The Journal of Tehran University Heart Center

Case Report

Cornelia De Lange Syndrome: A Case Report

Mohammad Yousef Aarabi Moghaddam, MD, Hojatollah Mortezaian, MD, Seyed Reza Miri, MD*

Shaheed Rajaei Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.

Received 23 June 2008; Accepted 24 December 2008

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.

J Teh Univ Heart Ctr 4 (2009) 244-247

Keywords: *De Lange syndrome • Dyspnea • Heart murmurs • Congenital abnormalities*

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 , anti-mongoloid slant, low front and back hairlines, ptosis, depressed bridge of the nose with anteverted nares , down-turned 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

*Corresponding Author: ***Seyed Reza Miri,*** *Associate Professor of Pediatric Cardiology, Shaheed Rajaei Cardiovascular Medical and Research Center, Vali-Asr Ave, Adjacent to Mellat Park. 1996911151. Tehran, Iran. Tel: +98 21 2392542. Fax: +98 21 2042026. Email: godronlym@yahoo.com.*

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.

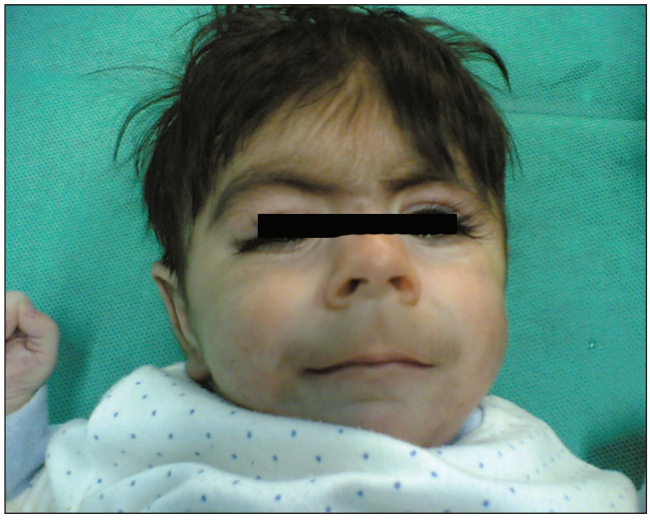

Figure1. Facial appearance of the patient

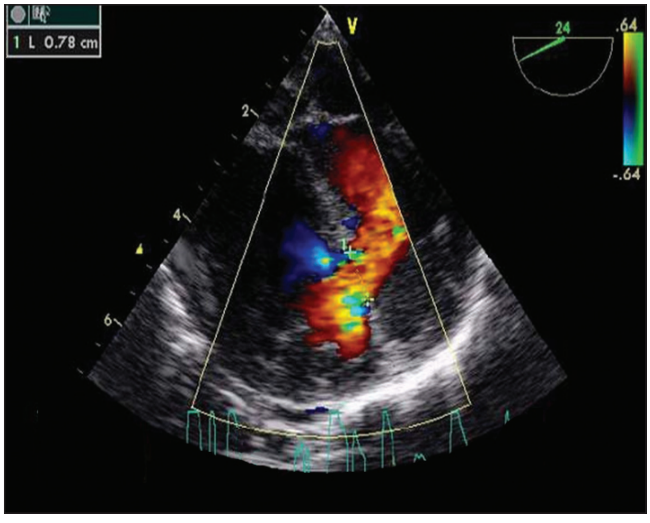

Figure 2. Large ventricular septal defect in echocardiography

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.[1-4] 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, micromelia, and oligodactyly 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.[13-16] 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.[2-5] 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.[2-3]

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;[12] they have prenatal growth deficiency, moderate-to-profound 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, while it is always present at birth in the classic phenotype. The characteristic facial appearance decreases with time in the mild phenotype. Craniofacial pattern profiles shows that both type I and type II groups have microbrachycephaly, but that the dimensions of the mild group are somewhat closer to normal.[22-25]

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.[16-18] 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.[16-17]

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

1. Filippi G. The de Lange syndrome. Report of 15 cases. Clin Genet 1989;35:343-363.
2. Ireland M. Cornelia de lange syndrome: clinical features, common complications and long term prognosis. Curr Pediatr 1996;6:69-73.
3. Van Allen MI, Filippi G, Siegel-Bartelt J, Yong SL, McGillivray B, Zuker RM, Smith CR, Magee JF, Ritchie S, Toi A. Clinical variability within Brachmann de Lange syndrome: a proposed classification system. Am J Med Genet 1993;47:947-958.
4. Allanson JE, Hennekam RC, Ireland M. De Lange syndrome: subjective and objective comparison of the classical and mild phenotypes. J Med Genet 1997;34:645-650.
5. Berney TP, Ireland M, Burn J. Behavioural phenotype of Cornelia de Lange syndrome. Arch Dis Child 1999;81:333-336.
6. Bull MJ, Fitzgerald JF, Heifetz SA, Brei TJ. Gastrointestinal abnormalities: a significant cause of feeding difficulties and failure to thrive in Brachmann-de Lange syndrome. Am J Med Genet 1993;47:1029-1034.
7. Deardorff MA, Yaeger DM, Krantz ID. Cornelia de Lange syndrome. GeneReviews [GeneTests Web site]. Available at: www.cigna.com/healthinfo/nord30.html (26 February 2009).
8. Fryns JP. Partial trisomy 4p and Brachmann-de Lange syndrome. Am J Med Genet 2000;95:406.
9. Gillis LA, McCallum J, Kaur M, DeScipio C, Yaeger D, Mariani A, Kline AD, Li HH, Devoto M, Jackson LG, Krantz ID. NIPBL mutational analysis in 120 individuals with Cornelia de Lange syndrome and evaluation of genotype-phenotype correlations. Am J Hum Genet 2004;75:610-623.
10. Ireland M, Donnai D, Burn J. Brachmann-de Lange syndrome. Delineation of the clinical phenotype. Am J Med Genet 1993;47:959-964.
11. Jackson L, Kline AD, Barr MA, Koch S. de Lange syndrome: a clinical review of 310 individuals. Am J Med Genet 1993;47:940-946.
12. Krantz ID, McCallum J, DeScipio C, Kaur M, Gillis LA, Yaeger D, Jukofsky L, Wasserman N, Bottani A, Morris CA, Nowaczyk MJ, Toriello H, Bamshad MJ, Carey JC, Rappaport E, Kawauchi S, Lander AD, Calof AL, Li HH, Devoto M, Jackson LG. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. Nature Genet 2004;36:631-635.
13. Manouvrier S, Espinasse M, Vaast P, Boute O, Farre I, Dupont F, Puech F, Gosselin B, Farriaux JP. Brachmann-de Lange syndrome: pre- and postnatal findings. Am J Med Genet 1996;62:268-273.
14. Mau UA, Backsch C, Schaudt H, Trefz FK, Kaiser P. Three-year-old girl with partial trisomy 4p and partial monosomy 8p with resemblance to Brachmann-de Lange syndrome--another locus for Brachmann-de Lange syndrome on 4p? Am J Med Genet 2000;91:180-184.
15. Russell KL, Ming JE, Patel K, Jukofsky L, Magnusson M, Krantz ID. Dominant paternal transmission of Cornelia de Lange syndrome: a new case and review of 25 previously reported familial

recurrences. Am J Med Genet 2001;104:267-276.
16. Sakai Y, Watanabe T, Kaga K. Auditory brainstem responses and usefulness of hearing aids in hearing impaired children with Cornelia de Lange syndrome. Int J Pediatr Otorhinolaryngol 2002;66:63-69.
17. Selicorni A, Sforzini C, Milani D, Cagnoli G, Fossali E, Bianchetti MG. Anomalies of the kidney and urinary tract are common in de Lange syndrome. Am J Med Genet 2005;132:395-397.
18. Stefanatos GA, Musikoff H. Specific neurocognitive deficits in Cornelia de Lange syndrome. J Dev Behav Pediatr 1994;15:39-43.
19. Van Allen MI, Filippi G, Siegel-Bartelt J. Clinical variability within Brachmann-de Lange syndrome: a proposed classification system. Am J Med Genet 1993;47:947-958.
20. Wygnanski-Jaffe T, Shin J, Perruzza E, Abdolell M, Jackson LG, Levin AV. Ophthalmologic findings in the Cornelia de Lange syndrome. J AAPOS 2005;9:407-415.
21. Yamaguchi K, Ishitobi F. Brain dysgenesis in Cornelia de Lange syndrome. Clin Neuropathol 1999;18:99-105.
22. Tekin M. Cornelia de Lange syndrome: differential diagnoses & workup (typus amstelodamensis). Arch Med Enfants 1933;36:713-719.
23. Braddock SR, Lachman RS, Stoppenhagen CC, Carey JC, Ireland M, Moeschler JB, Cunniff C, Graham JM Jr. Radiological features in Brachmann-de Lange syndrome. Am J Med Genet 1993;47:1006-1013.
24. Beck B, Fenger K. Mortality, pathological findings and causes of death in the de-lange sSyndrome. Acta Paediatr Scand 1985;74:765-769.
25. O'Donnell D, Davis PJ, King NM. Management problems associated with Cornelia de Lange syndrome. Spec Care Dentist 1985;5:160-163.
26. Grau Carbó J, López Jiménez J, Giménez Prats MJ, Sànchez Molins M. Cornelia de Lange syndrome: a case report. Med Oral Patol Oral Cir Bucal 2007;12:E445-448.
27. Stevenson RE, Scott CI Jr. Discordance for Cornelia de Lange syndrome in twins J Med Genet 1976;13:402-404.
28. Jones KL. Smith's recognizable patterns of human malformation. In: Jones KL, ed. Smith's Recognizable Patterns of Human Malformations. 5th ed. Philadelphia: WB Saunders; 1997. p. 88-91.
29. Kaga K, Tamai F, Kitazumi E. Auditory brain stem responses in children with Cornelia de Lange syndrome. Int J Pediatr Otorhinolaryngol 1995;31:137-146.
30. Husain K, Fitzgerald P, Lau G. Caecal volvulus in the Cornelia de Lange syndrome. J Pediatr Surg 1994;29:1245-1247.
31. Hawley PP, Jackson LG, Kurnit DM. Sixty four patients with Brachmann-de Lange syndrome: a survey. Am J Med Genet 1985;20:453-459.
32. Goodban MT. Survey of speech and language skills with prognostic indicators in 116 patients with Cornelia-de Lange syndrome. Am J Med Genet 1993;47:1059-1063.
33. Robinson LK, Wolfsberg E, Jones KL. Brachmann-de Lange syndrome: evidence for autosomal dominant inheritance. Am J Med Genet 1985;22:109-115.
34. Wilson GN, Heiber VC, Schmickel RD. The association of chromosome 3 duplication and the Cornelia de Lange syndrome. J Pediatr 1978;93:783-788.
35. Van Allen MI, Filippi G, Siegel-Bartelt J, Yong SL, McGillivray B, Zuker RM, Smith CR, Magee JF, Ritchie S, Toi A. Clinical variability within Brachmann-de Lange syndrome: a proposed classification system. Am J Med Genet 1993;47:947-958.