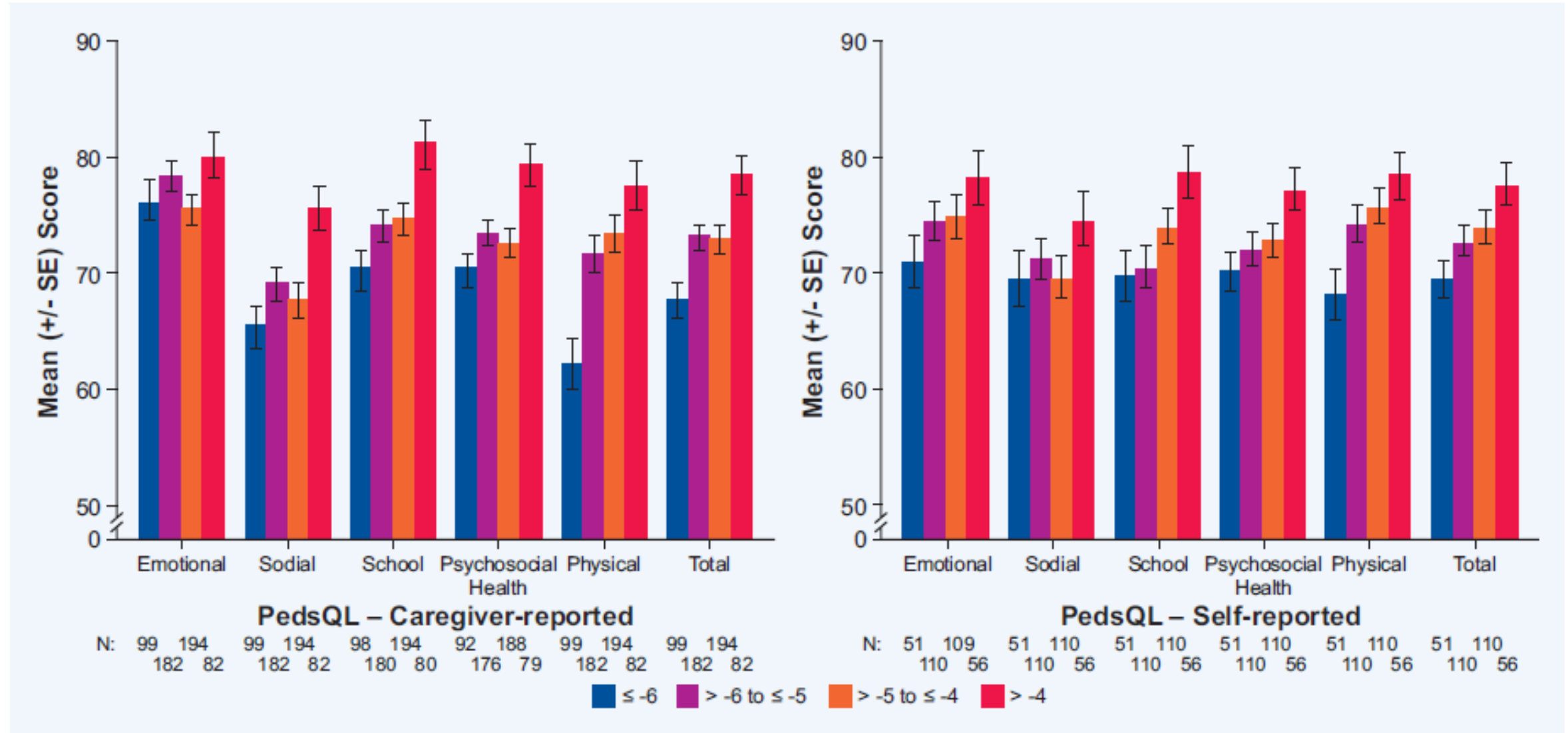
| DOMAIN | <5 th % | 5-25 th % | 25-50 th % | 50-75 th % | 75-95 th % | N= |
|------------------|--------------------|----------------------|-----------------------|-----------------------|-----------------------|----|
| Daily activities | 9 | 12 | 4 | 4 | 1 | 30 |
| Mobility | 21 | 6 | 2 | 0 | 0 | 29 |
| Social-cognitive | 6 | 10 | 5 | 6 | 0 | 27 |
| Responsibility | 4 | 3 | 4 | 3 | 1 | 15 |

MG23122013 for Identification Number Daily Activities Item Map
Score = 60, SE = 0.68, Fit = -1.44

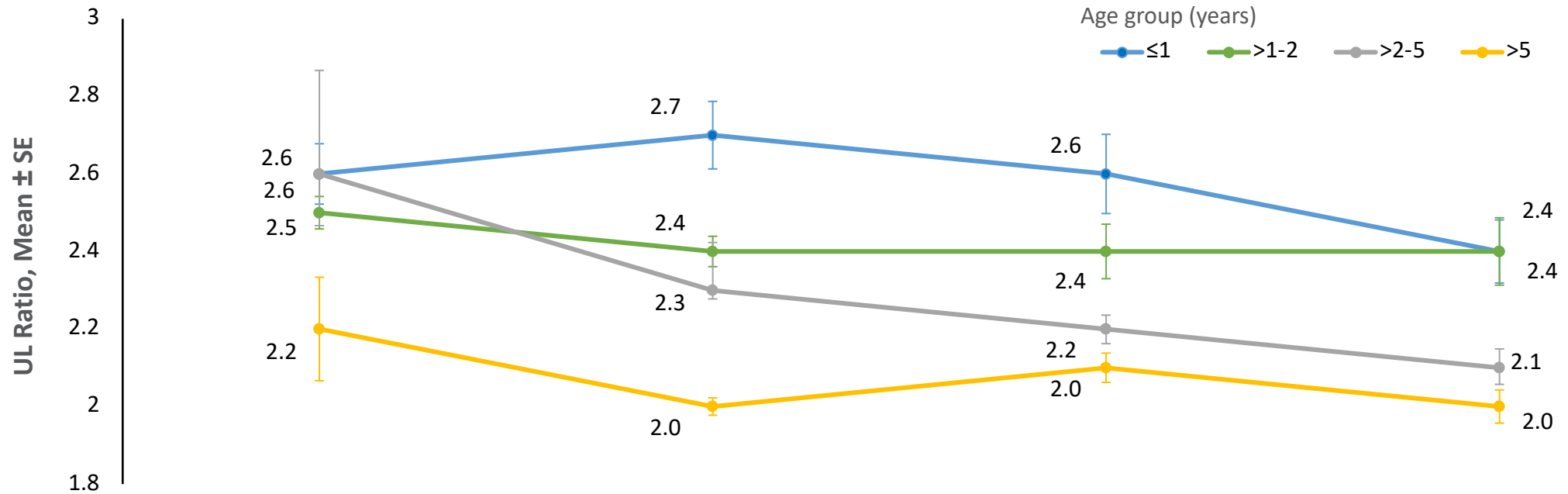


HRQOL tools and height Z-score

PedsQL and height Z-score



UL Ratios by Age Subgroups Over Time

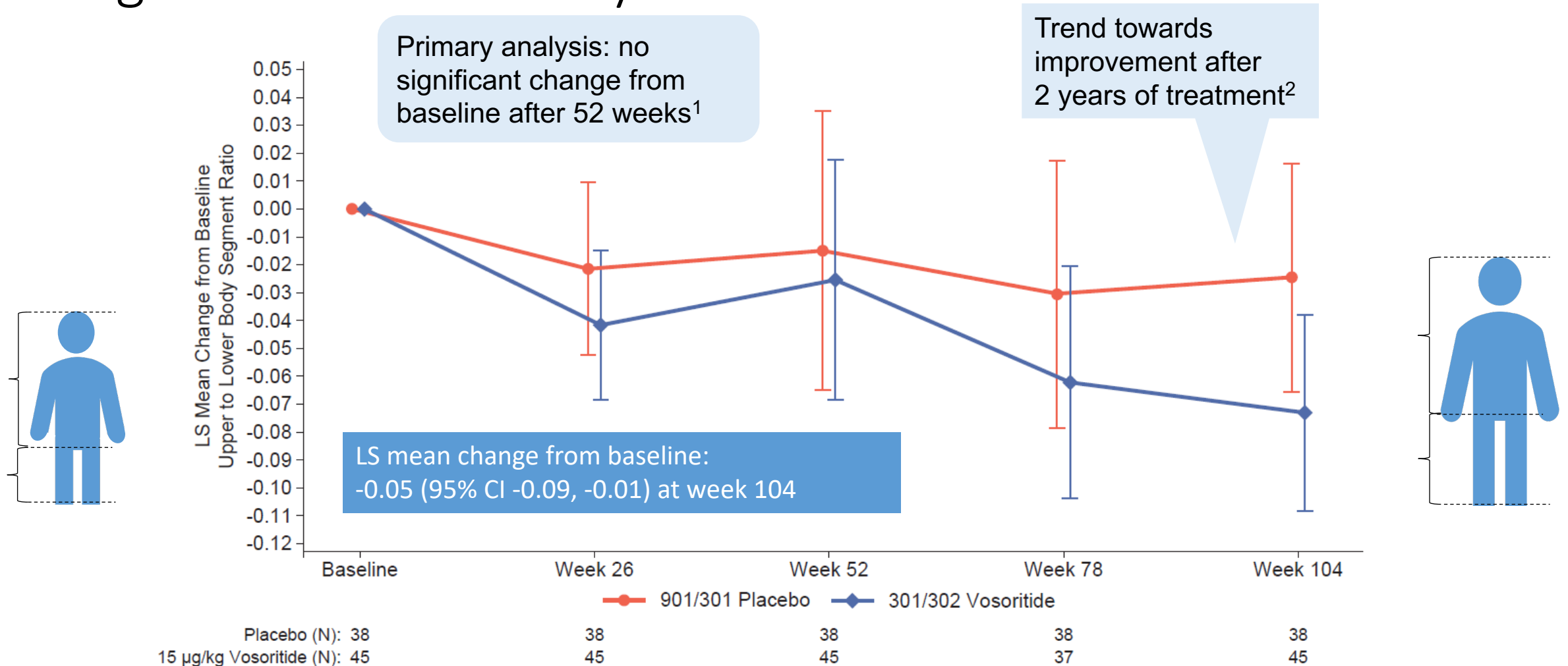


| Age Group, n | Baseline | 6 Months | 12 Months | 18 Months |
|--------------|----------|----------|-----------|-----------|
| ≤1 | 15 | 13 | 9 | 6 |
| >1-2 | 23 | 18 | 11 | 6 |
| >2-5 | 61 | 47 | 21 | 8 |
| >5 | 52 | 36 | 20 | 9 |

Participants are arranged in sub-groups by age at enrollment into the ACHieve study.
UL ratio, upper to lower body proportion ratio.

All product candidates are investigational. Intended for education and scientific exchange only. Not for use in promotion or product commercialization

Trend towards improvement in upper to lower body segment ratio after 2 years

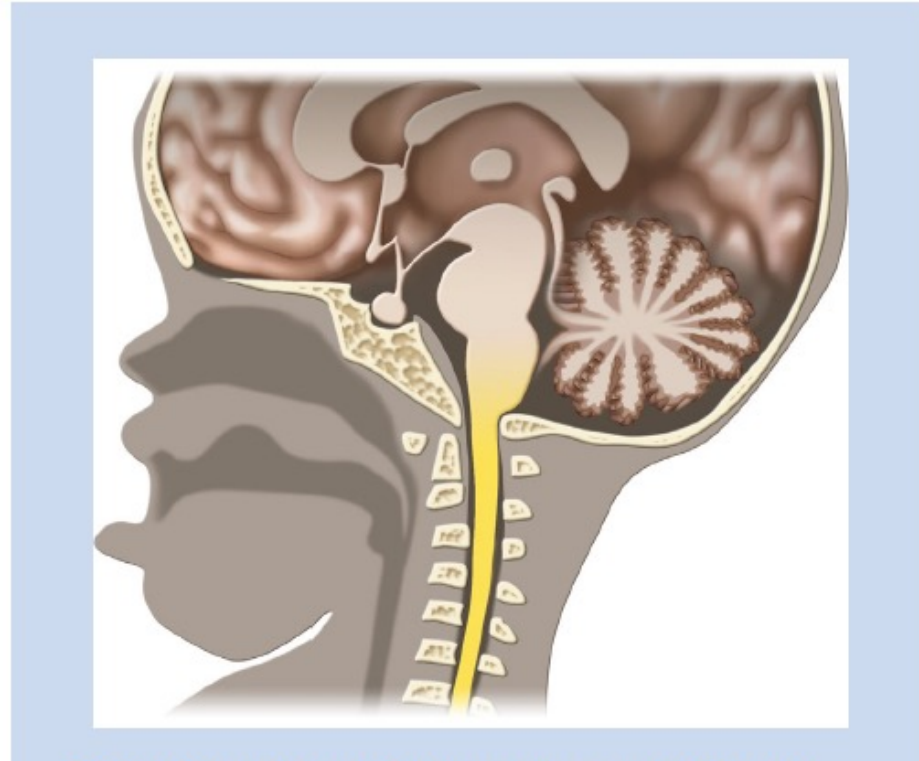


1. Savarirayan R et al. Lancet 2020;396:684-92;



2. Savarirayan R et al. Genet Med 2021;doi:10.1038/s41436-021-01287-7

Baseline defined as time of initiation of vosoritide treatment

Foramen magnum stenosis



Achondroplasia Foramen Magnum Score: screening infants for stenosis

Moira S Cheung ¹, Melita Irving,² Alessandra Cocca ¹, Rui Santos,³
Meera Shaunak,¹ Harry Dougherty,¹ Ata Siddiqui,⁴ Paul Gringras,⁵ Dominic Thompson⁶

Cheung MS, et al. *Arch Dis Child* 2021;**106**:180–184.

Ach foramen magnum stenosis score (AFMSS)

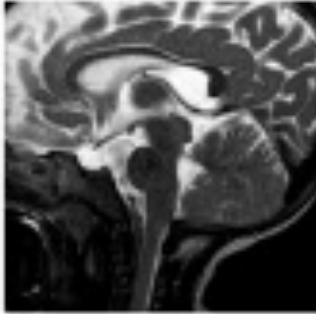




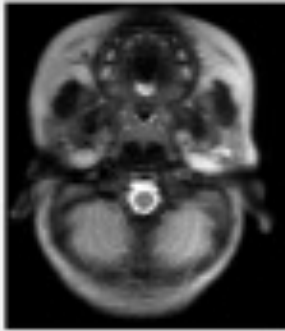
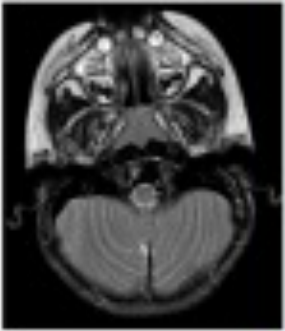
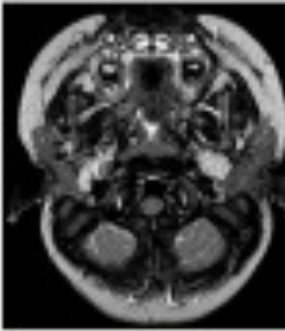

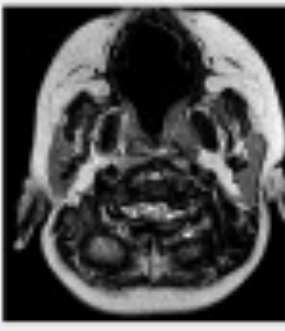
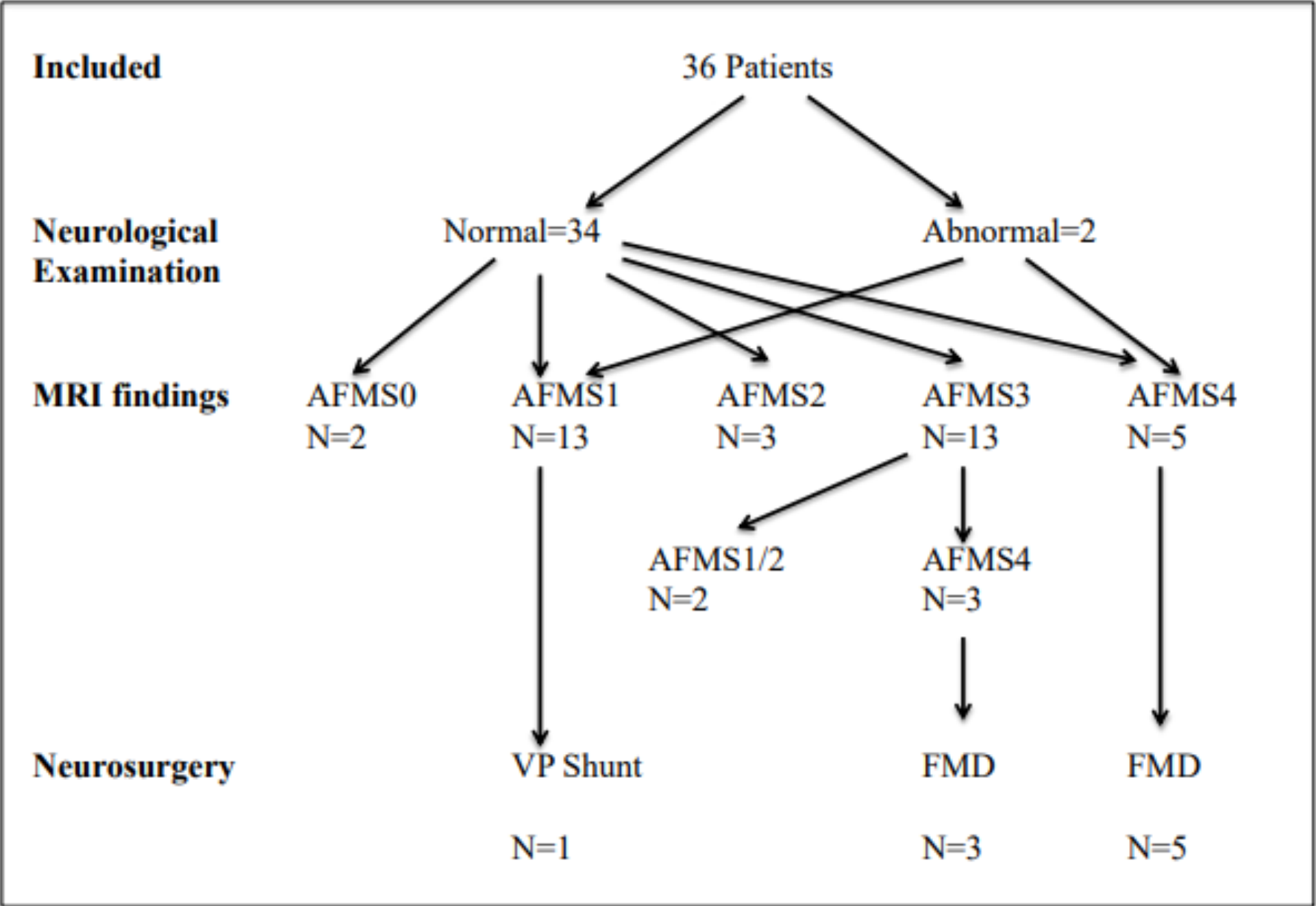
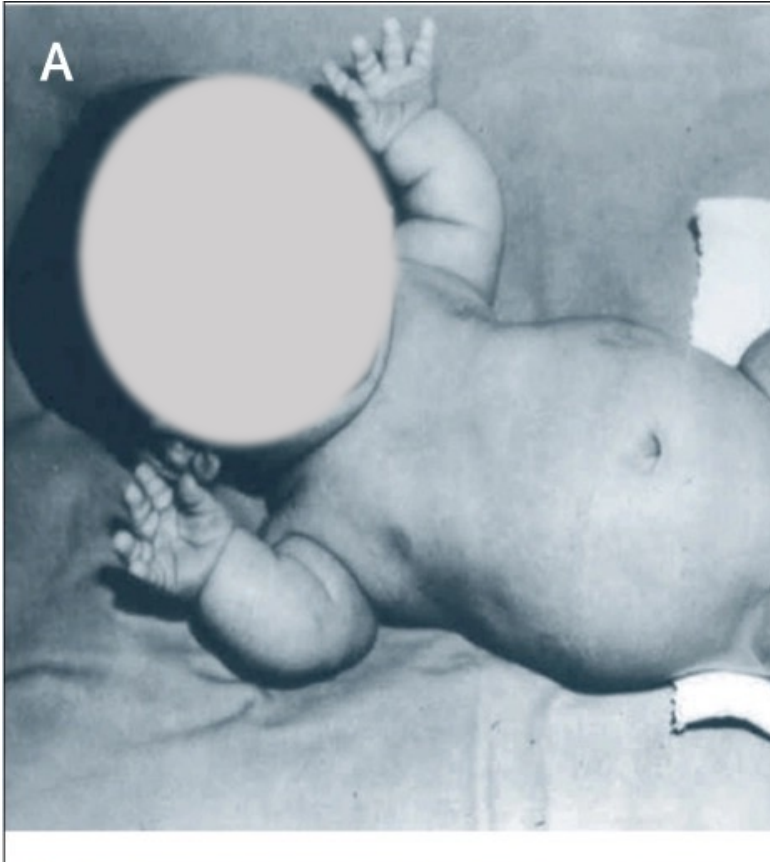
| AFMS0 | AFMS1 | AFMS2 | AFMS3 | AFMS4 |
|--|--|--|--|--|
| Normal foramen magnum | Constitutional narrowing of the foramen magnum with preserved CSF (no cord distortion) | Narrowing of the foramen magnum with loss of CSF space surrounding the cord | Loss of the CSF space with cord compression | Cord compression and signal changes (Myelomalacia) |
|  |  |  |  |  |
|  |  |  |  |  |

Table 1 Baseline characteristics of patients

| Characteristic | Number of infants (n=36) |
|----------------------------------|--------------------------|
| Gender | |
| Male | 18 (50%) |
| Female | 18 (50%) |
| Timing of diagnosis | |
| Antenatal period | 23 (64%) |
| Postnatal period | 12 (33%) |
| Unknown | 1 (3%) |
| Diagnostic investigations | |
| Genetic testing (<i>FGFR3</i>) | 33 (92%) |
| Skeletal survey only | 3 (8%) |



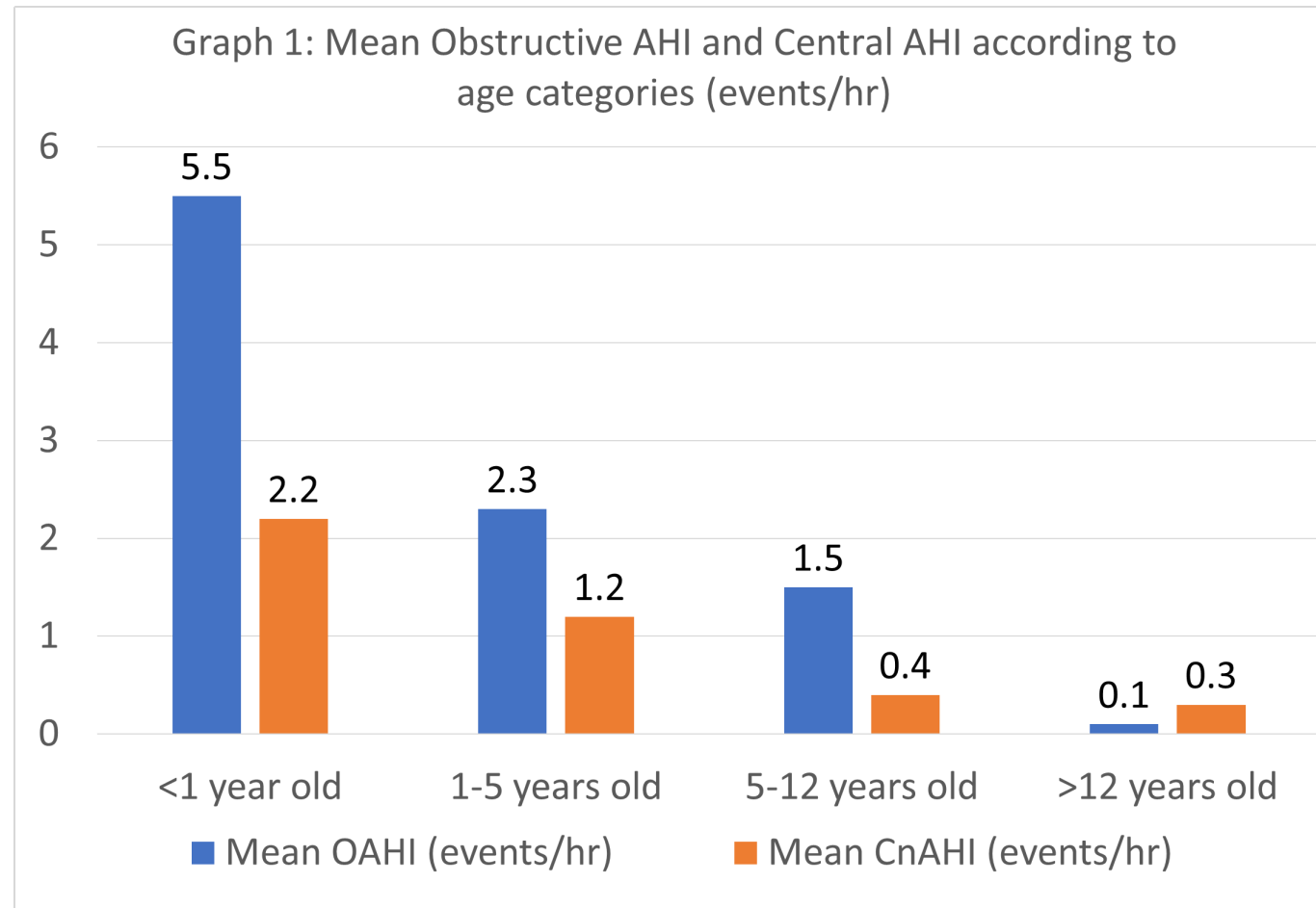
Sleep-disordered breathing



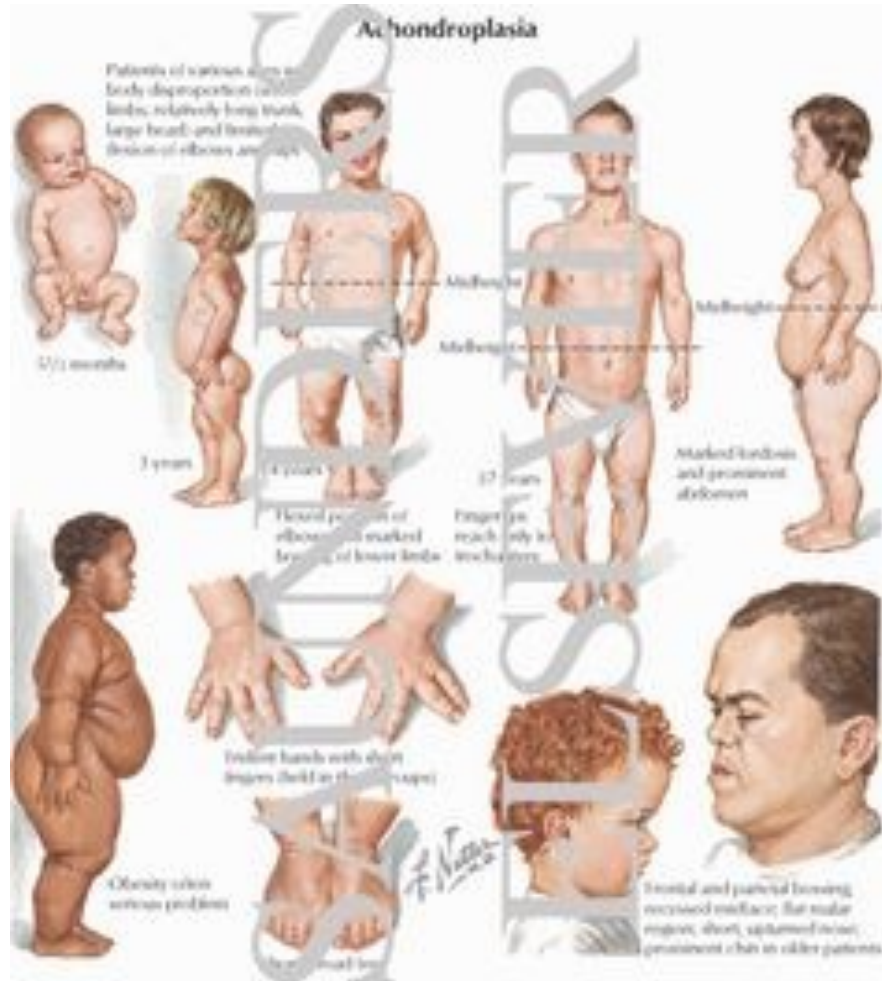
Incidence of sleep disordered breathing

- 61.1% (22) reported snoring and/or sleep apnoea
- Cardiorespiratory sleep studies performed on 35 infants
- Sleep disordered breathing detected in 88.5% (31/35)
 - Mild obstructive sleep apnoea (OSA) in 11.4% (4)
 - Mod OSA in 11.4% (4)
 - Severe OSA in 43.8% (12)

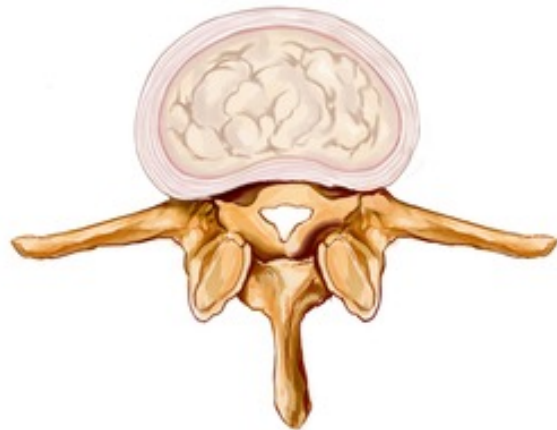
Sleep disordered breathing n=81 Achondroplasia



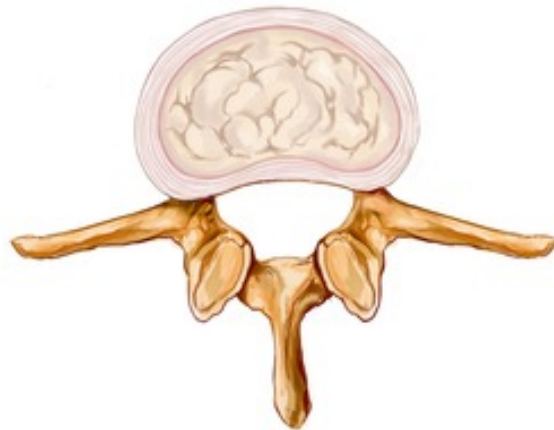
Across the life course:



Pain in Ach



Stenosis



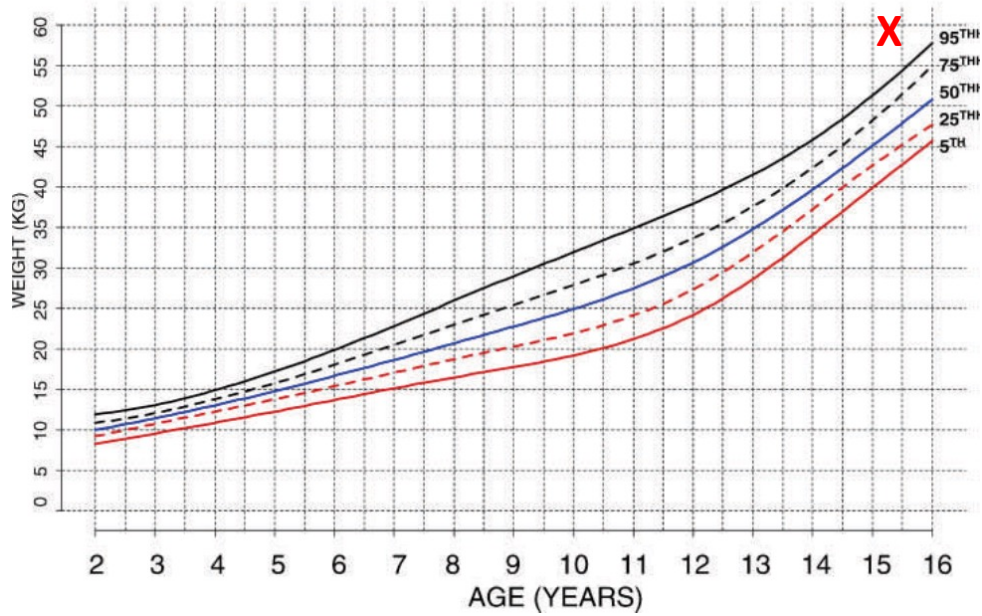
Normal



Pain

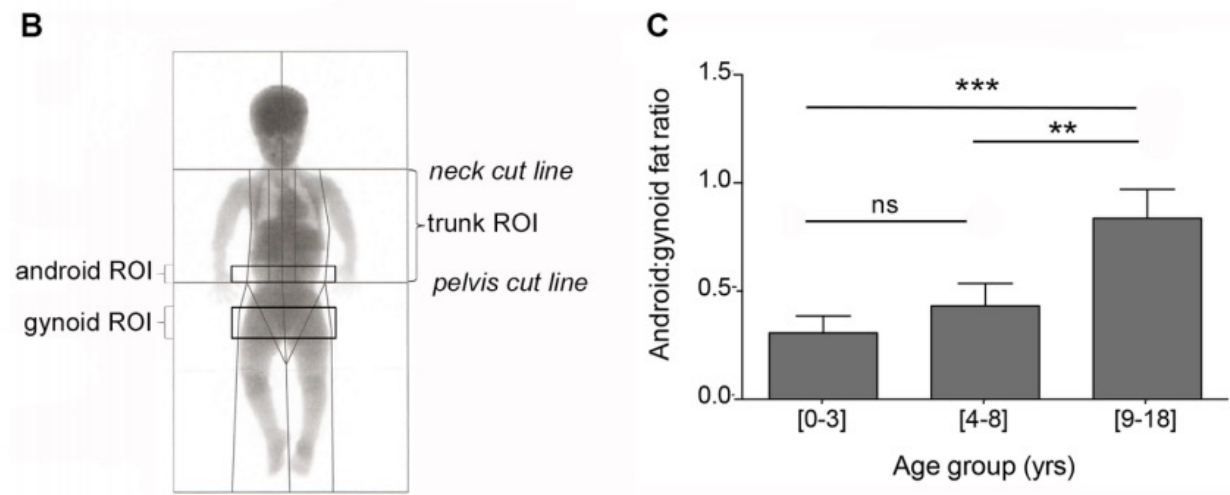
- Alade *et al.* 2013:
 - 316 with short stature skeletal dysplasia
 - 153 with Ach
 - Chronic pain prevalence (brief pain inventory): 70.3%
 - 63.1% in Ach group

Weight management in Ach

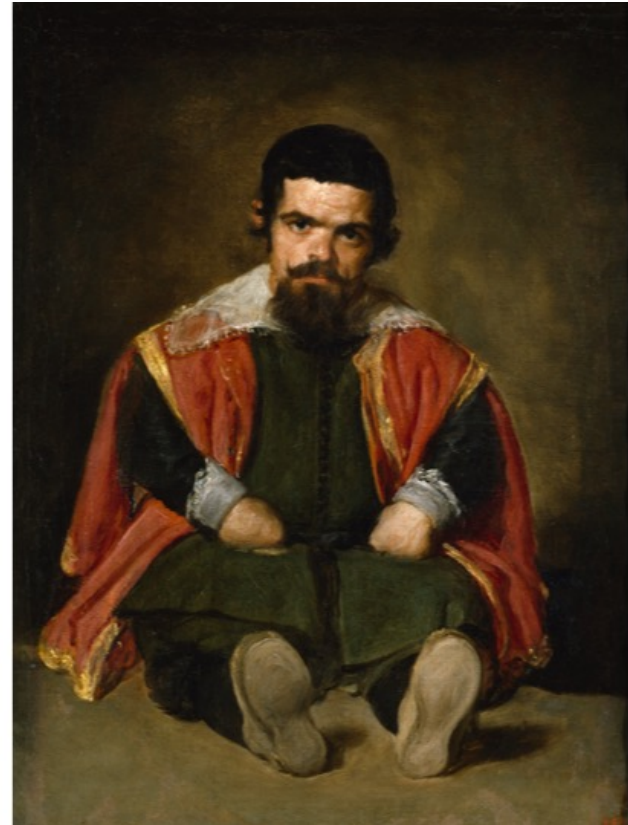


Obesity

- 50% in Ach - abdominal
- Without typical secondary complications (normoglycaemia)
- Worsens overall clinical status



Mental Health



Higher rates of non-skeletal complications in achondroplasia compared to the general population: A UK matched cohort study using the CPRD-GOLD database

Melita Irving, Jeanne M. Pimenta, Moira Cheung, Louise Mazzeo, Sarah Landis, Swati Mukherjee

Matched retrospective cohort study using UK Clinical Practice Research Datalink (CPRD-GOLD)

- Study index date was first ACH record within study period of 01/01/1987–31/12/2018
- Control patients defined as those without evidence of skeletal/growth disorders

We identified 541 cases and 2,052 matched controls

| Body system | Rate Ratio, RR (95% CIs) | Specific complications | | | |
|------------------|--------------------------|---|--|--|--|
| | | Statistically significantly higher RR in ACH compared to controls | No difference in RR between ACH cases and controls | Condition included in body system but <5 events ¹ | |
| Any Non-skeletal | 1.76 (1.56–1.98) | | | | |
| Developmental | 8.84 (4.18–18.72) | Developmental delay Speech delay | 8.80 (3.02–25.68) 7.61 (3.03–19.13) | – | Motor delay |
| Neurological | 7.56 (4.24–13.50) | Seizures Hydrocephalus/ ventriculomegaly | 4.01 (1.52–10.58) Cases only | Dementia | Craniocervical stenosis Failure to thrive Subdural haematoma |
| Respiratory | 4.15 (2.51–6.88) | Apnoea/sleep disordered breathing | 25.81 (10.0–66.60) | Sleep disorder | – |
| ENT | 2.98 (2.43–3.65) | Enlarged tonsils Hearing loss/ deafness Otitis media | 3.34 (1.26–8.86) 3.50 (2.50–4.89) 3.11 (2.45–3.94) | Sinusitis Voice abnormality | Middle ear dysfunction Tracheomalacia Bronchomalacia |
| Metabolic | 1.65 (1.24–2.18) | Obesity | 2.59 (2.26–2.97) | Diabetes Hyperlipidaemia | – |
| Mental Health | 1.62 (1.21–2.17) | ADD/ADHD/ adjustment disorder Depression/anxiety Self-harm/suicidal ideation | 3.44 (1.13–10.51) 1.51 (1.09–2.08) 3.71 (1.17–11.77) | Substance abuse | 'Other' mental health |
| Cardiovascular | 1.17 (0.92–1.49) | – | – | Chest pain/angina Coronary disease Hypertension Myocardial infarction Stroke | – |
| Other | 1.76 (1.52–2.03) | Gastrointestinal issues Pain-musculoskeletal | 1.66 (1.31–2.09) 1.84 (1.58–2.15) | Headache Sexual health/ gynaecological issues | – |

¹Due to database requirements, data for cases or controls which have less than 5 events are not permitted to be reported.

Summary – benefits beyond height wish-list:

- Reduced medical and surgical burden
- Improved functionality and independence skills
- No sleep disordered breathing or foramen magnum stenosis.....
- Benefits lasting into adulthood:
 - Pain
 - Obesity
 - Spinal stenosis
 - Mental health

Thanks for listening



EAAF

European Achondroplasia Forum

