CASE REPORT

First-degree Atrioventricular Block as an Early Marker of Advanced Disease of the Conduction System in a Patient with Hereditary Val142Ile Cardiac Amyloidosis

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Introduction

Cardiac amyloidosis (CA) is a type of restrictive cardiomyopathy secondary to amyloid infiltration in the heart. The most common clinical forms are immunoglobulin light chain amyloidosis (AL) and amyloidosis resulting from amyloid deposits secondary to the destabilization of the protein tetramer transthyretin (ATTR), which is divided into two types: the hereditary form (ATTRm) and the wild type (ATTRwt).[1]

Cardiac impulse conduction disorders and atrial arrhythmias are more frequent in ATTR than in the AL form, and this seems to reflect the longer survival of patients affected by ATTR, given that the AL form manifests with high mortality up to 6 months from diagnosis,[2] because conduction system disease appears to be a later manifestation.

Electrocardiogram (ECG) is a useful tool for follow-up of patients with cardiac arrhythmias and conduction system disorders. This exam, which is widely used and easy to perform, can predict the future need for pacemaker (PM) implantation in the general population and, potentially, in this population.[3,4]

Keywords

Cardiomyopathy; Familial Amyloidodis/complications; Atrioventricular Block/genetics; Artificial Pacemaker; Bradycardia/complications; Sick Sinus Syndrome/genetics; Diagnostic Imaging.

Case report

A white, 66-year-old, male patient, with body mass index of 20.7 kg/m², was attended for the first time in 2017 after his first episode of post-exertion syncope, without any other symptoms. He referred only treatment for benign prostatic hyperplasia with finasteride, without any other comorbidities. His first-degree uncle had died suddenly at the age of 60 years. He brought the following tests that had been performed during the same year: transthoracic echocardiogram with left ventricular hypertrophy (septum: 16 mm and posterior wall: 14 mm), left ventricular ejection fraction (LVEF) of 76%, E/A: 2.02, and indexed left atrial volume: 40 ml/m². Initial ECG showed sinus rhythm, low voltage QRS in frontal plane, amputation of anteroseptal R waves, heart rate (HR): 94 bpm, PR interval: 160 ms, and normal ventricular repolarization (Figure 1). Due to the mismatch between the degree of left ventricular hypertrophy on the transthoracic echocardiogram and the ECG findings, an investigation focused on CA was initiated. The following were ordered: cardiac magnetic resonance imaging (Figure 2), which showed a pattern suggestive of CA; 24-hour urine and blood immunofixation; and serum free light chain assay, which excluded the AL type as the cause of amyloid deposition. Myocardial scintigraphy with technetium pyrophosphate showed grade 3 uptake in the cardiac area (Figure 2), which raised high suspicion of ATTR, and, finally, genetic testing confirmed the Val142Ile mutation. Six months after diagnosis, the patient began complaining of fatigue on exertion and systemic venous

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congestion, which subsided after the association of furosemide 120 mg/day and spironolactone 25 mg/day, as well as initiation of cardiac rehabilitation. He started Tafamidis meglumine 20 mg/day in March 2018.

During the 4 years of follow-up, an unexplained drop occurred in 2018, and a loop recorder was implanted in November of that year, after initial investigation without diagnostic definition (24-hour Holter, normal tilt test, and conventional ECG without relevant changes in progression). During the following years, there was a progressive increase in PR interval, and first-degree atrioventricular block (AVB) emerged in 2019, preceding the manifestation of trifascicular block in 2020, the year when additional increase of the PR interval was observed (Figure 1).

The last transthoracic echocardiogram performed in August 2020 showed LVEF: 45%, left ventricular hypertrophy (septum and posterior wall: 18 mm), indexed left atrial volume: 53 ml/m^2, global longitudinal

strain of −11% with "cherry on the top" pattern, E/E' ratio: 15, and pulmonary artery systolic pressure: 30 mmHg. A treadmill stress test carried out during the same period revealed worsened functional class, compared to the exam performed in 2017 (in 2020, 6.5 METs; in 2017, 8.98 METs), worsening of chronotropic deficit (in 2020, 71% of maximal HR; in 2017, 74% of maximal HR), and drop in blood pressure during exertion and pressure rebound during recovery; the patient only complained of tiredness at peak exertion (in 2017, hemodynamic response was normal). There was no worsening of conduction disturbance on exertion, and the PR interval remained prolonged and fixed.

Prolonged monitoring with implantable loop recorder, except for atrial fibrillation flare-ups with low HR (which motivated the initiation of anticoagulation in 2019), did not show any arrhythmias that were symptomatic or subject to low brain output, until January 2021, when extreme bradycardia was recorded
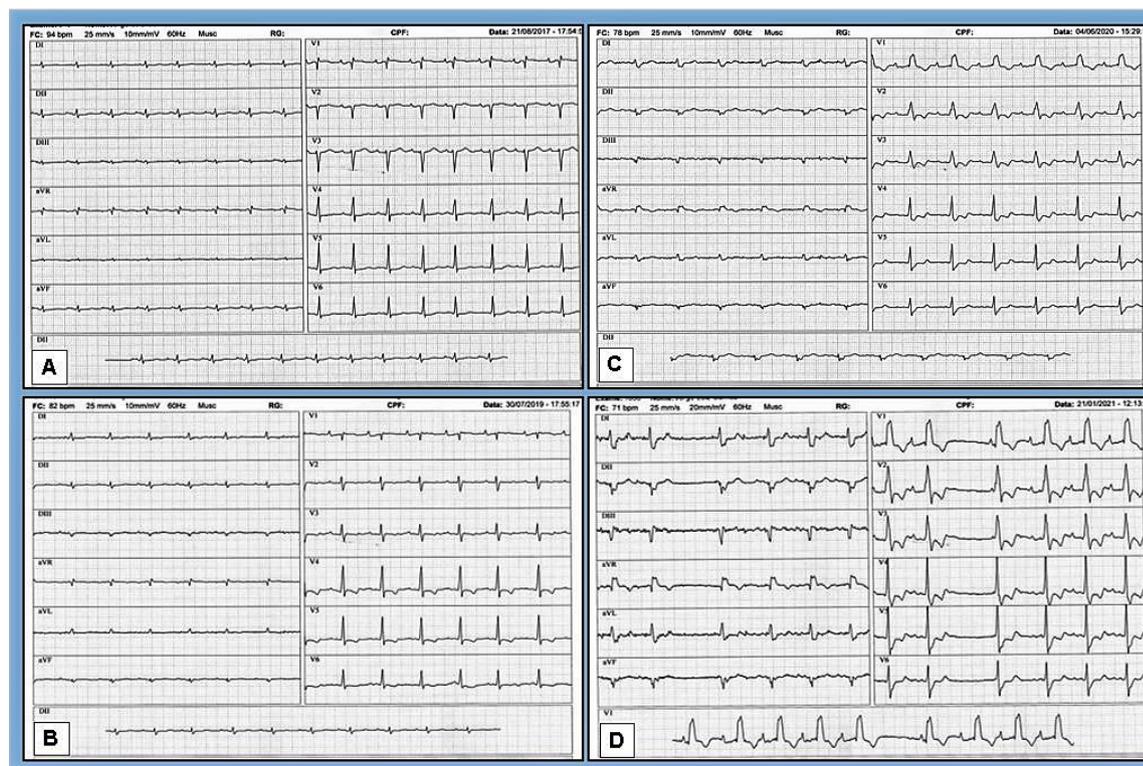

Figure 1 – Electrocardiograms performed annually.

A – ECG from 2017: sinus rhythm, HR: 94 bpm, PR interval: 160 ms, left and right atrial enlargement, low voltage in the frontal plane, and amputation of the anteroseptal R wave. B – ECG from 2019: sinus rhythm, HR: 82 bpm, PR interval: 220 ms (first-degree AVB), more marked alteration in ventricular repolarization from V4 to V6. C – ECG from 2020: sinus rhythm, HR: 78 bpm, PR interval: 240 ms (progression of first-degree AVB), onset of third-degree right bundle branch block and left anterior fascicular block. D – ECG from 2021 in 2N: sinus rhythm, HR: 71 bpm, PR interval: 280 ms, third-degree right bundle branch block, left anterior fascicular block, and 2:1 sinoatrial block, followed by junctional escape.
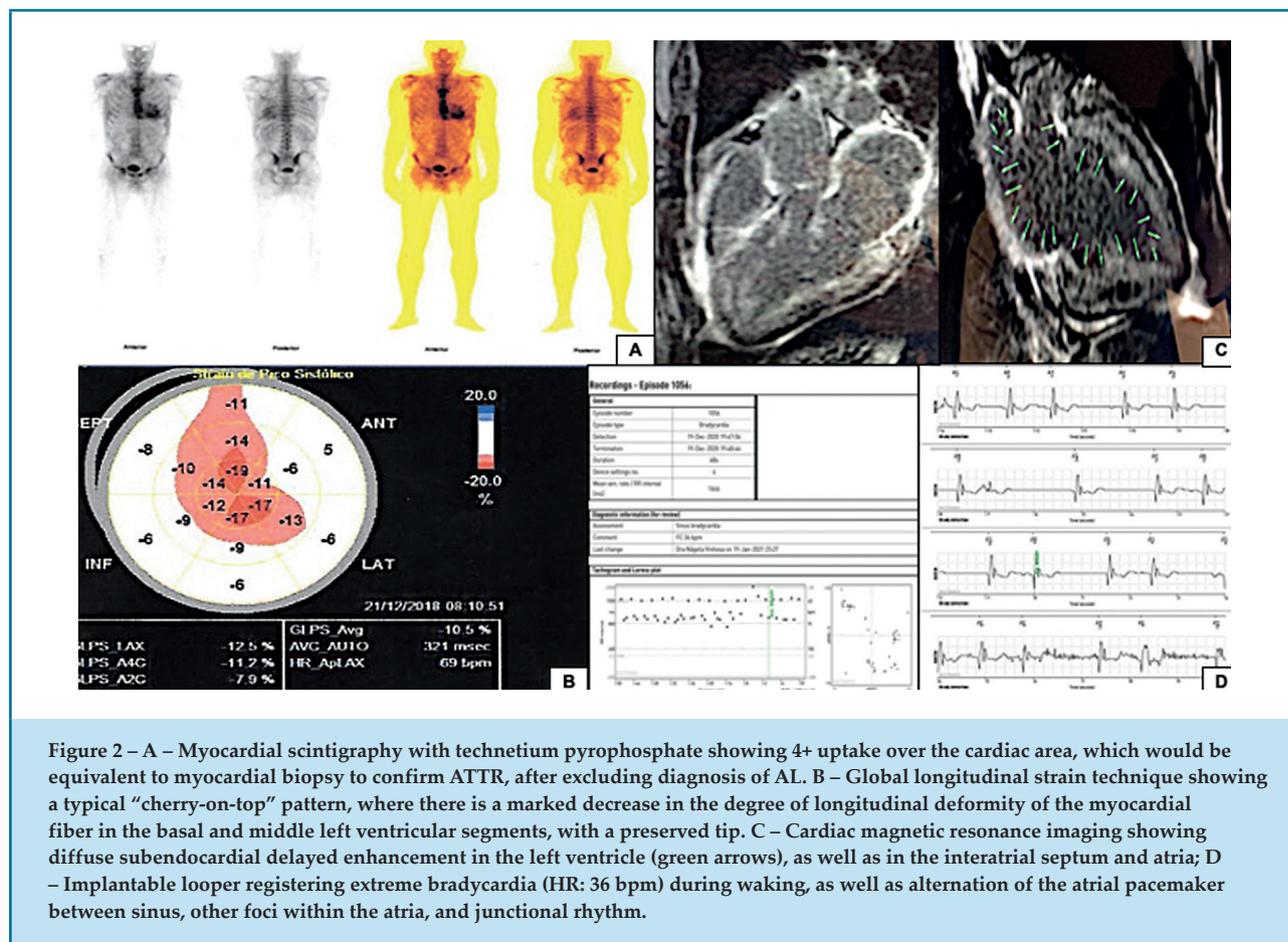
Figure 2 – A – Myocardial scintigraphy with technetium pyrophosphate showing 4+ uptake over the cardiac area, which would be equivalent to myocardial biopsy to confirm ATTR, after excluding diagnosis of AL. B – Global longitudinal strain technique showing a typical "cherry-on-top" pattern, where there is a marked decrease in the degree of longitudinal deformity of the myocardial fiber in the basal and middle left ventricular segments, with a preserved tip. C – Cardiac magnetic resonance imaging showing diffuse subendocardial delayed enhancement in the left ventricle (green arrows), as well as in the interatrial septum and atria; D – Implantable looper registering extreme bradycardia (HR: 36 bpm) during waking, as well as alternation of the atrial pacemaker between sinus, other foci within the atria, and junctional rhythm.

(HR: 33 bpm) during waking (Figure 2). The last ECG in 2021 also showed a 2:1 sinoatrial block, making both findings compatible with sick sinus syndrome (Figure 1). Implantation of a dual-chamber PM was indicated, with activity sensor on, with programming in the future to adjust PR interval during exertion.

Discussion

CA occurs as a result of deposition of insoluble amyloid fibrils within the cardiac tissue, which causes progressive myocardial (early diastolic and late systolic) dysfunction and arrhythmias. In the case reported, the disease is due to the mutation of the Val142Ile transthyretin gene (ATTRm) that makes this protein (which has the form of a tetramer) unstable, leading to its dissociation into unfolded monomers, which will in turn be deposited in the heart. This specific mutation has variable penetrance and a predominant (sometimes exclusive) heart disease phenotype, and is the most common mutation in the United States, occurring in 3% to 4% of African Americans,

with median survival of 3.5 years.[5,6]

The natural history of ATTR includes complicated progressive heart failure (HF), which initially manifests with a phenotype of HF with preserved ejection fraction (HFpEF),[7] due to arrhythmias and conduction system disorders. The extent of cardiac involvement is the major prognostic determinant. Approximately 13% of adult patients hospitalized for HFpEF have ATTR.[1,6] Furthermore, a study conducted in London found that, in the Afro-Caribbean population with HFpEF, Val142Ile ATTRm was responsible for the etiology in 8.5% of cases, and 11.4% of cases were caused by all types of CA.[8]

Diastolic dysfunction plays a key role in the pathophysiology of HFpEF, which leads to increased filling pressures at rest and/or during exertion, leading to symptoms such as dyspnea and decreased functional capacity. Numerous other cardiovascular system abnormalities contribute to the clinical syndrome of HFpEF, including decreased systolic reserve, left atrial dysfunction, pulmonary hypertension, vascular stiffness, pericardial restriction, microvascular dysfunction, and

chronotropic incompetence.[9] It is believed that both decreased contractile reserve (evident from altered global longitudinal strain, even with normal LVEF, since the degree of longitudinal fiber strain contributes to contractility) and chronotropic incompetence contribute to decreased cardiac output (marked during exertion), which is compatible with the symptoms of fatigue and pre-syncope on exertion in the case reported as present from 2020 onwards.

In the patient whose case has been reported, the onset of first-degree AVB preceded the presence of trifascicular block by 1 year (Figure 1); it also preceded the implantable looper's recording of bradycardia (HR < 40 bpm) during waking by 2 years (Figure 2).

First-degree AVB has always been considered a benign finding, given that it is only a delay in conduction through the atrioventricular node, and it is usually supra-Hisian. However, extreme forms of first-degree AVB (PR interval > 300 ms) can cause symptoms compatible with PM syndrome, as atrial systole occurs very early during diastole, resulting in an ineffective or diminished contribution to cardiac output, culminating in shortened diastole and mitral and tricuspid diastolic regurgitation.[10] This deleterious effect may be more pronounced in HF patients with a long PR interval, as in the case reported, where the PR interval was 280 ms. Furthermore, 2 studies derived from the Framingham cohort drew attention to the potential negative impact of the presence of first-degree AVB on overall cardiovascular morbidity and mortality. In the first, Schnabel et al.,[11] developed a risk score for the development of atrial fibrillation, and, along with advanced age, hypertension, and HF, first-degree AVB was also a predictor event.[11] In the other study, Cheng et al.[12] investigated 7575 individuals, and 124 (1.6%) of whom had first-degree AVB, which was associated with a 2-fold increase in the incidence of atrial fibrillation and a 3-fold increase in the incidence of PM implantation, in addition to moderately increased risk of all-cause mortality.[12]

Bradyarrhythmias secondary to both autonomic dysfunction and infiltration of the sinus node and the conduction system (which seems to have occurred in this case, analyzing the electrocardiographic evolution) are commonly found in ATTR; however, the ideal time for definitive PM implantation has yet to be defined[1]. Among cohorts of patients with advanced CA, electrophysiological study has demonstrated a high burden of conduction system disease, including increased HV intervals, even among patients with normal QRS duration.[13]

Donellan et al.[14] found a high prevalence of high-grade AVB requiring definitive PM implantation in a cohort of 369 patients with ATTR. Approximately 9.5% were diagnosed with ATTR at the time of definitive PM indication, and, at an additional 28-months of follow-up, 10% of patients with ATTRm and 12% of patients with ATTRwt had high-grade AVB with indication for definitive PM. The most evident conduction abnormalities on baseline ECG were increased QRS duration (present in 51% of patients with ATTRwt and 48% of patients with ATTRm), followed by first-degree AVB (present in 39% of patients with ATTRwt and 43% of patients with ATTRm), but only increased QRS duration was associated with the development of subsequent high-grade AVB in their study.[14] This may reflect that progression of the deposition intensity in the conduction system of the heart with first-degree AVB is an early, but not a categorical marker of the future need for definitive PM implantation, depending on the evolution of the disease and the early initiation of treatment.

Therefore, conduction system abnormalities present on surface ECG, including first-degree AVB, seem to be a manifestation of advanced disease. In the case reported, PM was indicated due to the presence of sinus node disease, in spite of its coexistence with trifascicular block, which also infers impairment of the infra-His conduction system, but we were not able to confirm this hypothesis, because the patient did not undergo electrophysiological study.

Similarly to ATTR, other heart diseases that affect the cardiac conduction system, as well as the autonomic innervation of the heart, such as Chagas disease and Fabry disease (a lysosomal storage cardiomyopathy of uncleaved glycosphingolipids) also evolve with bradyarrhythmias and impairment of the cardiac conduction system that manifests as sinus node disease and AVB as the disease progresses. In Fabry disease, PR interval > 200 ms (3% of cases) and increased QRS duration > 120 ms (9% of cases) are independent predictors of the future need for definitive PM implant,[15,16] which is compatible with the clinical evolution of the patient in the case reported.

In the absence of symptomatic chronotropic deficit on exertion (which was documented in the 2020 treadmill stress test), the current ACC/AHA/HRS guidelines[10] recommend definitive PM implantation in the presence of second-degree, Mobitz II AVB, high-grade AV block, and third-degree AVB, or sinus pause > 3 seconds; however, there is no specific recommendation for patients with CA, particularly in those (as in the case described) at risk of developing severe conduction system disorders, still

without a formal indication for definitive PM. In small cohorts of patients with the AL form and advanced heart disease, routine looper implantation showed that all cases of death were preceded by bradycardia (the majority with complete AVB).[1,17] Therefore, a lower threshold for indicating PM in patients with AC may be a reasonable decision, which still needs to be tested in future studies.

Regarding the best mode of cardiac pacing, the literature is still scarce in relation to whether the indication of cardiac resynchronization therapy is preferential to single right ventricular pacing in these patients, because the population of patients with HF for whom cardiac resynchronization therapy is more effective are those with left bundle branch block morphology, with the aim of reducing symptoms and LV size and to increase LVEF. In contrast, patients with CA have a small LV cavity, ECG with various manifestations of non-left bundle branch block conduction disturbances, and they often develop atrial fibrillation, which makes them less eligible for cardiac resynchronization therapy.[1] On the other hand, some case reports have demonstrated clinical and echocardiographic improvement in patients with advanced CA and HF. In a recent retrospective study including 78 patients with ATTR, cardiac resynchronization therapy led to improved LVEF and functional class, reduced mitral regurgitation, and stabilization of NT-ProBNP levels, in comparison with patients with only right ventricular pacing > 40%.[18] Considering that PM implantation in patients with ATTR can precipitate worsening of ventricular function with only right ventricular pacing > 40%, given the high incidence of first-degree AVB and high-grade AVB in this population, it is possible that a high percentage of right ventricular pacing occurs.[14] Furthermore, observational studies have shown that mechanical and electrical resynchronization seems to be more effective with His or left bundle branch stimulation (deep transseptal),[19] which makes it a candidate, in the near future, to be the preferred resynchronization method. While randomized studies have yet to be published to answer these questions, the decision regarding type of stimulation for patients with CA should be made after a multidisciplinary discussion, weighing the severity of symptoms and the risks, combined with the expected benefit. In our case, the decision was made to use dual-chamber stimulation with a right ventricular cable positioned in the high septum, initially, aiming to stimulate the conduction system in the most proximal region possible.

Conclusion

Clinical follow-up of patients with Val142Ile ATTRm should cover annual ECG as screening for progression of conduction system disease. The appearance of first-degree AVB during the course of the disease may predict the need for definitive PM 2 years in advance. This finding, however, requires further scientific evidence.

Author contributions

Conception and design of the research: Nunes NSV. Acquisition of data: Nunes NSV. Analysis and interpretation of the data: Nunes NSV. Writing of the manuscript: Nunes NSV, Benchimol-Barbosa PR. Critical revision of the manuscript for intellectual content: Mesquita ET, Mesquita CT, Benchimol-Barbosa PR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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