CASE REPORT

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Cornelia De Lange Syndrome In A 4-Year-Old Child From India: Phenotype Description And Role Of Genetic Counseling

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ABSTRACT

Introduction: Cornelia de Lange syndrome (CdLS) is a congenital disorder marked by distinctive facial features, severe growth restriction, cognitive disability, global developmental delay, and anomalies involving multiple body organs. Majority cases of CdLS are caused due to sporadic mutations in the NIPBL, SMC1A, SMC3, RAD21, or HDAC8 genes, which form/regulate a multiprotein complex called cohesin. Cohesin is required for the separation of sister chromatids during cell division. **Case report:** We present a rare case of a 4-year-old child from India depicting classical features of CdLS. The patient was managed symptomatically by a multidisciplinary team and was requested regular follow-ups. **Conclusion:** Phenotype description according to ethnicity may help in diagnosing CdLS. A multipronged approach by a team of physicians from various faculties is required for providing comprehensive medical care to patients with CdLS.

Keywords: Cornelia de Lange syndrome, NIPBL, limb malformations.

1. INTRODUCTION

Cornelia de Lange syndrome (CdLS) is a congenital multisystem developmental disorder. The prevalence of CdLS is estimated to be around 1/10000 to 1/80000 live births (1). Common features of CdLS include characteristic facial dysmorphism, growth deficiency, global developmental delay, cognitive disability, along with several cardiac, gastrointestinal, genitourinary, limb, ophthalmic, and neurosensory anomalies (2). Mutations in the NIPBL (Nipped-B-like protein), SMC1A (structural maintenance of chromosomes 1A), SMC3 (structural maintenance of chromosome 3), RAD21 (human homolog of *Schizosaccharomycespombe*radio-sensitive mutant 21), and HDAC8 (histone deacetylase 8) genes are linked with CdLS. CdLS cases are mostly sporadic. However, autosomal and X-linked dominant modes of inheritance have also been reported (3). We present a rare case of a 4-year-old child from India with CdLS and discuss its etiology, pathogenesis, and management.

2. CASE REPORT

A 4-year-old boy was brought to the pediatric out patient department by his parents with complaints of poor growth, poor appetite, chronic regurgitation of food, and numerous congenital anomalies. The parents of the child did not have a consanguineous marriage. None of the close family members had similar features. The child was born via simple vaginal home delivery without complications. Developmental milestones were grossly delayed, as per the history elaborated by the mother. Vitals of the patient were normal. Height and weight were lower than WHO prescribed standards for his age. Facial examination showed undeveloped orbital arches, synophrys, curly eyelashes, down turned angle of the mouth, thin lips, hirsutism, long philtrum, micrognathia, and abnormally-shaped/missing teeth (Figure 1). Fixed flexion of the right elbow was present. The third and fourth fingers of the right hand showed clinodactyly (Figure 2). The left lower limb showed absence of the second toe and syndactyly of the third and fourth toes (Figure 3). Cognitive skills and speech were impaired. On auscultation heart sounds were normal. Genital, ophthalmological, and ear examinations were unremarkable. A clinical diagnosis of CdLS was made. Routine blood and urine investigations did not show any ab-

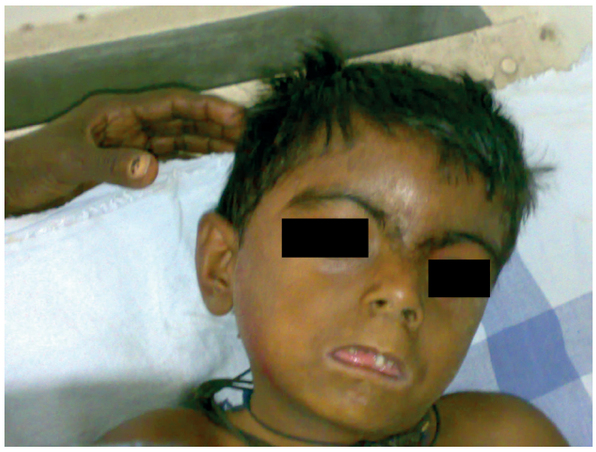

Figure 1. Facial dysmorphism characterized by undeveloped orbital arches, synophrys, curly eyelashes, downturned angle of the mouth, thin lips, hirsutism, long philtrum, micrognathia, and abnormal dentition

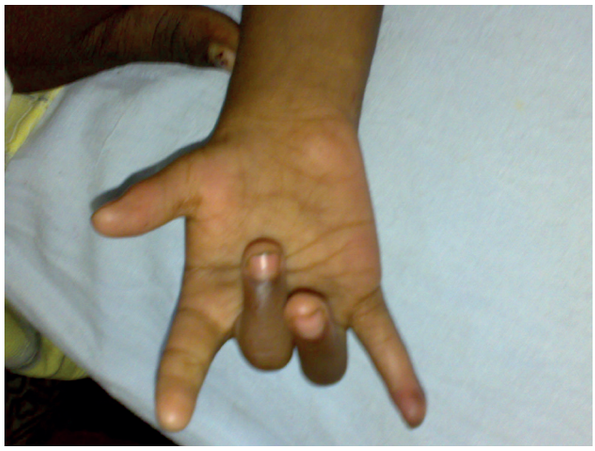

Figure 2. Clinodactyly of the third and fourth fingers of the right hand

normalities. Echocardiography, chest X-ray, audiometry, and abdominal ultrasound findings were normal. Karyotyping revealed normal male 46, XY karyotype. Further genetic tests could not be conducted due to the economic constraints of the patient. The symptom of heartburn due to regurgitation was treated with a proton-pump inhibitor. Genetic counseling and anticipated guidance was provided to the parents. The patient was requested to follow-up on regular intervals.

3. DISCUSSION

CdLS is classified according to the expression of the phenotype. Classical phenotype (Type-I) is the severe form of CdLS with typical facial and skeletal anomalies, as seen in our patient. Type-I CdLS is usually caused due to NIPBL mutations. Mild phenotype (Type-II) is the milder atypical variant of Type-I CdLS with fewer facial and skeletal anomalies. Type-II CdLS is usually associated with SMC1A, SMC3, RAD21, and HDAC8 mutations. Type-III CdLS have phenotypic manifestations similar to Type-II CdLS but is related to chromosomal aneuploidies or teratogenesis. Type-II and Type-III CdLS have better prognosis as compared to Type-I CdLS (4). The above mentioned genes help in the formation/functioning of cohesin, a multiprotein complex, which

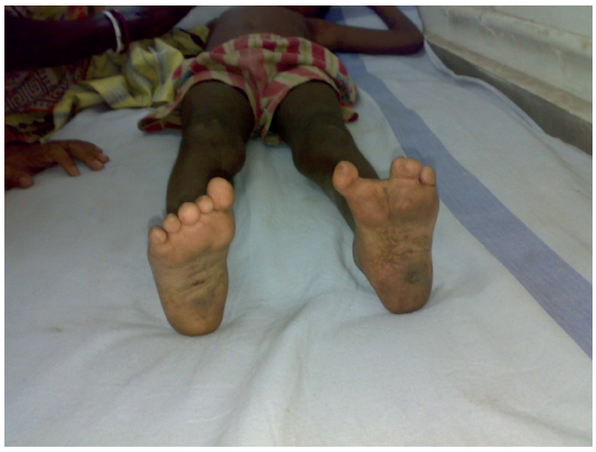

Figure 3. Left lower limb showing absence of the second toe and syndactyly of the third and fourth toes

helps in chromosomal structural organization required for genomic maintenance and gene expression (5).

CdLS due to NIPBL, RAD21, and SMC3 mutations is inherited via the autosomal dominant mode. CdLS due to SMC1A and HDAC8 mutations is inherited via the X-linked dominant mode. However, majority of the cases (99 %) are caused due to *de-novo* mutations (3). CdLS in our patient is most likely caused by a sporadic mutation as both the parents and other close relatives of the patient did not express any features of CdLS. Mutational analysis for genotype-phenotype correlation could not be carried out as these facilities were lacking in our hospital and funds weren't available for testing in private laboratories.

Ultrasound combined with genetic testing helps diagnosing CdLS in the in utero period. Periodic detailed ultrasound scans may detect findings suggestive of CdLS such as intrauterine growth restriction, limb anomalies, facial abnormalities, diaphragmatic hernia, and heart defects. Such high-risk fetuses could be subjected to genetic analysis to identify the mutated genes and confirm diagnosis (1).

Management of CdLS is mostly symptomatic and involves a multidisciplinary team (2). In our patient the gastroesophageal reflux was treated by pharmacotherapy. However, if symptoms persisted surgical treatment was advised. Orthopedic surgical intervention for the affected limbs was not advised as the patient had only a modest functional impairment. Physical and speech therapy was advised to optimize psychomotor development and communication skills. Dental consultation was also sought with regular follow-up visits.

During the genetic counseling, the parents of the patient were informed in details about the nature of the disorder, and the modalities available for its early detection. As the loci of the genetic mutation was not truncated, the mode of inheritance of the disorder in the patient's offspring could be either autosomal dominant (NIPBL, RAD21, or SMC3 mutations) or X-linked dominant (SMC1, or HDAC8 mutations). If the NIPBL, RAD21, or SMC3 genes are mutated, then there is a 50 % chance of the offspring of the patient being affected, irrespective of gender. If the SMC1A or HDAC8 genes are mutated,

then all the daughters of the patient would be affected but the sons would be unaffected. As the parents of the patient are healthy, the chances of their next child being affected is 1.5 % due to a possibility of germline mosaicism (4, 6). Hence, they were advised to follow strict vigilance while planning their next pregnancy.

4. CONCLUSION

CdLS is a rare congenital multisystem disorder. Most cases are diagnosed clinically. Phenotype variations maybe present due to variability in ethnic background. Hence, phenotype descriptions according to ethnicity may help in diagnosis. Mutational analysis is required for phenotype-genotype correlation. Efficient management requires a multidisciplinary approach.

- **Author's contribution:** All authors were included in all steps of preparations of this case report.
- **Conflict of interest:** none declared.
- **Declaration of patient consent:** Authors certify that they have obtained patient consent form.

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