Cornelia De Lange Syndrome: A Case Report of an Iranian Turkmen Girl with Clinical Presentation

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ABSTRACT

Cornelia de Lange Syndrome (CdLS) is a genetic disorder, with approximately one per 10,000-30,000 prevalence. The most frequent clinical abnormalities include typical face dysmorphia, anomalies of the hands and feet, multiple malformations, microcephaly and other characteristics include feeding difficulties in the newborn period and mental delay. The reported genes associated with CdLS include NIPBL, SMC1A, SMC3, RAD21 and HDAC8. We report a 20-day-old Iranian Turkmen girl with this syndrome.

Keywords: Cornleia de Lange Syndrome; Hirsutism; Genetic Disorder; Early Diagnosis

INTRODUCTION

Cornelia de Lange Syndrome (CdLS) is a genetic disorder which can result in several alterations affecting both physical and cognitive development. The abnormalities consist of facial dysmorphia (including arched eyebrows, synophrys, depressed nasal bridge, long philtrum-down-turned angles of the mouth), abnormal upper-extremity, hirsutism, cardiac defects, and gastrointestinal alterations [1]. The prevalence of this syndrome is approximately one per 10,000-30,000 [2]. Several genes including Nipped-B-like (NIPBL), structural maintenance of chromosomes 1A (SMC1A), structural maintenance of chromosomes 3 (SMC3), cohesin complex component (SCC1 or RAD21), histone deacetylase 8 (HDAC8) genes have been implicated in this genetic syndrome. Some CdLS cases appear to be sporadic and 10% of the cases show chromosomal changes, such as translocation of the 3q 26:2-q23, 5p13.2 [3-5]. However, a report in Iran highlighted the NIPBL mutations as the underlying cause [6].

CASE REPORT

The patient was a 20-day-old Turkmen girl who presented to our hospital for well-baby visits. She was the second child of a non-consanguineous marriage, born after a 38 weeks gestation and via normal vaginal delivery.

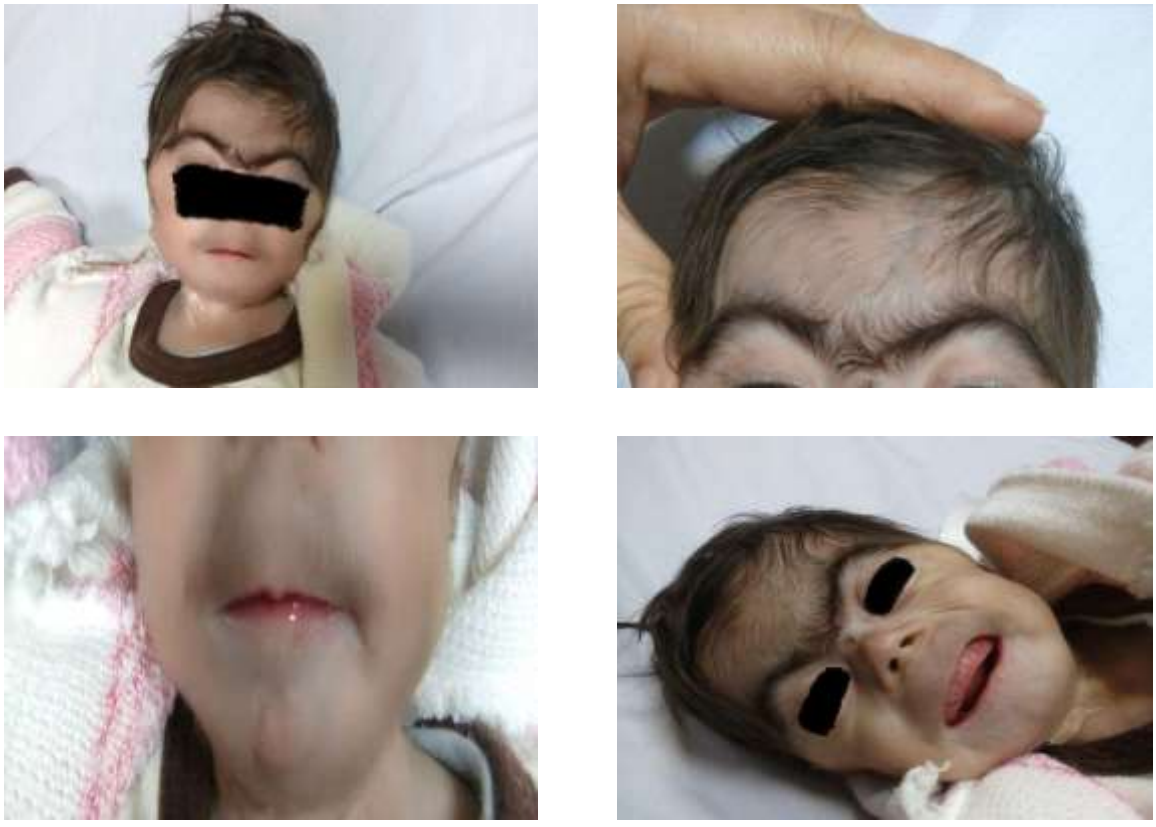
Her physical examination showed confluent eyebrow with well-defined and arch liked, long curly eyelashes, low front and back hairline, depressed nasal bridge, turned up nose, down-turned angles of the mouth and thin lip, short neck, microcephaly, excessive body hair, small broad hands with simian crease, short leg, hyper tonicity, and small labia major. Her weight was 2kg with a birth weight of 1500gram and she was 43cm tall. Her head circumference was 29cm. Ophthalmologic investigations were normal. On cardiac auscultation, ejection systolic soufflé of 2/6 intensity in the pulmonary area was heard. Her transthoracic echocardiography revealed severe pulmonary stenosis (PS), patent ductus arteriosus (PDA) as well as partial anomalous pulmonary venous drainage (PAPVD).

Table 1: Clinical Features of CdLS in the Diagnosed Cases

Clinical Features	Present case
Prenatal onset growth retardation (68%)	+
Initial hypertonicity (100%)	+
Low-pitched weak cry in infancy (74%)	+
Feeding difficulties in the newborn period and infancy (71%)	+
Micro-brachycephaly (93%)	+
Bushy eyebrows and synophrys (98%)	+
Long, curly eyelashes (99%)	+
Depressed nasal bridge (83%)	+
Anteverted nares (85%)	+
Down-turned angles of the mouth (94%)	+
High arched palate (86%)	+
Micrognathia (84%)	+
Spurs in the anterior angle of the mandible, prominent symphysis (66%)	-
Short neck (66%)	+
Hirsutism (78%)	+
Low anterior and posterior hairline (92%)	+
Hypoplastic nipples and umbilicus (50%)	-
Micromelia (93%)	-
Phocomelia and oligodactyly (27%)	+
Clinodactyly of fifth fingers (74%)	-
Simian crease (51%)	+
Proximal implantation of thumbs (72%)	-
Hypoplastic external genitalia (57%)	+
Ophthalmologic manifestations (50%)	-
Cutis marmorata and perioral pale cyanosis (56%)	-
Seizures (23%)	+
Congenital Heart Defect (33%)	+

"(%)" prevalence among the diagnosed cases
"-/+ "presence in the current case

Figure 1 (A-D): Clinical Features of CdLS in our mentioned case



Laboratory analysis including complete blood count, biochemical parameters and urinalysis were normal. Cranial magnetic resonance imaging was also normal. Her report of cytogenetic investigation revealed 46 XX compatible with apparently normal female neonate cytogenetically.

DISCUSSION

As a multisystem malformation syndrome, CdLS is recognized primarily by the morphological characteristics (malformations of the cranial, cardiac, gastrointestinal, and skeletal systems) [7]. However, wide clinical variability with milder phenotypes has been reported. Ascertaining these disorders may be difficult on the basis of physical features. If ultrasound examination is not performed accurately, the diagnosis may be missed in certain cases [8]. This disorder has widely varied features among affected individuals ranging from relatively mild to severe. A neonatal case with confluent eyebrows, depressed nasal bridge, turned up nose, hirsutism, down-turned angles of the mouth and thin lip, short neck, low anterior and posterior hairline and phocomelia presented in the right hand was reported by Hoseininejad et al. [9], but in the current case phocomelia was not seen. Our patient is the second case of CdLS from Golestan province, northern Iran. Table 1 summarizes and compares detailed features of patients reported in the literature.

CdLS is caused by mutations in the NIPBL, SMC1L1, orSMC3 genes. In 2004, it was reported by two independent groups [4,10] that 26–56% of patients with CdLS carry a heterozygous mutation of the NIPBL gene localized on 5p13.2. Belonging to the family of chromosomal adherins involved in chromatid cohesion processes and enhancer-promoter communications, the NIPBL gene is the human orthologous of Drosophila Nipped-B and yeast Scc-2 [11,5]. Both SMC3 and SMC1L1 mutation-positive patients exhibit very mild facial dysmorphism, no absence or reduction of limbs or digits, and no other major structural anomalies [12,13]

Hakan Uzun et al reported a one-day old new born female with complaints of seizure and multiple congenital anomalies with arched like confluent eyebrows and well-defined, long curly eyelashes, low anterior and posterior hairline, short neck, depressed nasal bridge, down-turned angles of the mouth and thin lips, cleft palate, microcephaly, excessive body hair and small broad hands with simian creases, clinodactyly of left fifth fingers, short leg, hypertonicity, and small labia majora. On cardiac auscultation, 1–2/6 holosystolic murmur was heard. Ophthalmologic examinations had normal findings, just like our present case [3].

CONCLUSION

CdLS is a rare but well characterized syndrome with key diagnostic features including the distinctive facial features, limb anomalies, and growth retardation. The patient was diagnosed as CdLS on the recognition of distinctive facial features as well as the pre- and post-natal growth retardation, feeding problems, and physical malformations. Reporting CdLS cases of different ethnic backgrounds could be helpful in diagnosis and add nuances to the syndrome description.

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