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Cornelia de Lange Syndrome: A Rare Case

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Abstract

Cornelia de Lange Syndrome (CdLS) is a genetic disorder. It has an autosomal dominant pattern of inheritance and is characterized by multisystem malformations. In this report, we present a case of a newborn having distinctive features such as: Facial dysmorphia (arched eyebrows, synophrys, depressed nasal bridge, long philtrum, down-turned angles of the mouth), upper-extremity deficiency or shortening, hirsutism, cardiac defects, cognitive retardation and gastrointestinal abnormalities. The purpose of this report is to highlight the importance of screening in children with congenital cognitive and growth defects, and to raise a high index of suspicion for this particular syndrome, whenever such features are observed in a newborn.

Keywords: Cornelia de Lange syndrome; Genetic disorder; Autosomal dominant; Malformation; Facial dysmorphia; Synophrys; Depressed nasal bridge; Hirsutism; Cardiac defects; Retardation.

Introduction

Cornelia de Lange syndrome (CdLS) is a multisystem disorder with physical, cognitive and behavioral defects. It is named after the Dutch pediatrician, Cornelia de Lange, who first described this developmental disorder in two infants in 1933. It is easily recognizable at birth due to its distinctive and unique facial appearance such as: Synophrys, prenatal and postnatal growth deficiency, psychomotor delay, behavioral problems, and malformations of the upper extremities etc [1,2]. Cardiac defects and gastrointestinal anomalies are also common. Additional physical features include: Myopia, palatal abnormalities, genitourinary abnormalities, congenital diaphragmatic hernias and hearing loss. Facial dysmorphism includes arched eyebrows, synophrys, and short nose with anteverted nares, long philtrum, thin upper lip, and micrognathia. There is a spectrum of findings which may range from severe to mild. This case report describes a newborn with typical features of Cornelia de Lange syndrome.

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Case report

A male newborn weighing 2kg (less than 3rd centile), was referred to the neonatal unit for his unique features and routine examination. He was the only child from a non-consanguineous marriage, born at 37 weeks of gestation through spontaneous vaginal delivery, to a 30-year-old mother (Gravida four, para three).

The child was born in a good condition with good reflexes. There were no signs of jaundice, cyanosis, respiratory distress or fits during the postnatal period. On examination (Figure 1,2,3), the child was vitally stable with a short length (less than 3rd percentile), microcephaly (head circumference less than 3rd percentile), brachycephaly, generalized excessive body hair (hirsutism), arch like confluent eyebrows (synophrys), prominent long curly eyelashes, low anterior and posterior hairline, micrognathia, short neck, broad nose, depressed nasal bridge, broad forehead, low set ears, down-turned angles of the mouth, thin upper lip, long philtrum, widely spaced small nipples also noted with excessive body hair. There were small broad hands, bilateral syndactyly of the toes. No vertebral defects were noticed. Moreover, there was hypoplastic male genitalia and micro-penis. Cardiovascular, respiratory, gastrointestinal and neurological examinations were normal. Fundoscopic and otoscopic examinations were also normal.

The complete blood count and biochemical profile of the neonate was found to be within the reference range. A full septic and biochemical work-up was negative for an underlying infectious pathology. The x-ray baby gram was normal for an underlying skeletal defect. Ultrasound abdomen showed bilateral multiple renal cysts of variable sizes with poorly defined intervening echogenic parenchyma and cortico-medullary architecture. The findings were consistent with bilateral multicystic dysplastic kidneys.

Since there were no active complaints, the child was orally allowed and kept on direct mother feed. Prophylactic vitamin K and routine immunizations were given. The parents were counseled about the nature of illness, its treatment options and long term complications. Prognosis was also discussed. They were then referred to a tertiary care facility for multidisciplinary management and follow-up care.

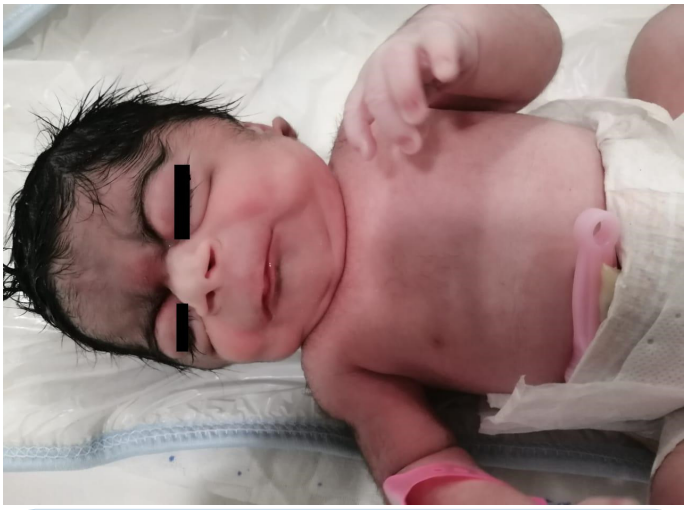

Figure 1: Classic craniofacial features of Cornelia de Lange syndrome.

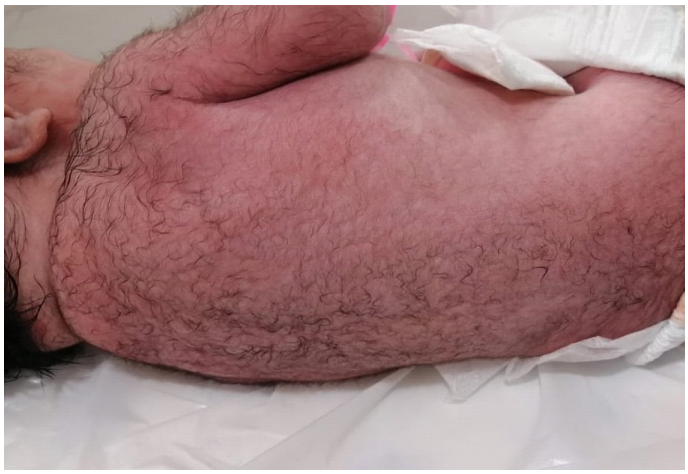

Figure 2: Excessive body hair (Hirsutism).

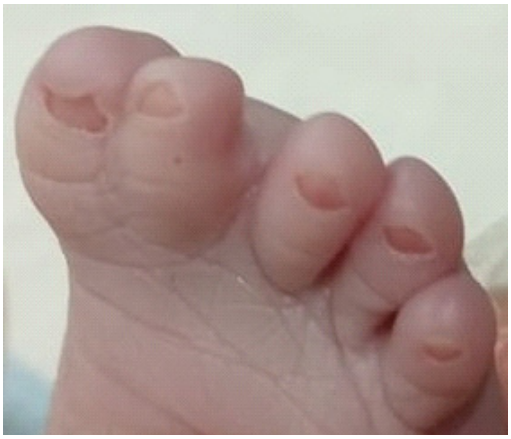

Figure 3: Syndactyly of toes.

Discussion

Researchers have shown Cornelia de Lange Syndrome (CdLS) as a rare genetic disorder characterized by multisystem malformations. The pathogenic variants of particular genes such as: NIPBL, SMC1A, SMC3, RAD21 and HDAC8 contribute to its unique presentation. The exact incidence is estimated to be 1 in 10,000 but still it is very well-known due to its distinctive phenotype. Most of the cases are reported to be sporadic, however familial inheritance and parental consanguinity are also significant factors. One-third of the population of such cases are associated with premature birth [3,4]. The clinical diagnosis is based on certain signs and symptoms. Severe or the classic type is described as having distinctive craniofacial features including synophrys, highly arched eyebrows, long lashes , short nasal bridge and microcephaly. Growth restrictions (<5th centile), hypertrichosis and upper limb deformities ranging from subtle phalangeal abnormalities to oligodactyly. Mild phenotypes have less severe deformities but unique facial features consistent with CdLS. Across the CdLS spectrum Intelligence Quotient (IQ) ranges from below 30 to 102 (mean: 53). Autistic and self-destructive behavioral tendencies are also noticeable [5].

Scoring Criteria

A Clinical scoring criteria [6] is based on the following cardinal and suggestive features.

Cardinal features:

- synophrys and/or thick eyebrows
- short nose, concave nasal ridge and/or upturned nasal tip
- Long and/or smooth philtrum
- thin upper lip vermilion and/or downturned corners of mouth
- Hand oligodactyly and/or adactyly
- Congenital diaphragmatic hernia

Suggestive features:

- Global developmental delay and/or intellectual disability
- Prenatal growth retardation
- Postnatal growth retardation
- Microcephaly (prenatal and/or postnatal)
- small hands and/or feet

Each feature is given a score of one.

- ≥11 points (of which at least three are cardinal): Classic CdLS.
- 9 or 10 points (of which at least two are cardinal): Non-classic CdLS.
- 4–8 points (of which at least one is cardinal): Molecular testing is required for the diagnosis.
- <4 points: insufficient to indicate molecular testing for diagnosis.

A molecular diagnostic criteria exists to detect abnormalities in the genes responsible for chromatin regulation especially those involving cohesion complexes. NIPBL, SMC1L1 and SMC3 mutations are the major cause of CdLS. Studies based on Genotype-phenotype correlations suggest significant variations in patients with and without mutations in terms of extent of growth and developmental retardation [7,8].

The clinical score of our patient was estimated to be eight which indicated the need for molecular testing. Analyses for mutations in the NIPBL, SMC1L1 and SMC3 genes are not currently available in Pakistan. Therefore, a genotype-phenotype correlation could not be performed in our patient.

Once the diagnosis of CdLS is made, a multidisciplinary approach is taken with the pediatrician playing a central role in clinical care. Focus is given on the major malformations and their management along with surveillance. Echocardiography and renal sonography are routine tests that are indicated in every child diagnosed as CdLS. CNS imaging also needs to be done in case the child presents with neurological symptoms. Early intervention is necessary for congenital heart diseases, urinary system abnormalities, feeding problems, psychomotor delay, hearing and visual impairment. Surgery may be indicated for some of the birth defects. Preferably, all infants and children diagnosed as CdLS need a routine follow-up at least once a year [6].

Conclusion

Cornelia de Lange syndrome is a genetically inherited multisystem disorder characterized by a set of distinctive physical features which can be easily identified by a detailed neonatal examination. This case report signifies the importance of screening of all newborn children for possible cognitive and growth defects. Knowledge about this particular syndrome and keeping a high index of suspicion are imperative for a prompt diagnosis and timely management.

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