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Cornelia De Lange Syndrome: A Case Report

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Abstract

Objective: Cornelia de Lange syndrome (CDL) is a congenital disease characterized by severe mental retardation, pre and postnatal symmetric growth delay, limb defects, visceral defects and a typical dysmorphic face with hirsutism. In our case, a patient with CDL syndrome is presented in the highlights of previous literature.

Case: A 31 year old patient, gravida 2, para 1, was referred at 30 weeks of gestation to the perinatology department for assesment of early intrauterine growth retardation (IUGR). The early onset symetrical IUGR was diagnosed on the basis of the fetal biomethric parameters. Mild flexion deformity was also identified. Micrognathia and a 4 mm in size hypoplastic nasal bone were identified with a dysmorphic face pattern.

Conclusion: A suspected CDL syndrome must be on mind in cases of early onset symmetrical IUGR with the coexistence of extremity anomalies and dysmorphic facial apperance. Postnatal diagnosis of this syndrome is therefore based on the characteristic clinical phenotype. Similarly, antenatal detection depends on ultrasonographic identification of typical phenotypic features seen in infants with CDL syndrome.Because of the prenatal genetic diagnosis possibility and the recurrence risk for the next pregnancy the prenatal counselling must be given for the suspected cases of CDL syndrome patients.

Keywords: Cornelia de Lange syndrome, early onset entrauterine growth retardation, dismorphic face.

Cornelia de lange sendromu: olgu sunumu

Amaç: Cornelia de Lange (CDL) sendromu, mikrosefali, sinofriz (orta hatta birleşen kaşlar, uzun kirpikler, antevert burun delikleri, uzun filtrum, ince dudaklar gibi karakteristik yüz görünümü bulgularının bulunduğu, gelişme geriliği, mental retardasyon, hirsutizm ve çoklu kongenital anomalilerin eşlik ettiği nadir görülen bir genetik sendromdur. Olgumuzda, CDL sendromu literatür bilgileri ışığında tartışıldı.

Olgu: 31 yaşında, G2 P1, 30 haftalık gebe erken intrauterin gelişme kısıtlılığı saptanması üzerine kliniğimize refere edildi. Kliniğimizde yapılan 30. hafta detaylı fetal ultrasonografisinde, fetal biyometrik ölçümlere göre erken simetrik intrauterin gelişme geriliği tespit edildi.Burun kemiği 4 mm olarak normalden kısa (hipoplastik) ölçüldü. Dismorfik yüz görünümü mevcuttu. Mikrognati ve üst ekstremitede fleksiyon deformitesi belirgindi. Detaylı yapılan fetal ultrasonografik muayene ile fetusta genetik bir anomali olabileceğinden şüphelenildi.

Sonuç: CDL sendromu, dismorfik yüz görünümü, üst ekstremite defektleri ve erken başlangıçlı simetrik IUGK tespit edilen her vakada ayırıcı tanıda yer almalıdır. Yapılacak detaylı ultrason muayenesi ile diğer anomaliler kolaylıkla saptanabilir. Hastalığın prenatal genetik tanısının mümkün olması ve tekrarlama riskinin bulunması nedeniyle aileye genetik danışma verilmelidir.

Anahtar Sözcükler: Cornelia de Lange sendromu, erken başlangıçlı intrauterin gelişme geriliği, dismorfik yüz görünümü.

Introduction

Cornelia de Lange syndrome (CDL) is a rare genetic syndrome accompanied by mental retardation, hirsutism and multiple congenital anomalies with diagnoses of face characteristics such as microcephaly, synophrys (eyebrows combining on midline), long eyelashes, anteverted nostrils, long philtrum, thin lips etc.[1] CDL syndrome also known as Brachmann de Lange syndrome was first defined in 1933. CDL syndrome mostly

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appears sporadically. The prevalence of the disease varies between 1/10,000 and 1/50,000.[1] The risk of repeating at next pregnancy is 2-5%.[2] The syndrome considered as having multifactorial etiology generally appears sporadically; however its genetic transition can be low penetrated autosomal dominant or recessive.[3] In prenatal diagnosis of CDL syndrome, there are certain face anomalies and fetal growth retardation, hypertrichosis, visceral anomalies, upper extremity defects and serious neurological damage.[4] In an epidemiological study performed on a wide-scale population, CDL syndrome rate was determined as 1/81,000.[5]

In the light of literature, we discussed Cornelia de Lange syndrome case which was suspected in prenatal period and established certain postnatal diagnosis in our presentation.

Case

Thirty-one years old case at her 30th gestational week with G 2 P 1 was referred to our clinic due to early intrauterine growth retardation (IUGR). At her first pregnancy, 3500 gr girl baby was delivered by cesarean at her 40th gestational week. There were no kin marriage and no known disease in the medical histories of the patient and her husband. At first trimester scanning test, nuchal translucency was measured as 2 mm. However, biochemical marker results could not be reached. Biochemical markers at her 16th gestational week were found as AFP 19.6 IU/ ml (0.81 MoM), HCG 23634 mlU/ml (1.12 MoM), unconjugated estriol 0.756 ng/ ml (0.46 MoM). Biochemical risk calculated for Trisomia 21 was 1/278, the risk calculated for Trisomiy 18 was 1/1124 and the risk calculated for neural tube defect was below 1/10,000. It was learnt that it was decided to maintain the pregnancy without diagnosing as a result of genetic consultation given to the patient by other center.

In detailed fetal examination on 30th gestational week performed in our clinic, fetal abdomen circumference was measured as below -2 standard deviation (SD) and approximate birth weight as below -2 SD. Early symmetric intrauterine growth retardation was detected according to the fetal biometric measurements. Humerus length was found below -3 SD, radius and ulna heights were found below -4 SD at upper extremity measurements. There was a slight flexion deformity. No abnormality was seen in the hand carpal and metacarpal bones. Slight microcephaly and micrognathia were observed. It was observed that nasal root was depressed and nasal bone was shorter than normal (4 mm) and hypoplastic. The face had a dysmorphic view. No pathology at medulla spinalis and cranial structures are observed. Diaphragmatic hernia and pyelectasis could not be detected. There was no distinctive pathology at lower extremities. Four chambers and major vessel outputs were observed at fetal heart examination. There was no distinctive atrial or ventricular septal defect. Pulsatility index (PI) and resistance index (RI) of right uterine artery were found as 0.5 and 0.39, respectively in Doppler examination and no indent was observed. PI was 0.5 and RI was 0.41 in left uterine artery and again there was no indent. The "a" wave was positive in ductus venosus. Amniotic fluid volume was normal.

Required genetic consultation was provided to the patient who had findings such as symmetric IUGR, distinctive upper extremity shortness, hypoplasia of 5th phalanx, micrognathia and hypoplastic nasal bone and prenatal diagnosis was suggested. The patient specified that she did not want to have prenatal diagnostic invasive test (amniocentesis, cordocentesis etc.) and that she decided to maintain the pregnancy. Thereon, the follow-up of the pregnancy was continued at Perinatology Department. In the detailed examination of the patient at her 34th gestational week, approximate delivery weight was 1835 gr (below -2 SD) and symmetric IUGR was continuing. Umbilical artery PI was 1.55 and RI was 0.82.

2520 gr girl baby was delivered by cesarean at her 38th gestational week. Head circumfer-

ence was measured as 30 cm (below -2 SD). First minute Apgar score was 3 and fifth minute Apgar score was 7. Common face, depressed nasal root, long philtrum, anteverted nostrils, micrognathia, microcephaly (Fig. 1), shortness and flexion deformity at upper extremity, simian line at hand, distinctive hypertrichosis at back and femur (Fig. 2) and low birth weight were observed in the newborn examination. At the second examination performed in pediatrics and genetics department, postnatal diagnosis was established as Cornelia De Lange syndrome according to the literature information.

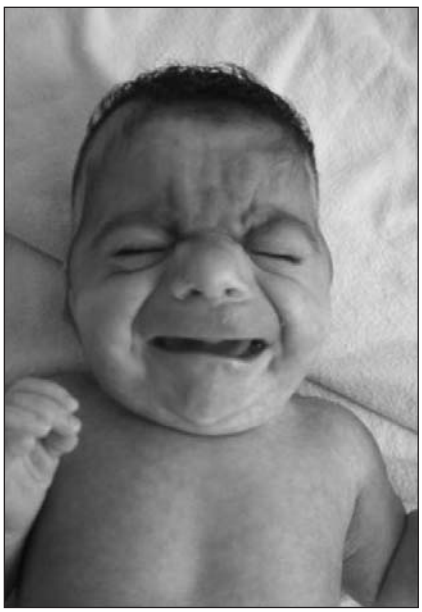

Figure 1. CDL syndrome (dysmorphic face view).

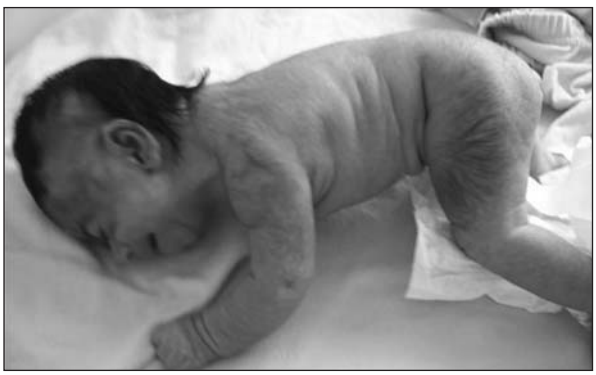

Figure 2. CDL syndrome (hypertrichosis).

Discussion

Cornelia De Lange syndrome is clinically well defined syndrome though it is rare, and it is observed in all cases with dysmorphic face characterized by growth and development retardation, microcephaly, synophrys, long curved eyelashes, downward looking thin lips, long philtrum.1,4,6 3 q 26. 3 chromosomal defect are seen in cases with defined familial history and kin marriage where etiology of syndrome is not known well.[2,7] In sporadic and familial cases, mutation was defined on NIPBL (Nipped – B – like) with cohesin regulator on 5th chromosome.[7,8] Also mutations were detected in SMAC 1A gene on X chromosome and SMC 3 gene on 10th chromosome which are the structural components of cohesin complex. Last two gene defects are related with slighter forms.[9,10] In our case, kin marriage and familial history was not detected. Chromosome analysis performed on the patient and her husband was normal; however mutation analysis was not performed.

In the literature, 15 studies were examined which were diagnosed as CDL syndrome in pre- and postnatal period.[11-24] According to the data of these studies, 95% of patients had IUGR, 81% of them had skeletal anomalies, 50% of them had facial dysmorphism and 50% of them had fetal diaphragmatic hernia. There was polyhydramniosis in two cases and there was increase in nuchal thickness in four cases. Prenatal diagnosis could only be established on six cases (Table 1).[16-19]

Early symmetric IUGR at prenatal diagnosis is the most evident ultrasonographic finding and becomes evident in between 20th and 25th gestational weeks. In our case, early symmetric IUGR was also detected as the most evident pathological finding. The reason that the patient was referred to our clinic was the early beginning IUGR. In IUGR etiology, there are many factors varying according to IUGR type. Intrauterine infections, genetic factors, maternal diseases, malnutrition, drugs, radiation, multiple pregnancies and uteroplacental factors are

among these factors. In our case, it was considered that symmetric IUGR developed according to genetic factor.

While there are several skeletal anomalies, the most significant findings are the defects evident at upper extremity.[25,26] Classical extremity anomalies are micromelia, oligodactylia and terminal transverse hemimelia.

In our case, humerus and radius lengths were measured as below -3 SD. At the same time, there was a slight flexion deformity in upper extremity. Hypoplasia of 5th phalanx and 1st metacarpal bone was seen in 90% of cases in the literature.[25] In our case, no pathology was detected in metacarpal bones except 5th phalanx hypoplasia.

Among facial anomalies, long eyelashes, anteverted nostrils, long philtrum, micrognathia, low ear (dysmorphic face) are the diagnoses that can be observed in prenatal period.[15-19] In our case, micrognathia and hypoplastic nasal bone among facial anomalies were detected in prenatal period (Table 1).

The existence of hypertrichosis is also one of the findings helping to diagnose. The existence of long eyelashes together with hypertrichosis is typical for CDL syndrome (Fig. 2).[19]

Bilateral diaphragmatic hernia, single umbilical artery and unilateral pyelectasis are seen in some cases.[12-15,23] These pathological findings were not observed in our case.

Congenital cardiac anomalies may accompany the syndrome less frequently. These anomalies are ventricular septal defect (VSD), atrial septal defect (ASD), aortic or pulmonary stenosis, Fallot tetralogy, single ventricle, atrioventricular septal defect and aortopulmonary window.[11,13,17] In our case, no cardiac anomaly with prenatal diagnosis was detected.

Less frequently, nuchal cystic hygroma and increased nuchal thickness were seen in some cases.[11,22,24] At first trimester scanning of our case, nuchal thickness was measured as 2 mm.

Another finding helping to diagnose is alpha feto protein (AFP) value below 0.4 MoM measured at 15th gestational week.[11] In our case, AFP value was 0.81 MoM at her 16th gestational week. Findings guiding prenatal diagnosis of CDL syndrome are increased nuchal thickness at first trimester, early beginning symmetric IUGR, evident defects especially at upper extremities and dysmorphic face.[20,23,24,27] Due to non-specific prenatal ultrasonographic diagnoses, the diagnosis can be established after delivery in many cases as in our case. Apert syndrome, Trisomia 18, Fanconi anemia, Holt-Oram syndrome, Multiple pterygium syndrome, Roberts syndrome, Smith-Lemli-Opitz

Table 1. CDL syndrome cases with prenatal diagnosis.

	Goolsby et al[16]	Manouvrier et al.[17]	Ackerman and Gilbert-Barness[18]	Ranzini et al.[19]	Boog et al.[20]	Urban and Hartung[21]	Our case
Gestational week	18	33	20	34	20	22	Postnatal diagnosis established
IUGR	+	+	+	+	+	-	+
Microcephaly	-	-	+	+	+	-	+
Extremity defects	+	+	micromelia	+	+	+	+
Congenital heart diseases	-	-	-	-	-	-	-
Diaphragmatic hernia	+	-	+ (bilateral)	-	-	-	-
Abnormal face	+	+	+	+	+	+	+
Other anomalies				Single umbilical artery, Dandy-Walker variant, unilateral renal pyelectasis, polyhydramniosis		Cleft palate cerebellar vermis hypoplasia	Hypoplasia of 5th phalanx

syndrome, thrombocytopenia and absent radius syndrome (TAR) should be brought to mind in prenatal differential diagnosis of CDL syndrome.

Conclusion

CDL syndrome should be within differential diagnosis in each case where dysmorphic face, upper extremity defects and early beginning symmetric IUGR are detected. Other anomalies can be detected easily by performing a detailed ultrasonographic examination. Genetic consultation should be provided to family since it is possible to establish prenatal genetic diagnosis of disease and there a risk for recurrence.

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