Case Report:
Perinatal Lethal Form of Hypophosphatasia

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Abstract

Background: Hypophosphatasia is a rare inherited metabolic disease which is sometimes fatal and is characterized by defective bone and teeth mineralization. The disease is due to loss of function mutation in the gene encoding tissue-nonspecific alkaline phosphatase (TNAP or TNSALP).

Case Report: We report a full term female baby whose parents were first cousins and her mother had a history of a previous abortion and one neonatal death with an antenatal diagnosis of achondrogenesis. The baby was born depressed and needed intubation in the labor room and mechanical ventilation in NICU. The baby had some dysmorphic features, lung hypoplasia and very low alkaline phosphatase level. Skeletal survey findings were consistent with hypophosphatasia. She had progressive deterioration of her respiratory condition and expired at the age of 25 days.

Conclusion: The perinatal lethal form is the most severe type of hypophosphatasia. Prenatal testing for mutations in the TNSALP gene allows genetic counseling and prenatal diagnosis of the disease in families with severe forms of hypophosphatasia.

Key Words: Hypophosphatasia – Perinatal lethal form – TNSALP gene.

Introduction

HYPOPHOSPHATASIA is a rare inherited metabolic disease which is sometimes fatal and is characterized by defective bone and teeth mineralization and deficiency of serum and bone alkaline phosphatase activity [1-4].

The disease can be classified according to patient age when the first signs and symptoms manifest into: Perinatal (lethal), infantile, childhood and adult. Additional clinical forms include odonto-hypophosphatasia where there are only dental manifestations and a rare benign perinatal form characterized by in utero detection but much better prognosis than the other perinatal form [1,4].

Case Report

We report a female baby whose parents were first cousins, mother was 27 years old at the time of delivery, her blood group was B+ve with a history of a previous abortion at 2 months of age and one neonatal death at the age of one week for a baby whose ante-natal ultrasound examination revealed a picture suggestive of achondrogenesis. The prevalence of the severe hypophosphatasia was estimated to be one every 100,000 live birth [5]. It is especially prevalent in Mennonites population in Manitoba, Canada, where 1:2500 newborns manifests severe disease [6].

The disease is due to mutations in the Liver/bone/kidney alkaline phosphatase gene (ALPL; OMIM# 171760) encoding the tissue-nonspecific alkaline phosphatase (TNAP or TNSALP) [1,7]. The trait may be inherited as autosomal recessive (perinatal and infantile) or autosomal dominant (perinatal benign) or (childhood, adult and odonto-hypophosphatasia) [1].

The diagnosis is based on the characteristic prenatal ultra-sonographic and postnatal radiographic findings, clinical examinations, laboratory investigations (low serum levels of alkaline phosphatase, high serum pyridoxal 5’-phosphate and increased urinary phospho-ethanolamine) and may need to be confirmed by gene study [1,4,7-9].

There is no approved curative treatment of hypophosphatasia and management consists of palliating the symptoms, maintaining calcium balance and applying physical, occupational, dental and orthopedic interventions as necessary [2]. Enzyme replacement using human recombinant bone targeted alkaline phosphatase which has been tried in infants and juveniles provides promise for improving the outcome [10-12].

Case Report

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The baby was 40 weeks +3 days gestation with birth weight 3.575Kg (AGA), a product of normal vaginal delivery with an APGAR scoring of 2,6 and 8 at 1.5 and 10 minutes respectively. The baby was born depressed and needed intubation in the labor room and was transported to NICU where she was connected to mechanical ventilator.

Chest X-ray revealed lung hypoplasia for which the baby was given one dose of surfactant on admission. She needed high parameters on conventional ventilator and sometimes high frequency oscillator during the stay in NICU. Nitric oxide and sildenafil were used upon echocardiographic diagnosis of pulmonary hypertension but both did not result in any improvement of the ventilatory parameters of the baby.

On examination, the baby was short, length was 45cm (below the 3rd centile) with the lower segment length 17.5cm (disproportionate short stature). Head circumference was 34cm (10th centile) while the weight was between the 10th and the 50th centile. The baby had some dysmorphic features in the form of frontal bossing, bitemporal narrowing (narrow forehead), flat nasal bridge, small chest, fusiform fingers and there were creases in both forearms and legs in addition to clinodactyly.

Chromosomal study revealed 46 XX normal female karyotyping.

Liver function tests showed very low alkaline phosphatase level, 17mmol/L with subsequent results not exceeding 20mmol/L while other hepatic enzymes, renal function tests, electrolytes as well as Calcium, Phosphorous and Magnesium had been always within the normal ranges. Complete blood counts did not show any striking abnormalities. TORCH screening for the mother and the baby, neonatal screening and thyroid function tests were all normal.

Results

Skeletal survey revealed:

Generalized skeletal under-ossification, with marked under-ossification of the membranous calvarial bones and pseudo-widening of the calvarial sutures. Platyspondyly with defective ossification in the paravertebral neural arches Figs. (1,2).

Small triangular scapulae and small irregular pelvic bones Fig. (1).

Metaphyseal ossification defects seen as metaphyseal radiolucencies (celery stalk-like) extending into diaphyses of tubular bones Fig. (3).

On day 24 of life, the baby had severe deterioration of her respiratory condition, needed higher ventilatory parameters; CRP rose with no positive blood cultures and was started on antibiotics. The general condition continued to deteriorate and the baby passed away on the next day.

Fig. (1): Skeletal X-ray showed marked bone under-ossification with long bones metaphyseal radiolucencies, platy-spondyly and thin gracile ribs.

Fig. (2): Skull X-ray showed marked under-ossification of the membranous calvarial bones with islands like areas of ossification of parietal bones and to a lesser extent the occipital bones as well as pseudo-widening of the sutures and fontanels.

Fig. (3): Left upper limb X-ray showed abnormally ossified short bones with classic (Celery stalk like) metaphyseal radiolucencies.
Discussion

Hypophosphatasia is an inborn error of metabolism caused by a loss of function mutation in the Tissue Nonspecific Alkaline Phosphatase (TNALPL) gene [8,13,14].

Tissue nonspecific alkaline phosphatase hydrolyzes several substances, including inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP) (major form of vitamin B6) and Phosphor-Ethanolamine (PEA) [1,7].

When (TNALPL) is low, inorganic pyrophosphate (PPi) accumulates extracellularly inhibiting mineralization of bones causing rickets in infants and children and osteomalacia in adults.

Pyridoxal 5'-phosphate (PLP) will not be able to cross over the cell membranes which impair the brain synthesis of neurotransmitters and leads to seizures [15,16].

The clinical symptoms are heterogeneous ranging from still birth with profound skeletal hypomineralization to early loss of teeth without bone symptoms [4,7,8].

Six clinical forms of hypophosphatasia have been identified depending on the time of diagnosis: The perinatal (lethal), infantile, childhood, adult, odonto-hypophosphatasia and a rare benign perinatal form [1,7,17].

In the lethal perinatal form there is profound hypomineralization, deformed or shortened limbs of the fetus during gestation which will be evident at birth [18]. Skin may be covered with osteochondral spurs protruding from fore-arms or legs [19].

There may be peculiar partial or complete absence of ossification in one or more of the vertebrae. In the skull the individual membranous bones may calcify only at the centers leading to areas of unossified calvarium giving the illusion that the cranial sutures are widely separated when they are in fact functionally closed. The radiologic findings are diagnostic [7].

Stillbirth is not uncommon; neonates who survive will suffer from respiratory complications due to hypoplastic lungs, rachitic deformities of the chest and ultimately respiratory failure. Seizures can occur and are ultimately lethal [20].

In perinatal benign form, despite prenatal symptoms, there is a spontaneous improvement of skeletal defects and mineralization during the third trimester [4,21,22]. The patients manifest limb shortening and bowing and often dimples overlying the long bone deformities. The disease has a mild postnatal course [4].

Patients with infantile and childhood forms present with signs of rachitic deformities with possible spontaneous mineralization and remission of clinical problems [1,5,23].

Adult hypophosphatasia presents during middle age with osteomalacia and pseudo gout due to the deposition of pyrophosphate crystals in the joints [24].

Odonto-hypophosphatasia is characterized by premature exfoliation of fully rooted primary teeth and/or dental carries, often not associated with skeletal deformities [1].

The most important diagnostic laboratory finding is subnormal serum Alkaline Phosphatase (ALP). The severer the disease, the lower the serum ALP appropriate for age [7,8].

Other conditions that may be associated with low levels of alkaline phosphatase include: Pregnancy, drug administration, hypothyroidism, anemia and Celiac disease [1].

The most sensitive substrate marker for hypophosphatasia is increased pyridoxal 5'-phosphate (PLP) plasma level which correlates with the disease severity [8].

An increased urinary Phosphor-Ethanolamine (PEA) level which may be present even in heterogeneous carrier supports the diagnosis of hypophosphatasia but is not pathognomonic [9].

Radiologic diagnosis by ante-natal ultrasound is possible for perinatal (lethal) and perinatal benign forms while post natal X-ray is considered diagnostic in these forms together with infantile form despite patient to patient variability and the diversity of radiographic findings [1,19].

Gene study may be needed when the biochemical and the clinical data are not clear to offer genetic counseling or to offer molecular prenatal diagnosis to families affected by severe forms of the disease [1].

The differential diagnosis of the perinatal form includes:

1- Achondrogenesis type Ia in which the bodies of the spines (as opposed to the neural arches in hypophosphatasia) are not ossified. The calvarium will show ossification in achondrogenesis while in hypophosphatasia it is absent.
2- Osteogenesis imperfecta type II where in contrast to the thickened long bones of osteogenesis type II, the long bones in hypophosphatasia tend to be thin or may be absent [25].

In our case, although the ante-natal U/S did not diagnose perinatal hypophosphatasia, it picked up changes that were attributed to achondrogenesis which is one of the differential diagnoses of the perinatal hypophosphatasia. The baby was born with short stature, hypoplastic lungs and evident respiratory problems consistent with the clinical picture of the disease. Alkaline phosphatase level had always been very low with other causes of low levels being ruled out which is the most important laboratory evidence of hypophosphatasia. Radiological findings were typical for the disease.

On revising the records of the sibling who died before and had been diagnosed as a case of achondrogenesis she was found to have small chest and short limbs, her alkaline phosphatase was 4mmol/L which raises the possibility of a wrong diagnosis and possible affection of the previous baby with hypophosphatasia.

References

الملخص العربي

هيبيفوسباتازيا: هو مرض وراثي نادر من أمراض الأيض وقد يكون في بعض الأحيان قاتلاً. يتميز هذا المرض بقلة ترشيب المعادن في العظام والاستناد نتيجة فقدان وظيفة الجين الذي ينظم عملية تكوين إنزيم (الأنثيلين فيسوتاز).

بأن تعذر تقرير حالة طفقة حديثة الولادة، أولاً أقارن من الدرجة الأولى والمابع حسب تاريخ سابق من الإجهاض وطفل توفى في الشهر الأول من العمر. وكان قد تم تشخيصه قبل الولادة. حددت حالاتنا من صعوبة في التنفس بعد الولادة وتقلها إلى العناية المركزية للأطفال وتم وضعها على جهاز التنفس الصناعي. كانت تسعة منهم من الصغر حجم الرئة وتقص في مستوى الـALP. ولقد أظهر فحص الأشعة صورًا متوافقة للخصائص اللازمة تشخيص الهيبوفوساتازيا. عانت الطفلة من تدهور حالها التنفسية وتوفيت في اليوم الخامس والعشرين من العمر.

نستنتج من هذا أن الهيبوفوساتازيا التي تحدث قبل الولادة هي اخطر أنواع هذا المرض وأن الفحص الجيني أثناء الحمل يسمح بتشخيص الحالة قبل الولادة وتقديم المشورة الوراثية للآباء في العائلات التي عندما تاريخي عائلة لهذا المرض.