

Cardiomyopathy Related to Transthyretin Val30met Mutation in Hereditary Systemic Amyloidosis

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Introduction

Amyloidosis due to transthyretin (TTR) is the most common type of hereditary systemic amyloidosis. It is also known as familial amyloid polyneuropathy type I in view of its neurological manifestations. It is a condition with autosomal dominant inheritance mainly caused by a Val30Met mutation, in which the valine in position 30 is replaced by methionine, creating a mutant TTR protein¹. The TTR protein normally runs as a tetramer, but due to mutation, it tends to dissociate into monomers that assemble into amyloid fibrils that get deposited in the tissues. Such protein deposition is the essence of the pathogenesis of amyloidosis due to TTR accumulation mainly in the peripheral nervous system and heart. In the latter, it mainly causes ventricular wall hypertrophy, diastolic dysfunction and conduction disorders².

There is a relationship between amyloidosis and the nationality of those affected by it, being more frequent in people of Portuguese, Japanese and Swedish origin. Therefore, its recognition and study in Brazil is highly relevant due to the Portuguese colonization³.

Objectives

We describe the case of a patient with familial amyloidosis presenting heart complications, in order to discuss diagnostic advances, especially in the field of cardiovascular imaging, as well as therapeutic advances about this condition.

Case Report

Female patient, 32 years old, previously healthy, of Portuguese descent; four years ago she started having diarrhea, abdominal cramps, nausea and weight loss; she presented improvement with use of loperamide hydrochloride 2 mg, 1 tablet every 8 hours, and Thiorphan 100 mg, 1 tablet every 8

hours, associated with oral rehydration therapy. About three and a half years ago, she presented episodes of dizziness, muscle weakness and loss of sensation in the lower limbs. The patient underwent electromyography and biopsy of the left sural nerve, in which staining by Congo red showed amyloid substance deposits around vessels and endoneurium, giving grounds to the conclusion of a chronic axonal neuropathy by amyloidosis.

The patient has a family history of amyloidosis. Thus, a DNA sequence analysis in Exon2 of the TTR gene was requested, showing point mutation at position 1208, generating the G/A (Heterozygous) genotype, responsible for the Val30Met missense mutation. The diagnosis was of TTR-related hereditary amyloidosis, and a liver transplantation was therefore recommended; the patient awaits transplantation.

A year ago, she started having dyspnea on great effort, syncope, urinary incontinence, weakness, difficulty in walking and worsening of the sensitive condition.

Due to such condition and to the likelihood of cardiac involvement by the disease, the patient was sent to the Department of Cardiology of Hospital Universitário Antônio Pedro (HUAP) for further investigation. Her test showed hypophonic sounds, B4, systolic murmur (2+/6+) audible in all areas, especially in the aortic area and in the left sternal border, without irradiation and unchanged to dynamic auscultation. In the neurological test she was lucid and oriented, without focal signs, slowed walking, decreased algic, light tactile and thermal sensitivity, and reduced deep tendon reflexes in upper limbs and none in lower limbs.

Laboratory tests were ordered for diagnostic investigation purposes, whose results evidenced troponin of 0.01 ng/mL and Pro BNP of 581 pg/mL. Then, an electrocardiogram (Figure 1) and speckle tracking echocardiography were performed, showing increased parietal average thickness, even without an increase in the LV mass index (Figure 2).

The procedure indicated was the placement of cardiac pacemaker, beginning treatment of oral anticoagulation with warfarin, 10 mg, 1 time a day, monitoring the INR; prescription of Tafamidis 20 mg, 1 time a day. The patient, however, awaits a court decision for the drug, not sold in Brazil. The patient was invited to participate in the research project on the evaluation of imaging methods in cardiovascular amyloidosis, approved by the ethics committee no. 384150. She filled out an informed consent form to authorize the use of her medical records in the research. Then, a skeletal scintigraphy was performed with ^{99m}Tc-MDP and ^{99m}Tc-DPD, showing no evidence of radiopharmaceutical uptake in heart topography and physiological distribution of the radiotracer by the bone scaffold (Figure 3).

Keywords

Cardiomyopathies/complications; Amyloidosis, Familial/ complications; Mutation; Prealbumin/genetics; Amyloid/genetics; Echocardiography.

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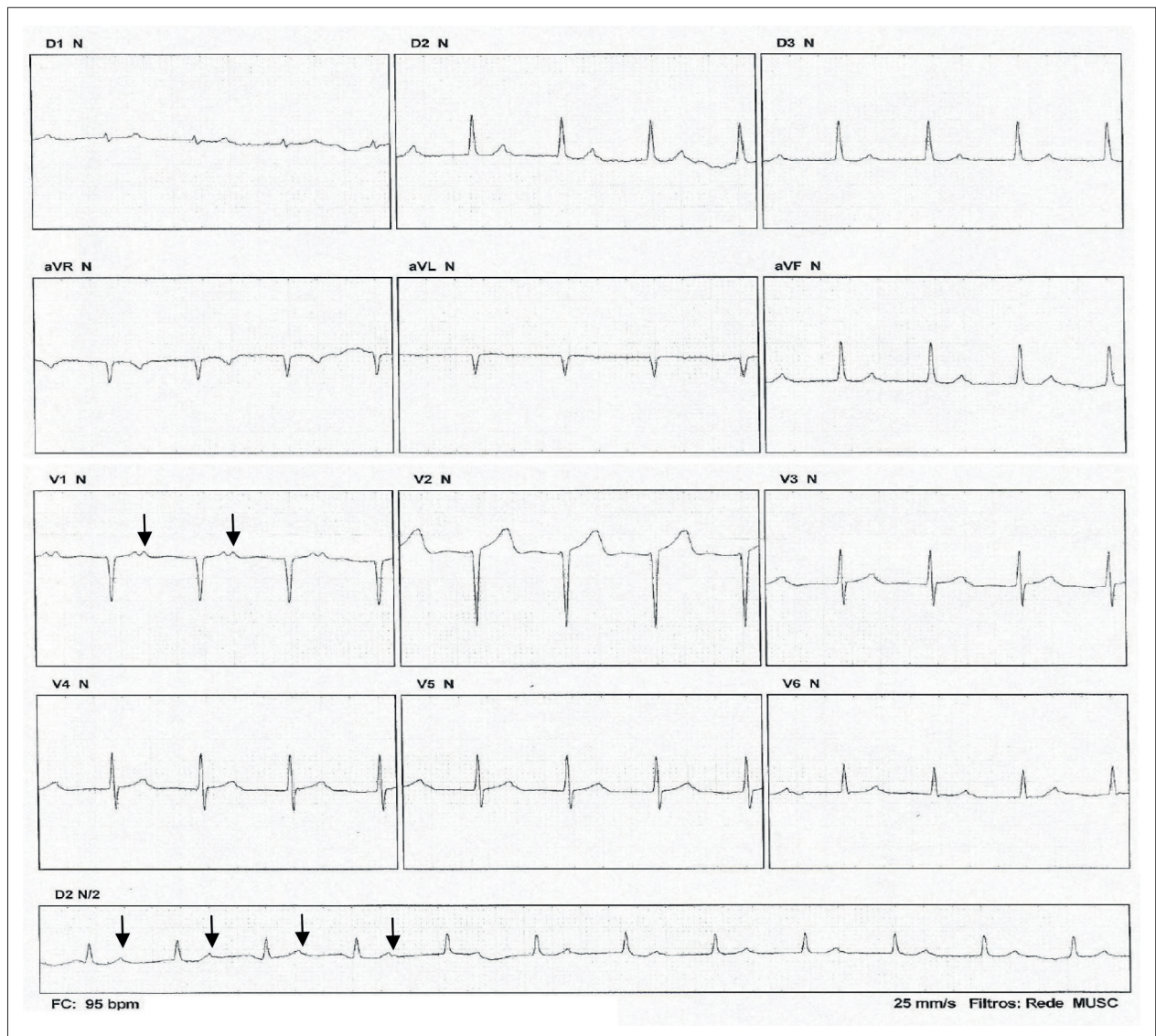


Figure 1 – Electrocardiogram with atrioventricular isorhythmic dissociation with 95 bpm heart rate, QRS angle of +90°, PR interval of 720 ms, low voltage in PF and decreased septal forces. The arrows show the P waves next to the end of the T wave. Arrows indicating p wave.

Discussion

TTR amyloidosis is a condition with autosomal dominant inheritance usually caused by a Val30Met mutation that generates the mutant TTR protein, although other mutations are associated with the disease⁴.

Most patients have nervous system involvement and may develop cardiac amyloidosis, both conditions observed in the case presented herein. Mutations that often induce cardiac involvement are SSA, V122I, V30M and T60A. The population of immediate risk to the clinical expression of cardiomyopathy by TTR are afrodescendants over 65 years old, with the V122I mutation. TTR deposits can occur in other tissues and produce a variety of symptoms¹.

Diagnosis requires histological identification of amyloid deposits with Congo red dye. Immunohistochemistry identifies the type of amyloidosis, but the electronic microscopy and mass spectrometry are more sensitive and specific. Cardiac biopsy remains the benchmark for the diagnosis of cardiac amyloidosis, but the approach integrating clinical treatment with noninvasive tests and the identification of amyloid deposits in extracardiac tissues can also be used⁴, as done in this case. The most frequent complementary tests for this purpose are echocardiography, cardiac MRI, ECG, whole-body skeletal scintigraphy with Technetium-99m Pyrophosphate, and heart scintigraphy with MIBG; and serum biomarkers, including B-type natriuretic peptide (BNP) and cardiac troponins (T or I)^{1,5}.

Case Report

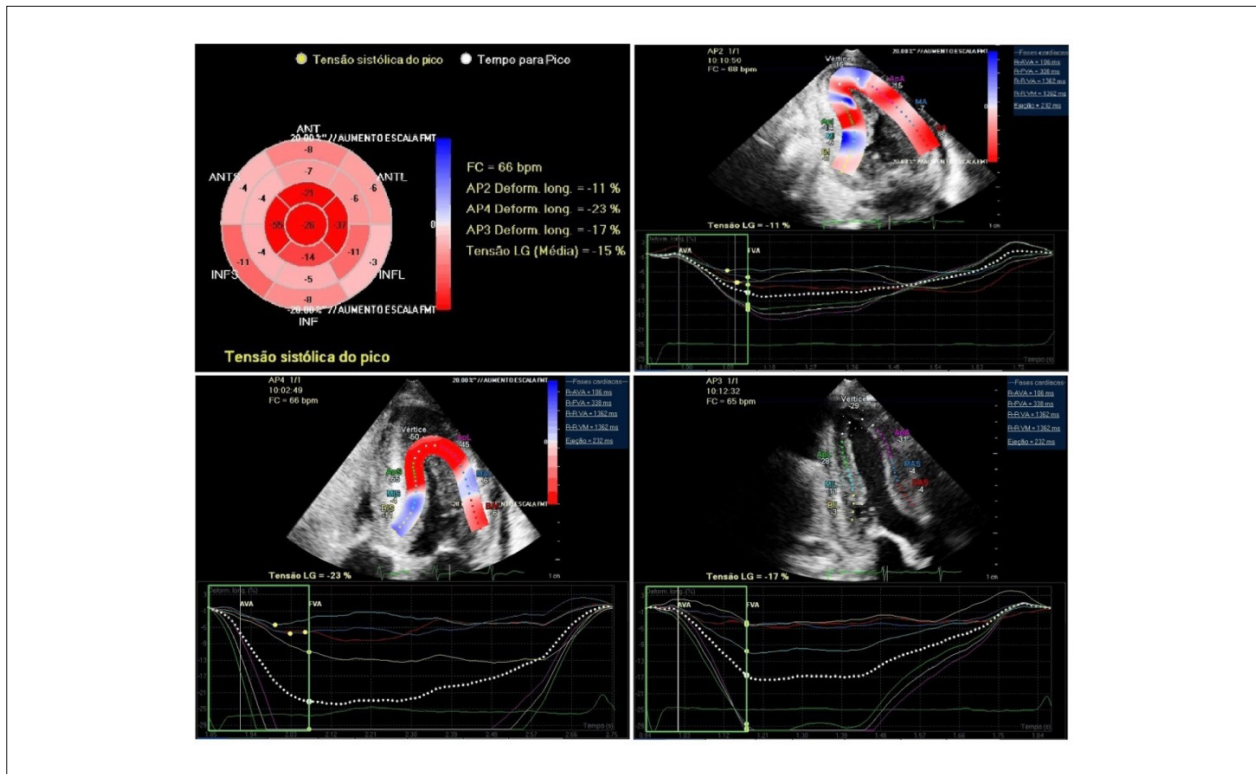


Figure 2 – Speckle Tracking Echocardiography of patient with amyloidosis. Videos and complete medical report attached.

Primary systemic amyloidosis has a strong relation with serum biomarkers, often detectable in disease. In TTR amyloidosis there is minor change in troponin T and troponin I levels, where pro BNP is a more sensitive marker⁶, as seen in our case. The changed plasmatic values of troponin in patients with amyloidosis are associated with the severity of cardiac involvement, and its use associated with pro BNP proved to be useful for monitoring the treatment and prognosis⁶. The typical findings in echocardiography are hypertrophy of the ventricular wall with myocardial speckled appearance, a reduction in left ventricle volume, valve thickening, atrial enlargement and signs of elevated filling pressures⁴. The increase in left ventricular wall thickness greater than 12 mm, in the absence of hypertension or other cause of hypertrophy are the main diagnostic features of amyloidosis. Our patient presented an increased parietal average thickness, even without an increase in LV mass index; this parameter is compatible with cardiac amyloidosis, and the patient has a genotype for ATTR and positive biopsy evidencing active disease in other organ. Patients with right ventricular hypertrophy, diastolic dysfunction and normal blood pressure should be considered for endomyocardial biopsy⁷. The Speckle Tracking echocardiogram has shown excellent accuracy in differentiating hypertrophy by hypertrophic cardiomyopathy from hypertrophy by amyloidosis⁸. The typical ECG findings are: low voltage associated with increased ventricular wall thickness; conduction abnormalities, such as atrioventricular blocks, presence of inactive areas, ventricular repolarization changes

and arrhythmias, atrial fibrillation¹. In our report, the patient presented an atrioventricular isorhythmic dissociation with 95 bpm heart rate, QRS angle of +90°, PR interval of 720 ms, low voltage in PF and decreased septal forces.

Myocardial scintigraphy with drugs sensitive to TTR protein offers a new possibility for noninvasive diagnosis. Studies with ^{99m}Tc-DPD radiotracer suggest that this drug is better than others in detecting the disease⁹. Nevertheless, ours tests with ^{99m}Tc-MDP and ^{99m}Tc-DPD tracers were negative in the case presented herein.

Treatment of cardiac amyloidosis is based on the symptomatic control of heart failure, using loop diuretics and spironolactone. Beta blockers are often poorly tolerated. The calcium channel blockers and digitalis are contraindicated due to the binding of amyloid fibrils and the potential toxicity of these agents. The management of arrhythmias should be compliant with the electrical function presented, often requiring anticoagulation¹. Liver transplantation is used in the treatment, but cardiac tissue reinfiltration is observed through years of monitoring. Heart transplantation associated with liver transplantation has been studied too, presenting good results⁴. Inhibitors of tetramers dissociation, as Tafamidis, a TTR tetramer stabilizer¹, have been studied, but they are not sold in Brazil, besides being expensive. The interference RNA (RNAi) therapy, which inhibits the transcription of RNAm that encodes TTR is in phase 1 of testing, and has shown a reduction of more than 80% of TTR serum levels in healthy volunteers¹⁰.

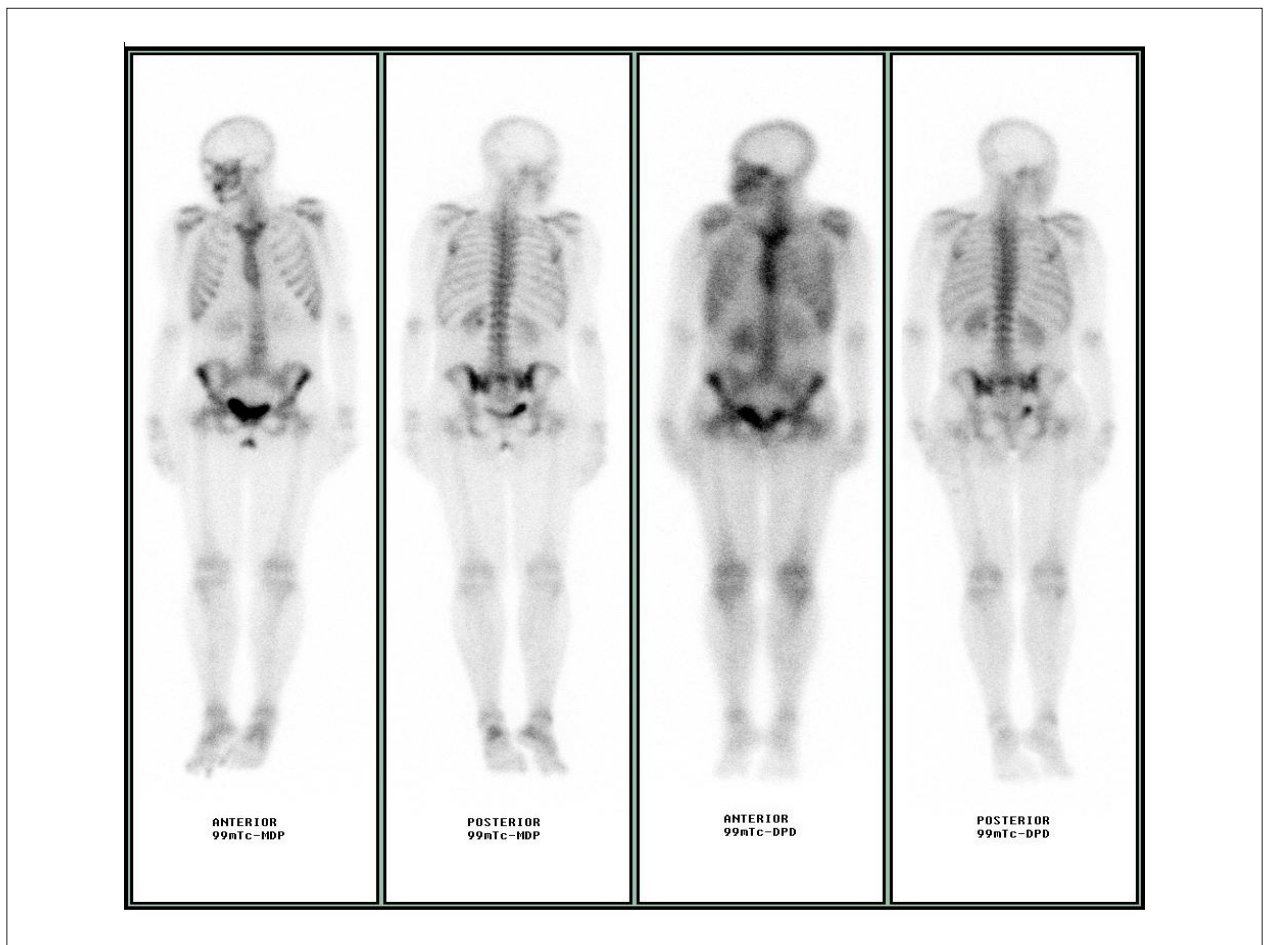


Figure 3 – Skeletal scintigraphy with ^{99m}Tc -MDP and ^{99m}Tc -DPD showed no abnormalities.

We presented a case of hereditary systemic amyloidosis by mutation in the gene that encodes the TTR protein, with cardiac repercussions. Although endomyocardial biopsy remains as the benchmark procedure, the evidence of amyloid deposits in other tissues, associated with abnormal cardiovascular imaging tests, has proven to be a feasible possibility of less invasive diagnosis. In our case, the echocardiogram with Speckle Tracking analysis proved useful for this purpose. Scintigraphy with ^{99m}Tc Technetium, which has shown encouraging results in several studies⁹, was negative in our case, with ^{99m}Tc -MDP and ^{99m}Tc -DPD, reinforcing the need for further studies in this field.

Authors' contributions

Research creation and design: Cordeiro CP; Pozzatti RR; Ferreira SG; Freitas MS; Rocha AM; Ribeiro ML; Nascimento OM; Mesquita CT. Data collection: Cordeiro CP; Pozzatti RR; Ferreira SG; Freitas MS; Rocha AM; Ribeiro ML; Nascimento OM; Mesquita CT. Data analysis and interpretation:

Cordeiro CP; Pozzatti RR; Ferreira SG; Freitas MS; Rocha AM; Ribeiro ML; Nascimento OM; Mesquita CT. Statistical analysis: Ferreira SG. Obtainment of funding: Mesquita CT. Manuscript drafting: Cordeiro CP; Pozzatti RR; Ferreira SG; Freitas MS; Rocha AM; Ribeiro ML; Nascimento OM; Mesquita CT. Critical revision of the manuscript for important intellectual content: Cordeiro CP; Pozzatti RR; Ferreira SG; Ribeiro ML; Nascimento OM; Mesquita CT.

Potential Conflicts of Interest

No relevant potential conflicts of interest.

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Academic Association

This study is not associated with any graduate program.

References

1. Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. *Circulation*. 2012; 126(10):1286-300.
2. Sattianayagam PT, Hahn AF, Whelan CJ, Gibbs SDJ, Pinney JH, Stangou AJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J*, 2012; 33(9):1120-7.
3. Planté-Bordeneuve V. The diagnosis and management of familial amyloid polyneuropathy. *Rev Neurol (Paris)*. 2006; 162(11):1138-46.
4. Banyersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review. *J Am Heart Assoc*. 2012; 1(2):e000364
5. Fadel B, Baldini L, Pergola V, Bulbul ZA, Di Salvo G. Myocardial deformation imaging and rare cardiomyopathies with hypertrophic phenotype: a review focused on Fabry disease, Friedreich ataxia and amyloidosis. *Cardiogenetics* 2013; 3:e4;
6. Biomarcadores em cardiologia – Parte 1 – Na insuficiência cardíaca e nas cardiomiopatias específicas. *Arq Bras Cardiol*. 2014; (online). ahead print. p.0-0.
7. Gertz M, Comenzo R, Falk R, Fermand J, Hazenberg B, Hawkins P, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol*. 2005; 79(4):319-28.
8. Baccouche H, Maunz M, Beck T, Gaa E, Banzhaf M, Knayer U, et al. Differentiating cardiac amyloidosis and hypertrophic cardiomyopathy by use of three-dimensional speckle tracking echocardiography. *Echocardiography*. 2012; 29(6):668-77.
9. Rossi P, Tessonnier L, Frances Y, Mundler O, Granel B. ^{99m}Tc DPD is the preferential bone tracer for diagnosis of cardiac transthyretin amyloidosis. *Clin Nucl Med*. 2012; 37(8):e209-10.
10. Coelho T, Adams D, Silva A, Lozeron P, Hawkins PN, Mant T, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med*. 2013; 29(9):819-29.