Recurrent Syncope: Initial Presentation of Transthyretin Amyloidosis. Benefits of Disease-Modifying Treatment

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Introduction

Syncope is a symptom that can occur in normal hearts, but it may also have multiple causes, both cardiological and neurological.¹ It is not frequently reported as an initial manifestation of cardiac amyloidosis, but, when it occurs, it can be determined by severe atrioventricular block, ventricular tachyarrhythmia, or, as we will describe in the following case report, autonomic dysfunction and postural arterial hypotension.² The objective of this study is to describe the case of a patient with transthyretin (TTR) cardiac amyloidosis, with the Val50Met mutation, historically known as Val30Met,, whose initial clinical presentation was syncope.

Case Report

JLS, a 63-year-old, white, male goldsmith, who was born in Bahia and resided in São Paulo, had a condition of recurrent syncope 2 years before he was first attended in the emergency room. It was preceded by feeling of heat and visual blackout, with quick recovery and without sphincter release or traumas; the episodes occurred immediately after the patient stopped walking. He also reported feeling precordial heaviness during routine exertion, weight loss of 15 kg over the past 6 months and erectile dysfunction for 2 years. He did not report any comorbidities or medication use. He reported paternal family history of heart failure without a defined etiology.

Physical examination did not show any significant alterations. Heart rate (HR) was 67 bpm, and blood pressure was 110/70 mmHg (lying) and 90/50 mmHg (standing). Laboratory test results included NT-proBNP of 898. Electrocardiogram showed sinus rhythm, inactive area of the inferior wall, poor R wave progression from V1 to V3. Holter showed no alterations, with average HR of 75 bpm, minimum of 63 bpm and maximum of 104 bpm. Exercise test showed depressed HR (chronotropic deficit of 58% and chronotropic index of 0.18). A pathological drop in systolic blood pressure was observed upon exertion, with

paradoxical increase during recovery and normal diastolic blood pressure, as well as rare, isolated polymorphic supraventricular extrasystoles. Carotid Doppler, cranial tomography, and myocardial scintigraphy with MIBI showed no alterations.

Tilt test was performed using a passive protocol without sensitization, showing chronotropic deficit (absence of HR increase after tilting), with postural hypotension 3 minutes after tilting (asymptomatic), and pre-syncope 5 minutes after tilting, as well as a significant drop in blood pressure, without alterations in HR, thus indicating a response of postural hypotension. (Figure 1) Echocardiogram showed preserved biventricular systolic function, grade I diastolic dysfunction, cardiac chambers with normal dimensions, widespread increase in the myocardial thickness of the left ventricle (septum 17 mm and posterior wall 13 mm) and the right ventricle, and absence of pulmonary arterial hypertension. Global strain was 15.1% with greater reduction in the middle and lower basal, lateral, anterior, and inferoseptal segments. There was mild pericardial effusion, largest lamina of 4 mm. (Table 1) Cardiac magnetic resonance imaging showed standard non-coronary, semi-circumferential endocardial late enhancement, in the basal and middle portions (sparing the inferolateral segment) and circumferential enhancement in the apical portion of the left ventricle, also involving the right ventricle, atria, and interatrial septum.

Laboratory exams were negative for light chain amyloidosis, with kappa:lambda ratio of 1.1 (reference value: 0.26 to 1.65). Serum and urine immunofluorescence showed no monoclonal peak. Dosage of the enzyme alpha-galactosidase A = 6.26, thus excluding Fabry disease. Technetium-99m labeled pyrophosphate scintigraphy for amyloidosis screening showed grade 3 and HTE/HTD ratio of 2.0.

During neurological evaluation, the patient demonstrated complaints of dysphagia, constipation, dysphonia, cough, pain in the lower limbs, muscle weakness in the legs and hands, weight loss, red eyes, and erectile dysfunction. Neurological examination revealed predominantly distal sensorimotor tetraparesis and distal muscle atrophy, with preserved proximal strength and reduced skin appendages in the distal region of the lower limbs. He showed distal lower and upper limb anesthesia for painful stimuli, postural kinetic change, areflexia, gait disorder, and reduced deep sensitivity. Conclusion: familial amyloidotic polyneuropathy stage I. Electroneuromyography showed chronic peripheral sensorimotor polyneuropathy affecting the lower limbs; it was primarily axonal in pattern, with total degeneration of the sensory nerve fibers, moderate to severe degeneration of the motor nerve fibers, and signs of chronic reinnervation.

Keywords

Familial Amyloidosis; Cardiomyopathy, Restrictive; Syncope; Primary Dysautonomias.

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Case Report

Genetic study provided evidence of the Val50Met mutation, confirming the diagnosis of hereditary TTR cardiac amyloidosis, with stage I neurological impairment. Treatment was subsequently initiated with tafamidis 20 mg on November 8, 2019, associated with fludrocortisone 0.1 mg per day. The patient evolved without any new complaints of syncope after receiving instruction to ingest more fluids, postural exercises, and physiotherapy, and he did not have any new cardiac symptoms. On August 13, 2021, he presented symptoms of dyspnea, and, upon physical examination, signs of visceral congestion were observed. During this evaluation, the fludrocortisone was discontinued, and furosemide 40 mg per day was prescribed. The patient lost 4 kg and relapsed to recurrent syncope, including a syncope episode when standing up at the doctor's office. Fludrocortisone was reintroduced; the diuretic was discontinued, and the patient became asymptomatic again.

NT-proBNP serum levels showed a elevation over time after the introduction of tafamidis, increasing from the initial value of 898 to 1823, and, on August 30, 2021, echocardiogram revealed preserved systolic function, a slight increase in wall thickness (19 mm), increased degree of diastolic dysfunction, and change from grade I (previously) to II, maintaining the degree of change in global longitudinal strain. (Table 1)

Discussion

The initial presentation of recurrent syncope is not a common diagnostic scenario for amyloidotic cardiomyopathy.³ Among the causes of syncope due to cardiomyopathy, atrioventricular block and ventricular tachyarrhythmia are common. In this patient, these causes were ruled out, and the tilt test was conclusive for the diagnosis of postural hypotension due to dysautonomia, thus indicating involvement of the autonomic

nervous system, rather than cardiomyopathy, even though the echocardiogram and resonance findings unequivocally showed structural findings of amyloidotic cardiomyopathy, considered without clinical repercussion. The absence of heart failure made it possible to use steroids with mineralocorticoid action, which efficiently suppressed new episodes of syncope.

The exact determination of the cause of the multiple episodes of syncope presented by this patient allowed for adequate treatment and suppression of new episodes. Temporary discontinuation of fludrocortisone due to hypervolemia led to the recurrence of syncope episodes. In the current phase of the disease, when constant hypervolemia is not occurring due to heart failure, the use of fludrocortisone has been appropriate for the treatment.¹ If the disease progresses, treatment becomes challenging, given that there will be a need for constant optimization of the blood volume status, so that hypovolemia and recurrence of syncope do not occur. The use of tafamidis at a dose of 20 mg per day in this patient made stabilization of the disease possible, without progression of neurological symptoms over almost 2 years. In the historical series, there is a very significant evolution of symptoms evaluated by the NIS scale over a period of 1 year.⁴ In the ATTR-ACT study, a difference in mortality and hospital admissions was observed starting at 18 months, which is precisely the patient's current period.⁵

Conclusion

Early identification of hereditary amyloidosis has become relevant in clinical settings, not only due to the specific details of managing cardiac and neurological involvement, but also due to the possibility of specific treatment for the disease. In this case report, we underscore the benefit of the disease-modifying treatment in relation to the stabilization of neurological and cardiological symptoms.

Figure 1 – Tilt test indicating response of postural hypotension. DP: diastolic pressure; HR: heart rate; SP: systolic pressure. Hor.: horizontal position; Incl: inclined position; e Tren.: trendelenburg.

Case Report

Table 1 – Progressive echocardiograms

ECHO parameter	2019	2021
Aorta	30 mm	32 mm
Left atrium	33 mm	34 mm
Septum	17 mm	19 mm
Posterior wall	13 mm	14 mm
LV	42 mm 28 mm	40 mm 28 mm
LVEF	62%	63%

LV: left ventricle; LVEF: left ventricular ejection fraction.

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Author Contributions

Conception and design of the research: Correia EB, Bruscky LVR, Valério BCO, Murta ACS; Acquisition of data: Correia EB, Bruscky LVR, Murta ACS, Albrecht FC; Analysis and interpretation of the data: Correia EB, Bruscky LVR, Murta ACS, Albrecht FC, Pinto IMF; Statistical analysis: Smanio PEP; Writing of the manuscript: Correia EB, Bruscky LVR, Valério BCO, Murta ACS, Albrecht FC, Pinto IMF, Smanio PEP; Critical

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