Prenatal Caffey Disease

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Two forms of cortical hyperostosis or Caffey disease (OMIM *114000) have been described: prenatal and infantile. The classical mild infantile form was described by Roske in 1930 and further characterized by Caffey and Silverman in 1945. It is characterized by a massive subperiosteal new bone formation that typically involves the diaphyses of long bones, mandible and clavicles [1]. In addition, painful swelling of soft tissues, irritability and fever are quite common. The time of onset is usually within the first 6 months of life with resolution before age 2 years. The clinical course is variable and unpredictable [2]. The prenatal form of Caffey disease has a more severe course characterized by extensive hyperostotic bone involvement, angulations and shortening of long bones, polyhydramnios, and fetal hydrops. This is a rare disorder with a high mortality rate due to prematurity and lung hypoplasia [3]. We report a case of prenatal Caffey disease that presented prenatally with polyhydramnios, fetal hydrops and hepatomegaly followed by prematurity and pulmonary hypoplasia; the diagnosis was based on the abnormal skeletal appearance in the initial chest X-ray.

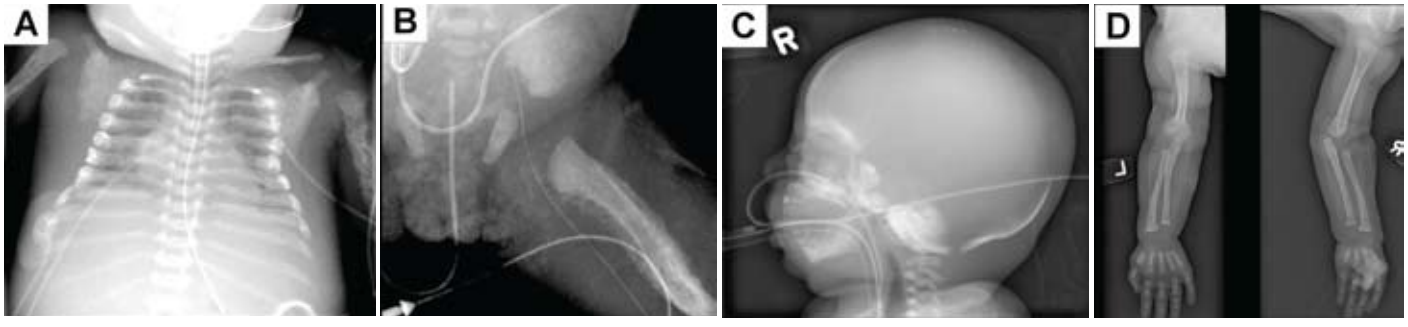
PATIENT DESCRIPTION

Our patient was born at 28 weeks 5 days gestation with a birth weight of 1455 g, head circumference 27.5 cm and length 40 cm. Her mother was a healthy 38 year old, gravida 4, para 1. The mother had received good prenatal care and the ultrasound scans performed at 11 and 19 weeks were normal. She was immune to rubella, and serology was negative for hepatitis B, human immunodeficiency virus and syphilis. Pregnancy was unremarkable until 27 weeks gestation when an ultrasound scan showed polyhydramnios and fetal hydrops, moderate ascites and hepatomegaly. No specific prenatal diagnosis was found at that point. A decompression amniocentesis was performed at 28 weeks 5 days gestation due to an increased amount of amniotic fluid. Labor began soon after the procedure.

The infant girl was born by spontaneous vaginal delivery. She was depressed and apneic at birth, was intubated in the delivery room and received bovine surfactant. Initial physical examination was remarkable for generalized edema, mild ascites, hepatomegaly and a bent and bruised left arm. A chest X-ray showed moderate hyaline membrane disease and an exuberant periosteal reaction involving the humeral diaphyses and the ribs [Figure A]. Skeletal X-rays demonstrated an extensive symmetrical involvement of other bones, including the femurs [Figure B] and the mandible [Figure C]. The periosteal reaction seen in the X-rays is consistent with prenatal-onset infantile cortical hyperostosis, also known as prenatal Caffey disease.

Investigations for possible causes of hydrops fetalis in our patient were negative. These included white blood cell count, hemoglobin and platelet count,

[A] Lung appearance consistent with hyaline membrane disease. There was an exuberant periosteal reaction involving the humeral diaphyses and the ribs. **[B]** Periosteal reaction involving the entire length of the femoral diaphysis. **[C]** Periosteal reaction involving the mandible. **[D]** X-rays of both upper limbs at 3 months of age: There is evidence of bony remodeling and increased osseous definition seen at the humeral, ulnar and radial diaphyses. No periosteal reaction is noted.



heart anatomy on echocardiogram, ophthalmological examination, serology for congenital infections (TORCH, syphilis and parvovirus), and metabolic screen for urine organic acids, serum amino acids, storage disease (mucopolysaccharides, oligosaccharides) and hexosaminidase.

Her course in the neonatal intensive care unit was complicated by hyaline membrane disease and persistent pulmonary hypertension. She was ventilated for 5 weeks, followed by continuous positive airway pressure, with supplemental oxygen and diuretic therapy for an additional 3 months. She had conjugated hyperbilirubinemia, with normal liver enzymes from the first day of life, treated with ursodiol and resolving after several weeks. She was treated with supplementation of vitamin D, calcium and phosphate. The periosteal reaction resolved completely before discharge at age 3.5 months [Figure D].

COMMENT

Histological analysis of cortical areas in Caffey disease reveals abnormal deposition of hyperplastic, immature lamellar bone that replaces the original cortical bone. Additional findings include thickening of the periosteum, intense proliferation of subperiosteal cells and fibrosis of bone marrow [4]. Collectively, these findings suggest a common pathway of an inflammatory reaction [5]. The appearance of this process early in gestation may explain the lethality of prenatal-onset Caffey disease. The fibrotic bone marrow generates hepatic myeloid extramedulary hematopoiesis that leads to significant hepatomegaly which, combined with a small thoracic cavity due to the widened ribs, results in the development of hypoplastic lungs. Furthermore, exuberant extramedulary hematopoiesis in the periportal areas might also compress the terminal portal venules, resulting in presinusoidal portal hypertension leading to anasarca and hydrops that may also contribute to the development of pulmonary hypoplasia [5].

Schweiger et al. [1] reviewed 44 reported cases of Caffey disease with antenatal onset, identifying severe and mild forms of the condition. Severe prenatal cortical hyperostosis was present in 26 patients: 11 were stillborn, of whom 6 had pulmonary hypoplasia; 15 were liveborn, 6 of whom died in the neonatal period due to respiratory problems. Polyhydramnios was the first presenting manifestation in most of these pregnancies. Additional findings included fetal hydrops or skin edema (50% of cases) and hepatosplenomegaly (31% of cases). In all survivors, a remarkable resolution of hyperostosis was observed after several weeks. Eighteen patients, classified as having the mild form, were born at term, and fetal hydrops, hepatomegaly or bone abnormalities were not detected before the 35th week of gestation [1].

The prenatal diagnosis of prenatal Caffey disease is based on ultrasound findings (as early as 14 weeks of gestation, average 27 weeks) of short and angulated bones with irregular diaphyses and increased echogenicity and, typically, the absence of fractures. The differential diagnosis of prenatal Caffey disease includes hypophosphatasia and camptomelic dysplasia, both of which can present bowing and angulation of long bones, and osteogenesis imperfecta type 2, usually associated with fractures. Congenital syphilis can present with periosteal new bone formation [3]. Three-dimensional computed tomography may be useful in the prenatal diagnosis of lethal infantile cortical hyperostosis.

Caffey disease can be sporadic or transmitted as an autosomal dominant disorder with variable penetrance (OMIM #114000). Affected members of some families with Caffey disease were found to be heterozygous for a missense mutation (3040 C→T) in exon 41 of the gene encoding the α1 chain of type I collagen (COL1A1), altering residue 836 (R836C) in the triple-helical domain of this chain [2,4]. This mutation was found in cases of the infantile as well as prenatal form of this disease. The COL1A1 gene is responsible for other collagen diseases such as osteogenesis imperfecta and Ehlers-Danlos syndrome [2]. In other familial cases, autosomal recessive inheritance has been suggested [2].

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"The television, that insidious beast, that Medusa which freezes a billion people to stone every night, staring fixedly, that Siren which called and sang and promised so much and gave, after all, so little"

Ray Bradbury (born 1920), American fantasy, horror, science fiction and mystery writer, many of whose works have been adapted into television shows or films