



Case Report

Growth hormone therapy in HHRH[☆]

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ABSTRACT

Background: Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) (*SLC34A3* gene, OMIM 241530) is an autosomal recessive disorder that results in a loss of function of the sodium-phosphate NPT2c channel at the proximal tubule. Phosphate supplementation rarely improves serum phosphate, hypercalciuria, nephrocalcinosis, 1,25(OH)₂ vitamin D (1,25(OH)₂D) levels or short stature.

Methods: We describe ²³Na MRI and the successful use of recombinant human growth hormone (rhGH) and Fluconazole to improve growth (possibly confounded by puberty) and hypercalciuria in a now 12-year-old male with HHRH (novel homozygous *SLC34A3* mutation, c.835_846 + 10del.T).

Results: The patient had chronic bone pain, hypophosphatemia (0.65 mmol/L [reference interval 1.1–1.9]), pathological fractures and medullary nephrocalcinosis/hypercalciuria (urinary calcium/creatinine ratio 1.66 mol/mmol [<0.6]). TmP/GFR was 0.65 mmol/L [0.97–1.64]; 1,25(OH)₂D was >480 pmol/L [60–208]. Rickets Severity Score was 4. Treatment with 65 mg/kg/day of sodium phosphate and potassium citrate 10 mmol TID failed to correct the abnormalities.

Adding rhGH at 0.35 mg/kg/week to the phosphate therapy, improved bone pain, height z-score from -2.09 to -1.42 over 6 months, without a sustained effect on TmP/GFR. Fluconazole was titrated to 100 mg once daily, resulting for the first time in a reduction of the 1,25(OH)₂D to 462 and 426 pmol/L; serum phosphate 0.87 mmol/L, and calcium/creatinine ratio of 0.73.

²³Na MRI showed normal skin (z-score + 0.68) and triceps surae muscle (z-score + 1.5) Na⁺ levels; despite a defect in a sodium transporter, hence providing a rationale for a low sodium diet to improve hypercalciuria.

Conclusions: The addition of rhGH, Fluconazole and salt restriction to phosphate/potassium supplementation improved the conventional therapy. Larger studies are needed to confirm our findings.

Keypoints

What is known about this subject: Hereditary Hypophosphatemic rickets with Hypercalciuria (HHRH) is a rare autosomal recessive disorder that affects the *SLC34A3* gene, resulting in a loss of function of the NPT2c channel (type IIc sodium phosphate cotransporter) in the proximal tubule. A key feature of this condition is a substantially elevated

1,25(OH)₂ vitamin D level. Currently, the only therapy is phosphate supplementation which rarely normalizes serum phosphate, 1,25(OH)₂ vitamin D levels or the short stature. Potassium citrate is used to reduce the hypercalciuria, but rarely prevents the progressive nephrocalcinosis.

What this study adds: We describe the successful use of recombinant human growth hormone (rhGH), in a male with HHRH due to homozygosity of a novel *SLC34A3* mutation (c.835_846 + 10del.T)

[☆] A case of hypophosphatemic rickets with hypercalciuria (HHRH): response to therapy with rhGH and fluconazole.

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inherited from consanguineous parents, based on a previous case report. This patient had chronic bone pain, hypophosphatemia, pathological fractures and medullary nephrocalcinosis due to substantial hypercalciuria. Treatment with copious amounts of sodium phosphate (up to 65 mg/kg/day) resulted in intermittent diarrhea, and failed to correct the hypophosphatemia, high 1,25(OH)₂ vitamin D levels or the short stature. In an effort to help this patient and based on a previous report (Dreimane et al., 2020), rhGH was added to the phosphate therapy at a dose of 0.35 mg/kg/week. The treatment was safe and without side effects (no hyperglycemia, hyperlipidemia or worsening of joint pain), but while bone pain and catch-up growth improved, rhGH only normalized serum phosphate and TmP/GFR for a short-term and the elevated 1,25(OH)₂ vitamin D levels remained unchanged. The addition of Fluconazole, as suggested by Bertholet-Thomas et al. (2019), at 100 mg once daily was prescribed to inhibit the 1-alpha-hydroxylase, reduced the 1,25(OH)₂ vitamin D levels and hypercalciuria to almost normal levels.

Even though this tubulopathy affects a sodium transporter thought to be due to compensatory increase of the sodium hydrogen antiporter 3 (NHE3) activity (presumed to be the most important sodium transporter in the proximal tubule), sodium-23 (²³Na) Magnetic Resonance Imaging (MRI) did not demonstrate reduced skin and muscle sodium after starting sodium phosphate therapy. Insulin, growth hormone and insulin-like growth factor 1 regulate the expression of NPT2a and NPT2c through unknown mechanisms. While we do not have biopsy evidence, we postulate that NPT1c became upregulated, in part compensating for the NPT2c deficiency as IGF-1 stimulate the Na/Pi cotransport in OK cells (Jehle et al., 1998). Our case study suggests the combination of sodium phosphate supplementation, rhGH, Fluconazole and salt restriction in patients with HHRH due to *SCL34A3* mutations.

1. Introduction

Hereditary hypophosphatemia rickets with hypercalciuria (HHRH, OMIM: 241530) is a rare autosomal recessive disorder with an estimated prevalence of 1/250,000 due to loss of function mutation of the *SCL34A3* gene, resulting in a defect sodium-phosphate co-transporter NPT2c (Bergwitz and Miyamoto, 2019). This condition presents with urinary phosphate wasting, hypophosphatemic rickets, bowing, short stature, as well as elevated 1,25(OH)₂D levels; setting this fibroblast growth factor 23 (FGF23)-independent disorder apart from the more common X-linked hypophosphatemia (XLH, OMIM: 307800, caused by mutations of the *PHEX* gene), or autosomal dominant hypophosphatemic rickets (ADHR, OMIM: 193100, caused by mutations of the *FGF23* gene). As a matter of fact if measured, FGF23 levels are appropriately suppressed in HHRH (Colazo et al., 2020). Renal sodium wasting and high 1,25(OH)₂D levels cause hypercalciuria and nephrocalcinosis (Bergwitz and Miyamoto, 2019), which should trigger a referral to a pediatric nephrologist. Despite that, the journal *Pediatric Nephrology* has only one published HHRH case report (Vargas-Poussou et al., 2008).

The treatment of HHRH consists of monotherapy with oral phosphate supplements, while active vitamin D analogs are contraindicated (Bergwitz and Miyamoto, 2019). Unfortunately, there are no long-term studies to show whether the phosphate supplementation can ameliorate the bone changes or prevent the progression of the nephrocalcinosis. Also, phosphate supplementation alone does not alter the histological changes, normalize the serum phosphate, nor does it seem to overcome the growth failure in many cases (Colazo et al., 2020). Milder mutations may result in some catch-up growth with phosphate supplementation in select cases, but the results are inconsistent, and diarrhea is a major limiting factor for this treatment (Bergwitz and Miyamoto, 2019; Yu et al., 2012). The use of potassium citrate has also not been evaluated systematically (Dasgupta et al., 2014).

Recently, recombinant human growth hormone (rhGH) was reported as additional therapy for the short stature in one patient with HHRH

(Dreimane et al., 2020). In that case report, there was also a description of improved serum phosphate but the mechanism was not explained, no long-term data were provided, and the elevated 1,25(OH)₂D levels were not altered by rhGH therapy alone (Dreimane et al., 2020). In 2019, Bertholet-Thomas et al. proposed the use of Fluconazole, an inhibitor of 1 α -hydroxylase, as a therapeutic tool to manage patients with *SLC34A3* mutations (Bertholet-Thomas et al., 2019). We describe the successful and safe use of rhGH (at a dose of 0.3 mg/kg/week) in combination with Fluconazole (100 mg once daily, 2.7 mg/kg) and its impact on bone pain, tubular phosphate wasting, hypercalciuria and short stature in a prepubertal male with HHRH who did not respond to, nor tolerated oral phosphate supplementation well.

2. Case report

2.1. History and initial presentation

A 9-year-old male presented in May of 2017 after immigration from the Middle East and 4 years of refugee camp in Lebanon with chronic pain in hips, knees, ankles and a history of fluid in his right knee. Initial x-rays demonstrated general osteopenia, focal areas of linear increased sclerosis of femoral and proximal tibial metaphysis with areas of subchondral lucency. The diagnosis of rickets was made. He sustained fractures of the forearm and the femur. A provider in the community treated him with 2000 units of oral vitamin D3 once daily and repeated the x-rays one year later, showing worsening of the rickets severity score of 4 (Thacher et al., 2000). A renal ultrasound demonstrated bilateral medullary nephrocalcinosis. This resulted in a referral to endocrinology and nephrology.

Birth history and past medical history were unremarkable. The family history revealed that the parents were second degree cousins. The boy had 6 siblings aged 5 months to 13 years. One infant died for unknown reasons. The other siblings are all healthy. The family members were of normal height, and his younger brother whom we assessed to rule out the same disorder was on the 53rd percentile. His mother was 165 cm (61st percentile WHO) and his father was 172 cm (29th percentile WHO). While this patient's target final height would be 175 cm (44th percentile), he was at the <3rd height percentile with a z-score of -1.91. His bone age was not delayed at 9 years \pm 9.3 months (chronological age of 9 years, 7 months). His weight was at the 10th percentile and his blood pressure was normal at 111/63 mmHg. Physical exam revealed mild double contours of medial knees, but no bowing of the femur or the tibiae, and was otherwise unremarkable. Laboratory findings at initial visit are given in Table 1.

Table 1
Laboratory findings at presentation.

Parameter	Value	Unit	Reference interval
Age	9	Years	n/a
Calcium	2.41	mmol/L	2.30–2.69
Magnesium	0.84	mmol/L	0.80–1.50
Serum albumin	41	g/L	36–47
Alkaline Phosphatase	1075	U/L	142–335
Phosphate	0.79	mmol/L	1.22–2.00
Microalbumin/creatinine ratio	2.9	mmol/mmol	0.0–1.9
Luteinizing Hormone	0.55	iU/L	<1.3 for Tanner stage I
Follicle stimulating Hormone	1.0	iU/L	0.3–3.1 for Tanner stage I
Testosterone	<0.4	nmol/L	<0.4 for Tanner stage I
IGF-1	295	ug/L	23–386
24-h urine calcium	10.93	mmol/d	2.50–7.50
24-h urine phosphate	25.6	mmol/D	
TRP	77	%	85–95
TmP/GFR	0.65	mmol/L	0.97–1.64
iPTH	4.2	pmol/L	1.6–6.9
25(OH) vitamin D	61	nmol/L	75–250
1,25(OH) ₂ vitamin D	>480	pmol/L	60–208

2.2. Management

The diagnosis of HHRH was made and treatment was initiated with 30 mg/kg of elemental phosphate and slowly increased to a maximum of 65 mg/kg/day. Treatment with active vitamin D is contraindicated in the condition, so it was stopped. He was started on 10 mmol of oral potassium citrate three times daily to form chelate complexes with calcium and the patient developed diarrhea. Hydrochlorothiazide was not considered as the presence of a sodium phosphate cotransporter could lead to profound sodium wasting. His serum phosphate did not improve, nor did his TmP/GFR (Brodehl, 1994). Unfortunately, his height z-score dropped as low as -2.09 and did not respond to the oral phosphate treatment (Fig. 1). Growth hormone stimulation tests (Clonidine and L-Arginine) ruled out growth hormone deficiency, for instance, growth hormone levels increased to $16.3 \mu\text{g/L}$ on clonidine stimulation test. We started compassionate growth hormone therapy as suggested by Dreimane et al. (2020) Only after 6 months of receiving rhGH at 0.3 mg/kg/week , he achieved a catch-up growth to a z-score of -1.42 . His growth velocity improved from 3.12 cm/year pre-therapy, to 6.92 cm/year after starting phosphate supplementation and it further increased to 14.1 cm/year on rhGH. However, the patient also turned stage II Tanner.

Not unexpectedly, rhGH treatment did not alter the $1,25(\text{OH})_2\text{D}$ level and the improvement of the serum phosphate was short-lived. Because hypercalciuria and $1,25(\text{OH})_2\text{D}$ remained unchanged, and the phosphate dropped to 0.53 mmol/L , we started Fluconazole at 50 mg once daily, based on the report by Bertholet-Thomas et al. (2019), resulting in a reduction of the $1,25(\text{OH})_2\text{D}$ (which could be quantitated for the first time) to 462 pmol/L , and a slight increase in phosphate to 0.65 mmol/L . Increasing Fluconazole to 100 mg once daily, further decreased the $1,25(\text{OH})_2\text{D}$ level to 426 pmol/L and the hypercalciuria almost normalized with a calcium/creatinine ratio of 0.73 mmol/mmol [normal <0.6]. At the last follow up, his serum phosphate improved to

0.87 mmol/L . The evolution of the laboratory parameters and height z-score are depicted in Fig. 1.

2.3. Genetic studies

Genetic testing identified that the patient is homozygous for a pathogenic variant in *SLC34A3*, denoted c.835_846 + 10del.T. Previously, a mutation affecting a similar region of the genome, c. 846G > A, had been described (Lorenz-Depiereux et al., 2006). The findings suggested that this silent mutation in exon 8 could lead to aberrant splicing (Lorenz-Depiereux et al., 2006). Since our patient had a mutation in the same region, resulting aberrant splicing in the *SLC34A3* gene was likely to cause HHRH. This unusual splicing may result in the loss of a transport domain vital for the protein's cotransport function (Fig. 2). The patient's mutation affects a hydrophilic region of the gene (Bergwitz and Miyamoto, 2019). The loop occurs between a scaffold and transport domain, therefore deleting amino acids could affect the protein's function (Fig. 2).

2.4. $^{23}\text{Sodium}$ MRI study

Since the homozygous *SLC34A3* mutation (c.835_846 + 10del.T) in our patient resulted in reduced or non-functioning sodium phosphate cotransporter activity, which could lead to sodium wasting, we wanted to investigate the sodium levels in skin and muscle and performed a $^{23}\text{Sodium}$ MRI study (Filler et al., 2021a; Filler et al., 2021b). The $^{23}\text{Sodium}$ MRI study took place while our patient was on sodium phosphate supplements, but before the addition of rhGH and Fluconazole. In contrast to our hypothesis about sodium wasting, the $^{23}\text{Sodium}$ MRI was normal and did not reveal evidence of reduced whole leg, skin or muscle sodium content, compared to healthy age-matched controls (Fig. 3) (Sarleno et al., 2022). We hypothesize that due to compensatory increase of the sodium hydrogen antiporter 3 (NHE3) activity, normal

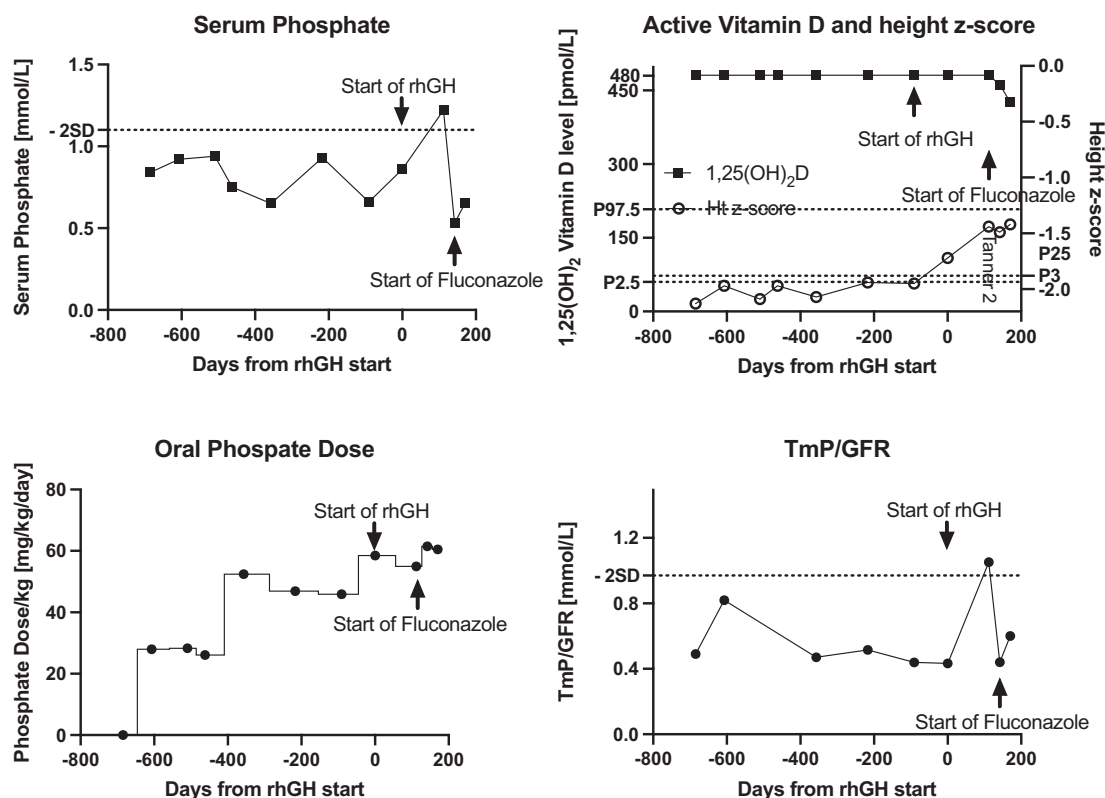


Fig. 1. (black and white): Evolution of serum phosphate, $1,25(\text{OH})_2$ vitamin D, height z-score, oral phosphate dose and TmP/GFR in relationship to the initiation of the therapy with recombinant growth hormone.

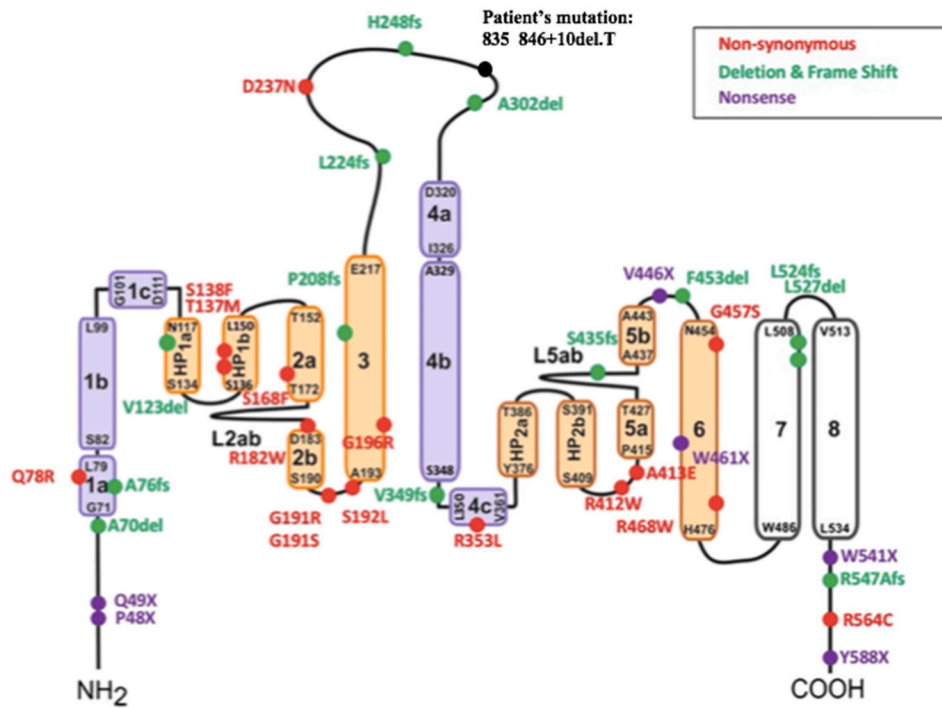


Fig. 2. (color). HHRH mutation map with novel patient mutation. Figure adapted from Bergwitz and Miyamoto, 2018 (Bergwitz and Miyamoto, 2019; Dasgupta et al., 2014), represents mutations in SLC34A3 gene resulting in HHRH. The patient's novel mutation is represented by a black circle in the loop region of intron 8. The orange boxes represent a transport domain whereas the purple boxes represent a scaffold domain.

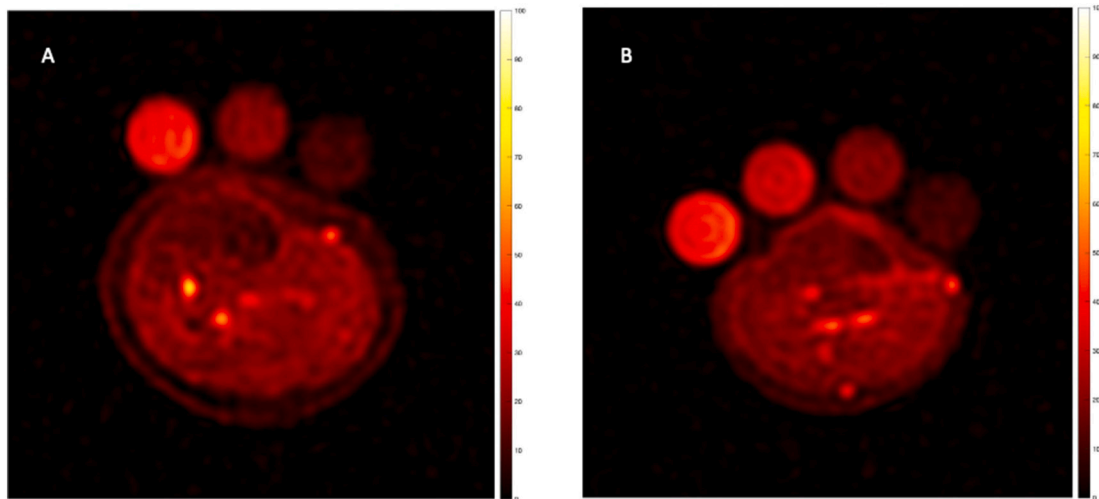


Fig. 3. (color): ²³Na MRI of the leg in a healthy 11-year-old male (A) and the 11-year-old male patient with HHRH (B). Images show a normal whole leg [Na^+] (18.4 mmol/L, z-score + 1.31), skin [Na^+] (14.5 mmol/L, z-score + 0.68) and triceps surae muscle [Na^+] (21.2 mmol/L, z-score + 1.5) despite a defect in a sodium transporter. [Na^+] measurement was possible by linear trend analysis as detailed in (Filler et al., 2021a; Filler et al., 2021b; Qirjazi et al., 2020), using four calibration vials containing increasing concentrations of NaCl solution (from left to right: 40, 30, 20, 10 mmol/L). Tissue [Na^+] is displayed as heat map, with greater signal intensity proportional to tissue [Na^+].

tissue sodium levels were maintained. Another explanation could be related to the phosphate supplementation (Jemp® phosphate), which, while being the lowest sodium option, still contains a large amount of sodium (phosphorous 500 mg, potassium 123 mg, sodium 469 mg).

3. Discussion

We describe the successful use of rhGH and Fluconazole in a patient with HHRH who did not respond adequately and had side effects to traditional oral phosphate therapy in combination with potassium

citrate therapy for the hypercalciuria. While previously described by Dreimane (Dreimane et al., 2020), we are unaware of any other more detailed report that focuses on all aspects of this disorder. In our patient, rhGH alone did not ameliorate the undetectably high 1,25(OH)₂D levels, nor did it affect the hypercalciuria, and based on a case report (Bertholet-Thomas et al., 2019) we added Fluconazole. Our patient's ²³Na MRI findings did not support any sodium wasting, so we implemented of a low sodium diet. This change in the diet, also improved his hypercalciuria.

While the mechanism of rhGH on tubular phosphate transport is not

fully elucidated, there are animal and human data that suggest an increase of tubular reabsorption of phosphate due to growth hormone. Corvilain et al. showed in 1964 that growth hormone leads to an increased tubular phosphate reabsorption in the absence of an effect of intact parathyroid hormone (Corvilain and Abramow, 1964). Improved phosphate retention due to rhGH therapy was also demonstrated in XLH patients (Smith and Remington, 2021). In patients without any defect in their phosphate transport but with growth hormone deficiency, an increase in serum phosphate was also observed when treated with rhGH (Ahmad et al., 2003). The putative mechanism is through NPT2A regulated phosphate transport which is influenced by insulin-like growth factor 1 and insulin and growth hormone (Mamonova and Friedman, 2021).

rhGH therapy did not alter the very elevated 1,25(OH)₂D levels, which is not surprising given the mechanism of action. We therefore added Fluconazole as described by Bertholet-Thomas et al. (2019). Fluconazole is an inhibitor of the 1 α -hydroxylase. The idea is based on the use of ketoconazole in patients with increased 1,25(OH)₂D levels with loss-of-function mutations in *CYP24A1* or *FGF23* (Tebben et al., 2012; Claramunt-Taberner et al., 2018). However, ketoconazole is associated with liver toxicity, therefore Fluconazole was deemed to be a better choice (Bertholet-Thomas et al., 2019). Fluconazole has also been used successfully in patients with *CYP24A1* mutations (Sayers et al., 2015). The putative mechanism as proposed by Bertholet-Thomas is as follows: The hypophosphatemia upregulates 1,25(OH)₂D levels to increase intestinal phosphate reabsorption, but in turn it also results in hyperabsorptive hypercalciuria, which is responsible for the progressive nephrocalcinosis and urinary stone disease. Azoles are effective inhibitors of 1 α -hydroxylase, decreasing 1,25(OH)₂D levels (Bertholet-Thomas et al., 2019). Our treatment approach confirmed the effects observed in Bertholet-Thomas' patient with a compound heterozygous mutations in *SLC34A3* (c.925 + 20_926-48del [a deletion in intron 9 that leads to abnormal splicing] and c.1055_1058dup [a duplication in exon 10 predicted to lead to a frameshift and premature termination of the protein] (Bertholet-Thomas et al., 2019)), who had a very similar clinical presentation as our patient.

An unexpected fact was that despite having a defect in a sodium phosphate co-transporter, our patient did not exhibit reduced tissue sodium, based on ²³Na MRI. Putatively, the effect of the sodium phosphate co-transporter on proximal tubule sodium reabsorption is lower than that of other transporters such as the sodium hydrogen antiporter 3 (NHE3) (Onishi et al., 2020). The important consequence of our finding is that a sodium restricted diet may be safe and assists in the management of hypercalciuria since sodium and calcium in the urine correlate positively (Osorio and Alon, 1997). Hypercalciuria improved substantially on 100 mg of Fluconazole to almost normal levels.

Although in our case, the addition of rhGH, Fluconazole and salt restriction appear to have improved the conventional therapy of phosphate supplementation and potassium citrate, which do improve rickets/osteomalacia, if tolerated, larger studies are needed to confirm our findings. While both growth hormone therapy and fluconazole have previously been described, to the best of our knowledge, the combination of both therapies has not previously described, and may provide patients with better quality of life and renal function outcomes. Potassium phosphate supplements may also be preferable, but these are not available in Canada.

4. Conclusion

Taken together, oral phosphate therapy and potassium citrate are insufficient to ameliorate the pathophysiological changes of HHRH. The addition of rhGH, Fluconazole and salt restriction appear to have improved the conventional therapy of phosphate supplementation and potassium citrate. Larger studies are needed to confirm our findings, as this novel approach may provide patients with better quality of life and renal function outcomes.

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Ethics approval

Case reports are ethics exempt in our institution, however, written informed consent about publication was obtained by the caregivers. The ²³Na MRI study received full approval from the Research Ethics Board.

Consent to participate

The authors declare that they have obtained consent to participate from the caregiver and the consenting minor for the publication of this study.

CRedit authorship contribution statement

Guido Filler conceived this project, wrote the drafts, collated the results, made multiple edits, collated all changes, added intellectual content, and approved the final version.

Clara Schott conducted the thorough literature review, developed the figure of the NPT2c transporter with the novel mutation, the provided major intellectual input into the design of the study, helped with the interpretation of the results, carefully edited, and revised the various versions of the manuscript and approved the final manuscript.

Fabio Salerno performed the sodium-23 (²³Na) MRI study, provided major intellectual input into the analysis of the results, carefully edited, and revised the various versions of the manuscript and approved the final manuscript.

Andrea Ens provided major intellectual input into the initial design of the study, helped with the interpretation of the results, carefully edited, and revised the various versions of the manuscript and approved the final manuscript.

Christopher William McIntyre provided major intellectual input into the design of the study, facilitated the sodium-23 (²³Na) MRI, helped with the interpretation of the results, carefully edited, and revised the various versions of the manuscript and approved the final manuscript.

Dr. Maria Ferris provided major intellectual input into the design of the study, provided major intellectual input into the analysis of the results, carefully edited, and revised the various versions of the manuscript and approved the final manuscript.

Robert Stein provided major intellectual input into the design of the study, helped with the interpretation of the results, carefully edited, and revised the various versions of the manuscript and approved the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of competing interest

All authors declare that they have no relevant financial interest.

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