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Lobster Claw Hand Deformity - Cornelia de Lange Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. Author SD conceived the idea for the manuscript. Authors MJ and PK were involved directly in patient care. Author VG drafted the manuscript. Authors SD, HAK and MK provided necessary revisions to the manuscript. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Background: Cornelia de Lange syndrome is a genetic syndrome characterized by intellectual disability, facial features with synorphrys or fused eyebrows, upper limb anomalies and atypical growth. It is caused by spontaneous mutations in genes responsible for structural or regulatory function of cohesin complex.
Report: We present two newborns cases admitted to our NICU with characteristic dysmorphic features of microcephaly, ectrodactyly and thick eyebrows. One baby also had associated congenital heart defect and sensorineural hearing loss. Both babies are under followup with developmental early intervention programs. Parents were offered genetic counselling for future pregnancies.
Conclusion: Cornelia de Lange is predominantly a clinical diagnosis by identifying typical dysmorphic features. Labelling a syndromic diagnosis helps to provide genetic counselling to the parents, identify associated co-morbidities at earlier stages and improve the quality of living of such children.

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Keywords: Cornelia de lange syndrome; synorphrys; dysmorphism; ectrodactyly.

1. INTRODUCTION

Cornelia de-Lange syndrome (CdLS) is a multisystem syndrome encompassing congenital malformations, growth retardation and neurodevelopment delay, with incidence estimated to be 1in 10,000 [1]. Characteristic facial dysmorphic features with microcephaly, arched eyebrows, synophrys, depressed nasal bridge, long philtrum, down-turned angles of the mouth; upper-extremity malformations, hirsutism, cardiac defects, and gastrointestinal alterations define this syndrome [2] and is usually fatal by 2 years of life in severe cases. We report two such newborns with this syndrome in this report.

2. CLINICAL DESCRIPTION

Case 1

A term, low birth weight (Weight = 2.3kg, Length = 46cm, Head circumference = 31.5 cm; all values <3rd centile for gestation), female neonate, was admitted to our Level III NICU at a South Indian tertiary care hospital, in view of congenital anomaly detected at birth. She was third born child of non consanguineous marriage, with no significant antenatal or family history. Baby had microcephaly (<3SD), low set posteriorly placed ears, prominent occiput, short neck, thick bushy eyebrows, short nose, high arched palate, long philtrum, retrognathia, thin upper lip, proximally implanted thumb over left forearm, claw hand, short fingers, hirsutism and tuft of hair over the lower back. (Fig. 1)

Case 2

A late preterm (Gestational age = 36weeks), low birth weight (Weight = 1.8kg, Length = 42cm, Head circumference = 29cm; all values <3rd centile for gestation), female neonate was admitted to our NICU with Lobster claw hand deformity. She was the second born to a non-consanguineously married couple with normal antenatal history. Baby also had microcephaly (<3SD), short neck, thick bushy eyebrows, short nose, high arched palate, excessive body hair and long philtrum similar to the neonate described prior. Micromelic shortening of upper extremities and polythelia were also noted in her. (Fig. 2).

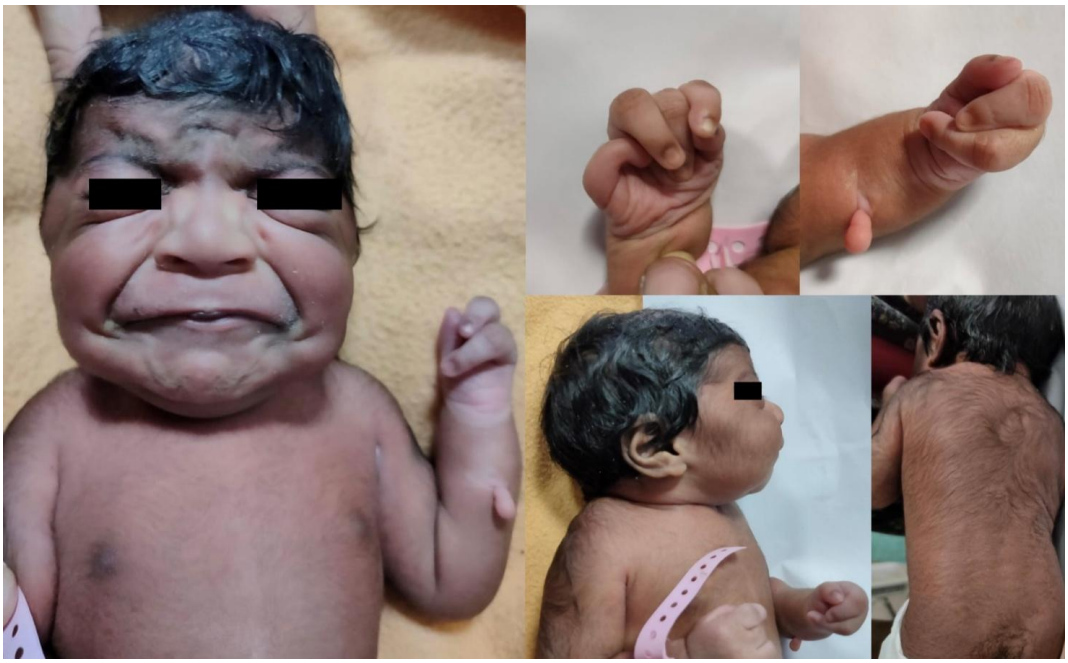

Fig. 1. Images of first neonate showing short neck, thick bushy eyebrows, depressed nasal bridge, long philtrum, retrognathia, thin upper lip, proximally implanted thumb over left forearm, claw hand with oligodactyly, clinodactyly in right hand, hirsutism and tuft of hair over the lower back

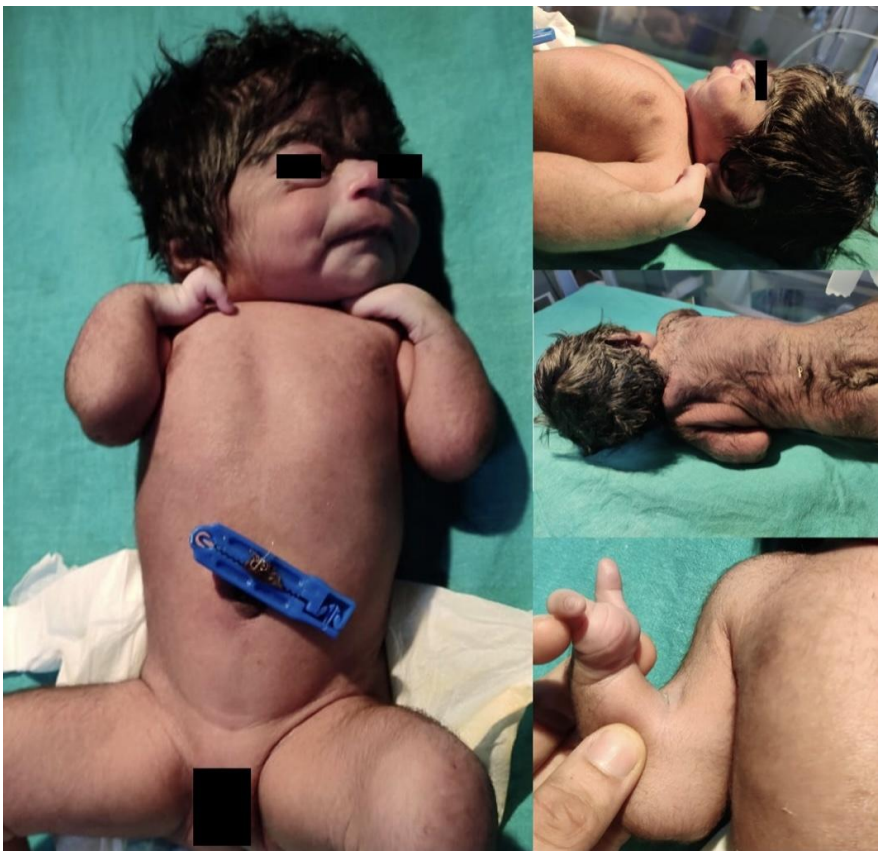

Fig. 2. Images of second neonate showing bilateral lobster claw hand deformity, short neck, thick bushy eyebrows, depressed nasal bridge, excessive body hair, long philtrum, micromelic shortening of upper extremities and left sided polythelia

3. MANAGEMENT AND OUTCOME

The first neonate's imaging studies of heart, cranial vault, abdomen and pelvis were normal. Karyotyping turned out as 46XX, female. Screening ophthalmological and hearing evaluation were also normal. While the second neonate's 2D Echocardiography revealed multiple defects including osmium primum atrial septal defect, patent ductus arteriosus and apical ventricular septal defect, all with left to right shunts and moderate pulmonary hypertension with tricuspid regurgitation. Baby also had bilateral sensorineural hearing loss. Other laboratory parameters were normal in both neonates.

The diagnosis of Classical Cornelia de Lange syndrome was made on clinical grounds with the presence of typical phenotypic features. Parents were not affordable for genetic testing. Genetic counselling was offered and long term prognosis of their children were explained. Both neonates were enrolled in developmental early intervention centres and offered supportive care with multidisciplinary interventions to improve quality of life and are under followup.

4. DISCUSSION

Cornelia de lange (CdLS) is a multi-system disorder with physical, cognitive and behavioral characteristics that is named after the Dutch paediatrician Cornelia de Lange, who first described the developmental disorder in two infants in 1933 [3]. Brachmann described similar features at autopsy in 1916, hence also known as Branchmann-de Lange syndrome [4].

The facial characteristics are the most diagnostic: microcephaly, well defined and arched eyebrows growing across the base of nose (synophrys or confluent eyebrows), long curly eyelashes, short neck with low anterior hair line , long philtrum, generalised hirsutism, thin downturning upper lips, microganthia, a small nose with low bridge, low set ears and crescent shaped mouth. These patients show marked

growth retardation of prenatal onset, and fail to thrive. Weight at birth is usually below the 5th percentile, and height, weight and head circumference all remain below the ranges for the general population.

Micromelia with oligodactyly, clinodactyly, proximal implantation of thumb, syndactyly of toes are common. Feeding difficulties with gastroesophageal reflux, with higher predisposition to Barrett oesophagus and adenocarcinoma later in life. There is evidence of premature aging in these individuals. Hearing loss secondary to canal stenosis, cochlear anomaly or ossicular malformation and visual disturbances secondary to high myopia, strabismus, nystagmus are common. 25% individuals with CdLS have cardiac anomaly while 10% have renal malformation. Cardiac defects like pulmonary stenosis, VSD, ASD and coarctation of aorta show higher incidence. Intellectual disability, severe language and speech delay, hyperactivity, autism spectrum disorder are developmental and behaviours issues noted. Even as adults they are short statured and obese [5,6].

Classic (or typical) CdLS is easily recognized from birth by experienced paediatricians owing to a distinctive craniofacial appearance and growth pattern, as well as limb malformations. However, not all individuals have the classic phenotype, and presentation is a spectrum with the disorder can varying widely, from mild to severe phenotypes, caused by pathogenic variants in genes involved in cohesin functioning. Cohesin is an essential regulator of most aspects of chromosome biology, including chromosome segregation, maintenance of genome stability, regulation of gene expression, chromatin structure and genome organization [7,8].

CdLS score of ≥11 indicates classic CdLS if at least three cardinal features are present; a score of 9–10 indicates non-classic CdLS if at least two cardinal features are present; a score of ≥4 is sufficient to warrant molecular testing for CdLS if at least one cardinal feature is present [6,9]. (Table 1) Both our neonates scored >11, confirming classical CdLS. Next generation sequencing (NGS) based screening for known CdLS genes are warranted in Non-Classical varieties.

Over 500 genetic mutations have been associated with the condition; occurring on 7 different genes. Inheritance maybe autosomal dominant or sporadic when there are mutations in NIPBL gene (50%) or X linked when SMC1L1 gene (5%) is affected [10,11]. SMC3, RAD21, BRD4, HDAC8 and ANKRD11 are the other genes tested in the NGS gene panel for CdLS. In the case of negative results, NIPBL and subsequently the other CdLS genes should be tested for mosaicism using tissues other than blood, for example, fibroblasts, buccal swabs or bladder epithelial cells from urine. Deletion and duplication testing of NIPBL can be carried out using multiplex ligation-dependent probe amplification (MLPA) or chromosome microarray.

Table 1. Clinical features of CdLS - international consensus score

	Neonate 1	**Neonate 2**
Cardinal features (2 points each if present)		
1. Synophrys and/or thick eyebrows	Yes	Yes
2. Short nose, concave nasal bridge and/or upturned nasal tip	Yes	Yes
3. Long and/or smooth philtrum	Yes	Yes
4. Thin upper lip vermilion and/or downturned corners of mouth	Yes	Yes
5. Hand oligodactyly and/or adactyly	Yes	Yes
6. Congenital diaphragmatic hernia	No	No
Suggestive features (1 point each)		
1. Global developmental delay and/or intellectual disability	N/A	N/A
2. Prenatal growth retardation (<2SD)	Yes	Yes
3. Postnatal growth retardation (<2SD)	N/A	N/A
4. Microcephaly (pre- and/or postnatally	Yes	Yes
5. Small hands and/or feet	Yes	Yes
6. Short fifth finger	Yes	N/A
7. Hirsutism	Yes	Yes
Total score	**15**	**14**

Genetic testing is necessary for determination of recurrence risk and genetic counselling of the family. Prenatal testing is warranted for all future pregnancies. If no molecular evaluation can be performed, the empirical recurrence risk is 1.5% [12]. Foetal ultrasound findings of symmetric IUGR, limb anomalies, abnormal facial profile, increased nuchal thickness, congenital diaphragmatic hernia and cardiac malformations must prompt evaluation of CdLS in the foetus [13].

An interdisciplinary approach is recommended with paediatrician helming the central role. A team for promoting the child's well-being includes speech, occupational and physical therapists along with parents. Most go through puberty, while only a small number of women with CdLS have given birth [14]. Teenagers with CdLS can become overweight or develop overt obesity, hence regular evaluation for weight is essential [15].

Neurobehavioural comorbidities like impaired adaptive behaviour, autism spectrum disorder, learning disabilities are common. Intellectual disability in CdLS children ranges from profound to mild. Child psychologists and psychiatrists are involved in the mental and social rehabilitation of these children. Environmental enrichment strategies are employed to stimulate cognitive and learning abilities. Child neurologists and physiotherapists involve in amelioration of developmental delay and seizures [9]. Recurrent respiratory infections are common in these children and are thought to be secondary to altered anatomy, hypotonia and coordination of swallowing and coughing and frequent cause for morbidity and mortality. Severe forms of CdLS are fatal by 2years with other causes of mortality being cardiac anomalies, congenital diaphragmatic hernia and gastrointestinal problems [16].

5. CONCLUSION

Cornelia de Lange syndrome has distinctive craniofacial appearance and the classical variety can be easily diagnosed at birth on typical phenotypic presentation of arched, confluent eyebrows or synophrys and limb anomalies. These children need early developmental interventions and care directed towards management of specific organ involvement to improve their quality of life.

CONSENT

As per international standard, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bhuyian ZA, Zilfalil BA, Hennekam RC. Amalay boy with the cornelia de lange syndrome: Clinical and molecular findings. Singapore Med J. 2006;47:7247.
2. Noor N, Kazmi Z, Mehnaz A. Cornelia de Lange syndrome. J Coll Physicians Surg Pak. 2012;22(6):412–3.
3. DeLange C. Sur un type nouveau de degenerescence (typhus Amsterlodamensis). Arch. Med. Enfants. 1933;36 :713–719.
4. Brachmann W. Ein fall von symmetrischer Monodaktylie durch ulnadefekt mit symmetrischer Flughautbildung in den Ellenbeugen, sowie anderen Abnormitaten (Zwerghaftigheit, Halsrippen, Behaarung), Jahrb Kinderheilk. 1916;84:225–235.
5. Ireland M, Burn J. Cornelia de Lange syndrome-photoessay. Clin Dysmorph. 1993;2:151-160.
6. Kline AD. Cornelia de Lange syndrome: clinical review, diagnostic scoring system, and anticipatory guidance, Am J Med Genet. 2007;143A:1287–1296.
7. Michaelis C, Ciosk R, Nasmyth K. Cohesins: Chromosomal proteins that prevent premature separation of sister chromatids. Cell. 1997;91:35–45.
8. Kagey MH. Mediator and cohesin connect gene expression and chromatin architecture. Nature 2010;467:430–435.
9. Kline AD, Moss JF, Selicorni A. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018;19:649–666.

10. Krantz ID, McCallum J, DeScipio C, Kaur M, Gillis LA, Yaeger D, et al. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of the Drosophila Nipped-B gene, Nat Genet. 2004;36:631–635.
11. Musio A, et al. X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations, Nat Genet 2006;38:528–530.
12. Jackson L, Kline AD, Barr MA, Koch S. de Lange syndrome: A clinical review of 310 individuals. Am. J. Med. Genet. 1993; 47:940–946.
13. Dempsey MA. Molecular confirmation of nine cases of Cornelia de Lange syndrome diagnosed prenatally. Prenat. Diagn. 2014;34:163–167.
14. Huisman SA. Phenotypes and genotypes in 51 individuals with SMC1A variants. Am. J. Med. Genet. 2017;173A:2108–2125.
15. Kline AD. Natural history of aging in Cornelia de Lange syndrome. Am. J. Med. Genet. C Semin. Med. Genet. 2007; 145C:248–260.
16. Schrier SA. Causes of death and autopsy findings in a large study cohort of individuals with Cornelia de Lange syndrome and review of the literature. Am. J. Med. Genet. 2011;155A:3007–3024.

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