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AUTHORS' CONTRIBUTIONS

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Propionic acidemia: a rare cause of dilated cardiomyopathy and long QT syndrome

Acidemia propiónica: una causa poco habitual de miocardiopatía dilatada y síndrome de QT largo

To the Editor,

Organic acidemias are among the rarer causes of dilated cardiomyopathy (DCM). They form a group of inherited metabolic diseases characterized by excessive accumulation of organic acids leading to systemic disease. Among this group, propionic acidemia is the type that frequently involves the heart. We present a case of DCM with a diagnosis of propionic acidemia. The patient gave informed consent to undergo tests and to the publication of the case, which was approved by the ethics committee of our hospital.

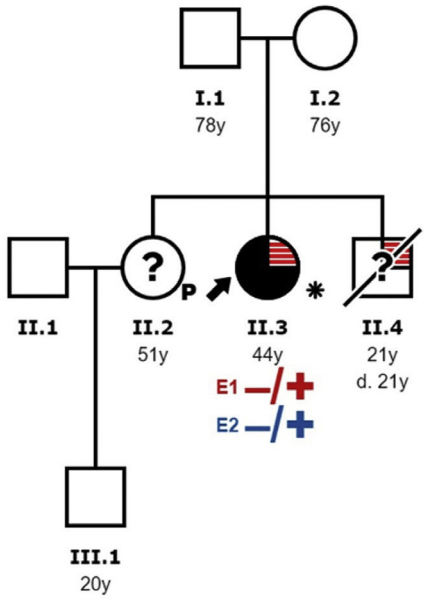
A 38-year-old woman was referred to the cardiology department because of a finding of DCM on echocardiography. The family history included a brother diagnosed with DCM of unidentified etiology, who died at 21 years of age while undergoing cardiac transplant (figure 1). The personal history referred to episodes of hypoglycemic ketotic crises in childhood and highlighted a diagnosis of chronic kidney disease of unclear etiology in 2015. In 2019, due to the progression of renal disease, renal transplant was performed without subsequent complications.

At the time of the diagnosis of DCM, the patient was in New York Heart Association (NYHA) functional class II, with a spherical dilated (end-diastolic diameter, 65 mm) left ventricle (LV) with severe LV systolic dysfunction (LV ejection fraction [LVEF], 33%) and severe relaxation deficit with elevated filling pressures (E/E', 14) (figure 2). The electrocardiogram (ECG) showed a long QTc interval (figure 2). Coronary angiography showed no lesions.

A genetic study was performed using a general DCM panel (figure 1), which was negative. Decompensated heart failure was not observed on optimized drug therapy; in March 2021, the patient was in NYHA functional class I, had achieved partial echocardiographic remission with a slightly dilated LV (end-diastolic diameter, 59 mm) with a recovered LVEF (55%), and diastolic normalization (E/E', 7), but with decreased global longitudinal strain (figure 2). Improvement was seen on electrocardiography with QT shortening (figure 2).

In July 2021, the patient was admitted to the psychiatry department for behavioral disturbances. Brain magnetic resonance imaging (MRI) showed a hypersignal in the basal ganglia, so the patient was referred to neurology. The etiological study included a urine organic acid study; we highlight increases in 3-hydroxypropionic acid (146 mmol/mol creatinine; normal, < 5) and methylcitric acid (99 mmol/mol creatinine; normal, < 5), with normal levels of methylmalonic acid. Whole exome sequencing targeting genes related to propionate and biotin metabolism disorders showed 2 heterozygous mutations in the *PCCB* gene (figure 1). Both are described in the Human Gene Mutation Database. As predictors of pathogenicity, and according to the criteria of the American College of Medical Genetics, they are classified as pathogenic variants, thus confirming the diagnosis of propionic acidemia.

Propionic acidemia is an inherited autosomal recessive disease characterized by the accumulation of propionate and its metabolites due to mutations in propionyl-CoA carboxylase (PCC), which



Propionic acidemia
Clinically affected

Propionic acidemia
Unknown, possibly affected

Dilated cardiomyopathy
Clinically affected

E1 PCCB (c.683C>T, p.Pro228Leu)
+/+: homozygous –/+: heterozygous +: hemizygous –/–: not found –: not found

E2 PCCB (c.1218_1231delinsTAGAGCACAGGA, p.Gly407fs)
+/+: homozygous –/+: heterozygous +: hemizygous –/–: not found –: not found

✱ Verified by our medical team

Dilated cardiomyopathy panel
ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CAV3, CRYAB, CSRP3, DES, DMD, DSC2, DSC2, DSG2, DSP, EDM, EYA4, FHL1, FHL2, FKRP, FKTN, GATAD1, HFE, ILK, JUP, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYPN, NEXN, PDLIM3, PKP2, PLN, PRDM16, PSEN1, PSEN2, RAF1 RBM20,RYR2, SCN5A, SDHA, SGCD, TAZ, TBX20, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TXNRF2, VCL
Genes related to propionate and biotin metabolism disorders
ALDH6A1, BTD, HIBCH, HLCS, MCCC2, PCCA Y PCCB

Figure 1. Genealogical tree (June 2022) and genes studied in the index case.

is a mitochondrial enzyme that catalyzes a reaction prior to entry into the Krebs cycle. The PCC enzyme is composed of PCCA and PCCB subunits, which are encoded by the *PCCA* and *PCCB* genes. Propionic acidemia can result from mutations in these genes.

In clinical terms, the disease leads to chronic multiorgan involvement and ketotic hypoglycemia in the presence of precipitating factors (infections or fasting).[1]

Cardiac involvement is common in the form of cardiomyopathy and long QT syndrome. Cardiomyopathy occurs in 25% of cases,[2] with a mean age at presentation of 7 years.[3] It may be the only manifestation of the disease and the most frequent form of presentation is DCM (> 90%).[2] The incidence of long QT syndrome varies (22%-70%)[1] and increases with age. Both cardiomyopathy and a long QT interval may be caused by the toxic effects of propionate and its metabolites. The prognosis of patients with cardiomyopathy is poor, with a mortality rate of 50% due to progression of cardiomyopathy[2] and sudden cardiac death due to ventricular arrhythmias. Some cases have required cardiac transplant.[4]

Diagnosis is based on a urine organic acid study in which elevated levels of 3-hydroxypropionate and 2-methylcitrate are observed together with normal values of methylmalonic acid.[1] The diagnosis is confirmed by genetic study, detecting pathogenic variants of the *PCCA* or *PCCB* genes. Of note, these genes are not included in the recommended DCM panel.[5] Although this disease is not often suspected, it causes systemic disease and particularly affects the heart: thus, some studies have suggested that these

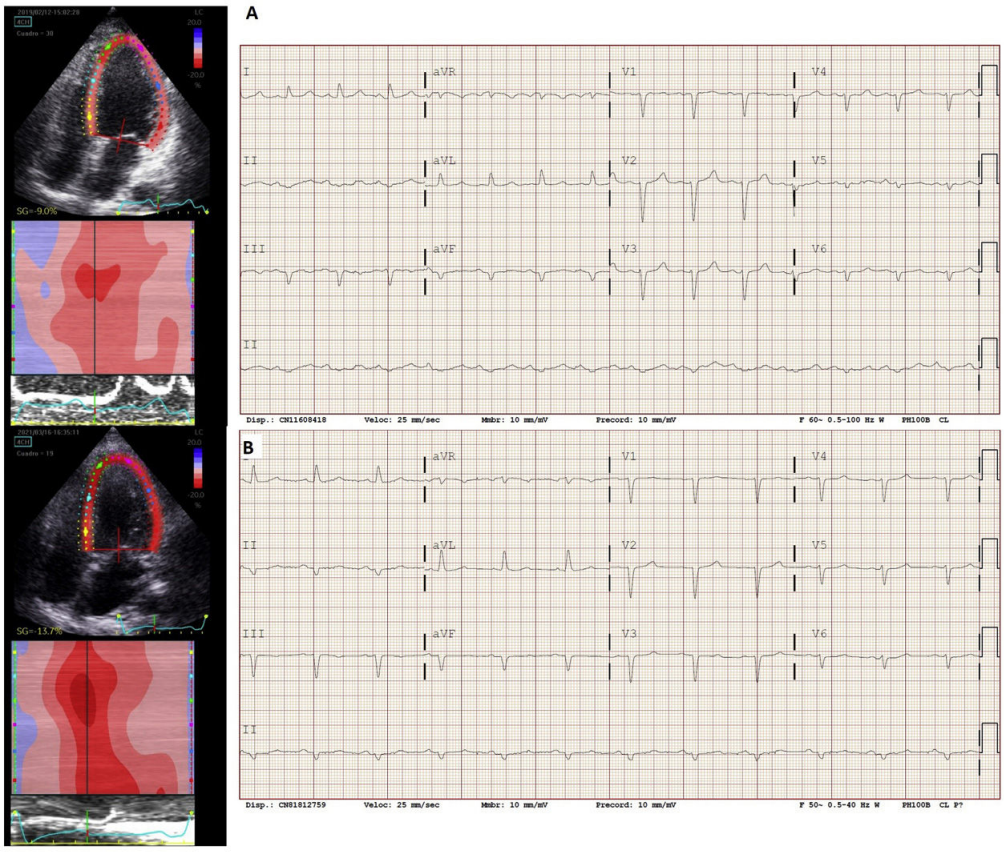


Figure 2. A: In 2019, a global longitudinal strain (GLS) of -9% was observed on echocardiogram and a QTc of 485 ms (Bazett's formula) on electrocardiogram. B: In 2021, we observed an improvement in GLS (-14%) and QTc (436 ms) on echocardiogram.

genes should be included in the general DCM panel to achieve early diagnosis.[6]

Propionic acidemia should be suspected in a case of DCM accompanied by a long QT interval, acute or intermittent neurological symptoms, ketotic hypoglycemia, and a family history of cardiomyopathy or sudden cardiac death.

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AUTHORS' CONTRIBUTIONS

J Siquier wrote the original text. J Pons and A Grau reviewed the original text in detail and provided the transthoracic echocardiography images. D Heine-Suñer performed and interpreted the patient's genetic study. All authors actively participated in this case, reviewed the manuscript, and approved its submission.

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Double lung transplantation in pulmonary arterial hypertension associated with congenital heart disease

Trasplante bipulmonar en hipertensión arterial pulmonar relacionada con cardiopatías congénitas

To the Editor,

Pulmonary arterial hypertension (PAH) affects almost 4% of patients with congenital heart disease (CHD),[1] worsening their prognosis. After pulmonary vasodilator therapy, the only remaining therapeutic option is double lung transplant, frequently accompanied by heart transplant. Nevertheless, access to heart-lung transplant is increasingly limited by the scarcity of donor organs and the high risk involved.

In the present study, we retrospectively analyzed the case histories of patients with PAH-CHD who underwent double lung transplant at our center from September 2010 to January 2022. This is the first such patient series described in Spain. The indication for transplant was high-risk PAH despite optimized medical treatment with triple vasodilator therapy including intravenous prostacyclins. During the study period, 12 of the 135 PAH-CHD patients treated at our center were considered for transplant (figure 1). Of these 12 patients, 6 underwent double lung transplant, representing 13% of patients undergoing this procedure for PAH at our center during the study period. The patients gave informed consent for the intervention and for the publication of the study findings. The mean age of the patients was 39 ± 10, and 67% were women. All the patients had a history of heart failure. Of the 6 patients, 4 had typical atrial flutter and were treated by ablation of the cavotricuspid isthmus; arrhythmia recurrence was recorded in 2 of these patients, 1 with atypical incisional atrial flutter and another with atrial fibrillation. Pulmonary artery trunk aneurysm with a maximum diameter of 53 mm was found in 4 patients; in 1 patient the aneurysm was complicated by symptomatic extrinsic compression of the left coronary artery, requiring implantation of an intracoronary stent, and another patient had in situ thrombosis in the pulmonary artery trunk. Finally, 1 patient had life-threatening hemoptisis requiring bronchial artery embolization. Regarding etiology, 2 patients had residual PAH years after closure of the intracardiac defect, and the remaining 4 had an incidental intracardiac shunt. Due to suspicion of pleural adhesions in the 2 patients with residual PAH after previous defect repair, extracorporeal circulation was established with femoral cannulation. In the 4 patients with open defects, central cannulation was used, and the defects were closed during the transplant procedure, with the exception of a restrictive interventricular communication that was left open. Defect closure did not significantly increase the duration of extracorporeal circulation (284 minutes without closure vs 299 minutes with closure). The presence of pulmonary aneurysm increased the complexity of arterial anastomosis, whereas no modification of the procedure was required in the patient with in situ thrombosis. There were 2 severe postsurgery complications: 1 patient developed interstitial pulmonary edema, prolonging intubation and requiring hemofiltration; and another patient had bleeding with hemodynamic consequences related to the clamshell incision and required

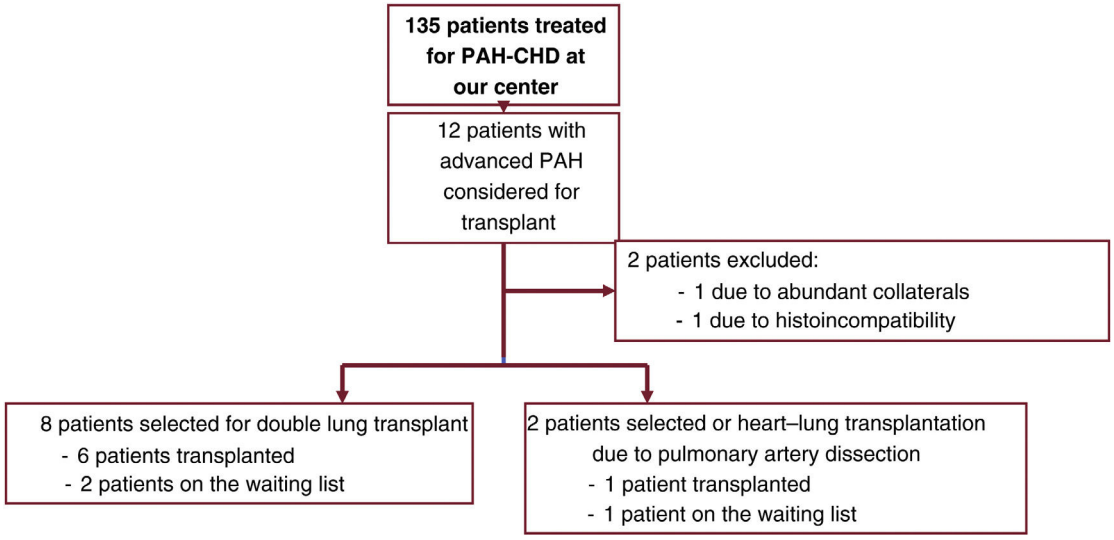

Figure 1. Flow chart of PAH-CHD patients selected for double lung transplant. PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease. Tx, transplant.