Pediatric Insights

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An Update from the Division of Pediatric Endocrinology, Diabetes, and Metabolism

About the Division

The Division of Pediatric Endocrinology, Diabetes, and Metabolism at Children's Hospital of Pittsburgh of UPMC provides diagnostic and therapeutic services for children with diabetes mellitus, hypoglycemia, and disorders of physical growth, sexual maturation, thyroid function, pituitary function, and calcium and phosphorous metabolism, as well as other gender disorders. Patients are evaluated in collaboration with multidisciplinary teams to come to a unifying diagnosis and provide the best outcomes for patients and families.

For a referral or consultation, please contact us at 412-692-5170. Visit us online at **CHP.edu/diabetes**.

Nursen Gurtunca, MD
Assistant Professor, Pediatrics
University of Pittsburgh
School of Medicine

Pushpa A. Viswanathan, MD
Assistant Professor, Pediatrics
University of Pittsburgh
School of Medicine

Children's Hospital of Pittsburgh of UPMC

DIAGNOSE IT

For decades, the experts of the Division of Pediatric Endocrinology, Diabetes, and Metabolism at Children's Hospital of Pittsburgh of UPMC have played a major role in the care of children with diabetes and all types of hormone-related disorders. • Children's Hospital has one of the largest pediatric endocrine clinics in North America and is a leader in both clinical care and research in many of the issues surrounding childhood diabetes mellitus and endocrine issues. • We offer this case presentation to help educate other health care professionals about our most interesting and complex cases.

Case Presentation

A 31-month-old Caucasian female was referred to endocrinology for evaluation of short stature, hypophosphatemia, and elevated alkaline phosphatase (AP) level. She was on a normal diet. Her height was at the 7th percentile and weight at the 44th percentile. She had mild frontal bossing, widening of the wrists, and marked bowing of the legs that had first been observed at age 15 months and managed conservatively. No dental abnormalities were present. Both parents are of normal stature.

Initial Laboratory Values

	Level	Ref Range
Ca (mg/dL)	10.1	8.8–10.8
Phos (mg/dL)	2.9	4.5–5.5
Alk phos (IU/L)	477	<290
PTH (pg/mL)	13	8.5–72.5
1,25OH Vit D (pg/mL)	71	31–87
25OH Vit D (ng/mL)	63	25–100

What steps would you take next to diagnose this patient?

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Additional Studies

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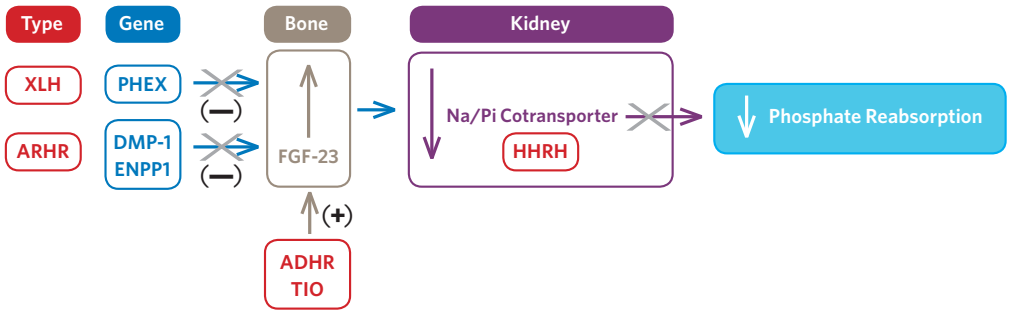
	Level	Ref Range
Phos Tubular Absorption	84%	>90
TmP/GFR (mmol/L)	0.18	1.15–2.44
C-terminal FGF-23	197 RU/mL	(expected value <230)

DNA Gene Sequencing	
PHEX	Normal Sequences
FGF-23	Normal Sequences

Differential Diagnosis

- The most common cause of hypophosphatemic rickets (HR) is inactivation of the PHEX gene, causing X-linked hypophosphatemic rickets (XLH) mediated by elevated levels of fibroblast growth factor 23 (FGF-23), a phosphaturic factor.
- Other genetic forms of HR are autosomal recessive hypophosphatemic rickets (ARHR) due to dentin matrix protein 1 *(DMP-1)* gene mutations (ARHR1) and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) gene mutations (ARHR2). Few cases are reported in the literature.
- XLH and ARHR have similar clinical phenotypes due to shared pathophysiology of increased FGF-23 expression, which accounts for renal phosphate wasting with hypophosphatemia, reduced generation of calcitriol, and defective skeletal mineralization.
- Mutations in FGF-23 prevent its proteolytic cleavage, resulting in increased FGF-23 levels in autosomal dominant hypophosphatemic rickets (ADHR).
- Mesenchymal tumors that cause acquired HR (tumor-induced osteomalacia — TIO) also are associated with elevated expression of FGF-23.
- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is caused by defective renal sodium-potassium cotransporter. It is inherited in an autosomal recessive fashion. It differs from FGF-23 mediated HR in that the calcitriol level is not low.

Mechanism of Renal Phosphate Wasting in Hereditary Hypophosphatemic Rickets and Tumor-Induced Osteomalacia



- FGF-23 levels are increased by inactivating mutations in PHEX (as in XLH), DMP-1 and *ENPP1* (as in ARHR), by activating mutations in FGF-23 (as in ADHR), or by tumor production of FGF-23 (as in TIO).
- Excessive activity of FGF-23 suppresses the Na/Pi cotransporter and causes renal phosphate wasting.
- In HHRH, the renal phosphate wasting is caused by a mutation in the Na/Pi cotransporter itself.

XLH: X-linked hypophosphatemic rickets. **ADHR:** Autosomal dominant hypophosphatemic rickets. **ARHR:** Autosomal recessive hypophosphatemic rickets. **TIO:** Tumor-induced osteomalacia. **HHRH:** Hereditary hypophosphatemic rickets with hypercalciuria. **PHEX:** Phosphate-regulating endopeptidase on the X chromosome. **DMP-1:** Dentin matrix protein 1. **FGF-23:** Fibroblast growth factor 23. **ENPP1:** Ectonucleotide pyrophosphatase/phosphodiesterase 1.

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DIAGNOSE IT *(Continued from Page 2)*

Diagnose It

- DNA gene sequencing for the most common genetic causes of hypophosphatemic rickets was performed, with normal results.
- FGF-23 level was normal. However, the FGF-23 level can be normal or even low prior to phosphate replacement. The fact that it was measurable in the face of hypophosphatemia suggests that the patient's phosphate loss is driven by FGF-23. Further investigations for ARHR associated with elevated FGF-23 levels were carried out.
- Sequence analysis of DMP-1 revealed a single nonsense mutation, c.403G>T (p.Gly135X) in exon 6, that is predicted to generate a truncated DMP-1 protein with no putative biological function.
- Copy number analysis revealed a heterozygous intragenic DMP-1 deletion of approximately 8.15 kb encompassing exons 1–3.
- Unaffected mother and father were heterozygous for the nonsense and deletion mutations, respectively, confirming that the mutations were on different alleles. A younger, unaffected brother was wild type.

Treatment

Treatment with calcitriol and neutral phosphate led to improvement in the patient's growth velocity, bone deformities, and alkaline phosphatase level.

Discussion

- Hypophosphatemic rickets is often misdiagnosed in early infancy as physiological bowing.
- Treatment with phosphate supplementation and calcitriol at an early age is important to eliminate bone deformity, short stature, and secondary hyperparathyroidism.
- PCR-based sequencing analysis has limitations in the evaluation of mutations.
- Although intragenic deletions are an uncommon cause of gene inactivation, these mutations must be considered when standard tests do not reveal mutation(s) in candidate genes.

About Children's Hospital of Pittsburgh of UPMC

Regionally, nationally, and globally, Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, Children's Hospital has fulfilled this mission since its founding in 1890. Children's is named consistently to several elite lists of pediatric hospitals, including ranking No. 9 in the prestigious *U.S. News & World Report* annual Honor Roll of America's Best Children's Hospitals for 2017–2018 and ranking 10th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY16).

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