CASE REPORT

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Hereditary Hypophosphatemic Rickets with Hypercalciuria-Importance of Further Evaluation when Clinical Suspicion is Strong

Chathupani Anuradha Wettasinghe, Ishara Minuri Kumarasiri, Mahendralingam Vidushajini, Thabitha Jebaseeli Hoole, Manimel Wadu Akila Nimanthi, Imalka Jayasundara, Reha Balasubramaniam, Navoda Atapattu

Lady Ridgeway Hospital, Clinic of Pediatric Endocrinology, Colombo, Sri Lanka

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ABSTRACT

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare genetic condition with autosomal recessive inheritance and a prevalence of 1 in 250000. It is due to mutation of the *SLC4A3* gene. Correct diagnosis of this condition is important as treatment with active vitamin D metabolites is contraindicated. Evolution of the disease despite initial completely normal biochemistry has been observed, potentially creating diagnostic confusion. The first child presented at the age of 5.5 years with features of rickets. He had an abnormal bone profile with normal vitamin D levels. Urinary phosphate studies were compatible with HHRH. He was treated with phosphate supplementation and potassium citrate. He has well responded well to treatment. The second child initially presented at 1.5 years of age with leg bowing and a family history of hypercalciuria. All investigation findings, including urinary phosphate studies, were within normal limits. At the age of 2.5 years, he again presented with worsening of bowing. Biochemical and urinary investigations were repeated and laboratory findings were now compatible with HHRH. These cases highlight the importance of repeated investigations despite initial normal parameters, if the initial clinical suspicion is strong. Clinical- and investigation-based diagnosis of this rare genetic disease, HHRH, is feasible in resource limited setting.

Keywords: Hereditary hypophosphatemic rickets with hypercalciuria, evolution of investigation findings, clinical diagnosis of the disease

What is already known on this topic?

Hereditary hypophosphatemic rickets with hypercalciuria is a rare genetic disease. Correct diagnosis is essential as vitamin D metabolites which are commonly used in the treatment of rickets is contraindicated in this unique disease.

Corresponding Author: Navoda Atapattu, Lady Ridgeway Hospital, Colombo, Clinic of Pediatric Endocrinology, Colombo, Sri Lanka
E-mail: navodaa@gmail.com **ORCID:** orcid.org/0000-0002-3398-2536
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What this study adds?

This study shows the possibility of evolution of biochemical findings over time despite completely normal initial reports. This report also highlights the role of clinical- and laboratory-based diagnosis in resource limited settings, where genetic diagnosis is not feasible.

Introduction

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH-OMIM: 241530) is a genetic condition with autosomal recessive inheritance (1). It is a rare condition with a prevalence of 1 in 250000 (1). HHRH occurs due to a loss of function mutation in *solute carrier family 34 member 3* (*SLC4A3*) gene located on chromosome 9q34, which encodes a sodium dependent phosphate transporter (NaPi-IIc) that is highly expressed in the proximal tubule of the nephron (2,3). Dysfunction of the transporter results in phosphate wasting. It is a distinct form of hypophosphatemic rickets compared to other types as affected individual present with hypercalciuria (2).

HHRH was first described by Tieder et al. (4) in 1985. Investigators identified consanguineous Bedouin kindreds consisting of six members with hypophosphatemic rickets and hypercalciuria. The condition began in early childhood with short stature, clinical features of rickets and increased renal clearance of phosphate and hypercalciuria. Apart from that these patients had low or low-normal parathyroid hormone (PTH) levels. Supplementation with phosphate resulted in complete resolution of symptoms and biochemical findings except for the maximal tubular reabsorption of phosphate (TRP) to glomerular filtration rate ratio (TmP/GFR).

Twenty-one years after the initial diagnosis of HHRH the genetic abnormality causing the disease was identified by Bergwitz and Miyamoto (2) in 2006. They identified a homozygous single nucleotide deletion (c.228delC) in all individuals affected with HHRH by nucleotide sequencing analysis.

Hypophosphatemia in patients with HHRH causes an appropriate stimulation of renal 1α-hydroxylase leading to increased synthesis of the biologically active vitamin D metabolite 1,25 dihydroxyvitamin D [1,25(OH)2D] (5). Active vitamin D metabolites cause increased intestinal absorption of calcium and reduced PTH-dependent calcium absorption in distal renal tubules resulting in increased urinary calcium excretion.

HHRH usually presents in early childhood with features of rickets, bone pain, skeletal deformities, muscle weakness and short stature (6). It has been reported that HHRH is strongly associated with renal cysts (7).

Diagnosis of the condition depends on several biochemical investigations combined with imaging studies and genetic tests. Biochemical tests may include a fasting bone profile demonstrating low serum phosphate with normal corrected calcium, elevated 1,25 OH vitamin D levels and low or low normal PTH level. Urinary studies will show hypercalciuria with phosphate wasting (inappropriately low Tmp/GFR) in the absence of features of Fanconi syndrome. Imaging studies are likely to provide evidence of rickets with ultrasound (US) scan evidence of nephrocalcinosis or renal stones (8,9).

As there is a marked heterogenicity in clinical spectrum of HHRH and investigation findings may evolve with time, periodic close follow-up is mandatory in this unique disease. Here in we describe patients from two different kindreds reflecting the diversity of clinical presentation in HHRH.

Clinical Presentation

Patient 1

A five years eight months old boy presented with leg bowing. He was the first born to non-consanguineous, healthy parents with two healthy younger siblings. His past history was unremarkable. He had no clinical features of malabsorption. On examination, there was widening of wrists and bilateral genu valgum deformity, suggestive of a clinical diagnosis of rickets.

Imaging studies also revealed evidence of rickets. Initial biochemical results are depicted in Table 1 which shows normal biochemical findings with the exception of elevated alkaline phosphatase (ALP).

During follow-up investigations he had both normal and low serum phosphate values. Due to normal vitamin D level, persistently elevated ALP level and intermittent subnormal serum phosphate levels, he underwent urinary phosphate and calcium studies. Results are depicted in Table 2. These investigations showed hypophosphatemia, renal phosphate wasting and hypercalciuria.

US of kidney, ureter and bladder revealed bilateral grade II-III medullary nephrocalcinosis, mild hydronephrosis and proximal hydroureter on the left side, a 3.2 mm size calculus within the left sided pelvicalyceal system and bilateral simple renal cysts. He was started on phosphate buffer due to unavailability of phosphate tablets at that time. Hydrochlorothiazide and potassium citrate were also added. With treatment his ALP and serum phosphate levels became normal, rickettsial changes resolved on X-rays and bowing of legs completely resolved.

Table 1. Initial biochemical findings of Patient 1

Test	Value	Reference range
Corrected Calcium (mmol/L)	2.22	2.2-2.7
ALP (U/L)	650	60-425
Serum phosphate (mmol/L)	1.27	1.25-2.1
Serum creatinine (umol/L)	51	26-62
Vitamin D (nmol/L)	63	>50 sufficient
PTH (pmol/L)	2.42	1.54-7.2

ALP: alkaline phosphatase; PTH: parathyroid hormone

Table 2. Follow-up results of Patient 1

Test	Value	Reference range
Serum phosphate (mmol/L)	0.86	1.25-2.1
Urine phosphate creatinine ratio (mmol/mmol)	7.54	1.2-12
TRPO4 (%)	68%	>90%
TmPGFR (mmol/L)	0.8	1.15-2.6
Urine calcium creatinine ratio (mmol/mmol)	1.92	0.07-1.5

Currently, he is 10 years and 1 month old and the bowing of legs has completely disappeared with no progression of medullary nephrocalcinosis or calculi. The renal functions are within normal limits. He is on phosphate supplements and potassium citrate with good compliance. He is studying in grade 5 with good scholastic skills.

Patient 2

The second case presented was a 2 year 6-month-old boy who presented with bowing (mild genu valgum deformity) who had completely normal investigation findings one year earlier. However, due to the worsening clinical features and a high degree of clinical suspicion, he was re-evaluated and found to have abnormal investigation findings one year after the initial presentation. This underlines the importance of a combination of high degree of clinical suspicion triggering periodic re-evaluation, despite completely normal initial biochemical findings.

He initially presented to our unit at the age of one year six months with bilateral bowing of the legs. He was the first of dizygotic twins, born at term with a birth weight of 2.37 kg to second degree consanguineous parents with a healthy elder sister and a twin sister. Antenatal and post-natal periods were unremarkable. He was on formula and breast milk from the second week of life. Weaning started from 5 months of age and his diet was rich in calcium and vitamin D-containing food. There was no history of convulsions or tetany. He exhibited no features to suggest malabsorption. There was a family history of hypophosphatemia with hypercalciuria in two of paternal cousins, a boy and a girl, neither of whom were evaluated. The pedigree chart is shown in Figure 1.

This boy was extensively investigated during the admission, including urinary phosphate studies, urinary calcium excretion, intact PTH levels and all were within normal limits.

Results are depicted in Table 3. X-ray examinations did not show any evidence of rickets and US of kidney, ureter, and bladder was normal. He was followed up at a local hospital with a healthy diet rich in calcium and vitamin D. One year later he was referred to our unit due to worsening of bowing and cloudy urine. Due to the high degree of clinical suspicion, he was re-evaluated. These results are also depicted in Table 4. Repeat investigations revealed hypercalciuria, hypophosphatemia, renal phosphate wasting with a TmpGFR of 0.92, compatible with a diagnosis of HHRH. He was started on oral phosphate and potassium citrate and is being followed up at our clinic routinely.

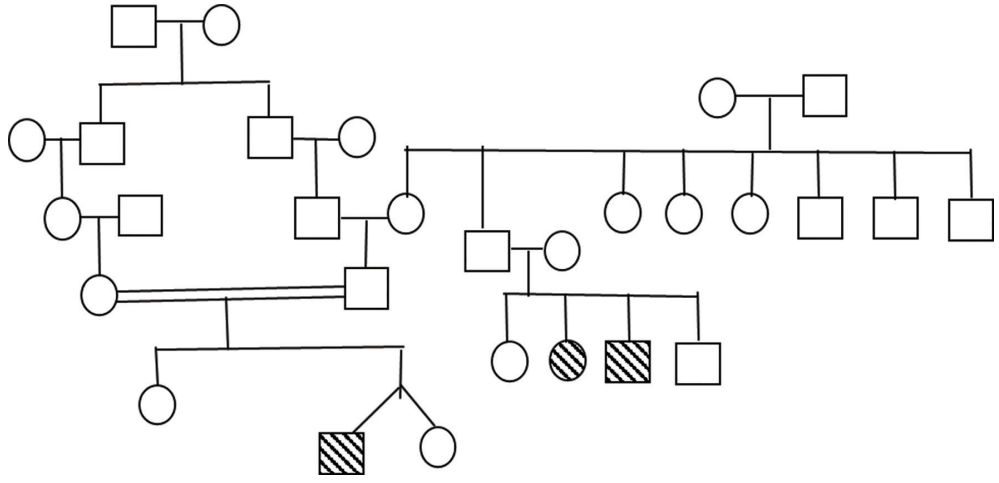

Figure 1. Pedigree chart of case 2 patients

Discussion

Correct diagnosis of HHRH is important due to the unique nature of treatment modalities, but may be challenging because of initial phenotypic variability. This heterogenicity may vary from full-blown HHRH at the most severe to asymptomatic idiopathic hypercalciuria in the other. According to Tieder et al. (4), the magnitude of the hypophosphatemia which regulates active vitamin D levels appeared to determine which subjects would have hypercalciuria combined with bone disease.

Table 3. Initial evaluation of Patient 2

Test	Value	Reference range
Corrected calcium (mmol/L)	2.52	2.2-2.45
Serum phosphate (mmol/L)	1.46	1.25-2.1
ALP (U/L)	416	60-425
Serum creatinine (umol/L)	21	26-62
Serum sodium (mmol/L)	137	135-145
Serum potassium (mmol/L)	5.1	3 5-5.5
Urine phosphate: creatinine ratio (mmol/mmol)	5.5	1.2-12
TRPO4 (%)	92.04%	>90%
TmpGFR (mmol/L)	1.53	1.15-2.6
Urine calcium: creatinine ratio (mmol/mmol)	0.85	0.07-1.5
PTH (pmol/L)	1.0	1.54-7.2
Vitamin D (nmol/L)	60	>50 Sufficient

ALP: alkaline phosphatase; PTH: parathyroid hormone

Table 4. Follow-up results in Patient 2

Test	Value	Reference range
Corrected calcium (mmol/L)	2.5	2.2-2.7
Serum phosphate (mmol/L)	1.08	1.25-2.1
ALP (U/L)	446	60-425
Serum creatinine (umol/L)	28	26-62
Serum sodium (mmol/L)	137	135-145
Serum potassium (mmol/L)	4.5	3.5-5.5
Urine phosphate: creatinine ratio (mmol/mmol)	5.68	1.2-12
TRPO4 (%)	85%	>90%
TmpGFR (mmol/L)	0.92	1.15-2.6
Urine calcium: creatinine ratio (mmol/mmol)	1.8	0.07-1.5
Urine magnesium: creatinine ratio (mmol/mmol)	0.59	0.3-1.6
PTH (pmol/L)	0.77	1.54-7.2
Vitamin D (nmol/L)	55.5	>50 Sufficient

ALP: alkaline phosphatase; PTH: parathyroid hormone

Zhu et al. (3) reported that compound heterozygous/homozygous carriers showed >90% penetrance for kidney and bone phenotypes. The biochemical phenotype for heterozygous carriers was intermediate, with decreased serum phosphate, TRP%, fibroblast growth factor 23 and intact PTH, but increased serum 1,25-dihydroxyvitamin D and urine calcium excretion, causing idiopathic hypercalciuria in 38%, with bone phenotypes observed in 23% of patients. Some heterozygous NaPi-IIc mutations have been associated with isolated hypercalciuria which may increase the risk of nephrocalcinosis (3).

Patients may initially present with normal laboratory investigations with a mild degree of rickets symptoms, as in Patient 2. These patients, when undergoing periodic evaluation, may develop biochemical evidence of HHRH. A rare case of initially normal biochemical findings, later manifesting as abnormal laboratory values compatible with HHRH was reported by Karakilic-Ozturan et al. (10). These authors described two siblings with a similar condition. The first sibling was a sixteen year old boy with severe deformity of lower limbs and recurrent fractures. His lower limb X-rays did not suggest rickets but his biochemical profile revealed low phosphate, high ALP, and hypercalciuria with low TRP. Renal US suggested bilateral renal calculi. He has underwent genetic analysis, revealing *SLC34A3* homozygous mutation. As his younger sibling had mild genu valgum deformity with bone pain, she underwent biochemical investigation and genetic analysis. In her case, biochemistry revealed phosphate in the lower region of normal with elevated ALP but without hypercalciuria. TRP was normal at that time. There were no X-ray changes suggestive of rickets in her lower limbs. However, her genetic analysis also showed she harbored a homozygous *SLC34A3* mutation.

Due to the expected risk of developing the full clinical spectrum of HHRH she was periodically followed up in clinic. Two and half years after initial presentation, she developed hypophosphatemia and reduced TRP and was started on phosphate supplementation. This was the first case history reflecting the evolution of clinical and biochemical changes over time, despite initial normal biochemical parameters. These authors proposed that the phenotypic variation in HHRH may be due to genetic and epigenetic factors. The clinical sequence and biochemical progression of the younger sibling is very similar to the progression seen in Patient 2 in the present report.

Unfortunately, as a developing country with economic constraints, genetic testing is not available for our patients. Close clinical follow-up and timely re evaluation enabled us to diagnose these two patients with HHRH.

Treatment of HHRH includes phosphate supplementation which is the main stay of treatment. Clinical features of rickets improve rapidly with phosphate supplementation and hypercalciuria resolves as FGF 23 levels increase. Activated vitamin D analogues are contraindicated in HHRH because they compound the effect of excess endogenous 1,25 vitamin D in hypercalciuria. There is a lack of long-term data to determine whether oral phosphate supplementation alone is sufficient to prevent renal calcification and bone loss. The monitoring frequency and biochemical parameters are also not well established (1).

Conclusion

HHRH is due to genetic mutation in *SLC34A3* gene mutation causing variable clinical presentations ranging from completely asymptomatic, isolated hypercalciuria with or without nephrocalcinosis or nephrolithiasis and HHRH causing rickets and related sequelae HHRH is diagnosed by clinical history, examination, biochemical and imaging findings, while specific genetic mutational analyses, where available, are used to confirm the diagnosis. However, HHRH may present a diagnostic challenge due to the phenotypic variability and completely normal initial investigations, as in Patient 2, although findings later progressed to those suggestive of HHRH. This case report highlights the importance of periodic monitoring of biochemical parameters despite completely normal initial biochemistry, if the clinical suspicion is high. These two cases also provide a description of the diagnosis of HHRH using clinical presentation and laboratory parameters in a resource limited setting.

Ethics

Informed Consent: Written informed consent was obtained from the patients' parents.

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Footnotes

Authorship Contributions: Concept: Chathupani Anuradha Wettasinghe, Ishara Minuri Kumarasiri, Navoda Atapattu, Design: Chathupani Anuradha Wettasinghe, Reha Balasubramaniam, Manimel Wadu Akila Nimanthi, Navoda Atapattu, Data Collection or Processing: Chathupani Anuradha Wettasinghe, Mahendralingam Vidushajini, Thabitha Jebaseeli Hoole, Imalka Jayasundara, Navoda Atapattu, Analysis or Interpretation: Chathupani Anuradha Wettasinghe, Ishara Minuri Kumarasiri, Navoda Atapattu, Literature Search: Chathupani Anuradha Wettasinghe, Ishara Minuri Kumarasiri, Mahendralingam Vidushajini, Thabitha Jebaseeli Hoole, Manimel Wadu Akila Nimanthi, Imalka Jayasundara, Reha Balasubramaniam, Navoda Atapattu, Writing: Chathupani Anuradha Wettasinghe, Navoda Atapattu.

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