Case Report

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Cornelia De Lange Syndrome with Left Heart Hypoplasia: A Case Study

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Abstract

Cornelia de Lange syndrome (CdLS) is characterized by slow growth that can lead to short stature. Despite mutations in the NIPBL, RAD21, or SMC3 genes, CdLS is thought to be inherited in an autosomal dominant manner. Findings include intellectual disability bone abnormalities in the upper extremities and distinct facial features. It has similar characteristics to autism spectrum disorder, which is a developmental condition that affects communication and social interaction. The physical and clinical findings of a one-and-a-half-year-old girl patient diagnosed with CdLS were reported. In addition to NIPBL gene mutation, atrioventricular septal defect (AVSD), an overriding aorta, and a hypoplastic left heart (HLH) were observed in our case. This study revealed the patient's physical and clinical findings consistent with the diagnosis of CdLS. Additionally emphasized HLH. The importance of performing corrective surgery immediately following the evaluation of congenital heart diseases in CdLS patients can be emphasized..

Keywords: Cornelia de Lange syndrome, congenital heart diseases, overriding aorta, HLH

Introduction

Cornelia de Lange syndrome is characterized by slow growth that can lead to short stature before or after birth. Findings include moderate to severe intellectual disability, and bone abnormalities in the upper extremities. Different facial features such as arched eyebrows (synophrys) meeting in the middle, long eyelashes, low-set ears, small and widely spaced teeth, and a small and upturned nose are also observed. It has similar characteristics to autism spectrum disorder, which is a developmental condition that affects communication and social interaction (1).

In addition, excessive body hair (hypertrichosis), an unusually small head (microcephaly), hearing loss, and digestive problems may occur. Some cases of this condition are born with an opening in the roof of the mouth, called a cleft palate. Seizures, heart defects, and eye problems have also been reported in cases of this disorder (1).

Cornelia de Lange syndrome occurs as a result of mutations in the NIPBL, RAD21, or SMC3 genes, however, it is thought to be inherited in an autosomal dominant manner. Autosomal dominant inheritance means that the presence of one changed chromosome in the cells is sufficient for the disease to occur (2).

This study aimed to reveal the physical and clinical findings of the patient diagnosed with Cornelia de Lange syndrome.

Case Report

A female baby was born by cesarean section (C/S) on March 9, 2022, weighing 2130 g, 43 cm tall, with a head circumference of 28 cm, and an APGAR score of 7/8. She was born at 37 weeks 4 days and has 0 Rh+ blood group. The other family members were all healthy. There was no consanguineous marriage. The double Screening Test result showed cystic hygroma. Herfree fetal DNA result was low risk. She was placed under a radiant warmer as soon as she was born, and she had a peak heart rate (HRV) of more than 100/min, free-flow oxygen was started because her breathing was irregular. Her general condition was stable during follow-up. Corrective surgery for a hypoplastic left heart (HLH) was performed. She was fed with formula. There was motor retardation.

The patient was diagnosed with Cornelia Delange syndrome. Her general condition was good, consciousness

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was clear, color was natural, and turgor and tone were normal. There was no problem with vision. Heterozygous variants of unknown clinical significance have been detected in the NIPBL gene. Dysmorphia was present and there was no weight gain. It was followed by nephrology. A consultation was requested from pediatric gastroenterology to regulate weight-gaining nutrition.

Antenatal intrauterine development delay and oligohydramnios were present. It was observed that the baby had a single umbilical artery. Atrioventricular Septal Defect (AVSD) and Overriding Aorta were present. The left side of the heart was hypoplastic compared to the right. Ventricular Septal Defect (VSD), and large mitral atresia or hypoplasia in the ultrasonographic (USG) imaging in the patient diagnosed with Unstable AVSD. Double Outlet Right Ventricle was determined because both large vessels originate from the right ventricle (Figure 1A).

No epileptogenic potential was detected as a result of sleep electroencephalography (EEG), where age-appropriate maturation was observed. The general condition of the patient was moderate, consciousness was clear and active. A short forehead and low-set ears were observed. Doublehemi thoraxes were ventilated equally. Coarse rales and tachypnea were observed in the respiratory system. In the cardiovascular system, S1, and S2 were normal, and the heart was rhythmic. No additional sound was heard, there was a murmur. The control of femoral artery pulses (AFN) was positive. The abdomen was comfortable in the gastrointestinal system. There was no rebound defense, hepatosplenomegaly, or dysmorphic findings. The liver and spleen were nonpalpable. Bowel sounds were normoactive. There was no mass. Extremities were natural. There was a sacral dimple. The fingers were short and had simian lines. There was a location anomaly in the lower extremities. In the neurological examination, newborn reflexes were taken, and the tone was normal (Figure 1B).

Atrioventricular (AV) valve insufficiency (mild-moderate), Patent Ductus Arteriosus (PDA) and Patent Foramen Ovale (PFO) were present. Pulmonary artery band (PAB) application was performed at 2-3 weeks of clinical follow-up. Infarction has been started and GLENN surgery would be planned.

In neck USG examination, thyroid gland sizes were within normal limits. Thyroid gland parenchyma was homogeneous. No nodule was detected. Lymphadenopathy (LAP) was not detected in the bilateral neck lymphatic chain. The size and echo of bilateral submandibular and parotid glands were normal.

The evaluation was suboptimal since the entire abdominal USG was performed with a bedside mobile Ultrasound (US) device in the intensive care unit. The size of the liver was within normal limits. Liver contours were smooth and marginal angles were sharp. Parenchymal echo was homogeneous. No solid or cystic mass lesion was observed in the liver. The gallbladder

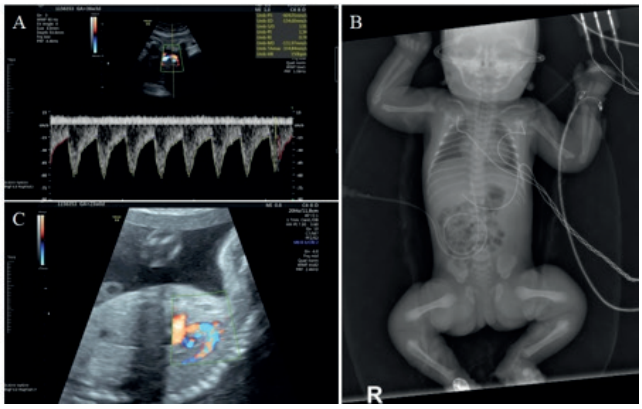

Figure 1. Echocardiography, X-ray, and prenatal ultrasonography of the patient were taken before and after birth. A) Atrioventricular Septal Defect (AVSD) was detected in Echocardiography. B) Abnormal extremities were shown in vertebra, lower and upper extremity radiography. C)Uterus didelphys anomaly was observed in USG.

was contracted. No dilatation was observed in the intrahepatic bile ducts. Both kidneys' size and localization were normal. Kidney contours were smooth and cortex thickness was natural. A corticomedullary distinction could be made clearly in both kidneys. No visible calculus or a dilated renal pelvis and calyces were observed in both kidneys. Grade 1 pelviectasis was observed in the left kidney. Pancreas and midline structures could not be evaluated due to intense gas superposition. Spleen size was within normal limits. Its echo structure was homogeneous. The bladderlumen was homogeneous, and no pathological state was observed. Uterus didelphys anomaly was observed. The right ovary could not be evaluated due to gas, and the left ovary appearednatural. Parenchymal organ evaluation could not be performed due to extensive dressing materials in the abdomen. Pelvic minimal free fluid was detected in the abdomen. Gallbladder sludge was observed. Fluid reaching a depth of 2cm was observed in all quadrants of the abdomen (Figure 1C).

The patient's Papanicolaou smear (PAP) result was HPV subtype 90, 92. The cornea and lens were transparent. Papilla, macula, and vascular structures were natural.

During the checks, the general condition was found to be good. The Glasgow Coma Scale (GCS) score was determined as 15. The skin, oropharynx, tonsils, and bilateral tympanic membrane are natural. Direct-indirect light reflex was positive. There was no sign of meningeal irritation.

Discussion

Our case reported a novel cardiac finding (AVSD, Overriding Aorta, and HLH) associated with CdLS. According to several studies, the most common defects were pulmonary stenosis and ventricular and atrial wall defects, followed by aortic coarctation, bicuspid aortic valve, hypertrophic cardiomyopathy, and others (3,4). The presence of heart disease is associated with a higher need for neonatal hospitalization and a mortality rate that triples that of non-

cardiac patients, with 19.2% of cases requiring cardiac surgical correction (3).

We found in our case, the heterozygous variants of unknown clinical significance in the NIPBL gene. Gillis et al. reported NIPBL mutations in a large well-characterized cohort of individuals with sporadic or familial CdLS (2). Another study supported the idea that the NIPBL gene was mutated in individuals with CdLS (5). Avagliano et al. revealed that many genes were associated with chromatinopathies classified as "Cornelia de Lange Syndrome-like". It is known that the phenotype of these patients becomes less recognizable, overlapping with features characteristic of other syndromes caused by genetic variants affecting different regulators of chromatin structure and function. Therefore, the diagnosis of Cornelia de Lange syndrome can be difficult due to the occasional discrepancy between the unexpected molecular diagnosis and clinical evaluation (6).

In the present study, we found no mental retardation in our case. However, Berney et al. used a mailed questionnaire to examine 49 people with Cornelia de Lange syndrome to determine behavioral phenotype. Ages range from early childhood to adulthood, with the degree of mental retardation ranging from borderline (10%), mild (8%), moderate (18%), severe (20%), and very profound (43%). A wide range of symptoms occurred frequently, particularly hyperactivity (40%), self-harm (44%), daily aggression (49%), and sleep disturbance (55%). These were closely related to the presence of autistic-like syndrome and the degree of mental retardation. The frequency and severity of the disorder, which continues after childhood, were important when planning the amount and duration of support needed by parents (7).

Moreover, we detected no motor retardation in the present case. This was not in accordance with a case study that was reported recently. Deardorff et al. reported a wide range of findings, from mild to severe CdLS. Severe CdLS was characterized by distinctive facial features, growth restriction, hypertrichosis, and upper limb reduction defects ranging from thin phalanx abnormalities to oligodactyly. Craniofacial features include synopsis, highly arched and/or thick eyebrows, long eyelashes, short nasal bridge with forward-facing nostrils, small, widely spaced teeth, and microcephaly. Individuals with a milder phenotype have less severe growth, cognitive, and limb involvement but often have facial features consistent with CdLS. Other common findings include hearing loss, myopia, and cryptorchidism or hypoplastic genital organs (8).

In addition, no digestive system abnormalities were found in our patient. It was supported by Husain et al. that a variety of gastrointestinal anomalies have been described, including malrotation, colonic duplication, and non-fixation of the colon (9). In the Husain et al. study, two patients with CdLS were admitted to the hospital due to acute distal intestinal obstruction. In both cases, cecal volvulus was observed with necrosis in the terminal ileum, cecum, and ascending colon secondary to non-fixation of the colon during emergency laparotomy (9). However, in our case, cystic hygroma, oligohydramnios, uterus didelphys anomaly, and a single umbilical artery were detected.

Conclusion

The findings of this study provide valuable insights into the physical and clinical manifestations that align with the diagnosis of CdLS. Furthermore, a noteworthy emphasis is placed on the recognition of HLH in the context of CdLS. These findings underscore the significance of promptly conducting corrective surgical interventions upon the identification of congenital heart diseases during the assessment of CdLS patients. Meanwhile, parents of children with CdLS should be counseled about the possibility of intestinal obstruction resulting from cecal volvulus. This awareness may lead to earlier identification and treatment of this potentially fatal gastrointestinal tract anomaly. The implications of these revelations suggest that early surgical intervention can play a crucial role in optimizing patient outcomes and managing associated health complications. This underscores the importance of a comprehensive and timely approach to the medical care of individuals with CdLS.

References

1. DeScipio C, Kaur M, Yaeger D, Innis JW, Spinner NB, Jackson LG, et al. Chromosome rearrangements in Cornelia de Lange syndrome (CdLS): report of a der (3) t (3; 12) (p25. 3; p13. 3) in two half sibs with features of CdLS and review of reported CdLS cases with chromosome rearrangements. Am J Med Genet Part A2005; 137(3): 276-82.
2. Gillis LA, McCallum J, Kaur M, DeScipio C, Yaeger D, Mariani A, et al. NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype–phenotype correlations. Am J Hum Genet 2004; 75: 610–23.
3. Ayerza Casas A, PuisacUriol B, Teresa Rodrigo ME, Hernández Marcos M, Ramos Fuentes FJ, Pie Juste J. Cornelia de Lange syndrome: Congenital heart disease in 149 patients. Med Clin (Barc). 2017;149(7):300-2.
4. Chatfield KC, Schrier SA, Li J, Clark D, Kaur M, Kline AD, et al. Congenital heart disease in Cornelia de Lange syndrome: phenotype and genotype analysis. Am J Med Genet A. 2012;158a(10):2499-505.
5. Tonkin ET, Wang TJ, Lisgo S, Bamshad MJ, Strachan T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. Nat Genet2004; 36(6): 636-41.
6. Avagliano L, Parenti I, Grazioli P, Di Fede E, Parodi C, Mariani M, et al. Chromatinopathies: A focus on Cornelia de Lange syndrome. Clin Genet 2020; 97(1): 3-11.
7. Berney TP, Ireland M, Burn J. Behavioural phenotype of Cornelia de Lange syndrome. Arch DisChild 1999; 81(4): 333-6.
8. Deardorff MA, Noon SE, Krantz ID. Cornelia de Lange syndrome.2020.
9. Husain K, Fitzgerald P, Lau G. Cecal volvulus in the Cornelia de Lange syndrome. J Pediatr Surg1994; 29(9): 1245-7.