Diagnosis and management of a case of Hypophosphatasia

Linda Touman1, Mandeep Singh2.
Kypros Nicolaides Fetal Medicine Unit (FMU), Southend University Hospital NHS Foundation Trust, Essex, UK.

Introduction:
- Perinatal hypophosphatasia is a lethal autosomal recessive skeletal abnormality with a birth prevalence of about 1 per 100,000.
- It is characterized by deficiency of the tissue nonspecific isoenzyme of alkaline phosphatase causing abnormal bone mineralization.
- The homozygote has a severe deficiency of tissue and serum alkaline phosphatase and is uniformly fatal.
- The heterozygote is generally normal but may be mildly affected.

Case:
- A 25 yrs old, Para 1, Referred at 28 weeks by the sonographers for a short femur. Scanned at FMU, both femurs and tibiae were shown to be sharply bent and blotted below the 5th centile. Fractured femur and right sided talipes were demonstrated. Suspected osteogenesis Imperfecta (OI). Referral to geneticist who suspected OI. Aminocentesis was performed for OI screen. Results came back as negative for OI.
- Follow up. Small chest and a suspicion of a rib fracture. Normal skull/brain shape, normal amniotic fluid and normal fetal movements. Later on multiple fractures of the long bones were shown. Conservative management.
- Delivery at 39+4 weeks by ELCS. Alive boy, 3070 grams with bilateral femurs fractures, old fracture in Tibia, no fractured ribs.
- Evaluated by OI team and diagnosed as a case of hypophosphatasia.

Discussion:
- The sonographic findings of Hypophosphatasia include: 1) general underossification of the bones of the fetus, 2) limb shortening, 3) lack of ossification of groups of vertebral bodies, 4) lack of ossification of the neural arches of the spine and 5) lack of ossification of the hands. In addition, the pelvic bones are small, and there may be major portions of the calvaria, base of skull and facial bones which are not calcified. Of the various sonographic findings the most notable in addition to the limb shortening are the marked demineralization of the fetal calvarium and absent segments of the spine. Patients with the heterozygous form of the disease are often normal or may be mildly affected.

- Differential Diagnosis:
This condition may be indistinguishable from osteogenesis imperfecta (Type II). The sporadic segmental vertebral lack of ossification may be a helpful differentiating feature, if present. Likewise, in contrast to the thickened bones of osteogenesis type II, the long bones in hypophosphatasia tend to be thin or may be absent. Camptodemic dwarfism may also involve an absent spinal segment. Achondrogenesis may also cause lack of ossification of the spine however it is the bones of the spine that are not ossified as opposed to the neural arches in hypophosphatasia. In addition, the calvarium will be ossified in achondrogenesis as opposed to hypophosphatasia where it will be absent.
- The disease hypophosphatasia is clinically classified according to the age of onset of symptoms and subdivides into perinatal, infantile, childhood and adult forms. The most severe type is perinatal hypophosphatasia, which has an autosomal recessive mode of inheritance. The later onset forms of the condition have a more varied inheritance pattern and etiology.
- The severe form is due to abnormalities in the tissue-nonspecific isoenzyme of alkaline phosphatase (TNS-ALP). This causes severe skeletal abnormalities due to abnormal bone mineralization. The most likely mechanism responsible for the defect is inhibition of mineralization because of the phosphocompounds that accumulate due to the inactive enzyme. Typically, the placental and bowel isoenzymes are of normal activity.
- Mutations in the TNS-ALP gene at 1p36 have been identified as causing severe hypophosphatasia and thus where mutations can be identified in an affected family member accurate molecular prenatal testing can now be offered in a subsequent pregnancy.
- In new cases or in cases when the mutation has not been isolated, prenatal diagnosis of hypophosphatasia relies on ultrasound examination and enzyme activity studies in chorionic villi, amniotic fluid, fibroblasts and fetal serum.
- The diagnosis of severe perinatal hypophosphatasia by ultrasound examination has been reported from as early as 14 weeks of gestation and is characterized by poor ossification of all bones, most pronounced in the calvarium, shortening and bowing of the long bones and narrow chest.

Conclusion:
- Pregnancies at risk of Hypophosphatasia can be offered prenatal diagnosis, or an early scan to detect signs of hypomineralization and to be offered termination of the pregnancy if appropriate.

References:
- Atsushi Watanabe, Hideo Orimo, Toshiyuki Takeshita and Takashi Shimada. Prenatal Diagnosis of Severe Perinatal (Lethal) Hypophosphatasia. Prenatal Diagnosis - Morphology Scan and Invasive Methods. 29, June, 2012