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Case Report

Campomelic dysplasia: a case report

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ABSTRACT

Campomelic dysplasia is a rare, lethal, and autosomal dominant inherited disorder with reversal of sex in genotypic male in two third cases. An eight-month-old phenotypic female infant was admitted with respiratory distress and failure to thrive. She had facial dysmorphism, cleft in soft palate, pectus excavatum deformity, bowing of lower limbs, dimpling at right knee area and bilateral congenital talipes equinovarus deformity. Radiographs shows 11 pairs of ribs, hypoplastic scapula, bowing of bilateral tibia and hypoplastic bilateral fibula. Karyotyping was 46XYchromosome and whole exome sequencing reveals autosomal dominant affecting SOX9 (NM_000346.4) gene, pathogenic variant of c.583C>T (p.Gin195Ter) which is stop gained variant. She was managed according to hospital protocol and discharged. Prenatal diagnosis, genetic counselling and multidisciplinary approach for management of survival cases is important to reduce mortality.

Keywords: Campomelic dysplasia, SOX9 gene, Skeletal dysplasia, Genetic counselling

INTRODUCTION

Campomelic dysplasia (CD) is an autosomal dominant genetic disorder, first reported by Maroteaux et al.[1] Name of the disease is derived from the Greek words' campo, meaning bent, and melia, meaning limb. Reliable data regarding the prevalence of CD is unknown however, estimated prevalence to be in the range of 1:40,000 to 1:80,000.[2] Typically, it is manifested as bowing of lower limbs, hypoplastic scapula, missing of one pair of ribs, Robin sequence, pelvic malformations, bilateral clubfeet; and around two-thirds of affected genetic males have sex reversal due to dysgenetic testis.[2,3] An overall three-fourth patients died in neonatal period due to respiratory failure arising from chest defect, hypoplastic lungs and tracheobronchial hypoplasia, and mortality reaches to 90% by 2 years of age due to recurrent respiratory infections while few cases may survive longer because of variable penetration of gene and variable organ anomalies.[4,5] It is usually due to mutation in the SOX9 gene-a member of the SOX (SRY-related HMG box) gene family-located on 17q24.3, and have diverse' role during embryogenesis of multiple tissues and organs including cartilages, testis, nervous system, retina, lung, cardiac tissues.[6]

CASE REPORT

An eight months old phenotypically female infant of non-consanguineous Indian couple (father age 33 years, mother age 25 years), second by birth order (first sibling 3 years and 6 months of age, female, healthy) was admitted with fever and respiratory distress. She had history of 3-4 times hospitalization for similar complaints. Mother also revealed child is on bottle feeding, not gaining weight adequately, and history of delayed development compared to her 1st baby. Antenatally, mother spontaneously conceived and pregnancy was diagnosed at one and half months of gestation. There was no history of drug intake (sodium valproate, thalidomide, carbamazepine) except routine iron and calcium preparations. Mother had no history suggestive of diabetes, seizure disorder, pregnancy induced hypertension/thyroid disorder. Ultrasonography at 28th week gestation showed apparently short bilateral femur with bowing at acute angulation and bilateral short

tibia and fibula with CTEV on left side with polydactyly. Child was delivered vaginally, at term with birth weight of 2.4 kg and had cried immediately after birth. Child was hospitalized in neonatal period for respiratory distress for period of 5 days.

On examination, her weight was found to be 5.2 kg (expected of 7.5 kg, inference<3rd SD), length of 55 cm (expected 67 cm, inference<3 SD), head circumference was found to be 44 cm (expected 41 cm, inference +1 to +2 SD). Child had large head, sparse hair, frontal bossing, parietal prominence, and scalp had nodular swelling over right post auricular area of size 1.5×1 cm. Facial dysmorphism was noted in form of epicanthal folds, hypertelorism, flat nasal bridge, low set ears and high arched palate and cleft of 0.5cm was noted in soft palate however lips were normal with microstomia and retrognathia (Figure 1 A and B). Chest had pectus excavatum deformity, lower limbs bowing in anterior tibia bilaterally, dimpling was present around right knee area and she had bilateral congenital talipes equinovarus deformity with sandal gap present in bilateral lower limbs, however bilateral upper limbs were normal (Figure 1 C). Child had phenotypic female genetalia with bilateral labial swellings, vaginal opening could be seen and anal opening was patent. Bilateral Spine and back examination were within normal limit.

Radiological examination revealed following findings: radiography of chest shows 11 pairs of ribs, hypoplastic scapula with normal thoracic cavity and vertebrae. Skull radiograph revealed disproportionately large skull bones while radiograph of lower limb showed bowing of bilateral tibia, hypoplastic bilateral fibula without obvious any dislocation (Figure 2 A-D). Ultrasound abdomen and pelvis described uterus of size 1×0.8×1.6 cm but bilateral ovaries were obscured. Computed tomography brain scan showed bilateral benign enlargement of subarachnoid spaces in frontal lobes while multi-slice spiral computed tomography of thorax revealed mosaic attenuation of bilateral lung parenchyma, absent 12th pair of rib, hypoplastic bilateral acetabulum, hypoplastic bilateral scapula, deficient posterior bony arch of lower lumbar and sacral vertebrae suggestive of spina bifida occulta and multi-slice spiral CT of abdomen showed distended gall bladder without hyperdense calculi, normal pancreas, kidneys, spleen and urinary bladder while soft tissue measuring of 1.9×0.8×2.4 cm noted in recto-vesical space and it could represent uterus. 2D Echocardiography suggested small ostium secondum atrial septal defect. Karyotyping was suggestive of 46XY chromosomal pattern while whole exome sequencing reveals autosomal dominant affecting SOX9 (NM_000346.4) gene, pathogenic variant of c.583C>T (p.Gin195Ter) which is stop gained variant. Amino acid glutamine at 195th position is signaled as termination protein and it is a nonsense mutation. The predicted cause of loss of function of protein is by protein truncation.

She was treated with injectable antibiotics, oxygen supplementation and adequate diet. Mother was counselled about diagnosis/prognosis and genetic counselling about reversal of sex. Child was in follow-up after 1 month and she had no acute problem. Genetic study of parents and other sibling was not done due to financial issues.

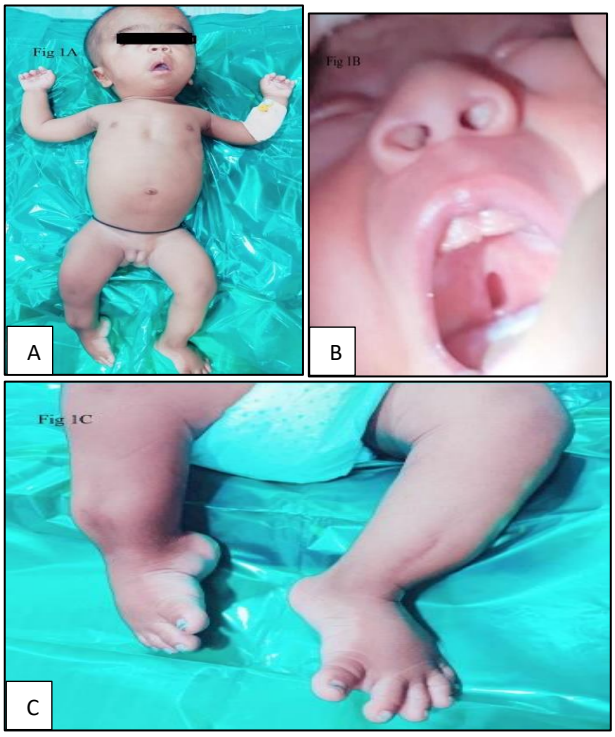

Figure 1 (A-C): Showed facial features, cleft palate and lower limb deformity.

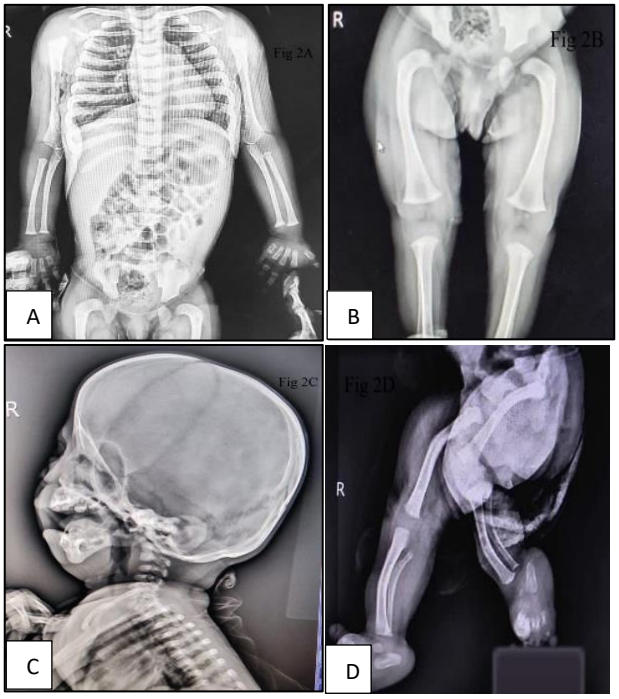

Figure 2 (A-D): Radiological changes in patients.

DISCUSSION

Skeletal dysplasias are a heterogenous group of disorders of skeleton-genesis. CD is one of the life threatening skeletal dysplasia; closely differentiated with thanatophoric dysplasia, osteogenesis imperfecta type II, hypophosphatasia achondrogenesis, atelosteogenesis, mesomelic dysplasia and kypomelic dysplasia, etc.[7] Our case had typical clinical features of CD those reported in literature including respiratory difficulty since birth, typical bony deformities in form of bowing of lower limb/dimpling on right knee, hypoplastic scapulla, 11 pairs of ribs, bilateral clubfeet and robin's sequence. Other associated malformations like ischio-pubic-patella syndrome (IPP), 10 pairs of rib instead of 11 pair, fibula aplasia-tibia campomelic-oligosyndactyly syndrome, and bilateral gonadoblasoma is reported by various authors with CD.[7-12]

Sex-determining region of the Y chromosome (SRY)-related box 9 (SOX9) play a crucial role in sexual organ differentiation; mutation in this gene results into disorder of sex development, associated with dysgenetic gonads and such dysgenetic gonads are prone for malignancies like gonadoblastoma.[12,13]

CD is reported equally in both sexes, however, 75% of male genotype have female phenotype or ambiguous genitalia. In our case, we noted female external genitalia, uterus-like structure on computed tomography but ovaries were not demonstrated and genetic sex was male (46XY).

Most of the cases of CD succumb during neonatal phase of life as a complication of respiratory failure due thoracic cage defect, laryngo-tracheomalacia and hypoplastic lungs as well as cardiac, renal and central nervous system anomalies. However, around 10% cases survive beyond 2 years of age; oldest patient of CD is 41 years old reported in literature.[12]

In patients who survive up to longer, they have multiple complications of spinal abnormalities.[14] Present case was 8 months old female who had recurrent respiratory infections, feeding problems and multiple hospitalization.

CD is mainly results from de novo heterozygous SOX9 mutation; including nonsense, missense, frameshift, spice mutation/chromosomal aberration impairing enhancer region because of translocation, inversions and deletion.[15-17] Exome sequencing in our patient reveals heterozygous, autosomal dominant affecting SOX9 (NM_000346.4) gene, pathogenic variant of c.583C>T (p.Gin195Ter) which is stop gained variant.

Amino acid glutamine at 195th position is signaled as termination protein and it is a nonsense mutation. Predicted cause of loss of function of protein is by protein truncation. Similar type of observations is reported by various researchers.[18-20]

CONCLUSION

Prenatal early diagnosis of such lethal skeletal dysplasia can be markedly improved with integrated expertise of ultra sonographer, obstetrician, pediatrician and clinical genetics. Familial genetic screening and counselling plays an important role in early diagnosis particularly in family with such disorders for reproductive planning and early interventions. Genetic test should be easily available and it should be reachable to poor people particularly in developing countries. A multidisciplinary team approach is crucial in the management of CD due to the complex and diverse range of complications associated with this condition in surviving cases.

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