

Antenatal Diagnosis of Prenatal Cortical Hyperostosis: Case Report

Prenatal Kortikal Hiperostozisin Antenatal Tanısı

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ABSTRACT Caffey disease or cortical hyperostosis is characterized by massive subperiosteal new bone formation at diaphyses of long bones mandible and clavicle as a result of a multifocal inflammatory skeletal process and classified into two forms regarding the onset of the disease: infantile form and prenatal form. Prenatal form with earlier onset tends to be more severe and a less frequently encountered diagnosis while late onset infantile form is usually presents with a self limiting disease. Polyhydramnios, irregularly shaped bones and hepatomegaly should raise suspicion about this rare disease when detected on ultrasonographic examinations. Here we present a case of severe prenatal cortical hyperostosis diagnosed by ultrasonographic examinations performed at 31 weeks of gestation that was revealed to have polyhydramnios, hepatomegaly, pulmonary hypoplasia and irregularly shaped long bones.

Key Words: Hyperostosis, cortical, congenital; abnormalities; hepatomegaly; polyhydramnios; lung agenesis

ÖZET Caffey sendromu ya da kortikal hiperostozis, iskelet sistemindeki multifokal inflamatuvar bir sürecin sonucu olarak uzun kemiklerin diafizlerinde, mandibulada ve klavikulada masif subperiosteal kemik formasyonu ile karakterize bir hastalıktır. Hastalığın başlangıç zamanına göre infantil ve prenatal olmak üzere iki formu bulunmaktadır. Daha erken başlangıçlı olan prenatal form daha şiddetli olmakla beraber daha nadir rastlanmaktadır. Buna karşın geç başlangıçlı infantil formu çoğunlukla kendi kendini sınırlayan bir hastalık tablosu ile prezente olmaktadır. Ultrasonografik incelemelerde polihidramniyoz, anormal yapılı kemikler ve hepatomegali saptandığında ayırıcı tanılar arasında bu hastalık da düşünülmelidir. Burada 31. gebelik haftasında yapılan ultrasonografik inceleme ile tanı konulmuş, polihidramniyoz, hepatomegali, pulmoner hipoplazi ve uzun kemiklerde düzensizlikler ile kendini gösteren şiddetli bir prenatal kortikal hiperostozis olgusu sunulmaktadır.

Anahtar Kelimeler: Hiperostozis, kortikal, konjenital; anormallikler; hepatomegali; polihidramniyoz; akciğer agenezi

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Infantile cortical hyperostosis or Caffey disease is first described by Roske in 1930 and it is characterized by massive subperiosteal new bone formation at diaphyses of long bones mandible and clavicle as a result of a multifocal inflammatory skeletal process.¹ Caffey disease is classified into two forms (infantile form and prenatal form) and it is self limiting when presented near or after birth. Disease gets more severe as presentation occurs earlier. Infantile form of the disease is seen 3/1000 infants while there is only handful of cases reported about prenatal form of the disease.²

CASE REPORT

The patient was 32 years old nulligravid woman attended at her first pregnancy provided by in vitro fertilization after 6 years of infertility. Both partners are free from any co-morbidities and family history was unremarkable. There is no consanguinity between partners. Hemoglobin, TSH, free T3, free T4 levels were within normal limits. Rubella IgM, syphilis, hepatitis B and human immune deficiency virus were all found negative. First and second trimester screening tests were within normal limits. Pregnancy follow-up of the patient was unremarkable until the pregnancy proceeds to 20 weeks of gestation. Detailed obstetric ultrasonography that was performed at 22 weeks of gestation revealed bilateral clinodactyly at 5. phalanx and 2 weeks of retardation was found in fetal biometric measurements moreover bilateral lateral ventricle diameters were found at upper limits of normal range (9,6 milimeter). Due to the suspicion about chromosomal anomaly amniocentesis was performed 15 days later and revealed a normal 46XX karyotype. Polyhydramnios, hepatomegaly, pulmonary hypoplasia and irregularities in long bones were found at ultrasonographic examination performed at 31 weeks of gestation and also hydrocephaly was observed to be developed. Termination was offered to family due to the fetal anomaly that was considered incompatible with life however the family refused pregnancy termination. At 33 weeks 5 days of gestation patient administered with regular contractions and ruptured amniotic membranes. Ultrasonography revealed the fetal demise and fetal biparietal measurement was found compatible with 38 weeks of gestation. Digital vaginal examination revealed full dilatation and effacement of cervix. After 30 minutes a 2400 g female fetus was stillborn. The fetus has facial swelling, generalized edema, retrognathia, microstomia, relative macrocephaly, angulated thighs and legs, protuberant abdomen and fragile skin (Figure 1, 2). Radiographic evaluation of fetus demonstrate cortical hyperostosis, curved tibia, and irregularities on bone cortex as well as reduced size of thoracic cavity (Figure 3, 4). Tissue samples ob-



FIGURE 1, 2: Facial swelling, generalized edema, retrognathia, microstomia, angulated thighs and legs, protuberant abdomen and fragile skin could be seen in these figures.

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tained from fetus evaluated for COL1A1 (c.3040 C>T) mutation and found negative.

Ethical issues: A written informed consent was obtained for publication of this case report.

DISCUSSION

Infantile cortical hyperostosis or Caffey disease is first described by Roske in 1930 and it is characterized by massive subperiosteal new bone formation at diaphyses of long bones mandible and clavicle as a result of a multifocal inflammatory skeletal process.¹ Caffey disease is classified into two forms (infantile form and prenatal form) and it is self limiting when presented near or after birth. Disease gets more severe as presentation occurs earlier. In infantile, mild form onset of disease was seen at 6 months after birth and resolves spontaneously at 2 or 3 years of age.³ Prenatal, severe form of the disease usually emerges before 35 weeks of gestation and usually follows a lethal course.¹ Fetal anemia has been previously demonstrated in prenatal form of Caffey disease.⁴ Severity of the early onset prenatal form of the disease was attributed to



FIGURE 3, 4: Cortical hyperostosis, curved tibia, and irregularities on bone cortex as well as reduced size of thoracic cavity could be seen on plain radiographs.

hepatomegaly as a consequence of hepatic myeloid extramedullary hematopoiesis caused by fibrotic bone marrow, small thoracic cavity and subsequent pulmonary hypoplasia. Moreover, increased compression on terminal hepatic venules results with presinusoidal portal hypertension, anasarca and ascites that may further contribute the development of pulmonary hypoplasia in the course of disease process.⁵ Some authors also suggest that vascular occlusion secondary to thrombocytosis may also have a role in pathogenesis.⁶ Prognosis of prenatal

form of Caffey disease is poor usually due to prematurity and pulmonary hypoplasia.

Irregularly shaped bones could be misinterpreted as fractures in ultrasonographic examination so Caffey disease should be differentiated from osteogenesis imperfecta. In this case we also face the diagnostic dilemma about ultrasonographic appearance of irregularly shaped bones. We should note that it could be extremely easy to misinterpret them as fractures so attentive ultrasonographic examination has crucial importance in differential diagnosis of prenatal Caffey disease. Existence of irregularly shaped bones with polyhydramnios should raise suspicion of prenatal form of Caffey disease.

Inheritance pattern of Caffey disease is still not clear. Both dominant and recessive patterns are suggested and mild forms are considered to be inherited in a dominant fashion. Moreover high rates of postnatal improvement could be associated with reduced penetrance.¹ Recently, a mutation in gene coding alpha 1 chain of type 1 collagen (COL1A1) described in both infantile and prenatal form of Caffey disease.⁷ This gene is considered to be inherited in an autosomal dominant pattern with variable penetrance. Inheritance pattern in the other cases that do not demonstrate this mutation is thought to be autosomal recessive.³ Our case was found negative for COL1A1 gene mutation without affected parents so an unknown gene with autosomal recessive inheritance pattern could be responsible from the disease in this case as well as other cases of prenatal Caffey disease that do not show COL1A1 mutation.

Schweiger et al. published the largest review about antenatal onset Caffey disease.¹ They assessed 44 reported cases of prenatal Caffey disease. They classified prenatal Caffey disease as severe if fetal hydrops, hepatomegaly and bone abnormalities detected before 35 weeks of gestation and as mild if these abnormalities detected after 35 weeks of gestation. Twenty-six of 44 cases were classified as severe prenatal cortical hyperostosis in whom prognosis was poor. Eleven of the 26 fetuses were stillborn and 6 of the remaining 15 liveborn fetuses

died in the neonatal period due to respiratory problems. Fetal hydrops and skin edema detected 50% and hepatomegaly was detected 31% of these cases. Polyhydramnios was found to be the first finding in most of the cases.¹ In one case a transient ventriculomegaly was the first abnormality detected in a fetus with prenatal Caffey disease however our case is the first report of prenatal severe Caffey disease with hydrocephaly in the literature.⁸

Diagnosis of prenatal form of Caffey disease largely depends on ultrasonographic examinations. Bone changes in prenatal Caffey disease averagely

detected at 27 weeks of gestation however there are reports that demonstrate bone changes as early as 14 weeks of gestation in literature.⁹ Hypophosphatasia and camptomelic dysplasia could be both presented with angulations in long bones. Osteogenesis imperfecta type 2 is usually associated with fractures and fractures could be easily misinterpreted as bone irregularities in ultrasound examination. Congenital syphilis is also associated with periosteal bone formation. All of these conditions should be considered in differential diagnosis of prenatal Caffey disease.

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