Case Report

Newborn with classical Cornelia de Lange syndrome: A rare case report

Ayush Sopori[1], Mohit Bajaj[2], Jyoti Sharma[3], Chetna Jangwal[1]

From [1]Junior Resident, [2]Senior Resident, [3]Associate Professor, Department of Pediatrics, Dr. Rajendra Prasad Government Medical College, Sadarpur, Himachal Pradesh, India

ABSTRACT

Cornelia de Lange syndrome (CdLS) is a rare multisystem developmental disorder associated with multiple congenital malformations including facial dysmorphism, upper-extremity malformations, hirsutism, cardiac defects, gastrointestinal abnormalities, and central nervous system anomalies. In the neonatal period, typical facial features help in diagnosing it. Here, we report a neonate with facial features (bushy eyebrows, synophrys, long eyelashes, micrognathia, hirsutism, and low hairline), gastroesophageal reflux disease, large atrial septal defect, and neonatal seizures diagnosed as classic CdLS.

Key words: Cornelia de Lange syndrome, Dysmorphic features, Growth retardation, Neonate

Cornelia de Lange syndrome (CdLS), also known as Brachmann de Lange syndrome, is a rare multisystem congenital anomaly syndrome characterized by facial dysmorphism, limb anomalies, growth retardation (prenatal and postnatal), and neurological developmental delay along with the involvement of respiratory, cardiac, and musculoskeletal system. Facial dysmorphism includes low hairline anteriorly and posteriorly, arched eyebrows, synophrys, short nose with anteverted nares, long philtrum, thin upper lip, and micrognathiamainly [1]. The incidence varies from 1:30,000 to 1:50,000. It is slightly more common in females as compared to males (F:M:1.3:1) [2]. Most cases are sporadic but familial transmission with an autosomal dominant hereditary pattern has also been reported [3].

At present, the diagnosis in neonates is made on the basis of clinical observations as suggested by the CdLS Foundation and Scientific Advisory Committee of the World CdLS Federation [4]. A thorough medical evaluation including history and physical examination, family history, laboratory tests, X-rays, and karyotyping is usually conducted before keeping its possibility [5]. Here, we report a case of neonatal CdLS with characteristic facial features and physical findings that can help pediatricians and general practitioners all over the world to easily identify such classical cases and to provide the family with information on this syndrome and its course of illness.

CASE REPORT

A 20-day-old female neonate brought in the neonatal intensive care unit (NICU) with complaints of regurgitation of feeds for 3 days followed by fast breathing for 1 day. There was a history of thick secretions coming from the mouth post-breastfeeds intermittently for the past 1 week. The newborn was delivered by vaginal route with a gestation of 38 weeks and born out of a non-consanguineous marriage. There was no history of birth asphyxia. The birth weight was 1.8 kg (asymmetric intrauterine growth retardation). The Apgar scores at birth were 7 and 8. The newborn had passed urine and meconium within 24 h and was discharged after 72 h.

At admission, the newborn was sick looking with a weak cry, tachycardia, tachypnea (>70/min), and respiratory distress in the form of suprasternal and intercostal recession with SPO_2 of 84% on room air with secretions coming from the mouth. Newborn also had subtle seizures at admission. The occipitofrontal circumference (OFC) was 32.8 cm and the length was 47 cm. Her facial characteristics included bushy eyebrows, synophrys, long eyelashes, depressed nasal bridge, downturned angle of the mouth, micrognathia, and hirsutism. The newborn had low anterior and posterior hairline along with clinodactyly of both hands. On the central nervous system examination, bilateral lower limbs had a high tone in the form of scissoring posture (Figs. 1 and 2a). Cardiovascular system examination revealed systolic murmur Grade 5 in the 2nd and 3rd intercostal space parasternal region with palpable liver and spleen. Respiratory system examination revealed crepitations in the right apical and inframammary region. Genitalia were normal. Based on the clinical examination, a possibility of CdLS (classical) with associated late-onset sepsis and pneumonia was kept.

Laboratory analysis including complete blood count, cerebrospinal fluid study, biochemical parameters, urinalysis,

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Corresponding to: Dr. Mohit Bajaj, Department of Pediatrics, Dr. Rajendra Prasad Government Medical College, Sadarpur, Himachal Pradesh, India. E-mail: tandian427@gmail.com

arterial blood gas (ABG), thyroid profile, and karyotyping (46, XX) was normal. Random blood sugar was 110 mg/dl. X-ray chest showed consolidation in the right apical lobe and in the inframammary region along with cardiomegaly (Fig. 2b).

Newborn received positive pressure support for 2 days and was weaned off gradually. Empirical antibiotics cefotaxime 100 mg/kg/day in three divided doses/amikacin 15 mg/kg/day in single dose were started. For gastroesophageal reflux disease (GERD), ranitidine was added, and frothing decreased significantly. The blood culture was sterile. Transthoracic echocardiography revealed a large atrial septal defect (ASD) with RA/RV dilation. Neurosonogram and ultrasound (USG) abdomen were normal.

After completion of 14 days of antibiotics, the newborn improved gradually and was discharged. At discharge, phenobarbitone was continued, and on examination, the cry had improved with a bilateral tone of lower limbs on the higher side with the same posture. The eye examination was normal. At 2 months of life, the infant was readmitted with seizures. At admission, the weight was 2200 gm, OFC was 33.1 cm, and the length was 47 cm. The rest of the examination was similar with the increased tone of lower limbs. The phenobarbitone dose was increased and the child is on follow-up and doing well (Fig. 3).

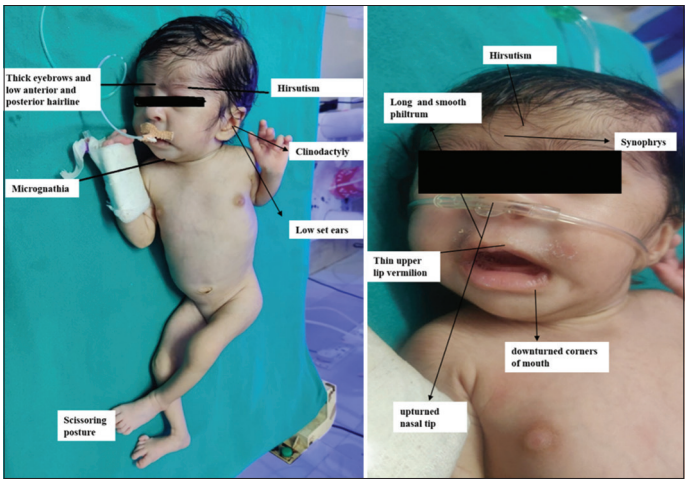

Figure 1: Facial features of newborn

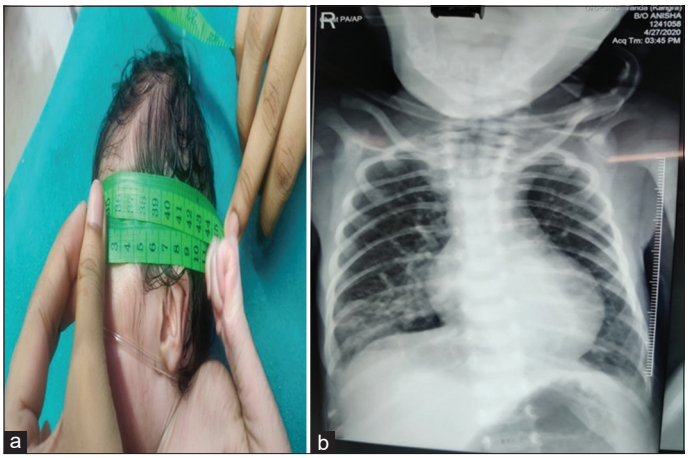

Figure 2: (a) Microcephaly; (b) chest X-ray of newborn showing the right lower lobe consolidation with pneumonia and cardiomegaly

DISCUSSION

CdLS is a very complex congenital disorder with unknown etiology. It was first reported by Dr. Cornelia de Lange, a Dutch pediatrician in 1933. Brachmann in 1916 had observed similar features with additional features of deficiencies of the upper limb in a child with the autopsy. For their contributions, both names have been attached to the name of this syndrome [6].

The diagnosis is primarily clinical and is based on signs and symptoms of a distinct phenotype, mainly in the face and limbs. Van Allen *et al*. proposed a classification system [7]. Type 1 denotes "classic" patients having characteristic facial and skeletal changes. Type 2 shows "mild" patients having similar facial and minor skeletal abnormalities that were noted in type 1, however, these changes may develop later in 1–2 years of life or maybe partially expressed. Type 3 is "phenocopies" that includes the patients who have phenotypic manifestations, which are related to chromosomal aneuploidies or teratogenic exposures. In our case, the newborn was a classic CdLS. At present, consensus criteria are used to diagnose and classify it at birth [5]. In our case, the newborn had 13 points suggesting classical CdLS (Table 1).

GERD is the most commonly seen gastrointestinal sign and can present as dystonic Sandifer-like events [8]. GERD may present in a highly variable manner, including feeding problems, recurrent (chemical) pneumonia, failure to thrive, agitation, restlessness, or poor sleep. GERD tends to persist or to worsen with time. The index case had admission due to pneumonia secondary to GERD which relieved after giving intravenous ranitidine. On follow-up, GERD had improved after the addition of ranitidine.

The symptoms are very vast affecting the entire body affecting cardiac, skeletal, gastrointestinal, vision, and auditory systems. Our case had facial features including microcephaly, high forehead, short neck, bushy eyebrows, small nose, anteverted nostrils, thin upper lip, fish-like mouth, long philtrum, and micrognathic mandible. Skeletal features can include malformations which include an absent forearm, abnormal fusion of the radius and ulna (radioulnar synostosis), absent radius or ulna, and oligodactyly. Small hands are present in almost all individuals with CdLS.

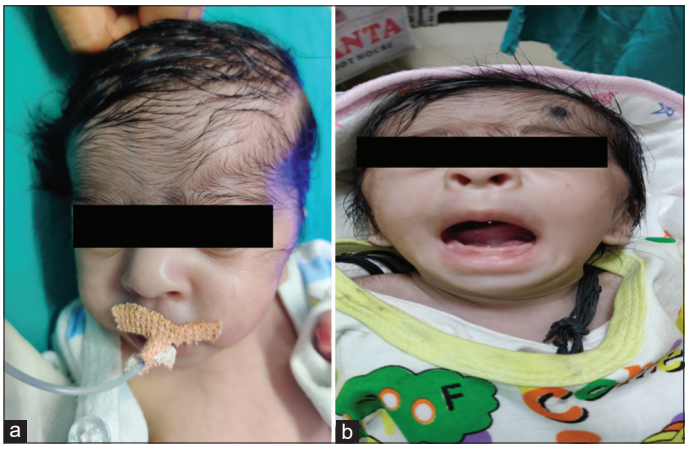

Figure 3: Taken at (a) 1 and (b) 3 months of age. On follow-up, the newborn was showing low hairline with increase hirsutism along with characteristic facial features

Table 1: Clinical criteria of CdLS for diagnosis

Cardinal features (2 points each if present)	Suggestive features (1 point each if present)
a. Synophrys and/or thick eyebrows	a.Global developmental delay and/or intellectual disability
b. Short nose, concave nasal ridge, and/or upturned nasal tip	b. Prenatal growth retardation (<2SD)
c. Long and/or smooth philtrum	c. Postnatal growth retardation (<2SD)
d. Thin upper lip vermilion and/or downturned corners of mouth	d. Microcephaly (prenatally and/or postnatally)
e. Hand oligodactyly and/or adactyly	e. Small hands and/or feet
f. Congenital diaphragmatic hernia	f. Short fifth finger
	g. Hirsutism

Clinical score

- ≥11 points, of which at least 3 are cardinal: Classic CdLs
- 9 or 10 points, of which at least 2 are cardinal: Non-classic CdLs
- 4–8 points, of which at least 1 is cardinal: Molecular testing for CdLs indicated
- <4 points, insufficient to indicate molecular testing for CdLS.

Radial head underdevelopment and radial dislocation are present in 79% of individuals [9].

Our case included clinodactyly of toes and fingers and proximally placed thumbs. Vision problems can include nystagmus, strabismus, ptosis, or myopia. Eye examination of the child was found to be normal on both admission and follow-up. Auditory defect includes mild to moderate or even severe hearing loss. They have narrow ear canals leading to problems with chronic ear drainage. However, in our case, the auditory examination was normal on both admission and follow-up. The cardiac defect can include congenital heart disease, most common being the ventricular septal defect. Our case had a large ASD. The child is on follow-up by the cardiology department for ASD.

DNA testing is helpful for the confirmation of clinical diagnosis, but the sensitivity is only 50% for mutations in the NIPBL gene as CdLS is caused by other genes that are yet to be identified. Thus, no genetic testing was done. Jackson *et al*. reported that 33% of these children were delivered prematurely or intrauterine growth retardation (IUGR) [10]. Our case also had prenatal and postnatal growth retardation. Seizures are seen in 45–60% of children and antiepileptic drug (AED) valproic acid has been found to be effective in controlling it. Our child had subtle seizures at admission and after 2 months of age. At present, she is on phenobarbitone and doing well.

CONCLUSION

Early recognition of CdLS is very important for pediatrician/neonatologists as treatment involves a team approach. Antenatal history along with ultrasound between 20 weeks and 25 weeks of gestation showing missing or abnormally short upper limb provides clues to the diagnosis as CdLS in 30% of cases. In such cases, a 3D ultrasound examination should be performed which reveals low hairline, hypertrichosis, and micrognathia.

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