Ellis–van Creveld Syndrome with Sagittal Craniosynostosis

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Abstract

Keywords

- Ellis–van Creveld syndrome
- chondroectodermal dysplasia
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- scaphocephaly

Ellis–van Creveld syndrome (EVC) is a rare disorder (the incidence is estimated at around 7/1,000,000) characterized by the clinical tetrad of chondrodystrophy, polydactyly, ectodermal dysplasia, and cardiac anomalies. Sagittal synostosis is characterized by a dolichocephalic head shape resulting from premature fusion of the sagittal suture. Both are rare disorders, which have never been reported together. We present a case of EVC and sagittal synostosis. We report the clinical features of a Hispanic boy with EVC and sagittal craniosynostosis who underwent cranial vault remodeling. The presentation of this patient is gone over in detail. A never before reported case of EVC and sagittal synostosis is presented in detail.

Ellis–van Creveld syndrome (EVC) is an inherited, autosomal recessive disorder characterized by the clinical tetrad of chondrodystrophy, polydactyly, ectodermal dysplasia, and cardiac anomalies.^{1–3} Affected individuals manifest clinically with disproportionate short-limb dwarfism, short ribs, post-axial polydactyly, and dysplastic nails and teeth. Cardiac defects occur in approximately 50 to 60% of cases and often involve the atrial septum.^{2,4} Cognitive and motor development is unaffected.

Richard W. B. Ellis of Edinburgh and Simon van Creveld of Amsterdam first described the condition in 1940.¹ Since then, only 300 cases reported as of 2000.⁵ The incidence is estimated at around 7/1,000,000.² The condition is more common among the American Amish, but it is known to affect all races with equal sex predilection.^{2,3} Consanguinity is implicated in approximately one-third of the cases.⁵ EVC has been linked to mutations in the *EVC1* and *EVC2* genes on the short arm of chromosome 4.⁵ Individuals with mutations in either *EVC1* or *EVC2* are phenotypically indistinguishable, and one-third of individuals clinically diagnosed with EVC are not found to

have either mutation.^{6,7} Definitive diagnosis is made based on mutations in *EVC1* and *EVC2*.

Sagittal craniosynostosis is characterized by the premature fusion of the sagittal suture. Growth is inhibited perpendicular to the sagittal suture, leading to dolichocephaly. Sagittal craniosynostosis occurs in approximately 1/2,000 to 1/7,000 births, and is the most common craniosynostosis.^{8,9} The purpose of this article is to present a case of EVC and sagittal synostosis, the combination of which has never been reported in the literature.

Case Report

A Hispanic male was found to have polydactyly on prenatal ultrasound in a mother with polyhydramnios. A subsequent fetal MRI showed body wall edema, mesomelic shortening and mild bowing of the long bones, bilateral postaxial polydactyly, short ribs, premature ossification of the femoral epiphysis, a dolichocephalic skull, and a possible lumbosacral vertebral anomaly. Fetal echo showed mild right ventricular

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Fig. 1 (a) Frontal view of skull demonstrating sagittal suture ridging, significant soft tissue swelling about the neck and short, and angular ribs. (b) Lateral view of the skull shows dolichocephalic head shape and a posterior parietal buckle fracture.

hypertrophy and dilation with systolic function. Amniocentesis was done for amnioreduction and genetic testing at 33 weeks. Routine karyotype was 46,XY, normal male. The chromosomal microarray analysis was normal, but the whole-exome sequencing revealed a heterozygous mutation in the *IFT140* gene. The mother's medications included pre-natal vitamins and steroids before amnioreduction.

The patient's older sister carries a clinical diagnosis of EVC. She underwent sequencing and deletion/duplication analysis, and no mutation was found in *EVC1* or *EVC2*, which can occur in one-third of cases. A third-generation pedigree was collected and there was no known consanguinity—both the mother and father's families were from the same region of Mexico but from different cities.

At birth, the patient was diffusely edematous, particularly pronounced in the lower face and eyes, with a dolichocephalic head, small anterior fontanelle, narrow temporal region, and overriding sutures. Ears were pointed, low set, and posteriorly rotated. Right ear measured in the 3rd percentile at 3 cm. There was unfolding of the helices bilaterally with attached

ear lobes. The palate was intact with a posteriorly set tongue. Excessive nuchal skin was noted. The nipples were widely spaced at 12 cm. The right hand, palm, and finger all measured approximately in the 3rd percentile (5.25, 3.25, and 2 cm, respectively), consistent with disproportionate dwarfism. Upper and lower extremities showed a predominance of rhizomelic to mesomelic shortening and excessive skin folds. Postaxial polydactyly of the upper and lower extremities was present. Hypoplastic nails of the toes bilaterally were seen as well. Extremities exhibited decreased tone.

Skeletal survey confirmed sagittal craniosynostosis and a posterior parietal buckle fracture (→Fig. 1). Shortening and mild angular deformities of the bilateral ribs were noted. Upper extremities showed bilateral valgus deformities of the humeri, varus deformities of the proximal ulnas, radial head dislocations, and postaxial polydactyly exhibiting fusion at the base of the fifth and sixth metacarpals (→Fig. 2). Lower extremities showed bilateral mild varus deformities of the femurs, mesomelic shortening, relative overgrowth of the fibulas, and mild brachydactyly (→Fig. 3). An echocardiogram confirmed a

Fig. 2 Skeletal survey. (a) Left upper extremity demonstrates valgus deformity of the humerus, varus deformity of the proximal ulna, radial head dislocation and postaxial polydactyly, similar findings were seen on the right. (b) Right hand demonstrates postaxial polydactyly with fusion at the base of the 5th and 6th metacarpals.

Fig. 3 Radiograph of the right leg demonstrates mild varus deformity of the femur, mesomelic shortening, relative overgrowth of the fibula and mild brachydactyly, similar findings on the left.

moderately dilated and hypertrophied right ventricle with normal systolic function and revealed a small patent ductus arteriosus and a small secundum atrial septal defect.

The patient underwent surgery for cranial vault remodeling at 9 months to correct the scaphocephalic deformity. Preoperative computed tomographic scan demonstrated mild cervical kyphosis and a hypoplastic dens in addition to shortened mandibular rami and scaphocephaly with com-

plete fusion of the anterior suture and frontal bossing (►**Fig. 4**). Thorax was narrowed as well as the cervical vertebral bodies with a more focal narrowing at the level of C1 secondary to an unfused Kerckring ossicle. The patient underwent middle posterior cranial vault remodeling. A sagittal craniectomy and multiple parietal barrel stave osteotomies were performed via the modified Pi technique for sagittal suture craniosynostosis. The patient tolerated surgery well without complications.

Discussion

EVC is an autosomal recessive skeletal dysplasia. Recently, EVC has been included in a group of human genetic disorders known as ciliopathies characterized by a dysfunctional molecular mechanism in the primary cilia.¹⁰ Mutations in the *EVC1* and *EVC2* genes have been found in approximately two-thirds of the EVC cases.^{5,6} No known mutation has been identified in the other one-third.⁷ In this case, the patient and his older sister both carried a clinical diagnosis of the EVC, without mutation in either *EVC1* or *EVC2*.

The cardinal features of EVC—short-limb dwarfism, polydactyly, ectodermal dysplasia of the nails, hair, and teeth, and congenital heart defects—are all present in our patient.^{1–3} Polydactyly of the ulnar side of the hands is seen in all individuals with EVC. Polydactyly of the feet, a condition reported in only 10% of EVC cases, was also present in our patient.¹¹ Cardiac anomalies are reported in roughly half of EVC cases, most commonly involving the atrium.^{2,4} Cardiac defects are associated with a higher morbidity in the EVC.¹²

Sagittal craniosynostosis is not known to be associated with EVC, and this case appears to be the first report of sagittal synostosis in a patient with EVC. It was first believed that this case may have been a presentation of cranioectodermal dysplasia. Cranioectodermal dysplasia is a rare developmental disorder that resembles EVC. Affected individuals often have pronounced dolichocephaly with sagittal suture synostosis, narrowed thorax, ciliopathy, rhizomelic shortening of the long bones, and congenital heart disease. However, polydactyly, as was seen in this patient, is not characteristic of this disorder.¹³ It is possible that this case represents a variant

Fig. 4 Preoperative computed tomographic three-dimensional reconstruction (a) top-down view demonstrates anterior sagittal suture fusion (b) oblique view demonstrates frontal bossing.

of cranioectodermal dysplasia with polydactyly, but given the sister's clinical diagnosis of EVC it was considered more consistent with EVC. Cranioectodermal dysplasia and EVC have significant overlap in their phenotypes and can be difficult to distinguish. This is the first known case of EVC and sagittal synostosis.

Products/Devices/Drugs

None.

Financial Disclosures/Commercial Associations

None.

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