



## Cornelia De Lange Syndrome in a Torch Positive Infant: Case Report

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### Abstract

Cornelia de Lange syndrome (CdLS) is a rarely seen autosomal dominant syndrome presented with facial dysmorphism ( Microbrachycephaly, synophrys, arched eyebrows, low set ears, long eyelashes, wide spaced teeth, upturned nose), characteristic cry, behavioral problems, feeding problems, growth retardation, motor delay, upper limb reduction defects that range from subtle phalangeal abnormalities to oligodactyly (missing digits), systemic defects etc. Heterozygous mutation in NIPBL or cohesion structural components, SMC1L1, SMC3 identified in major number of patients. Genetic study shows the association of chromosome no. 10, 5 and X most commonly. We present a case of mild CdLS which was TORCH screen positive in her newborn period. Clear cut diagnosis was made from morphological features of the child after ruling out all systemic complications of the child it was marked mild variant of CdLS.

**Key Words:** Cornelia de Lange syndrome (CdLS), TORCH infection, Facial abnormality, cohesion complex

## INTRODUCTION

CdLS is a multisystem developmental commonly autosomal dominant disease. Incidence is around 1 to 2.2 in 100,000 populations according to

EUROCAT (European surveillance of congenital and rare disease)<sup>1</sup>. It causes distinct facial, systemic, behavioral abnormality, hearing

impairment, vision anomaly, limb defects etc. Diagnosis of Cornelia de Lange syndrome (CdLS) is made on a clinical basis.

*Craniofacial appearance* is most prominent feature (>95%): Micro brachycephaly (mean occipital frontal circumference [OFC] <2nd centile) Synophrys, arched eyebrows in 98% Long, thick eyelashes Low-set posteriorly rotated and/or hirsute ears with thickened helices. Depressed nasal bridge, upturned nasal tip with anteverted nares, and prominence of the lateral aspects Long smooth philtrum, thin border of the upper lip with a midline "drip" appearance (lowering of the apical part of the upper lip at the base of the philtrum below the arc of the upper lip), downturned corners of the mouth High and arched palate with clefts in 30% Small widely-spaced teeth Micrognathia in 80%; mandibular spurs in 42% Short neck.

*Growth failure* is also prominent (>95%): Growth failure occurs prenatally. Height and weight remain below the 5th centile throughout life.

*Intellectual disability* (>95%): Severe-to-profound pervasive developmental delay. IQ ranges from below 30 to 102 (mean: 53). Many individuals demonstrate autistic and self-destructive tendencies.

*Limb abnormalities* (>95%): Upper extremities are primarily involved. Limb abnormalities may be symmetric or asymmetric. Upper extremity deficiencies ranging from severe reduction defects with complete absence of the forearms to various forms of oligodactyly (missing digits) occur in approximately 30%. In the absence of limb deficiency, micromelia (small hands), proximally placed thumbs, and fifth finger clinodactyly occur in nearly all individuals. Radioulnar synostosis may result in flexion contractures of the elbows. The feet are often small and two-three syndactyly of the toes occurs in more than 80%.

*Hirsutism* (>80%): Thick scalp hair extends onto the temporal regions and at times involves the face, ears, back, and arms<sup>2</sup>.

*Systemically* heart defects, convulsions, GERD, ear abnormality, vision abnormality are very common<sup>2</sup>.

Two varieties are documented generally. The classic CdLS variety presents with all the abnormalities in severe forms but in another form (mild CdLS) the abnormalities are in less severe form<sup>2</sup>. Biochemically the disease is found a defect in cohesin complex, which has a role in regulating gene expression, DNA repair, chromatin remodelling and maintaining genetic stability<sup>3</sup>. As CdLS is a rare developmental disorder and cases of uncomplicated CdLS associated with TORCH infection in newborn period is very rarely reported. Therefore we are presenting this case to have a broad view on CdLS and its association with intrauterine infection.

## CASE REPORT

A 7 month female child was presented to our OPD with chief complaint of delay in neck holding and eyes half open during sleep since birth. Previously she had history of admissions due to LRTI. She was first order child of consanguineous marriage and was born by LSCS due to footling presentation. The mother was undergoing regular antenatal check up. In third trimester USG abdomen revealed some congenital anomaly. The child did not cry for 2 hours after birth and was bottle fed from birth. Birth weight was 2.25 kg. She was immunised according to her age. Till 7 months she hadn't attained neck control.

On examination child had microcephaly, synophrysis, long eyelashes, long philtrum, thin upper lip, depressed nasal septum, retrognathia (fig-1), low set ears (fig-2), high arched palate, low posterior hairline (fig-3), b/l curved little finger (fig-4). Anterior fontanelle was open. Heart rate and respiratory rate were within normal limits. The respiratory system examination showed b/l conducted breath sounds. All other

CNS examination and abdominal examination were within normal limits. Ophthalmic examination showed exposure keratitis with a normal fundus.

The complete blood count was normal except TLC 15400, biochemical parameters, urine were within normal range. ECG, ECHOCARDIOGRAPHY and upper G.I. endoscopy were normal. The mother was HIV Screen negative. The child had undergone TORCH screening during her newborn period and was positive for toxoplasma IgG {2360 IU/ML – N<7.20} CMV IgG {124U/ML-N<12} CMV IgM{1960U/ML-N<18} HSV I &II IgG 2.20 U-N<0.9}



Fig01



Fig03



Fig04



Fig02

### DIAGNOSIS AND MANAGEMENT

On basis of such varied clinical presentation and investigation a diagnosis of mild CdLS with TORCH infection with LRTI was made. She was treated for exposure keratitis and LRTI by antibiotics and artificial tears .

### DISCUSSION

Most commonly CdLS is a sporadic disease, but it can be familial, and may be seen in high incidence in consanguinity<sup>4</sup>. Classic variety presents in severe manifestations. Life expectancy depends upon the systemic complications. It is rare in mild variety. The cause of death aspiration pneumonia , recurrent apnea , congenital heart disease, volvulus and intestinal obstruction, post-

surgical complications (thrombocytopenia and intracranial bleeding), and cerebral edema and herniation after spine surgery. Severe broncho pulmonary dysplasia, mediastinitis, uremia, bronchial asthma, coronary artery occlusion, and pulmonary embolus were other causes of death<sup>2</sup>. A study shows high frequency of antibody deficiency in CdLS subjects. Screening and management of immunodeficiency needed in CdLS patients with severe or recurrent infections. Results indicate that impaired T-cell populations may be associated with antibody deficiency in CdLS<sup>5</sup>. The prognosis for patients with mild form of Cornelia de Lange syndrome (CdLS) is much better than that for patients with the classic form. Life expectancy is generally normal. The differential diagnosis of Cornelia de Lange syndrome includes fetal alcohol syndrome and various other genetic syndromes. Prenatal diagnosis is made after careful evaluation of CdLS abnormalities on prenatal ultrasonography. These include growth retardation, limb defects, diaphragmatic hernia, hypoplastic forearms, underdeveloped hands and typical facial defects<sup>4</sup>. Several genetic study showed the cause of this syndrome lies in chromosome 5,10,3,X chromosomes. Heterozygote mutation of NIPBL gene in chromosome no 5 which produces defect in delangin protein which is a part of cohesin complex. This complex is needed for several critical role in mitosis and gene expression. X linked SMC1L1 defect causes defect in another locus of cohesin complex but produces a mild variety<sup>6</sup>. It is also thought that milder form is associated with partial trisomy of chromosome 3. One third of the cases associated with preterm delivery. The association of CdLS and intrauterine infection is neither much investigated nor reported.

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