



Ellis-van Creveld Syndrome: A Case Report of Two Brothers

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ABSTRACT

Ellis-van Creveld (EVC) syndrome is a rare genetic disorder with autosomal recessive transmission, clinically presenting as bilateral postaxial polydactyly, chondrodysplasia of long bones resulting in acromesomelic dwarfism and ectodermal dysplasia. Mutation in EVC1 and EVC2 gene located in a head to head configuration on chromosome 4p16 has been associated with this syndrome. In Amish community of Pennsylvania, EVC prevalence rate is 1/5,000 and, in non-Amish population, the birth prevalence is 7/1,000,000. Prenatal abnormalities include narrow thorax, shortening of long bones, hexadactyly and cardiac defects. Heart defects, especially atrial septation defects, occur in about 60% of cases. Cognitive and motor development is quite normal. The oral manifestations include upper labiogingival fusion, partial harelip, conical teeth, enamel hypoplasia, hypodontia and neonatal teeth. This case report focuses on striking oral findings and main diagnostic features of this syndrome.

Keywords: Chondroectodermal dysplasia, Ellis-van Creveld syndrome, Postaxial polydactyly.

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INTRODUCTION

Ellis-van Creveld syndrome (EVC) or meso/chondroectodermal dysplasia is a rare congenital, autosomal recessive disease.¹ The first case of EVC syndrome was reported by McIntosh in 1933, but a thorough description was given by Richard WB Ellis of Edinburgh and Simon van Creveld of Amsterdam in 1940, coined the term chondroectodermal dysplasia, which is now referred as EVC syndrome.²

It is commonly prevalent in the Amish community of Pennsylvania, with a rate of 1/5,000 and in non-Amish population, the birth prevalence is 7/1,000,000.³

Characteristic features of this syndrome include bilateral postaxial polydactyly, chondrodysplasia of long bones resulting in acromesomelic dwarfism and ectodermal dysplasia. Heart defects, especially atrial septation defects, occur in about 60% of cases.^{4,5} Cognitive and motor development is moderately normal. The oral manifestations include upper labiogingival fusion, partial harelip, short upper lip, multiple musculo-fibrous frenula, conical teeth, enamel hypoplasia, hypodontia, neonatal teeth, premature eruption, and/or exfoliation.^{4,5} Taurodontism affecting both deciduous and permanent teeth were also reported with EVC syndrome.⁶ This syndrome does not have any gender predilection, but parental consanguinity was reported in 30% of cases.²

The syndrome is known to result from an underlying genetic mutation in EVC1 and EVC2 (LBN) located in chromosome 4p16. Ellis-van Creveld syndrome is considered part of an emerging class of diseases called ciliopathies. The underlying cause may be a dysfunctional molecular mechanism in the primary cilia structures of the cell, organelles present in many cellular types in the human body.⁷ The chondrocyte primary cilia are a crucial organelle for skeletal development.⁸ The cilia defects adversely affect 'numerous critical developmental signaling pathways' essential to cellular development, and thus offer a plausible hypothesis for the often multisymptom nature of a large set of syndromes and diseases.

The clinical and radiographic evaluations help in diagnosis and treatment of EVC syndrome. As more than half of the cases with EVC have cardiac malformation, dental treatment must be performed under prophylactic antibiotic coverage. This article describes cases of EVC syndrome with most of the diagnostic clinical features.

CASE REPORT

A 15 years old boy presented with a chief complaint of missing front teeth in the upper and lower regions of the jaws. Parents gave a history of eruption of four malformed deciduous maxillary anterior teeth at 1 year of birth with their exfoliation at 5 years of age with no eruption of their successors. Eruptions of posterior teeth in both dentitions were normal. Medical history revealed congenital bone dysplasia of legs (bowing) for which the patient had undergone surgery at around 4 years of age. He also gave a history of intermittent chest

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infection since birth. The patient was the first born of a nonconsanguineous marriage and healthy parents with no history of hereditary disorders. The child was born as a result of infertility treatment taken by the mother. His younger brother aged 10 years also presented with a similar history with congenital heart valve defect and had undergone surgery for the same at 5 years of age. He also had a leg surgery at 4 years. Permanent central incisors were present in both jaws. The psychosomatic and mental development of both the siblings was within normal limits.

On general physical examination, patient had short disproportionate stature with 1.30 meter height and his gait was abnormal. Hands were presented with bilateral postaxial polydactyly and lower limbs had bowing. Hyponychia and dystrophy of all finger and toe nails were evident (Figs 1A to E). Partial upper harelip (Figs 2A to E), hypertrophy of upper labial frenum, notching of alveolar ridge and obliteration of upper labial sulcus were noticed on oral examination. Oral hard tissue examination revealed underdeveloped maxilla, missing all permanent anteriors and third molars. There is also evidence of retained deciduous canines. The orthopantomography (OPG) and cephalometry (Figs 2A to E) confirmed inspeutory findings. Hand wrist radiograph showed 6 metacarpals (Figs 1A to E).

DISCUSSION

Ellis-van Creveld belongs to short rib-polydactyly group with autosomal recessive transmission most often described in families with a history of consanguinity.² In the present case, there was no history of parental

consanguinity as well as there was no history of genetic disorders. The most striking features of EVC syndrome include bilateral postaxial polydactyly of the hands (100% of cases) as well as feet polydactyly (10% of cases) occasionally, ectodermal dysplasia (93% of cases) and congenital heart defects (60% of cases).⁹ This case demonstrated characteristic features of EVC syndrome except cardiac defect, which manifested in the sibling. Chondrodystrophia is also a most common clinical feature, affecting the tubular bones producing a serious ossification defect, leads to mesomelic shortening.⁵ Both brothers had surgical correction of lower limbs for the same.

Congenital heart malformations include single atrium, defects of the mitral and tricuspid valves, patent ductus, ventricular septal defect, atrial septal defect, and hypoplastic left heart syndrome. Genitourinary anomalies, such as agenesis and renal dysplasia, ureterectasia and nephrocalcinosis account for 20% of cases.⁵ Other uncommon anomalies seen are strabismus, congenital cataracts, cryptorchidism, and epi- and hypospadias.⁶ A case of EVC syndrome with dyserythropoiesis and another with associated perinatal myeloblastic leukemia was reported in literature.^{10,11} Digoy et al reported a unique case of EVC syndrome with congenital stridor due to the appearance of a cyst in the upper airway which impeded autonomous breathing on displacing the larynx.¹²

The diagnostic oral signs of present case were evident with hypertrophic upper labial frenum, labiokingival adherence, and oligodontia of 16 permanent teeth. After an extensive literature search, we found that our case presented with maximum number of missing permanent teeth with EVC syndrome.



Figs 1A to E: Clinical features of Ellis-van Creveld syndrome: (A) Short stature with bowing of legs, (B) bilateral postaxial polydactyly, (C) hand wrist radiograph shows six metacarpals and (D and E) dysplastic toenails



Figs 2A to E: Clinical and radiological features of Ellis-van Creveld syndrome: (A) Normal skin and hair, (B) partial upper cleft lip, (C) missing permanent anterior teeth, (D) cephalometry shows underdeveloped maxilla, (E) OPG shows all missing permanent anterior teeth and third molars, retained deciduous canines

Ellis-van Creveld syndrome comes under ciliopathies, which are caused by abnormalities in the primary cilia. Cilia dysfunction in EVC syndrome has been linked to a mutation in two adjacent genes, *EVC* and *EVC2* on chromosome 4. The *EVC* gene, identified in 2000, controls the development of (codes for) *EVC1* protein, while *EVC2*, identified in 2002, codes for a protein called limbin. Ellis-van Creveld individuals with mutations in *EVC1* or *EVC2* are phenotypically indistinguishable.¹³

The essential differential diagnoses include Jeune dystrophy, McKusick-Kaufman syndrome and Weyers syndrome. Jeune dystrophy is characterized by thoracic dystrophy, shortening of the extremities and generalized bone dysplasia but congenital heart disease, supernumerary digits and ectodermal dysplasia are absent.⁹ Ellis-van Creveld and McKusick-Kaufman syndromes (MKK), both recessively inherited disorders, share postaxial polydactyly and congenital heart defect. Distinguishing features are the absence of osteochondrodysplasia and ectodermal anomalies and presence of hydrometrocolpos in MKK syndrome. Weyers acrodistal dysostosis, the heterozygous manifestation of *EVC* gene, is an autosomal dominant condition characterized by the absence of disproportionate dwarfism, heart defect and thoracic dysplasia.⁹ Other differential diagnoses of EVC syndrome include Saldino-Noonan syndrome, McKusick-Kaufman

syndrome, Verma-Naumoff syndrome, Beemer-Langer syndrome.⁶

Prenatal diagnosis of EVC syndrome can be made by ultrasonography after the 18th gestation week, which shows growth retardation, narrow thorax, marked shortening of the long bones, hexadactyly of hands and feet, and cardiac defects. Diagnoses are also possible using chorionic villi or amniotic fluid using linked-microsatellite markers if there is previous history.¹⁴ Increased fetal nuchal translucency thickness in association with EVC has been described at 13th week of gestation.¹⁵ Diagnosis at birth can be made by observing the typical symptoms of the disease. Skeleton radiography, ECG, and echocardiography may also help in diagnosis of EVC syndrome. The definitive diagnosis is made by molecular diagnostic methods, based on homozygosity for a mutation in the *EVC1* and *EVC2* genes by direct sequencing.⁶ In this case, both brothers had ultrasound scanning during fetal life, but no diagnosis was made. Genetic counseling was not given, so prenatal evaluation for second baby was not done.

One-third of these patients die at the early age or at infancy from cardiorespiratory problems. Treatment is usually symptomatic accomplished with multidisciplinary approach of pulmonologist, cardiologist, orthopedist, physiotherapist, plastic surgeon, dental specialist, and

psychologist.⁶ The present case was referred for further dental esthetic rehabilitation.

CONCLUSION

Ellis-van Creveld syndrome is a rare AR trait with a high mortality rate in the early life. Ellis-van Creveld 1 and EVC2 do not account for the totality of EVC cases. Moreover, apart from a few constant clinical features, patients have some variable components also. Prenatal diagnosis related to intrauterine growth retardation, skeletal malformations and cardiac defects can be perceived on ultrasound scans. Further molecular exploration on other genes is needed to understand exact pathogenesis of this syndrome.

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