CAMPOMELIC DYSPLASIA: A LONG SURVIVING PATIENT WITH SEX REVERSAL

KAMPOMELİK DİSPLAZİ : UZUN ÖMÜRLÜ XY KARYOTİPLİ DİŞİ BİR OLGU

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SUMMARY: Campomelic dysplasia is a rare disorder characterised by rhizomelic dwarfism, and numerous cartilage and osseous anomalies including bowed femora and tibiae with dimples on the pretibial regions, and associated extraskeletal findings. Except for a small number of cases, patients are lost within the first ten months, mainly due to respiratory distress. Here we present the first campomelic dysplasia case with sex reversal reported from Turkey, together with a review of the literature. The relatively long survival up to the age of 4 is another distinctive property of the case.

Key Words: *Campomelic Dysplasia- Sex Reversal-Respiratory Distress.*

ÖZET: Campomelic Displazi cücelik, pretibial bölgede gamzeler, femur ve tibiada bükülmeleri de içeren bir grup kıkırdak ve kemik anomalisi ve eşlik eden iskelet sistemi dışı bulgularla karakterize nadir görülen bir bozukluktur. Bildirilen az sayıda vaka dışındaki hastalar genellikle solunum yetmezliğine bağlı olarak ilk on ayda hayatlarını yitirmektedirler. Bizim vakamız bildiğimiz kadarıyla Türkiye'den bildirilen ilk XY karyotipli dişi campomelik displazi vakası olup bu vakanın bulgularıyla birlikte literatür bilgisi de gözden geçirilmiştir. Ayrıca vakanın 4 yaşına kadar yaşamış olması da diğer bir özelliğidir..

Anahtar Kelimeler: *Kampomelik Displazi, Sex Reversal, Respiratuar Distres.*

INTRODUCTION

Campomelic dysplasia (CD), derived from the union of the latin words campo: bent, and melos: extremity, is a rare form of congenital dwarfism characterised by congenital bowing and angulation of the femora and tibia and various associated skeletal and extra-skeletal anomalies. It was first reported by Proudfoot et al. as a form of dwarfism (1). However, in 1971 CD was first described as a syndrome by Maroteaux et al. (2) and Bianchine et al. (3) separately. Today there are more than a hundred cases reported. Here we present a 14-month-old girl who meets the criteria for CD. To our knowledge she is the first case of CD with sex reversal reported from Turkey (4-6), and she led a relatively long life, up to the age of four.

CASE REPORT

A 14-month-old girl was admitted with respiratory distress and coughing. She had multiple anomalies such as a flat nasal bridge, cleft palate, low-set ears, micrognathia, tracheomalacia, facial hypoplasia, an atypical simian line in the right hand, bilateral angulation of the lower extremities, pretibial skin dimples, talipes equinovarus and hypotonia (Fig. 1a). She had rough respiratory sounds. Her body weight and length were under the 5 percentile and head circumference was under the 25 percentile. Her mental development was consistent with 7.5 months according to the Denver developmental screening test.

She was delivered via caesarean section at 32 weeks of gestation because of polyhydramnios

and preeclampsia. Her mother was 28 years of age and her father was 35 years of age at the time of delivery. The family history revealed three miscarriages and one dilatation and curettage. The patient had an 11-year-old healthy brother. The parents were healthy and nonconsanguineous and the pregnancy history was uncomplicated without drug use, any illness or exposure to mutagenic-teratogenic agents.

All the biochemical values and thyroid function tests were within normal limits.

Micrognathia and facial hypoplasia were evident on cranial X-ray studies (Fig. 1b). A chest roentgenogram revealed that sternal mineralisation was absent, the thorax was bell-shaped and the scapulas were hypoplastic (Fig. 1c).

Pelvis and lower extremity images showed vertically oriented narrow iliac wings, increased acetebular angles, bilateral hip dislocation, anterolateral angulation of the tibiae and femora, hypoplastic fibulae, pes equinovarus and a lack of ossification of the epiphysis except for in the femur distal (Fig. 1d).

Her transcranial ultrasonography via the anterior fontanel revealed minimal dilatation of the 3rd and lateral ventricules. Cranial magnetic resonance imaging was normal except for a mild cerebral and cerebellar atrophy. Abdominal sonography was normal. Echocardiography did not reveal any pathologic findings.

Chromosome analysis revealed 46 XY. The patient's external genitalia were totally feminine and the uterus and ovaries were visualised by pelvic sonography.

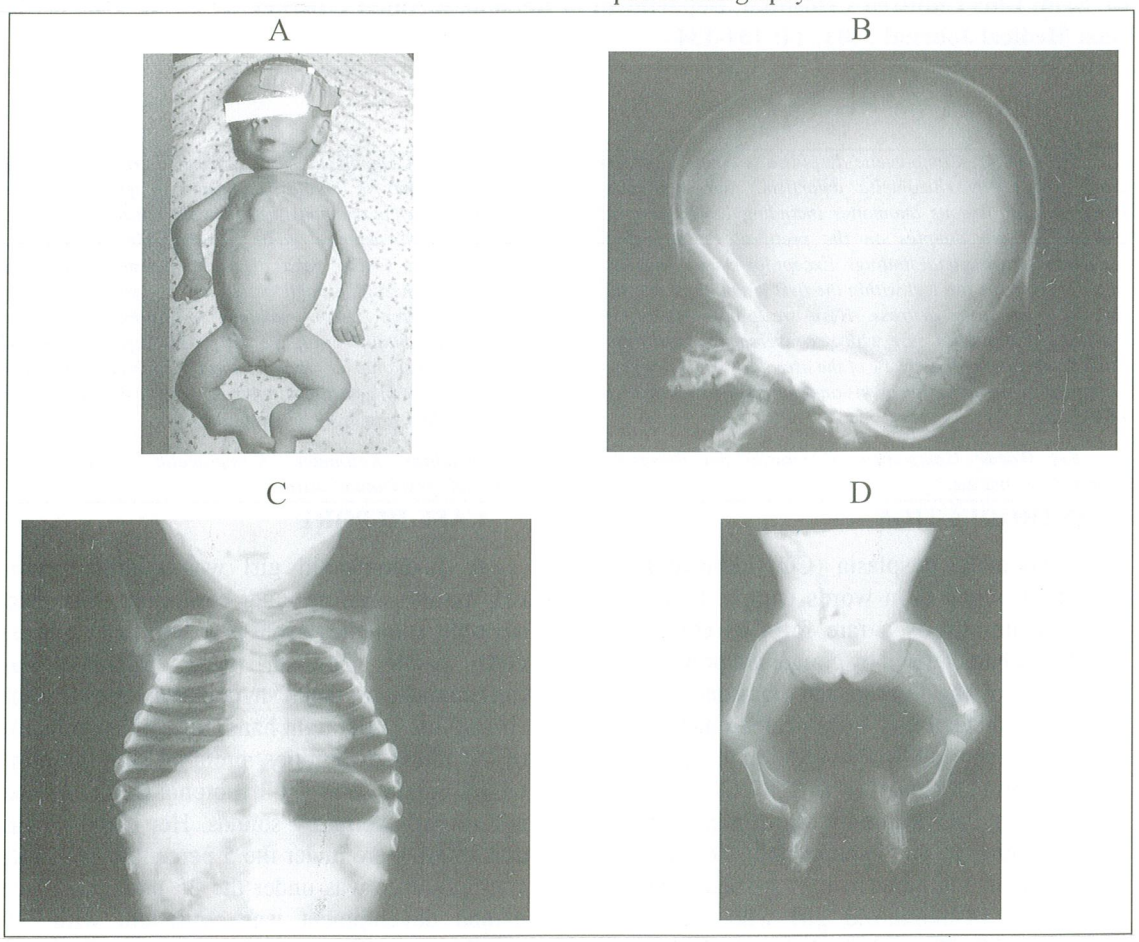

Fig. 1: The appearance of the 14-month-old child with the clinical diagnosis of CD (A). Lateral cranial X-ray; Facial hypoplasia and micrognathia are evident (B). PA thorax roentgenogram: Narrow, bell-shaped thorax and hypoplastic scapulae are striking. There is no sternal mineralisation (C). Frontal projection of the pelvis and lower extremities: Note narrow iliac wings, increase in the acetebular angles, dislocation of the hip joints, insufficent mineralisation of the pubic bone, femoral and tibial angulation, hypoplastic fibulas and lack of mineralisation of the epiphysis except for in the femur distals (D).

The final diagnosis was campomelic dysplasia with sex reversal and she was medicated for her respiratory distress. After being discharged from the hospital the child was not brought to the department for follow-up but we learnt from the family that she had had several severe respiratory distress episodes and had died at the age of four during one of these.

DISCUSSION

CD is a rare skeletal dysplasia with an incidence of 0.05-0.09/10,000 live births (7). Although its exact aetiology has not been determined yet, CD is assumed to be recessively inherited. Cytogenetic studies have described an unexceptionally high incidence of 46 XY karyotypes in phenotypic females, as in our case. Evidence of autosomal dominant inheritance was shown by Lynch et al. (8) in some families with CD, while Wagner et al. (9) found that in campomelic patients with sex reversal, mutations of the SOX 9 gene, which takes place in the long arm of chromosome 17, might be an autosomal dominant condition. Cameron et al. (10) reported that paternal stem cell mosaicism containing the mutant SOX 9 gene may be the reason for different 46 XY gonadal phenotypes. They explained this variability by enviromental factors, variable penetrance of mutation or a high activity of non-mutant SOX9 allele. Today CD is now known to be caused by mutations in the SOX9 gene (6). SOX9 protein regulates the expression of type 2 collagen gene. This explains why abnormalities of this pathway lead to the abnormal skeletal development seen in CD (6).

The designation of campomelic dwarfism was proposed by Maroteaux et al. (2) and refers to bowing of the legs. Beluffi et al. (11) have reported the rate of radiologic signs in a series of 133 CD cases. In their study group 99% of the patients had micrognathia, 91% facial hypoplasia, and 90% macrocephaly as cranial findings. Hypoplastic scapulas were present in 92% of cases, bell-shaped narrow thorax in 80%, lack of sternal mineralisation in 79%, tracheomalacia in 72%, eleven cots in 68% and nonmineralised pedincules in 78%, and kyphoscoliosis in 70%. Pelvis and lower extremity findings were as follows: angulated femur 99%, angulated tibia 100%, hypoplastic fibula 97%, narrow iliac wings 98%, increased acetebular angles 97%, insufficient development of the pubic bones 97%, hip dislocation 91%, lack of secondary ossification centres- proximal tibial 96%- distal femoral 89%- talar 66%. The present case has the vast majority of the described radiographic findings. Autopsies of 56 cases revealed associated findings like the absence of olfactory bulbus and tractus, hydrocephaly, hypoplastic lungs, congenital cardiac and renal malformations, hydronephrosis and tracheolaryngomalasia. There is a history of polyhydramnios during pregnancy in many of the cases (12). Mental retardation is not crucial. Our case also had a polyhydramnios history and she was mentally retarded. Glass et al. (13) described shallow orbits and Aslan et al. (5) reported cleft mandibula as further radiographic variations accompanying CD. In CD the probability of survival is very low. Nearly all patients die within 10 months (11). There are a few cases reporting children living up to 4 years (14) and one case up to 17 years (2). Our case is one of the rare CD patients having a long survival. There is also a rare clinical 'acampomelic' variant, characterised by the absence of the most striking component-bowing of the long bones (15-16). It has been reported in 10 cases to date (6).

To our knowledge the case presented here is the first case with sex reversal reported from Turkey. There are three cases of CD reported from our country in the literature to date, excluding this one. Again the patient's long survival should be emphasised, with regard to the minority of patients with a relatively long life. We also want to stress that the diagnosis of CD should be considered in a neonate or infant with respiratory stress and minor or major anomalies.

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