

Ellis-van creveld syndrome with unusual Genitourinary findings: A case report

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Abstract

Ellis-van Creveld syndrome (EVC) also known as Chondroectodermal dysplasia or Mesoectodermal dysplasia, is a chondral and ectodermal dysplasia characterized by short ribs (chondrodystrophy), polydactyly, growth retardation, ectodermal and heart defects. It is a rare disease with approximately 300 cases reported worldwide. After birth, cardinal features are short stature, short ribs, polydactyly, dysplastic fingernails and teeth. Heart defects, especially abnormalities of atrial septation, occur in about 60% of cases. Cognitive and motor development is normal. This rare condition is inherited as an autosomal recessive trait with variable expression. Mutations of the EVC/EVC1 and EVC2 genes, located in a head to head configuration on chromosome 4p16, have been identified as causative. EVC belongs to the short rib-polydactyly group (SRP). The management of EVC is multidisciplinary. Management during the neonatal period is mostly symptomatic, involving treatment of the respiratory distress due to narrow chest and heart failure. Orthopedic follow-up is required to manage the bone deformities. Professional dental care should be considered for management of the oral manifestations. Prognosis is linked to the respiratory difficulties in the first months of life due to thoracic narrowness and possible heart defects. Prognosis of the final body height is difficult to predict.

Keywords: Ellis-van Syndrome, Polydactyly, SRP, Chondrodystrophy.

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Introduction

Ellis-van Creveld (EVC) syndrome was first described in 1940 by Ellis and Creveld, as an autosomal recessive disorder and is characterized by short stature and ribs, ectodermal defects and polydactyly.¹ More than half of EVC patients present with congenital heart defects.² Ellis-van Creveld syndrome is a rare disease. A prevalence of 0.7/100,000 live birth has been noted and only around 300 cases reported worldwide.^{3,4} It is mainly reported in highly consanguineous populations such as the Amish population in Lancaster Country, Pennsylvania, US, where the largest pedigree has been described: 52 cases in 30 sib ships.⁵ The exact prevalence of this rare syndrome is still unknown. This syndrome does not have any gender predilection but 30% of cases reported with parental consanguinity.⁶ The syndrome can be diagnosed either by ultrasonography starting from 18th week of gestation or through clinical examination right after birth. Diagnosis after birth is based on clinical observation of features and symptoms described above. It is also supported by X-ray of the skeleton, chest radiography, ECG, and echocardiography.⁴ The definitive diagnosis is molecular, based on homozygosity for a mutation in the EVC and EVC2 genes by direct sequencing.³ EVC syndrome is one of a group of diseases called

ciliopathies, which is caused by abnormalities in the primary cilia. It has been found that the affected EVC individuals with mutations in EVC or EVC2 are phenotypically indistinguishable.⁷ Prenatal abnormalities include narrow thorax, marked shortening of the long bones, hexadactyly of hands and feet, and cardiac defect leading to the diagnosis of SRPs.⁸ After birth, the cardinal features are disproportionate small stature with increasing severity from the proximal to distal portions of the limbs, polydactyly affecting hands (usually bilateral), hidrotic ectodermal dysplasia mainly affecting the nails, hair and teeth and congenital heart malformations occurring in about 50–60% of cases and comprising of single atrium, defects of the mitral and tricuspid valves, patent ductus, ventricular septal defect, atrial septal defect and hypoplastic left heart syndrome. The presence of congenital heart disease may support the diagnosis of the EVC syndrome and appears to be the main determinant of longevity.^{9,10} In this paper we are presenting a case report diagnosed with the typical features of EVC syndrome.

Case Report

A 10 year old male child patient of Indian origin presented to the Dept. of Oral Medicine and Radiology at Maulana Azad Institute of Dental Sciences, New Delhi with a chief complaint of teeth missing in the lower front teeth region. He was the third child of non-consanguineous parents. Two elder sisters and a younger brother were normal. Parents were healthy and normal. Pregnancy and delivery were uneventful and the child was born at the end of 37th week of gestation. The mother gave history of surgery in the child for bilateral genu valgum at the age of 7 years. The mental

age was normal. Developmental milestones were attained on time.

Patient at 10 years of age showed short stature with long narrow thorax, shortening of limbs with paucity of hair (Fig. 1a and 1b). The nails of both hands and feet showed extreme degree of dysplasia with incomplete webbing between 2nd and 3rd toes. Hands and feet were stubby with fingers of same size. Poataxial polydactyly (hexadactyly) was seen (Fig. 1c, 1d). The upper lip was hypoplastic/short compared with the broad and thick lower lip.

The patient presented with mixed deciduous dentition. Teeth present were first permanent maxillary and mandibular molars in all four quadrants, first permanent premolar of third quadrant, second primary molars of all four quadrants, first primary molars of first, second and fourth quadrants and primary canines of all four quadrants. Primary incisors of the first and second quadrants were retained. The primary molars in the maxillary and mandibular ridges showed carious involvement. The permanent maxillary and mandibular central and lateral incisors were missing. Hypoplastic enamel was seen. The crowns of the anterior teeth i.e. 11 and 21 were morphologically altered (shovel/peg shaped) (Fig. 2a). Multiple hyperplastic and fleshy labial freni were seen attached to the gingiva on the maxillary and mandibular ridges. In the upper jaw, the labial frenum was tightly attached into the crestal alveolar region, resulting in a diastema between the central incisors. Bilateral incomplete cleft of the

primary palate was present. (Fig. 2a, 2b). Mild serration of the anterior mandibular ridge was present.

On the basis of clinical findings and patient's history a provisional diagnosis of Ellis-van Creveld syndrome was made. Other differential diagnosis considered were Curry-Hall (CH) syndrome, Jeune Asphyxiating Thoracic Dystrophy (JATD) and McKusick-Kaufman syndrome (MKK). Following investigations were advised:

Transthoracic echo-doppler report showed normal echo study. **Orthopantomogram(O.P.G.)** showed true partial anodontia and congenitally missing 11, 12, 21, 22, 31, 32, 33, 41, 42, 43. (Fig. 2c)

Skeletal survey showed Postaxial polydactyly with an extra metacarpal and 2 phalanges in the extra digit. There was evidence of fusion of capitates and hamate on the left hand and partial fusion of capitates and hamate on the right hand. (Fig. 3a, 3b) Shortening of bilateral tibia and fibula was seen. There was evidence of screws in bilateral tibia and fibula. Patient underwent surgery for genu valgum in 2007 followed by post surgery screws placement in tibia and fibula. (Fig. 3c, 3d).

The mother complained of small sized genitalia (Fig. 4a, 4b) with history of difficulty in micturition. Genitourinary examination was suggestive of webbed penis, phimosis (Fig. 4c) and left retractile testis. There was an additional complaint of inability to read from the blackboard in the classroom.

Table 1: Comparison between features present in EVC Syndrome, Weyer's dysostosis/ Curry Hall (CH Syndrome) and JATD (Jeune Asphyxiating thoracic dystrophy)

| Clinical features | EVC Syndrome ^{1,3} | CH Syndrome ^{3,11} | JATD Syndrome ^{3,12} |
|----------------------------------|-----------------------------|-----------------------------|--|
| Thoracic dysplasia | + | - | + |
| Pulmonary hypoplasia | - | - | + |
| Respiratory insufficiency | - | - | + |
| Polydactyly | Usually involving the hands | Usually involving the hands | Inconsistent: Involving hands and feet |
| Onychodystrophy | + | + | - |
| Lip abnormality | + | + | - |
| Multiple freni | + | + | - |
| Cardiac Abnormalities | + | - | - |
| Neonatal death | +/- | - | - |
| Renal/hepatic/pancreatic changes | +/- | - | - |
| Ectodermal dysplasia | + | +/- | + |
| Disproportionate dwarfism | + | (mild)+/- | +/- |



Fig. 1 a,b: Shows short stature with long narrow thorax, shortening of limbs
c, d: Shows postaxial polydactyly of hands and dysplastic nails in hands and feet



Fig. 2A: Shows hypoplastic enamel with shovel shaped primary incisors and multiple hyperplastic labial freni, **B:** Shows mild serration of the anterior mandibular ridge with multiple labial freni, **C:** Orthopantomogram shows true partial anodontia with congenitally missing 11, 12, 21, 22, 31, 32, 33, 41, 42, 43



Fig. 3A, B: Skeletal survey shows postaxial polydactyly with extra metacarpal and 2 phalanges in the extra digit, **Fig. C, D** show post-surgery screws in bilateral tibia and fibula



Fig. 4A, B: Show small sized genitalia, 4C: Shows phimosis

Discussion

The first case of EVC syndrome was reported by McIntosh in 1933, but Richard W.B. Ellis of Edinburgh and Simon van Creveld of Amsterdam in 1940, first described this condition and defined it as EVC syndrome.¹³ Birth prevalence of EVC has been estimated to be 7 per 10,00,000 population whereas Zanwill KM *et al.* reported that among 300 reported cases of EVC syndrome, 93% had ectodermal dysplasia.⁶ Some important clinical features of this syndrome are: 1) disproportionate small stature with increasing severity from the proximal to distal portions of the limbs, and shortening of the middle and distal phalanges 2) polydactyly affecting hands, which can be unilateral or bilateral and occasionally, the feet 3) hidrotic ectodermal dysplasia mainly affecting the nails, hair, and teeth 4) congenital heart malformations occurring in about 50-60% of cases and comprising of single atrium, defects of the mitral and tricuspid valves, patent ductus, ventricular septal defect, atrial septal defect, and hypoplastic left heart syndrome. 5) There may be a valgus deformity of the knees or lumbar lordosis. Other uncommon anomalies may include urinary tract anomalies, strabismus, congenital cataracts, cryptorchidism, and epi and hypospadias. Our patient presented with small, webbed penis and left retractile testis. History of surgery for genu valgum was positive at the age of 7 years although no cardiac anomalies were present.

Oral manifestations of EVC syndrome may include enamel hypoplasia, hypodontia, conical teeth, diastema, multiple labial gingival freni, labiogingival adherence, submucosal clefts, short upper lip, presence of neonatal teeth, premature eruption, and/or exfoliation, etc. The diagnosis in our case became easy because of presence of most of the classical signs of EVC.

Differential Diagnosis

Curry-Hall (CH) syndrome (Weyer's acrofacial dysostosis; OMIM193530) is an allelic variant of EVC syndrome. An autosomal dominant condition characterized by disproportionate dwarfism, nail and tooth abnormalities, polydactyly and dysostosis.¹⁴ The two syndromes differ in mode of inheritance and phenotypic severity.¹⁵ EVC is caused by homozygous mutations (2 copies) at 1 site in the EVC gene and CH is caused by heterozygous mutation (1 copy) at this site or elsewhere in the EVC gene. The features of Jeune Asphyxiating Thoracic Dystrophy (JATD) bear a striking resemblance to those of EVC. However, polydactyly is an inconsistent feature in JATD and when present usually affects both hands and feet.¹⁶ Nail dysplasia and upper lip abnormalities (typically partial cleft upper lip connected by multiple freni to the alveolar ridge) are not seen in JATD. Pulmonary insufficiency is more frequent in JATD whereas associated heart defects are more common in EVC.¹⁷ EVC and McKusick-Kaufman syndrome (MCK, MIM 236700), both recessively inherited disorders, share postaxial polydactyly and congenital heart defect. Distinguishing characteristics are the osteochondrodysplasia and ectodermal anomalies in EVC syndrome, and hydrometrocolpos in MCK syndrome.¹⁸ Other differential diagnosis of EVC syndrome includes Saldino-Noonan syndrome, Majewski syndrome, Verma-Naumoff syndrome and Beemer-Langer syndrome.

Increased first-trimester fetal nuchal translucency thickness in association with EVC has been described at 13th week of gestation.¹⁹ The definitive diagnosis can be made by molecular diagnostic methods, which is based on homozygosity for a mutation in the EVC and EVC2 genes by direct sequencing. There is no definite cure of EVC syndrome. Treatment is usually symptomatic, which can be accomplished with multidisciplinary approach. Particularly during the

neonatal period, these patients require treatment for respiratory distress and heart failure. Oral manifestations need intense professional attention. Prognosis is coupled to the respiratory problems during the first few months of life that are attributable to thoracic narrowness and heart defects. Patients generally need the consultation of Pulmonologist, Cardiologist, Orthopedist, Physiotherapist, Plastic surgeon, Dentist, Psychologist etc.¹⁸ Patients with cardiac abnormality should be first referred to pediatric cardiologist for surgical or non-surgical management of the defect. Treatment of polydactyly, i.e. surgical removal of extra finger or toe is usually carried out in first year of life. Orthopedic surgeon along with physiotherapist improves the strength and movement of fingers/toes. Surgical intervention of knee valgus alleviates pain and improves walking. Patients with EVC syndrome should seek dental treatment in early years of their life. Dental health education for patients and their parents should include diet counseling, methods of plaque control, oral hygiene instructions, and importance of timely dental check-up. Dental care after eruption of teeth includes oral hygiene instructions, dietary counseling and effective plaque control. Children with EVC syndrome are at a high risk for caries. The treatment of present case includes the extraction of retained deciduous, restoration of carious teeth, and replacement of edentulous spans with removable artificial prosthesis. Weak eye-sight was corrected by a pair of spectacles. Patient is currently under treatment for genito-urinary disorder and genetic analysis.

Why this clinical report is important to dentists?

- Improved oral hygiene devices (e.g. Battery powered toothbrushes) may be considered to achieve adequate oral hygiene, as the dexterity is affected by polydactyly.
- Multiple freni in the mouth may result in notching/serrations of the alveolar ridges and malocclusion.
- Children with EVC are at an increased risk for dental caries.

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