New homozygous mutation in ALPL gene in Saudi patient with infantile hypophosphatasia

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Abstract
Hypophosphatasia (HPP) is a rare genetic disorder characterized by the abnormal development of bones and teeth. These abnormalities occur due to defective bone and tooth mineralization associated with low serum and bone alkaline phosphatase activity. Which caused by a number of loss-of-function mutations in the ALPL gene leading to diminished activity of the enzyme in bone, liver, and kidney. The clinical presentation of this disease is extremely variable. Ranging from extreme life-threatening forms revealed at birth in young infants presenting with severely impaired bone mineralization, seizures, and hypercalcemia, to young adults with premature exfoliation of their teeth without any other symptom. Herein, we report a case of HPP who presented with pyridoxine-responsive seizures in the early neonatal period and was found to have hypercalcemia, low alkaline phosphate and skeletal demineralization.

Introduction
Hypophosphatasia (HPP) [Online Mendelian Inheritance in Man (OMIM) 146300, 241500 and 241510] is a rare metabolic disease defined by a deficiency of serum tissue nonspecific alkaline Phosphatase (TNSALP). It was first described in 1948 (Rathbun 1948) and has a variable clinical presentation. Seven forms have been reported based primarily on the age at which skeletal lesions are discovered [1].

Perinatal HHP: associated with profound inactivity of alkaline phosphatase and markedly impaired mineralization with clinically apparent skeletal deformities and pathognomonic radiographic changes with rapidly progressive clinical course. Some pregnancies end in stillbirth. In other cases, affected newborns pass away from respiratory failure in several days.

Prenatal benign HHP: is associated with bowed limbs at birth. The skeletal malformations associated with this form improve after birth. Infantile HHP: has symptoms similar to, but typically less severe, than perinatal form and recognized before 6 months of age. Childhood HHP: is highly variable, from severe to mild forms, but are less severe than the infantile form. Affected children may sometimes have craniostenosis and exhibit signs of intracranial hypertension.

Adult HPP: osteopenia, recurrent fractures, and pseudofractures with early loss of adult dentition common. Ondohyphosphatasia: is characterized by the premature loss of deciduous teeth in childhood, or loss of teeth in adulthood. Pseudohyphosphatasia: is similar to infantile HPP but with unremarkable ALP levels.

The genes of the other, tissue-specific, ALP isoenzymes are located on the long arm of chromosome 2 (2q34-37) [2-4]. The main symptoms are diagnosis before age 6 months because of pyridoxine-responsive seizures, failure to thrive, muscular hypotonia, mainly in perinatal and infantile forms of hypophosphatasia and the common clinical signs are rickets, osteomalacia, fractures, teeth loss, nephrocalcinosis, craniostenosis, fractures and respiratory failure. The severely affected babies often die at or soon after birth from respiratory insufficiency due to pulmonary hypoplasia, a consequence of poorly mineralized bones of the chest [5,6].

The main diagnostic laboratory abnormalities are low serum ALP and TNSALP activity (hypophosphatasemia) and increased levels of ALP substrates (inorganic pyrophosphate (PPI), pyridoxal-5'-phosphate (PLP, the active metabolite of vitamin B6), and phosphoethanolamine (PEA))

Case report
Nine months old female infant was referred to genetic metabolic physician at age of on week due to neonatal seizure since birth and hypercalcemia. She was born at the 37th week of gestation with a birth weight of 2010 g and the Apgar score was 8 at 1 minute and 10 at 5 minutes after birth. Her prenatal ultrasound was normal and she the second child of consanguineous Saudi parents with was significant family history, the oldest sibling baby girl was died at age of 4 months with respiratory failure and unclear diagnosis. Metabolic acidosis and seizures were observed in the first day of life. She kept in NICU and intubation was attempted. She has frequent myoclonic seizures that were not controlled after phenobarbital and phenytoin therapy. On her physical examination at one month old, her weight was 2370 g (<3th centile), her height was 48.6cm (3th-10th centile), and her head circumference was 35.6 cm (10th-50th centile). A flattened facial appearance, broad forehead, flattened nasal bridge, bilateral low-set ears, short neck, narrow thorax, no organomealy and heart examination murmur was normal. (Figure 1)
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Figure 1. At age of 4 months. Facial phenotype showing broad forehead, flattened nasal bridge, bilateral low-set ears, short neck.

Figure 2. (A, B) Radiographic imaging of the patient before Asfotase alfa treatment showing distorted trabeculation, reduced mineralization in the epiphyses and metaphyses, demineralization in the skull.

Figure 3. After 20 weeks of ERT, substantial mineralization is apparent.

Material and methods

Exon 2 to 12 of ALPL gene (NM_000478) were amplified by PCR. The amplified products were then sequenced using ABI 3730 sequencers and analyzed for sequence variations. The significance of the variations was determined by comparison with wild type sequence, previously reported mutations, and correlation with the structure of the alkaline phosphatase enzyme (liver/bone/kidney type). Although DNA sequencing is a highly sensitive methodology, mutation detection may not be 100% DNA based testing is confirmatory. A negative test result reduces but does not eliminate a genetic cause for this individual's phenotype.

Results

Molecular analysis performed by Saudi diagnostic laboratory SDL in Saudi confirmed the diagnosis of HPP. A homozygous c.173T>C.
transition in exon 3 pf the ALP gene. This change converts a codon for leucine (CTG) to 3 codon for proline (CCG). This change has not been previously reported as either amutation or a polymorphism. Additionally, this change is not listed in the dbSNP or ESP database. The molecular gene diagnosis also done for the parents and both heterozygous for same gene ALPL.

An established treatment for HPP was not available until the recent development of ERT with a modified human TNAP (asfotase alfa) it was shown to prevent their infantile hypophosphatasia including its associated seizures and dental abnormalities [10-12]. Asfotase Although enzyme replacement therapy may provide a therapeutic option, but still there is no current therapy for HPP till now.

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