

## CASE REPORT

# Ellis–van Creveld syndrome

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### Abstract

Ellis–van Creveld syndrome is a rare autosomal recessive disorder caused by mutations in the *EVC* and *EVC2* gene (4p16), characterized by chondrodystrophy, postaxial polydactyly, ectodermal dysplasia and cardiac anomalies. We present the case of a 24 years old female patient with unaffected parents and an affected sister, with a personal history of surgically corrected postaxial polydactyly of both hands and atrioventricular canal. Clinical features were: a marked acromesomelic short stature (135 cm height), narrow thorax, *genu valgum*, club feet, brachydactyly, malposed toes, hypoplastic nails and teeth, diffuse alopecia, atrioventricular canal, hypoplastic mammary glands and a small goiter. Radiologic evaluation revealed short metacarpals and phalanges, capitat and hamat fusion on the left, left ulnar epiphysis with areas of osteolysis and osteocondensation, *genu valgum*, short fibulae, narrow thorax, cardiac enlargement with hilar congestion. Echocardiogram showed absence of the atrial sept and the basal portion of the ventricular sept and electrocardiogram – right bundle branch block, left anterior fascicular block and left ventricular hypertrophy. Free thyroxine, TSH and usual laboratory parameters were in the normal range with exception of ionic calcium which was low (3.8 mg/dL).

**Keywords:** Ellis van Creveld syndrome, acromesomelia, *genu valgum*, common atrium, atrioventricular canal.

### Introduction

Ellis–van Creveld syndrome is a rare autosomal recessive disorder caused by mutations in two non-homologous genes – *EVC* and *EVC2* located 4p16 in a head to head configuration. Such head to head configuration may be a common feature of the human genome and the two genes could be coordinated by the same promotor or shared elements of overlapping promoters, so, mutations of any of these genes emerge to the same phenotype [1].

The murine and bovine orthologue of *EVC2*, *LBN* which codes for limbin is strongly expressed in proliferating chondrocytes, osteoblasts and osteoclasts [2].

Analysis of the human, mouse and pufferfish genome sequence indicated that *EVC* and *EVC2* lie within a syntenic region with conserved gene order and transcription orientation encompassing the genes *NSG1*, *STX18*, *MSX1*, *C17*, *EVC* and *EVC2* [1].

Mutations in the *EVC* or *EVC2* gene also cause Weyers acrofacial dysostosis, an allelic disorder showing autosomal dominant inheritance.

Phenotypic features are comparable; Weyers acrofacial dysostosis is characterized by mild short stature, postaxial polydactyly, nail dystrophy and dental anomalies and Ellis–van Creveld syndrome is characterized by marked short stature with shortening of the distal part of the extremities (acromesomelic type), postaxial polydactyly, nail dystrophy, dental anomalies, upperlip anomalies and a cardiac malformation, usually a septal defect and often a single atrium [3, 4].

It was suggested that midline orodontal anomalies are present only in cases of *EVC* [5].

The clinical features of the Ellis–van Creveld syndrome appear indistinguishable whether the disorder is caused by mutation in the *EVC* gene or in the *EVC2* gene [1, 6]. Since *EVC* gene was identified in 2000 [7] and *EVC2* in 2002 [6] only a few mutations have been described.

### Patient and methods

We present a 24 years old female patient referred for goiter, palpitations, fatigue and tetanic crises with a personal history of bilateral postaxial hexadactyly of the hands surgically corrected at the age of six months and atrioventricular canal with Eisenmerger syndrome at the age of 18 years. Her parents were unaffected and her sister shared the same phenotypic features as the proband. Our patient was born at a normal gestational age with a birth weight of 3100 grams according to the mother.

Clinical features were: round face with erythematous cheeks, discrete palpebral oedema, hypoplastic, widely spaced teeth with frequent decays and brownish coloration, 135 cm height below the 5<sup>th</sup> centile, 47 kg weight, BMI = 27.5 kg/m<sup>2</sup>, short arms and legs with most striking shortening in the distal part (acromesomelia), *genu valgum*, club feet with malpositions of the toes, brachydactyly, diffuse alopecia, hypoplastic nails, an intense cardiac murmur on the left sternal border, hypoplastic mammary glands with hypopigmented areolae, scarce axillary and pubic hair (she reported regular menses), a small goiter and present Chvostek sign (Figure 1).

Ultrasound evaluation revealed a thyroid volume of 15.7 mL, enlargement of inferior vena cava (35 mm)

and suprahepatic veins (right suprahepatic vein 13.3 mm); echocardiogram showed absence of the atrial sept and the basal portion of the ventricular sept, mitral and tricuspid valve regurgitation (Figure 2). Electrocardiogram findings were: right bundle branch block, left anterior fascicular block, left ventricular hypertrophy with QRS enlargement (Figure 3).

Radiologic evaluation revealed a small sella turcica, hypoplasia of the metacarpals and phalanges, capitat and hamat fusion on the left, left ulnar epiphysis with areas of osteolysis and osteocondensation (Figure 4), bilateral *genu valgum*, short fibulae, periosteal tibial reaction on the anterior-lateral side (Figure 5), narrow thorax, cardiac enlargement, hilar congestion (Figure 6).

CBC, haemoglobin, ESR, BUN, cholesterol, glycemia, fT4 and TSH were in the normal range; ionic calcium was decreased (3.8 mg/dL).

### Discussions

Family history suggests autosomal recessive inheritance. Short stature is explained both by the severe cardiac defect with reduction of the cardiac index and by the presence of skeletal dysplasia.

Histopathologic examination of the fetuses with Ellis–van Creveld syndrome revealed chondrocyte disorganisation in the physal growth zone of long bones and to a lesser extent in the central physal growth zone of the vertebrae [8].

The short stature is present at birth and limb shortening is progressive, symmetrical and affects especially the distal parts, leading to disproportionate dwarfism (adult height ranges between 105 and 155 cm). Polydactyly is bilateral and postaxial in the hands and in 10% of cases is observed in the feet. Other skeletal anomalies include narrow thorax, *genu valgum*, lumbar lordosis, broad hands and feet [3, 4, 7].

Oral anomalies are represented by short upper lip, multiple frenula, and broad alveolar ridges. Dental anomalies include neonatal teeth, partial anodontia, small teeth with delayed eruption and enamel hypoplasia [9].

Nails are hypoplastic or absent and hair is occasionally sparse. Cardiac anomalies occur in 50–60% of patients: common atrium (40%), atrio-ventricular canal, septation defects, patent *ductus arteriosum* [10, 11].

In some cases genitor-urinary anomalies (hypospadias, epispadias, cryptorchidia, vulvar atresia, renal agenesis, megaureters, nephrocalcinosis) and central nervous system anomalies are reported [12].

In our patient the association of acrosomic short stature, hexadactyly of the hands, *genu valgum*, ectodermal dysplasia and atrioventricular canal allowed the positive diagnosis of Ellis–van Creveld syndrome.

### Conclusions

Ellis–van Creveld syndrome is a rare recessive disorder with a complex phenotype (disproportionate dwarfism and cardiac defects that might be life threatening) imposing multidisciplinary approach.

Prenatal diagnosis is desirable considering the high mortality rate and the poor quality of life of affected subjects and would also provide the basis for genetic counseling.

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Figure 1 – Phenotypic aspect

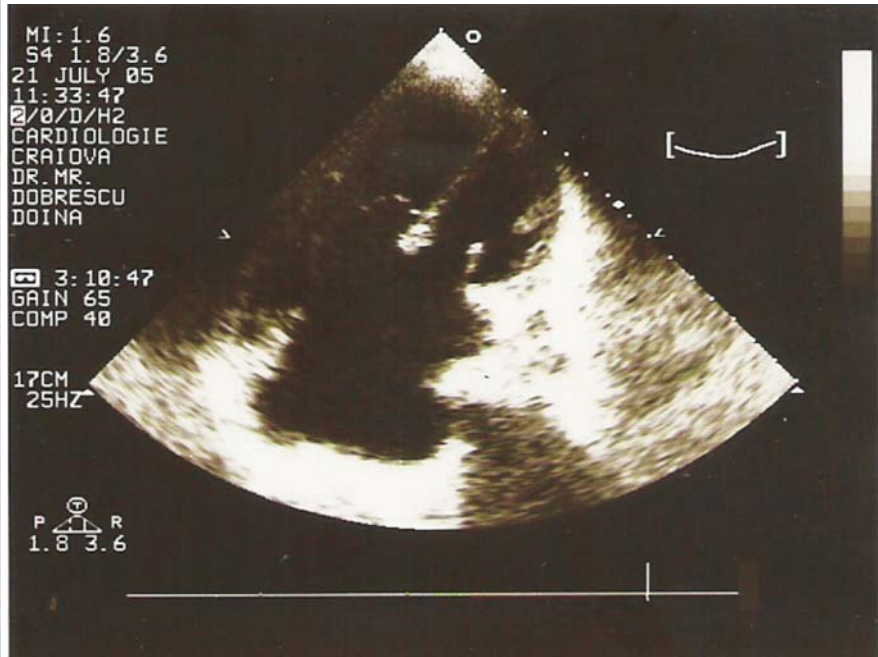


Figure 2 – Echocardiogram absent atrial sept, ventricular basal septal defect, atrioventricular canal

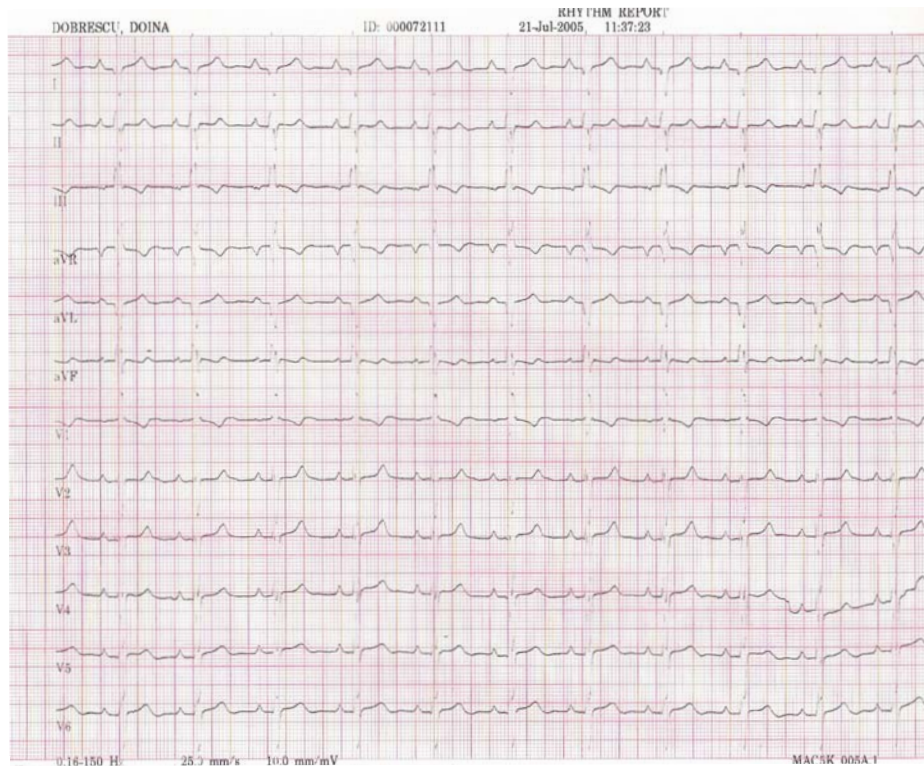
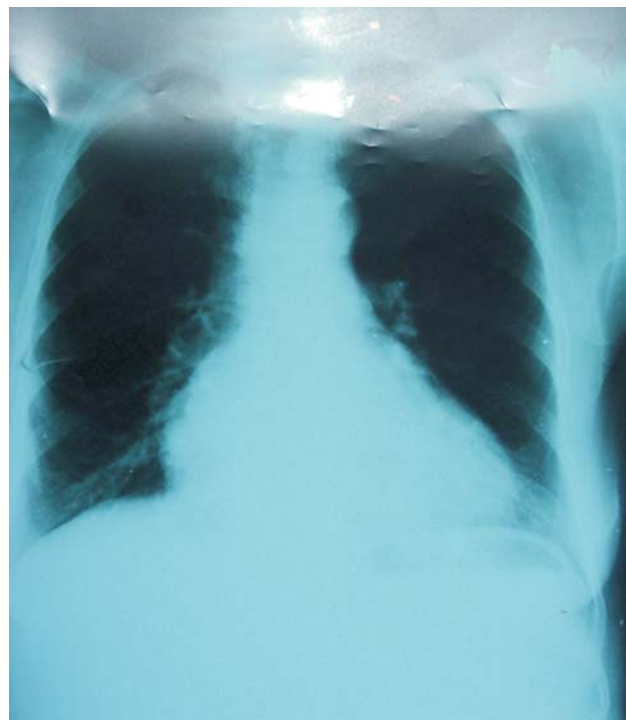
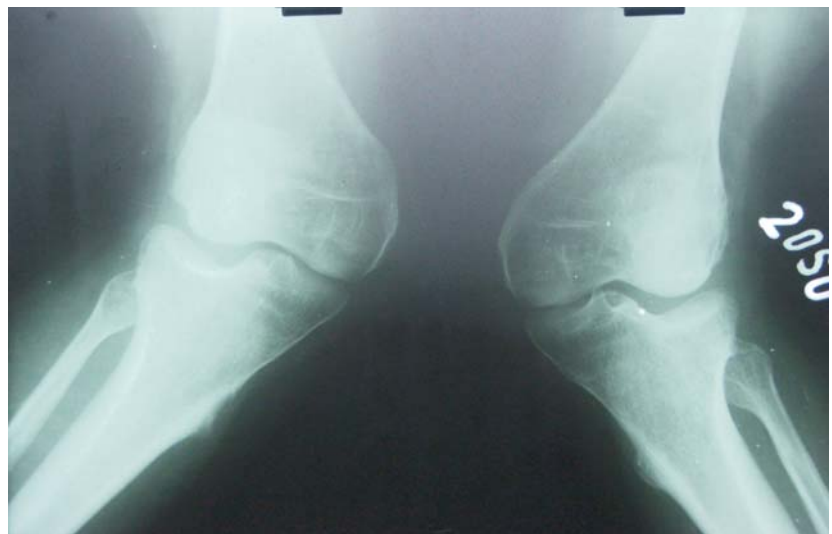


Figure 3 – Echocardiogram showing right bundle branch block, left anterior fascicular bloc, left ventricular hypertrophy



**Figure 4 – Hand X ray: surgically corrected hexadactyly, hypoplastic metacarpals and phalanges, abnormal left ulnar epiphysis**

**Figure 5 – Genu valgum, short fibulae, periosteal tibial reaction**



**Figure 6 – Chest X-ray narrow thorax, cardiac enlargement, hilar congestion**