

## Scientific letters

**Cardiac Involvement Secondary to a Familial Form of Transthyretin Amyloidosis Resulting From the *Glu54Gln* Mutation*****Amiloidosis cardiaca secundaria a la mutación familiar Glu54Gln del gen de la transtiretina*****To the Editor,**

A 43-year-old-woman, originally from Romania and resident in Spain, with a previous medical history of bilateral carpal tunnel syndrome, was admitted to our hospital due to progressive exertional dyspnea and bilateral edema in both lower extremities.

At admission, she did not have fever, blood pressure was 101/72 mmHg, and heart rate was 95 beats per minute. On examination, the patient had no jugular ingurgitation and cardiac auscultation was rhythmic without murmurs. The lungs showed mild crackles, and pitting edema was found in both lower extremities.

Laboratory tests revealed a serum creatinine concentration of 1.17 mg/dL, 0.3 g/24-h proteinuria, and calculated creatinine clearance (Modification of Diet in Renal Disease formula) was 55.95 mL/min/1.73m<sup>2</sup>. The N-terminal pro-B-type natriuretic peptide value was 6.932 pg/mL. All other laboratory studies, including biochemical, hematological and protein electrophoretic values, were normal. An electrocardiogram showed sinus rhythm, low electric potentials, and sporadic ventricular extrasystole. Chest x-ray revealed cardiomegaly and bilateral pleural effusion.

Transthoracic echocardiography highlighted a biventricular thickening (ventricular septum of 15 mm, left ventricular weight of 209 g, and left ventricular mass index of 131 g/m<sup>2</sup>) and an abnormal filling pattern compatible with restrictive cardiomyopathy.

After a magnetic resonance imaging scan with gadolinium enhancement, subendocardial ring uptake was demonstrated on the left ventricle, the free wall of the right ventricle, the septum, and the back wall of the right atrium (Figure 1).

Because of a high index of suspicion for amyloidosis, an abdominal subcutaneous fat biopsy was performed, revealing birefringence with Congo red staining, consistent with amyloid deposits.

A Tc-99m 2,3-dicarboxypropane-1, 1-diphosphonate (Tc<sup>99m</sup>-DPD) bone scintigraphy and a single-photon emission computed tomography scan combined with a conventional computed tomography scan of the chest were carried out in 2 phases and an increase in biventricular myocardium blood pool was observed during the early phase, in addition to strong radiotracer uptake in both ventricles during the late phase (Figure 2).

Subsequently, a kidney biopsy ruled out amyloid deposits, and sequencing of the transthyretin gene was performed, showing the c.220G > C variant (also called *Glu54Gln*), present in the third exon of one of the alleles.

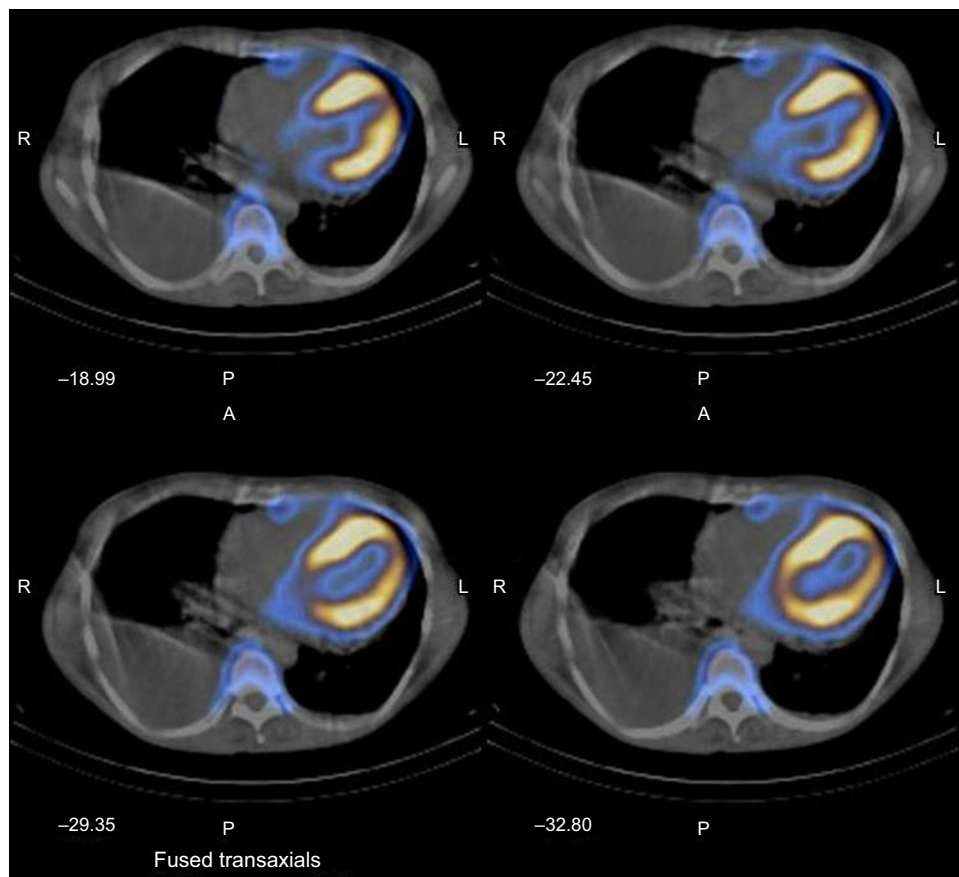
The patient accepted to be included on the national waiting list for a double heart-liver transplant. One month after diagnosis, while waiting for the transplant, the patient died after a large ischemic stroke.

Amyloidosis is a systemic disease caused by deposition of misfolded protein in various human tissues and organs.<sup>1,2</sup> This fibrillary deposition generates organ dysfunction.<sup>2</sup> Myocardium is one of the most frequently organs, and amyloidosis should be suspected in patients with heart failure with preserved ejection fraction and ventricular hypertrophy without previous hypertension,<sup>2</sup> especially in young people such as our patient. There are different types of amyloidosis, but cardiac involvement is strongly related to transthyretin gene-associated mutations and, to a lesser extent, to light-chain amyloidosis,<sup>1</sup> being highly uncommon in amyloid A amyloidosis.<sup>2</sup>

We present the case of a young woman with heart failure with preserved left ventricular ejection fraction and with rapid and aggressive progression who was finally diagnosed with amyloidosis. In this case, we suspected this entity after the echocardiographic study and typical magnetic resonance images with late gadolinium enhancement,<sup>2,3</sup> and diagnostic confirmation was provided by subcutaneous fat aspirate, which is the gold standard technique.<sup>1</sup>



**Figure 1.** Magnetic resonance imaging with gadolinium shows a subendocardial ring uptake on the left ventricle, the free wall of the right ventricle, the septum, and the back wall of the right atrium.



**Figure 2.** Tc-99m 2,3-dicarboxypropane-1, 1-diphosphonate bone scintigraphy and single-photon emission computed tomography combined with a conventional computed tomography shows an increase in biventricular myocardium blood pool observed during the early phase in addition to a strong radiotracer uptake in both ventricles during the late phase. A, anterior; L, left; P, posteroanterior; R, right.

We reasonably excluded light-chain amyloidosis due to the absence of light-chain immunoglobulins on immunoelectrophoresis, in both serum and urine. In addition, we observed radiotracer uptake in both ventricles during TC<sup>99m</sup>-DPD scintigraphy, and in line with current literature, this technique binds to transthyretin in the myocardium, but not to immunoglobulin light chains.<sup>2</sup>

Finally, the genetic study of the transthyretin gene confirmed the *Glu54Gln* variant, excluding a wild-type-transthyretin-related amyloidosis. This is the first time that the transthyretin gene variant, *Glu54Gln*, which is related to myocardial involvement, has been isolated in Spain. In contrast, this mutation has been previously described in the international Mutations in Hereditary Amyloidosis database in 2 Romanians.<sup>4</sup> This is relevant due to the high prevalence of Romanian immigration in Spain (especially in our area: Zaragoza, Aragon, Spain). Moreover, in line with previous reports of patients with the *Glu54Gln* mutation, our patient initially presented with peripheral neurology and subsequently developed serious cardiomyopathy (typical in family amyloidosis) with several hospitalizations for acute heart failure.

Because the abnormal transthyretin is synthesized in the liver, we proposed a double heart-liver transplant for this patient, since orthotopic liver transplant-with/or without cardiac transplant-has been considered a potentially curative treatment for this entity.<sup>2</sup> However, liver transplant has been less effective in other transthyretin gene mutations different from Val30Met.<sup>5</sup> Unfortunately the patient experienced a serious complication and did not survive to receive the transplant.

Given that amyloidosis is an autosomal dominant inheritance disease with high penetrance, we also studied the gene sequence of

the patient's descendants (daughter, son and grandson). We found her daughter positive for the same mutation with no clinical symptoms or signs. She is currently being studied and under consideration for a potential prophylactic liver transplant.

We believe this case highlights the need to include amyloidosis in the differential diagnosis of heart failure with preserved ejection fraction, especially in young people, due to the high mortality of this disease.

#### CONFLICT OF INTEREST

Authors do not have conflicts to disclose  
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## Selection of the Best in 2016 in Congenital Heart Diseases



### Selección de lo mejor del año 2016 en cardiopatías congénitas

#### To the Editor,

Last year saw a continuation of the trend to publish more articles on congenital heart diseases (CHD), a trend characterized by intensified interest in the epidemiological importance being acquired by this population.

One of the more notable studies on the consequences of modern interventions in CHD was the Finnish National Registry of late causes of death among patients younger than 15 years who underwent surgery between 1953 and 2009 (10 964 patients, 98% follow-up).<sup>1</sup> This study compared causes of death with those in the general population, subdividing the results into 2 periods: 1953 to 1989 and 1990 to 2009. Total survival was higher in the second period, and the main cause of CHD-related death was heart failure (HF); however, the rate of HF-death declined significantly over the long-term among patients who underwent surgical correction of ventricular septal defects and transposition of the great arteries. An especially notable finding was the near complete absence of sudden death in the second period among patients with tetralogy of Fallot and transposition of the great arteries. Also of interest is the higher death rate from neurological diseases and infections among CHD patients and a higher incidence of neoplasms, especially in the second period.<sup>1</sup>

Although HF is the main cause of death among CHD patients, the indications and optimal timing for transplantation are less well defined than for other heart conditions. Patients with CHD are less likely than other heart disease patients to be fitted with a defibrillator or ventricular assist device or to be included on high-priority wait-lists, and their wait-list mortality is higher. These specific concerns prompted the American Heart Association to issue a scientific statement reviewing the particular characteristics of CHD patients that can affect transplant surgery, such as complex anatomies frequently requiring additional surgery, HLA antibody sensitization, and difficult vascular access.<sup>2</sup> The review also examines evidence on the effectiveness of ventricular assist devices in the treatment of CHD and proposes therapeutic strategies to improve transplant outcome, including specific changes to the criteria used to assign urgency status to CHD patients on transplant wait-lists.<sup>2</sup>

Studies examining sudden death among CHD patients included a meta-analysis of the use of implantable cardioverter-defibrillators in a total of 2162 individuals followed up over  $3.6 \pm 0.9$  years.<sup>3</sup> In this population, 1 or more appropriate shocks were recorded in 22% of patients in primary prevention and 35% of those in secondary prevention; inappropriate shocks were recorded in 25% of patients, and other defibrillator-related complications in 26%.<sup>3</sup> These findings point to the need for continuing improvements in risk stratification and implantation programs.

There is also increasing awareness of the influence of CHD on psychosocial factors, reproductive function, and noncardiac conditions. A study published last year sought to characterize the effects of CHD on brain function, describing how neurodevelopment before birth and during infancy is influenced by a close interaction among genetic and epigenetic factors, direct disease consequences, such as severe cyanosis, and even therapeutic interventions; moreover, the cumulative burden of CHD continues into adulthood, when disease progression and the appearance of HF, arrhythmias, and comorbidities contribute to brain damage in the form of neurovascular disease.<sup>4</sup> The article also suggests interesting future directions for translational research to improve prognosis and quality of life in this population. Several studies have explored the multiorgan consequences of univentricular circulation, examining post-Fontan-procedure hemodynamics and the prevalence of liver fibrosis; however, these studies have not yet been translated into a specific therapeutic program. It is nonetheless worth highlighting a small, single-center study that presented a new therapeutic option for plastic bronchitis, a serious complication after single-ventricle palliation; the authors used a percutaneous embolization technique to reduce lymphatic flow to the pulmonary parenchyma, reporting significant symptomatic improvement in 15 of the 17 patients treated.<sup>5</sup> Plastic bronchitis is associated with high morbidity and mortality, and this new treatment could therefore represent an important advance if confirmed in a larger population over a longer follow-up.

Cardiac magnetic resonance is undoubtedly one of the most important imaging tools for diagnosis, risk stratification, and treatment planning. A recent review summarized advances applied to CHD such as 3 D flow imaging, which helps to elucidate underlying pathophysiology, and tissue characterization techniques such as T<sub>1</sub> mapping, which can detect clinical features of tetralogy of Fallot and systemic right ventricle.<sup>6</sup> The article also emphasizes the need to carefully manage gadolinium contrast agent administration to patients who will require repeat examinations throughout life from an early age.

On a final note, the past year saw a continued dearth of randomized studies in large CHD cohorts; moreover, a high proportion of published articles reported retrospective single-center studies, demonstrating the enormous potential for future research in this area.

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