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Growth in achondroplasia, from birth to adulthood, analysed by the JPA-2 model

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Abstract

Objectives: In general population, there are three phases in the human growth curve: infancy, childhood and puberty, with different main factors involved in their regulation and mathematical models to fit them. Achondroplasia children experience a fast decreasing growth during infancy and an “adolescent growth spurt”; however, there are no longitudinal studies that cover the analysis of the whole post-natal growth. Here we analyse the whole growth curve from infancy to adulthood applying the JPA-2 mathematical model.

Methods: Twenty-seven patients, 17 girls and 10 boys with achondroplasia, who reached adult size, were included. Height growth data was collected from birth until adulthood. Individual growth curves were estimated by fitting the JPA-2 model to each individual’s height for age data.

Results: Height growth velocity curves show that after a period of fast decreasing growth velocity since birth, with a mean of 9.7 cm/year at 1 year old, the growth velocity is stable in late preschool years, with a mean of 4.2 cm/year. In boys, age and peak height velocity in puberty were 13.75 years and 5.08 cm/year and reach a mean adult height of 130.52 cm. In girls, the age and peak height velocity in puberty were 11.1 years and 4.32 cm/year and reach a mean adult height of 119.2 cm.

Conclusions: The study of individual growth curves in achondroplasia children by the JPA-2 model shows the three periods, infancy, childhood and puberty, with a similar shape but lesser in magnitude than general population.

Keywords: achondroplasia; FGFR3; growth curves; growth velocity; height; puberty.

Introduction

Achondroplasia (ACH), an autosomal-dominant disorder, is the most common form of inherited severe and disproportionate short stature, occurring with birth prevalence between 1 in 10,000 and 1 in 30,000 live births [1]. It is caused by a gain of function mutation in the type 3 fibroblast growth factor receptor gene (*FGFR3*), located on chromosome 4p16.3 that leads to abnormal endochondral ossification [2, 3].

In the general population, the pattern of human linear growth is very well documented [4, 5]. There are three phases in the growth curve: infancy, childhood and puberty. These periods are the additive effect of various biological processes with different main factors involved in their regulation, as well as different mathematical models to fit them [4, 5]. From birth, the rapidly decelerating growth in the first 2 years of life is a prolongation of foetal growth. This is the infancy component, which appears to be mainly nutritionally determined and guided by thyroid hormones. Until the age of 3 years, growth is an additive combination of the infancy and childhood components. The childhood component is a period with a lower and slowly decreasing velocity, which lasts up to puberty and is under the additional strong influence of growth hormones. The final component of the human growth curve is puberty, in which sexual hormones initiate the pubertal spurt and subsequently lead to the end of growth, through the closure of the epiphysis [4, 5].

In the ACH population, Horton et al. published the first growth charts from birth until adulthood, in 1978 [6]. They observed a period of fast decreasing growth, experienced during infancy and childhood, which was also later described by other authors [6–10]. Unfortunately, beyond 10 years of age, there were limited measurements, and Horton [1978] could not be certain if there was a pubertal growth spurt [6]. Hoover Fong [2017] and Merker [2018] did not see a pubertal growth spurt when they analysed the average curves in cross-sectional design studies [9, 11]. Nevertheless, the inspection of some individual growth patterns by Merker showed a clear acceleration in growth velocity during early pubertal ages [9]. However, as a result of longitudinal design studies, del Pino et al. [2018] showed that ACH adolescents experience a period of rapid increase

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of height growth velocity with a later slowdown, the “adolescent growth spurt” [12]. In all periods, the ACH growth curve was similar in shape but lesser in magnitude in comparison to the general population [4, 5, 10, 12]. Nevertheless, none of these studies included a longitudinal analysis of the whole post-natal growth curve from birth until adulthood.

Analysis of the whole post-natal growth curve would help us to understand the growth dynamics in a condition with severe and disproportionate short stature and to analyse the effect of emerging potential therapeutic strategies on the different phases of growth [13]. Some of the potential treatments are aimed at reducing the excessive activation of FGFR3, which has a negative influence on the epiphyseal growth plates of the limbs, inhibiting endochondral ossification and disturbing their growth [14].

This investigation is an observational, descriptive, cohort study. In this study, the longitudinal growth in ACH children is described, applying a mathematical model to include the whole post-natal growth.

Patients and methods

Sample

Growth was analysed in children with a confirmed diagnosis of ACH, attending our growth clinic at Garrahan Hospital, with measurements of height from birth until adulthood. A total of 27 out of 385 children, 17 girls and 10 boys, provided sufficient data to analyse growth. Some anthropometric data of these patients were published previously [10, 12].

Inclusion criteria were children who had a birth length record, a first length measurement in our growth clinic between 0.42 and 0.59 years old, and at least one measurement annually until adulthood. The median (interquartile range) number of measurements per child was 22.5 (18.75, 24).

Exclusions criteria were pre-term children (born before 37 weeks of gestational age); a presence of any other chronic disease or comorbidities that could affect growth; and patients who underwent surgical leg lengthening or spinal arthrodesis. In this way, eight children were excluded because they underwent surgical leg lengthening and four because of spinal arthrodesis.

Diagnosis of the disease was made based on clinical examination and X-ray specific signs, according to Spranger [15]. Molecular testing was carried out in 22 out of 27 children, and all were heterozygous.

The following information was collected: date of birth, gestational age, length and weight at birth, age, sex, height and information about any other disease which may affect growth. Anthropometric data at birth were obtained from perinatal records provided by parents.

Methods

All children's measurements were initially taken and followed up by the same trained observer (AP) during routine visits, with

standardized techniques [16]. The supine length was measured until 4 years of age and, from then onwards, the standing height was measured with Harpenden instruments.

The individual's growth records were plotted. At the time of the last measurement, all patients had reached their adult height with the apparent indication of an upper plateau. To obtain comparable data, individual growth curves were estimated by fitting the JPA-2 model to each individual's height for age data [17].

JPA-2 model

The JPA-2 model [17] was designed to fit post-natal growth and includes three components that match with natural periods of human growth – infancy, childhood and puberty – utilizing post-natal age because this model has been proven to fit post-natal data very well from birth [17, 18]. It includes eight parameters and has the following mathematical expression:

$$y = a \left\{ 1 - \frac{1}{1 + [(t + e)/b_1]^{c_1} + [(t + e)/b_2]^{c_2} + [(t + e)/b_3]^{c_3}} \right\}$$

In this function, y = height reached at age t ; t = post-natal age; a = adult height, b_1 , b_2 , and b_3 = time-scale factors; c_1 , c_2 and c_3 = dimensionless exponents; and e = estimated pre-natal duration of growth [17].

The following biological parameters were obtained from JPA-2 fits on each individual's serial growth data: age, size (height) and velocity at 1 and 5 years of age, at take-off (the point of minimal pre-pubertal growth velocity), at peak velocity in puberty and at adulthood.

The goodness of fit was assessed by the residual standard deviation (RSD). In this study, we considered a fit to be acceptable if the RSD was no higher than 0.5 cm. The pooled RSD in the sample was 0.31 cm, with a range of 0.24–0.49 cm.

The mean-constant curve was obtained by feeding the mean values of the function parameters into the model [18].

The software used was KaleidaGraph 4.5.3.

The project was approved by the research review committee and the ethics review committee from Garrahan Paediatric Hospital.

Results

Twenty-seven children, 17 girls and 10 boys, provided sufficient data to analyse growth from birth until adulthood.

Figures 1 and 2 show the distance and velocity mean-constant curves for height for girls and boys, respectively. The shapes of the growth curves are similar and have the three periods described in children from the general population [4, 5]: infancy, childhood and puberty. The velocity curves show that, after a period of fast decreasing growth velocity from birth, with a mean growth velocity of approximately 9.7 cm/year at 1 year of age, the mean growth velocity is 4.2 cm/year in the late preschool years, in both sexes. After a period of slightly decreasing growth velocity, the pubertal spurt is initiated and growth velocity increases, achieving its maximum at age of peak height

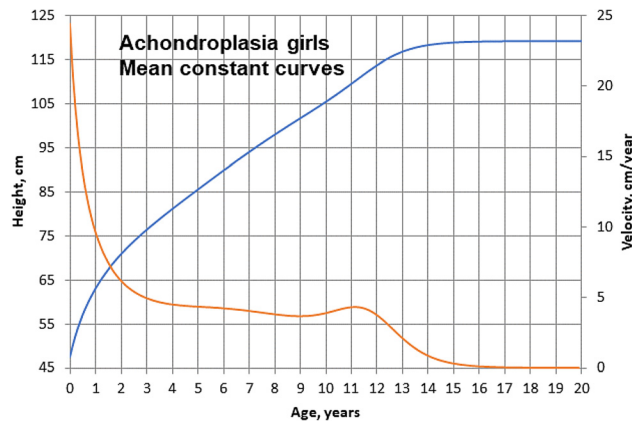


Figure 1: Distance and velocity mean-constant growth curves for height of JPA-2 model fitted to 17 girls. The growth curve shows the three periods of the human growth curve: infancy, childhood and puberty [4, 5].

velocity. In girls, the age and the peak velocity in puberty are 11.1 years and 4.32 cm/year, and they reach a mean adult height of 119.2 cm. In boys, the age and the peak velocity in puberty are 13.75 years and 5.08 cm/year, and they reach a mean adult height of 130.52 cm. After the age of peak height velocity, growth velocity decreases until they stop growing.

Table 1 shows the mean and standard deviations of the derived biological variables, obtained by fitting JPA-2 to the growth, in height. Growth velocity during infancy and childhood are similar in both sexes. During adolescence, ACH boys entered puberty 2 years later than girls, and the peak height velocity is slightly higher in boys. The difference in adult height between boys and girls (11.3 cm) comes from the later onset of the pubertal growth spurt (or longer childhood growth) in boys.

The curves of Figures 3, 4, and 5 represent the JPA-2 model fitted to the longitudinal data of three children, including all measurements since birth. A girl with puberty close to the mean (Figure 1), a boy with early puberty (Figure 2) and a boy with late puberty (Figure 3).

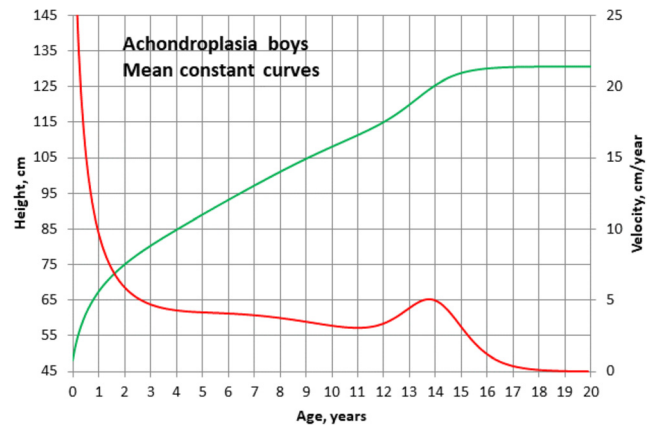


Figure 2: Distance and velocity mean-constant growth curves for height of JPA-2 model fitted to 10 boys. The growth curve shows the three periods of the human growth curve: infancy, childhood and puberty [4, 5].

Discussion

This is the first study on growth in the ACH population, from birth to adulthood, applying a parametric model, the JPA-2, to analyse growth longitudinally [17]. This analysis helps us to understand the growth process in ACH children.

In the general population, the growth pattern in height, which is constituted by the growth as a total of the legs and trunk length, is characterized by a gradually decreasing velocity during infancy and childhood, followed by a substantial acceleration that marks the beginning of the pubertal growth spurt in the early teens. This growth velocity increases and achieves its maximum at the age of peak height velocity [5]. The pubertal growth spurt is a persistent feature of the normal growth curve; however, sometimes differences in tempo among adolescents are very pronounced. The range of the peak height velocity is about 3 years for boys and girls. In early adolescence, some children grow at peak height velocity while others still have to start

Table 1: Mean and standard deviations of the JPA-2 model derived biological variables in achondroplasia children.

| | Boys N=10 | | | Girls N=17 | | |
|---------------|---------------------|-----------------|-------------------------------|---------------------|-----------------|-------------------------------|
| | Decimal age (years) | Height (SD), cm | Growth velocity (SD), cm/year | Decimal age (years) | Height (SD), cm | Growth velocity (SD), cm/year |
| | 1 | 67.3 (2.1) | 9.73 (1.08) | 1 | 63.2 (2.5) | 9.62 (1.4) |
| | 5 | 88.9 (3.2) | 4.16 (0.6) | 5 | 85.6 (3.6) | 4.35 (0.6) |
| Take off | 10.90 (1.25) | 110.98 (7.15) | 3.07 (0.57) | 8.90 (1.5) | 101.36 (6.15) | 3.68 (0.4) |
| Peak velocity | 13.75 (1.12) | 123.86 (5.7) | 5.08 (0.49) | 11.1 (0.88) | 110.0 (3.46) | 4.32 (0.7) |
| Adult height | 17.7 | 130.5 (5.0) | 0.01 (0.02) | 16.4 | 119.2 (5.4) | 0.003 (0.02) |

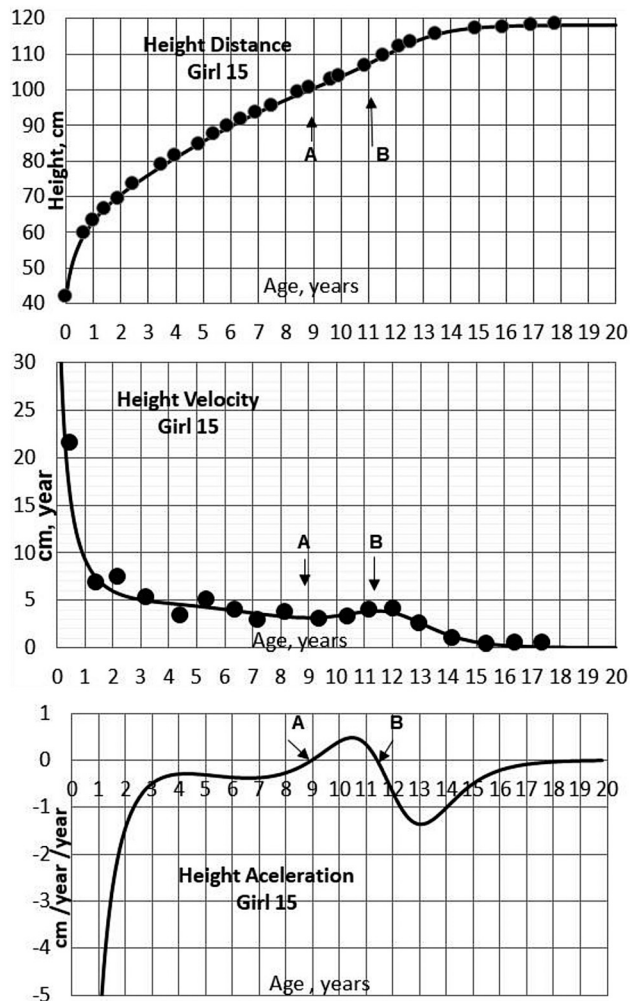


Figure 3: A plot of the JPA 2 model fitted to the longitudinal data of an ACH girl (N° 15) including all measurements since birth. The upper curve represents the distance curve. The middle curve represents the first derivative, depicting the speed of growth in cm/year, while solid dots represent observed speeds in the individual child considered. The lower curve represents the second derivative: the acceleration of the growth in cm/year/year. The arrows A and B indicate the ages at which the acceleration curve vanishes (zero acceleration), that is to say, the age of the onset (take-off) and the peak of the pubertal growth spurt: for this girl at 9.0 (A) and 11.4 years of age (B). This girl had a take-off and peak height velocity close to the mean age and reached an adult height of 118.22 cm. The growth curve shows the three periods of the human growth curve [4, 5]: infancy, childhood and puberty. The curve has a similar shape but lesser magnitude, with a growth velocity of 3.89 cm/year vs. 7.7 cm/year of a girl from the general population [21–23].

their growth spurt. In mid-adolescence, early maturing children will approach their final height while others grow at maximum velocity. As a consequence of these variations in tempo, the pubertal growth spurt can be observed when measurements are taken at reasonable intervals and when

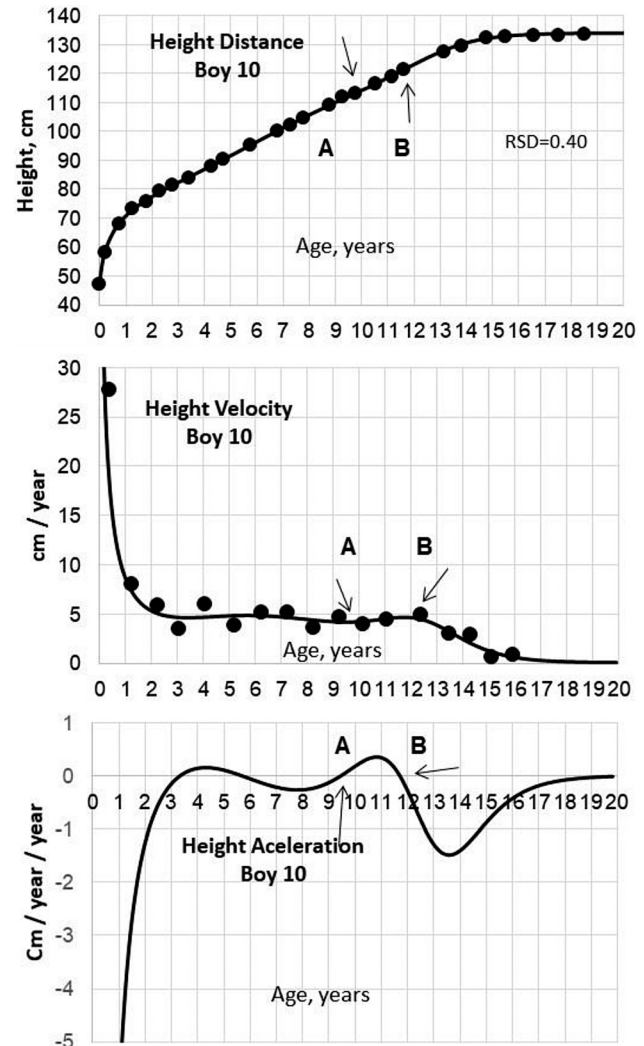


Figure 4: A plot of the JPA 2 model fitted to the longitudinal data of an ACH boy (N° 10) including all measurements since birth. The upper curve represents the distance curve. The middle curve represents the first derivative, depicting the speed of growth in cm/year, while solid dots represent observed speeds in the individual child considered. The lower curve represents the second derivative: the acceleration of the growth in cm/year/year. The arrows A and B indicate the ages at which the acceleration curve vanishes (zero acceleration), that is to say, the age of the onset (take-off) and the peak of the pubertal growth spurt: for this, boy at 9.5 (A) and 11.7 years of age (B). This boy had the take-off and the peak height velocity before mean age, approximately 2 years earlier (early puberty) and reached an adult height of 133.9 cm. The growth curve shows the three periods described by Karlberg [4]: infancy, childhood and puberty. The curve has a similar shape but lesser magnitude with a growth velocity of 5.08 cm/year vs. 9.3 cm/year of a boy from the general population [22, 23].

longitudinal growth data is analysed with appropriate mathematical models [4, 5, 18]

The gain of function of the *FGFR3* mutation plays an important role in pre-natal skeletal development, with a

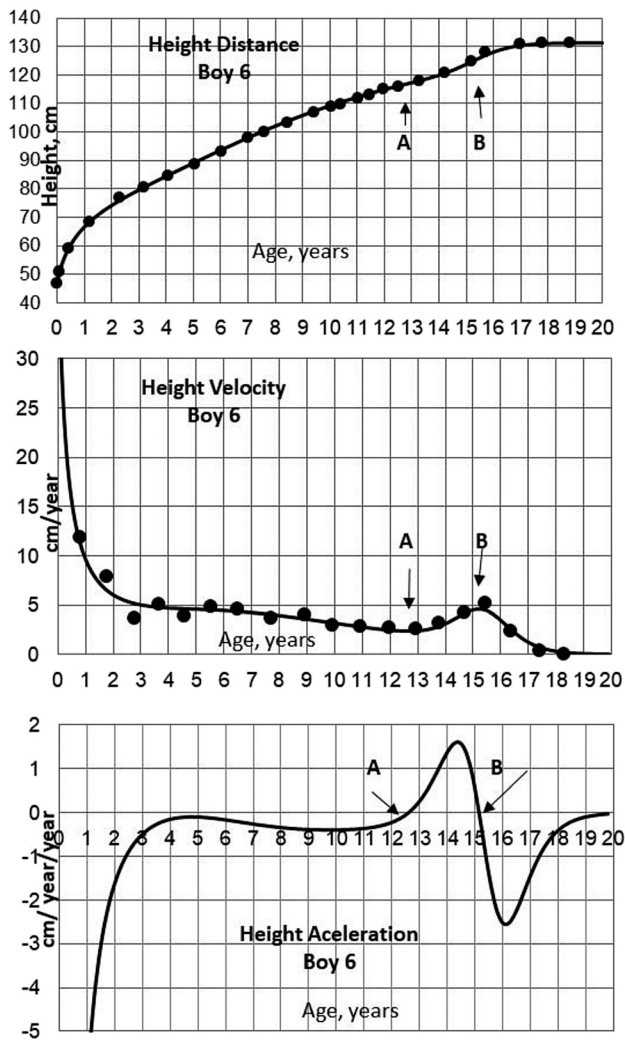


Figure 5: A plot of the JPA 2 model fitted to the longitudinal data of an ACH boy (N° 10) including all measurements since birth. The upper curve represents the distance curve. The middle curve represents the first derivate, depicting the speed of growth in cm/year, while solid dots represent observed speeds in the individual child considered. The lower curve represents the second derivate: the acceleration of the growth in cm/year/year. The arrows A and B indicate the ages at which the acceleration curve vanishes (zero acceleration), that is to say, the age of the onset (take-off) and the peak of the pubertal growth spurt: for this, boy at 12.6 (A) and 15.15 years of age (B). This boy had the take-off and the peak height velocity after the mean age, approximately 1.75 years later (late puberty) and reached an adult height of 131.37 cm. The growth curve shows the three periods of the human growth curve [4, 5]: infancy, childhood and puberty. The curve has a similar shape but lesser magnitude with a growth velocity of 4.60 cm/year vs. 9.3 cm/year of a boy from the general population [22, 23].

greater negative influence in the epiphyseal growth plates of the limbs, inhibiting endochondral ossification and disturbing limb growth more severely than the trunk [14]. Consequently, ACH children have a severe disproportionate

short stature [6, 8, 9, 10, 11, 19, 20], with short legs and arms, and a total growth velocity reduced in comparison to the growth velocity in the general population [4, 5, 10, 12]. Therefore, only a study of growth with a longitudinal design and suitable mathematical models can help us describe the growth patterns and analyse the dynamics of the growth process in ACH.

Applying the JPA-2 model to the growth data, we identified the three phases of growth (infancy, childhood and puberty) with a similar shape but lesser magnitude than the general population [4, 5]. If we compare our results with general population growth data, analysed with JPA-2, the growth velocity of ACH children is lesser in magnitude. The mean growth velocities are 6.2 and 4.2 cm/year vs. 10 and 7 cm/year at 2 and 5 years old, respectively [21]. During puberty, the age at take-off is similar in comparison to Polish girls and Finn children [21, 22]. The age at peak height velocity in ACH is similar to Polish girls and Chinese and Finn children and is half the magnitude: approximately 5.08 and 4.32 cm/year vs. 9.3 and 7.7 cm/year for average stature boys and girls, respectively [21, 22, 23].

The comparison of height data between ACH boys and girls shows that the difference (11 cm at adulthood) arises mainly during adolescence, as in the general population [24]. Differences in adult height between sexes in ACH have previously been described by different authors [6, 8, 9, 11, 19].

There are differences between heights in the present study and the results of our previous report [8]. This can be explained by the difference in sample size: only 17 girls and 10 boys were included in the present study.

In ACH children, the presence of the three phases of the growth curve with a similar shape to the general population shows that the negative influence of the *FGFR3* mutation in the epiphyseal growth plates does not completely nullify nutritional, endocrinological and other factors involved in the growth process. On the other hand, the present study reinforces the existence of the pubertal spurt in ACH adolescents, which is still under discussion in the scientific literature [9, 11, 25]. The reason why the pubertal spurt is often not observed in growth studies may be because time intervals between measurements are too long or the result of measurement errors. In this report, the same trained observer was used (AP), and they have been carrying out anthropometry since 1991.

Regarding growth-promoting treatments in ACH children, several therapies are being developed [13]. These potential new treatments propose to stimulate linear growth, improving stature, decreasing disproportion and preventing further complications [13]. Understanding the growth process in ACH would help us to analyse the effect

of these potential treatments in the different phases of growth.

There are manifold reasons for studying human growth. One motivation is mainly scientific and relates to an understanding of the growth process [18]. The traditional approach is to identify a suitable parametric model for the given measurement and age range, in order to analyse growth longitudinally. Thus, the growth curve is characterized and summarized by the fitted parameters of the model, which can be used instead of the raw data. The JPA-2 is a parametric model that was originally designed to fit post-natal growth in the general population and covers the whole growth process: infancy, childhood and puberty [17, 18]. We used the eight-parameter JPA-2 model because it is robust, extensively tested and provides an excellent fit from birth onwards [17, 21–23]. We focused on studying height from birth until adulthood in ACH children where the JPA-2 curve, with its eight estimated parameters, fits individual growth curves very well, with an RSD of 0.24–0.49 cm. Thus, this model could be applied in other growth disorders in which size and growth dynamics are affected in a general way. However, applying the JPA-2 model involves fitting many curves individually, and the ideal approach would be to fit a form of the curve to all subjects simultaneously. This could be done with the alternative SuperImposition by Translation And Rotation (SITAR) model, a shape-invariant growth curve model [26]. The SITAR model summarizes individual growth curves with a single curve and subject-specific random effects. The random effects reflect each patient's size, growth tempo and growth velocity, all of them biologically meaningful, and explains the heterogeneity in growth between individuals [26]. Analysing growth data with the most recently available SITAR method will be our next goal for studying growth in ACH.

Conclusion

This is the first study on growth in the ACH population, from birth to adulthood, applying a parametric model to analyse growth longitudinally. The height growth curve in ACH children shows the three periods described in the general population (infancy, childhood and puberty) with a similar shape but lesser magnitude than the general population. Our results reaffirm previous reports that ACH children have a “pubertal growth spurt” during adolescence.

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Ethical statement: The project was approved by the research review committee and the ethics review committee from Garrahan Paediatric Hospital.

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