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The Role of Prenatal Fetal Ultrasound in the Diagnosis of Cornelia de Lange Syndrome

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Abstract

Background: Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder characterized by distinct facial features, limb malformations, and growth abnormalities, often diagnosed postnatally. Prenatal detection remains challenging due to its variable presentation and the reliance on high-resolution imaging and genetic analysis. This report aims to highlight the importance of integrating detailed prenatal ultrasound findings with molecular diagnostics for early identification of CdLS.

Case Report: We present three cases of CdLS diagnosed through prenatal ultrasound and confirmed by genetic analysis identifying de novo mutations in the NIPBL gene. Key ultrasound findings included limb reduction defects, facial dysmorphisms such as synophrys and micrognathia, and intrauterine growth restriction. Two pregnancies were terminated due to poor prognosis, while the third resulted in a live birth with severe anomalies. Postnatal and autopsy findings corroborated the prenatal diagnoses and provided additional insights into the genotype-phenotype correlation, highlighting the variability of clinical presentations.

Conclusion: This study underscores the critical role of prenatal ultrasound in identifying suggestive features of CdLS and the necessity of molecular testing for definitive diagnosis. The findings expand the spectrum of prenatal manifestations associated with CdLS and advocate for refining diagnostic criteria to improve early detection and perinatal management. This approach facilitates informed decision-making and optimizes outcomes for affected families.

Keywords: Cornelia de Lange Syndrome, CdLS, Prenatal Ultrasound Diagnosis, NIPBL Gene.

* Introduction

Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder often arising sporadically due to de novo mutations, with minimal reproductive fitness. While familial cases exhibiting X-linked dominant, autosomal dominant, and paternal gonadal mosaicism inheritance patterns have been reported, approximately 60% of CdLS cases are associated with de novo mutations in the NIPBL gene (1). The estimated prevalence of CdLS is approximately 1 in 10,000 live births(2).

The most commonly described prenatal features of CdLS include fetal growth restriction (FGR), limb abnormalities, and distinctive facial characteristics. FGR is a hallmark of classic CdLS but is typically mild during early gestation, becoming more pronounced in later stages. Although prenatal diagnosis of CdLS is possible through ultrasound during the second and third trimesters, the condition is more frequently identified postnatally (3). In a recent review of 53 prenatal cases of CdLS, FGR was observed in 81% of cases as early as 16 weeks gestation, while characteristic facial features were detectable in 49% of cases around 19–20 weeks (4).

Key diagnostic ultrasound findings include facial anomalies such as a smooth and convex philtrum, anteverted nostrils, an upturned nose, synophrys (thick eyebrows meeting at the midline), a thin upper lip, low-set ears, and micrognathia. Limb abnormalities are often asymmetric and predominantly affect the distal upper extremities, including syndactyly, clinodactyly of the fifth finger, and oligodactyly. Additional malformations, such as congenital diaphragmatic hernia, congenital heart defects, and genitourinary anomalies, have also been reported in association with CdLS, though these are not specific to the syndrome (5).

In this review, we report three cases of CdLS caused by de novo

mutations in the NIPBL gene. Two pregnancies were terminated via therapeutic abortion, one during the early second trimester and the other in the third trimester. The third case presented with multiple anomalies, and the parents chose to continue the pregnancy. This study discusses the prenatal ultrasound findings, autopsy results, mutational analysis of the NIPBL gene, and the genotype-phenotype correlations in these cases. The prognosis for individuals affected by CdLS depends heavily on timely prenatal diagnosis and optimized perinatal care, as many health complications associated with CdLS may present as neonatal emergencies requiring urgent surgical intervention(6,7).

*** Case Reports**

*** Case 1**

The mother was a 33-year-old gravida 3, para 2 (G3P2), with a history of two cesarean sections due to obstructed labor secondary to cephalopelvic disproportion. She had two healthy male children born in 2011 (birth weight: 2970 g) and 2014 (birth weight: 3560 g). Both parents were of Cape Verdean descent, healthy, non-consanguineous, and with an unremarkable family history.

The current pregnancy was initially complicated by maternal complaints of hyperemesis and hepatic cytolysis in early gestation. At 12 weeks of gestation, a fetal nuchal translucency (NT) measurement exceeded 5 mm, accompanied by significant cervical and truncal edema and a polymalformative syndrome involving the limbs. A follow-up ultrasound at 12 weeks and 4 days confirmed increased NT above 5 mm and revealed upper limb malformations, raising suspicions of retrognathism.

At 13 weeks and 4 days of gestation, a detailed fetal ultrasound documented the following parameters: crown-rump length (CRL) of 68.5 mm, nasal bone (NB) of 3.4 mm, biparietal diameter (BPD) of 24.6 mm, and abdominal circumference (AC) of 74.7 mm. Anomalies included abnormal upper limb development with the forearms and hands held in a flexed position. Rupture of membranes occurred following a therapeutic amniocentesis to further investigate the malformations.

The couple opted for pregnancy termination at 13 weeks and 6 days of gestation. Delivery occurred spontaneously via vaginal delivery, and the sex of the fetus was indeterminate. The family was subsequently referred to the clinical genetics service. Written informed

consent was obtained for a comprehensive postmortem examination and genetic testing.

Postmortem findings were limited due to the small size of the fetus and early signs of maceration. Measurements included a crown-rump length of 8 cm, a crown-heel length of 13 cm, a foot length of 1 cm, and a weight of 44 g, all of which were significantly below normal ranges for 14 weeks of gestation. Despite the limitations, these findings were consistent with the estimated gestational age.

Fetal autopsy did not reveal the classical facial features of CdLS. However, notable findings included macrocephaly, marked cervical edema, and a small, triangular chin. Bilateral severe upper limb reduction defects were observed, including absent ulnae, shortened radii, and a single digit on each limb without clear ossification (Figure 1). The chest and abdomen appeared normal.

Chorionic villus sampling revealed a 46,XX karyotype. Genetic analysis of the NIPBL gene identified a heterozygous de novo sequence variation, c.7297G>C (p.Asp2433His) in exon 43. This variant has not been previously reported in the literature or mutation databases. However, a variant affecting the same amino acid (p.Asp2433Asn) has been documented in association with Cornelia de Lange syndrome.

*** Case 2**

The patient was a 32-year-old gravida 2, para 1 (G2P1), with one previous cesarean section for a healthy male child born in 2015. Her medical history included type 2 diabetes managed with insulin and hypothyroidism treated with Thyrofix (100 µg/day). Her husband, a 36-year-old man, was in good health. Both parents were of Pakistani descent, non-consanguineous, and with no significant family history.

The current pregnancy was initially uneventful. First-trimester ultrasound and routine screening results were normal. However, a detailed fetal ultrasound at 22 weeks of gestation revealed fetal hypotrophy. Bi-monthly ultrasound follow-up examinations showed additional anomalies, including ventricular septal defect (VSD), a small aortic arch, choroid plexus and paraventricular cysts, a single umbilical artery, and slight retrognathism. The estimated fetal growth was below the 5th percentile, consistent with intrauterine growth restriction (IUGR).

At 26 weeks of gestation, a fetal MRI was performed and revealed supra- and subtentorial

cerebral hypotrophy with mild delayed gyration. Amniocentesis showed a normal male karyotype (46,XY), with no evidence of 22q11.2 microdeletion. Array-comparative genomic hybridization (CGH) analysis was also normal.

A fetal echocardiogram at 30 weeks of gestation identified asymmetry of the great vessels with a hypoplastic aortic arch, a subaortic VSD, and left ventricular (LV) hypoplasia. Based on these findings and the progressively poor prognosis, the couple opted to terminate the pregnancy at 34 weeks of gestation.

The pregnancy was terminated, and fetal autopsy was performed. Autopsy findings confirmed IUGR, with the following measurements: crown-rump length of 29.5 cm (<10th percentile), crown-heel length of 43 cm (<10th percentile), foot length of 6.5 cm, and weight of 1872.8 g (<10th percentile). Dysmorphic facial features included a receding forehead, low hairline, synophrys with arched eyebrows, long eyelashes, marked infraorbital folds, anteverted nostrils, a long and bulging philtrum, a small mouth with drooping corners, micrognathia, and large, poorly hemmed, posteriorly tilted ears. A diastema was also noted.

Upper limb anomalies included high implantation of the fifth finger on the left hand and brachymetacarpy. Bone X-rays revealed bilateral brachymetacarpy of the first metacarpus, hypoplasia of the second phalanx of the fifth fingers, narrowing of the third phalanges, absence of ossification centers at the distal femur, and a small presacral dimple.

Cardiovascular abnormalities included hypoplasia of the horizontal part of the aortic arch, a narrowed aortic ring (3 mm), absence of a VSD, asymmetry of the great vessels with LV hypoplasia, and a single large, high coronary ostium.

These findings were consistent with a polymalformative syndrome suggestive of Cornelia de Lange syndrome (CdLS). Genetic analysis of the NIPBL gene identified a heterozygous de novo sequence variation, c.4734G>A (p.Trp1578*), in exon 23. This mutation resulted in a premature stop codon at amino acid position 1578, predicted to produce a truncated NIPBL protein.

*** Case 3**

The patient was a 2-year-old girl of non-consanguineous Malian parents, born to a 32-year-old mother (gravida 4, para 3). She was delivered at 36 weeks' gestation via normal vaginal delivery, with a birth weight

of 1865 g, length of 42.5 cm, and head circumference of 28.5 cm—all values below the 1st percentile. She was referred to the genetics clinic at 3 months of age for evaluation of a polymalformative syndrome.

There was no relevant family history. The pregnancy was initially uncomplicated. First-trimester screening showed a low risk for trisomy 21, with a calculated risk of 1/3420. At 20 weeks' gestation, fetal ultrasound revealed cysts in the left kidney and a single umbilical artery. Detailed fetal ultrasound at 25–26 weeks' gestation showed significant intrauterine growth retardation (IUGR) with measurements below the 5th percentile, especially affecting the crown-rump length. Additional findings included the right kidney located in the pelvis, a very large gallbladder, and dysmorphic facial features. Fetal MRI at 32 weeks' gestation revealed microcephaly, enlargement of the pericerebral spaces, delayed gyration, and hypoplasia of the brainstem. The parents declined consent for prenatal genetic testing.

Postnatal investigations showed a normal male karyotype (46,XY). CGH-array and fluorescence in situ hybridization (FISH) analysis for chromosomes 13, 18, 21, and 4p were normal. Echocardiography revealed a 1.8 mm ductus arteriosus shunt.

Molecular analysis of the NIPBL gene revealed a heterozygous de novo deletion, c.1864delG>A (p.Glu622Asnfs*19), in exon 10. This base pair change resulted in a frameshift at codon 622, predicted to produce a truncated or absent protein product. This specific deletion has not been previously reported in the literature or listed in population databases.

These findings were consistent with Cornelia de Lange syndrome (CdLS), confirmed by the presence of this pathogenic mutation in the NIPBL gene.

Prenatal fetal ultrasound		Case1	Case2	Case3
1st Trimester	fetal nuchal translucency (NT)	↑	no	yes
	IUGR	no	no	no
	Other abnormality	-Malformation of the upper limbs -Micrognathia		
2ed Trimester	Cardiac anomalies	no	yes	no
	Malformation of the upper limbs		Yes autopsy	no
	Micrognathia	yes	yes	yes
	Renal malformation	no	yes	yes
	IUGR	yes	yes	yes
	Single umbilical artery.	no	yes	yes
3rd Trimester	Neural malformation	no	yes	yes
Molecular genetic analyses	Gene	NIPBL	NIPBL	NIPBL
	Exon	43	23	10
	c.DNA mutation	c.7297G>C	c.4734G>A	c.1864delG>A
	Protein change	p.(asp2433His)	p.(Trp1578*)	p.(Glu622Asnfs*19)
	Zygosity	Heterozygote	Heterozygote	Heterozygote
	Type of mutation	frameshift	Non-sense	frameshift
Therapeutic abortion		yes	yes	no

Table 1: Prenatal fetal ultrasound presentation of three CdLS cases and molecular genetic analyses.

Cardinal Features	Suggestive features
Synophrys	Global developmental delay
Long and/or smooth philtrum	intellectual disability
Short nose, concave nasal ridge	Prenatal growth retardation
Hand oligodactyly and/or adactyly	Postnatal growth retardation
Congenital diaphragmatic hernia	Microcephaly
	Small hands and/or feet
	Short fifth finger
	Hirsutism

Table 2: The main cardinal and suggestive features of Cornelia de Lange Syndrome find In Prenatal ultrasound diagnosis are reported

* Discussion

The prenatal diagnosis of Cornelia de Lange Syndrome (CdLS) presents significant challenges due to its wide variability in clinical presentation. These challenges are further compounded by the presence of a normal karyotype in many cases and the identification of mutations in the NIPBL gene, as observed in our study, where a heterozygous de novo mutation was detected in all three cases (8). A cardinal feature consistently observed in all our cases was fetal growth restriction (FGR), as detailed in Table 1.

The prenatal diagnosis of CdLS may be supported by a combination of cardinal and suggestive features Table 2. Cardinal features include synophrys, a short nose with a depressed nasal ridge and anteverted nares, a long and smooth philtrum, a thin upper lip, downturned corners of the mouth, hand oligodactyly or adactyly, congenital diaphragmatic hernia, fetal growth restriction, microcephaly, and a short fifth finger. Severe limb reduction defects, diaphragmatic hernias, renal malformations, and cardiac anomalies are also suggestive of the syndrome (6). Limb defects, particularly, should be carefully evaluated on prenatal ultrasound. Mild malformations are detectable via detailed ultrasound examination. Limb defects can vary from unilateral to bilateral involvement, with bilateral defects often being asymmetrical. These defects may range from complete limb absence to conditions such as clinodactyly, oligodactyly, and ectrodactyly.

In cases of fetal growth restriction, the diagnosis of CdLS should be considered in the presence of limb reduction defect(9,10) . The Delphi consensus statement (2018) proposed a scoring system for prenatal ultrasound diagnosis of CdLS. According to this system, two points are assigned to each cardinal feature and one point to each suggestive feature. A total score of ≥4 points is required for a possible diagnosis of CdLS, while a score of ≥11 points confirms the diagnosis,

irrespective of the presence or absence of a pathogenic variant in the known CdLS genes. In our cases, the total scores were as follows: Case 1 = 3, Case 2 = 3, and Case 3 = 1, which indicates that none of these cases achieved the threshold score for confirming the diagnosis based on this scoring system. This observation suggests that the Delphi scoring system may not be fully applicable to our cases.

Despite this, the autopsy findings in Case 1, Case 2, and Case 3, as well as the postnatal evaluation of these cases, revealed the presence of nearly all the cardinal features of CdLS. This underscores the importance of employing high precision and skill during routine 3D ultrasound examinations to ensure the safety of the fetus and to improve the accuracy of prenatal detection of CdLS (11).

CdLS is caused by mutations in genes associated with the cohesin pathway. The inheritance patterns are primarily autosomal dominant, involving genes such as NIPBL, SMC3, and RAD21, or X-linked inheritance involving the SMC1A and HDAC8 genes (12,13). In our study, we identified de novo heterozygous mutations in the NIPBL gene in all three cases. The NIPBL gene, located on chromosome 5p13.2, plays a crucial role in cortical neuron migration during brain development. It contains 47 exons and is essential for proper development during embryogenesis. NIPBL mutations are responsible for approximately 70–80% of CdLS cases (6,14).

In our cases, three distinct mutations were identified: a missense mutation (c.7297G>C) in exon 43 in Case 1, a nonsense mutation (c.4734G>A) in exon 23 in Case 2, and a frameshift deletion (c.1864del) in exon 10 in Case 3. These mutations were identified through next-generation sequencing of DNA extracted from fetal tissue in Case 1 and Case 2, and from saliva collection in Case 3. Notably, missense mutations in the NIPBL gene are often associated with less severe phenotypes, including absent or milder limb abnormalities and less severe developmental and growth deficiencies. In contrast, frameshift mutations or nonsense mutations tend to lead to a more severe phenotype, characterized by pronounced developmental delay and severe structural malformations.

For instance, in Case 1, the fetus presented with bilateral severe upper limb reduction, absent ulnae, shortened radii, and a single digit, suggesting a more severe phenotype

despite the missense mutation. This finding is in line with previous studies that report less severe phenotypes in cases with missense mutations, such as milder growth retardation and intellectual disability (15). In Case 3, where a frameshift mutation was identified, the phenotype included multiple congenital anomalies and severe limb abnormalities, including bilateral upper limb malformations, cardiovascular anomalies, and facial dysmorphisms such as a receding forehead, low hairline, and marked infraorbital folds. These features are consistent with the more severe presentations associated with loss-of-function mutations in NIPBL (16).

*** Conclusion**

This study presents three cases of CdLS with different structural fetal anomalies and mutations in the NIPBL gene. The findings reinforce the importance of detailed prenatal ultrasound in detecting malformations associated with CdLS. While the scoring system proposed by the Delphi consensus did not achieve diagnostic confirmation in our cases, the identification of characteristic cardinal features during postnatal evaluation and autopsy highlights the potential for early detection and improved management of CdLS. Further studies are necessary to refine diagnostic criteria and improve the applicability of prenatal diagnostic tools for CdLS.

*** Referance**

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