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Prenatal Detection of Cleidocranial Dysplasia: A Case Report Highlighting the Importance of Exploring Insignificant Ultrasound Signs

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Abstract

Cleidocranial dysplasia is a rare autosomal dominant skeletal disorder characterized by clavicular hypoplasia, delayed closure of fontanels, dental abnormalities, and other skeletal anomalies. This case report presents the prenatal detection of cleidocranial dysplasia by exploring a subtle abnormality during routine prenatal ultrasound examination, subsequent genetic confirmation, and postabortal X-ray analysis. The aim is to emphasize the importance of taking into account any apparently insignificant ultrasound finding to diagnose a fetal genetic abnormality.

Keywords

- cleidocranial dysplasia
- supernumerary ribs
- 3D ultrasound
- amniocentesis
- microarray

Introduction

Cleidocranial dysplasia (CCD), also known as cleidocranial dysostosis or Marie-Sainton syndrome, is caused by heterozygous mutations in the runt-related transcription factor 2 (RUNX2) gene and has a reported incidence of one in a million people.[1] It usually has an autosomal dominant mode of inheritance, though de novo mutations are also possible. About 70% of CCDs have a genetic basis, while the causes of the remaining are still unknown.[1] It affects multiple aspects of skeletal development and is characterized by delayed or absent clavicular ossification, open fontanels and sutures, dental anomalies, along with other skeletal abnormalities including supernumerary ribs.[2] While CCD is typically diagnosed postnatally or in childhood based on clinical and radiographic features, advancements in prenatal imaging techniques have enabled early detection and improved management.[3]

Case Presentation

A 28 year old primigravida initially came to us at her 16th week of gestation with a low risk of aneuploidy on first trimester screening (nuchal translucency scan and double marker test), which showed a risk ratio of 1:5095 for trisomy21 and 1:227 for trisomy 18/13. Her reason for referral to our center was a very low PAPP A value of 0.15 MoM in her double marker test report.

We decided to perform a genetic sonogram for her. The ultrasound examination was normal except for a subtle finding. We found a very small (3.6×1.9mm), highly echogenic linear structure unilaterally developing at the transverse process of the 7th cervical vertebra (►**Fig. 1A and B**). Following three-dimensional (3D) analysis with different rendering techniques, we were of the opinion that the structure might be a rudimentary cervical rib (►**Fig. 2A–C**). Looking for fetal clavicles is not within the typically recommended routine

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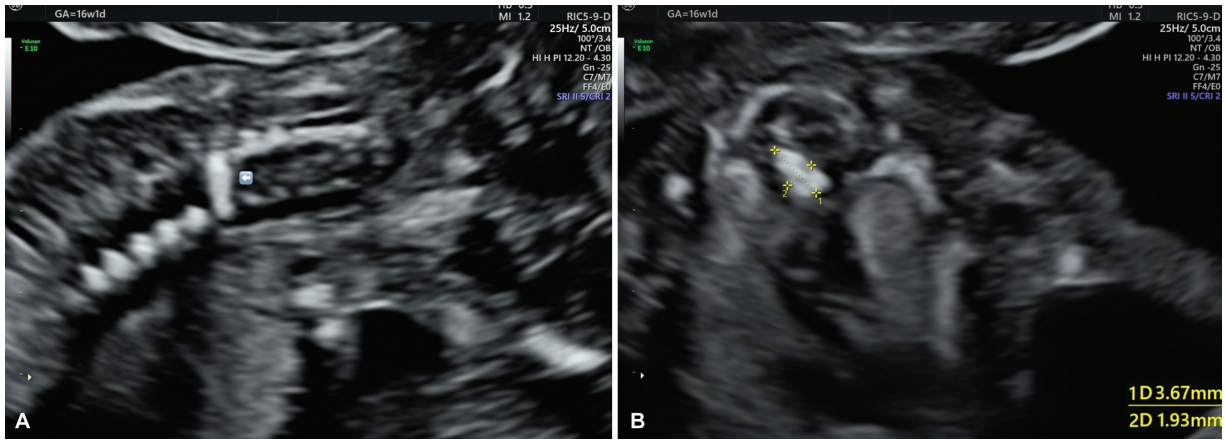

Fig. 1 (A) Sagittal image of fetal spine showing a linear echogenic projection. (B) Axial image of the fetal spine showing the echogenic projection and its size.

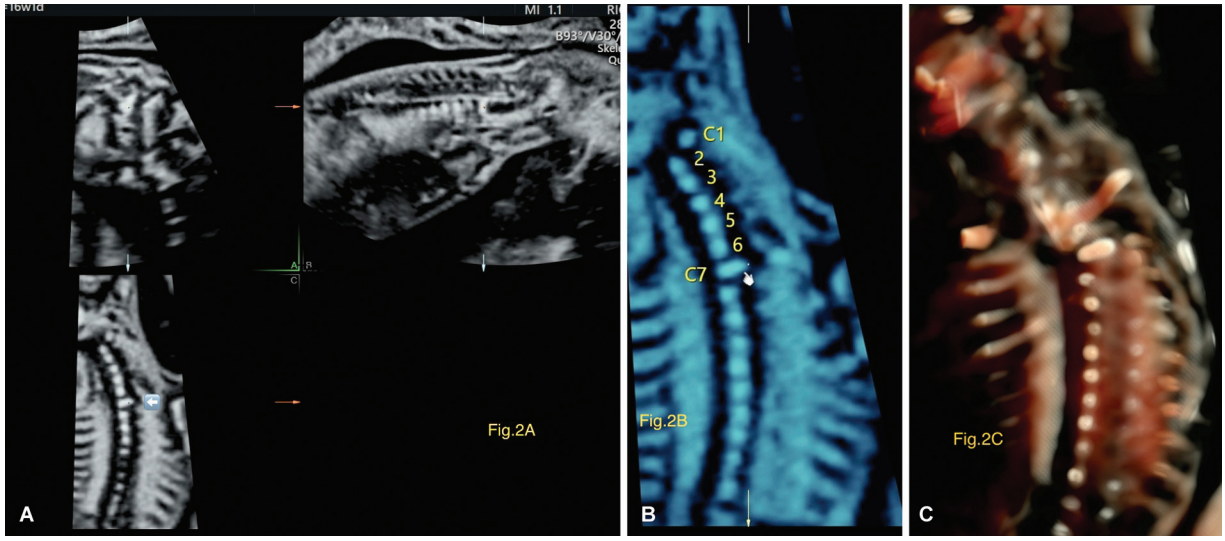

Fig. 2 (A) Three-dimensional (3D) volume-contrast imaging (VCI) multiplanar image of the spine localizing the echogenic projection. (B). Fetal spine in 3D VCI skeletal mode showing the bony projection at cervical 7 vertebral body. (C) Fetal spine in HDLive rendered mode with enhanced visualization of the bony projections.

ultrasound scan protocol. But we tried to image the fetal clavicles and found them on both sides. They could be well demonstrated by 3D techniques (►**Fig. 3A–C**). The fetal clavicles subjectively seemed to be short in length.

This observation was extremely important as any abnormalities of clavicles are considered a strong marker of CCD. To rule out any possible genetic association, we counseled the parents, and informed consent for invasive testing was obtained. Amniocentesis was performed at 16 weeks of gestation, and the sample was sent for chromosomal microarray for genetic analysis. The analysis revealed a deletion on chromosome 6p spanning approximately10,946.8kbp (~1MB) (►**Fig. 4**). This deletion on chromosome 6p21.1 hosting RUNX2 gene is reported to be causing CCD.[4] Following the confirmation of CCD, the couple opted for termination of the pregnancy due to the potential challenges associated with the diagnosis. Finally, they completed the process of abortion at 19 weeks. Postabortal fetal radiography was performed to further characterize the skeletal anomalies. The X-ray examination of the fetus exhibited radiological features of CCD, validating the prenatal diagnosis. The images revealed bilateral hypoplastic and poorly mineralized clavicles, macrocrania due to wide-open fontanels and sutures, and delayed ossification of the pubic and ischial bones (►**Fig. 5A–C**). However, the prenatal ultrasound finding of a very small echogenic bony structure present unilaterally at the C 7 vertebra could not be visible at postabortal X-ray, possibly due to its smallness and intrathoracic location obscured by adjacent vertebrae.

Discussion

CCD is a rare skeletal disorder with highly variable presentation and a lack of typical genotype phenotype match. The main features are aplasia to just partial hypoplasia of clavicles, open fontanelles that may remain nonossified permanently, and supernumerary teeth placed haphazardly in a crowded manner.[5] Prenatal detection is thus difficult, though ultrasound

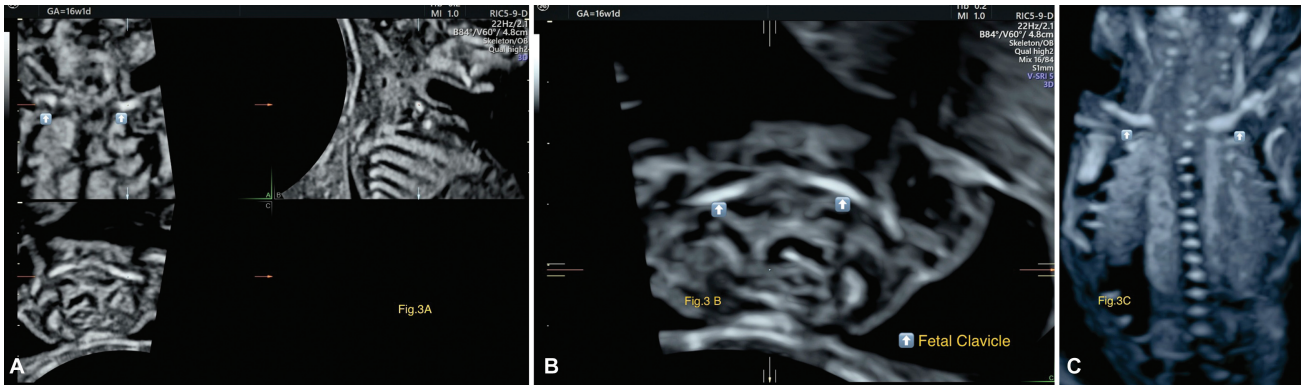

Fig. 3 (A) Three-dimensional (3D) multiplanar image showing the fetal clavicles, apparently small in size. (B) Axial 3D image of upper chest showing fetal clavicles. (C) Coronal 3D image showing fetal clavicles.

CN State	Type	Chr. No	Cytoband start	Size (kbp)	No. of Genes	Genomic Coordinates	Interpretation
1	Loss	6	p21.1-p12.3	10946.8	145	arr[GRCh37] 6p21.2p12.3 (37,520,993_48,467,869)x1	PATHOGENIC

Interpretation : The CMA analysis shows a deletion on chromosome 6p spanning about 10946.8kbp (~1MB). This deletion on chromosome 6p21.1 hosting RUNX2 gene is reported to be causing Cleidocranial Dysplasia.

Cleidocranial dysplasia (CCD) is a rare autosomal dominant skeletal dysplasia due to mutations causin haploinsufficiency of RUNX2, an osteoblast transcription factor specific for bone and cartilage. Cleidocranial dysplasia (CCD) spectrum disorder is a skeletal dysplasia that represents a clinical continuum ranging from classic CCD (triad of delayed closure of the cranial sutures, hypoplastic or aplastic clavicles, and dental abnormalities) to mild CCD to isolated dental anomalies without the skeletal features. Most individuals come to diagnosis because they have classic features. At birth, affected individuals typically have abnormally large, wide-open fontanelles that may remain open throughout life. Clavicular hypoplasia can result in narrow, sloping shoulders that can be opposed at the midline. Moderate short stature may be observed, with most affected individuals being shorter than their unaffected sibs. Dental anomalies may include supernumerary teeth, eruption failure of the permanent teeth, and presence of the second permanent molar with the primary dentition. Individuals with CCD spectrum disorder are at increased risk of developing recurrent sinus infections, recurrent ear infections leading to conductive hearing loss, and upper-airway obstruction. Intelligence is typically normal.

Fig. 4 The microarray report showing deletion in runt-related transcription factor 2 (RUNX2) gene consistent with cleidocranial dysplasia.

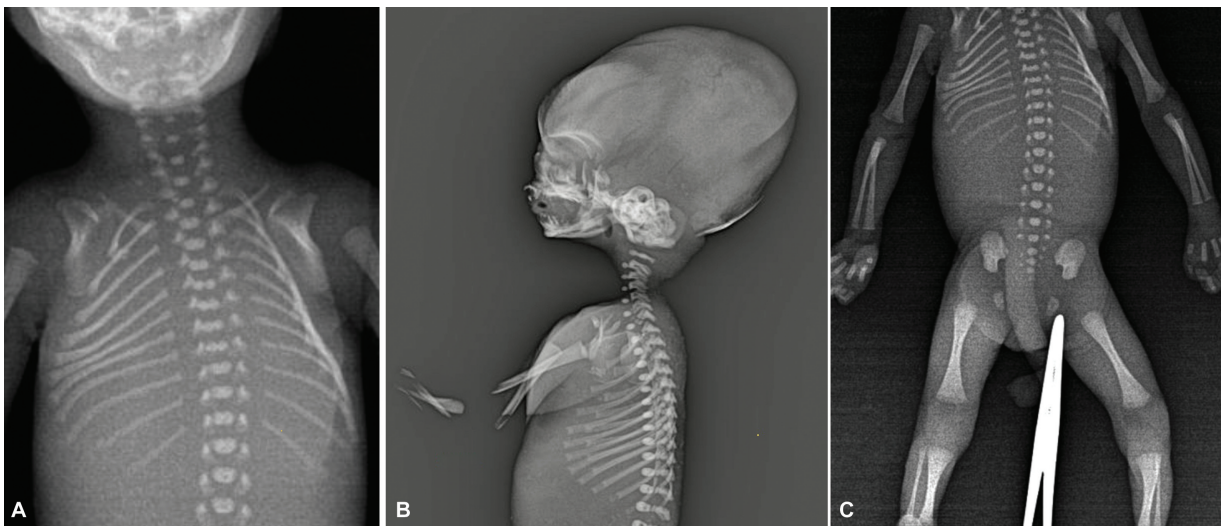

Fig. 5 (A) Chest X-ray of the abortus showing short clavicles specially at lateral ends. (B) X-ray Lateral view of the skull showing an elongated head shape. (C) X-ray of the abortus showing hypo mineralization of pelvic bones.

may play a crucial role in the early detection of CCD through a high index of suspicion. The characteristic ultrasound features include hypoplastic clavicles, wide fontanels, brachycephaly, hypoplastic mandible, delayed ossification of the pubic and ischial bones, and other skeletal abnormalities, including supernumerary ribs.[5] As the clavicles are involved and show some detectable changes in CCD, identifying clavicular anomalies, even without any other abnormalities, strongly points toward possible CCD. During prenatal ultrasound, it may sometimes be difficult to identify both the clavicles properly where 3D techniques can image them in full length and clarity. 3D ultrasound imaging techniques with different rendering modes are important adjuncts for identifying subtle skeletal abnormalities. These findings, in combination with a detailed family history, should prompt genetic testing for the identification of the RUNX2 gene mutation for confirming the diagnosis of CCD.[5]

The RUNX2 gene encodes a transcription factor essential for osteoblast differentiation from stem cells and thus plays a central role in skeletal development.[6] Pathogenic variants in this gene disrupt normal bone formation and result in the skeletal abnormalities observed in CCD. Different mutations in the RUNX2 gene have been reported in CCD cases, including point mutations, small insertions AND or deletions, and larger genomic rearrangements.[7] Genetic confirmation is crucial for accurate diagnosis and appropriate genetic counseling. It helps in estimating the recurrence risk for future pregnancies and guiding the management of affected individuals. Here, in this case, it appears to be de novo as there was no relevant family history; however, it is difficult to diagnose clinically because of widely varied and subtle asymptomatic presentations in many cases, even within the same affected families.

Conclusion

This case report highlights the significance of exploring apparently subtle findings on prenatal ultrasound examination. In this case, the finding of a linear echogenicity on the C7 vertebra, which we suspected to be a unilateral supernumerary rib (cervical rib), ultimately led to the diagnosis of an underlying genetic condition.[8,9] Early detection through detailed prenatal imaging enables timely genetic counseling, facilitating informed decision-making regarding pregnancy management. Integration of postabortal X-ray findings here further consolidates the diagnosis of CCD. Detailed ultrasound examination with a high index of suspicion is vital for the early recognition and comprehensive management of this rare skeletal condition.

Conflict of Interest
None declared.

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