Placental and Radiographic Findings in a Pre-Term Infant with Galactosialidosis
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Introduction:
Galactosialidosis is a rare lysosomal storage disorder caused by mutations in CTSA, which encodes Cathepsin A. We report a case of a newborn male with galactosialidosis who had unusual radiographic and placental findings.

Case Report:
Viable male infant delivered prematurely at 34 weeks gestation. Birth weight 1.73 kg, length 39 cm.

Prenatal concerns for:
- Fetal growth restriction
- Small diaphragmatic hernia
- Possible skeletal dysplasia

Physical exam:
- Small phallus with hypospadias
- Single umbilical artery
- Mild rhizomelic shortening of the extremities
- No cataracts, corneal clouding, or retinal abnormalities
- No hydrops or organomegaly
Radiographic Findings:
- Osteopenia and punctate calcifications of multiple epiphyses, suggestive of chondrodysplasia punctata

Laboratory Results:
- Newborn screen: Abnormal amino acid profile, suggestive of Maple Syrup Urine Disease
- PTH (intact): 1,247.3 pg/mL (High)
- Serum very long chain fatty acids: Normal
- Peripheral blood smear: Leukopenia with frequent atypical lymphocytes with cytoplasmic vacuolization
- Placental histology: Diffuse fine vacuolization of multiple cell types, suggestive of a lysosomal storage disorder
- Urine oligosaccharide profile (Mayo): Abnormal—consistent with galactosialidosis
- SNP microarray:
  - Small heterozygous deletion of 8q24.1 (“Variant of uncertain significance”)
  - Absence of heterozygosity of several regions, including a portion of chromosome 20 which includes the CTSA locus
- Oligosaccharide mutation panel: Homozygous for a “likely pathogenic” mutation in exon 3 of CTSA: c.308G>T (p.Gly103Val)

Clinical Course:
The patient experienced increasing respiratory distress and multi-organ failure and died at 3 weeks of age.
Radiographs demonstrate osteopenia, periosteal elevation, metaphyseal irregularities, and punctate calcification ("stippling") of the epiphyses (arrows). There was trace abdominal fluid and elevation of the right hemidiaphragm (abdominal ultrasonography, not shown).

Microscopic placental examination reveals a single umbilical artery (A), marked fine vacuolization of the amniocytes seen in the fetal membranes (B). Striking diffuse fine vacuolization is also seen within the Hofbauer cells of the chorionic villi and syncytiotrophoblasts lining those villi (C and D) and within the extravillous intermediate trophoblasts (X-cells) (E and F).
Discussion:
Galactosialidosis is an autosomal recessive storage disease caused by biallelic mutations in CTSA, the gene that encodes Cathepsin A. Affected patients are deficient in both β-galactosidase and α-neuraminidase. The consequences can vary from a severe early infantile presentation to presentation in childhood or even adolescence.

The patient whom we describe did not have ophthalmologic abnormalities, fetal hydrops, or ascites—findings that are common in the early infantile form of galactosialidosis. Punctate stippling of the epiphyses and abnormalities on placental histology were clues that galactosialidosis was a possibility, with abnormalities in urine oligosaccharide analysis and subsequent mutation testing for mutations in CTSA confirming that diagnosis.

“Stippling” of the epiphyses has been reported in several other infants with galactosialidosis. Patel et al (1999) described an infant with hydrops and a coarse facial appearance who had stippled epiphyses. Those authors provided an extensive differential diagnosis of that radiographic finding. Vacuolization of various cell types in the placenta is seen in multiple lysosomal storage disorders; however, the constellation of syncytiotrophoblast, villous stromal cell, extravillous trophoblast, and amniocyte vacuolization is seen in galactosialidosis and I-cell disease.

Conclusion:
Histologic examination of the placenta and review of skeletal radiographs can provide important clues to aid in the diagnosis of infants with unusual clinical presentations, and can guide more definitive diagnostic testing.

References: