Clinical Presentation of Autosomal Recessive Hypophosphatemic Rickets Type 2 (ARHR2)

Hypophosphatemic rickets comprise a group of rare genetic disorders that are characterized by pathologically low levels of serum phosphate, rickets and osteomalacia that is unresponsive to vitamin D. The disease is usually hereditary, with 20% of cases inherited in an autosomal dominant (ADHR) or autosomal recessive (ARHR) fashion while the remaining 80% arise from an X-linked inherited mutation (XLH) or are caused by mesenchymal tumors (tumor-induced osteomalacia).

INTRODUCTION

Autosomal recessive hypophosphatemic rickets type 2 (ARHR2) has been genetically linked to a homozygous loss-of-function of the *ENPP1* gene. *ENPP1* encodes the ENPP1 protein, a major generator of extracellular pyrophosphate (PPi), a potent inhibitor of vascular and ectopic calcification. As in all cases of hypophosphatemic rickets, patients with ARHR2 have low circulating blood levels of phosphate. Phosphate is essential for normal development of bones and teeth.

The frequency of ARHR2 is unknown. In addition to ARHR2, inactivation of the ENPP1 protein has been linked to several disorders of ectopic mineralization, most notably generalized arterial calcification of infancy (GACI), which is usually fatal to patients in the first 6 months of life. Patients who survive GACI often develop ARHR2.

ARHR2 is a heterogenous disease that usually presents within the first decade of life. The disorder manifests clinically with short stature, abnormal gait, bowing limbs, bone abnormalities, bone pain, dental caries, calcification of the ligaments at bony insertion sites, limited movement of the spine and hip and fusion of the cervical spine, nephrocalcinosis, tortuosity of vessels, and hearing loss. Diagnosis of ARHR2 is based on the association of clinical, radiological, biochemical, and genetic assessments. Differential diagnoses are essential due to overlapping phenotypic characteristics of the various forms of hypophosphatemic rickets (Table 1).

Table 1. Characteristics of hypophosphatemic rickets with renal phosphate wasting

Disorder	Gene (location)	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	FGF23
XLH (X-linked hypophosphatemia)	*PHEX* (Xp22.1)	N	↓	↑, ↑↑	↓	↑	↓	N, ↑[b]	N	N[c]	↑, N
ADHR (Autosomal dominant hypophosphatemic rickets)	*FGF23* (12p13.3)	N	↓	↑, ↑↑	↓	↑	↓	N, ↑[b]	N	N[c]	↑, N
ARHR1 (Autosomal recessive hypophosphatemic rickets 1)	*DMP1* (4q22.1)	N	↓	↑, ↑↑	↓	↑	↓	N, ↑[b]	N	N[c]	↑, N
ARHR2 (Autosomal recessive hypophosphatemic rickets 2)	*ENPP1* (6q23.2)	N	↓	↑, ↑↑	↓	↑	↓	N, ↑[b]	N	N[c]	↑, N

[a]Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; [b]PTH may be moderately elevated; [c]Decreased relative to the serum phosphate concentration.

N, normal; ↓, decreased; ↑, elevated; ↑ ↑, very elevated; 1,25 $(OH)_2D$, 1,25-dihydroxyvitamin D; 25 (OH)D, cholecalciferol; ALP, alkaline phosphatase; Ca, serum levels of Ca; FGF23, fibroblast growth factor 23; P, serum levels of phosphate; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate per glomerular filtration rate; U_{Ca}, urinary calcium excretion; U_P, urinary phosphate excretion

Table 1. The genetic linkage and biochemical characteristics are shown for the group of rare disorders that comprise the category of hypophosphatemic rickets with renal tubular phosphate wasting due to elevated FGF23 levels and/or signaling.

Patients with ARHR2 present biochemically with hypophosphatemia (low levels of phosphate in the blood), hyperphosphaturia (excess phosphate in the urine), and elevated plasma alkaline phosphatase. In patients with ARHR2, high circulating levels of FGF23, fibroblast growth factor 23 have also been observed. FGF23 is a secreted protein that is essential for the renal regulation of phosphate homeostasis. It reduces renal phosphate resorption by downregulating the expression of NPT2, a sodium-phosphate cotransporter, in the proximal tubule, resulting in renal wasting. The exact mechanism linking mutations in the *ENPP1* gene to increased FGF23 levels is unclear.

Currently, no approved therapies for patients diagnosed with ARHR2 exist, and treatment primarily consists of phosphate and vitamin D dietary supplementation. Patients afflicted with this disorder will require lifelong follow-up and management, with some requiring surgical intervention and/or long-term pain management.

TYPICAL PATIENT PROFILE CASE STUDY

A 7-year-old boy was referred to the pediatric endocrinology clinic for evaluation of bowing legs and hip pain. On physical examination, short stature (< 3rd percentile for age), mild dental carries, slight widening of the wrist, and significant deformity of the knees (genu valgum) were observed. Radiological analysis of the lower extremities of the patient was performed, and the result is shown in Figure 1. The radiograph demonstrates the presence of bilateral genu valgum as well as partial fraying and irregularity of the distal femoral and proximal tibial growth plates. In addition, the patient was found to have mild renal impairment with nephrocalcinosis.

Biochemical analyses were also performed on the patient. Laboratory results showed that he had hypophosphatemia, hyperphosphaturia, elevated plasma alkaline phosphatase, and reduced calcium excretion. The patient had normal levels of PTH and vitamin D metabolites (25OH and 1,25 $(OH)_2$). The results also revealed elevated levels of FGF23. The laboratory evaluation was consistent with that of a patient with hypophosphatemic rickets (see Table 1). Based on the clinical presentation, the child was diagnosed as having XLH, the most common form of rickets. Treatment with oral phosphate and vitamin D supplements was initiated. Evaluation of the patient after several weeks on this regimen demonstrated an inadequate response to treatment.

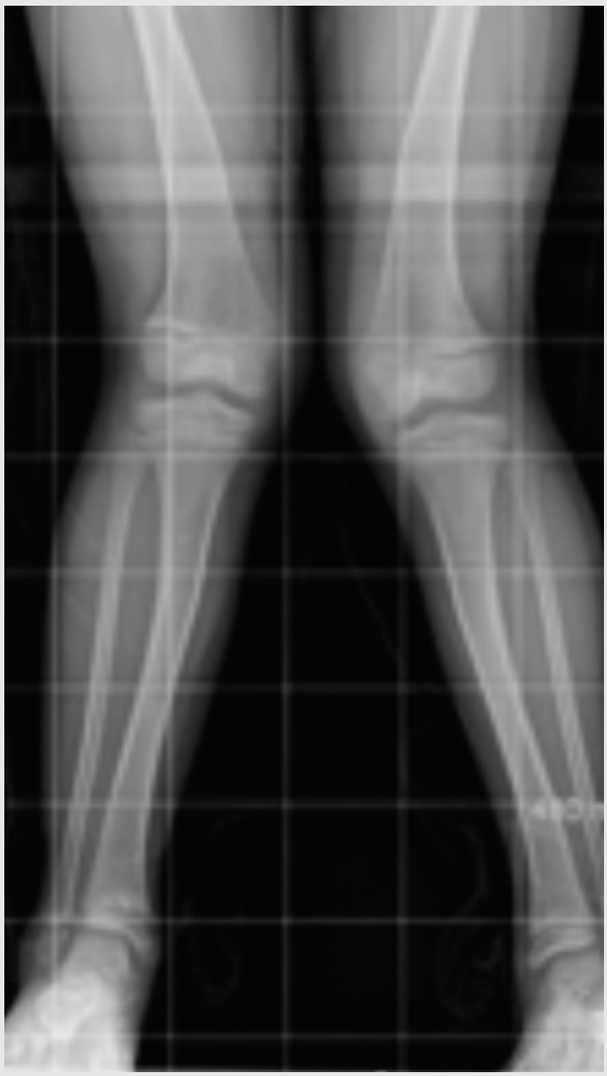

Figure 1. Shown is the radiograph of the lower extremities of the patient. The child presented with short stature and bilateral genu valgum.

Genetic analysis did not identify mutations in the *PHEX*, *FGF23*, or *DMP1* genes, suggesting that perhaps the patient may not have XLH. In addition, there was no family history of rickets. Sequencing of additional genes known to be involved in hypophosphatemia revealed a mutation in the patient's *ENPP1* gene, which confirmed a diagnosis of ARHR2. A homozygous splice donor site mutation was found at the exon–intron junction of exon 21 of the *ENPP1* gene, which resulted in a truncated, inactive ENPP1 protein. The patient's treatment regimen was changed to include additional phosphate supplementation and high-dose calcitriol (activated vitamin D_3). The altered plan led to improvement in serum calcium and phosphate. Within a few weeks of starting therapy, the alkaline phosphatase levels in the patient's blood improved.

The patient's bone profile parameters continue to be routinely evaluated, and his treatment with phosphate and vitamin D supplements continues. Though the patient's biochemical profile improved, he still has significant bowing in his legs. The bilateral genu valgum has remained stable, without progression or improvement, and the child will be routinely followed up as an outpatient in the clinic and may require an orthopedic consultation for possible surgical correction of the deformity in his legs. He will also be followed by the nephrology service for management of his nephrocalcinosis.

DISCUSSION

Different forms of hypophosphatemic rickets, all characterized by renal phosphate wasting, present with similar symptomology, which can make accurate diagnosis difficult. Misdiagnosis may lead to ineffective treatment that can ultimately compound clinical consequences in cases of ARHR2. Early and accurate diagnosis via laboratory testing, in conjunction with timely genetic analysis is essential to avoid preventable outcomes such as bone and dental deformities, which can worsen over time.

Current approaches with phosphate supplements and vitamin D analogs for patients with rickets result in outcomes that are still not optimal; they only partially correct the disorder by slowing down or halting further progression of the disease. Genetic analysis is necessary for the correct diagnosis of inherited hypophosphatemic rickets to effectively differentiate between the several forms of the disease, which exhibit overlapping and sometimes identical phenotypic and biochemical characteristics.

SUMMARY

- Autosomal recessive hypophosphatemic rickets type 2 (ARHR2) is a rare form of hypophosphatemic rickets (HR). Several forms of HR have been identified which present identically both phenotypically and biochemically.
- Homozygous loss-of-function mutations in the *ENPP1* gene have been genetically linked to the ARHR2 form of the disease.
- Early identification via genetic testing/screening should lead to improved outcomes for many more patients afflicted with rare diseases such as ARHR2.

INOZYME GENETIC TESTING PROGRAM

Inozyme Pharma is partnering with PreventionGenetics to offer a no-cost genetic testing program to improve the detection and understanding of the rare calcification/ hypophosphatemic rickets disorder, ARHR2 (autosomal recessive hypophosphatemic rickets type 2). Offered globally, the program tests for mutations in the *ENPP1* gene, which is implicated in this severe calcification disorder. The genetic test can identify individuals who may have the condition or are carriers for the ENPP1 deficiency.

For additional information, please contact **PreventionGenetics** at **1-715-387-0484** and/or mail **clinicaldnatesting@preventiongenetics.com**

or

visit https://www.preventiongenetics.com/specialOrders?sp=sp051

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