Picture stories

Ellis-van Creveld syndrome with homozygous deletions in exons 1 to 11 of the EVC gene and exons 1 to 22 of the EVC2gene

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Introduction

Ellis-van Creveld syndrome (EVS) is an autosomal recessive disorder of children, initially described by Richard Ellis and Simon van Creveld[1]. EVS is caused by mutations of the EVC and EVC2 genes, located on chromosome 4p16, leading to abnormally small EVC and EVC2 proteins[1,2]. Consanguineous marriage is found in about 30% of cases[3,4]. Clinical features include postaxial polydactyly, ectodermal dysplasia, disproportionate short stature, congenital heart defects, partial harelip, multiple frenulae in lips, short ribs, narrow chest, epispadias, hypospadias, cryptorchidism, low iliac wings with spur-like projections at acetabula and genu valgum[5]. Around 50 percent of children may die due to respiratory complications before reaching adulthood and the rest may need various procedures to survive[6].

Case report

A 4 year old boy, born of a non-consanguineous marriage, presented with dental abnormalities, including malocclusion of the teeth and hypodontia involving primary dentition. On further inquiry, the parents revealed that the child also had global developmental delay and was not attaining height appropriately. On physical examination, the child had disproportionate short stature, postaxial polydactaly of hands, clinodactaly of extra finger and knock knees. The stature of the child was 104cm (Z score of height for age <-2) and upper segment (63.5cms) to lower segment (40.6cms) ratio was -1.5. The child had normal facial and trunk development, but small distal extremities, especially fingers and toes with bilateral ulnar polydactyly and dystrophic nails (Figures A and B). Knock knees were present bilaterally with tibial segment disproportionately shorter than the femoral segment.

Examination of the oral cavity revealed the absence of two lower incisor teeth, hyperplastic frenula, dystrophic philtrum, V-shaped notching of upper lip, labio gingival adherence in the anterior region of lips, malocclusion of teeth, serrated incisor margins, diastema and conical teeth (Figures C and D).

Cardiovascular system examination revealed a heart rate of 112/min, oxygen saturation of 92% in room air and a pansystolic murmur, most prominent in the parasternal region. There was hepatomegaly with a span of 10 cm, and liver was palpable 3cm below the right subcostal margin. On diagnostic evaluation, X-ray of wrist and shoulder joint showed fusion of 5th and 6th metacarpals and capitohamate fusion with an estimated bone age of 3-6 years (Figure E).

The electrocardiogram showed T wave abnormality in V1, V2, V3 and V4 and right atrial enlargement. 2D-echocardiogram revealed acyanotic congenital heart disease in the form of endocardial cushion defect, partial atrioventricular septal defect, common AV ring, atrial septal defect (6 mm) with left to right shunt, cleft anterior mitral leaflet and mild to moderate mitral regurgitation. Ultrasound scan of abdomen showed mild hepatomegaly. Haematological parameters, liver and renal function tests were unremarkable. On neuropsychological evaluation, intelligence quotient (IQ) was found to be 65 (mild intellectual disability). Magnetic resonance imaging of brain was normal. Genetic sequencing revealed pathogenic homozygous deletions in contiguous regions encompassing exons 1 to 11 of the EVC gene (ENST00000382674.2) and exons 1 to 22 of the EVC2gene (ENST00000344408.5), confirming

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the diagnosis. Deletions involving these particular exons of these two genes were not found in the genetic database ClinVar.

The child is currently planned for dental reconstruction and correction surgery for acyanotic congenital heart disease. The procedure planned for the child is extraction of the unerupted teeth, orthotic intervention in the form of braces for malocclusion of teeth and correction of congenital teeth by composite or fixed crown. The child is receiving occupational therapy and also going to school for formal education. The parents have been provided with appropriate genetic counselling.

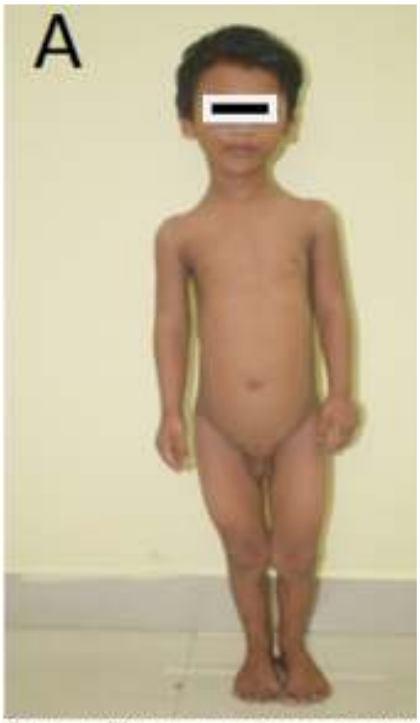

Figure A: ***Tibial segment disproportionately shorter than femoral segment***

**Permission given by parents to publish photograph*

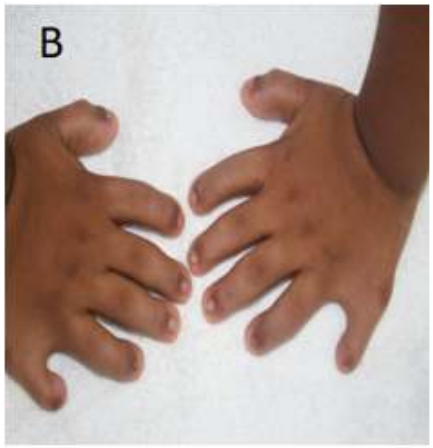

Figure B: ***Polydactyly and dystrophic nails***

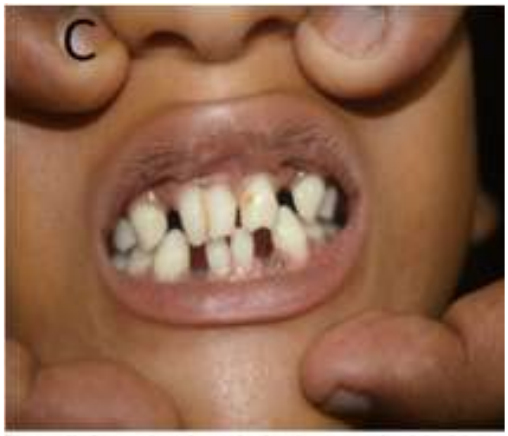

Figure C: *Lower dental arcade showing agenesis of the 2 lower incisors and hypertrophy of labiogingival frenulum*

Figure D: ***Frontal view of the mouth. Multiple musculo-fibrous frenula***

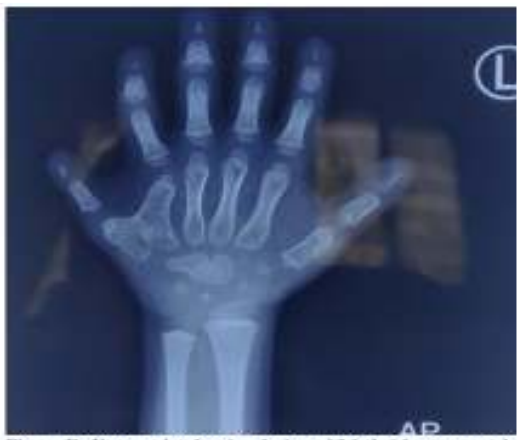

Figure E: *X-ray wrist showing fusion of 5th & 6th metacarpals and capitohamate fusion with estimated bone age of 3-6 years*

Discussion

The atypical features observed in our case were intellectual disability, knock knees and mild hepatomegaly, which have been observed only in a minor proportion of children with EVS. Gupta *et al* in 2017 reported correction of a case of severe genu

valgum in EVS using a two-step procedure[7]. Bohm *et al* have reported a case of EVS with hepatomegaly, portal fibrosis, bile duct hyperplasia and dysplasia[8]. Although most patients have normal intelligence, occasional central nervous system anomalies or mental retardation has been reported[9,10]. Genetic sequencing revealed pathogenic homozygous deletions in contiguous regions encompassing exons 1 to 11 of the EVC gene and exons 1 to 22 of the EVC2gene. Deletions involving these particular exons of these two genes were not found in the genetic database ClinVar.

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