Reminder of important clinical lesson

Corrected ASD: case closed?

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Summary

Ellis-van Creveld syndrome (EvC) is a rare autosomal recessive chondroectodermal dysplasia, associated with mutations in the EVC1 and EVC2 genes (4p16). The management of EvC is multidisciplinary, and early diagnosis is of the utmost importance for efficient and timely treatment. The main prognostic determinant is presence of a heart defect. The authors describe the case of a 42-year-old man referred to our outpatient cardiology clinic, following surgical repair of an atrial septal defect. He had presented to different medical specialties on numerous occasions since childhood, but remained without a clear diagnosis for more than 40 years. This case reinforces the need for a holistic view when assessing a patient with congenital heart disease. Moreover, this illustrates the importance of communication and discussion between different medical specialties.

BACKGROUND

Ellis-van Creveld syndrome (EvC) is a rare autosomal recessive skeletal dysplasia, often associated with cardiac abnormalities. Prevalence, although not well established, is estimated to be around 1 per 60 000.¹ Since the first full description of the syndrome in 1940, by Richard W B Ellis and Simon van Creveld,² around 150 cases have been described worldwide.³

EvC affects multiple organs and has a variable phenotype. It is characterised by small stature, disproportionate extremities, short ribs, postaxial polydactyly, and dysplastic teeth and nails.³ A congenital heart malformation occurs in about 50–60% of cases, most often a single atrium. Other cardiac abnormalities include atrioventricular canal, ventricular septal defect, atrial septal defect (ASD) and patent ductus arteriosus. Approximately 50% of the patients die in the few first months of life due to cardiorespiratory complications and the heart defect is the main determinant of life expectancy.^{4–6}

The differential diagnosis of EvC includes other clinically similar entities, known as short-rib polydactyly syndromes, difficult to distinguish by the clinical presentation alone. Mutations in the EVC1 and EVC2 genes (4p16) allow diagnostic confirmation in the majority of cases,^{7–9} but only a few gene mutations have been described.

CASE PRESENTATION

A 42-year-old man was referred to our outpatient cardiology clinic by his general practitioner for evaluation of a surgically corrected ASD.

His extensive medical history included orthopaedic procedures/interventions from an early age; surgical correction of the bilateral polydactyly and bilateral club foot at 2 years of age, and 12 cm leg lengthening using an Ilizarov external fixator at 17 years of age (figure 1).

In early adulthood, he developed dyspnoea upon moderate exertion, associated with a systolic heart murmur II/VI grade at the left 2nd intercostal space. Radiological evaluation of the thorax revealed cardiomegaly with an enlarged right heart border. The ECG revealed right axis deviation, incomplete right bundle branch block, first-degree atrioventricular block and right atrial and ventricular hypertrophy. His transthoracic echocardiogram identified an ostium primum ASD with large left-right shunt, moderate right ventricular dilatation and tricuspid regurgitation, and no signs of pulmonary hypertension. The haemodynamic study confirmed the presence of the ASD, with a ratio of pulmonary to systemic blood flow (Qp:Qs) >1.5, but no evidence of pulmonary hypertension. At the age of 22, cardiac surgery was performed with successful correction of the ASD using a pericardial patch. The procedure was uneventful.

OUTCOME AND FOLLOW-UP

When reassessed in our Cardiology outpatient clinic, he was 42 years old and asymptomatic. Clinical findings were normal coloration of skin and mucous membranes, unusual facies with atypical features, multiple oral frenulae, enamel hypoplasia and hypodontia, low stature (148 cm) and disproportional extremities with most striking shortening in the distal part (acromesomelia), genu valgum and bilateral clubfeet, brachydactyly, bilateral scar in the ulnar aspect of the hands (supernumerary digit amputation) and partial inability to form a clenched fist, hypoplastic nails and sparse hair (figure 2, table 1). There were no signs of respiratory distress or heart failure. Heart sounds were regular and no murmurs were detected. Ancillary tests: Holter monitoring showed sinus rhythm, right bundle branch block and periods of second-degree atrioventricular block Mobitz I. The transthoracic echocardiogram confirmed absence of residual shunt on the interatrial septum,

Figure 1 Short stature/disproportionate extremities.

normal right heart cavities and preserved left ventricle global systolic function. He had normal exercise tolerance on the treadmill.

Careful analysis of the medical history, the multiple clinical features and data from complementary exams raised suspicion about a possible rare genetic syndrome since simultaneous heart and bone involvement is uncommon. The patient was referred to a clinical geneticist, and the presumptive clinical diagnosis of EvC was later confirmed by the mutations in the EVC1 and EVC2 genes. Family consanguinity was not present.

DISCUSSION

EvC is rare. It is recognised that nearly one-third of patients have a history of consanguinity in their families which

predisposes to EvC autosomal recessive inheritance.^{10 11} The syndrome is commonly diagnosed during the prenatal period, from 18th week of gestation by ultrasonography, or at birth by observation of the exuberant phenotype.¹² Even though our patient's clinical findings coincide with most published reports, there are no specific or constant characteristics that confirm EvC. Congenital heart malformations, supernumerary digits, ectodermal dysplasia as well as normal cognitive and motor development are features that support the diagnosis.^{1 6} The combination of severe bone and heart malformations should raise suspicion of an underlying genetic syndrome. Although detection of EVC1 or/and EVC 2 gene mutations can confirm diagnosis in two-thirds of patients, this molecular technique is still recent and not widely available.

Figure 2 (A,B) Supernumerary digit surgical correction and disproportionate fingers; (C) inability to form a clenched fist; and (D) oral frenulae and hypodontia.

Table 1 Principal clinical characteristics of Ellis–van Creveld syndrome

Main clinical findings of Ellis–van Creveld syndrome	
Chondrodystrophy (most common)	
Low stature	
Disproportionate distal limb shortening (acromesomelia)	
Polydactyly (constant finding)	
Hands bilaterally (most cases)	
Feet occasionally	
Ectodermal dysplasia (observed in many)	
Nails: dystrophic and friable	
Teeth: hypodontia/small and enamel hypoplasia	
Hair: sparse and fine	
Congenital cardiac anomalies (in 50% cases)	
Atrial septal defect leading to single atrium (most common)	
Ventricular septal defect/patent ductus arteriosus/valve defects	

The management of EvC is multidisciplinary and early diagnosis is of utmost importance. During the neonatal period, care is mostly supportive with management of respiratory distress due to a narrow thorax and heart failure, the main determinants of short-life expectancy. These patients warrant removal of neonatal teeth that could impair feeding and other orthodontic procedures to improve mastication, aesthetics and speech. Surgical correction is required for polydactyly and other bony malformations, and most importantly for cardiac anomalies which need to be recognised early.^{13 14}

This case report describes long-term longitudinal follow-up of an EvC patient, enabling analysis of the initial clinical findings, disease evolution and management

efficiency. Our patient was submitted to multiple surgeries and evaluated by many different medical specialties, but nevertheless remained without a clear diagnosis for more than 40 years. This demonstrates the difficulties faced when assessing patients with multisystem disease. Recognition of the many potential complications that can compromise quality of life and life expectancy is important, particularly those that can be prevented if recognised early. Clinical discussion between medical specialties is vital, as increasingly the supraspecialisation of medicine can mislead physicians to consider only symptoms or signs in their specialist area. In the presence of multiorgan pathology, the clinician needs to be able to embrace a global and holistic approach.

In this case, the skeletal and cardiac complications of EvC were minimised or treated. Our patient's heart anomaly went undetected until adolescence, by which time he presented with moderate exercise intolerance. Further investigation revealed an ostium primum ASD, already associated with electrical and haemodynamic changes within the right atrium and ventricle. Fortunately, cardiac surgery was still able to reverse the haemodynamic impact of the large and long-standing ASD, as confirmed by the patient's clinical stability, echocardiography and other ancillary tests on recent follow-up.

Our understanding of this disorder is still limited, given that EvC clinical features are not well delineated at present and genetic analysis is not able to confirm it in all the cases. Long-term follow-up and advances in genetics will likely provide additional understanding of the disease and further demarcation of EvC from the other short rib-polydactyly syndromes.

Learning points

- ▶ EvC is a rare autosomal recessive disorder, often described in consanguine families.
- ▶ The simultaneous presence of heart and bone malformations is uncommon and associated with genetic disorders.
- ▶ A comprehensive evaluation of the patient with multiple organ disease is important, screening for potentially preventable complications such as congenital heart disease.

Competing interests None.

Patient consent Obtained.

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