CASE REPORT

CORNELIA DE LANGE SYNDROME: A CASE REPORT

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ABSTRACT

Cornelia de Lange syndrome (CdLS) is an uncommon congenital condition. It is also often called as Amsterdam dwarfism.[1] It often manifests in a child as low body weight at birth. As the child grows, it shows distinctive features like delayed growth and development, hirsutism, short stature and unique facial characteristics. Often the child shows retarded physical and mental development. This syndrome is often diagnosed based on clinical features as there are no biochemical or chromosomal markers for CdLS which presents itself as a diagnostic challenge[2-4].

INTRODUCTION

Dr. Cornelia de Lange first described it as a distinct syndrome in 1933, although Brachmann had described a child with similar features in 1916.[1]

The incidence is 1 case per 10,000-50,000 live births. No differences based on sex or race have been described More than 99% of cases are sporadic. Cornelia de Lange syndrome is occasionally transmitted in an autosomal dominant pattern. Although possible autosomal recessive inheritance has been reported in some families, these instances were likely to be due to germline mosaicism. The *NIPBL* gene provides instructions for making a protein called *delangin,* which plays an important role in human development. Before birth, delangin is found in the developing arms and legs, the bones of the skull and face, the spinal column, the heart, and other parts of the body.[1,5] Delangin helps control the activity of chromosomes during cell division.[1,4,5] More than 300 mutations in the *NIPBL* gene have been identified in people with Cornelia de Lange syndrome, a developmental disorder that affects many parts of the body. Mutations in this gene are the most common known cause of Cornelia de Lange syndrome, accounting for more than half of all cases.[4]

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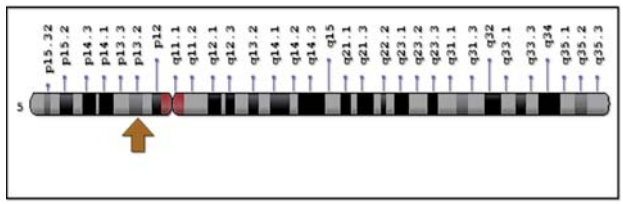
Fig. 1: Cytogenetic Location: 5p13.2, which is the short (p) arm of chromosome 5 at position 13.2. Molecular Location: base pairs (NCBI)



The history of patients with Cornelia de Lange syndrome (CdLS) may include the following, Intrauterine growth retardation (68%). Average birth weight is less. In most patients,growth occurs at rates lower than those on normal growth curves throughout life. Height velocity is equal to the reference range, but pubertal growth is slowed. Weight velocity is lower than the reference range until late adolescence. Average head circumferences remain less.[2,5] CdLS has a variable phenotype, with classic and mild types. Diagnosis is based on clinical and radiological findings as well as characteristic facies.[6]

Complications in individuals with CdLS require the support of a multidisciplinary health team. Family support is also essential, especially at the time of diagnosis. It is important to provide the family with information on the syndrome, which could help parents/caregivers to cope emotionally with the diagnosis and cooperate with regard to the child's treatment. A case report of a 7 year boy from the state of Haryana in India presenting with mild features of the disease establishes further the knowledge of this rare condition.

CASE REPORT

A 7 year old male patient from Bundakhera district of Haryana visited the Department accompanied by his parents with a chief complaint of poor growth and short stature, with multiple decayed teeth in upper & lower teeth region since 2-3 years.Patient was apparently abnormal since birth. The infant was born at full term through natural childbirth. The parents had no systemic abnormalities. The child was not the product of consanguineous marriagehoweverthe child reports to have suffered frompneumonia during first month of life for which he was hospitalized for 10 days in a Government set up hospital. Routine immunization was done for the child. Patient was unable to take breast milk

in initial 1 month of life due to weakness (as reported by parents) and his size was almost that of a palm. Soon the parents observed delayed development in terms of physical and mental abilities. Patient had delayed growth milestones and was unable to cope with studies at school and was dropped out from regular schooling. Patient also reports of multiple decayed teeth in the upper and lower back region due to a habit of feeding sweetened milk. Parents report of behavioral abnormalities (sudden change in behavior from jolly to extreme reclusion) with a habit of lip biting. Frequent episodes of gastric reflux disorders with presentations of intermittent poor appetite & vomiting were reported by the parents.

Fig. 2: Shows profile views of patient showing synophrys with long curly eye lashes and low anterior hairlines.

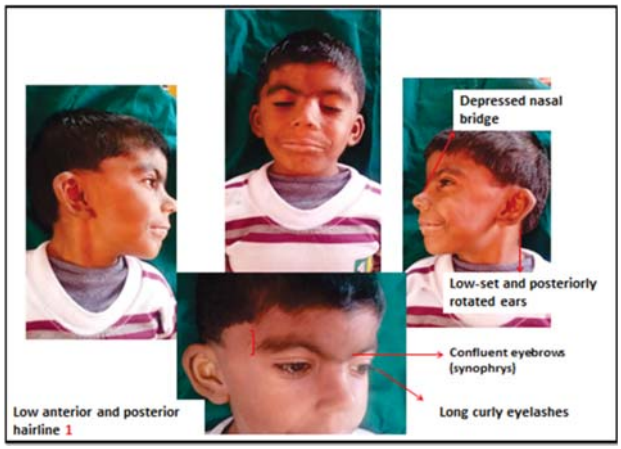
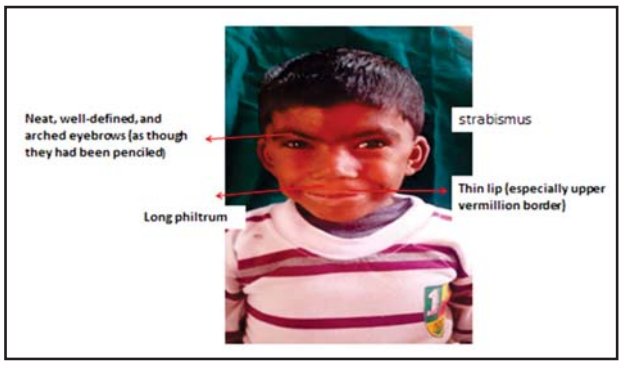
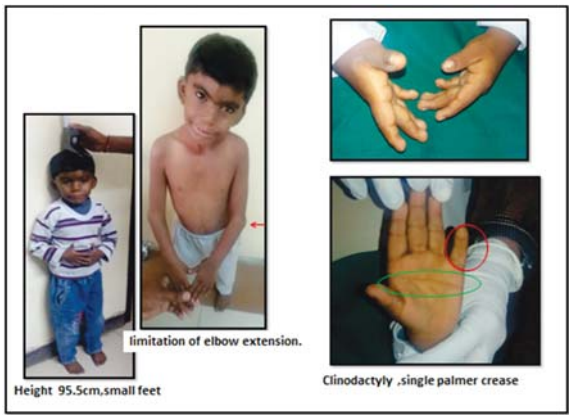


Fig. 3: Shows thick well-defined eyebrows, long philtrum, thin lip and strabismus in eyes



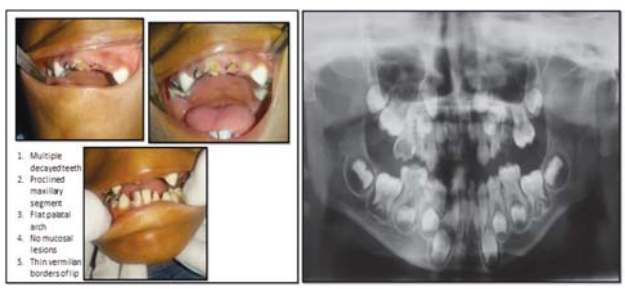
General examination revealed an apparently friendly behavior of the child with short stature [height (95.5cm); weight (10.3kg) : Head (micro cephalic) OFC:43cm (NORMAL for 7 years 55-60cm)]; physical features were apparent of a dysmorphic face with characteristic facial features like Thick eye lashes which typically meet at the midline (synophrys), arched eyebrows, long eye lashes with strabismus in eyes. Short nose and

Fig. 4: Shows typical features of hand and elbow joint



down turned lips with a long philtrum (increased distance between nose and upper lip) lips were thin and curved downwards producing a mask like appearance.Low set ears which appeared larger compared to facial profile. Excessive body hair, low hairline anteriorly and behind neck "Hirsutism". Hair growth on upper lip presents, incurved 5th finger (clinodactyly), with single palmer crease, protruded mandible with relative hypertrophied maxillary facial appe Intra oral examination revealed,multiple decayed teeth,proclined maxillary segment, flat palatal arch, no mucosal lesions, thin vermilian borders of lip with a cresent shaped mouth (Fig.5). Behavior management of the child was a challenge as the patient showed sudden disinterest towards examinations and refused to cooperate and hesitant to talk or communicate. His general health was good without any cardiac or respiratory defects and on psychiatric evaluation patient scored 60 on the Stanford Binet IQ scale which fell into the interval of 40-50 suggestive of moderate mental deficiency.ENT consultation suggested an conductive hearing loss with audiometery testing .

Fig. 5: Showing intra oral features, with panoramic radiographical assessment



Panaromic radiography revealed a multiple unerupted teeth with developing folicles of 11,21 seen with apparent morphological abnormality. Developing tooth bud 13,23,14,24,15,25,46,36,17,27,37,47. Grossly decayed 51,52,54,55,64,65,74,75,81,82,84 [Fig. 6]

To rule out a suspected morphological variation of unerrupted 11, 21, Intra Oral Peri Apical (IOPA) radiograph (Fig. 6) were advised which revealed Broad and morphologically altered 11,21 with a radiolucent inverted "v" observed extending from the incisal region till the cervical third suggestive of dens invaginatus with lack of cervical constriction (possibility of overlap of developing 12, 22).

Skeletal analysis to assesses the skeletal variation if any and to determine the skeletal age of the patient was done.

Fig. 6: IOPA w.r.t. 11,21

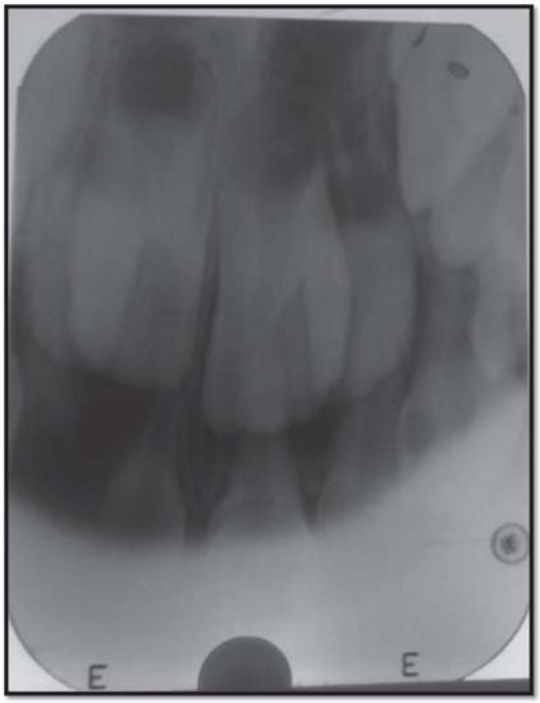
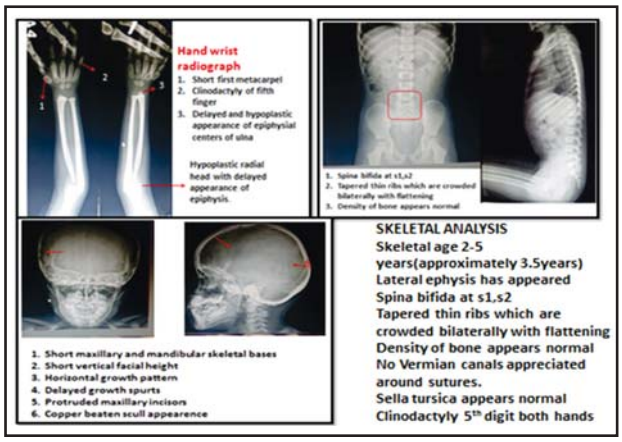


Fig. 7: Skeletal analysis suggestive of typical features of CdLS



On the basis of facial features oral and radiographic findings, the provisional diagnosis of Cornelia de lang syndrome was confirmed [Table.1]

Table 1: Correlates features reported in literature and identified in our case

FEATURES	COMMON MANIFESTATION OF CDLS[1,2,5,7]	REPORTED IN LITERATURE	IN OUR CASE
Cranium	Microbrachycephaly[2]	+	+
Forehead	Pilosity on forehead	+	+
	Low anterior and posterior hairline[3]	+	+
Eyes	Bushy and confluent eyebrows (synophrys)	+	+
	Long curly eyelashes	+	+
	Ptosis, nystagmus[1,5]	+	+
Nose	Anteverted nostrils[5]	+	+
Mouth	Thin lips	+	+
	High arched palate	+	_
	Long philtrum	+	+
	Cleft palate, perioral cyanosis (rare)	+	_
	Disturbance of nasopharyngeal function[1,2,3,5]	+	+
Mandible	Micrognathia, Macroglossia	+	_
	Spurs in the anterior angle of the mandible[1,2,7]	+	+
Ears	Low set , outwardly placed ears Hypoacusis[2,5,7]	+	+
Feet	Limb and digital anomalies[1,7]	+	+

Other general features present in our case are listed in Table 2:

Table 2: Shows other common general features present in our case

Other general features	• Hirsutism • Retarded bone age • Structural anomalies of limbs • Clinodactyly of fifth finger • Delayed growth and development • Cardiac, respiratory and GI abnormalities • Mental retardation (varying degrees) • Self injurious tendencies (report of lip biting) • Gastroesophageal reflux • Child hood pneumonia

Some features identified in our case not previously been reported in literature are enlisted in Table 3.

Table 3: Features present in the case not reported in literature

Features	In our case	Reported in literature
Flat palatal arch	+	-
Spina bifida	+	-
Thin tapered ribs	+	-
Crowding of developing tooth buds	+	-
Middle lobe hypoplasia of developing incisor	+	-

A final diagnosis of Cornelia de Lang syndrome was given with a multidisciplinary approach towards the management of the patient including pediatric, ENT, medicine, pedodontics and oral maxillofacial surgery and orthopedic consultation was conducted.

DISCUSSION

Cornelia de Lange syndrome (Brachmann syndrome, Typusdegenerativusamstelodamensis) is a multiple congenital anomaly, first documented in 1916 by W. Brachmann followed by Cornelia de Lange in 1933.[2,3] Van Allen et al classified CdLS into 3 types:

Type I or classic patients: show characteristic facial and skeletal changes of CdLS[7]

Type II or mild patients: show characteristic facial features and minorskeletal abnormality.[7]

Type III show phenotypic manifestations of CDLS, related to chromosomal aneuploidies or teratogenic exposures. Based on given classification, the present case falls into Type II.[7]

The principal clinical characteristics of this syndrome are the delay in growth and development, hirsute, anomalies in the structure of the limbs and distinctive facial characteristics.[5,9] At birth and during the length of their life, these patients present a weight and size inferior to that corresponding to their age. The intellectual coefficient is not over 50%. Our patient was also of short stature [height (95.5cm); weight (10.3kg) Head (micro cephalic) OFC:43cm (NORMAL for 7 years 55-60cm)] and underweight (10 kgs.) corresponding to his age. According to Stanford Binet IQ test he was found to be moderately mental deficient and was unable to cope with normal schooling of his age and had dropped out from main stream schooling. Our patient also had limited mobility of the elbow and fifth finger clinodactyly. The feet of our patient were short and wide.

The characteristic facial features reported in the literature are present in our case which is evident in the case analysis,also Braddock et al. (1993) presented a review of the classic radiological features of CdLS which includes microcephaly, limb and digital anomalies and delayed skeletal maturation.[10] In our patient radiographs revealed unerrupted multiple teeth though the patient is 7.5 year of age. with apparent morphological abnormality of unerrupted 11,21 suggestive of middle lobe hypoplasia of the developing permanent incisors. However a frequently reported finding of a high arch palate and spacing was absent in our case on the contrary our case presented a picture of a flat palatal arch with crowding and multiple grossly decayed teeth. The feature of copper beaten scull appearance has been previously reported by Reddy SS[11] is present in our case and suggest an increase in intracranial pressure during developmental stages.

Early intervention in patients with Cornelia de Lange syndrome (CdLS) is necessary for feeding problems, hearing and visual impairment, congenital heart disease, and urinary system abnormalities.Early intervention for psychomotor delay is also indicated. Computer programs that emphasize visual memory are more beneficial than standard methods of verbal instruction.Perceptual organizational tasks should be emphasized.Tactile stimulation during indirection helps the children remember and perform maximally. Fine motor activities, when physical impairments do not limit them, should be stressed in education, especially activities related to activities of daily living. Children with special health care needs and increased risk of oral problems require an interdisciplinary health care team.[7,12]

Cooperation between medical and dental services is essential to patient well-being. Oral health includes the interrelation of all aspects of child development, genetic potential and environmental circumstances. Abnormalities in the growth and development of the maxillar lead to dental misalignments. Mental impairment, delayed motor skills, dental misalignment, and type of diet may contribute to periodontal disease. Complications in individuals with CdLS require the support of a multidisciplinary health team. Family support is also essential, especially at the time of diagnosis. It is important to provide the family with information on the syndrome, which could help parents/caregivers to cope emotionally with the diagnosis and cooperate with regard to the child's treatment.[3,5,12]

CONCLUSION

Considering the clinical manifestations, it is clear that the occurrence of CdLS places serious limitations on the lives of affected individuals. A multidisciplinary

approach to caring for patients with CdLS is essential. Dentists play a fundamental role in caring for these individuals, as oral manifestations are very common in the syndrome, a better understanding of the etiopathological aspects and clinical manifestations of this condition, which could allow establishing measures for the improvement of health care and quality of life of affected individuals and their families.

REFERENCES

1. **Verma L, Passi S, Gauba K.** Brachman de lange syndrome. Contemp Clin Dent 2010 ;1:268-70
2. **Malik LM, Khan GA, Azfar NA, Jahangir M.** Cornelia de Lange Syndrome - a cause of hypertrichosis in children: case report and of literature. Journal of Pakistan Association of Dermatologists 2011; 21 (3): 211-214
3. **Carbó JC, Jiménez JL, Prats MJG, Molins MS.** Cornelia de Lange syndrome: A case report. Med Oral Patol Oral Cir Bucal. 2007 Oct 1;12(6):E4458.
4. **Lalatta F, Russo S, Gentilin B, Spaccini L, Boschetto C, Cavalleri F, Masciadri M, Gervasini C, Bentivegna A, Castronovo P, et al.** Prenatal neonatal pathology in two cases of Cornelia de Lange symptoms harboring novel mutations of NIPBL. Genet Med. 2007;9:188–194.
5. **Gillis LA, McCallum J, Kaur M, DeScipio C, Yaeger D, Mariani A, Kline AD, Li H, Devoto M, Jackson LG, et al.** NIPBL Mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. Am J Hum Genet. 2004;75:610–623
6. **Scarpelli AC, Pordeus IA, Resende VL, Castilho LS, Marques LS, Paiva SM.** Cornelia De Lange syndrome: a case report of a Brazilian boy. The Cleft palate-craniofacial journal. 2011 Jul;48(4):490-3.
7. **Toker AS, Ay S, Yeler H, Sezgin I.** Dental Findings in Cornelia De Lange Syndrome. Yonsei Med J. 2009;50(2):289-92.
8. **Allanson JE, Hennekam RC, Ireland M.** De Lange syndrome: subjective and objective comparison of the classical and mild phenotypes. J Med Genet 1997;34:645-50.
9. **Carbó JC, Jiménez JL, Prats MJG, Molins MS.** Cornelia de Lange syndrome: A case report. Med Oral Patol Oral Cir Bucal. 2007 Oct 1;12(6):E445 8.
10. **Braddock SR, Lachman RS, Stoppenhagen CC, Carey JC, Ireland M, Moeschler JB, et al.** Radiological features in Brachmann-de Lange syndrome. Am J Med Genet 1993;47:1006-13
11. **Reddy SS, Shweta V, Chauhan P, Sahana K.** CORNELIA DE LANG SYNDROME. e-Journal of Dentistry. 2012;2(4):269-72.
12. **Grau-Carbó J, López-Jiménez J, Giménez-Prats MJ, Sànchez-Molins M.** Cornelia de Lange Syndrome: A case report. Med Oral Patol Oral Cir Bucal. 2007;12(6):445-48.