Treatment of hypophosphataemic rickets in children remains a challenge

Line Hougaard Nielsen[1], Elise Torp Rahbek[1], Signe Sparre Beck-Nielsen[2, 3] & Henrik Thybo Christesen[3, 4]

ABSTRACT

INTRODUCTION: Hypophosphataemic rickets (HR) is a rare hereditary disease characterised by hypophosphataemia, defects in bone mineralisation and rickets.

MATERIAL AND METHODS: We searched the hospital files at H.C. Andersen Children's Hospital, Odense University Hospital, Denmark, for children with the International Classification of Diseases 10 codes E83.3B (vitamin D resistant rickets) and E83.3A1 (familiar hypophosphataemia) from 1 February 2012 to 1 May 2012. Data were collected retrospectively.

RESULTS: Fifteen HR children were identified. X-linked hypophosphataemia with mutations in the phosphate-regulating endopeptidase homologue, X-linked were present in 80%; three had autosomal recessive HR with dentin matrix protein mutations. The children were treated with phosphate and alphacalcidol for an average of 7.7 years ± 5.1 standard deviations (SD). At the latest follow-up, the mean age was 10.1 (+5.4) years, and the mean height had declined 0.8 SD from the first contact. A total of 40% had an actual height below –2.0 SD, and 40% underwent surgery for leg deformities. Among the medically treated patients, five had genu varus with a mean medial femoral condyle distance of 6.6 cm (+ 2.79), and two patients had genu valgus with a mean medial malleolus distance of 12.3 cm (+ 1.77). Episodes of secondary hyperparathyroidism were seen in 87%, and one patient developed transient nephrocalcinosis.

CONCLUSION: The current medical treatment for HR is insufficient. The rarity of the disease and the treatment difficulties of HR call for centralised management. International multi-centre trials including novel treatment options are warranted.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Hypophosphataemic rickets (HR) is a type of hereditary rickets characterised by hypophosphataemia secondary to urinary phosphate loss and defective bone mineralisation. X-linked dominant hypophosphataemic rickets (XLH) is the most common form with an estimated incidence of 3.9 per 100,000 live births [1]. XLH is caused by a dominant inactivating mutation in the *gene phosphate-regulating endopeptidase homologue X-linked (PHEX)*. Autosomal recessive hypophosphataemic rickets (ARHR1) is a more seldom variant which is caused by mutation in the *dentin matrix protein (DMP1)*. Autosomal dominant hypophosphataemic rickets (ADHR) is another rare type of HR caused by mutation in fibroblast growth factor 23 (FGF23). These gene mutations all result in increased FGF23, which regulates the phosphate homeostasis [2].

There is a tendency for men with XLH to have more severe skeletal affection than women. This may be due to the fact that men only carry activated, mutated X chromosomes, whereas women, carrying two X chromosomes per cell, inactivate a proportion of the mutated X chromosomes [3].

Medical treatment is difficult and consists of oral phosphate and alphacalcidol (1-alpha-hydroxy vitamin D). The optimum dose of phosphate is uncertain, but some clinicians recommend 20-40 mg/kg/day, with higher doses during high-growth periods. Phosphate needs to be administered 3-5 times daily, which often leads to gastrointestinal side effects [4]. A dosage of 0.03-0.05 microgram/kg of alphacalcidol is recommended once daily [5]. Some clinicians advocate for a higher alphacalcidol dose in the initial phase, but this has not been evaluated compared to lower doses.

Even timely treatment with a high level of adherence cannot completely normalise bone growth, and various degrees of bone deformity and reduced height are unavoidable [3, 6]. Furthermore, side effects to the treatment are likely to arise, such as secondary hyperparathyroidism (SHPT) and nephrocalcinosis [7].

We made a retrospective follow-up of children with HR followed at the Hans Christian Andersen Children's Hospital, Odense University Hospital (OUH), Denmark, to evaluate the efficacy and any complications of the current treatment regimen.

MATERIAL AND METHODS

We identified HR patients at OUH by searching the hospital files for children with the the International Classification of Diseases (ICD) 10 codes E83.3B (D-vitamin resistant rickets) and E83.3A1 (familiar hypophosphataemia) during the period from 1 February to 1 May 2012. Permission was granted from the Danish Data Protection for collecting sensitive personal data. Existing records were reviewed for gender, age and height at diag-

ORIGINAL ARTICLE

1) Faculty of Health, University of South Denmark, Odense
2) Department of Paediatrics, Hospital of Southwest Denmark, Esbjerg
3) Institute of Clinical Research, University of South Denmark, Odense
4) Hans Christian Andersen Children's Hospital, Odense University Hospital

Dan Med J 2014;61(7):A4874

TABLE 1

Basic characteristics of hypophosphataemic rickets patients.

Patient no.	Gender	Age, yrs; months: time of diagnosis	Age, yrs; months: latest follow-up	Treatment duration, yrs	Affected gene	Family member with known HR
1	Girl	0; 6	2; 7	2.08	*DMP1*	Yes
2	Girl	1; 2	16; 10	15.54	*PHEX*	Yes
3	Girl	3; 3	11; 5	8.17	*PHEX*	No
4	Girl	0; 7	6; 5	5.83	*PHEX*	Yes
5	Girl	0; 5	2; 7	2.17	*PHEX*	Yes
6	Girl	2; 6	11 11	9.42	*PHEX*	No
7	Girl	6; 1	13; 7	2.31	*PHEX*[a]	Yes
8	Girl	1; 8	7 5	5.75	*PHEX*[a]	Yes
9	Girl	2; 6	14; 5	11.92	*PHEX*	N/A
10	Boy	3; 8	10; 11	7.25	*DMP1*	Yes
11	Boy	1; 8	5; 1	3.42	*DMP1*	Yes
12	Boy	2; 6	19; 2	16.5	*PHEX*	Yes
13	Boy	0; 2	11; 5	11.12	*PHEX*	Yes
14	Boy	2; 3	15; 5	13.17	*PHEX*	No
15	Boy	1; 3	2; 9	1.5	*PHEX*[a]	Yes
Average	–	2; 0	10; 2	7.7	–	–

DMP1 = *dentin matrix protein*; HR = hypophosphataemic rickets; N/A = data not available; PHEX = *phosphate-regulating endopeptidase homologue X-linked*.
a) Mutation associated with the *PHEX* gene detected by linkage analysis [3].

TABLE 2

Height data and parathyroid hormone values.

Patient no.	Height SD: baseline	Height SD: latest follow-up	Δ height SD	PTH_{max} for patients with SHPT, pmol/l
1	0.02	–1.50	–1.52	8
2	–2.05	–0.92	1.13	–[a]
3	–0.45	–2.12	–1.67	9.9
4	0.99	–2.63	–3.62	12.5
5	0.92	–0.99	–1.91	16.4
6	–2.86	–1.36	1.50	9.5
7	–0.20	0.11	0.31	13.4
8	–0.79	–0.93	–0.14	–[a]
9	–2.30	–2.72	–0.42	10.1
10	–1.23	–1.32	–0.09	9.7
11	–1.51	–1.21	0.30	10.6
12	–3.10	–2.80	0.30	16.5
13	–0.30	–2.70	–2.4	11.5
14	–1.05	–2.87	–1.82	15.7
15	–0.24	–1.79	–1.55	7.5
Average	–0.9	–1.7	–0.8	11.6

PTH = parathyroid hormone; SD = standard deviation; SHPT = secondary hyperparathyroidism.
a) No elevated PTH values.

nosis and at follow-up. Furthermore, we registered gene mutations, known HR in the family, number of visits per year, the most recent medial femoral condyle distance and medial malleolus distance, medical treatment, bone deformity correcting surgeries and nephrocalcinosis detected by ultrasound of the kidney/urinary tract. Furthermore, the average phosphate and alphacalcidol dosages were registered from the initiation of medical treatment to the end of the study period or until bone deformity-corrective surgery. Based on these data, we calculated an average dose for each patient and the overall median/(range) dosage.

The average number of reported phosphate administrations per day during the years of medical treatment was used as an estimate of treatment adherence. Phosphate administrations 4-5 times/day was defined as good adherence, 3 times/day was medium adherence and 1-2 times/day was poor adherence.

SHPT was defined as the detection of at least one measurement of serum parathyroid hormone (S-PTH) above the upper reference value (> 6.90 pmol/l).

Height standard deviations (SD) score was calculated from the reference curve used at the department [8] using the software NordiNet 3.2. For statistical calculation, the Shapiro-Wilk test, t-distribution and Welch's unpaired t-test were used. A p-value < 0.05 was considered statistically significant.

Trial registration: not relevant.

RESULTS

Fifteen patients with HR were identified. The patients came from Funen (n = 11), other parts of the Region of South Denmark (n = 1) and other areas of Denmark (n = 3).

XLH represented 80% (n = 12). The remaining 20% (n = 3) had ARHR1 (**Table 1**). The sex ratio (girl:boy) was 3:2. Eleven patients had relatives with known HR at the time of their diagnosis. The average age ± standard deviation (± SD) at diagnosis was 2.0 ± 1.6 years, whereas the mean baseline height SD was –0.9 ± 1.2 (**Table 2**). In 20% of the patients (n = 3), the height was below –2.0 SD. At the time of diagnosis, the patients who were diagnosed before the age of seven months had a higher height SD than patients diagnosed after the age of seven months. The median number of visits per year was three (**Table 3**).

The average duration of treatment was 7.7 ± 5.1 years, Table 1. At the end of the study period, one patient was not receiving any medical treatment due to SHPT and poor compliance. All other patients were being treated with phosphate and alphacalcidol. The overall median phosphate dosage was 32.8 mg/kg/d (range 4.6 to 82.0); alphacalcidol 0.04 microgram/kg/d (range 0.0 to 0.15). A good adherence to treatment was observed in 67%, whereas 27% had medium adherence and 6% had poor adherence to treatment, Table 3. The adherence to treatment was not correlated with height SD (p = 0.10).

TABLE 3

Dosage, adherence and visit frequency.

Patient no.	Mean phosphate dosage, mg/kg/d	Mean alpha-calcidol dosage, µg/kg/d	Adherence	Visits/yr, n
1	26.5	0.03	Good	4
2	31.2	0.04	Medium	3
3	82.0	0.02	Good	2
4	54.2	0.15	Good	3
5	14.2	0.01	Good	1
6	74.3	0.06	Good	4
7	4.6	0.00	Poor	2
8	16.9	0.004	Medium	1
9	67.4	0.05	Good	2
10	32.8	0.04	Good	4
11	39.7	0.03	Good	4
12	30.3	0.06	Medium	3
13	57.8	0.06	Good	3
14	47.6	0.10	Good	3
15	8.5	0.01	Medium	2
Median (range)	32.8 (4.6-82.0)	0.04 (0.0-0.15)	–	3 (1-4)

At the latest follow-up, the average age was 10.1 ± 5.4 years and the mean height SD –1.7 ± 0.9, Table 2). Mean Δ height SD from baseline was –0.8 ± 1.4. At the last follow-up, 40% (n = 6) had a height below –2.0 SD. Initiation of treatment before the age of two years was not correlated with increased height SD at the latest follow-up (p = 0.57).

Among the XLH patients, there were no differences in Δ height SD between genders, (girl:boy) ratio (2:1).

A total of 40% (n = 6) went through one or more bone deformity corrective surgeries of the lower limbs, with an average of two surgeries per patient. At the most recent follow-up, three patients were below the age recommended for surgical intervention.

Of the patients with no surgeries, five had genu varus (**Figure 1**) with an average medial femoral condyle distance of 6.6 ± 2.8 cm, and two patients had genu valgus with an average medial malleolus distance of 12.3 ± 1.8 cm. Two patients (girls) aged 14 and 16 years had no deformities of the lower limbs. Only one patient had transient nephrocalcinosis following an accidental overdosing of phosphate. Among the patients, 87% (n = 13) had at least one case of SHPT with an average PTH_{max} of 11.6 pmol/l, (Table 2).

DISCUSSION

Despite an average of 7.7 years of medical treatment at a specialist centre with median dosages within the internationally recommended range, many patients remained severely affected at the most recent follow-up with either genu valgus or varus, and 40% had an actual height below –2.0 SD. Furthermore, 40% had undergone surgery for leg deformities. A decline in the height SD with age was present among medically untreated as well as among medically treated patients. Thus, in our study, HR was associated with a progressive decrease in height SD, which was not compensated for by the current methods of treatment.

Other studies [3, 7, 9] also find that HR often results in growth retardation with a reduced final height and leg deformities requiring surgery despite medical treatment.

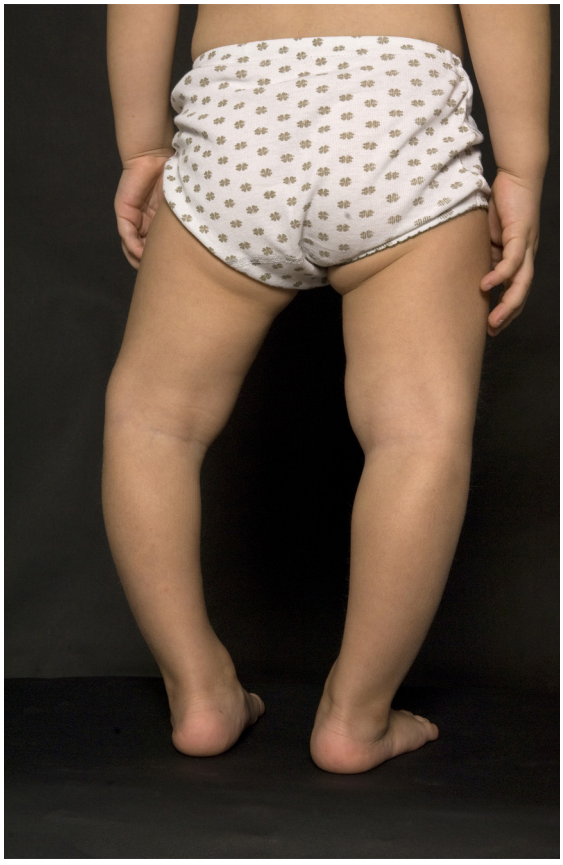
The disease exerts its effect on bone mineralisation already before HR becomes clinically symptomatic. The leg deformities are usually already present at the time of diagnosis. Studies [10, 11] find a trend towards increased height when treatment is initiated within the first year of life. In families with known cases of HR, diagnosis and treatment shortly after birth may decrease the severity of bone deformations. In our study, 73% of the included patients had relatives with HR. Eight patients initiated medical treatment before the age of two years. Nevertheless, no difference in height SD at the latest follow-up could be detected between this group and the group with later on-set of treatment. This may be due to low statistical power.

We argue that the number of phosphate administrations per day is the best estimate of adherence, given that only a few clinicians followed the patients in the outpatient clinic and hence adjusted the number to adherence. However, no difference in Δ height SD could be detected between daily phosphate dose groups.

The incidence of nephrocalcinosis visualised by ultrasound in the present study was low compared with other studies [7]. The presence of nephrocalcinosis in one patient in our study was entirely caused by an unintended, increased phosphate dosage. We found no difference by gender in Δ height SD among XLH patients, whereas previous studies including adults with HR show a tendency towards a more severe skeletal affection in men [6]. This may be due to young age among our patients, a possible lack of diagnosis and referral of mildly affected girls, or low statistical power.

SHPT was a very frequent complication, which would lead to a necessary reduction of the phosphate dosage. Low phosphate dosage and SHPT in itself may both lead to decreased bone mineralisation. Thus, preventing SHPT has high priority. In our series, experimental treatment with Cinacalcet was not performed. Cinacalcet has been used in some patients with HR [12-14], but a recent case describing hypocalcaemia with fatal outcome during Cinacalcet treatment in children has lead to a current suspension of all paediatric clinical trials with Cinacalcet.

As increased FGF23 is part of the pathogenesis of



Hypophosphataemic rickets patient with genu varus.

HR, some experimental trials for future treatment focus on decreasing the FGF23 level. In mouse models of XLH (HYP-mice), treatment with FGF23 antibodies has resulted in partial healing of rickets [15]. In addition, treatment of HYP-mice with FGF23 antagonist has shown improvement of bone mineralisation and growth [16]. One available study showed promising results after one single treatment with FGF23 antibodies/antagonists in HR adults [17].

A strength of our study was the inclusion of a relatively large number of patients, the rarity of the disease taken into account, and the use of a uniform treatment strategy. Limitations included the retrospective design and the risk of intra- and inter-observer variability in the clinical assessment of genu valgus/varus and medial malleolus distance. In addition, we did not correct for the physiological genu varus and valgus, which is primarily present below the age of five years [18].

CONCLUSION

In summary, we showed that despite a modern treatment regimen, HR causes reduced height and considerable lower limb deformities. The rarity of the disease and its complexity justify centralised management. New treatment options should be tested in international multicentre controlled studies.

CORRESPONDENCE: *Henrik Thybo Christesen*, Afdeling H, H.C. Andersen Børnehospital, Odense Universitetshospital, Søndre Boulevard 29, 5000 Odense C, Denmark. E-mail: henrik.christesen@rsyd.dk.

ACCEPTED: 5 May 2014

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

LITERATURE

1. Beck-Nielsen SS, Brock-Jacobsen B, Gram J et al. Incidence and prevalence of nutritional and hereditary rickets in Southern Denmark. Eur J Endocrin 2009;160:491-7.
2. Beck-Nielsen SS, Brixen K, Gram J et al. Mutational analysis of PHEX, FGF23, DMP1, SLC34A3 and CLCN5 in patients with hypophosphatemic rickets. J Hum Genet 2012;57:453-8.
3. Beck-Nielsen SS, Brusgaard K, Rasmussen LM et al. Phenotype presentation of hypophosphatemic rickets in adults. Calcif Tissue Int 2010 2010;87:108-19.
4. Carpenter TO, Imel EA, Holm IA et al. A clinician's guide to X-linked hypophosphatemia. J Bone Mineral Res 2011;26:1381-8.
5. Cheung M. Drugs used in paediatric bone and calcium disorders. Endocrine Dev 2009;16:218-32.
6. Rahbek ET, Nielsen LH, Beck-Nielsen SS et al. Medicinsk behandling af hypofosfatæmisk rakitis hos børn. Ugeskr Læger 2014;176:V10130629.
7. Baroncelli GI, Bertelloni S, Sodini F et al. Genetic advances, biochemical and clinical features and critical approach to treatment of patients with X-linked hypophosphatemic rickets. Pediatric Endocrin Rev 2004;1:361-79.
8. Wikland KA, Luo ZC, Niklasson A et al. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. Acta Paediatr 2002;91:739-54.
9. Zivicnjak M, Schnabel D, Billing H et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. Pediatr Nephrol 2011;26:223-31.
10. Makitie O, Doria A, Kooh SW et al. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. J Clin Endocrin Metab 2003;88:3591-7.
11. Quinlan C, Guegan K, Offiah A et al. Growth in PHEX-associated X-linked hypophosphatemic rickets: the importance of early treatment. Pediatr Nephrol 2012;27:581-8.
12. Alon US, Levy-Olomucki R, Moore WV et al. Calcimimetics as an adjuvant treatment for familial hypophosphatemic rickets. Clin J Am Soc Nephrol 2008;3:658-64.
13. Raeder H, Shaw N, Netelenbos C et al. A case of X-linked hypophosphatemic rickets: complications and the therapeutic use of cinacalcet. Eur J Endocrin 2008;159(Suppl 1):S101-S105.
14. Yavropoulou MP, Kotsa K, Gotzamani Psarrakou A et al. Cinacalcet in hyperparathyroidism secondary to X-linked hypophosphatemic rickets: case report and brief literature review. Hormones (Athens) 2010;9:274-8.
15. Aono Y, Yamazaki Y, Yasutake J et al. Therapeutic effects of anti-FGF23 antibodies in hypophosphatemic rickets/osteomalacia. J Bone Min Res 2009;24:1879-88.
16. Wohrle S, Henninger C, Bonny O et al. Pharmacological inhibition of FGFR signaling ameliorates FGF23-mediated hypophosphatemic rickets. J Bone Min Res 2013; 28:899-911.
17. Carpenter TO, Imel EA, Ruppe MD et al. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. J Clinical Invest 2014;124:1587-97.
18. Hvid I, Bünger C, Sneppen O et al. Ortopædisk kirurgi. 7 ed. Copenhagen: FADL, 2010:688.