Prenatal Caffey Disease
Case Report and Review of the Literature

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Abstract

Background: Two forms of Caffey disease or cortical hyperostosis were described, a severe prenatal form and a milder infantile one. Both are characterized by massive periosteal bone formation that typically involve the diaphyses of long bones.

Case Report: We report a 26 week +4 days old baby girl whose mother had severe polyhydramnios. The baby was born with hydrops fetalis and some dysmorphic features. During routine chest X-ray, periosteal hyperostosis was observed in the ribs and both humeral diaphyses. Skeletal survey showed symmetrical extensive hyperostotic changes affecting the diaphyses of long bones, ribs, skull base and the mandible. These features were consistent radiologically with Caffey disease. The baby had lung hypoplasia, needed high ventilator parameters throughout her life and expired on day 33 of life.

Conclusion: Prenatal Caffey disease is a rare condition which when presented before the age of 35 weeks of gestation is characterized by extensive periosteal hyperostotic bone involvement, angulations and shortening of long bones, polyhydramnios, and hydrops fetalis with high lethality due to prematurity and lung hypoplasia.

Key Words: Prenatal caffey disease.

Introduction

CORTICAL hyperostosis is a rare condition that has been described in two forms: Prenatal and infantile forms. The classical infantile form was first described by Roske in 1930 and further characterized by Caffey and Silverman 1945. The classical infantile form is presented by an episode of massive periosteal new bone formation typically involves the diaphyses of long bones, ribs, mandible and clavicles [2,3]. Irritability, fever, bone ache (that may be severe enough to result in pseudo-paralysis), hyperesthesia, soft tissue swelling and redness involving one or several areas of the body are the main symptoms [4,5]. Other reported clinical findings include: Dysphagia, proptosis, nasal obstruction and individual nerve involvement that may result in localized palsies [6,7].

The manifestations usually appear before the age of 6 months. The clinical course is variable and unpredictable but usually the acute symptoms resolve over few months. The outcome is generally good with symptoms resolution usually before the age of one year [8,9]. Sometimes when paired bones such as tibia and fibula have been affected, a long term complication may be that of cross fusion and if this involves adjacent ribs it may result in progressive thoracic scoliosis with respiratory compromise [10]. Relapses may occur several years later [11-13].

The prenatal form of Caffey disease has a more severe course if the onset starts before 35 weeks of gestation with hyperostotic bone involvement, angulations and shortening of long bones, polyhydramnios, fetal hydrops, lung hypoplasia, prematurity and high lethality. If the condition started after 35 weeks, it will have a milder course [14,15].

Case Report

We report one baby girl who was born at 26 weeks +4 days of gestation with birth weight 1100 gm, head circumference (25cm) and length (31cm). The baby was a product of normal vaginal delivery with Apgar scores of 4 and 7 at one and five minutes respectively. She was depressed at birth and needed intubation in the labor room. The baby was generally edematous and there were some dysmorphic features in the form of; depressed nasal bridge, low set ears, short upper limbs, and bilateral simian creases.

The mother who was 22 years, primigravida and her blood group was A +ve. Antenatal ultrasound revealed severe polyhydramnios and shortening of long bones suggestive of skeletal dysplasia. She received course of dexamethazone before delivery.
The baby was admitted directly to NICU. Chest X-ray showed hyaline membrane disease, increased bone density and periosteal reaction involving humeral diaphyses and the ribs. The baby received 2 doses of surfactant and she needed high parameters of mechanical ventilation then high frequency ventilation for most of her life. Echo-cardiography done on the 2nd day of life revealed minimal pericardial effusion with no major structural anomalies. Inhaled nitric oxide was started on day 10 for treatment of pulmonary hypertension that was diagnosed by echocardiography. The condition was complicated by bilateral pneumothorax and pneumo-mediastinum on day 13 and Pulmonary interstitial emphysematous (PIE) changes.

The abdomen had been distended since birth with mild hepatomegaly. Abdominal US revealed moderate ascites with no evidence of other intra-abdominal anomalies.

Neurologically, the baby had been hypoactive and hypotonic since birth with no evident abnormal movements. Cranial US revealed lissencephaly as a co- incidental finding and there was no evidence of intra-cranial hemorrhage.

An attack of clinical sepsis complicated the condition on day 7 which was manifested by deterioration of the general condition, higher ventilatory parameters, deterioration of renal functions (which had been initially normal), marked hypo-albuminemia, thrombocytopenia and further rise of CRP which had been always high. There were no positive blood cultures but ETT secretions revealed Pseudomonas Aeruginosa colonization and there was relative improvement in the general condition as well as laboratory findings after starting Meropenem and AmBisome empirically.

The baby deteriorated again on day 30 in absence of any laboratory proof of sepsis. She was hypotensive with severe metabolic acidosis, thrombocytopenia, positive CRP and she needed higher ventilatory parameters. Her condition kept on deteriorating till she expired on day 33 of life.

Renal functions had always been normal since birth except during the course of clinical sepsis when they temporarily rose. Hepatic functions (including ALT, AST, GGT and Alkaline Phosphatase) also had been always normal with mild cholestatic jaundice.

TORCH screening for both the baby and the mother and metabolic screening using (Neogen) filter paper were both normal. Chromosomal study revealed 46 XX normal female karyotype.

Skeletal X-rays taken on the first day of life showed symmetrical extensive hyperostotic changes affecting the diaphyses of long bones and the ribs which became markedly irregular with diaphyseal cortical thickening, no osteolytic changes or pathological fractures. Those changes spared phalanges, vertebrae and hip bones (Fig. 1). Cortical periosteal new bone is noted at the mandible and skull base (Fig. 2). There was some improvement of the radiological findings with less hyperostosis and less cortical thickening of the long bones diaphyses during the stay in the hospital (Fig. 3).
Two forms of cortical hyperostosis or Caffey Disease have been described, the prenatal and the infantile ones [1,15]. The prenatal form was further described into two forms: 1- A severe form with an onset before 35 weeks of gestation and generally associated with polyhydramnios, lung disease, prematurity, and high lethality. 2- A mild form with an onset after 35 weeks of gestation and without complications [15].

Both autosomal recessive and dominant inheritance has been suggested with some sporadic cases reported. The dominant inheritance seems to be more common in the mild prenatal form. All races are affected with equal ratio in males and females [8,15].

The proposed mechanism includes hypoxia due to inherited defects of the arterioles of the periosteum resulting in hypoxic damage which acts as an inciting event of periosteal reaction followed by subperiosteal bone formation with new lamellar immature bone that replaces the original cortical bones [14,16]. Histologically there is thickening of the periosteum, intense proliferation of subperiosteal cells and fibrosis of the bone marrow [17]. These findings suggest a common pathway of an inflammatory reaction [18].

Fibrosis of bone marrow generates hepatic myeloid extra-medullary hematopoiesis that leads to hepatomegaly which, when combined with small thoracic cavity due to widened ribs results in hypoplastic lungs. Exuberant extramedullary hematopoiesis in the peri-portal areas might also compress the terminal portal venules, resulting in pre-sinusoidal portal hypertension leading to ana-sarca and hydrops that may contribute to the development of pulmonary hypoplasia [18].

There are no diagnostic laboratory tests for Caffey Disease in general but the condition is usually associated with high ESR, CRP, alkaline phosphatase, white blood cells, platelet count and immunoglobulin levels [10,19,20].

The differential diagnosis of prenatal Caffey Disease includes: Hypophosphatasia, camptomelic dysplasia, osteogenesis imperfecta and congenital syphilis [14].

Our case was born prematurely at 26 weeks +4 days of gestation with an antenatally diagnosed polyhydramnios and postnatally diagnosed hydrops (generalized edema, pericardial effusion and ascites) which are all consistent with severe form of Prenatal Caffey Disease [15]. Lung hypoplasia was suggested by the need for high frequency oscillator from the first day of life, the air leak and the pulmonary hypertension which is also consistent with severe Prenatal Caffey Disease [15,18]. There was hepatomegaly and CRP had always been high as described in most of the cases of Caffey Disease [18,20], while, ESR and Platelet count were low and alkaline phosphatase was normal in the contrary to most of the reported cases but these again are not specific for the diagnosis [18,20].

Hypophosphatasia was ruled out as alkaline phosphatase was normal. Camptomelic dysplasia was ruled out clinically and radiologically as vertebrae, pelvic bones and phalanges were spared and ribs’ number was 12 and not 11 as usual in this condition [21]. Osteogenesis imperfecta was ruled out also clinically and by the absence of the characteristic multiple fractures radiologically.

Congenital Syphilis was ruled out by negative ante-natal serology and radiologically by the confined bony affection to the diaphyses of the bones and not the metaphyses, absence of destructive lesions and the improvements without specific anti-syphilitic treatment [22].

The radiological findings were typical for Caffey Disease with extensive irregular hyperostotic bone involvement which was confined to the diaphyses of long bones and ribs, sparing metaphyses and epiphyses and also sparing the spine, phalanges and the pelvis with no evidence of fractures or erosions [23].

References
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