Familial Transthyretin Cardiac Amyloidosis with Homozygous Val122Ile Mutation Mimicking Hypertrophic Cardiomyopathy

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Abstract

Systemic amyloidosis is a group of diseases caused by the deposition of an amyloid protein that forms fibrils and deposits in tissues. With respect to age and phenotype, patients with the Val122Ile transthyretin (TTR) mutation are similar to those with wild-type cardiac amyloidosis, causing a late-onset restrictive cardiomyopathy with minimal neuropathy, whose median age of onset is 69 years. Homozygous mutation is rare. We report the case of a male patient who had recent-onset heart failure and phenotype of hypertrophic cardiomyopathy. Technetium scintigraphy showed cardiac uptake and absence of circulating immunoglobulins, suggesting TTR cardiac amyloidosis. Genetic analysis confirmed cardiac amyloidosis caused by the homozygous Val122Ile mutant TTR protein.

Introduction

Amyloidosis is a group of diseases caused by the deposition of an insoluble and abnormally folded protein that can accumulate in various organs, causing progressive and irreversible dysfunction.¹ Diseases caused by mutations in the transthyretin gene (TTR), known as hereditary or variant cardiac amyloidosis (ATTRv), are endemic to certain geographic regions. There is a genotype-phenotype correlation, and specific TTR mutations are associated with purely neurological disease, heart disease, or both.²

The Val122Ile mutation, which almost exclusively affects individuals of African or African Caribbean descent, has a population prevalence of 3% to 4%. This mutation was first described in 1989 in a case of 3 patients with hereditary systemic amyloidosis.³ With respect to age and phenotype, patients with the Val122Ile TTR mutation are similar to those with wild-type cardiac amyloidosis (ATTRwt), causing a late-onset restrictive cardiomyopathy with minimal neuropathy, whose median age of onset is 69 years.^{4,5}

Keywords

Amyloidosis; Hypertrophic Cardiomyopathy; Restrictive Cardiomyopathy; Heart Failure.

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Manuscript received September 15, 2021, revised manuscript September 26, 2021, accepted September 26, 2021.

Most patients with ATTR are heterozygous, which means that they have a defect in only one of the homologous chromosomes. Although homozygous cases with defects in both chromosomes are rare, they have been reported. Homozygosity for the Val122Ile mutation may be associated with early onset of heart disease. The largest cohort of people with homozygous Val122Ile demonstrated symptom onset a decade earlier than individuals with a heterozygous mutation (62 versus 72 years); all of them were African American, and the disease was predominant in males at a ratio of 6:1.⁶

We report the case of a patient with a homozygous TTR gene mutation causing familial amyloid cardiomyopathy.

Case Report

A 64-year-old Afro-Brazilian man reported that, in May 2015, he felt tiredness, weakness, and weight loss of approximately 7 kg (from 71 to 64 kg). He had had history of stage I hypertension and carpal tunnel syndrome for 5 years. He reported that the fatigue had been progressive and associated with orthopnea, paroxysmal nocturnal dyspnea, and lower limb edema. The initial electrocardiogram revealed sinus rhythm, first-degree atrioventricular block, and left-axis deviation with normal voltage. Echocardiogram revealed left ventricular hypertrophy with symmetrical increases in the thickness of the septum and posterior wall.

Upon initial evaluation, syndromic diagnosis was heart failure with preserved ejection fraction, and etiological diagnosis was hypertensive heart disease or possible hypertrophic cardiomyopathy, and the patient was referred to our hospital, which is a reference center for hypertrophic cardiomyopathy.

Upon physical examination, the patient showed elevated jugular venous pressure and lower limb edema. Laboratory tests were as follows: leukocytes, 3320/mm³; hemoglobin, 14.6/mm³; platelet count 202/mm³; plasma urea 36 mg/dL; creatinine, 0.99 mg/dL; fasting glucose, 98 mg/dL; sodium, 141 mEq/dL; potassium, 4.2 mEq/dL; 24-hour proteinuria, 0.05 g/24 hour; ultrasensitive troponin I 135 ng/L (reference value < 46); and BNP 1191 pg/ml (reference value < 25). Echocardiography revealed left ventricular hypertrophy and diastolic dysfunction with a restrictive pattern, left atrial dilatation, increased valve thickness and interatrial septum, mild pericardial effusion, and left ventricular ejection fraction of 54% (Figure 1). Cardiac magnetic resonance imaging showed delayed gadolinium enhancement with a circumferential pattern, suggesting cardiac amyloidosis. Investigation to rule out light chain amyloidosis showed absence of monoclonal

DOI: <https://doi.org/10.36660/abchf.20210023>

gammopathy, by means of light chain assay and 24-hour serum and urinary immunofixation.

Technetium bone scintigraphy was performed, revealing grade 3 cardiac uptake, suggesting ATTR (Figure 2). Genetic analysis confirmed the hereditary form due to homozygous mutation of the transthyretin protein (Val122Ile).

Discussion

We have reported the case of an Afro-Brazilian man with homozygous Val122Ile mutation for amyloidosis. This is an extremely rare condition, with only 25 patients reported to date. Almost all reported mutations have been Val122Ile, and it has been most common in African American ethnicity, with only one case reported in a White man.⁷

The patient's symptoms began at 59 years of age, but diagnosis was made 5 years later. The mutation found (Val122Ile) causes cardiac amyloidosis in people over 60 years of age, with a phenotype similar to that of ATTRwt. Reddi et al. studied 13 patients with homozygous mutation, and they found a significantly earlier age of onset defined by age at diagnosis (62 ± 5.75 years) in comparison with 24 patients with heterozygous mutation (72 ± 8.14 years). An analysis of the literature has shown a higher percentage of male homozygotes compared to heterozygotes.

Notwithstanding the early onset, symptoms are usually the same as in heterozygotes. Restrictive cardiomyopathy and, rarely, neuropathy have been observed. Neuropathy may be peripheral and/or autonomic. Soft tissue involvement leads to an increased incidence of bilateral carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture.^{4,8} Prognosis may be worse. There has been a report of severe phenotype with rapid progression to heart failure, New York Heart Association functional class II/IV, left ventricular dysfunction, and considerably elevated NT-proBNP.⁷

In patients who are homozygous for the Val30Met ATTR mutation with familial amyloidotic polyneuropathy, there seems to be a greater likelihood of progressing with central nervous system involvement than in those who are heterozygous for the mutation.⁹

There is a lack of evidence regarding drugs that bind and stabilize the TTR homotetramer specifically in homozygotes. Supportive management is based on proper adjustment of blood volume and treatment of arrhythmias. In general, angiotensin-converting enzyme inhibitors and beta-blockers are not well tolerated in this group of patients, as in other types of cardiac amyloidosis.¹⁰ In severe cases of heart failure, there has been a report of heart transplantation.¹¹

Figure 1 – Echocardiogram showing increased thickness of the septal and inferior lateral walls, increased thickness of the interatrial septum and mitral and aortic valves, and pericardial effusion.

Case Report

Figure 2 – Cardiac pyrophosphate scintigraphy at 1 hour and 3 hours, showing grade 3 cardiac uptake.

In conclusion, our patient with a homozygous mutation had an early onset, simulating hypertrophic cardiomyopathy. Thus, amyloidotic heart disease should be considered as a differential diagnosis of cardiac hypertrophies, especially hypertrophic heart disease. Early diagnosis makes it possible to initiate specific treatment with stabilizing drugs, thus avoiding disease progression.

Author contributions

Conception and design of the research: Cafezeiro C, Alencar A. Acquisition of data: Bueno B, Rissato J. Writing of the manuscript: Cafezeiro C. Critical revision of the manuscript for intellectual content: Hotta V, Dabarian A. Supervision / as the major investigator: Fernandes F.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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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