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Antenatal Approach to Skeletal Dysplasia: Case Report of Chondrodysplasia Punctata

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Abstract: ***Chondrodysplasia punctata (CDP) is a rare skeletal dysplasia characterized by abnormal cartilage development and punctate calcifications. We report a case of a 32-year-old multigravida woman referred at 22 weeks' gestation for a routine anomaly scan that revealed stippled femoral epiphyses, flat facies, depressed nasal bridge, increased frontonasal angle, and polyhydramnios, raising suspicion for skeletal dysplasia. Amniocentesis identified a pathogenic variant in the EBP gene, confirming the diagnosis of X-linked dominant CDP. Following multidisciplinary counseling, the couple opted to continue the pregnancy with plans for palliative care. Serial ultrasounds monitored fetal growth. At 38 weeks, the patient underwent cesarean delivery of a female infant exhibiting characteristic CDP features, including limb shortening, dysmorphic facies, and epiphyseal calcifications. The neonate developed respiratory distress and metabolic abnormalities, necessitating admission to the neonatal intensive care unit for respiratory support, metabolic management, and genetic evaluation. This case highlights the importance of detailed prenatal ultrasound evaluation, genetic testing, multidisciplinary counseling, and anticipatory management in the care of fetuses with CDP. Early diagnosis enabled informed decision-making and preparation for postnatal care of this complex skeletal dysplasia.***

Keywords: Chondrodysplasia Punctata, Skeletal Dysplasia, Prenatal Diagnosis, Ultrasonography, Genetic Testing, Genetic Counseling

1. Introduction

Skeletal dysplasias also known as osteochondrodysplasias, are a large heterogeneous group of disorders consisting of skeletal abnormalities. Skeletal dysplasias are a heterogeneous group of genetic disorders characterized by abnormalities in bone and cartilage development, leading to disproportionate short stature and various skeletal deformities. The primary etiology is genetic mutations, which begin at an early stage of fetal development and continues to evolve throughout life.[1] Their overall prevalence has been reported to be 2.3-7.6 per 10000 births in various studies.[2]

According to Nosology Committee of the International Skeletal Dysplasia Society, the latest and tenth version of the Nosology comprises 461 different diseases which are further classified into 42 groups based on their clinical, radiographic, and/or molecular phenotypes.[3]

Chondrodysplasia punctata (CDP) is a rare, heterogeneous group of skeletal dysplasias characterized by abnormal cartilage development and punctate calcifications in various tissues. It is distinguished by sporadic tiny calcifications at the metaphysis of long bones and irregular calcium deposits in the metaphyseal cartilage that result in punctate calcification. Genetic mutations resulting in chromosomal aberration or congenital enzymatic metabolic abnormalities are the primary cause of this illness.[4]The etiological classifications, genetic makeup, and clinical symptoms are quite intricate.[5]The clinical manifestations of CDP can range from mild to severe, and include disproportionate short stature, craniofacial dysmorphism, limb shortening, and epiphyseal stippling.

Because of a multitude of characteristics, such as their high number and phenotypic variety with overlapping traits, foetal skeletal dysplasias are challenging to detect in utero. For many illnesses, there is no systematic strategy or accurate molecular diagnosis. The inability of ultrasonography to offer a comprehensive picture. The fluctuation in the period between discoveries in some skeletal dysplasias.[1]

Antenatal diagnosis plays a crucial role in the management of these conditions, allowing for early intervention and appropriate counseling. This case report illustrates the importance of a comprehensive antenatal approach in the diagnosis and management of skeletal dysplasia.

2. Case Report

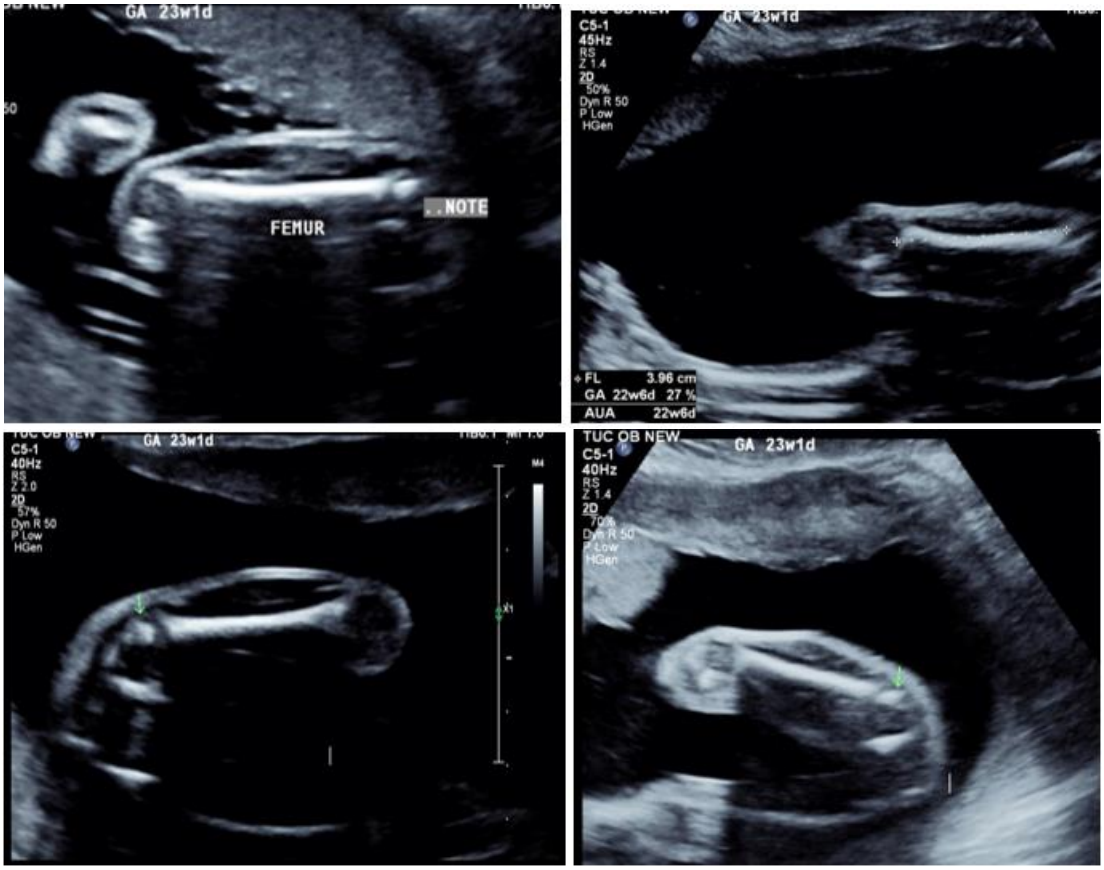
A 32-year-old G3P2L1 woman was referred to our tertiary care center at 22 weeks of gestation for a routine anomaly scan. GE LOGIQ P9 R3 Ultrasound machine with 1-5 curvilinear probe was used and Step by step fetal anatomical survey was done. The ultrasound findings revealed stippled femoral epiphyses, flat face, Depressed nasal bridge (saddle nose) with increased frontonasal angle (151 degree), however the nasal bone length was normal in this case and polyhydramnios was found raising concerns for a potential skeletal dysplasia.

The patient was advised further evaluation with Amniocentesis exome sequence. Given the significant findings, genetic counseling was provided, and the couple opted for invasive prenatal testing. Amniocentesis was performed, and the results revealed a pathogenic variant in the EBP(+) (ENST00000495186.6) gene, consistent with the diagnosis of Chondrodysplasia punctata,a X-linked dominant disease.

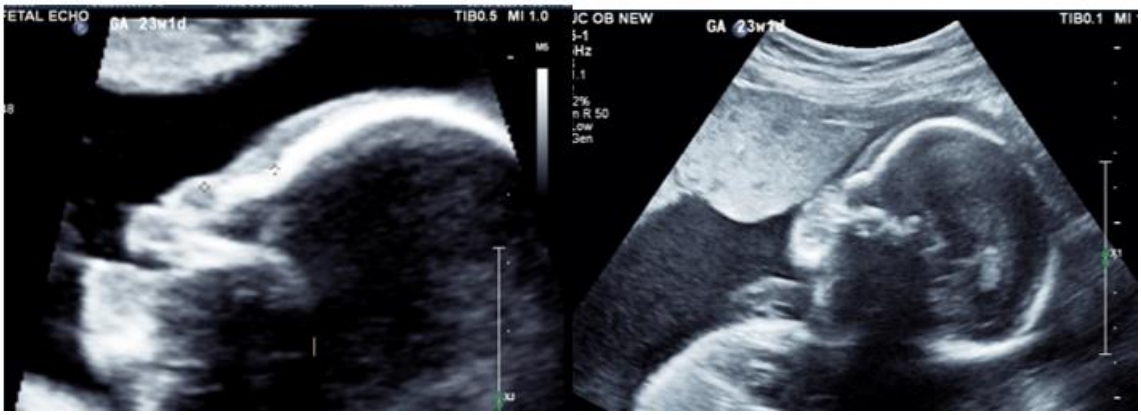
After extensive counseling and discussions with the multidisciplinary team, including maternal-fetal medicine specialists, geneticists, and neonatologists, the couple decided to continue the pregnancy with palliative care measures in place for the newborn.

The patient received regular antenatal follow-up, with serial ultrasound assessments to monitor fetal growth and well-being. At 38 weeks of gestation, she underwent an elective cesarean delivery, and a female infant was born with characteristic features of CDP, including shortening of the limbs, dysmorphic facial features, and punctate calcifications in the epiphyseal regions.

The infant was immediately evaluated by the neonatology team and was found to have respiratory distress and metabolic abnormalities consistent with CDP. She was admitted to the neonatal intensive care unit (NICU) for specialized care, including respiratory support, metabolic management, and genetic evaluation.



Picture 1: USG showing Stippled femoral epiphyses



Picture 2: USG showing depressed nasal bridge (saddle nose) with increased frontonasal angle (151 degree)

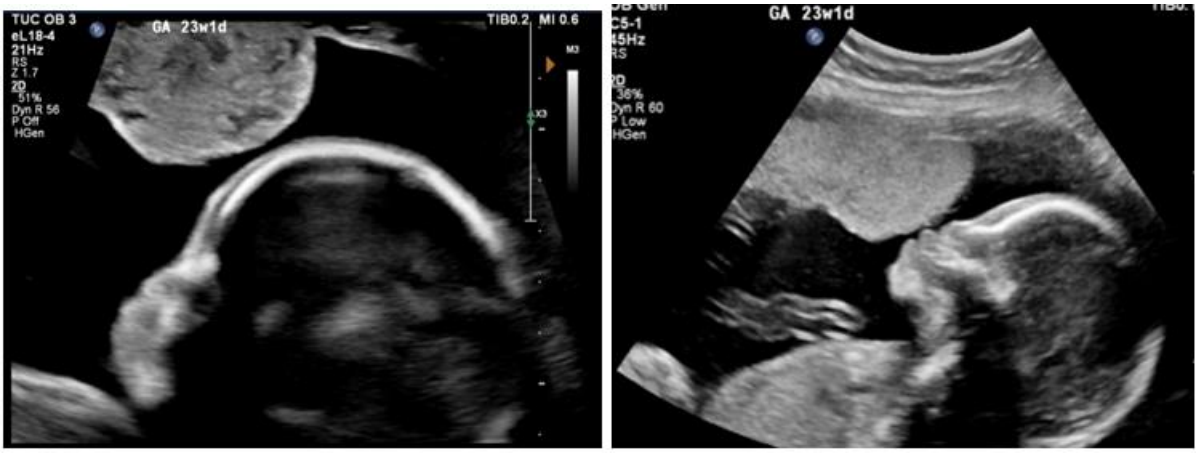


Figure 3: USG showing Flat face

3. Discussion

This case highlights the importance of a comprehensive antenatal approach in the diagnosis and management of skeletal dysplasias. Early detection through detailed ultrasound assessments, coupled with genetic testing and multidisciplinary counseling, allowed for an accurate diagnosis and informed decision-making by the parents.

The ultrasound findings described in our case report, such as shortening of long bones, punctate epiphyseal calcifications, and facial dysmorphism, are consistent with the typical prenatal ultrasound presentation of chondrodysplasia punctata reported in larger case series and studies.

Our case report emphasizes the importance of genetic testing for confirming the diagnosis and identifying the specific subtype of chondrodysplasia punctata. The identification of the EBP(+) (ENST00000495186.6) gene, consistent with the diagnosis of Chondrodysplasia punctata, is a crucial step in providing accurate genetic counseling and tailoring management strategies. EBP spans 7 kb of genomic DNA and is found on the short arm of the X chromosome (Xp11.22-p11.23). Its five exons code for a spliced transcript of one kilobase. EBP is found in the endoplasmic reticulum and is broadly expressed in all tissues. It has a molecular weight of 27 kDa and 230 amino acids, including 4 transmembrane domains. Over 70 EBP mutations have been found thus far. The final phase of sterol synthesis involves the isomerization of cholest-8(9)-ene-3β-ol to ketene sterols, which is catalysed by Δ8-Δ7 isomerase, an enzyme that is encoded by EBP. This process converts lanosterol to cholesterol.[6] Extensive problems arise from the accumulation of 8-dehydrocholesterol (8-DHC) and 8(9)-cholesterol in the epidermis, plasma, and other tissues, which is caused by a 6EBP mutation.

26 female patients with probable CDPX2 mutations were examined by Herman et al.[7] Twenty-two of the 26 individuals had EBP mutations, 13 of which were de novo. The majority of EBP mutations for CDPX2 are missense and nonsense single-nucleotide alterations in exons. Splice site mutations have also been documented, despite the fact that most mutations occur in exons. Although Trp61X, Arg110Gln, and Arg147His are often reported mutation sites, the reasons behind these recurrent hotspot mutations remain unclear.[8–12] Ikegawa et al.[13] (2013) came to the conclusion that missense mutation produces noncanonical CDPX2, while truncation of the protein owing to nonsense EBP mutation leads in canonical CDPX2.A growing number of experts think that the phenotype and genotype of CDPX2 are unrelated.[10, 11, 14] According to this research, CDPX2 was caused by a heterozygous EBP mutation (c.440G>A [p.Arg147His], a known causal mutation). This mutation, which changes arginine to histidine, is missense. The patient's parents were not carriers, according to a Sanger test, suggesting that the foetus' mutation happened from scratch. Cases involving this mutation location have previously been reported by Whittock et al., Has et al., and Cañueto et al.[9–11]

Several studies have highlighted the significance of molecular genetic testing in chondrodysplasia punctata. Our report aligns with the recommendations and practices outlined in other studies and case series, which emphasize the importance of a multidisciplinary approach and comprehensive counseling in the management of chondrodysplasia punctata.

A study by Catapano F et al.[15] (2022) underscored the need for a multidisciplinary team, including maternal-fetal medicine specialists, geneticists, neonatologists, and other specialists, to provide coordinated care and counseling for families affected by skeletal dysplasias, including chondrodysplasia punctata.

The postnatal management strategies and potential complications described in our case report, such as respiratory support, metabolic management, and specialized care in the neonatal intensive care unit (NICU), are consistent with the experiences and recommendations reported in other studies and case series.

Overall, our case report aligns with the existing literature in terms of prenatal ultrasound findings, the importance of genetic testing and subtype identification, the need for a multidisciplinary approach and comprehensive counseling, and the postnatal management strategies for chondrodysplasia punctata. However, it also highlights the individualized nature of each case and the need for tailored care based on the specific clinical presentation and circumstances.

The timely diagnosis of chondrodysplasia punctata, a form of skeletal dysplasia, enabled the healthcare team to provide appropriate counseling, support, and palliative care planning for the family. While the outcome was tragic, the antenatal approach ensured that the parents were fully informed and supported throughout the process.

4. Conclusion

Skeletal dysplasias pose significant challenges in antenatal management, requiring a multidisciplinary approach involving maternal-fetal medicine specialists, geneticists, and other healthcare professionals. Early detection through comprehensive ultrasound assessments and genetic testing is crucial for accurate diagnosis, counseling, and appropriate management strategies. This case underscores the importance of an antenatal approach in improving outcomes and providing compassionate care for families affected by these complex conditions.

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