Case Report

Cornelia De Lange Syndrome: A Case Report

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Abstract

Cornelia de Lange syndrome (CdLS) is a rare syndrome characterized by multiple congenital anomalies, mental retardation, characteristic facial appearance, developmental delay, skeletal malformation, hirsutism, and various cardiac and ophthalmological problems. The diagnosis of this syndrome is clinical. The patient of the present case report was the second case of CdLS from Iran; only a few cases of CdLS have thus far been reported from countries outside Europe and North America. Reporting CdLS cases of different ethnic backgrounds can add nuances to the phenotypic description of the syndrome and be helpful in diagnosis. Furthermore, an increased awareness of this syndrome may result in an early diagnosis and a decrease in morbidity.

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Introduction

Cornelia de Lange syndrome (CdLS) is a syndrome of multiple congenital anomalies characterized by a distinctive facial appearance, prenatal and postnatal growth deficiency, feeding difficulties, psychomotor delay, behavioral problems, and associated malformations that mainly involve the upper extremities.1 Mutations in a gene named Nipped-B homolog (NIPBL) is seen in some patients, but the vast majority of CdLS cases have normal karyotypes by chromosome banding.2 Diagnosing classic cases of CdLS is usually straightforward; diagnosing mild cases may, however, be challenging even for an experienced clinician.3 Apnea after respiratory aspiration, cardiac malformations, and complications related to gastrointestinal problems are causes of death.4

Case report

Herein we present a second case of CdLS from Iran, a 3-month-old male infant, who was referred as a case of heart murmur. He was then about 22 inches in height and 3 kilograms in weight, but he had been 2,900 kilograms and 22 inches high at birth. His skull circumference was 33cm (32 cm at birth). The baby had been born as a full-term baby and had jaundice at birth. Family history and medical history were not significant.

The patient was admitted because of dyspnea and systolic murmur accompanied by loud second heart sound. At presentation, the patient had synophrys (bushy eyebrows meeting in the midline) with long curly eye lashes, antimongolid slant, low front and back hairlines, ptosis, depressed bridge of the nose with anteverted nares, downturned angles of the mouth and thin lips, long philtrum, small lower jaw and protruding upper jaw, and low set and outwardly placed ears. Other findings supporting the diagnosis were: microcephaly, excessive body hair, small broad hands with simian crease and proximal insertion of the thumbs, clinodactyly of the fifth finger, short neck with limited movement, micropenis (3cm), bilateral high inguinal testes, and stiff muscle tone (Figure 1). He had a low-pitched

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cry and feeding problems, which is common in CdLS, and it was responsible for malnutrition. X-ray showed delayed bone development. Moreover, his brain-stem-evoked potential test showed conductive hearing loss. The karyotype was normal. Analyses for mutations in the NIPBL genes are not currently available in Iran. The patient’s angiography showed large ventricular septal defect (VSD) and moderately increased pulmonary artery pressure (Figure 2). He was candidated for pulmonary artery banding.

Discussion

Cornelia De Lange first introduced the disease described above as a distinct syndrome in 1933, although Brachmann had described a child with similar features in 1916. CdLS, also known as Brachmann de Lange syndrome (BDLS) or Brachmann Cornelia de Lange syndrome, is a multi-system developmental disorder. Other less frequently used synonyms are Brachman-De Lange Syndrome and typus degenerativus amstelodamensis.5-7 The syndrome is characterized by the following characteristics: Intrauterine growth retardation, prematurity, low-pitched weak cry in infancy, initial hypertonicity, respiratory and feeding difficulties, and hypertonic mental deficiencies. In addition, autism and self-injurious tendencies also frequently occur.8-13 Short stature, microcephaly, confluent eyebrows (synophrys), long curly eyelashes, low anterior and posterior hairline, long philtrum, anteverted nares, down-turned angles of the mouth, thin lip, low-set ears, depressed nasal bridge, high arched palate and reports of cleft palate, late eruption of widely spaced teeth, micrognathia, hirsutism, cutis marmorata and perioral cyanosis, microcornea, and oligodactaly or other deficiencies of the arms may be present.14-20 Less striking limb findings include single palmar flexion crease, clinodactyly of the fifth fingers, proximally placed thumbs, partial syndactyly of the second and third toes, and limitation of elbow extension.21-23 Hypoplastic external male genitalia, small labia majora, and hypospadias have also been reported.24-27 Myopia, ptosis, blepharitis, epiphora, microcornea, nystagmus, astigmatism, optic atrophy, coloboma of the optic nerve, aniridia, and congenital glaucoma have been described previously as well.24-27

Radiography may reveal the following: retarded bone age, spurs in the anterior angle of the mandible, a prominent symphysis, and long-bone abnormalities including ulnar aplasia and/or hypoplasia, aplasia and/or hypoplasia of the radial head, or fusion of the elbow.12-14 Ultrasonography at diagnosis to assess for kidney and urinary tract abnormalities may show horseshoe kidney, altered corticomedullary differentiation, pelvic dilation, vesicoureteral reflux, small kidneys, renal cysts, and renal ectopia.7-9 Echocardiography may be indicated if congenital heart disease is suspected (15-25%) and may display VSD, atrial septal defect (ASD), pulmonary stenosis (PS), and tetralogy of Fallot (TOF).27-32

CdLS is relatively rare and affects, according to sources, between 1:30,000 to 1:50,000 in different population groups.33-35 There is no racial predilection, but it is more frequent in women than men: 1, 3/1. It is thought to be the result of a dominant mutation. A large part of the cases diagnosed as CdLS seem to be sporadic and 10% of the cases present chromosomal alterations, translocation of the 3q26.2-q23. The vast majority of CdLS cases have normal karyotypes by chromosome banding. Heterozygous mutations in a gene named NIPBL was described in 56% of the individuals with CdLS in 2006.7-11 Mutation-positive patients are more severely affected in comparison to mutation-negative individuals with respect to weight, height, and mean head circumference at birth, facial dysmorphism, and speech impairment. Although the exact function of the protein product of NIPBL
in humans, delangin, remains unknown, it may play a role in developmental regulation and in cohesion of sister chromatids. More than 99% of cases are sporadic. CdLS is occasionally transmitted in an autosomal dominant pattern, and although possible autosomal recessive inheritance has been reported in some families, these instances were likely to be due to germline mosaicism. The recurrence risk is 0.5-1.5% if parents are unaffected and 50% if a parent is affected. The mutation-detection rate is approximately 50% with current molecular screening techniques; this observation may suggest genetic heterogeneity. The correlation between genotype and phenotype is not clear cut. Moreover, missense mutations in NIPBL might be associated with mild phenotypic features. A phenotype similar to that of CdLS may be observed in patients with a duplication of band q26-27 of chromosome 3, fetal alcohol syndrome, Coffin-Siris syndrome, and Fryns syndrome. Life expectancy is normal if no major malformations occur.

There have been two phenotypes differentiated: a classic and a milder. Be that as it may, the genetic bases of CdLS are still not clear. In Type I, or classic BDLS, patients have the characteristic facial and skeletal changes of the diagnostic criteria; they have prenatal growth deficiency, moderate-to-severe psychomotor retardation, and major malformations, which result in severe disability or death. Type II, or mild BDLS, patients have similar facial and minor skeletal abnormalities to those seen in type I; however, these changes may develop with time or may be only partially expressed. They have mild-to-borderline psychomotor retardation, less severe pre- and postnatal growth deficiency, and the absence of (or less severe) major malformations. Type III, or phenocopy BDLS, includes patients who have phenotypic manifestations of BDLS that are causally related to chromosomal alterations or teratogenic exposures. In the mild phenotype, the characteristic facial appearance may not appear until 2 to 3 years of age, at which time it is always present at birth in the classic phenotype. The characteristic facial appearance decreases with time in the mild phenotype. Craniofacial pattern profiles show that both type I and type II groups have microcephaly, but that the dimensions of the mild group are somewhat closer to normal.

Diagnosis of BDLS is dependent on the recognition of distinctive facial features in addition to the physical features as pre- and postnatal growth retardation, microcephaly, severe mental retardation with speech delay, feeding problems, major malformations including limb defects, and characteristic facial features. Most children cannot live more than 2 years and the main cause of death in such patients include pneumonia along with cardiac, respiratory, and gastrointestinal abnormalities. Medical care includes early intervention for feeding problems, hearing and visual impairment, congenital heart disease, and urinary system abnormalities. Management of such patients can be perfectly done by a team approach including geneticists, cardiologists, gastroenterologists and nutritionists, nephrologists (if recurrent urinary tract infections, impaired renal functions, or congenital abnormalities are present), ophthalmologists, and hearing specialists.

Because of the characteristic facial features and the physical findings as well as the presence of a normal karyotype, our patient was diagnosed as type I CdLS . The patient was the second case of CdLS from Iran; only a few cases of CdLS has been reported from countries outside Western countries. An increased awareness of this syndrome may result in an early diagnosis and a decrease in morbidity.

References