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Case Report

# Familial Cleidocranial Dysplasia in a Neonate: A Case Report

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## ABSTRACT

***Background:*** Cleidocranial dysplasia (CCD) is a rare inherited skeletal dysplasia, with an incidence of 1 case per 1000,000 individuals. It is a form of predominantly autosomal dominant inheritance and is associated with a mutation in runt related transcription factor-2 gene mapped on chromosome 6p21. This disease primarily affects the bones formed by intramembranous ossification and is characterized by the aplasia or hypoplasia of the clavicles, delayed closure of fontanelles, open skull sutures, supernumerary teeth, wide pubic symphysis, and short stature. The phenotypic spectrum can range from individuals with minor dental anomalies to severe manifestations, like syringomyelia. The early diagnosis of CCD may be difficult because the craniofacial abnormalities become obvious usually during adolescence.

***Case report:*** Herein, we reported a rare case of a neonate with features of classical CCD coupled with a positive family history extending over three generations. This report aimed to create awareness among the paediatricians regarding CCD and highlight the importance of the early diagnosis of this rare disorder to prevent the associated complications.

***Conclusion:*** Though the diagnosis of CCD in neonatal period is a challenge, the clinical features along with the characteristic family history and radiographic findings, help to establish the diagnosis with confidence.

***Keywords:*** Autosomal dominant, Cleidocranial dysplasia, Hypoplasia of clavicle, Neonate

## Introduction

Cleidocranial dysplasia (CCD), also known as Cleidocranial dysostosis, mutational dysostosis, and Marie-Sainton syndrome (named after the people who first described the medical condition), is a rare polyostoticskeletal dysplasia with a predominant involvement of the membranous bone. It is inherited in an autosomal dominant fashion with an incidence of 1 case per million individuals worldwide with no predilection for sex or ethnic group (1).

The CCD is primarily characterized by retardation in bone ossification, hypoplastic clavicles, as well as various craniofacial and dental abnormalities. Despite the presence of these clinical findings at birth, they are often either missed or diagnosed much later (2). Herein, we presented a case of CCD in a neonate with classical clinical features, coupled with a strong family history.

## Case report

A term female neonate was born to non-consanguineous parents at 38 weeks of gestation, with a history of CCD in mother, maternal grandmother and her sibling, and great-grandmother (Figure 1). The newborn was antenatally detected to have long bones less than the 5$^{th}$ centile for age and mid-facial hypoplasia. Her birth weight was 2,730 g with a height of 46 cm (between the 10 and 25$^{th}$ centile as per Lubchenco growth chart), and head circumference of 33 cm.

Upon examination, she was detected with the hypermobility of bilateral shoulder joints (Figure 2), wide fontanelles, open sutures, frontal bossing,

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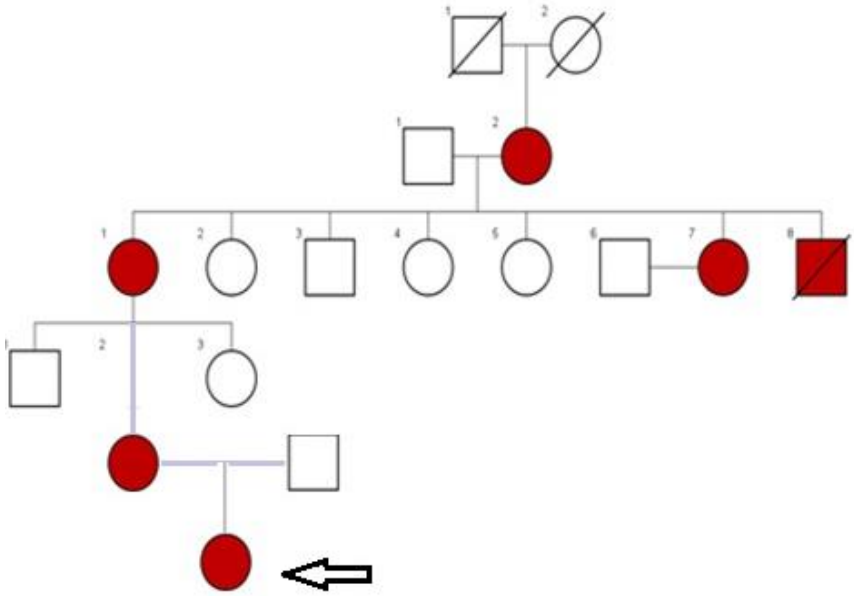

**Figure 1.** Pedigree chart showing affected members in every generation

**Figure 2.** Neonate with hypermobility of shoulders

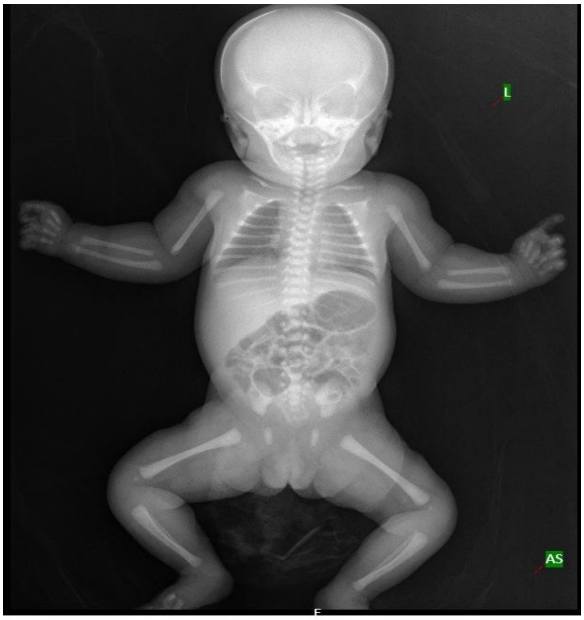

**Figure 3.** Infantogram of the neonate showing hypoplasia of bilateral clavicles

hypertelorism, and short limbs. X-ray findings revealed the hypoplasia of both clavicles with a bell-shaped thorax (Figure 3). Based on the positive family history, coupled with pathognomonic clinical and radiologic findings, the patient was diagnosed with CCD. The neonate remained asymptomatic during the hospital stay with no feeding or respiratory difficulty, and her parents were offered genetic counselling regarding the regular follow-up of the child.

## Discussion

Cleidocranial dysplasia is a form of predominantly autosomal dominant (AD) inheritance; however, autosomal recessive and sporadic cases have been also reported. This disease involves mutation in Runt related transcription factor -2 (*RUNX-2*)/core binding factor A1 gene on chromosome 6p21, which is responsible for the differentiation of

mesenchymal cells into osteoblasts (3).

In our case, genetic analysis was not performed due to the observation of a pathogenic sequence variant (c.470dupT, a novel truncating frameshift variant leading to premature stop codon) in exon 3 of *RUNX2* gene in the neonate's mother (4). Cleidocranial dysplasia manifests with several skeletal and dental defects, the most striking of which are the abnormalities of the skull, teeth, jaws, and shoulder girdle, as well as stunted long bones.

This disease has derived its name from the shoulder girdle defect, which ranges from the complete absence of the clavicles (in 10% of the cases) to the hypoplasia of the clavicles. This defect results in shoulder hypermobility, which was observed in our case. The delayed and imperfect ossification of the cranium leads to patent skull sutures with wide-open fontanelles, frontal bossing, hypertelorism, retention of primary teeth, failure of eruption, delayed maturation of the secondary dentition, and multiple impacted and supernumerary teeth (5, 6).

A variety of other skeletal abnormalities, such as bell-shaped thorax, brachydactyly, short stature, pubic symphysis, and hypoplasia of iliac bones, have been also mentioned in the literature. The clinical features noted in our case were the hypoplasia of the clavicles, hypermobility of bilateral shoulder joints, wide fontanelles, open sutures, frontal bossing, and hypertelorism. Familial history extending over three generations was a strong clue clinching an early suspicion in our case. Otherwise, diagnosis can be established based on characteristic clinical signs and radiographic findings.

Molecular genetic testing can be used to confirm the diagnosis in patients with atypical clinical and radiological findings. Moreover, antenatal ultrasound can be utilized to diagnose the problem as early as 14 weeks of gestation. The antenatal scan findings indicating the disease are abnormally short (<5$^{th}$ centile for gestational age) or absent clavicles, brachycephaly with undermineralisation, and generalised immature ossification (7).

Similar calvarial defects and delayed cranial ossification are also observed in other syndromes, such as Crane-Heise syndrome, Yunis-Varon syndrome, Pycnodysostosis, CDAGS syndrome, and hypophosphatasia. However, CCD can be differentiated from these disorders due to its specific features and genetic analysis (8). The complications of CCD include genu valgum, scoliosis, pes planus, recurrent sinusitis, recurrent otitis media, hearing loss, speech problems, and obstructive sleep apnea.

Therefore, the management of CCD requires a multidisciplinary, preventive, and long-term approach. This includes osteoporosis management, antibiotics administration for recurrent infections, speech therapy, removal of retained deciduous or supernumerary teeth, and implementation of cosmetic interventions, if required.

## Conclusion

In conclusion, though the diagnosis of CCD in neonatal period is a challenge, the clinical features of the disease, along with the characteristic family history and radiographic findings, help to establish the diagnosis. As rightly said, 'Prevention is better than cure', if the diagnosis is established early, one can also intervene early to prevent the associated complications. The time of CCD diagnosis may also affect the choice of the necessary treatment plan.

Parents need to be educated about this disease and advised for regular follow-up visits so that these complications can be addressed in the early stage. The malformations and complications associated with CCD would rarely result in significant disabilities with timely management, which also keep the prognosis at a favourable level.

## Acknowledgments

None.

## Conflicts of interests

None.

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