



## A Rare Case of Ellis Van Creveld Syndrome

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### Abstract

*Ellis-Van Creveld syndrome is an autosomal recessive disorder of skeletal dysplasia. It is also known as chondroectodermal dysplasia or mesoectodermal dysplasia. Six fingered dwarfism was an alternative designation used for this condition. It is characterized by chondroectodermal dysplasia, polydactyly, congenital heart defects and hypoplastic nails and teeth. Mutations of EVCI and EVC2 genes located in head to head configuration on chromosome 4p16 have been identified as causative along with parental consanguinity.*

### Introduction

Ellis-van Creveld (EvC) syndrome is an autosomal recessive chondroectodermal dysplasia, described by Richard Ellis and Simon van Creveld in 1940.<sup>1</sup> It is a generalised dysplasia of endochondral ossification, caused by mutations in a novel gene on chromosome 4p16, with high prevalence in Amish community of Lancaster.<sup>2</sup> There is parental consanguinity in 30% of the cases with 7/1 000 000 prevalence outside Amish community. Today, the syndrome has been described in other populations and it is known to affect all races.<sup>3</sup>

EvC presents a characteristic tetrad<sup>4</sup>:

1. Disproportionate dwarfism due to chondrodysplasia of the long bones and an exceptionally long trunk. The severity of short limbs increases from the proximal to the distal portions.
2. Bilateral postaxial polydactyly of the hands, with the supernumerary finger usually being

on the ulnar side. Occasionally a supernumerary toe may be present.

3. Ectodermal dysplasia with dystrophic, small nails, thin sparse hair and hypodontic and abnormally formed teeth.
4. Congenital heart malformations in 50–60% of the cases. The most common being a single atrium and a ventricular septal defect.

Other skeletal anomalies such as genu valgum (knock knees) have been occasionally reported. Patients' intelligence is usually normal.<sup>5</sup> Oral manifestations in EvC syndrome are remarkable and constant. The most common finding is a fusion of the anterior portion of the upper lip to the maxillary gingival margin, so that no mucobuccal fold exists, causing the upper lip to present a slight V-notch in the middle.<sup>1</sup> The anterior portion of the lower alveolar ridge is often serrated and multiple small and conical molars have abnormal cusps or accessory grooves,<sup>1</sup> and sometimes hypoplastic enamel is seen. Congenitally missing primary and

permanent teeth, dysmorphic conical-shaped roots and delay in eruption have also been reported.<sup>6</sup> Malocclusions occur secondary to these oral abnormalities as they are of no specific type.<sup>7</sup> Cardiac defects present in 50 – 60% of patients with EvC and require antibiotic coverage for the prevention of infectious endocarditis.<sup>4</sup> Almost half of these patients die during childhood because of cardiopulmonary complications; for this reason the life expectancy of EvC patients is determined by their congenital cardiac disease.

### Case Report

A 38 years old female patient reported to the department of General Medicine, GGH, Kakinada with chief complaints of sudden onset of shortness of breath, orthopnea associated with palpitations. Patient was 4<sup>th</sup> child of non-consanguineous marriage. Antenatal, natal and neonatal histories were non contributory. No significant family history.

General examination revealed that patient was of short stature (weight-29kgs; Height-72cm) with bilateral postaxial polydactyly of hands, both upper & lower limb dysplasia with bimanual hexadactyly noted on Ulnar side, hypoplastic Fingers and nail aplasia. Patient had Kyphoscoliosis since birth. Dental history revealed tooth aplasia, congenitally missing lower central and lateral incisors, enamel hypoplasia and conical teeth. The patient's intellectual ability was within the normal range.

Echocardiography shows large ASD with single atrium, trivial mitral regurgitation, mild tricuspid regurgitation cardiomegaly. Ultrasound abdomen revealed normal hepato-biliary and genitor-urinary development.



**Figure 1** The small distal extremities.



**Figure 2** Serrated lower anterior region with missing permanent incisors.





**Figure 3-** Hexadactyly on ulnar side with nail aplasia



**Figure 4** Kyphoscoliosis of spine



**Figure 5** 2D ECHO showing large atrial septal defect with single atrium.

### Discussion

Ellis Van Creveld Syndrome seen commonly in Amish population of Pennsylvania USA which does not show any gender predilection.<sup>2</sup> The diagnosis

can be made as early as 18th week of gestation by ultrasonography when the increased nuchal translucency is evident.<sup>4,7,8</sup> and later by clinical examination after birth.<sup>1,3,4</sup>

The most consistent clinical feature is chondrodystrophy due to defect in ossification affecting tubular bones resulting in shortened long bones of the limbs especially in distal and middle segments resulting in acromesomelic dwarfism.<sup>3,4,8</sup> The other features include polydactyly usually bilateral postaxial hexadactyly most often seen in upper limbs on ulnar side and involves lower limb in 10% of cases. They also have wide hands and feet, sausage shaped fingers and dysplastic fingernails.<sup>2,8</sup> Our patient had hexadactyly in both the upper and lower limbs with nail aplasia with no syndactyly and kyphoscoliosis of spine since birth. Other features include genu valga, curvature of the humerus, talipes equinovarus, talipes calcaneovalgus<sup>4</sup> and pectus carinatum with a long narrow chest.<sup>2-4,8</sup> Congenital heart malformations are described in a 50–60% of patients. The anomalies include defects of the mitral and tricuspid valves, patent ductus arteriosus, ventricular septal defect, atrial septal defect and hypoplastic left heart syndrome which are the principal causes of decreased life-expectancy in these patients.<sup>3,8,9</sup> our patient had large atrial septal defect resulting in single atrium, trivial mitral regurgitation, mild tricuspid regurgitation and cardiomegaly. The disease has characteristic oral manifestations that help early diagnosis at birth or during early childhood.<sup>5</sup> The most common among them include fusion of the upper lip to the gingival margin resulting in the absence of mucobuccal fold, broad maxillary labial frenum described as partial harelip, multiple small accessory frenula, ankyloglossia, malocclusion, conical, microdontia teeth, hypodontia, anodontia (commonly the absence of permanent mandibular central and lateral incisors) and enamel hypoplasia.<sup>5,7,8,10</sup> Our patient had all the above findings tooth aplasia and congenitally absent lower central and lateral incisors, enamel hypoplasia and conical teeth. Other minor or variable manifestations include retarded

eruption, supernumerary teeth, dental fusion, dysmorphic roots, taurodontism, abnormal occlusal anatomy with wide grooves and atypical cusps.<sup>5</sup>

Genitourinary abnormalities are seen in about 22% of the cases and include vulvar atresia, megaureters, nephrocalcinosis and renal agenesis.<sup>3,8</sup> Several inconstant additional clinical findings are described, including strabismus, epi- and hypospadias, cryptorchidism and thoracic wall and pulmonary malformations.<sup>3,7</sup> Exceptionally, hematological anomalies such as dyserythropoiesis and perinatal myeloblastic leukemia have been reported.<sup>3,7</sup> The cognitive and motor development are normal with occasional CNS anomalies and hydrocephaly.<sup>8,9</sup>

The definitive diagnosis is molecular based on the homozygosity for a mutation in the EVC 1 and/or EVC 2 genes by direct sequencing. However the genetic mutations are seldom required for the clinical diagnosis as gene mutations is positive in only 2/3rd of patients. Due to the lack of availability of genetic studies the diagnosis was achieved clinically based on the observation of the symptoms and manifestations as described and with the aid of additional tests such as radiology, laboratory and cardiac function.<sup>1,3,8</sup>

Differential diagnosis includes other short rib polydactyly syndromes like Weyers acrodistal dysostosis (Curry-Hall syndrome), asphyxiating thoracic dystrophy (Jeune syndrome), achondroplasia, chondroplasia punctata, orofaciadigital syndromes and Morquio's syndrome.<sup>3,4,7,8</sup>

EVC syndrome and Weyer's acrodistal dysostosis (Curry-Hall syndrome) are allelic conditions caused by loss of function mutation in EVC and EVC2. These are separated by 2–6 kb of genomic sequence on chromosome 4p16.10.<sup>2</sup> Clinical features in Curry-Hall syndrome are similar to Ellis Van Creveld syndrome, which includes normal stature and cardiac defects; however thoracic dysplasia is generally absent. Additional features of Curry-Hall syndrome include presence of osseous cleft of symphysis of the mandible, while fifth carpal in distal row of wrist and multiple ossification centres in hamate is absent.<sup>4</sup>

Asphyxiating thoracic dystrophy or Jeune syndrome is a rare, potentially lethal, autosomal recessive disease; characterized by thoracic dystrophy, short limbs which is rhizomelic rather than mesomelic, small stature, polydactyly and generalized bony dysplasia. There are anomalies in pigmentation of the retina, renal involvement and hypoplastic lungs<sup>2,3</sup> and absence of nail dystrophy and abnormal frenula.<sup>4</sup> The orofaciadigital syndromes result from dominant sex-linked inheritance, they are limited to women and clinically characterized by multiple gingivolabial frenula, hypoplasia of the nasal cartilages, moderate mental retardation, fissured tongue and in a third of the cases ankyloglossia.<sup>2,3</sup>

In achondroplasia, rhizomelic shortening of the limbs along with large calvarial bones and small cranial base and facial bones is seen. Chondroplasia punctata presents with severe and symmetrical rhizomelic micromelia, punctate calcifications and alterations to the ossification in metaphyses and epiphyses of the long bones, microcephaly, micrognathia and flattened nasal bridge. Morquio's syndrome shows short neck, lumbar kyphosis, hypermobility of metacarpal joints, general osteoporosis, short trunk with proportionately long limbs and coxa valga. The hands show shortening of the metacarpals, inclination of the distal portions of the radius and ulna toward each other and a prominent maxilla along with broad mouth.<sup>4</sup>

### Conclusion

This patient showed many characteristic changes mentioned in literature as short stature, limb dysplasia, short ribs, polydactyly, congenital nail aplasia and tooth aplasia with large atrial septal defect resulting in single atrium which is the most common cardiac anomaly associated with EVC syndrome. However the genetic mutations are seldom required for the clinical diagnosis as gene mutations is positive in only 2/3rd of patients. Due to the lack of availability of genetic studies the diagnosis was achieved clinically based on the observation of the symptoms and manifestations as described and with the aid of additional tests such as radiology, laboratory and cardiac function.<sup>1,3,8</sup>

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