Ellis-van Creveld Syndrome in Two Filipino Siblings

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ABSTRACT

We describe two siblings who presented with features of Ellis-van Creveld (EvC) syndrome or chondroectodermal dysplasia, a disproportionate short-limb dwarfism. They were born to a non-consanguineous Filipino couple. The older female child, who was examined at 6 years of age, had partial oligodontia on the upper anterior alveolar ridge with a short fixed frenulum between the inner upper lip and gum, a very large atrial septal defect (ASD) which was repaired at the age of 5 years, a long torso and short extremities, postaxial polydactyly on both hands with 5th digit clinodactyly, dysplastic and hypoplastic nailbeds on the fingers and toes, brachydactyly, and short stature. Her cognitive and gross motor development remained at par with age. Her radiologic findings which included short ribs, fusion of the capitate and hamate, cone-shaped epiphysis of the middle phalanges, and short tubular bones, were consistent with EvC syndrome. Orthopedic intervention was done to correct the genu valgum deformity while dental intervention included partial dentures fitted on her. The partial dentures had improved her facial profile, speech, and even her general disposition. The younger male sibling had a long neck, hyperextended back, a small chest circumference, and postaxial polydactyly. He died at 2 weeks of age due to respiratory complications from the narrow thoracic cage. The 38 y/o mother of both patients was counseled regarding the 25% recurrence risk, in line with the autosomal recessive pattern of inheritance of EvC syndrome.

Key Words: short limb dwarfism, Ellis-van Creveld syndrome, chondroectodermal dysplasia

Introduction

Ellis-van Creveld (EvC) syndrome, also called chondroectodermal dysplasia, is an autosomal recessive condition caused by a mutation on the *EVC1* or *EVC2* gene found on chromosome 4p16.[1] The classical phenotypic features are short rib/polydactyly skeletal dysplasia, natal teeth, oral frenulae, other features of ectodermal dysplasia, and congenital heart disease in 50-60% of the affected cases. Prevalence is estimated to be 1 in 200,000.[2] There are reports of this condition being found in Asian countries, aside from the classic reports among the Amish community and in an aboriginal kindred in Australia.[3,4,5,6] Here we present two Filipino siblings with the classical features of EvC.

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Case Report

The first child was a 6 year old female, the oldest child of a non-consanguineous Filipino couple. She was born to a 30 y/o G1P0 mother after an unremarkable pregnancy. No prenatal ultrasound examination was done. She was born term by normal delivery, with a birth weight of 2.9 kg, and with good activity. Polydactyly, growth retardation, and a cardiac murmur were noted in the neonatal period. A 2D-echocardiography revealed a large atrial septal defect (ASD). Cardiac surgery was done at 5 years of age. Medical consults during this period were for respiratory infections and occasional episodes of edema. Other physical abnormalities observed were missing midline teeth, long torso, broad hands, short fingers, and hypoplastic and dysplastic nails. Post surgery, she continued to have slow weight gain and short stature. At the time of examination at 5 years of age, her weight of 12.5 kg and height of 93 cm were both below the 5th percentiles. She had a broad bulbous nose, large ears, thin upper lip adherent to the gingivae, absent midline teeth, some carious teeth, a small barrel chest, widely spaced nipples, a midline surgical scar over the sternum, broad palms with short fingers and post-axial polydactyly, bilateral clinodactyly, and midphalanx hypoplasia of the last digit, hypoplastic fingers with absent nailbeds, dysplastic toenails, overlapping 3rd and 4th toes, genu valgum and a prominent bony sacral prominence (Figure 1). Examination of the heart, abdomen and genitalia were normal. She had a wide based gait and was unable to do a heel-to-toe walk. Certain fine motor skills were affected by her short digits such as doing up buttons and grasping certain objects. Her cognitive skills remained normal. The radiographic findings included short ribs, fusion of the capitate and hamate, cone-shaped epiphysis of the middle phalanges, short tubular bones, and poorly developed bilateral tibial epiphyses, an extra rib on L1 and spina bifida occulta at S1.

The second child was the younger male sibling of the proband. Upon delivery, he was noted to have a long neck, polydactyly in all four extremities, a small chest circumference, hyperextended back and an empty scrotum (Figure 2). He died after two weeks due to respiratory complications. There were no other investigations done.

Both parents are unaffected. The family pedigree showed a 2 month old 2nd degree cousin who died due to an isolated cyanotic heart problem and a 3rd degree relative with unilateral polydactyly but with no other features (Figure 3).

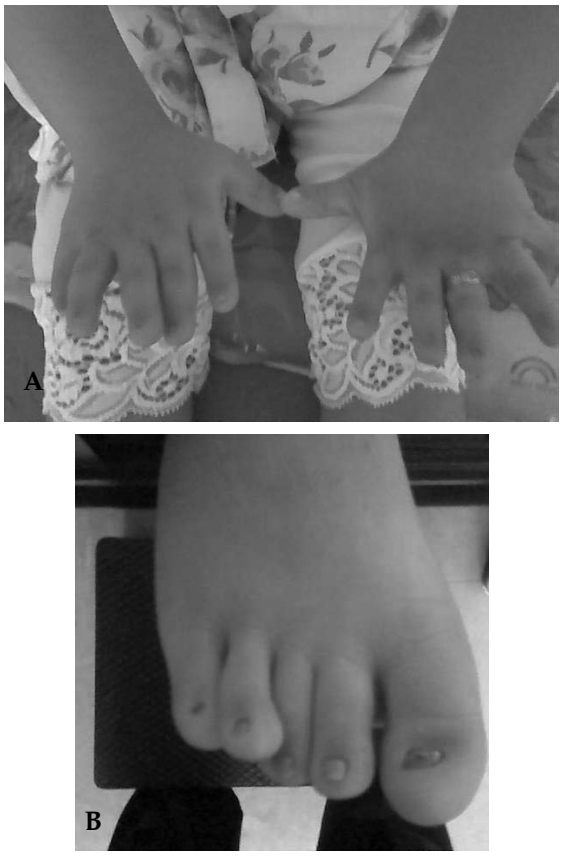

Figure 1. A) Bilateral postaxial polydactyly. B) Dystrophic toenails with overlapping toes.

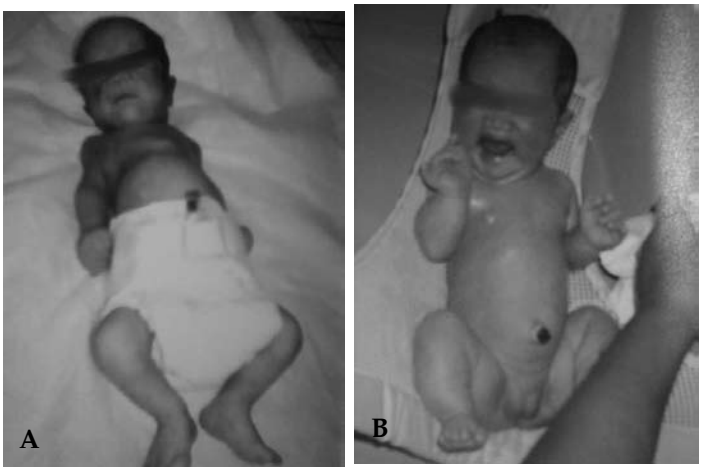

Figure 2. A) Male sibling (post-mortem). B) Female sibling during the neonatal period. Both exhibiting the long torso and short limbs.

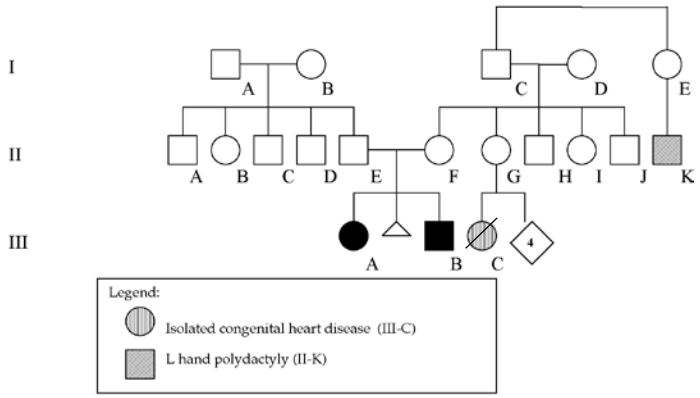

Figure 3. Family pedigree

Discussion

The features of the two siblings which included short stature with a long trunk, short limbs, congenital heart disease (ASD), dental abnormalities, and polydactyly are typical of EvC syndrome. However, the first child's extra rib and spina bifida occulta have not been reported as usual phenotypic features.[2,5] Moreover, only the male infant had polydactyly of the feet, which occurs in only 10-15% of affected cases.[7,8] He also had more severe complications from the small thorax while the sister managed to survive the neonatal period. These findings support the variable expression of the condition even among members of the same family. At the present time, clinical diagnosis of EvC syndrome is primarily based on physical features and characteristic radiographic findings.[9, 10]

The genes responsible for EvC are the *EVC1* or EVC gene and *EVC2* or Limbin gene. Identification of mutations in the *EVC1* and *EVC2* genes were seen in only two thirds of 65 affected patients.[1,11] Genetic heterogeneity has been used to explain why not all identified patients have mutations in the identified genes for EvC syndrome. The function of these genes are not fully understood but thought to be involved in regulation and differentiation signaling among ectodermal and mesodermal derivatives and in skeletal formation mechanisms.[12] Most recently, Ruiz-Perez, et al. discovered that EVC is involved in the regulation of bone growth, particularly as a positive mediator in the Indian hedgehog (Ihh)-regulated pathway.[13] This Ihh is one of the secreted signaling molecules which affects the chondrocyte proliferation and differentiation in the growth plates.[14] Genotype-phenotype correlations still remain to be elucidated. A role in cardiogenesis has also been theorized because of the high incidence of congenital heart disease in EvC syndrome, but has not been proven.

The management of patients with EvC necessitates a multidisciplinary approach which include consults to cardiology, pulmonary, dental, orthopedic, physical and occupational therapy, and plastic surgery evaluations.[4,10] Approximately 30% of affected children die early in infancy due to cardiorespiratory problems.[4] Such cardiorespiratory

problems contributed to the demise of the male infant while cardiac surgery improved the survival and prognosis of the older sibling. Dental problems are frequent and well described in many articles.[4,6,7,8,10] The oral findings of upper labiogingival adhesion with multiple short frenulae, adontia, microdontia, conical teeth with short roots, and serrated gums in the female patient are consistent with these reports. No malocclusion was noted in the older child. Dental treatment plans for EvC patients usually follow multiple stages, including the use of partial dentures and surgical orthodontic procedures.[15] Currently, she has been fitted with upper and lower partial U-shaped dentures which has improved her profile and even general attitude and well-being (Figure 4). Bone deformities, such as genu valgum and patellar dislocation which are present in the affected female patient require regular follow up. Treatment options include corrective osteotomy of the tibia for the valgus deformity which is considered a very serious complication of this condition.[16] A few patients have had limb lengthening at the tibia using distraction osteogenesis.[17] At present, no immediate surgery is planned on this patient. The final adult height has been reported to be between 119-161cm.[10] However, there has been a report of 8 patients treated with growth hormone for short stature with some of them having favorable results.[18]

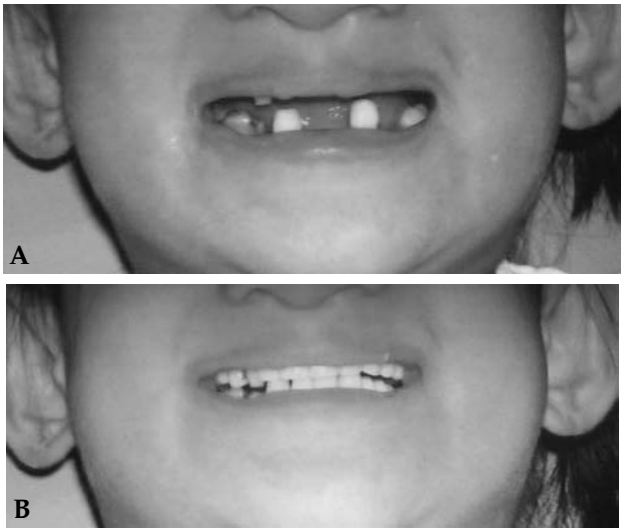

Figure 4. A) Dental anomalies in the patient. B) Patient wearing the partial dentures.

Since most survivors have normal intelligence, the finding of EvC syndrome in a child should warrant optimistic counseling for the family. The patient's cognitive development is at par with age.

Being an autosomal recessive condition, there is a 25% chance of having another affected child with every pregnancy and this must be stressed to the parents. Prenatal diagnosis in the local setting is possible through antenatal ultrasound examination by looking for features suggestive of EvC syndrome such as a narrow thorax, short femurs, polydactyly, and a congenital heart defect.[6,10]

Conclusion

Diagnosis of EvC syndrome can easily be done on clinical grounds, as seen in the 2 cases presented. It is important to recognize the classical features as well as the characteristic radiographic findings. A multidisciplinary team approach is essential in managing the associated medical complications.

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