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Short Communication
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Octogenarian Sisters with Transthyretin Cardiac Amyloidosis: Does Family Matter?

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Short Communication

Cardiac Amyloidosis (CA) is a disorder that can occur with different clinical manifestations due to an abnormal protein (Amyloid) that can be deposited in the heart tissues [1]. Cardiac amyloidosis has multiple subtypes, the most frequent forms in our country (Spain) being primary amyloidosis due to light chain deposits (LA-CA) and transthyretin deposit CA (ATTR-CA). The latter has an inherited variant (ATTRh) and a mutant or senile variant (ATTRwt) [2].

We present a curious report of two octogenarian sisters who were independently diagnosed in 2019 with ATTR-CA by two different cardiologists; the 87-year-old debuted at this age with a clinical scenario of Heart Failure (HF) with preserved ejection fraction and left ventricular hypertrophy (interventricular septum: 20 mm, left ventricular ejection fraction-LVEF 64%, left atrium volume 35 mL/m^2, NT-ProBNP 1737 pg/mL; Figure 1A), with a pseudoinfarction pattern (Q image) in V1 to V3 in the electrocardiogram (Figure 1B). An infiltrative deposit disease was suspected, because of this severe degree of ventricular hypertrophy. The younger sister, 82 year-old, had a previous history of syncope with mild conduction disorders in the electrocardiogram (left anterior hemiblock), and required implant of a pacemaker several years ago because of atrial fibrillation with slow ventricular rate (Figure 1C). She subsequently developed congestive HF with reduced ejection fraction (LVEF 20%, left atrium volume 39 mL/m^2, NT-pro BNP 16,246 pg/mL). Echocardiogram also showed a severe left ventricular hypertrophy, being interventricular septum 21 mm (Figure 1D). A diagnosis of transthyretin deposit was made in both sisters, according to Gillmore et al. [3]: Grade 3 uptake of Perugini's classification in bone scan ^{99m}Tc-DPD (Figure 1E, 1F), and exclusion of AL-CA by demonstrating the absence of a monoclonal peak in the serum and/or urine immunofixation test. Blood samples from the two sisters were sent for genetic study, and conventional sequencing by Sanger's method indicated that the TTR gene sequence was normal in both. This was quite a surprise, as we thought we were facing a clear case of ATTRh, and the absence of genetic alterations in the sequencing of the TTR gene showed two matching cases in the same ATTRwt family.

Reviewing this case, we would like to point out several essential aspects of ATTR-CA:

- **Variability in clinical presentation of the disease:** TTR-CA can presented with severe left ventricular hypertrophy, HF with preserved ejection fraction [4], HF with reduced ejection fraction [5], and conduction disorders leading to syncope and need for a pacemaker [2]. Al of them due to the progressive deposit of Amyloid material by transthyretin in the different cardiac structures (myocardium and conduction system).

- **The false belief that we are facing a low-prevalence disease.** This case shows it is necessary to test this diagnostic entity in certain patient profiles, because the prevalence is not low. Even in the same family, several sporadic cases of the disease (ATTRwt) may appear, as occurred in our report. There are already published series where up to 5% to 13% of patients with HF with preserved ejection fraction [4] and up to 11% with HF with reduced ejection fraction have Amyloid deposit per transthyretin [5].

- **The need for a genetic study to sequence the TTR gene for pathogenic variants.** As in this case, normal sequencing excludes the possibility of ATTRh, which has diagnostic implications for the family (they would not require a cardiological study or follow-up) and also therapeutic implications, because it excludes the possibility of using treatments thus far only approved for

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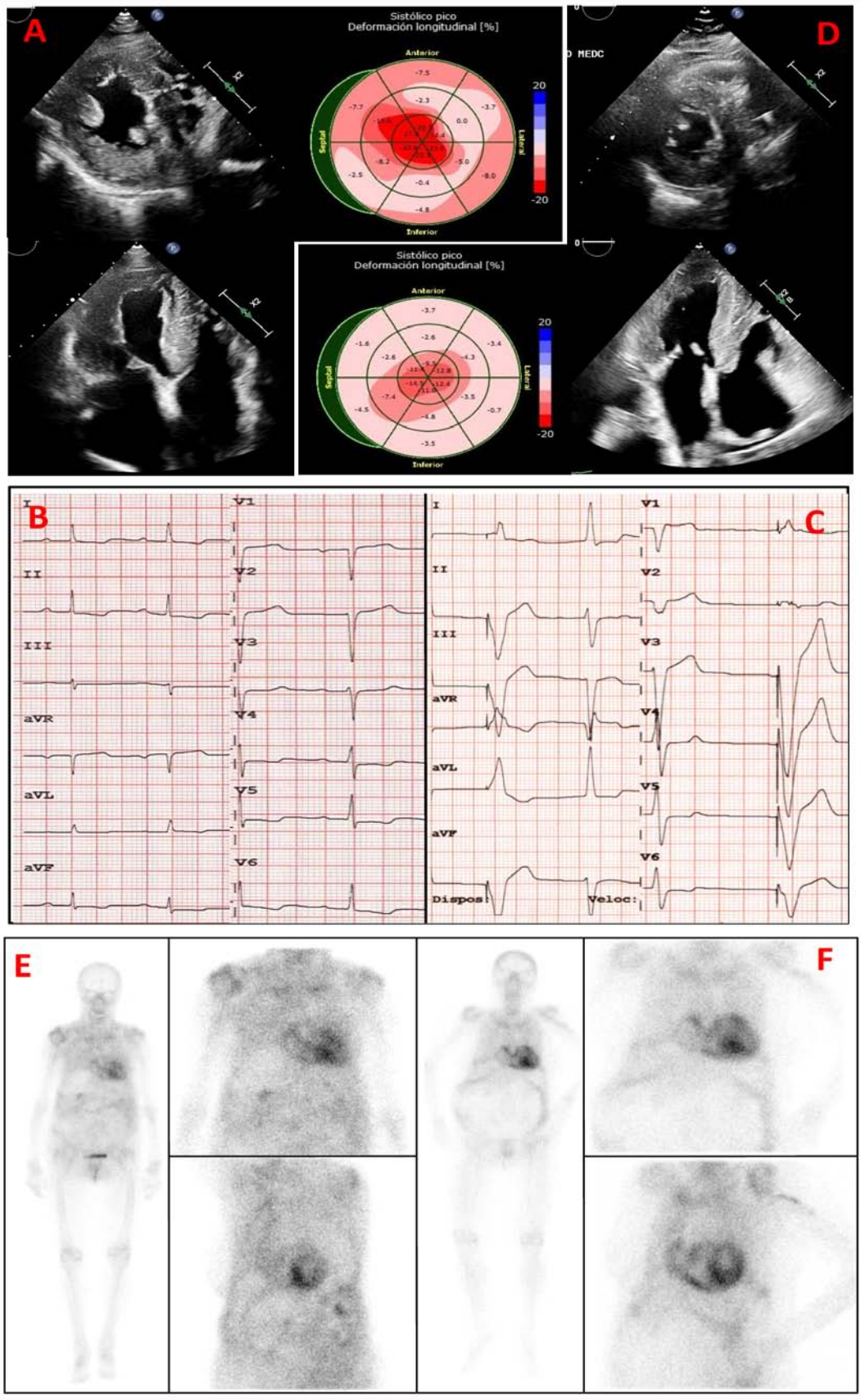

Figure 1: A, D) Transthoracic echocardiograms in short axis and apical four chambers with significant ventricular hypertrophy and left atrial dilation, as well as the typical pattern of cardiac amyloidosis in the longitudinal strain known as "bull's eye"; B) Surface electrocardiogram showing pseudo Q pattern in V1 to V3 derivations; C) Surface electrocardiogram showing a left anterior hemiblock in pacemaker-carrying patients; E and F) Uptake grade 3 of Perugini classification in bone scan with ^{99m}Tc-DPD.

ATTRh and not for ATTRwt.

Learning Points

1. Transthyretin Cardiac amyloidosis is an infiltrative cardiomyopathy that has a high variability in its clinical presentation.

2. Transthyretin Cardiac amyloidosis requires genetic testing to rule out hereditary causes.

3. There is a false belief in the low prevalence of transthyretin cardiac amyloidosis.

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