Incomplete Cleft Palate in Cornelia de Lange Syndrome

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Background: Cornelia de Lange Syndrome (CdLS) is a rare congenital anomaly inheritance syndrome. The prevalence is 1.6-2.2/100.000 of 8,558,346 births in Europe. Cleft palate is less frequent malformation of this syndrome (21,7%) than other associated malformations. The diagnosis can be obtained clinically based on CdLS diagnostic criteria by USA CdLS Foundation. This is the first case in our hospital.
Patient and Method: A case of a 4-year-old girl who came to our attention at Cleft and Craniofacial Center Cipto Mangunkusumo National General Hospital for incomplete cleft palate. Parents' major concerns was feeding problem. The clinical investigations showed that the child met diagnostic criteria for CdLS as described in literatures. We manage this case in collaboration with paediatric department and other related specialists, including radiologist and craniofacial orthodontist. We performed Veau-Wardill-Kilner's palataoplasty for the incomplete cleft palate. Paediatric department arranged provision of dietary.
Result: This patient with incomplete cleft palate whom we treated by palatoplasty was moderately involved by CdLS (severity score 17). After 3 weeks follow-up, we have overcome feeding problem and body weight gained.
Summary: Patient with CdLS needs early multidisciplinary team approach management for maximum outcome, because variety of associated malformations may present and life-threatening. Diagnostic criteria by USA CdLS Foundation assist health care personnel recognize this syndrome early.
Keywords: *CdLS, multidisciplinary team approach, incomplete palatoschisis, syndromic*

Latar Belakang: Sindrom Cornelia de Lange (CdLS) adalah sindrom kongenital yang jarang terjadi. Angka prevalensi sekitar 1.6-2.2/100.000 dari 8,558,346 kelahiran in Eropa. Celah langit-langit adalah malformasi yang paling jarang terjadi (21,7%) dibandingkan dengan malformasi lain. Diagnosis dapat ditegakkan secara klinis berdasarkan kriteria diagnosis yang dibuat oleh yayasan CdLS di Amerika Serikat. Ini adalah kasus pertama di rumah sakit kami.
Pasien dan Metode: Kasus pasien anak perempuan umur 4 tahun yang datang ke Cleft and Craniofacial Center Rumah Sakit Umum Pusat Cipto Mangunkusumo dengan masalah celah langit-langit inkomplit. Keluhan utama orang tua adalah masalah makan dan minum. Hasil pemeriksaan klinis terhadap pasien ini mengarah pada kriteria diagnostik CdLS sesuai literatur. Kami mengelola kasus ini bekerja sama dengan dengan Departemen Ilmu Kesehatan Anak, dan spesialis terkait, diantaranya spesialis radiologi dan spesialis ortodonti kraniofasial. Kami melakukan palatoplasti dengan teknik Veau-Wardill-Kilner.
Hasil: Pasien dengan celah langit-langit yang kami lakukan palatoplasty memiliki kriteria diagnosis CdLS sedang (skor 17). Setelah follow up selama 3 minggu, masalah makan dan minum telah teratasi dan peningkatan berat badan.
Ringkasan: Pasien dengan CdLS membutuhkan manajemen pendekatan awal tim multidisiplin karena mungkin saja terdapat malformasi yang dapat mengancam jiwa. Kriteria diagnosis oleh yayasan CdLS Amerika Serikat sangat membantu petugas kesehatan mengenali sindrom ini lebih dini.
Kata Kunci: *CdLS, multidisciplinary team approach, incomplete palatoschisis, syndromic*

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Cornelia de Lange Syndrome (CdLS) was first described by Cornelia de Lange, a Dutch paediatrician in 1933.[1,2] This syndrome is also called as Brachmann de Lange syndrome (BdLS) since he reported a patient with similar characteristics at autopsy in 1916.[1,2,3,4] It is slightly more common in woman than man (W/M=1,3/1).[1] There is no racial tendency.[1,2] Based on 23 years of epidemiologic monitoring (8,558,346 births in the 1980-2002 period), the prevalence of the classical form of CdLS to be 1.24/100,000 births or 1:81,000 births and estimated the overall CdLS prevalence at 1.6-2.2/100,000 in Europe.[5] The most frequent associated congenital malformations were limb defects (73.1%), congenital heart defects (45.6%), central nervous system malformations (40.2%), and cleft palate (21.7%).[5] First week survival of live born infants with CdLS is quite high (91.4%). Evidence showed that almost 70% of

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Table 1. Scoring System for Severity in CdLS

Parameter	1 Point	3 points	5 points
Birth weight	Above 2,500 g	2,000-2,500 g	Below 2,000 g
Sitting alone	Before 9 months	9-20 months	Over 20 months
Walking alone	Before 18 months	18-42 months	Over 42 months
Saying first word	Before 24 months	24-48 months	Over 48 months
Upper limb malformation	No defect	Partial defect (more than two digits)	Severe defect (less than two digits)
Number of other major malformations	0-1	2-3	More than 3
Hearing loss	Absent	Mild	Moderate-Severe

Scoring: >22 Points, severely involved;15-22 points, moderately involved; <15 points, mildly involved. Ages based on Kline et al. [1993b] using 25th-75th centiles of completing milestones. (based in part on Kline et al, 1996)

patients, born after the 37th week of gestation, weighed <or=2,500 g. Severe limb anomalies were more often present in males.[5] The etiology of this syndrome is still not clear.[6] Mutations in autosomal dominant inheritance of Nipped-B homolog (NIPBL) and SMC3-related CdLS also the x-linked inheritance of SMC1A-related CdLS have been suggested as probable cause of this syndrome.[6,7,8]

The characteristic of CdLS are generally divided into facial features, major and minor criteria and diagnostic criteria for CdLS were created by the CdLS Foundation's Medical Director Antonie Kline, M.D. in collaboration with members of the Clinical Advisory Board (CAB) of the CdLS Foundation and the Scientific Advisory Committee of the World CdLS (SAC) Federation (Figure 5). If genetic testing identified a mutation in one of the associated genes, the diagnosis of CdLS can be established. But by the presence of facial findings (eyebrows that meet at the midline, long eyelashes, short nose, anteverted nostrils, long and prominent area between upper lip and nose, broad or depressed nasal bridge, small or square chin, thin lips, downturned corners, high palate and widely spaced or absent teeth) and meet criteria from two major categories (growth, development, or behaviour) the diagnosis be enforced. Or facial findings meet criteria for at least one major categories and two additional categories (major or minor).[11] There are also severity scoring available (Table 1).

According to Kline et al, management and treatment of CdLS is based on the consensus of CAB and SAC, which focuses on prevention of treatable complications, and optimization of developmental ability. Routine medical evaluation for any abnormality condition is needed and each age group has its own particular issues.[9]

PATIENT AND METHOD

The patient is a 4-year-old female patient was brought by her parents' initiative to general surgery policlinic Cipto Mangunkusumo National General Hospital on November 2011 with cleft palate since birth. She was the first child in the family, born of a full-term sectio-caesarean delivery with a birth weight of 1500 gr, height of 40 cm and the birth head circumference was not measured. The present weight, height, and head circumference were 9400 gr, 85cm, and 42 cm. Both parents were normal and there was no history of deformity in their pedigree.

She was admitted at hospital when she was 16 days old because of the feeding problem she had and then returned home without feeding education to parents and also without any suggestion for feeding problem and the cleft palate. She often choked while drinking by using milk bottle and her weight was not gaining normally. She was sitting alone around the age of 18 months, walking alone in the age of 2 years and saying the first word when she was 12-month-old.

She was then suggested to come to Craniofacial Centre Cipto Mangunkusumo National General Hospital. Initially we diagnosed this child with Pierre Robbins Syndrome, based on the cleft palate, small jaw, glossoptosis and global development delay she had. Paediatric department found that this child

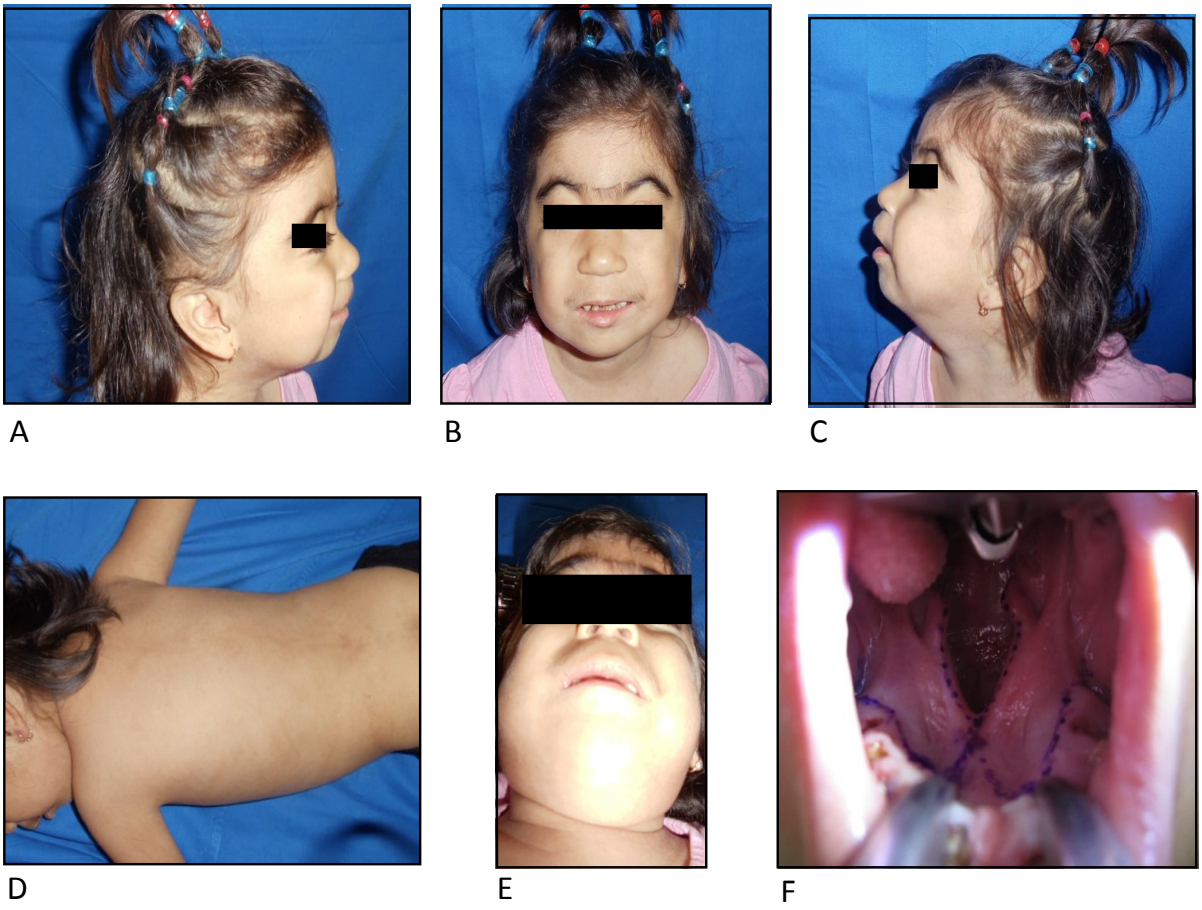

Figure 1. 4-year-old female patient with Cornelia de Lange Syndrome. She has synophrys, long eyelashes, droopy eyelid, short nose, broad and depressed nasal-bridge, small and square-chin, long philtrum, thin lips with downturned corners (A,B,C). Generalized hirsutism is present (D). She has incomplete cleft palate as minor criteria of CdLS (F).

had diagnostic criteria for CdLS. She presented several distinctive facial findings, developmental and growth delay and some behaviour problem (extreme shyness, withdrawal and hyperactivity). She has synophrys, long eyelashes, droopy eyelid, short nose, broad and depressed nasal-bridge, small and square-chin, long philtrum, thin lips with downturned corners (Figure 1.A, B, C). She has incomplete cleft palate as minor criteria of CdLS (Figure 1.F). The over-length of the philtrum is confirmed by OsiriX™ (Figure 2) and is interpretated by Growth Chart for Nose and Philtrum by Zankl et al (Figure 3). The techniques of measuring the philtrum is by drawing a straight line from the lower nose and then measured perpendicularly (Figure 4).[10] Her present weight and height is below 5th percentile for age. Generalized hirsutism is present with low frontal implantation of hair and long skin hair (Figure 1.A, B, C, D, E). There was no anomaly in extremities. According to CdLS diagnostic criteria checklist by CdLS Foundation, USA, she has 4 facial findings, 2 major criteria and 3 minor criteria those are sufficient to diagnose CdLS (Figure 5). Her severity score of CdLS was 15 (moderately-involved) [table 3].

Patient was coming back to our department on February 2012 and the patient was prepared for palatoplasty. Her general health was acceptable without cardiac or respiratory problem. The additional requirement tests (general analytical, radiology of thorax and electrocardiogram) did not show any alterations that might contraindicate the general anesthesia.

Under general anesthesia the palatoplasty was done using Veau-Wardill-Kilner's technique. Paediatric department arranged continue provision of dietary and

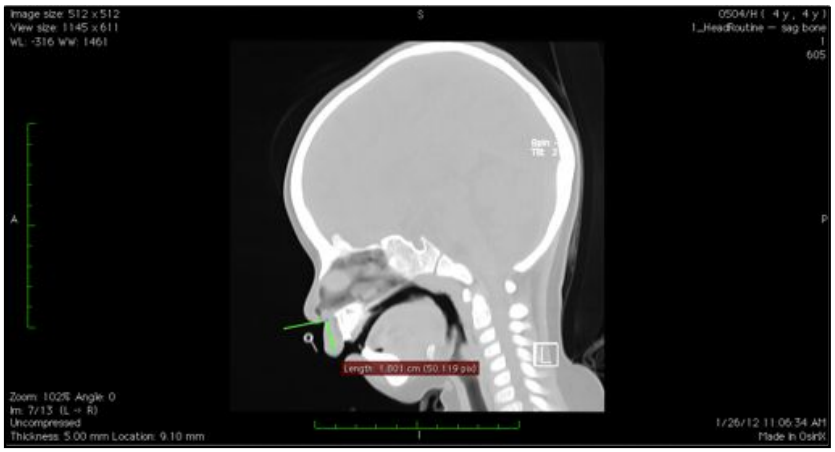

Figure 2. Philtrum measurement by OsiriX™: 1,801 cm

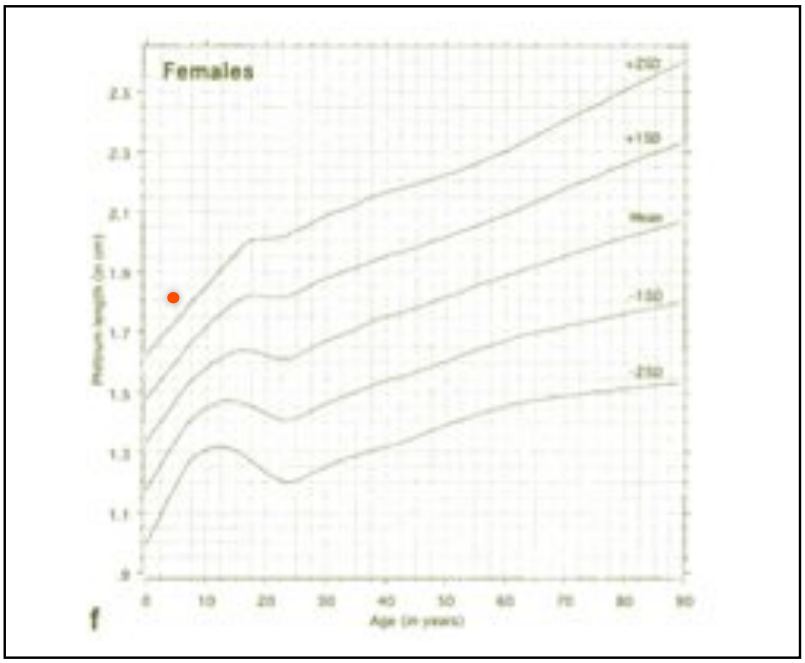

Figure 3. Philtrum length is interpreted by Growth Charts for Philtrum Length by Zankl, et al 2002[10]

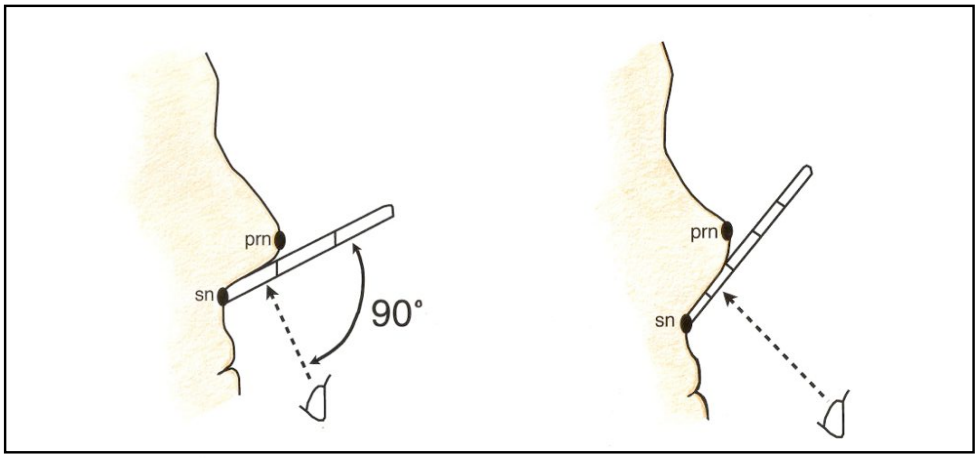

Figure 4. Illustration of measurement technique for philtrum length by Zankl et al 2002[10]

Coming to a Diagnosis:		Minor Criteria	
	Positive mutation on CdLS gene testing; OR		**Musculoskeletal** (>one or more of the following)
v	**Facial Findings and meet criteria from two major categories (growth, development or behaviour); OR**		Absent arms or forearms
			Three or more of the following or small hands and feet and/or missing digits with two or more of the following:
v	**Facial findings and meet criteria for at least one major categories and two additional categories (major or minor)**		Curved 5th finger
			Abnormal palmar crease
Facial Features			Dislocated elbow/abnormal elbow extension
v	**Eyebrows that meet at the midline and > three or more of the following:**		Short 1st knuckle/proximally placed thumb
v	Long eyelashes		
	Short nose, anteverted nostrils		Bunion
	Long, prominent area between upper lip and nose		Partial webbing between 2nd and 3rd toes
			Scoliosis
	Broad or depressed nasal bridge		Chest or sternum deformity
	Small or square chin		Hip dislocation or dysplasia
v	Thin lips, downturned corners		**Neurosensory/Skin** (three or more of the following)
v	High palate		
	Widely spaced or absent teeth		
Major Criteria		v	Droopy eyelid(s)
Growth (>two or more of the following)			Tear duct malformation or inflammation of eyelid
v	Weight below 5th percentile for age		
v	Height/length below 5th percentile for age		Nearsightedness
			Major eye malformation or peripapiillary
v	Head circumference below 5th percentile for age		Deafness or hearing loss
			Seizures
	Development (>one or more of the following)		Mottled appearance to skin
		v	Excessive body hair
v	Developmental delays or intellectual disability, with speech more affected than motor skills		Small nipples and/or belly button
			Other Major Systems (three or more of the following)
	Learning disabilities		Gastrointestinal malformation/malrotation
Behavior (>two or more of the following)			Diaphragmatic hernia
	Attention deficit disorder plus hyperactivity		Gastroesophageal reflux
		v	Cleft palate or submucous cleft palate
	Obsessive-compulsive characteristics		Congenital heart disease
	Anxiety		Micropenis
	Constant roaming		Abnormally placed opening or urethra on penis
	Agression		
	Self-injurious behaviour		Undescended testes
	Extreme shyness or withdrawal		Renal or urinary tract malformation
	Autistic like features		

Figure 5. Anomaly findings for diagnostic according to CdLS diagnostic criteria checklist. Adopted from Cornelia de Lange Syndrome Foundation. Diagnostic Criteria Checklist for Cornelia de Lange Syndrome 2010.[11]

Table 3. Patient's severity score of CdLS: 17 (moderately involved) [9]

Parameter	Data	Points
Birth weight	1500 g	5
Sitting alone	18 months	3
Walking alone	24 months	3
Saying first word	12 months	1
Upper limb malformation	No defect	1
Number of other major malformations	Incomplete cleft palate, droopy eyelid, hirsutism	1
Hearing loss	Absent	1
Total Score		**17**

growth monitoring.

Seven days after the treatment the patient was scheduled for a visit. First week after surgery chocking occurs sometimes. Three week after surgery we found no complaint in feeding and weight was increased to 10 kg.

DISCUSSION

CdLS is a rare multiple congenital genetic anomaly. The clinical hallmarks of this syndrome are the facial features.[2,9] Diagnosis is based upon phenotypic findings compiled by consensus among some members of the Clinical Advisory Board of CdLS Foundation USA (CAB) and the Scientific Advisory Committee of the World CdLS Federation (SAC).[8,11,13] This syndrome affect almost any organ system commonly neurodevelopment, craniofacial, gastrointestinal, and musculoskeletal. Some organ system requires early management protocol during the first day of life like craniofacial structures anomalies can affect the viability of a neonate because of their impact on airway/or swallowing.[12] So patients with this syndrome needs an immediate integrated team approached consists of specialist from a wide variety of disciplines, medical ethics, and social work to provide holistic care for maximum outcome.[13]

The patient in our case had her late first consultation with plastic surgeon at 4 years of age, due to her parents' concern about feeding problem those were choking when drinking, and her body weight was below the children on her age. Her severity of CdLS was moderate. As Kline et all purposed management and treatment since infancy continued by routine medical evaluation, it is now more arduous to treat this patient with maximum outcome. Our on going plan for this patient are monitoring growth via CdLS-specific growth charts, dentistry evaluation 6 months, paediatric ophthalmologic evaluation annually, audiology testing every 2-3 years. We also plan for speech therapy.

SUMMARY

Patient with CdLS needs early multidisciplinary team approach management for maximum outcome because variety of associated malformations may present that can lead to global developmental delay or even death. By knowing distinctive facial features of this syndrome, health care personnel will be greatly assisted to recognize this syndrome early.

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