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CASE REPORT

Ellis van Creveld syndrome in a Tunisian child revealed by an Eisenmenger syndrome

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Abstract Ellis-van Creveld syndrome (EvC) is an autosomal recessive inherited disease resulting from mutations in EVC1 or EVC2. Patients with this condition normally have chondrodysplasia, postaxial polydactyly, ectodermal dysplasia and congenital heart defects. We report the case of a 13-year-old Tunisian child who was admitted for cyanosis and acute heart failure. On clinical examination, he presented with typical features of EvC, cyanosis and dyspnea. EvC was confirmed by genetic tests, and echocardiography showed a partial atrioventricular canal defect with supra-systemic pulmonary artery pressure. The patient was treated; however, the evolution was fatal.

1. Introduction

Ellis–van Creveld syndrome (EvC syndrome, MIM 225500), or chondroectodermal dysplasia, is a rare autosomal recessive inherited disease that is characterized by a tetrad of cardinal features including disproportionate dwarfism, bilateral postaxial polydactyl of hands, ectodermal dysplasia, and congenital cardiac malformations [1].

List of abbreviations: ACE inhibitor, angiotensin-converting-enzyme inhibitor; CA, common atrium; EvC, Ellis–van Creveld syndrome; PAH, pulmonary arterial hypertension; PCCC, paediatric cardiac care consortium.

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Approximately two-thirds of affected individuals have a congenital heart disease, usually an atrial septal or atrioventricular septal defect [2]. However, in some cases, congenital heart diseases found in EvC syndrome mimic those found in patients with heterotaxia [3]. Recent data suggest that the EVC and EVC2 genes could have a role in establishing left—right asymmetry and thus may have a role in the development of heterotaxia [3].

Here, we report a Tunisian child with the typical features of the EVC syndrome who was hospitalized for cyanosis and dyspnea that complicated his congenital heart disease.

2. Case report

A 13-year-old boy was referred to our department for dyspnea. Family history revealed parental consanguinity, and one brother died at the age of 3 months from bronchiolitis. No autopsy was performed on the brother. However, there was no other affected sibling in the family. On admission, general examination showed that the patient had a short stature, with a height of 118 cm and a weight of 24 kg; additionally, the patient had multiple skeletal deformities, such as rhizomelic shortening of both limbs, valgus deformities in both knee joints and hexadactyly in both hands and feet (Figs. 1, 2). The patient's nails were hypoplastic and dystrophic. An oral examination revealed hypodontia with the congenital absence of the incisor teeth (Fig. 3). The canine teeth were deformed and hypoplastic. A radiological skeletal survey confirmed the above-described deformities and showed synmetacarpalism in the left 5th and 6th digits (Fig. 4).

During the cardiovascular examination, the child was tachycardic (126/min), cyanosed (oxygen saturation measured in room air = 62%), and tachypnic (35/min), with signs of respiratory difficulty and bilateral bronchi. His blood pressure was 126/72 mmHg. Cardiac auscultation revealed a loud systolic murmur at the left sternal margin and a widely split S2. Hepatomegaly with hepatojugular reflux were also detected.

A chest X-ray revealed cardiomegaly (cardiothoracic ratio = 70%) and an oligemic lung. Echocardiography showed situs solitus with enlarged right cardiac cavities. Using colour Doppler, an ostium primum atrial septal defect was identified with a large right-to-left shunt at the atrial level (Fig. 5a) and a severe mitral valve regurgitation secondary to a mitral cleft (Fig. 5b). There was evidence of pulmonary arterial hypertension (PAH), with a systolic pulmonary arterial pressure of 100 mmHg (Fig. 5c). The right ventricle was dilated, and there was paradoxical septal motion (Fig. 5d). The diagnosis of a partial atrioventricular canal defect with supra-systemic pulmonary pressure was made. Neurologic examination showed normal psychomotor and intelligence development with no neurologic anomalies. These clinical features were suggestive of EVC syndrome. The diagnosis was confirmed by genetic testing. Molecular studies found a homozygous mutation in exon 10 of the EVC gene (c.1327C > T); this mutation is predicted to generate a premature stop codon (p.(Arg443*)).

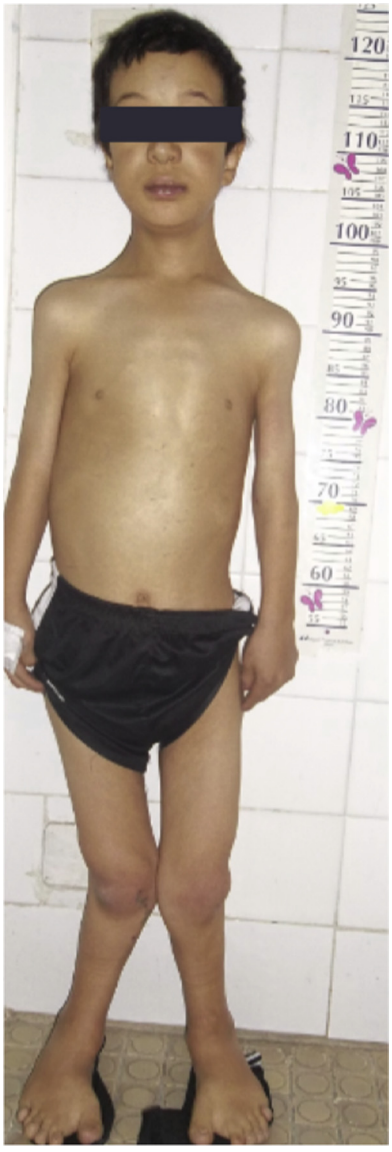

Figure 1 Skeletal deformities with rhizomelic shortening of both limbs and a valgus deformity in both knee joints.

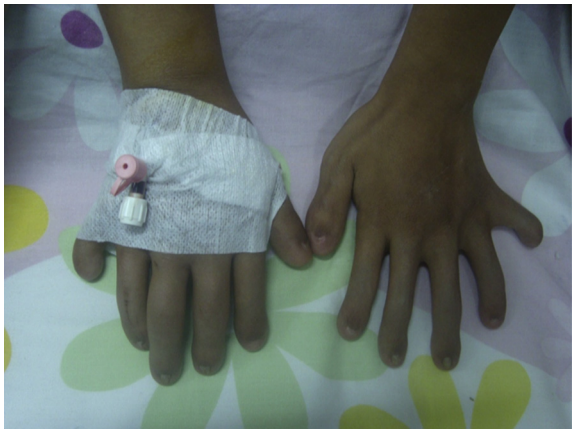

Figure 2 Photo showing hexadactyly in each hand.

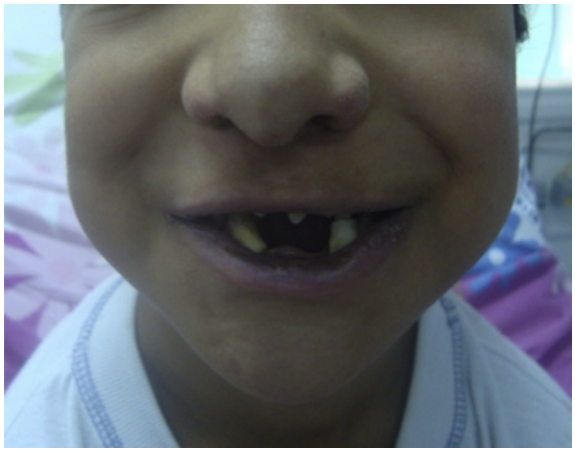

Figure 3 Oral examination showing the absence of incisor teeth and deformed canine teeth.

The patient was hospitalized in the pediatric intensive care unit. He was initially treated with diuretics and milrinone. Then, he was treated with diuretics and an ACE inhibitor, leading to the stabilisation of his heart failure. However, he died of refractory heart failure.

3. Discussion

EvC is a rare syndrome that was first described by Richard Ellis and Simon van Creveld in 1940. In most parts of the world, EVC syndrome occurs in 1 out of 60 000 to 200 000 live births [1]. This disease is characterized by skeletal disorders, including shortening of the limbs, short ribs, postaxial polydactyly and dysplastic nails. Patients also present a range of dental anomalies, including natal teeth, oligodontia, peg-shaped teeth and abnormalities of the enamel [2]. It is also associated with a high frequency of congenital cardiac defects [1]. However, most patients have intelligence in the normal range [1]. Our patient had all of the features that are suggestive of this syndrome.

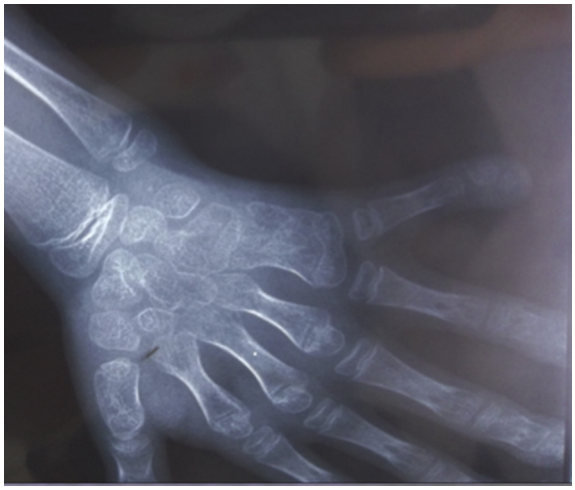

Figure 4 Radiological hand exam showing synmetacarpalism in the left 5th and 6th digits.

Genetic tests are necessary to confirm the diagnosis. Mutations of the EVC and EVC2 genes on chromosome 4p16 are responsible for the syndrome [4]. These genes encode a protein that acts as a positive mediator of Hedgehog signalling in normal endochondral growth and skeletal development [5,6]. The phenotype is identical in both of the mutations, and the incidence is equal in both genders [1]. Our patient had a homozygous mutation in exon 10 of the EVC gene (c.1327C $>$ T). To our knowledge, this is the first mutation identified in a Tunisian child with this syndrome.

One of the most interesting particularities of this syndrome is its association with congenital heart disease. Cardiac anomalies occur in approximately 60% of patients with EVC syndrome [7]. A common atrium (CA) is a common cardiac malformation that is found in patients with EVC [7]. Hills et al [7] performed a retrospective review of the cases submitted to the Pediatric Cardiac Care Consortium (PCCC) between 1982 and 2007. Thirty-two pediatric patients with congenital heart disease and EVC syndrome were identified in the PCCC database. The cardiovascular malformations that they identified included an atrioventricular canal defect in 28 patients (88%), with 15 of these having CA. Persistent left superior vena cava and pulmonary venous connection abnormalities were also common.

The mechanism by which EVC and EVC2 cause identical phenotypes with characteristic cardiac defects remains unknown [7]. It seems that EVC and EVC2 have a role in the development of the atrioventricular structure [7]. Lipscomb Sund et al showed colocalization of both the EVC and EVC2 gene mRNA proteins within the developing murine valvuloseptal structures, specifically at the tip of the primary atrial septum, atrio-ventricular cushions and outflow tract [8]. Furthermore, some authors have observed that the specific morphology of heart defects that are detected in EVC syndrome are strongly reminiscent of the cardiac phenotype found in patients with heterotaxia, in particular, in those with polysplenia [9]. In fact, CA, persistent left superior vena cava and pulmonary venous connection abnormalities that are associated with heterotaxia syndrome are common in EVC syndrome.

Molecular and developmental studies have demonstrated that nodal cilium dysfunction is a known cause of left—right axis defects in vertebrates [10] and that ciliary dysfunction is the result of defective processing of the Hedgehog proteins [10]. EVC syndrome is linked to abnormal processing of Hedgehog proteins, thus leading to ciliary dysfunction [10]. We know that EVC and EVC2 form a ciliary protein complex that interacts with Smo to allow the dissociation of Sufu/Gli3 inhibitory complexes and recruitment of Gli factors at the end of the cilia [6]. Our patient had a partial atrioventricular canal defect that was complicated by Eisenmenger syndrome. There was no evidence of either systemic venous or pulmonary venous connection abnormalities, suggesting a heterotaxy syndrome. Severe PAH precipitated his death. In the series of Hills et al [7], which is the largest series of patients with Ellis—van Creveld syndrome, there were no cases of Eisenmenger syndrome.

The management of EVC is multidisciplinary and involves orthopedic follow-up, dental and oral manifestation control

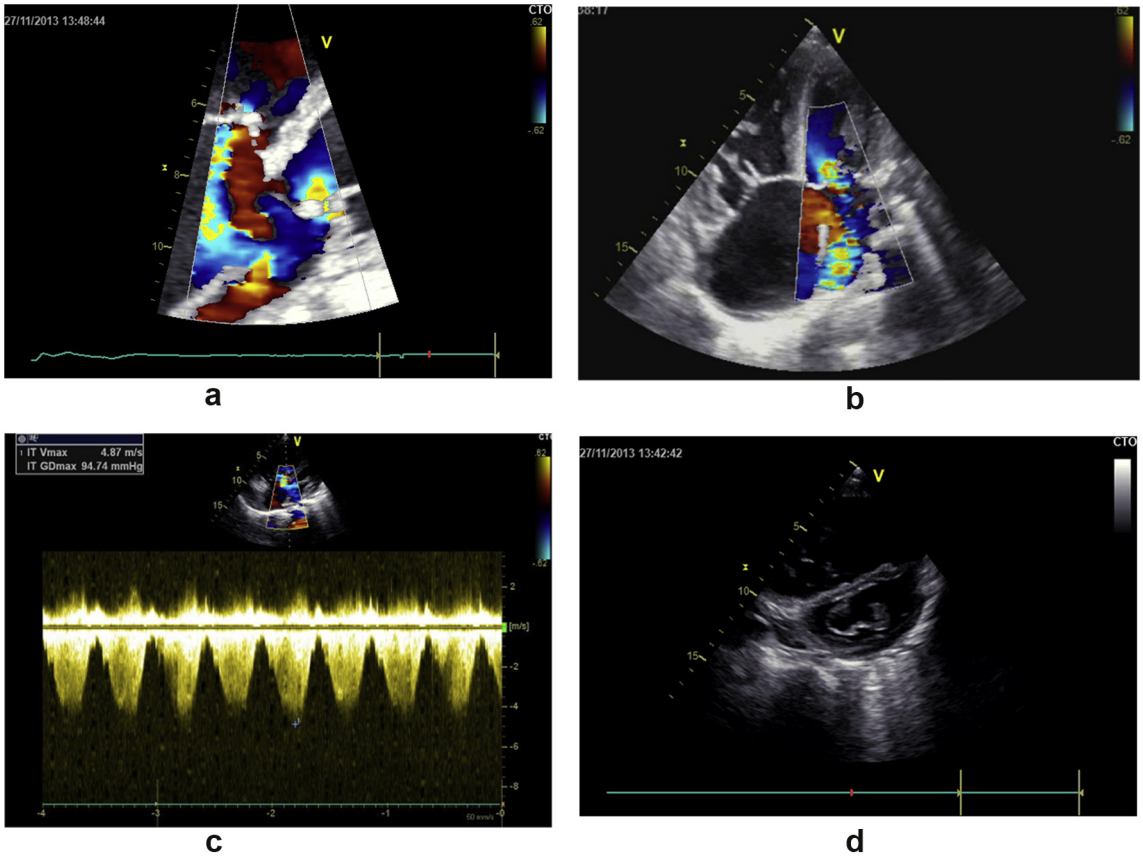

Figure 5 a: Echocardiography Doppler showing an ostium primum atrial septal defect with a right-to-left shunt. b: Echocardiography: apical view with colour Doppler showing grade III mitral regurgitation. c: Echocardiography: continuous Doppler estimating right ventricular systolic pressure to 100 mmHg. d:Echocardiography: parasternal short axis view showing paradoxical septal motion.

and, primarily, treatment of heart anomalies. In EVC syndrome patients, respiratory insufficiency because of a narrow thorax and cardiac anomalies are responsible for the majority of deaths in infancy [1].

4. Conclusion

EvC is a rare inherited disease. Congenital heart diseases are common in this syndrome. An atrioventricular canal defect is the most congenital heart disease associated with this syndrome. Recent data suggest that EvC can be associated with heterotaxy syndrome. The management of EvC involves a multidisciplinary approach, and the prognosis depends mainly on the associated cardiac disorders.

Conflict of interests

The authors have no competing interests to declare.

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