Original Article

Clinical and Echocardiographic Characterization of Patients with ATTR VAL142Ile

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Abstract

Background: **Transthyretin (TTR) amyloid cardiomyopathy associated with the VAL142Ile variant typically presents in patients in their sixth or seventh decades of life. It is among the most common hereditary forms of cardiac amyloidosis. This study aims to characterize the clinical, laboratory, and echocardiographic features observed in patients with the VAL142Ile variant, contributing to a deeper understanding of the phenotypic expression of this genetic variant.**

Method: **Cross-sectional study of 31 patients diagnosed with HF due to transthyretin amyloidosis (ATTR) VAL142Ile. Functional class, presence of atrial fibrillation (AF) and carpal tunnel syndrome (CTS), and NT-proBNP value were assessed. Diastolic and systolic dimensions, septum, posterior wall (PW), left atrial volume, ejection fraction (EF), diastolic function and global longitudinal strain (GLS) were quantified. Statistical analysis was performed using SPSS software version 26.0.**

Results: **Mean age at symptoms onset was 74.3 years (±5.9 years), with 61% being male. A total of 14 (45%) were identified with AF and 17 (55%) with CTS. Regarding New York Heart Association (NYHA) classification, 19 (61%) were in FC II and 8 (25.8%) in FC III. Measurements were diastolic diameter (DD) of 50.6 mm (±8.5), systolic diameter (SD) of 35.2 mm (±7.8), pw = 13.5 mm (±2.1) and ivs = 14.8 mm (±2.4). The left atrial volume was 54.3 mL/m² (±12) and the EF was 47.3% (±15.1). A total of 8 (25%) underwent strain echocardiography, and 7 (87.5%) showed apical sparing. Diastolic dysfunction grade II was observed in 8 (47%), and 14 (45%) had AF. The mean NT-proBNP was 3026 pg/mL (±1941 pg/mL).**

Conclusion: **Our findings underscore the importance of characterizing this population, highlighting the potential for early disease onset even with the VAL142Ile variant. Elevated NT-proBNP levels, along with the presence of AF and CTS, further elucidate the phenotypic patterns of patients with the ATTR VAL142Ile variant.**

Keywords: **Cardiac amyloidosis due to transthyretin, genetic variant Val142Ile, heart failure.**

Introduction

Transthyretin amyloidosis (ATTR) is an infiltrative, progressive, and often underdiagnosed disease caused by amyloid protein deposits in tissues, primarily affecting the heart and resulting in cardiomyopathy, heart failure, and arrhythmias.[1,2] There are two forms of ATTR: the hereditary form, caused by variants in the transthyretin (TTR) gene, and the wild-type form, which occurs independently of genetic mutations. The VAL142Ile genetic variant is prevalent in individuals of African descent, affecting up to 3.4% of this population, with a higher incidence in the elderly. In the United States, this condition accounts for up to 10% of heart failure cases among African Americans over age 65.[3] Amyloid cardiomyopathy associated with VAL142Ile generally appears in the sixth or seventh decades of life and is a leading hereditary form of cardiac amyloidosis,[3] clinically characterized by increased ventricular mass, heart failure symptoms, and arrhythmias. The slow progression of the disease and nonspecific symptoms make early diagnosis challenging, resulting in a high mortality rate when not treated appropriately.[1-4]

This study seeks to enhance the understanding of the clinical, laboratory, and echocardiographic profiles of patients with the VAL142Ile genetic variant, broadening our insight into its phenotypic manifestations (Central Illustration).

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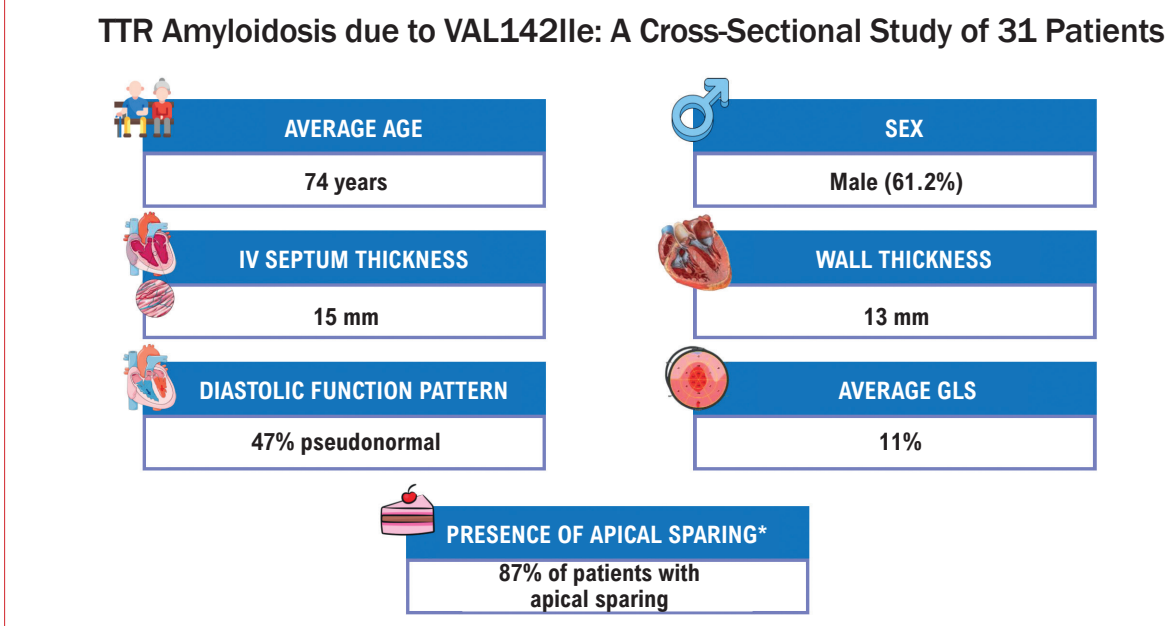
Manuscript received November 1, 2024; revised November 5, 2024; accepted November 5, 2024
Editor responsible for the review: Marcelo Tavares

DOI: https://doi.org/10.36660/abcimg.20240116i

Central Illustration: Clinical and Echocardiographic Characterization of Patients with ATTR VAL142Ile



Arq Bras Cardiol: Imagem cardiovasc. 2025;38(1):e20240116

TTR: Transthyretin; GLS: global longitudinal strain.

Notably, limited data are available in the medical literature, specifically addressing this increasingly prevalent variant in our population.

Methods

This is a cross-sectional, retrospective cohort study conducted at the Teaching-Care Outpatient Clinic of the Bahiana School of Medicine and Public Health (Salvador, Bahia). Data collection was conducted from February 2023 to September 2024 and included 31 patients diagnosed with VAL142Ile-associated cardiac amyloidosis. Diagnoses were based on clinical suspicion and confirmed by 12-lead electrocardiograms (ECG), echocardiography, cardiac resonance imaging, pyrophosphate scintigraphy, and genetic testing, in line with the latest diagnostic guidelines.[5-9] Exclusion criteria included patients with light chain (AL) amyloidosis. Clinical data collected included age, sex, New York Heart Association (NYHA) functional class, presence of atrial fibrillation (AF), and history of carpal tunnel syndrome (CTS). The age at symptoms onset was defined as the first event related to heart failure (signs and symptoms of HF, hospitalization due to HF, or emergency room visit due to congestive symptoms). NT-proBNP levels were measured as a prognostic marker and indicator of hemodynamic overload. The cutoff value of 3000 pg/mL was used as an indicator of severe ventricular dysfunction[1] (Table 1).

Echocardiographic measurements, including ejection fraction (EF), diastolic diameter (DD), systolic diameter (SD), septal thickness (S), and posterior wall thickness (PW), were calculated according to recommendations from the American Society of Echocardiography (ASE). Global longitudinal strain (GLS) was assessed per the Brazilian Society of Cardiology's Position Statement on Myocardial Deformation Imaging.[10] Apical sparing was identified in patients with preserved strain in the apical region compared to the basal and mid-myocardial areas.[11,12] Diastolic dysfunction was classified based on mitral flow and tissue Doppler criteria, with particular attention to the E/e' ratio, peak mitral annular velocity, and transmitral filling patterns (Table 2).

Statistical Analysis

Statistical analysis was performed using SPSS software version 26.0. Continuous variables, such as age at onset of symptoms, EF, GLS, and NT-proBNP levels, were described using mean, median, and standard deviation. Absolute and percentage frequencies were calculated for categorical variables, such as NYHA functional class, presence of AF, and CTS.

Results

Analysis of a sample of 31 patients diagnosed with VAL142Ile cardiac amyloidosis showed an average age of symptom onset at 74.3 years (±5.9 years), with males comprising approximately 68% of the sample. Among the patients studied, 14 (45%) had AF, and 17 (55%) reported a

Table 1 – Clinical characteristics of patients diagnosed with cardiac amyloidosis

Patient	Sex	Age at onset of symptoms	Functional class (NYHA)	CTS	AF	NT-proBNP
1	Male	72	II	Yes	No	Not performed
2	Male	70	III	No	No	Not performed
3	Female	77	II	No	No	Not performed
4	Male	74	II	No	Yes	Not performed
5	Male	78	III	No	No	Not performed
6	Female	74	II	No	Yes	Not performed
7	Female	76	II	No	No	Not performed
8	Male	70	II	No	No	Not performed
9	Male	78	III	Yes	No	Not performed
10	Male	66	II	Yes	No	2460 pg/mL
11	Male	71	I	Yes	Yes	Not performed
12	Male	79	III	Yes	Yes	3600 pg/mL
13	Male	79	II	No	No	Not performed
14	Female	81	III	No	Yes	Not performed
15	Male	72	II	Yes	Yes	Not performed
16	Female	81	II	No	No	Not performed
17	Female	72	II	Yes	Yes	3900 pg/mL
18	Female	75	III	No	Yes	4332 pg/mL
19	Female	79	II	Yes	No	650 pg/mL
20	Male	80	II	Yes	Yes	Not performed
21	Female	78	I	Yes	No	450 pg/mL
22	Male	69	II	No	No	1940 pg/mL
23	Female	74	III	Yes	Yes	4250 pg/mL
24	Male	69	IV	Yes	Yes	3900 pg/mL
25	Male	70	II	No	No	Not performed
26	Female	87	I	Yes	No	3100 pg/mL
27	Male	78	II	Yes	No	3747 pg/mL
28	Male	56	III	Yes	Yes	6471 pg/mL
29	Male	71	II	Yes	No	1400 pg/mL
30	Male	74	III	Yes	Yes	3203 pg/mL
31	Female	75	II	No	Yes	2000 pg/mL

CTS: Carpal Tunnel Syndrome; AF: Atrial fibrillation; NYHA: New York Heart Association.

history of CTS. Regarding functional class, 19 patients (61%) were in NYHA FC II, 8 (25.8%) in FC III, 3 (9.7%) in FC I, and 1 (3.2%) in FC IV. Mean measurements for left ventricular structure included a DD of 50.6 mm (±8.5), a SD of 35.2 mm (±7.8), a PW thickness of 13.5 mm (±2.1), and an interventricular septum thickness of 14.8 mm (±2.4). The mean left atrial volume indexed by body surface area was 54.3 mL/m² (±12) and the EF was 47.3% (±15.1). Of the 31 participants, 8 (25%) underwent echocardiography with assessment of ventricular deformation and of these, 7 (87.5%) had apical sparing visualized on echocardiography. Diastolic dysfunction was observed in 17 (55%) of the participants, with grades I (changed relaxation), II (pseudonormal) and III (restrictive), respectively in 3 (18%), 8 (47%), and 6 (35%) patients. Fourteen (45%) of the total 31 had a diagnosis of AF, and it was not possible to assess the left ventricular filling

Table 2 – Echocardiographic data of patients diagnosed with cardiac amyloidosis

Patient	EF	S	PW	DD	SD	Left Atrial Volume	Diastolic Function Pattern	Apical Sparing	GLS
1	60%	12	12	40	21	44 mL/m²	Pseudonormal	Present	14%
2	20%	18	16	60	54	64 mL/m²	Restrictive	N/A	N/A
3	48%	14	13	48	36	48 mL/m²	Pseudonormal	N/A	N/A
4	30%	14	14	59	50	64 mL/m²	N/A	N/A	N/A
5	27%	14	13	62	54	55 mL/m²	N/A	N/A	N/A
6	26%	12	12	50	44	52 mL/m²	N/A	N/A	N/A
7	33%	16	16	42	43	50 mL/m²	Restrictive	N/A	N/A
8	40%	16	16	48	33	42 mL/m²	Restrictive	N/A	N/A
9	38%	14	13	54	44	60 mL/m²	Restrictive	N/A	N/A
10	56%	14	15	54	38	26 mL/m²	Relaxation Alteration	N/A	N/A
11	60%	14	15	40	27	42 mL/m²	N/A	N/A	N/A
12	42%	17	14	45	37	50 mL/m²	N/A	Present	12%
13	68%	15	15	55	34	42 mL/m²	Relaxation Alteration	N/A	N/A
14	52%	14	12	55	40	47 mL/m²	N/A	N/A	N/A
15	41%	16	13	51	36	46 mL/m²	N/A	Present	8%
16	48%	11	11	52	40	42 mL/m²	Restrictive	N/A	N/A
17	56%	13	12	48	34	62 mL/m²	N/A	Present	10%
18	47%	22	18	46	35	71 mL/m²	N/A	Present	12%
19	62%	15	14	50	33	40 mL/m²	Pseudonormal	N/A	N/A
20	62%	15	15	50	32	80 mL/m²	N/A	N/A	N/A
21	80%	13	13	39	20	45 mL/m²	Pseudonormal	N/A	N/A
22	41%	18	12	43	39	52 mL/m²	Pseudonormal	Present	10%
23	55%	16	15	41	27	46 mL/m²	N/A	N/A	N/A
24	30%	19	18	64	55	84 mL/m²	N/A	N/A	N/A
25	50%	12	13	48	36	38 mL/m²	Pseudonormal	N/A	N/A
26	52%	14	14	49	36	50 mL/m²	Pseudonormal	Present	12%
27	60%	13	10	53	36	64 mL/m²	Relaxation Alteration	N/A	N/A
28	14%	11	11	68	64	50 mL/m²	N/A	Absent	7.2%
29	57%	16	15	40	28	54 mL/m²	Restrictive	N/A	N/A
30	46%	16	12	45	30	74 mL/m²	N/A	N/A	N/A
31	65%	12	12	48	31	40 mL/m²	N/A	N/A	N/A

EF: Ejection Fraction; S: Septum; PW: Posterior Wall; DD: Diastolic Diameter; GLS: Global Longitudinal Strain, SD: systolic diameter; N/A: doesn't apply.

pattern. NT-proBNP levels varied between patients, with an average of 3026 pg/mL (±1941 pg/mL) (Table 3).

Discussion

The findings of this sample reveal characteristics consistent with the findings in the literature on ATTR associated with the VAL142Ile variant.[3,4] The mean age of 74.3 years at symptoms onset and male predominance align with previous studies demonstrating a late manifestation and a greater impact on the male sex.[3,4] The patient in this cohort who presented the latest onset of HF symptoms was 87 years old, while the youngest developed heart failure due to TTR amyloidosis at the age of 56. This patient was homozygous for the TTR genetic variant, a condition that appears to have caused this pathology to manifest earlier.[3] The history

Table 3 – Results of clinical and echocardiographic evaluation

Variables	Mean	N (%)	Standard deviation
Male		19 (61%)	
Age	74.3 years		±5.9 years
Functional Class (NYHA)			
I		3 (9.7%)	
II		19 (61%)	
III		8 (25.8%)	
IV		1 (3.2%)	
DD	50.6 mm		±8.5 mm
SD	35.2 mm		±7.8 mm
Septum	14.8 mm		±2.4 mm
PW	13.5 mm		± 2.1 mm
EF	47.3%		±15.1%
Atrial volume	54.3 mL/m²		±12mL/m²
GLS	11%		
Apical sparing		7 (87.5%)	
CTS		17 (55%)	
AF		14 (45%)	
NT-proBNP	3026 pg/mL		±1941 pg/mL

GLS: Global Longitudinal Strain; N: Sample Number; CTS: carpal tunnel syndrome; EF: ejection fraction; AF: atrial fibrillation; NYHA: New York Heart Association; DD: diastolic diameter; SD: systolic diameter; PW: posterior wall.

of CTS in 55% of patients reinforces the association of TTR deposits in tendons and peripheral nerves, a marker that aids in the early diagnosis of the disease.[1,2,4,5] The mean EF was 47.3%, indicating a left ventricular systolic function impairment, which is usually seen in more advanced stages of this restrictive cardiomyopathy.[1,2,4,5] The increased thickness of the PW and interventricular septum reflect the deposition of amyloid in the interstitial space, with increased ventricular mass, diastolic dysfunction, and subsequent systolic dysfunction. In this study, diastolic dysfunction was prevalent, with most patients displaying grade II or higher dysfunction. This finding is expected regardless of the type of TTR-related genetic variant since amyloid infiltration in the myocardium causes ventricular stiffness and progressive impairment of diastolic function and HFpEF.[1,2,5] The reduced GLS value associated with apical sparing in approximately 87% of cases highlights the importance of GLS assessment in the diagnostic flow of patients with suspected ATTR. The presence of concentric left ventricular hypertrophy, atrial dilation, and the apical sparing pattern provides an echocardiographic profile that aids in distinguishing ATTR from other cardiomyopathies, such as hypertensive or hypertrophic types.[10-12] In this study, patients with NT-proBNP levels exceeding 3000 pg/mL showed lower GLS and more severe diastolic dysfunction, reflecting a higher degree of cardiac impairment. This finding aligns with previous studies that identified similar cutoff values for risk stratification in CA.[1] The AF (45%) among patients is consistent with other studies, which point to an association between amyloidosis and atrial arrhythmias.[1-4]

Although this study provides valuable information on the clinical manifestation of cardiac amyloidosis associated with the VAL142Ile variant, there are some limitations. The sample size was relatively small, and the lack of longitudinal follow-up prevents the evaluation of the temporal progression of clinical and echocardiographic markers. Additionally, underutilization of myocardial strain due to limited echocardiographic windows and availability may have affected the accuracy of GLS values and apical sparing detection in this subgroup with the VAL142Ile variant.

Conclusion

In conclusion, this study emphasizes the importance of characterizing this population and the potential for early onset, even in VAL142Ile variant cases. Furthermore, findings such as increased ventricular wall thickness, significant atrial dilation, reduced EF, and markedly low GLS (11%) indicate a late-stage diagnosis, a known marker of poor prognosis. High NT-proBNP levels, along with the presence of AF and CTS in a substantial proportion of patients, contribute to our understanding of the phenotypic patterns in patients with ATTR VAL142Ile.

Author Contributions

Conception and design of the research: Silva TO, Silva Filho TO, Tavares M, Ritt LEF; acquisition of data: Silva TO, Santos LTC, Fialho ML, Pereira GSS, Menezes EB, Rodrigues EG; analysis and interpretation of the data: Silva TO, Ritt LEF;

Statistical analysis: Silva TO; writing of the manuscript: Silva TO, Silva Filho TO, Santos LTC; critical revision of the manuscript for intellectual content: Silva TO, Tavares M, Machado MC, Ritt LEF.

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 study was approved by the Ethics Committee of the Escola Bahiana de Medicina e Saúde Pública under the protocol number 743825235.0000.5544. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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