The Genetics Corner: Hypophosphatasia

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Prenatal diagnosis of severe perinatal hypophosphatasia allowed early treatment with enzyme replacement therapy on the first day of life

Case History

This infant was born at 39 weeks gestation by scheduled primary Cesarean delivery to a young, healthy primigravida mother. The family history was negative, and the parents were not consanguineous. The pregnancy had been complicated by prenatal diagnosis of a skeletal dysplasia at 23 weeks 2 days gestation. Fetal ultrasound findings from an outside facility showed ventriculomegaly, multiple fractures, and a small chest. Amniocentesis was performed at 24 weeks, and a skeletal dysplasia gene panel was ordered. The results, which were available at 31weeks gestation, showed two variants in a gene, *ALPL:* one variant was classified as likely pathogenic: c.738G>C (p.Arg246Ser), and the other was classified as a variant of unknown significance: c.119C>T (p.Ala40Val). The mother was transferred to our facility at 35 weeks gestation. At that time, a fetal ultrasound examination showed brachycephaly, short ribs, curled, fairly well ossified, small chest circumference, and underossified vertebrae and long bones (transparent bone) with fractures and bowing. Based on the prenatal ultrasound findings and genetic test results, the diagnosis was made of the severe perinatal form of hypophosphatasia (HPP).

"Prenatal and postnatal genetics consultations were requested. The baby's clinical examination and bone survey confirmed the prenatal diagnosis of the severe perinatal form of hypophosphatasia."

Genetic Evaluation

Genetics was consulted shortly before delivery and soon after birth. We met the family several times and talked to them by phone. We explained that based on the fetal ultrasound findings and genetic testing results, we believe that each parent carried one of the variants for the autosomal recessive form of severe perinatal hypophosphatasia. Without therapy, this is considered a lethal form of skeletal dysplasia. Targeted parental testing was sent out before the delivery, and results returned one week after the delivery, confirming that the two variants are in trans (Figure 1). The original report was updated, and both variants were classified as likely pathogenic. After birth, on the physical exam, the baby had a small chest, shortened and bowed arms and legs (Figure 2.). A bone survey showed diffusely abnormal mineralization of all the bones of the visualized skeleton with multiple bones appearing non-mineralized. In addition, the mineralized bones show abnormal bony architecture with heterogenous and abnormal trabecular patterns and some sclerosis. Multiple long bones show metaphyseal flaring and angulated fracture of the right femoral diaphysis, as well as a gracile appearance of the ribs. Non-mineralization of posterior elements of the spine, bones of the skull (excluding the skull base), and multiple long bones as well as the phalangeal bones of the upper extremities (Figure 3) were evident. The diagnosis of HPP was further confirmed by the extremely low level of ALP <5. Additional labs showed a low level of PTH.

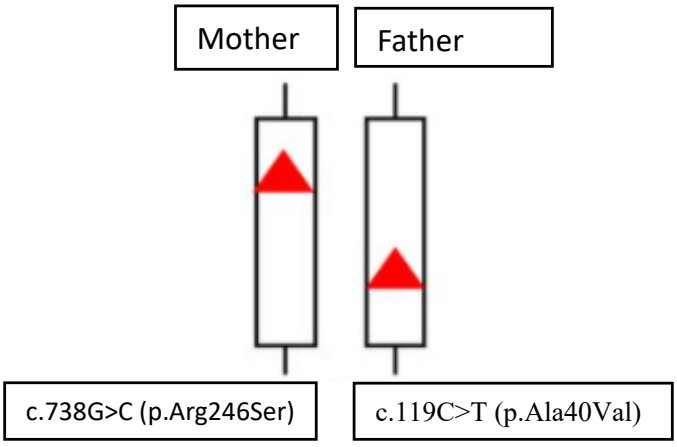


Figure 1. The baby is a compound heterozygote with 2 likely pathogenic variants in ALPL; parental testing confirmed that one variant was inherited from each parent.

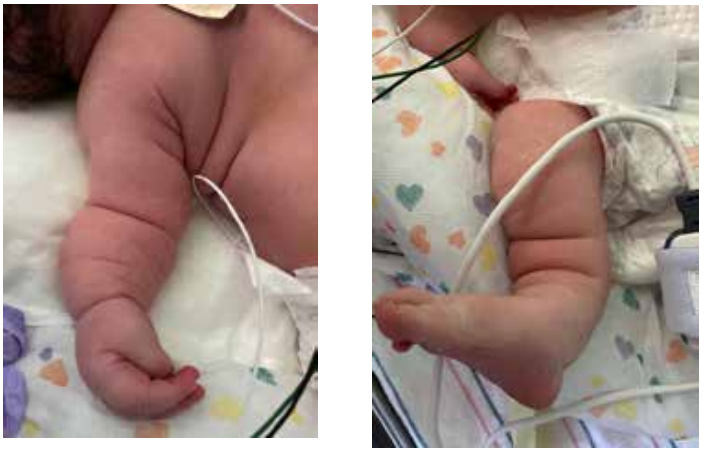
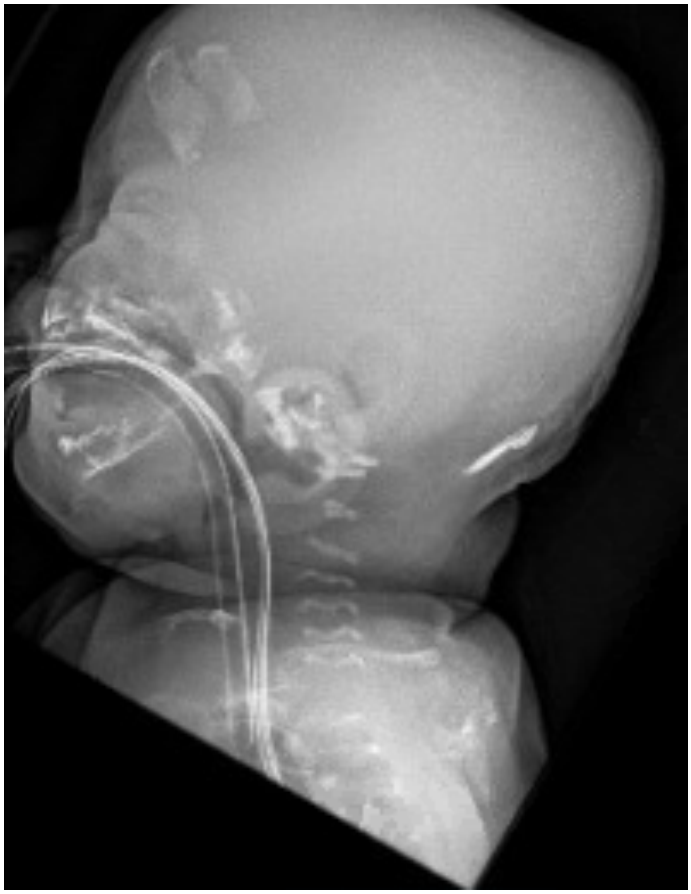
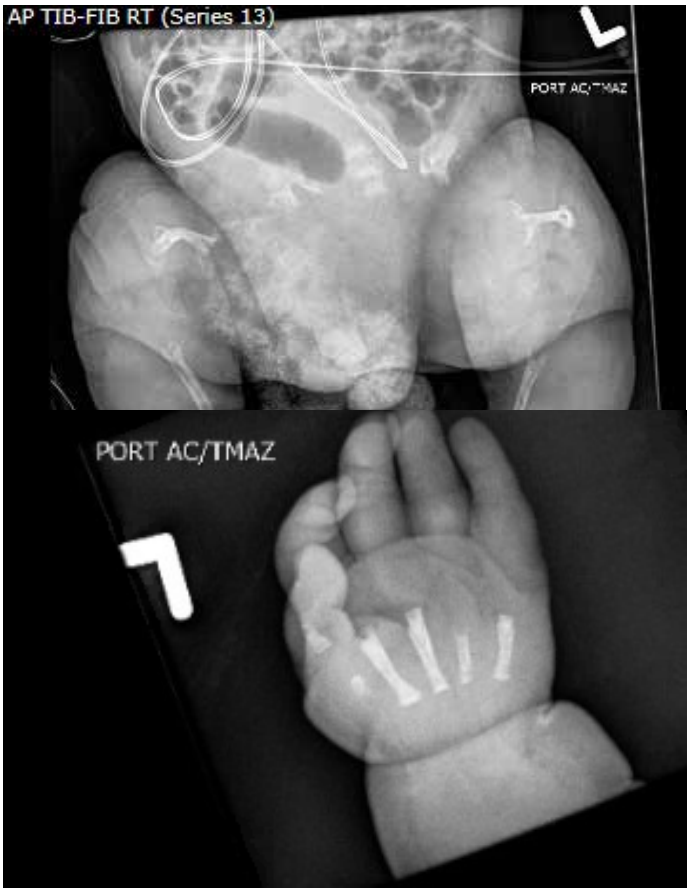
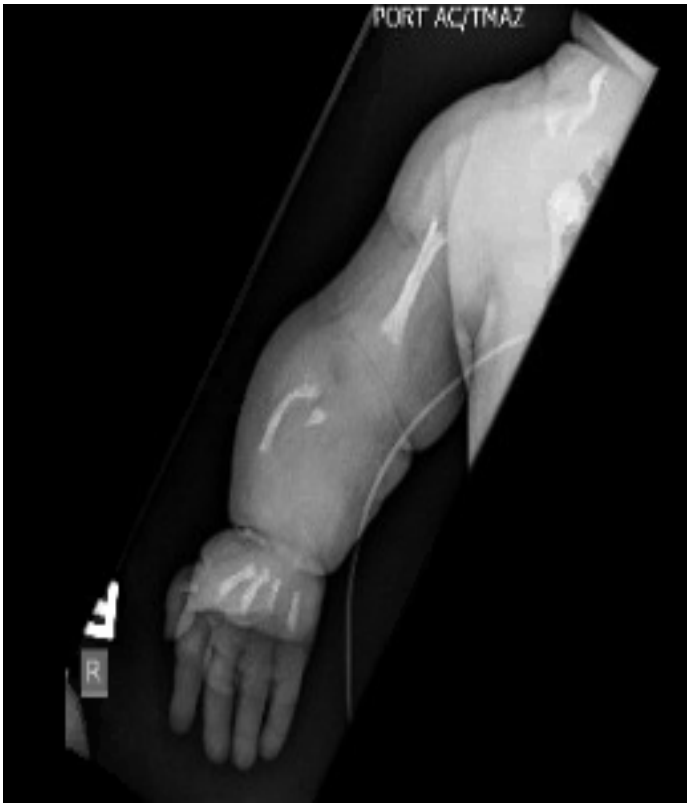


Figure 2. Shortened and bowed arms and legs.







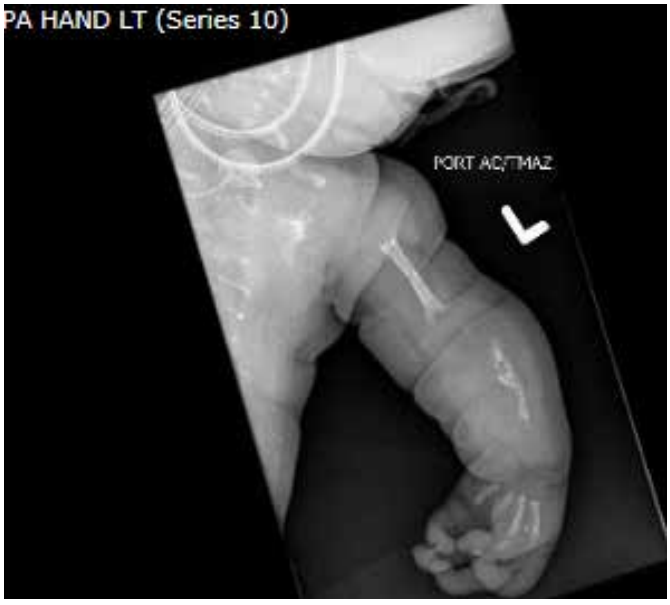


Figure 3. Diffuse undermineralization of all bones.

"Hypophosphatasia (HPP) should not be confused with hypophosphatemia- a different disorder secondary to pulmonary hypoplasia"

During the prenatal genetic consulting visit, the parents agreed to begin enzyme replacement therapy (ERT) with asfotase alfa as soon as possible after delivery. Treatment with asfotase alfa, 2mg/kg, three times per week by subcutaneous injection, was begun on the first day of life. The dose of asfotase alfa was escalated to 3mg/kg on day 18.

"Perinatal hypophosphatasia is the most severe type of HPP. It is complicated by respiratory insufficiency. This patient had additional findings of mild elevated pulmonary pressure and right ventricular hypertrophic cardiomyopathy likely "

After birth, the infant was orally intubated for hypoxia and respiratory distress. She required SIMV initially but transitioned to NAVA. Chest X-ray (Figure 4, left) at birth showed hypoplastic lungs with coarsened interstitial lung markings. Significant bone dysplasia was evident with absent ossification of vertebral bodies and ribs, bony stippling, and attenuated visualization of osseous structures. Echocardiogram on day one and day five showed mild elevation of pulmonary pressures, severe hypertrophy of the right ventricle, mild dilatation of the right ventricle, and moderate to severe narrowing of the LVOT due to septal wall motion without observed gradient. The mild elevated pulmonary pressure and right ventricular hypertrophic cardiomyopathy were likely secondary to pulmonary hypoplasia. An echocardiogram on day 18 showed normal biventricular systolic function, nonpatent ductus arteriosus, and mild elevation of pulmonary pressures, unchanged compared to prior study.

"Enzyme replacement therapy with asfotase alfa mineralizes the HPP skeleton, including the ribs, and improves respiratory function and survival in life-threatening perinatal and infantile HPP. "

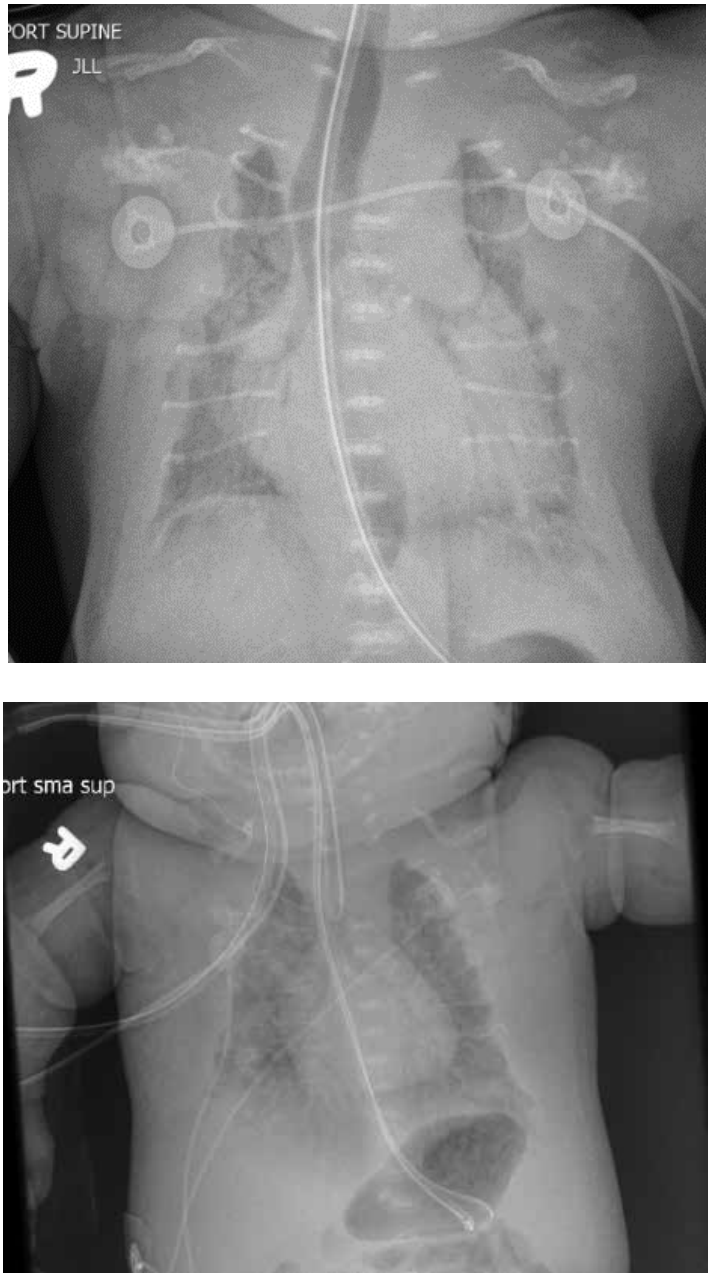


Figure 4. Chest X-rays at birth and at 17 days. Enzyme replacement therapy has not caused an appreciable change in bone mineralization at this point.

Discussion

Before the availability of treatment, the severe perinatal form of HPP often caused death *in utero* or soon after delivery. Affected neonates had rachitic defects in the chest wall, pulmonary hypoplasia, tracheobronchomalacia, causing severe respiratory compromise. Half of the affected infants died shortly after birth. Patients with perinatal or infantile hypophosphatasia were also at

risk for vitamin B6–dependent seizures,

The availability of enzyme replacement therapy (ERT) is transforming the care and outcome for patients with severe perinatal and infantile-onset HPP. Affected patients treated with asfotase alfa for up to 7-years showed early, sustained improvements in skeletal mineralization, respiratory function, growth, and cognitive and motor function. Asfotase alfa was generally well tolerated. Our patient is one of the few who have been treated at birth. In the report by Okazaki (2016), a patient with severe perinatal hypophosphatasia was successfully treated with ERT from day one of life with evidence of improvement in bone mineralization noted on X-ray after 21 days of therapy. At this writing, our patient is 18 days old. We plan to repeat the bone survey after 21 days of ERT. Figure 4 shows no significant difference in bone mineralization in radiographs taken at birth and 17 days. With asfotase alfa treatment, we anticipate improved bone mineralization after one month of treatment.

Practical Applications

1. Recognize that hypophosphatasia is a rare genetic bone disorder that should not be confused with hypophosphatemia, an electrolyte disorder in which there is a low level of phosphate in the blood.

2. Appreciate the clinical and radiologic features of the perinatal form of HPP, which is an extremely rare, autosomal recessive disorder that causes under mineralization of the skeleton, fractures, and life-threatening respiratory insufficiency due to pulmonary hypoplasia.

3. Appreciate that the pulmonary hypoplasia may cause pulmonary hypertension and further lead to right ventricular hypertrophic cardiomyopathy. Tracheobronchomalacia may cause ventilator dependence.

4. Offer enzyme replacement therapy for severe perinatal and infantile forms of HPP. Although ERT improves bone mineralization and survival in the severe forms of HPP, the treatment effect takes time. Evidence of improved bone mineralization may not be visible radiographically for several weeks or months.

References:

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The authors have no relevant disclosures.

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