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CASE REPORT

A case of Ellis-van Creveld syndrome in Palestine

Lila H. Abu-Hilal[1*], Balqees M. Mohamad[1], Bashar K. A. Douden[1], Mohammad Adwan[1], Rayan Salahaldin[1], Sajeda S. Subuh[2]

ABSTRACT

Background: Ellis-van Creveld syndrome causes chondral and ectodermal abnormalities. Although the precise prevalence is still unknown, the Amish group in the United States most frequently reports this uncommon sickness.

Case Presentation: The reported case was of a 2-year-old female patient who presented with dysmorphic facial and digital features, polydactyly, dwarfism, inability to walk normally, and multiple cardiac abnormalities. On examination, the patient's growth parameters were below the 5th percentile, with a weight of 10 kg, height of 72 cm, and head circumference of 45 cm (10th percentile). The patient had sparse, thin hair with bi-temporal narrowing and frontal bossing. The patient was advised to undergo surgery, which included atrioventricular canal repair, atrial septal defect closure, ventricular septal defect closure, mitral and tricuspid valve cleft closure, and left superior vena cava tunneling to the right atrium. One week after the operation, the patient developed sudden bilateral visual impairment, with no hemorrhage or space-occupying lesions. The patient was discharged on day 15 after surgery, and although stable, the visual impairment remained.

Conclusion: This case is believed to be one of the first cases in Palestine, as this disease is very rare worldwide. The outcomes of the condition are thought to be well predicted by prenatal discoveries.

Keywords: Ellis-van Creveld syndrome, chondral and ectodermal abnormalities, Palestine, case report.

Introduction

Ellis-van Creveld syndrome (EVC) is a rare genetic disorder that affects many different organs, including the heart, bones, nails, teeth, and skin. This disorder is characterized by short ribs, polydactyly (extra fingers or toes), growth retardation, and ectodermal and cardiac anomalies (1). The mutations in the *Ellis-van Creveld* genes (*EVC1* and *EVC2*) on chromosome 4p16 have been identified as the cause of this syndrome (2).

Regarding cardiac anomalies, about 50%-60% of people with EVC have congenital heart defects, with the most common being the single atrium. Other heart defects include atrioventricular (AV) canal defects, persistent left superior vena cava (LSVC), and tricuspid atresia. These heart defects can range from mild to severe and might require medical or surgical intervention (3).

The exact prevalence of EVC is unknown, but it is more common in certain populations, such as the Amish group in the United States. This disorder is inherited in an autosomal recessive manner, which means that a person must inherit two copies of the mutated gene, one from each parent, to develop the disorder (1).

In the presented case, a clinical case of a 2-year-old female with multiple dysmorphic features was described, she was presented to the study hospital for diagnostic and hemodynamic catheterization, as she was diagnosed with antenatal cardiac problems.

Case Presentation

A 2-year-old female toddler with bilateral hand polydactyly was referred to the study hospital for diagnostic and hemodynamic catheterization. Antenatally, she was diagnosed with a cardiac issue and dwarfism. The patient was born at full-term with a weight of 3.5 kg and exhibited

Correspondence to: Lila H. Abu-Hilal
*Medical Graduate, Faculty of medicine, Al-Quds University, Jerusalem, Palestine.
Email: lila_abuhilal@yahoo.com
Full list of author information is available at the end of the article.
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normal newborn behaviors, such as immediate crying and passing urine and meconium within 24 hours. Her mother noticed cyanosis around the patient's mouth and feet when she cried or after a bath, which spontaneously resolved. Additionally, she noted the presence of dysmorphic features.

The patient came from a consanguineous family with a healthy 25-year-old father and a 23-year-old mother. No other family members had similar hand deformities or dwarfism, but the patient's cousin on her mother's side had a cardiac issue, and his brother died at the age of 2 months from a similar cardiac condition (Figure 1).

The patient was breastfed for up to 4 months and then transitioned to formula. The introduction of solid food into her diet was delayed to 1 year of age due to delayed teething.

Developmentally, the patient was able to stand but experienced difficulty walking and had limited speech. The patient resides in a poorly ventilated and humid home with low socioeconomic status, but the environment is free of smoking and pets.

On examination, the patient's growth parameters were below the 5th percentile, with a weight of 10 kg, height of 72 cm, and head circumference of 45 cm (10th percentile). The patient had sparse, thin hair with bi-temporal narrowing and frontal bossing. In addition, the patient exhibited a depressed nasal bridge, prominent eyelashes, low-set ears of normal size, a thin upper lip, long philtrum, pink mucous membranes, and tongue, and multiple lower labial frenum with abnormal teeth and multiple cavities. The patient also had postaxial polydactyly on both hands, hypoplastic toenails, and short-limb dwarfism (Figure 2).

Neurological examination showed normal power and tone with normal reflexes but with difficulty walking and an unbalanced gait. These findings were consistent with EVC syndrome.

Vital signs included a temperature of 36.7°C, heart rate of 135 beats per minute, respiratory rate of 38/minute, blood pressure of 102/58 mmHg, and O_2 saturation of 88%.

Laboratory tests, including a complete blood count, and kidney and liver function tests, were normal. Echocardiography showed a unique presentation of a transitional AV canal, small ventricular septal defect (VSD), almost common atrium, mitral and tricuspid cleft, and left-sided SVC draining to the roof of the left atrium. Cardiac catheterization was performed, which showed a complete AV canal defect and severe pulmonary hypertension. The patient was advised to undergo surgery, which included AV canal repair, atrial septal defect closure, VSD closure, mitral valve cleft closure, tricuspid valve cleft closure, and LSVC tunneling to the right atrium. Post-procedure echocardiography showed complete AV canal repair, with no residual VSD or ASD.

One week after the operation, the patient developed sudden bilateral visual impairment, and an urgent brain computed tomography was performed, which showed no hemorrhage or space-occupying lesions. The ventricular system was normal, with no hydrocephalus or midline shift. An ophthalmic exam showed a clear cornea, clear lens in both eyes, and flat retina in both eyes.

Visual evoked potential testing was normal. A geneticist was consulted and found that the visual impairment was not related to the syndrome. Brain magnetic resonance imaging was done and showed a high-flare signal-diffusion restriction over the right occipital lobe, resembling subdural blood/empyema. The neurosurgery team was consulted, and no intervention was deemed necessary. The patient was discharged on day 15 after surgery, and although stable, the visual impairment remained.

The patient's mother was pregnant at this time, and it was discussed with the family that the condition is inherited. In future pregnancies, there is a 25% chance that the child would be affected, and whole exome sequencing was advised. However, due to the family's poor financial status, they couldn't afford the costs.

Discussion

Ellis-van Creveld syndrome (EVC) is an autosomal recessive disease caused by a mutation in *EVC1* which was identified in 2000 and *EVC2* which was identified in 2002. Both of these genes are located on chromosome 4p16 in the short arm of chromosome 4 (2), EVC is a rare disorder worldwide but it is most common in the Amish community of Pennsylvania in the USA and this is obvious by the huge difference between

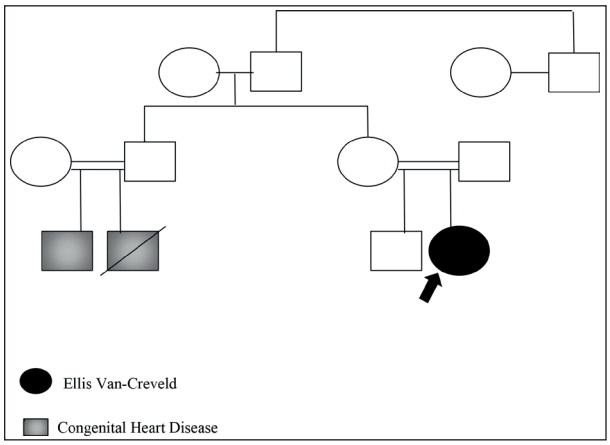

Figure 1. *Pedigree showing family members with congenital heart conditions.*

Figure 2. *Physical features of the patients. (A) Multiple lower labial frenulum, (B) dwarfism, and (C) postaxial polydactyly.*

Amish prevalence which is 1:5,000 and the worldwide prevalence which is 1:1,000,000 (1).

Chondroectodermal dysplasia is another term for EVC first reported by Richard W. B. Ellis and Simon Van Creveld in 1940, *EVC*1 and *EVC2* mutations disrupt Hedgehog signaling, and therefore, the ciliary function is important for vertebral development (3).

EVC patients have short stature, short forearms, bent lower limbs, nail abnormalities, small ribs, narrow thorax, teeth abnormalities, polydactyl (1) and 50%-60% of the patients have congenital heart defects like AV canal defect, VSD, common atria, persistent LSVC and pulmonary venous connection abnormalities (3). Diagnosis of EVC might be made based on a thorough clinical evaluation and medical history, as well as genetic testing.

Studies have shown that different mutations in *EVC1* or *EVC2* genes could result in a wide range of clinical phenotypes, including variation in the severity of skeletal and cardiac abnormalities, as well as differences in the development of teeth and nails. The genotype-phenotype connection in EVC is therefore complex, with multiple genetic and environmental factors contributing to disease manifestation. One study discusses the genotype-phenotype connection in individuals with EVC syndrome and profound deafness.

The authors identified mutations in the *EVC1, EVC2*, and *Transmembrane Channel-like 1* genes in affected individuals and found that different mutations in these genes resulted in a range of clinical phenotypes. Specifically, they observed variability in the severity of skeletal abnormalities, as well as differences in the age of onset and severity of deafness. The study highlights the complexity of the genotype-phenotype connection in EVC and the need for personalized approaches to the treatment and management of the disorder (4).

Individuals with EVC need to receive regular medical care from a team of healthcare professionals, including a cardiologist, pulmonologist, orthopedic specialist, and dentist. This multidisciplinary approach could help to manage the various symptoms and complications of the disorder.

Treatment for EVC depends on the specific symptoms and complications of the disorder. For example, heart defects might require surgical intervention or medication to manage symptoms. Individuals with EVC might also need physical therapy, orthopedic devices, and other supportive treatments to manage growth retardation, short stature, and other physical symptoms (5). On the bright side, if the patients survive the infancy stage they would have a life expectancy similar to that of ordinary people, with the record of the oldest living EVC patient being 82 years old (1).

Some prevention strategies that could be used to manage the condition include early diagnosis through genetic testing, genetic counseling for affected individuals and their families, and regular monitoring for complications such as heart defects and dental abnormalities. Additionally, lifestyle modifications such as a healthy diet and regular exercise could help to minimize the impact of EVC (6).

In recent years, gene therapy has emerged as a promising new treatment approach for rare genetic diseases. Gene therapy involves introducing healthy copies of the affected gene into the patient's cells, with the goal of correcting the underlying genetic defect. While gene therapy for EVC is still in the experimental stages, there have been some encouraging results in animal models. For example, a recent study in mice with EVC found that gene therapy was able to restore normal limb development and growth (7).

Overall, while there is still much research to be done, the future of gene therapy for rare genetic diseases like EVC is promising. As genetic technologies continue to advance, would be able to offer safe and effective treatments for these devastating conditions in the future (7).

The presented case is one of the first reports of EVC in Palestine and includes cardiac manifestations of transitional AV canal, small VSD, common atrium, mitral and tricuspid cleft, and LSVC draining to the roof of the left atrium. And this case adds to the understanding of the syndrome and might serve as a reference for future cases.

Conclusion

This patient presented with a unique combination of cardiac anomalies, including left persistent SVC draining into the left atrium. The rarity of this condition in Palestine makes this case a valuable addition to the medical literature. Given the potentially severe consequences of this disease, such as high mortality and reduced quality of life, it is important to consider the prenatal diagnosis. This would not only help diagnose affected fetuses but also facilitate early treatment and management. The reported case underscores the importance of recognizing and diagnosing EVC early in order to provide proper care and support for those affected by this condition. Further research into the genetic basis of this disease and its associated anomalies could lead to better understanding and treatment options in the future. To register such occurrences and raise awareness among groups with a high rate of consanguinity marriage, more work has to go into creating a national registry of uncommon conditions.

List of Abbreviations

AV	Atrioventricular
EVC	Ellis-van Creveld syndrome
LSVC	Left superior vena cava
SVC	Superior vena cava
VSD	Ventricular septal defect

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Consent for publication

Due permission was obtained from the parents of the patient to publish the case and the accompanying images.

Author contributions

All the authors listed in this article had a contribution to the acquisition of data from the patient's parents, drafting and writing the manuscript along with final approval of this version to be published.

Author details

Lila H. Abu-Hilal[1], Balqees M. Mohamad[1], Bashar K. A. Douden[1], Mohammad Adwan[1], Rayan Salahaldin[1], Sajeda S. Subuh[2]

1. Faculty of medicine, Al-Quds University, Jerusalem, Palestine
2. Faculty of Medicine, Mutah University, Amman, Jordan

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