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Cardiac Involvement in a Patient Cohort With Val30Met Mutation Transthyretin Amyloidosis

Daño cardiaco en una cohorte de pacientes con amiloidosis por transtiretina por la mutación Val30Met

To the Editor,

Hereditary transthyretin amyloidosis is an autosomal dominant disease caused by mutations in the transthyretin gene. Of the more than 100 such mutations reported, Val30Met is the most common; the condition is called familial amyloidotic polyneuropathy (FAP) or Corino de Andrade disease in patients with predominant neurological damage.[1] Identification of patients whose amyloidosis is due to a genetic defect is vital because such information affects the treatment strategy and is of great importance for relatives.[2] Although its worldwide prevalence is low, various endemic foci have been described. The island of Mallorca currently has the fifth highest number of affected individuals, behind Portugal, Sweden, Japan, and Brazil. In addition, Spain has another endemic focus, albeit smaller, in Valverde del Camino (Huelva).[3] Individuals with the Val30Met mutation generally present with peripheral neuropathy and progress to autonomic and motor neuropathy, with late onset of cardiac conduction disorders and without cardiac hypertrophy.[4] Currently approved treatments for FAP include liver transplant and tafamidis, a drug that stabilizes transthyretin. The other drugs under study show promising initial results. Current recommendations are to begin drug therapy or consider liver transplant at the first appearance of neurological signs and symptoms. Cardiac amyloidosis is one of the main causes of death in FAP but many of these patients with cardiac involvement are underdiagnosed.[5]

Our objective was to evaluate cardiac involvement in a large series of patients with FAP because this aspect of the disease is poorly characterized in the literature due to its low prevalence, particularly in Spain, for which there are no published data. We reviewed the medical records of patients with FAP (positive genetic study findings for the Val30Met mutation in the transthyretin gene in all patients and the presence of amyloid in subcutaneous fat, rectal, and salivary gland biopsy in all symptomatic patients). Demographic, clinical, electrocardiographic, echocardiographic, and Holter monitoring data were collected, as well as cardiac magnetic resonance imaging and diphosphonate scintigraphy data if they had been performed. Cardiac involvement was defined as the presence of specific signs or symptoms, arrhythmias, atrioventricular (AV) conduction disorders, left ventricular hypertrophy on electrocardiography (ECG) or echocardiography, or late enhancement on cardiac magnetic resonance imaging. Data from 132 patients were analyzed (Table): 104 symptomatic carriers (78.8%) and 28 asymptomatic carriers (21.2%). The mean ages were

Table
Clinical Data of the Patients Included in the Study

Variables	Total	Without cardiac involvement	With cardiac involvement	*P*
Sex (n = 132)				
Men	69 (52.2)	38 (50)	31 (55.4)	.2
Women	63 (47.8)	38 (50)	25 (44.6)	.1
Phenotype (n = 132)				
Asymptomatic carriers	28 (21.2)			
Symptomatic carriers	104 (78.8)	48 (46.2)	56 (53.8)	.05
Age at diagnosis, y	47.4 ± 17	42.9 ± 16	53.6 ± 17	0.03
Age at follow-up, y	57.2 ± 16.4	51.3 ± 15	65.3 ± 15	.01
Polyneuropathy (n = 104)	83 (79.8)	37 (50.7)	46 (85.2)	< .001
Nephropathy (n = 104)	22 (21.2)	5 (7.8)	17 (31.0)	< .001
Palpitations			19 (15.0)	
Dyspnea			13 (10.4)	
Syncope			5 (4.0)	
Heart failure			13 (9.8)	
Dysautonomia symptoms			26 (20.6)	
Pathologic ECG			39 (36.0)	
Conduction changes				
Sinus node dysfunction or atrial fibrillation			13 (9.8)	
AV block			17 (12.9)	

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Table *(Continued)*
Clinical Data of the Patients Included in the Study

Variables	Total	Without cardiac involvement	With cardiac involvement	*P*
First degree			11 (8.3)	
Second degree			3 (2.3)	
Third degree			3 (2.3)	
Branch block			12 (9.1)	
Left bundle-branch block			7 (5.3)	
Maximum thickness of the LV, mm (n = 81)			11.2 ± 3.2	
≥ 11 mm			19 (23.5)	
≥ 15 mm			10 (12.3)	
LVEF, % (n = 97)			61 ± 6	
< 50%			4 (4.1)	
Diastolic dysfunction			35 (46.0)	
Abnormal relaxation			24 (31.6)	
E/E', ms			11.5 ± 4	
Pacemaker			9 (6.8)	
Liver transplant	54 (41.0)	23 (30.3)	32 (57.0)	< .001
Death	22 (16.7)	4 (5.3)	18 (32.0)	< .001

AV, atrioventricular; ECG, electrocardiography; LV, left ventricle; LVEF, left ventricular ejection fraction.

47.4 ± 17 years at diagnosis and 57.2 ± 16.4 years at follow-up; 69 (52.2%) were men. Of the symptomatic carriers, 83 (79.8%) had polyneuropathy and 56 (53.8%) had some symptom of cardiovascular or cardiac involvement: 15% had palpitations; 10.4%, dyspnea; 4%, syncope; 20.6%, dysautonomia symptoms; and 9.8%, heart failure. The ECG was pathological in 39 patients (36%), due to signs of left ventricular hypertrophy, arrhythmias, or AV conduction changes: 13 (9.8%) with sinus node dysfunction or atrial fibrillation (bradycardia-tachycardia syndrome), 17 (12.9%) with different degrees of AV block, and 12 (9.1%) with His bundle-branch block. The mean maximum thickness of the left ventricular wall was 11.2 ± 3.2 mm, with a left ventricular ejection fraction of 61 ± 6%; 19 patients (23.5%) had a left ventricular wall thickness ≥ 11 mm and 10 (12.3%) had a thickness ≥ 15 mm. Of these 10, 5 underwent cardiac magnetic resonance imaging, with 3 showing late gadolinium enhancement in the subendocardial region in the characteristic ring shape (Figure). In addition, 46% had diastolic dysfunction and 9 (6.8%) required pacemaker implantation during follow-up due to sinus node dysfunction or advanced AV block. Liver transplant was performed in 54 patients (41%), as well as 1 combined heart-liver transplant; 11 patients received tafamidis in recent years. During follow-up, 22 patients (16.7%) died.

Although the cardiac involvement was clinically evident only in the late phase of the disease (these patients were 10 years older than those who only had the neurological phenotype), it was associated with greater comorbidity and was significantly linked to increased mortality (P = .003). On multivariable analysis, the parameters independently related to mortality during follow-up (P < .05) were pathological ECG, AV block, heart failure, pacemaker, neurological involvement, and renal failure. Mean duration from symptom onset to death was 7.3 years.

In conclusion, our results, based on a relatively large series given the low prevalence of the disease, provide additional information on FAP and help to describe its demographic characteristics, clinical presentation, diagnosis, and clinical course. FAP is a rare disease that not only causes classic neurological symptoms, as has been thought for many years, but also has a relatively frequent cardiovascular involvement, particularly pathological ECG, rhythm disturbances and AV conduction disorders, left ventricular hypertrophy with diastolic dysfunction, and dysautonomia symptoms, and is associated with increased

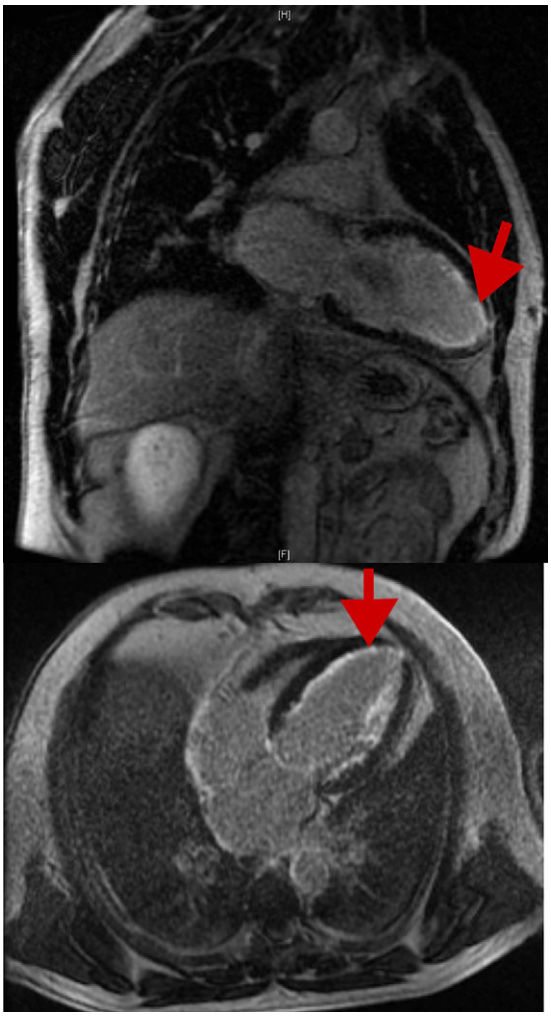

Figure. Cardiac magnetic resonance imaging of a patient with hereditary transthyretin cardiac amyloidosis. Diffuse subendocardial late gadolinium enhancement in the shape of a ring (arrows).

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morbidity and mortality. Compared with Portugal, Sweden, and Japan, the endemic area of Mallorca shows more frequent left ventricular hypertrophy and heart failure and worse prognosis. Cardiologists should perform close follow-up of these patients–with annual ECG, echocardiography, and Holter monitoring–and expand the evaluation (eg, cardiac magnetic resonance imaging, diphosphonate scintigraphy) in the presence of symptoms or changes.

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Coronary Angiography and Interventions in Patients With Hereditary Hemorrhagic Telangiectasia

Angiografía coronaria e intervencionismo en pacientes con telangiectasia hemorrágica hereditaria

To the Editor,

Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome is a rare autosomal dominant vascular disorder caused by mutations in the endoglin, *ACVRL1* or *SMAD4* genes that encode proteins involved in the transforming growth factor-beta superfamily, resulting in multiorgan vascular dysplasia. Clinical manifestations include spontaneous epistaxis, gastrointestinal bleeding, anemia, mucocutaneous telangiectasia, and multiorgan arteriovenous malformations.[1]

Cardiovascular involvement encompasses high-output heart failure, paradoxical emboli, and venous thromboembolism. Arrhythmias are common, whereas myocardial infarction rates appear to be low.[1,2]

Coronary angiography (CA) and percutaneous coronary intervention (PCI) in patients with HHT can be challenging in terms of the underlying coronary anatomy (atheromatosis, spontaneous coronary artery dissection [SCAD], and spasm), technical aspects, antithrombotic therapy, and increased bleeding risk.[2–4] We sought to assess the potential risks of CA and PCI in HHT patients by identifying retrospectively all HHT patients undergoing CA in the University Hospitals of Leuven between January 2002 and July 2017.

During this 15-year period, 655 HHT patients were followed up in our tertiary referral center and 18 underwent a CA. A full list of baseline characteristics is summarized in the Table. Six patients (33.3%) underwent CA due to an acute coronary syndrome (ACS), 2 patients (11.1%) due to stable angina, 5 (27.7%) due to heart failure, 3 (16.6%) due to valvular disease, and 2 (11.1%) as part of pretransplant work-up. Thirteen patients (72.2%) had normal coronaries whereas 5 (27.8%) had abnormal findings. Coronary artery disease was noted in 2 patients (11.1%), 1 presenting with a ST-segment elevation myocardial infarction (STEMI) treated with a bare-metal stent in the left anterior descending (LAD) and 1 with unstable angina treated with a bare-metal stent in the right coronary artery. Three patients (16.7%) exhibited SCAD of the LAD, 1 presenting as a STEMI treated with a drug-eluting stent and 2 as a non-STEMI treated conservatively. One ACS presenter had normal coronaries. Periprocedural complications occurred in 3 patients (16.6%), all ACS presenters. Accordingly, 3 out of 6 HHT patients (50%) undergoing CA in the context of an ACS had a major periprocedural complication, 2 of which occurred during PCI.

The first patient, a 67-year old man presenting with unstable angina, experienced a type-D dissection with a spiral luminal filling defect during PCI of the right coronary artery, which was treated with a bare-metal stent. The second patient, a 73-year old woman, presented with a STEMI and CA showed SCAD with TIMI flow 0 in the LAD. Predilatation with an undersized balloon,

Table
Baseline Characteristics (n = 18)

Age, y	61.6 ± 12.9
Male sex	5 (27.8)
Body mass index	19.6 ± 11.7
Current smoker	6 (33.3)
Hypertension	6 (33.3)
Hyperlipidemia	3 (16.7)
Diabetes mellitus	0 (0.0)
Renal dysfunction	1 (5.6)
Prior coronary artery bypass graft surgery	1 (5.6)
History of myocardial infarction	6 (33.3)
History of stroke	2 (11.1)
Peripheral vascular disease	3 (16.7)

Values are expressed as mean ± standard deviation or No. (%). Renal dysfunction was defined as serum glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.