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ORIGINAL ARTICLE

Growth in height and body proportion from birth to adulthood in hereditary hypophosphatemic rickets: a retrospective cohort study

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Abstract

Purpose Patients with hereditary hypophosphatemic rickets are short and disproportionate and very little information is available on segmental growth, but the body disproportion at adulthood leads us to think that the growth velocity of legs is slower.

Methods A total of 96 children were included and molecular testing was carried out in 42. Children who reached adult height were classified into two groups according to their compliance to conventional treatment (phosphate supplement and calcitriol). Individual growth records of height and sitting height/height were plotted using Argentine reference data in 96 children and growth curves were estimated by fitting Preece-Baines Model 1 in 19 of the children.

Results Molecular testing revealed sequence deleterious alterations or large deletions in 36/42 patients. During childhood, 76% of children grew below − 1.88 standard deviation score (SDS) and 97% had body disproportion. During adolescence, the mean peak height velocity for the good and poor compliance to treatment groups was 7.8 (0.6) and 5.4 (0.4) cm/year in boys and 7.0 (0.7) and 5.2 (0.8) cm/year in girls, respectively. At adulthood, the median sitting height/height ratio was 2.32 and 6.21 SDS for the good and poor compliance to treatment groups, respectively. The mean pubertal growth spurt of the trunk was –0.8 (1.4) SDS, with a short pubertal growth spurt of − 1.8 (0.4) SDS for limbs in the good compliance group. Median adult height in 13/29 males and 30/67 females was –4.56 and –3.16 SDS, respectively.

Conclusion For all patients the growth spurt was slower, secondary to a short growth spurt of limbs, reaching a short adult height with body disproportion that was more prominent in the poor compliance group.

Keywords Familial hypophosphatemic rickets · Puberty · Growth · Leg · Body height · Fibroblast growth factor 23

Introduction

Hereditary hypophosphatemic rickets (HHR) is a group of rare renal phosphate-wasting disorders [1–3]. Various genetic defects are known to cause the disease [4], among them, inactivating mutations in the *PHEX* (phosphate-regulating endopeptidase homologue, X-linked; MIM 300,550) gene lead to X-linked HHR (XLHR; MIM 307,800). This is the most common form of HHR, with an incidence of 3.9 per 100,000 live births [5–8]. XLHR is characterized by high

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circulating levels of fibroblast growth factor 23 (FGF23), which in excess leads to hypophosphataemia and inappropriately low circulating 1,25-dihydroxyvitamin D, with consequent skeletal and dental impairment, growth retardation, lower limb deformities and craneosynostosis [4, 9, 10]. During the last few years, a high level of FGF23 is the target to treat in this group of patients, and drugs aimed at inhibiting its side effects [11, 12].

Previous reports show that children with HHR at birth are of normal size but during infancy they grow slowly so that at the time of diagnosis they are short and disproportionate [13]. Conventional treatment (phosphate supplement and calcitriol) normalizes growth velocity in the majority of patients but no catch-up growth is observed, reaching adulthood with short stature and body disproportion, thus leading us to think that the legs grow more slowly [13–19]. Some authors describe an association between the height deficit at adulthood, the age at diagnosis and poor long-term adherence to treatment: an earlier diagnosis and good compliance to treatment leads to taller children [14, 20]. On the other hand, a wide spectrum of phenotype is described between individuals with the same genotype [21, 22].

This longitudinal retrospective cohort study analyses the long-term growth pattern, growth velocity, body disproportion and pubertal development in children with HHR under conventional treatment.

Patients and methods

Sample

The retrospective analysis was carried out in the hospital records of all patients diagnosed with HHR, attending our multidisciplinary team between 1992 and 2019, founding 96. No patient was excluded. Growth in height and sitting height was analyzed in all of them. Diagnosis of the disease was made based on clinical examination, laboratory test (reduced serum phosphorus, increased alkaline phosphatase, normal serum calcium, normal parathyroid hormone, reduced tubular reabsorption of phosphate and documentation of no glycosuria, bicarbonaturia or aminoaciduria) and X-ray (rachitic changes of the metaphyses: metaphyseal fraying, cupping and flaring; coarse trabeculae, bowing of the long bones) [23]. All children received conventional treatment with oral phosphate supplementation (multiple daily intakes to compensate for renal phosphate wasting) and calcitriol (to counter the 1,25-dihydroxyvitamin D deficiency) according to local recommendations [23].

The *PHEX* gene sequence and copy number variations were analyzed in 42 cases and the following information was collected: age, gender, height, sitting height (SH), Tanner stage of pubertal development, menarche and parental height. The percentage tubular reabsorption of phosphate (TRP; measured as $1-[(\text{urine phosphate/plasma phosphate})/(\text{urine creatinine/plasma creatinine})]\times 100$), alkaline phosphatase (IU/l) and serum phosphate (mg/dl) was analyzed at first appointment, before starting treatment.

Methods

All patients' measurements were initially taken and followed up by the same trained observer during the study period (1992–2019) using standardized anthropometric techniques [24, 25]. Height and SH were measured with Harpenden instruments. Mean intra-observer technical error of measurement for height and supine length was 0.10 and 0.11 cm, respectively [25]. Leg length (LL) was obtained by subtracting SH from height. Sitting height/height (SH/H) ratio was calculated as an indicator of body proportion. Individual growth records of height and SH/H were plotted using Argentine reference data [26, 27]. Patients reached adult height when their individual growth curve showed an apparent indication of an upper plateau for at least 2 years.

Patients who reached adult height were classified into two groups according to compliance to treatment and in accordance with the information in the clinical records. Good compliance was considered if the patient attended more than 80% of appointments and received more than 80% of treatment indicated, in agreement with local guidelines [23].

To compare objectively radiographic improvement, features were analyzed in the X-ray of the left wrist and knee during treatment (at baseline and at late follow-up) by radiographic scoring method (RSS) [28]. The score progressed from zero (normal) to 5 points (severe) Each radiograph was scored by one trained author (VF) and was blind to compliance of the treatment.

Pubertal development analysis

Growth during puberty was studied only in children with at least one measurement per year, from 5 years old until they reached adult height. To obtain comparable data, individual growth curves were estimated by fitting Preece-Baines Model 1 (PB1) to each individual's height, LL or SH for age data [29]. Growth in LL for severely affected children was not estimated because of their severe lower limb deformities.

Genital development in boys was scored visually on the Tanner scale. Testicular volume was measured by palpation using the Prader orchidometer [30, 31] A testicular volume of ≥ 4 ml was considered to be pubertal onset. Breast development in girls was scored both visually and by palpation to detect the budding in Stage 2 [30–32]. Menarche was recorded in each visit [31, 32].

Gene mutation analysis

Genomic DNA was isolated from peripheral blood leucocytes (42/96 patients, and family members when available) according to standard procedures. The entire coding region (exons 1–22) and splice sites in flanking intronic regions of the *PHEX* gene were polymerase chain reaction (PCR)-amplified and sequenced using automated analysers. After PCR, the products were assessed by electrophoresis on a 1% agarose gel stained with ethidium bromide, with the result showing as a single band of the expected size. The PCR products were purified (Qia Quick PCR purification kit, Qiagen, Buenos Aires, Argentina) and sequenced using a BigDye Terminator Version 3.1 cycle sequencing kit (Applied Biosystems, Buenos Aires, Argentina) on an ABI PRISM 3130 genetic analyser with capillary DNA sequencer (Applied Biosystems, Buenos Aires, Argentina). The primers used for sequencing were the same as those used for PCR [33]. Previously reported intronic mutations from the Human Gene Mutation Database (HGMD; www.hgmd.cf.ac.uk/) were also analyzed. The nucleotide sequences obtained were compared with those from Genebank accession number NG_007563.2 RefSeqGene. Nucleotide changes were reconfirmed in each sample DNA by antisense sequence and re-sequencing after a new PCR product was produced from the original DNA extract.

To detect gene deletions and duplications, multiplex ligation-dependent probe amplification was used (SALSA MLPA Probemix P223-B3, Tecnolab, Buenos Aires, Argentina).

In silico protein analysis

Nonsense and frameshift mutations that implicate a premature stop codon and a truncated protein were considered to be deleterious. To predict the pathogenicity of the previously undescribed missense variants, we used the recently established standards and guidelines of the American College of Medical Genetics and Genomics (ACMG) [34].

To evaluate the implication of a novel synonymous mutation and intronic variants, we used Human Splice Finder 3.1 (HSF; http://www.umd.be/HSF/) as a splice site prediction program. The original sequence of protein was obtained from the Ensembl and Uniprot/Swiss-Prot databases.

Statistical methods

Baseline characteristics were described using the mean or the median and interquartile range (IQR) for continuous variables. Differences among variables were analyzed using the median test, sign test or *t*-test.

Preece-Baines Model 1 (PB1) [29] was applied to estimate biological parameters. This model has the following mathematical expression:

$$Y = h1 - \frac{2(h1 - h\varnothing)}{e^{s0(t-\varnothing)} + e^{s1(t-\varnothing)}}$$

where Y = size and t = age. The five function parameters of the model were estimated by non-linear least-squares techniques [29].

The following biological parameters were obtained from PB1 fits to each individual's serial growth data: age, height and velocity at take-off (the point of minimal pre-pubertal growth velocity) and at peak velocity during puberty. Adolescent growth was calculated by subtracting height at take-off from the final height. The goodness of fit was assessed by the residual standard deviation (RSD).

The mean constant curve depicting the growth pattern of the 'average child' in the sample was obtained by feeding the mean values of the function parameters into the model [35]. This curve is not affected by the inter-individual variation in the tempo of growth.

Results

Ninety-six children (29 males) with HHR were included in the study. No child was excluded.

Molecular studies revealed sequence deleterious alterations or large deletions in 36 out of 42 patients analyzed (85.7%) (22 familial cases and 14 sporadic cases).

At diagnosis, the median (IQR) biochemical tests were: serum phosphate = 2.4 (2.2–2.7) mg/dl, alkaline phosphatase = 510 (400.6–723.9) IU/l and %TRP = 74 (62.2–85.5).

The mean (SD) height in non-affected parents was 158.22 (5.36) and 169.50 (7.37) cm for mothers and fathers, respectively, which is lower than the average Argentine adult height ($p = 0.0010$ and $p = 0.0023$) [26].

Prenatal growth

The mean (SD) birthweights and lengths were 3086 (703) and 3317 (586) g and 51.4 (2.77) and 50.0 (2.46) cm for boys and girls, respectively, which is no different from the Argentine reference data ($p = 0.06$, $p = 0.50$; $p = 0.50$, $p = 0.30$) [26].

Growth during infancy and childhood (*N* = 96)

At first appointment, the median (IQR) age was 3.5 (2.3–5.8) years and the median (IQR) time of follow-up was 6.8 (2.7–13.2) years. Median height standard deviation score

(SDS) was − 2.3(− 1.7 to − 3.2), with an SH/H ratio SDS of + 3.4 (1.9–4.8).

Height and SH/H growth curves for boys and girls are shown in Fig. 1. In 8/29 boys (27%) and 15/67 girls (22.4%) the growth pattern is within the normal range whereas all the other children are below –1.88 SDS. A total of 96% of the children have body disproportion (83/86) with an SH/H ratio above + 1.88 SDS (short legs) during follow-up.

Growth during puberty

Growth during puberty was studied in 19 of the 96 patients (11 females) by fitting the individual growth curves with PB1 [29]. The median (IQR) number of height measurements per child was 18 (15.5–20). The pooled RSD (IQR) was 0.42 (0.32–0.47) cm ($N = 19$), 0.30 (0.25–0.40) cm ($N = 12$) and 0.31 (0.29–0.34) cm ($N = 6$) for height, SH and LL, respectively. The height and growth velocity mean constant curves of PB1 fitted to males and females are shown in Fig. 2).

Table 1 shows the derived biological variables and the age of Tanner stages of pubertal development. Males and females with good compliance to treatment are taller at adulthood and have a higher growth velocity during take-off and at peak than the poor compliance groups. The growth velocity at peak is less in magnitude than the general population (for both the good and poor compliance groups: $p = 0.01$ and $p = 0.002$, respectively) [29].

Both in the general population and in the good compliance group, the adult gender difference in height (11.2 cm) was much more due to the late take-off of the boys' growth than to differences in the amount of pubertal spurt. The take-off age was later (1.5 years) in boys than in girls and the boys gained about 7.9 cm during that period.

Mean ages at Tanner II (11.07 years) in boys and girls and at menarche were not statistically different from those of the Argentine population [36, 37]; however, the group with poor compliance to treatment began puberty at a later age.

Table 2 shows the standard deviations of the derived biological variables of SH and LL growth. The growth velocity

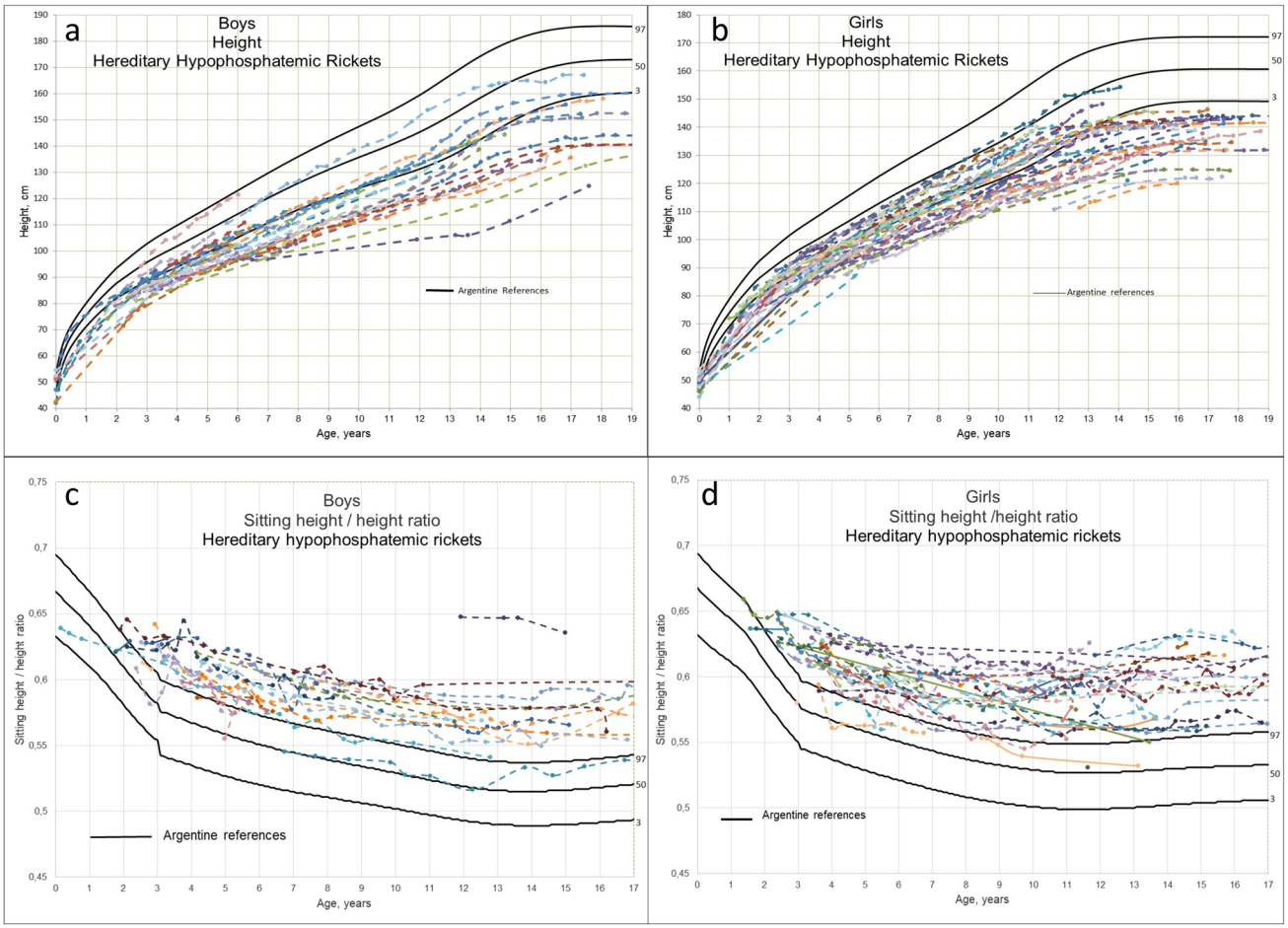

Fig. 1 Height and sitting height/height ratio growth curves for 29 boys (**a**, **c**) and 67 girls (**b**, **d**) with hereditary hypophosphatemic rickets, plotted using Argentine reference data [26, 27]

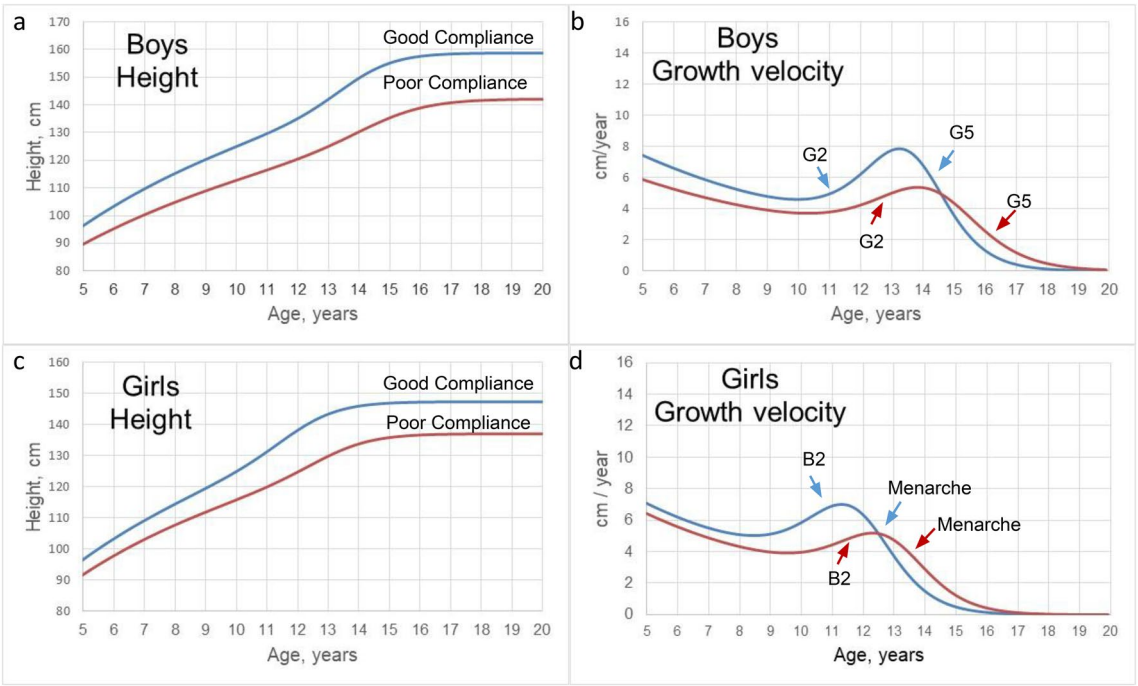

Fig. 2 Individual distance and velocity with mean constant curves for height of Preece-Baines Model 1 fitted to eight boys (**a**) and eleven girls (**b**). The shapes of the curves are similar to that for the general population [29]. The growth velocity curves show that after a period of slightly decreasing velocity, the pubertal spurt is initiated and growth velocity increases, achieving its maximum at the age of peak height velocity. After the age of peak height velocity, the growth velocity decreases until the patient stops growing. The peak height velocity was lower in the poor compliance to treatment group than the other group for both males and females. In males, Tanner II occurred during the increase of growth velocity. Mean age at Tanner V occurred after the age of peak height velocity, in the deceleration phase of the 'adolescent growth spurt'. In girls, Tanner II occurred during the increase of growth velocity. Menarche occurred when the peak height velocity had passed and the growth spurt was in its deceleration phase

in lower limbs is more compromised than the growth velocity of the trunk [39], so that the adult size in LL is significantly shorter than the trunk, thus explaining the body disproportion at adulthood. Figure 3 shows the mean constant curves for SH and LL fitted to males and females with good compliance to treatment compared with the general population. The curves show a pubertal spurt both in SH and LL, the spurt for LL being shorter [38, 39].

Adult height

Fourteen of 29 males reached adult height, with a median (IQR) height of 142.4 (138.1–155.7) cm and SDS = −4.3 (−4.8 to −2.1). Out of 67 females, 29 reached adult height, with a median (IQR) height of 141.5 (134.6–144) cm and SDS = −3.13 (−4.3 to −2.7). These values were different from the Argentine reference data for both genders ($p = 0.003$) [26]. Table 3 shows the height and SH/H ratio at first appointment and at adulthood. Patients with good compliance to treatment are taller and less disproportionate than the poor compliance group, both at the first appointment and at adulthood. The age at diagnosis in the good compliance group is earlier but this is not related to sporadic or familial cases.

The median (IQR) RSS rickets severity total score decreased from 3.25 (2.88/4.13) at 1st appointment to 2 (1.25/2.25) at late follow-up and from 4.88 (2.5/5) to 4.25 (2.5/4.6) for the good and poor compliance groups respectively.

Discussion

In this report, the long-term growth in height and change in body proportions of children with HHR are presented.

Unlike children with other genetic diseases in which prenatal growth is compromised, children with HHR are born with normal size [13–15, 17]. Similarly, in the present report, the size at birth is no different from the local reference data [26]. On the other hand, our patients are shorter than in other reports and this could be explained by different reasons [14, 20]. The clinical picture of children with HHR is highly variable, even among patients with the same genotype, and secondary to multiple factors, some unknown. On the other hand, in the population included, the height of the

Table 1 Mean and standard deviations of the Preece-Baines Model 1 derived biological variables of height and age of pubertal development stages in hipophosphatemic rickets, both sexes

	Males		Females		Total *Z* score	
	Good $N=5$	Poor $N=3$	Good $N=5$	Poor $N=6$	Good	Poor
Take-off						
Age, years	10.0 ± 0.99	10.4 ± 1.5	8.5 ± 1.3	9.6 ± 2.5		
Size, cm	125.1 ± 9.1	114.2 ± 5.2	117.2 ± 12	114.2 ± 12	− 1.5 ± 1[q]	− 2.9 ± 1[q]
Velocity, cm/year	4.6 ± 0.8	3.7 ± 0.5	5.0 ± 0.5	3.9 ± 0.6	− 0.5 ± 1.4[r]	− 2.7 ± 1.3[r]
Peak velocity						
Age, years	13.3 ± 0.8[a]	13.9 ± 1.3[b]	11.3 ± 0.6[c]	12.3 ± 1.6[d]		
Size, cm	144.4 ± 6	129.7 ± 4	133.8 ± 7.8	126.4 ± 8.4	− 1.1 ± 1.0[e]	− 3.1 ± 1.1[e]
Velocity, cm/ year	7.8 ± 0.6	5.4 ± 0.4	7.0 ± 0.7	5.2 ± 0.8	− 0.7 ± 0.6[f]	− 2.6 ± 0.8[f]
Growth, cm	33.6 ± 6.1	27.9 ± 5.6	30.3 ± 8.1	22.8 ± 9.5	1.2 ± 1.8[g]	− 0.4 ± 1[g]
Adult size, cm	158.7 ± 5.4	142.1 ± 2	147.5 ± 5.1	136.9 ± 7.4	− 1.9 ± 0.9[h]	− 4.2 ± 1.[h]
Tanner stage	Age, yrs, at Tanner II		Age, yrs, at Tanner II			
	11.1 ± 1.2[i]	12.9 ± 0.3[j]	10.9 ± 0.9[k]	11.7 ± 1.4[l]		
	Age, yrs, at Tanner V		Age at menarche, yrs			
	14.7 ± 1.5[m]	16.3 ± 1.3[n]	12.7 ± 0.4[o]	13.7 ± 1.[p]		

Sign test between patients and general population [a]$p=0.18$ [29]; [b]$p=0.5$ [29]; [c]$p=0.18$ [29]; [d]$p=0.65$ [29];[i]$p=0.31$[0.35] [j]$p=0.25$) [36]
[k]$p=0.5$ [36]; [l]$p=0.34$ [36]; [m]$p=0.50$ [36]; [n]$p=0.12$ [36]; [o] $p=0.50$ [37]; [p]$p=0.19$) [37]
Median test between groups [e] $p=0.018$; [f] $p=0.0001$; [g] $p=0.15$; [h] $p=0.0044$; [q] $p=0.018$; [r] $p=0.0044$

Table 2 Mean and standard deviations of the derived biological variables, obtained by fitting Preece-Baines Model 1 of growth in sitting height and leg length, in two groups according to compliance to treatment and for both sex

Variables	Peak velocity SDs	Growth SDs	Adult size SDs
Sitting height			
Good compliance	− 0.8 ± 1.4	1.6 ± 1.5	− 1.3 ± 0.6
Poor compliance	− 1.9 ± 1.7	1.1 ± 1.5	− 1.5 ± 1.8
Leg length			
Good compliance	− 1.8 ± 0.4	0.1 ± 1.0	− 2.6 ± 1.0

SDs standard deviation score

unaffected parents is lower than that of the Argentine population, reflecting the population that attends our institution. Another important point is that in Argentina a commercial pharmaceutical form of phosphate is not available and has to be imported or prepared as a master formula, which makes it difficult for many families to access treatment. Although adherence to replacement therapy was based on compliance with medical controls, this variable could not be fully verified.

It is recently reported that children with XLHR under conventional treatment show a decreased height gain from 1 year of age and remain below population reference data thereafter, reinforcing the importance of early diagnosis and treatment [13]. Unfortunately, in this report the growth data during teenage years was not evaluated due to limited measurements [13]. In 1992 Steendijk applied PB1 to the growth data of children with HHR and reported a normal growth spurt during adolescence; however, the SDS was not reported [19]. Interestingly, in the present report, in the group with good compliance to treatment the total pubertal growth spurt during adolescence is below normal (− 0.73 SDS) if we compare it with the general population, suggesting that good compliance to treatment is not enough to achieve completely normal growth, at least in some HHR patients [29]. As expected, pubertal growth is severely affected in the poor compliance to treatment group, secondary to growth retardation of the long bones and severely bowed legs.

Regarding the growth velocity of body segments, Zivičnjak [16] reported that the height, LL and arm length SDS in 76 patients decreased progressively during childhood and early adolescence, followed by an increase in SDS values later, understanding this to be a consequence of the delayed onset of puberty. However, they did not analyze this data in relation to the Tanner stages [16]. Interestingly, in our cohort, onset of puberty and age of menarche were no different from the general population [36, 37]. However, we have to take into account that our sample size analyzed to puberty is small, and this could explain why we found no differences from the general population.

On analyzing the segmental growth, in our study the peak velocity in LL is very compromised in both male and female adolescents with good compliance to treatment [38, 39]. However, at adulthood we find a taller height and lower

Fig. 3 Individual distance and velocity with mean constant curves for sitting height and leg length of Preece-Baines Model 1 in both males and females compared with the general population. The curves show a pubertal spurt in sitting height and leg length with an increase of growth velocity, its maximum at the age of peak height velocity. The peak growth velocity of the lower limbs is shorter than for the general population (^)

Table 3 Median (SDS) of height and sitting height / height ratio in children who achieve adult size

Both Sex	Good compliance to treatment $N=14$		Poor compliance to treatment $N=29$		Familial cases $N=18$		Sporadic cases $N=25$	
	Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
	1st appointment	Adulthood	1st appointment	Adulthood	1st appointment	Adulthood	1st appointment	Adulthood
Age, years	1.9 (1.5/3.1)[a]		5.1 (3.3/8.7)[a]		4.2 (2.3/7.3)[d]		3.5 (2.1/6.2)[d]	
Height, SDS	− 2.3 (− 2.8/− 1.4)[b]	− 2.4 (− 2.8/− 1.9)[c]	− 3.1 (− 3.9/− 1.9)[b]	− 4.3 (− 5.3/− 3.1)[c]	− 3.2 (− 3.9/− 2.6)	− 3.9 (− 4.9 / − 2.8)	− 2.3 (− 3.2,− 1.1)	− 3.1 (− 4.7/− 2.4)
SH/H	$N=6$ 2.4 (0.4/3.3)[d]	$N=10$ 2.2 (1.6/4.1)	$N=14$ 5.9 (7.3/3.3)[d]	$N=18$ 6.2 (7.7/4.9)[e]	$N=7$ 4.4 (3.4/6.5)	$N=11$ 5.1 (3.8/7.80)	$N=13$ 3.2 (1.7/6.9)	$N=17$ 5.0 (2.5/6.5)

The age at first appointment in the good compliance group is earlier than the poor compliance group ($p=0.0088$) and this is not related to being sporadic or familial cases ($p=0.34$)

Mean height SDS, [26], at first appointment and at adulthood, was significantly higher in the good compliance group in comparison to the poor compliance group. Body disproportion, evaluated with SH/H SDS [27], was more compromised in the poor compliance group at the 1st appointment and at adulthood

IQR interquartile range; *SH/H* sitting height/height ratio

[a]Median test between groups $p=0.0088$; [b]$p=0.019$; [c]$p=0.0001$; [d]$p=0.0034$, [e]$p=0.0016$, [d]$p=0.34$

LL in the good compliance to treatment group, reinforcing the concept that conventional treatment benefits adult height and particularly the growth in LL.

We also found differences in RSS score between groups with good and poor compliance to treatment [28]. However,

it is a small sample, secondary to the lack of x-rays of the whole sample, and this is a limitation of our study.

Molecular studies revealed sequence deleterious alterations or large deletions in 36 out of 42 patients analyzed (85.7%). Unfortunately, other methodology such as a NGS gene panel including genes related with HHR or other hypophosphatemic disorders, was not available to further investigate in the 6 patients with no proven mutation in *PHEX* gene.

Mutations in the *PHEX* gene are the most frequent cause of HHR [5–8]. The percentage of detection of *PHEX* mutation in our cohort, at 85.7%, was one of the highest among those reported, which range from 45 to 100% [21, 22, 40]. The high rate of mutation detection in the present study can be explained by the careful clinical and biochemical selection of patients before referring for genetic analysis and the methodology used for mutation detection. When the familial and sporadic cases were separated in this study, as in the other studies, the mutation detection rate was lower in the sporadic cases (14 of 19) than in the familial cases (22 of 23) [21, 22, 40].

Our study has the potential limitations commonly found in retrospective studies with missing data for patients that could not be included to analyze growth during puberty using PB1 [29]. Another limitation is that adherence to treatment was measured by the percentage of appointments attended and the missed dosing days, in accordance with local guidelines and not by drug accountability [23].

It would be useful to repeat this study in other children with HHR to be able to generalize the results. Nevertheless, we think it is important to have information about height growth velocity and body segment growth during puberty in children with HHR.

Conclusions

Patients with HHR and good compliance to treatment are born with normal size but during childhood, after starting conventional treatment, they grow without catching up. When puberty begins, adolescents experience a 'pubertal spurt' that is shorter than for the general population. This short growth spurt is mainly due to diminished growth capacity in the legs, meaning that when patients reach adulthood they are short and disproportionate.

Awareness of the characteristics and magnitude of the pubertal spurt of children with HHR and the changes in body proportions would help us to evaluate the effectiveness of new emerging therapies on longitudinal growth and body proportions.

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Author contributions All authors made substantial contributions to the study conception and design. Material preparation, data collection and analysis was performed by MdP, GLV and MAA. The first draft of the manuscript was written by MdP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability statement The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability KaleidaGraph 4.5.3 for Microsoft Windows. Copyright by Sinergy software. Serial no. 9009089.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Research involving human participants and/or animals This was a retrospective cohort study conducted in conformity with the World Medical Association and the Declaration of Helsinki for medical research involving human subjects. The study protocol was approved by the Research Review Committee and Ethics Review Committee from Garrahan Pediatric Hospital.

Informed consent For this type of study formal consent is not required.

Consent to participate Not applicable.

Consent for publication All authors approved the publication of the manuscript.

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