10.4274/jcrpe.galenos.2025.2025-1-15

Case Report

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

Wettasinghe CA et al. Hereditary Hypophosphatemic Rickets with Hypercalciuria – Need of Periodic Evaluation

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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 treatment for rickets is contraindicated in this unique disease.

What this study adds?
This study shows the possibility of evolution of bio chemical findings with time despite completely normal initial reports.
It also highlight the place for clinical and laboratory based diagnosis in resource limited setting, where genetic diagnosis is not feasible.

Abstract
Hereditaryhypophosphatemic rickets with hypercalciuria (HHRH) is a rare genetic condition with Autosomal recessive inheritance with a prevalence of 1 in 250000. It is due to mutation in SLC4A3 gene. Correct diagnosis of this condition is important as treatment with active vitamin D metabolites are contraindicated. Evolution of the disease despite initial completely normal bio chemistry has ben observed causing diagnostic confusion. First child presented at the age of 5.5 year with features of rickets. He had 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 to the treatment. Second child initially presented at 1.5 years of age with bowing and family history of hypercalciuria. All investigation findings including urinary phosphate studies were within normal limits. At the age of 2.5 year, he again presented with worsening of bowing. Bio chemical and urinary investigations were repeated. Laboratory findings were compatible with HHRH. It highlights the importance of repeated investigations despite initial normal parameters if the initial clinical suspicion is strong and clinical and investigation based diagnosis of this rare genetic disease in resource limited setting.
Keywords: Hereditary hypophosphatemic rickets with hypercalciuria, evolution of investigation findings, clinical diagnosis of the disease

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21.02.2025
26.06.2025

Epub: 18.08.2025

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) It occurs due to a loss of function mutation in solute carrier family 34 member 3, SLC4A3 located in chromosome 9q34, which encodes a sodium dependent phosphate transporter (NaPi-IIc) which 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).
It was first described by Tieder et al in 1985. Investigators have identified consanguineous Bedouin kindreds consisting of 6 members with hypophosphatemic rickets and hypercalciuria. It 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 elevated serum reduced parathyroid hormone levels. Supplementation with phosphate resulted in complete resolution of symptoms and biochemical findings except TmP/GFR (maximal tubular reabsorption of phosphate to glomerular filtration rate ratio) (4)
Twenty-one years after the initial diagnosis of Hereditary hypophosphatemic rickets with hypercalciuria the genetic abnormality causing the disease was identified by Bergwitz et al in 2006. They identified a homozygous single – nucleotide deletion (c.228delC) in all individuals affected with Hereditary hypophosphatemic rickets with hypercalciuria by nucleotide sequencing analysis (2).
Hypophosphatemia in patients with HHRH cause an appropriate stimulation of renal 1α- hydroxylase leading to increased synthesis of the biologically active vitamin D metabolite 1,25dihydroxyvitamin D (1,25(OH)2D) (5). Active vitamin D metabolite cause increased intestinal absorption of calcium and reduced PTH dependent calcium absorption in distal renal tubule resulting in increased urinary calcium excretion.
It usually presents in early childhood with features of rickets, bone pain, skeletal deformities, muscle weakness and short stature (6). According to Hanna et al Hereditary hypophosphatemic rickets 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 include a fasting bone profile demonstrating low serum phosphate with normal corrected calcium, elevated 1, 25 OH vitamin D levels and suppressed PTH level, urinary studies confirming hypercalciuria with phosphate wasting (inappropriately low Tmp/GFR) in the absence of features of Fanconi syndrome. Imaging studies revealing evidence of rickets with ultrasound 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.
hypercalciuria.
Here in we describe patients from two different kindred reflecting the diversity of clinical presentation in Hereditary hypophosphatemic rickets with hypercalciuria.

Clinical Presentation

Case 1

A five years eight months old boy presented with bowing. He was the first born to non-consanguineous healthy parents with two healthy younger siblings. His past `history was unremarkable. He didn't have clinical features of malabsorption. On examination, he has widening of wrists as well as bilateral genu valgum deformity suggestive of a clinical diagnosis of rickets.
Imaging studies revealed evidence of rickets. Initial biochemical evaluation is depicted in the Table 1. It shows normal biochemical findings except elevated ALP.
During follow up investigations he had normal serum phosphate values as well as low serum phosphate values. Due to normal vitamin D level and persistently elevated ALP level and on and off subnormal serum phosphate levels he underwent urinary phosphate and calcium studies. Results are depicted in Table 2. It shows hypophosphatemia, renal phosphate wasting and hypercalciuria.
USS Kidney ureter bladder revealed bilateral grade II-III medullary nephrocalcinosis, mild hydro nephrosis and proximal hydroureter in the left side, a 3.2mm size calculi 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, rickets changes disappeared on X-rays and bowing of legs completely resolved.
Currently, he is 10 years 1 month old and the bowing of legs has completely disappeared with no progression of medullary nephrocalcinosis and 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.

Case 2

Here in we report a 2 year 6-month-old boy who presented with bowing (mild genu valgum deformity) who had completely normal investigation findings one year ago and due to the worsening clinical features and high degree of clinical suspicion reevaluated and found to have abnormal investigation findings one year after the initial presentation.
This reflects the importance of high degree of clinical suspicion and periodic re-evaluation despite completely normal initial biochemical findings.
He initially presented to our unit at the age of one year six months with bi lateral bowing. He was the first of dizygotic twins, born at term with a birth weight of 2.37kg 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 since 5 month of age and diet was rich in calcium and vitamin D containing food. There was no history of convulsions or tetany. No features to suggest malabsorption. There is a family history of hypophosphatemia with hypercalciuria in two of the paternal side cousins, a boy and a girl. Pedigree chart – (Annexure 1).Neither of whom were evaluated.
Child 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 the Table 3 (Initial evaluation of patient described as case 2). It shows normal values in biochemical evaluation including urinary phosphate studies. X rays didn't show any evidence of rickets and ultrasound kidney, ureter, bladder was normal. He was followed up at a local hospital with healthy diet rich in calcium and vitamin D as for any growing child.
One year later in 2024, 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. Results are depicted in table 3(One year after initial presentation of the patient described as case 2) Repeat investigations revealed hypercalciuria, hypophosphatemia, renal phosphate wasting (TmpGFR 0.92) compatible with the diagnosis of Hereditary hypophosphatemic rickets with hypercalciuria.
He was started on oral phosphate and potassium citrate and is being followed up at our clinic routinely.

Discussion

Correct diagnosis of HHRH is very important due to variability in clinical presentation as well as unique nature of treatment modalities.
HHRH has phenotypic heterogenicity varying from hereditary hypophosphatemic rickets with hypercalciuria at the extreme end to asymptomatic idiopathic hypercalciuria in the other. According to Tider et al in 1987, it was identified that the magnitude of the hypophosphatemia which regulates active vitamin D levels appear to determine which subjects will have hypercalciuria combined with bone disease (4)
According to Zewu zhu et al in 2024 may, compound heterozygous/ homozygous carriers show above 90% penetrance for kidney and bone phenotypes. The biochemical phenotype for heterozygous carriers is intermediate, with decreased serum phosphate, tubular reabsorption of phosphate (TRP%), fibroblast growth factor 23 and intact parathyroid hormone, but increased serum 1,25- dihydroxy vitamin D and urine calcium excretion causing idiopathic hypercalciuria in 38%, with bone phenotypes still observed in 23% of patients. Some heterozygous NaPi-IIc mutations are frequently associated with isolated hypercalciuraia which increase the risk of nephrocalcinosis (3)
Patients can initially present with normal laboratory investigations with mild degree of rickets symptoms. These patients, with periodic evaluation, reveal bio chemical evidence of hereditary hypophosphatemic rickets with hypercalciuria. A rare case of initially normal bio chemical findings later manifesting as abnormal laboratory values compatible with hereditary hypophosphatemic rickets with hypercalciuria has been observed in a one study by Karakilic – Ozturan et al (10)
They have described two siblings with a similar condition. First sibling is a sixteen year old boy with severe deformity of lower limbs and recurrent fractures. His lower limb X- rays didn't show features of rickets but his bio chemical profile revealed low phosphate, high ALP, hypercalciuria with low tubular reabsorption of phosphate with ultra sound scan evidence of bi lateral renal calculi. He has underwent genetic analysis revealing SLC34A3 homozygous mutation. As his younger sibling had mild genu valgum deformity with bone pain she was further evaluated including bio chemical studies as well as genetic analysis. Bio chemical evaluation revealed phosphate in lower margin of normal with elevated ALP but without hypercalciuria. Tubular reabsorption of phosphate was normal at that time. There were no X ray changes of rickets in lower limbs. Her genetic analysis also revealed SLC34A3 homozygous mutation.
Due to the expected risk of developing full clinical spectrum of hypophosphatemic rickets with hypercalciuria she was periodically followed up in the clinic. Two and half years after the initial presentation, she developed hypophosphatemia and reduced tubular reabsorption of phosphate and started on phosphate supplementation. This was the only case history reflecting the evolution of clinical and bio chemical changes with time despite initial normal bio chemical parameters. According to authors this phenotypic variation can be due to genetic and epi genetic factors. The clinical sequence and biochemical progression of the younger sibling is exactly similar to the progression seen in our second patient.
Unfortunately as a developing country with economic constrains we don't have the facilities to arrange genetic testing in our patients. Close

clinical follow up and timely re evaluation have enabled us to diagnose the 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 hypophosphatemic rickets with hypercalciuria causing rickets and related squeal.
It is diagnosed by clinical history, examination, biochemical and imaging findings while specific genetic mutational analyses are used as diagnostic test
It can cause diagnostic dilemma due to the phenotypic variability and completely normal initial investigation findings later progressing to Hereditary hypophosphatemic rickets with hypercalciuria.
This case report highlights the importance of periodic monitoring of biochemical parameters despite completely normal initial biochemistry if the clinical suspicion is high.
Apart from that our two cases provide an example about the diagnosis of Hereditary hypophosphatemic rickets with hypercalciuria using clinical presentation and laboratory parameters in a resource limited setting.

Authorship Contribution

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Disclosure

No funding was received in the publication of this article.

Conflicts of interest

The authors report no conflicts of interest.

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Table 1. Initial biochemical findings of patient described in case 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

Table 2.Follow up investigation findings of patient described in case 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

Table 3 .Initial evaluation of patient described as case 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)	9.4	7.5- 53.1
Vitamin D (ng/ml)	24	20-40

Table 4 .Follow up investigation findings of the patient described as case 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)	7.3	7.5- 53.1
Vitamin D (ng/ml)	22.2	20-40
USS KUB	No nephrocalcinosis. Normal study	

Annexure 1 -Pedigree chart of case 2 patients