Tomás Ripoll-Vera,[a,b,*] Jorge Álvarez Rubio,[a,b] Mercedes Iglesias,[a] Inés Losada López,[b,c] Asunción Ferrer-Nadal,[b,d] and Juan González Moreno[b,c]

[a]*Servicio de Cardiología, Hospital Universitario Son Llàtzer, Palma de Mallorca, Balearic Islands, Spain*
[b]*Instituto de Investigación Sanitaria de Palma (IdISBa), Palma de Mallorca, Balearic Islands, Spain*
[c]*Servicio de Medicina Interna, Hospital Universitario Son Llàtzer, Palma de Mallorca, Balearic Islands, Spain*
[d]*Servicio de Nefrología, Hospital Universitario Son Llàtzer, Palma de Mallorca, Balearic Islands, Spain*

[*] Corresponding author:
E-mail address: tripoll@hsll.es (T. Ripoll-Vera).

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Neonatal myocardial ischemia and calcifications. Report of a case of generalized arterial calcification of infancy

Isquemia miocárdica neonatal y calcificaciones, presentación de un caso de calcificación arterial generalizada de la infancia

To the Editor,

Generalized arterial calcification of infancy (GACI) (Online Mendelian Inheritance in Man [OMIM] 208000) is a rare disorder affecting 1 in every 391 000 to 566 000 newborns. The condition is characterized by abnormal tissue mineralization, producing calcium build-up in the internal elastic lamina of medium-sized and large arteries of the body and proliferation in the tunica intima of muscular arteries, leading to narrowing of the arterial lumen and clinical repercussions in the territories perfused by those arteries.[1]

Clinical symptoms are myocardial ischemia, as well as vascular and periarticular calcifications in soft tissues. The diagnosis is confirmed by genetic study. In 70% of published cases, a mutation has been identified in the *ENPP1* gene (OMIM 173335). This gene encodes ectonucleotide pyrophosphate/phosphodiesterase 1, which produces inorganic pyrophosphate, an essential physiologic inhibitor of arterial calcification. In the rest of cases, mutations have been identified in the *ABCC6* gene, which encodes the MRP6 protein, a transmembrane adenosine triphosphate-binding cassette (ABC) protein transporter.[2]

There is no specific treatment, although bisphosphonates appear to increase survival in some patients. The prognosis depends on the extent of the calcification and associated complications, which lead to early death in many of these patients.[3]

Because only a few clinical cases have been published with a genetic study, we consider this report to be of interest.

We describe the case of an infant born at 33 weeks of gestation and hospitalized in the neonatal unit due to prematurity.

The initial examination revealed considerable limitation for elbow extension and hip mobilization. Limb X-rays disclosed periarticular calcifications (figure 1A). An electrocardiogram was also performed (figure 2D). Cardiac ultrasound on the third day of life showed a normal structure with preserved myocardial

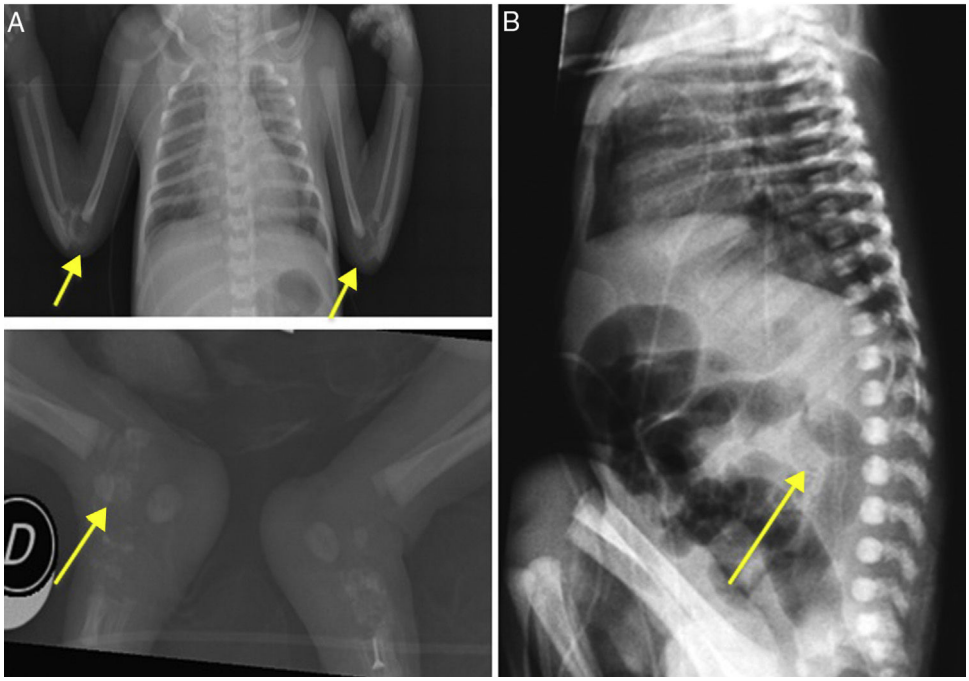

Figure 1. A, limb X-ray (calcifications indicated by arrows). B, abdominal X-ray: calcification of the descending aorta.

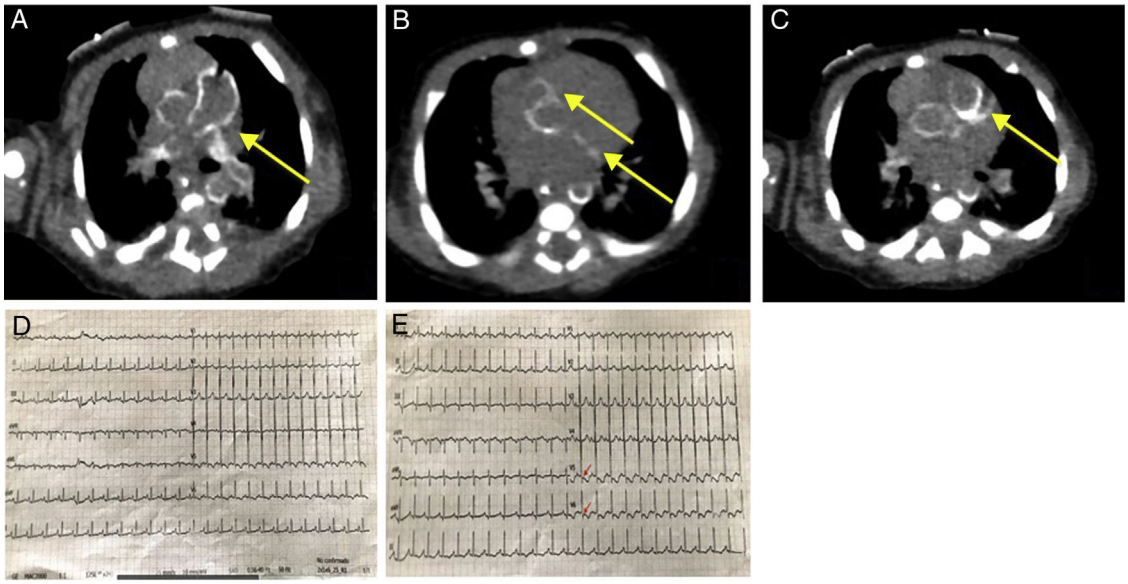

Figure 2. Computed tomography scan and electrocardiogram. A, calcification of the pulmonary artery and ascending aorta. B, right coronary (top) and circumflex (bottom) arteries. C, left anterior descending artery. D, initial electrocardiogram. E, subsequent electrocardiogram (ST-segment depression in V_5 and V_6 indicated by arrows).

function, but hyperechogenicity in the coronary arteries. On chest and abdominal computed tomography (CT), calcification was observed from the ascending aorta to the iliac branches and carotid and humeral arteries, with coronary and lung damage also visualized (figure 2A-C). Calcium and phosphate metabolism was normal.

On day 14 of life, the patient experienced a sudden episode of clinical worsening with respiratory pauses and evidence of low cardiac output, generalized pallor, slow filling, severe mixed acidosis, and associated severe hyperlactacidemia. Repeat echocardiography showed severe ventricular dysfunction with a left ventricular ejection fraction of 27%, as well as higher hypocontractility of the inferolateral segments. Electrocardiography revealed ST-segment depression in leads V_5 and V_6 (figure 2E). Cardiac biomarkers were elevated. Therefore, the diagnosis was non–ST-segment elevation acute myocardial infarction, complicated by cardiogenic shock. Inotropic support was started, and the patient was transferred to a tertiary hospital.

Following admission, ventricular function was partially restored and, in view of the probable GACI diagnosis, intravenous pamidronate therapy was started. The patient experienced progressive clinical worsening and died at 34 days of life.

In our patient, the genetic study was based on next-generation sequencing of coding exons and flanking intronic regions (NextGeneDx/Imegen panel, Spain, for GACI) of the *ABCC6* and *ENPP1* genes, using the Nextera XT kit (Illumina, United States). The study also included sequencing (MiSeq System, Illumina, United States) of libraries (2×150) plus Sanger sequencing of regions of interest with coverage of $< 100\times$ (exons 1 and 8 of *ENPP1* and exon 2 of *ABCC6*). The study revealed common variants and a heterozygous variant previously described[4] in the *ENPP1* gene, at the end of exon 4, c.556G >C, p.Gly186Arg, which is considered pathogenic (Sorting Intolerant from Tolerant Algorithm [SIFT], Polyphen2-HDIV [HumDiv; 0.999], Polyphen2-HVAR [HumVar; 0.986], MutationTaster [disease causing] and Combined Annotation Dependent Depletion [CADD] score of 34) due to a highly intact domain of somatomedin B2 protein. Another heterozygous mutation was found in intron 13 (c.1405+5G >C), not listed in the Genome Aggregation Database (gnomAD) and not previously described in the literature. These variants segregated in both parents, who were healthy, and each of these variants was found in an allele from each parent. The patient developed the disease due to compound heterozygosity (with trans configuration) similar to autosomal recessive inheritance, already described in several families affected by GACI.[2,5] However, according to in silico prediction (Human Splicing Finder) for this new variant, the variant would produce rupture of the splice donor site (variation, –40.36%), thus potentially affecting proper processing of the messenger RNA and favoring the pathogenic effect of this change. Nevertheless, some patients have only 1 pathogenic mutation of *ENPP1* in a single allele and a consistent pathologic phenotype.[2]

GACI is a very rare disorder, with variable clinical symptoms depending on the extent and location of the territory affected by vascular calcification.

Mutations in the *ENPP1* and *ABCC6* genes have been described as the cause in the case reports published to date.[2,3]

The prognosis is fatal in most patients, and clinical suspicion is important to direct a specific genetic study, as the family can receive appropriate genetic counseling once the mutation has been identified.[5]

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Ignacio del Castillo Velilla,[a,◇] Mercedes Ludeña del Río,[a] Jesús Cecilio López-Menchero Oliva,[a,b] Cristina Ramos Navarro,[c] Eva Bermejo-Sánchez,[d] and Natalia Bejarano Ramírez[a,b,◇,*]

[a]*Unidad de Cuidados Intensivos Neonatales, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*
[b]*Facultad de Medicina, Universidad de Castilla-La Mancha, Ciudad Real, Spain*
[c]*Unidad de Cuidados Intensivos Neonatales, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[d]*Unidad de Investigación sobre Anomalías Congénitas, Instituto de*

Investigación de Enfermedades Raras, Instituto de Salud Carlos III, Madrid, Spain

*Corresponding author at: Corresponding author:
E-mail address: nbejarano@sescam.jccm.es (N. Bejarano Ramírez).
◇The authors have contributed equally to this article.
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Changes in minimally invasive congenital cardiac surgery. Moving away from the midline

Evolución de la cirugía cardiaca congénita mínimamente invasiva: alejándose de la línea media

To the Editor,

Minimally invasive cardiac surgery (MICS) has emerged relatively recently for the surgical repair of congenital heart disease (CHD).[1–6] We have reported excellent results in terms of surgical outcomes when a MICS approach is employed, and our 20-year experience now comprises more than 1000 cases.[1] This includes different surgical approaches, ranging from minimally invasive lower minsternotomies (MS) to right anterior minithoracotomies and right lateral minithoracotomies (RLMT).

The transition process that led us from a full sternotomy to less invasive surgical strategies required improvements in the surgical instrumentation and perfusion strategies to enhance surgical exposure while maintaining a small incision, thus expanding implementation from simple cases, such as an atrial septal defect (ASD) closure, to more complex cases, such as ventricular septal defect (VSD) closure, partial atrioventricular septal defect repair, and partial pulmonary venous return repair.

Our current protocol includes a tailored approach that is based on patient sex and on the underlying pathology. The MS approach was predominantly used at the beginning of our experience and is now reserved mainly for small infants with VSD. A right anterior minithoracotomy was subsequently introduced for the treatment of simple CHD (mainly ASD) in female patients to avoid a midline incision. Most recently, we have moved our incision even more laterally and have introduced the RLMT (figure 1A). This has become our favored approach, as it can be applied for the correction of various CHD while offering excellent outcomes in terms of patient satisfaction and aesthetic results.[3]

In the RLMT approach, a right thoracotomy of 3 to 4 cm is created in the fourth or fifth intercostal space, depending on the main pathology to be addressed (figure 1B,C). The incision is extended from the mid-axillary line toward the anterior axillary line. Peripheral cannulation for cardiopulmonary bypass has been adopted as a standard practice in MICS cases, and currently, our institutional protocol allows a safe femoral arterial cannulation in patients weighing $\geq$ 15 kg and femoral venous cannulation in patients weighing $\geq$ 7 kg. The superior vena cava cannulation can be achieved either directly or percutaneously by cannulating the internal jugular vein.

At present, a total of 219 patients (110 females and 109 males) have undergone surgical correction of CHD by RLMT at our institution. Median age was 7.7 years [interquartile range [IQR, 4.9-13.2 years] and median weight 26.4 kg [IQR, 17.3-49.7 kg]. The diagnoses requiring surgical repair were ASD in 49% (107/219), partial pulmonary venous return in 25% (55/219), partial atrioventricular septal defect in 12% (27/219), and VSD in 8% (16/219) of the population, respectively. Other diagnoses (6%; 14/219) included aortic valve stenosis or left ventricular outflow obstruction (n = 6), inferior sinus venosus ASD (n = 6), and mitral valve stenosis (n = 2).

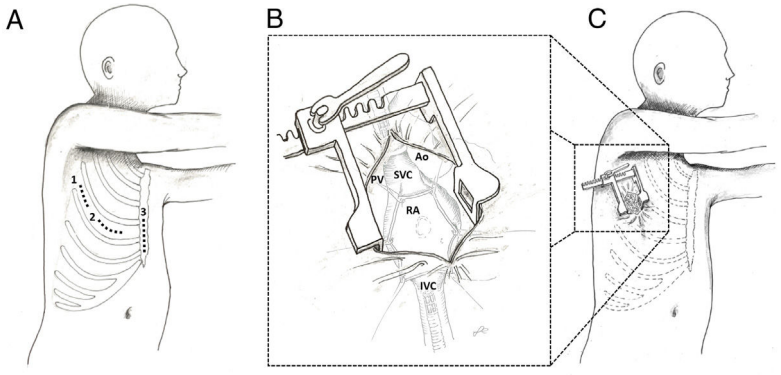

Figure 1. Different accesses for minimally invasive pediatric cardiac surgery. A: graphical representation of the 3 different types of access for minimally invasive cardiac surgery used at the University of Padua. 1, right lateral minithoracotomy. 2, right anterior minithoracotomy. 3, midline lower ministernotomy. B: close-up. C: graphical representation of a right lateral minithoracotomy with the anatomical structures that can be approached through this access. Ao, aorta; IVC, inferior vena cava; PV, pulmonary veins; RA, right atrium; SVC, superior vena cava.