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REVIEW ARTICLE

Cardiac Amyloidosis in Women: An Underappreciated Diagnosis

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Abstract

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that affects the heart mostly in two forms: immunoglobulin light chain amyloidosis (AL-CM) and transthyretin amyloidosis.

Transthyretin amyloid cardiomyopathy (ATTR-CM) predominantly affects the elderly population, mainly men (about 70-80%), and usually manifests with symptoms of heart failure (HF).

Despite technological advances in medicine, CA is still an underdiagnosed condition, especially in women, partly due to the known male predominance and high level of suspicion required for diagnosis. It is important to remember that amyloidosis is a systemic disease with a heterogeneous and non-specific presentation. It's worth paying attention to the patient's medical history and red flags in clinical and diagnostic tests (electrocardiogram [ECG], echocardiogram [ECHO], cardiac magnetic resonance [CMR]).

Accurate and timely diagnosis is crucial for appropriate management and prognosis.

So far, the under-representation of women in clinical trials may have also limited the evidence on sex-specific diagnosis, and outcomes.

Introduction

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy first described by Virchow in 1854. It is difficult to suspect and, therefore, often misdiagnosed. It affects the heart mostly in two forms: immunoglobulin light chain amyloidosis (AL-CM, a plasma cell dyscrasia) and transthyretin amyloidosis.

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, life-threatening form of restrictive disease caused by the extracellular deposition of insoluble amyloid fibrils in the myocardium. This leads to cardiac structural and functional abnormalities that clinically result in heart failure (HF). It predominantly affects the elderly population[1] and may be sporadic or inherited as an autosomal dominant pattern with variable penetrance.

Wild-type (ATTRwt), the most common form, is non-inherited and caused by amyloid formation in the presence of favorable conditions such as aging and oxidative stress.[1] Its incidence is around 13 to 17% in patients with HF with preserved ejection fraction (HFpEF) and increased left ventricular wall thickness (LVWT).[2] It presents later in life, with a median survival of 3–5 years.[2-4] According to Semigran (2016), it has been associated with HFpEF in one-third of the elderly population.[5]

The hereditary or variant form (ATTRv) is associated with TTR gene mutations and often presents earlier in life.[3] In all these genotypes, female patients are older than men at the time of diagnosis.[3]

In both types of ATTR-CM, there is a male predominance, with about 80% in the ATTRwt form and 70% in the ATTRv form.[2] For AL-CM, no significant sex imbalance has been described so far; male:female ratios are between 1:1 and 1.5:1. However, one type of amyloidosis is more pronounced in females: atrial amyloidosis secondary to chronic valvular atrial fibrillation (due to accumulation

Keywords

Diagnosis; Amyloidosis; Prognosis; Therapeutics; Women.

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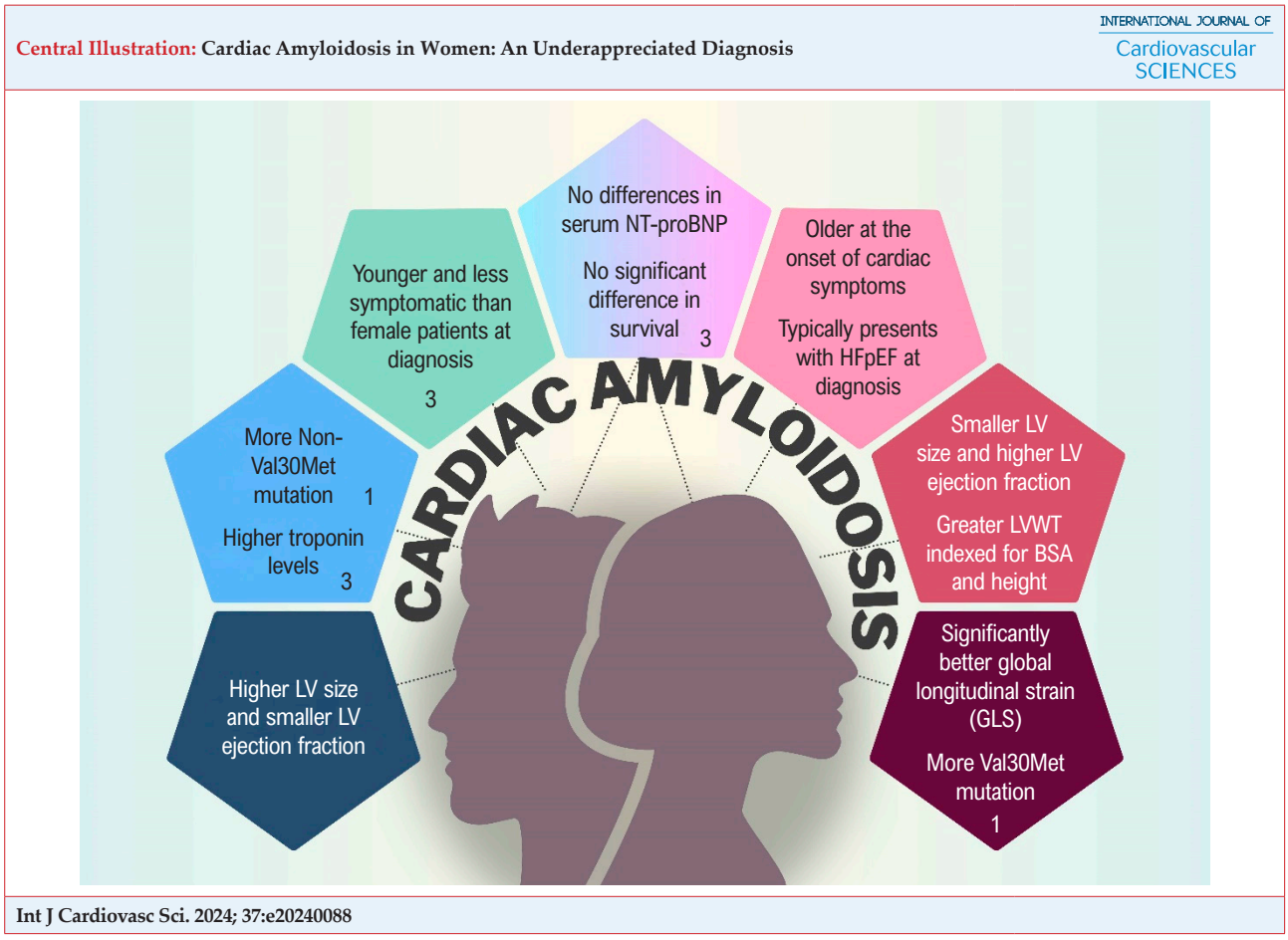

Differences of CA between men and women. LV: left ventricle; HFpEF: HF with preserved ejection fraction; LVWT: left ventricular wall thickness; GLS: global longitudinal strain; BSA: body surface area; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

of A-type natriuretic peptide).[2] Some reports suggest that estrogen seems to exert a cardioprotective effect in ATTR-CM by reducing the detrimental effects of amyloid fibrils on cardiac function.[1-3]

Figure 1 shows the main types of CA and their characteristics.

Epidemiology

Data from the literature indicate that in hereditary amyloidosis (cardiac and/or neurological forms) and systemic senile amyloidosis, over 80% of individuals affected are men.[2,6,7] In secondary systemic amyloidosis and AL amyloidosis, there is also a male predominance.[8,9]

In Brazil, from 1996 to 2022, data from the Mortality Information System (SIM-DATASUS) showed equivalent mortality due to amyloidosis in men and women (n = 1,174- CID10: E85) across all federative units (Figure 2 and 3). This information is highly relevant for the epidemiological assessment of the disease, considering that the pattern observed for all amyloidosis in scientific publications indicates male predominance. In this case, it can be inferred that, in Brazil, there is an equivalence between sexes regarding the incidence of amyloidosis. Data from a reference center for amyloidosis in Brazil demonstrated that women represent around 42% of the sample without specifying the type of amyloidosis.[10] It is worth noting that the severity of the disease with a cardiac phenotype also differs according to sex, as women usually develop less infiltration of amyloidogenic fibrils in the heart.[11]

Underdiagnosis in women

Despite its increasing recognition, CA remains an underdiagnosed condition, particularly in women. This can be partially explained by the non-indexed thresholds used for diagnosis, which assume an LVWT > 12 mm as a cut-off value for ATTR-CM diagnosis in both sexes, without accounting for the smaller cardiac

<table>
<tr><th colspan="3">CARDIAC AMYLOIDOSIS</th></tr>
<tr><th>AL</th><th colspan="2">ATTR</th></tr>
<tr><td rowspan="3">• No major sex imbalance (male : female = 1:1, or 1.5:1)[3]
• Rare disease
• Clonal hematological and neoplastic disease</td><td colspan="2">• Male predominance
• Women are older at presentation
• Mildly worse phenotype in females
• No significant difference between males and females in mortality in the overall population
• Female patients may have extracardiac symptoms more frequently than male patients</td></tr>
<tr><th>wtATTR</th><th>vATTR</th></tr>
<tr><td>• Non-inherited
• Most common phenotype
• Presents later in life
• Median survival of 3-5 years[1]</td><td>• Hereditary form (autossomal dominant pattern of inheritance with variable
• Presents earlier in life
• Variable course and survival</td></tr>
</table>

Figure 1 – CA main types and their main characteristics.
AL: light-chain amyloidosis; ATTR: transthyretin amyloidosis; wtATTR: wild-type; vATTR: hereditary.

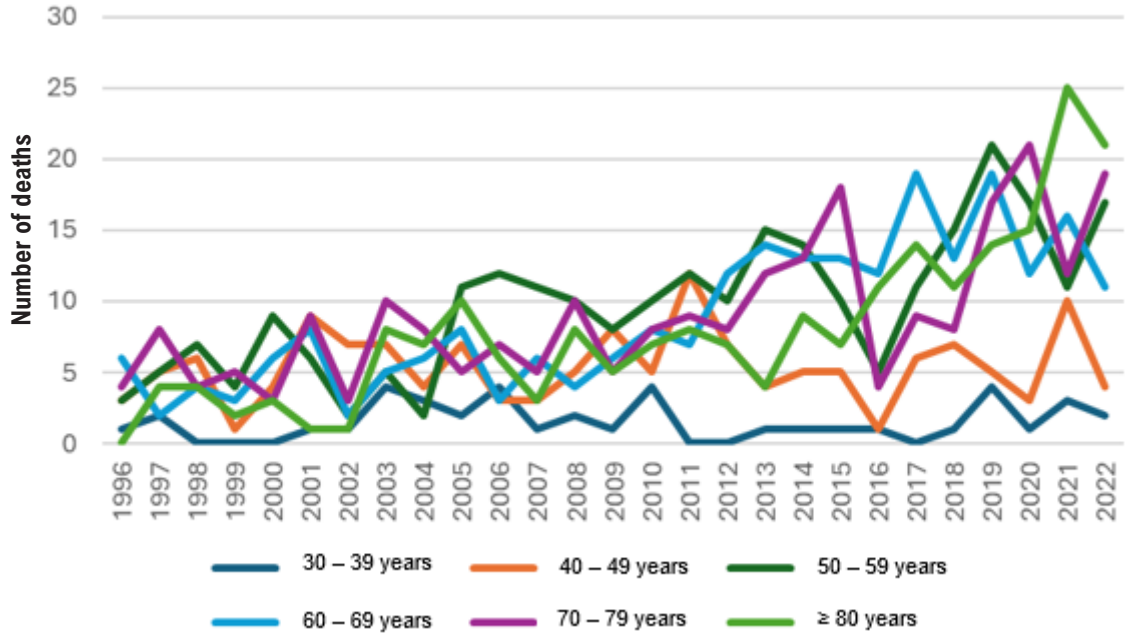

Figure 2 – Deaths from Amyloidosis (CID-10: E85) by age group in women in Brazil from 1996 to 2022. Source: Hospital Information System of the Unified Health System (SIH/SUS).[12]

anatomy in women.[1,3,13] Another possible explanation is the presumption of male predominance, which can reduce clinical suspicion in women, even when some red flags are present.[4]

In a study cohort comprising 1732 patients, Patel et al.[3] emphasized the importance of body size in assessing disease severity. Findings indicate a similar overall structural and functional phenotype between sexes when indexed to body

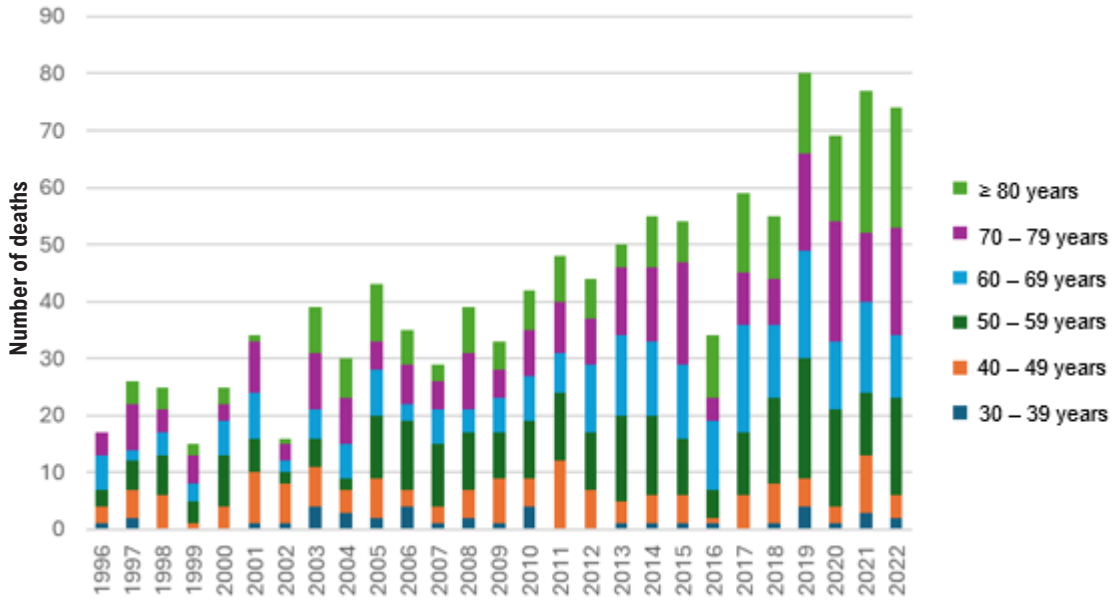

Figure 3 – Total deaths caused by amyloidosis (CID-10: E85) by age group in women from 1996 to 2022 in Brazil. Source: Hospital Information System of the Unified Health System (SIH/SUS).[12]

size, with significant differences pointing towards a mildly worse phenotype in females. This is better characterized by greater LVWT after indexing for body surface area and height, a higher degree of diastolic dysfunction, and more severe degree of atrioventricular (AV) valves regurgitation. Other results include significantly better global longitudinal strain (GLS) in women and similar disease progression and survival rates in both sexes.[3]

Non-myocardial manifestations of amyloidosis: sex differences

Amyloidosis is recognized as a systemic disease, which frequently delays the diagnosis of ATTR amyloidosis due to its heterogeneous and non-specific presentation. It affects not only the heart but also the eyes, kidneys, skin, musculoskeletal system, nervous system, and can manifest peripheral polyneuropathy, and autonomic dysfunction as a result of autonomic neuropathy. Almost all these extracardiac manifestations do not differ between sexes (Figure 4).

Amyloidosis manifests earlier and more severely in men, which contributes to the underdiagnosis in women. Thus, an important piece of information that could aid in early diagnosis in females is to attempt to associate features such as carpal tunnel syndrome (CTS) and lumbar spinal stenosis as a diagnostic track.[14] CTS, a musculoskeletal manifestation sometimes associated with amyloidosis, is the most prevalent manifestation in women and significantly impacts quality of life for many individuals. Because CTS is frequently associated with ATTR, it is established as a red flag for this disease.[1]

An analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) revealed that women with ATTRwt amyloidosis typically developed the disease at an older age and showed more severe neurologic impairment, such as walking disability, when compared to men. A larger proportion of females also had higher scores in THAOS compared to males (23% vs. 7%, with statistical significance), suggesting sex differences in certain clinical presentations of ATTRwt amyloidosis. This same study found that the incidence of autonomic neuropathy did not differ between sexes.[15]

Aortic stenosis is another typical finding in ATTR-CM, and according to a Japanese retrospective study, the moderate to severe form was more prevalent in women compared to men (45% vs. 5%; $p < 0.001$).[16]

Insights for early diagnosis of CA

The first step to early diagnosis in women involves raising awareness among clinicians about the possibility of CA affecting females despite its male prevalence.

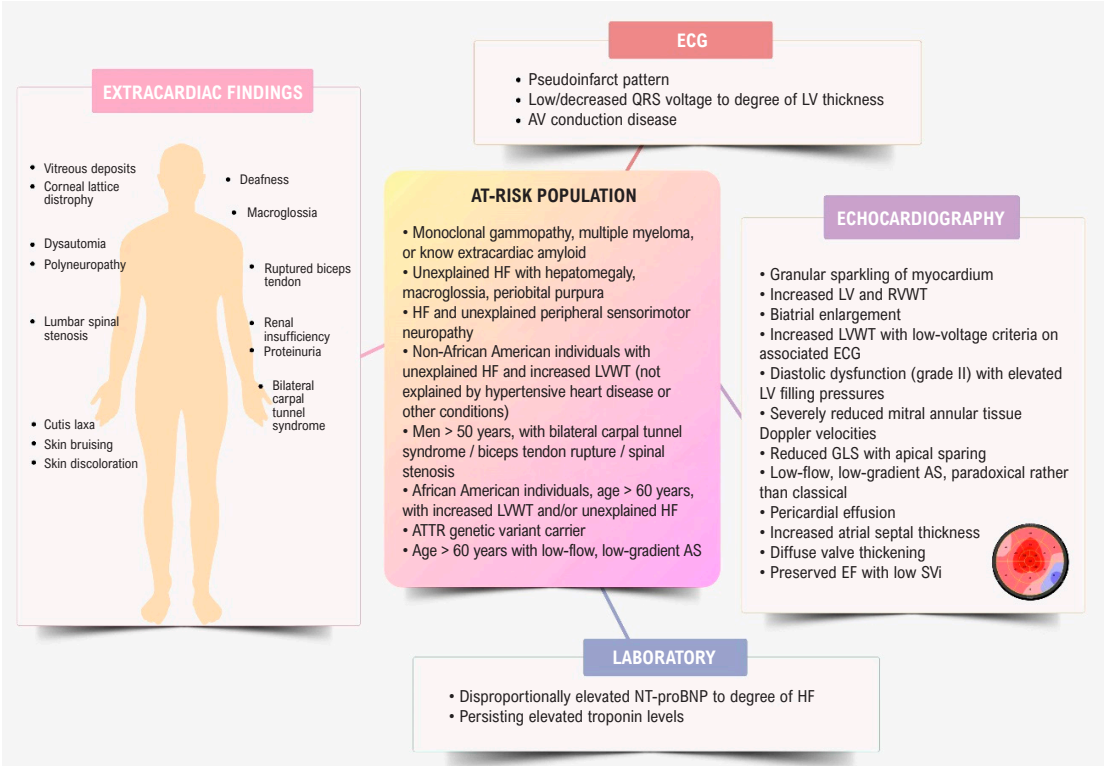

Figure 4 – Clinical, echocardiographic, and ECG red flags for CA diagnosis.
ECG: electrocardiogram; LVWT: left ventricular wall thickness; HF: heart failure; LV: left ventricle; GLS: global longitudinal strain; AS: aortic stenosis; SVI: stroke volume index; EF: ejection fraction; RVWT: right ventricular wall thickness.

Therefore, CA should be kept in mind, particularly in elderly patients presenting with HFpEF with concomitant valvular heart disease, sinoatrial and AV blocks, and advanced diastolic dysfunction. It is important to maintain a high level of suspicion if you come across a HF patient with guideline-directed medical therapy intolerance, a HF patient with concomitant peripheral neuropathy and/or dysautonomia, an older patient presenting with low-flow, low-gradient aortic stenosis, a HFpEF patient with bilateral CTS or spinal stenosis, and a HFpEF patient with atypical epidemiology (younger, lean, male), especially in the absence of typical comorbidities (hypertension, diabetes, obesity), as well as new hypertrophic cardiomyopathy diagnosis in older patients.

The diagnostic process begins with a comprehensive clinical history and physical examination, followed by an electrocardiogram (ECG), and transthoracic echocardiogram. It is essential to highlight that the level of suspicion can be heightened with multimodality imaging and follows a systematic approach where the first step involves assessing the presence/absence of monoclonal protein to screen for plasma cell disorder and, therefore, provide supportive evidence for AL-CM, as seen in Figure 5.

ECG red flags of ATTR-CM include atrial fibrillation, conduction system disease (AV or bundle branch blocks) or pacemaker placement, a pseudo-infarct pattern, and discordant QRS voltage for the degree of increased LVWT on imaging. Apparently, there are no differences in electrocardiographic findings between sexes.[13,17]

Echocardiography plays a significant role in the suspicion of the disease. It serves as an excellent tool for screening, highlighting some red flags for diagnosis, including features such as granular sparkling of the myocardium, increased wall thickness of both ventricles (especially in the absence of hypertension), marked biatrial enlargement, diastolic dysfunction with elevated LV filling pressures, and reduced GLS with apical sparing (the classical "cherry on top" that, if absent, does not rule out the disease), along with pericardial/pleural effusions.[18]

Cardiac magnetic resonance (CMR) imaging offers detailed cardiac tissue characterization and is essential for differential diagnosis from other forms of cardiomyopathy associated with increased LVWT and preserved EF. It is highly valuable for excluding amyloidosis in suspected cases. Characteristic CMR features of CA include expansion of the extracellular volume, abnormal gadolinium contrast kinetics, and diffuse late gadolinium enhancement.[17]

Women diagnosed with ATTR-CM typically present with HFpEF. In the presence of HFpEF and an LVWT > 12 mm accompanied by at least one red flag, amyloidosis should be considered as a possible diagnosis.[1]

There are other clues with some pathognomonic extracardiac manifestations of AL-CM (macroglossia, submandibular gland enlargement, and periorbital purpura) and ATTR-CM (musculoskeletal manifestations, such as spontaneous biceps tendon rupture and spinal stenosis).[17]

Figure 4 shows the clues for diagnosis, highlighting the clinical, echocardiographic, and ECG red flags. The Central Illustration highlights the differences between men and women.

In addition to imaging modalities, some cardiac biomarkers can contribute not only to diagnosis but also to disease management. Troponin levels typically remains mildly elevated throughout the course of the disease,[17,18] which can raise suspicion and serve as a laboratory red flag. Patel et al.[3] found no differences in serum NT-proBNP levels between sexes but observed higher troponin levels in men. In general, NT-proBNP levels are disproportionately elevated relative to the degree of HF.[18]

Prognosis in women

The true prevalence in women may be underestimated due to a sex-related bias in identifying the condition, as observed in other cardiovascular diseases. The under-representation of women in clinical trials may have

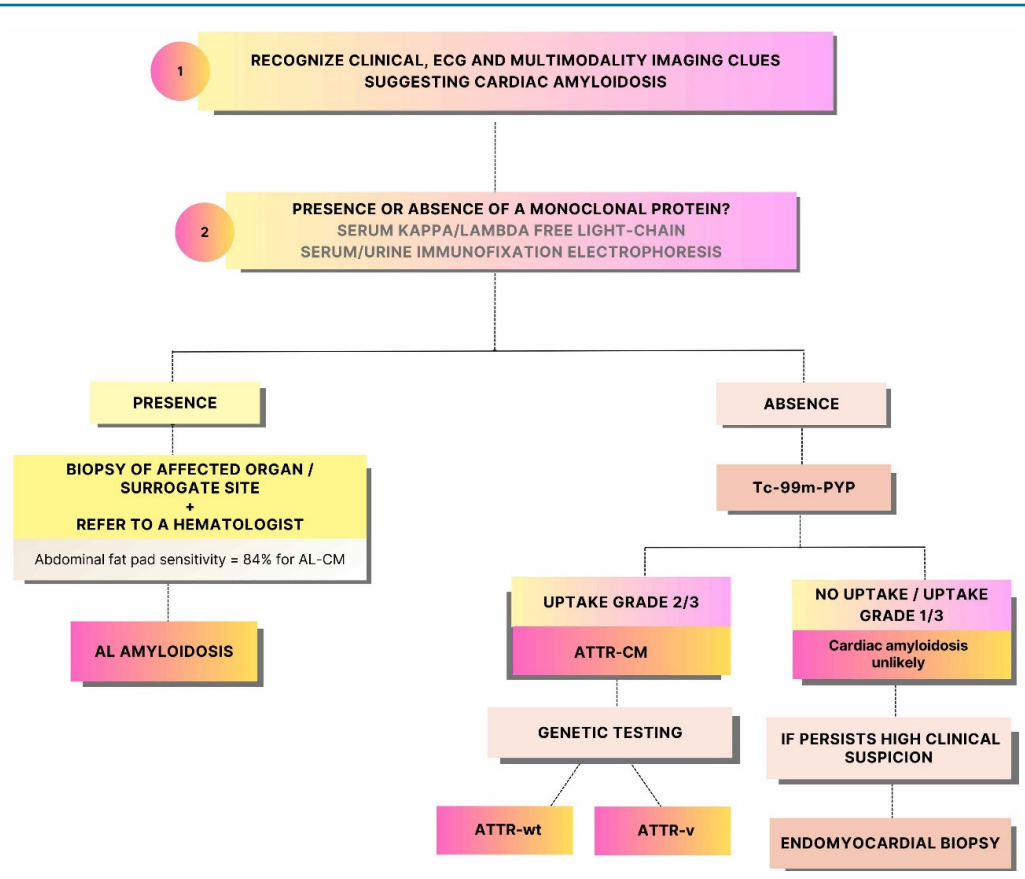

Figure 5 – Steps to the diagnosis of CA in female patients. ATTR-CM: transthyretin amyloid cardiomyopathy; ATTR-wt: ATTR wild type; ATTR-v: ATTR variant or hereditary.

also have restricted the evidence on sex-specific management and outcomes.

Suspecting CA is an essential step in achieving a precise diagnosis. Understanding the impact of sex differences on ATTR-CA is of paramount importance for the accurate diagnosis, treatment, and prognosis of this condition.[1] The prognosis of ATTR-CA begins with a correct diagnosis, and it is affected by multiple factors: the genetic mutation that can lead to a more aggressive course of the disease, the severity of myocardial infiltration and functional impairment, and the associated comorbidities such as diabetes and renal insufficiency.[19]

Few studies have examined prognostic differences based on sex and have not demonstrated any significant differences, even if a certain level of myocardial protection seems to be present in premenopausal women. Maraey et al. observed an increased risk of acute ischemic stroke and major bleeding events in females, as compared to males, but found no difference in the in-hospital mortality outcome between both groups in a cohort of all HF hospitalizations between January 2016 and December 2019.[20]

With advancements in diagnostic imaging and the emergence of novel TTR-targeted therapies, the prognosis of ATTR-CM is improving. However, for those undiagnosed or who cannot access novel treatments, there remains significant morbidity and mortality.[19] Women are diagnosed up to four years later than men, although this does not seem to translate into a worse prognosis in the medium term. When CA is diagnosed, its prognosis is quite similar in women and men.[21]

Treatment considerations

For AL amyloidosis, diuretics are the cornerstone of therapy. Most patients do not tolerate renin-angiotensin-aldosterone inhibitors (RAAS-I), although RAAS-I is better tolerated in ATTR amyloidosis. Also, beta-blockers are poorly tolerated. Orthostatic hypotension is commonly encountered due to autonomic dysfunction. Mineralocorticoid receptor antagonists and loop diuretics, hence, remain the vital therapy options for HF management in CA.[22,23] In patients with predominantly CA resulting from ATTRv or ATTRwt, Tafamidis is indicated in those with NYHA class I to III, and early initiation appears to slow disease progression. The benefit of Tafamidis has not been observed in patients with class IV, severe aortic stenosis, or impaired renal function (glomerular filtration rate < 25 mL/min per 1.73 m²).[23]

For patients with ATTR-CM with stage D HF, the use of a left ventricle (LV) assist device is challenging because of the small LV cavity size and concomitant right ventricular dysfunction. Orthotropic heart transplant in AL amyloidosis is associated with a high risk of disease recurrence in the transplanted heart. However, in carefully selected patients (especially in clinically isolated heart involvement), a heart transplant can be considered if the patient agrees to undergo intensive chemotherapy for plasma cells after the heart transplant. A heart transplant followed by aggressive chemotherapy may result in an expected 5-year survival of 60%. If there is autonomic neuropathy, most patients would require combined liver and heart transplants to prevent the recurrence of amyloid disease in the transplanted heart.[22,23]

Catheter ablation for atrial fibrillation in the setting of amyloidosis carries a high recurrence rate. Patients require anticoagulation because of the increased risk of thrombosis and thromboembolism. In the case of an AV block, one should aim for biventricular pacing, as the right ventricle's pacing alone in a stiff myocardium setting would be disadvantageous. Implantable cardioverter-defibrillator for primary prevention provides no clear benefit and is not indicated. It is reserved for secondary prevention, as otherwise generally indicated.[22,23]

Conclusion and future perspectives

CA is still an underdiagnosed condition specially in women. Accurate and timely diagnosis is crucial for appropriate management and prognosis. So, considering the patient's medical history and the clinical and echocardiography red flags, a higher level of suspicion is an essential step toward the correct diagnosis. The prevalence of HFpEF is higher in women, so it is important to remember that CA can be the etiology.

Echocardiography is the first imaging test used for patients with cardiovascular complaints. Increased LVWT can raise the suspicion of CA in the absence of diseases or if disproportional to that attributed to common comorbidities, such as hypertension, obesity, and atrial fibrillation, that trigger HFpEF.

The treatment of amyloidosis has significantly changed in recent years. Even though we currently have only a few drugs to use for the treatment of

CA, very promising new treatments will be available to cardiologists soon. Future research will need to individualize the therapy, analyze the different pharmacokinetics and pharmacodynamics according to gender, age and body surface area, propose combinations of drugs to optimize the beneficial effects, identify the selection criteria for starting the treatment, and refine the prognostic evaluation criteria.[24]

Author Contributions

Conception and design of the research, acquisition of data and writing of the manuscript: Espíndola LN, Oliveira GMM, Castro ML, Almeida MC; critical revision of the manuscript for intellectual content: Freire CMV; illustration: Espíndola LN.

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

References

1. Aimo A, Panichella G, Garofalo M, Gasparini S, Arzilli C, Castiglione V, et al. Sex Differences in Transthyretin Cardiac Amyloidosis. Heart Fail Rev. 2024;29(2):321-30. doi: 10.1007/s10741-023-10339-w.
2. Caponetti AG, Rapezzi C, Gagliardi C, Milandri A, Dispenzieri A, Kristen AV, et al. Sex-Related Risk of Cardiac Involvement in Hereditary Transthyretin Amyloidosis: Insights From THAOS. JACC Heart Fail. 2021;9(10):736-46. doi: 10.1016/j.jchf.2021.05.005.
3. Patel RK, Ioannou A, Razvi Y, Chacko L, Venneri L, Bandera F, et al. Sex Differences Among Patients with Transthyretin Amyloid Cardiomyopathy - from Diagnosis to Prognosis. Eur J Heart Fail. 2022;24(12):2355-63. doi: 10.1002/ejhf.2646.
4. Bruno M, Castaño A, Burton A, Grodin JL. Transthyretin Amyloid Cardiomyopathy in Women: Frequency, Characteristics, and Diagnostic Challenges. Heart Fail Rev. 2021;26(1):35-45. doi: 10.1007/s10741-020-10010-8.
5. Semigran MJ. Transthyretin Amyloidosis: A "Zebra" of Many Stripes. J Am Coll Cardiol. 2016;68(2):173-5. doi: 10.1016/j.jacc.2016.05.020.
6. Damy T, Kristen AV, Suhr OB, Maurer MS, Planté-Bordeneuve V, Yu CR, et al. Transthyretin Cardiac Amyloidosis in Continental Western Europe: An Insight Through the Transthyretin Amyloidosis Outcomes Survey (THAOS). Eur Heart J. 2022;43(5):391-400. doi: 10.1093/eurheartj/ehz173.
7. González-López E, Gagliardi C, Dominguez F, Quarta CC, Haro-Del Moral FJ, Milandri A, et al. Clinical Characteristics of Wild-type Transthyretin Cardiac Amyloidosis: Disproving Myths. Eur Heart J. 2017;38(24):1895-904. doi: 10.1093/eurheartj/ehx043.
8. Raimondi A, Salinaro F, Mussinelli R, Boldrini F, Cappelli F, Perfetto G, et al. The Role of Gender and Age in Cardiac AL Amyloidosis, Eur Heart J. 2013;34(1):2996. doi: 10.1093/eurheartj/eht309.P2996.
9. Ayar Y, Ersoy A, Oksuz MF, Ocakoglu G, Vuruskan BA, Yildiz A, et al. Desfechos Clínicos e Sobrevida em Pacientes com Amiloidose AA. Rev Bras Reumatol. 2017;57(6):535-44. doi: 10.1016/j.rbre.2017.02.002.
10. Arvidsson S, Pilebro B, Westermark P, Lindqvist P, Suhr OB. Amyloid Cardiomyopathy in Hereditary Transthyretin V30M Amyloidosis - Impact of Sex and Amyloid Fibril Composition. PLoS One. 2015;10(11):e0143456. doi: 10.1371/journal.pone.0143456.
11. Sequeira VCC, Penetra MA, Duarte L, Azevedo FR, Sayegh RSR, Pedrosa RC, et al. Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy: Baseline Anthropometric, Demographic and Disease Characteristics of Patients from a Reference Center. Arq Neuropsiquiatr. 2022;80(3):262-9. doi: 10.1590/0004-282X-ANP-2020-0590.
12. Brasil. Ministério da Saúde. Hospital Information System of the Unified Health System (SIH/SUS) [Internet]. Brasília: Ministério da Saúde; 2024 [cited 2024 April 09]. Available from: http://tabnet.datasus.gov.br/
13. Zadok OIB, Porter A. Overcoming the Diagnostic Pitfalls of Women With Cardiac Amyloidosis. JACC Heart Fail. 2022;10(1):71-2. doi: 10.1016/j.jchf.2021.09.010.
14. Kroi F, Fischer N, Gezin A, Hashim M, Rozenbaum MH. Estimating the Gender Distribution of Patients with Wild-Type Transthyretin Amyloid Cardiomyopathy: A Systematic Review and Meta-Analysis. Cardiol Ther. 2021;10(1):41-55. doi: 10.1007/s40119-020-00205-3.
15. Panichella G, Garofalo M, Gasparini S et al. Sex differences in transthyretin cardiac amyloidosis. Heart Failure Reviews. 2024. 29;321- 330.
16. Campbell CM, LoRusso S, Dispenzieri A, Kristen AV, Maurer MS, Rapezzi C, et al. Sex Differences in Wild-Type Transthyretin Amyloidosis: An Analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Cardiol Ther. 2022;11(3):393-405. doi: 10.1007/s40119-022-00265-7.
17. Takashio S, Yamada T, Nishi M, Morioka M, Fujiyama A, Nakashima N, et al. Sex-related Differences in the Clinical Characteristics of Wild-type Transthyretin Amyloidosis Cardiomyopathy. J Cardiol. 2022;79(1):50-7. doi: 10.1016/j.jjcc.2021.10.007.
18. Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023;81(11):1076-126. doi: 10.1016/j.jacc.2022.11.022.
19. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and Treatment of Cardiac Amyloidosis: A Position Statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021;42(16):1554-68. doi: 10.1093/eurheartj/ehab072.
20. Obi CA, Mostertz WC, Griffin JM, Judge DP. ATTR Epidemiology, Genetics, and Prognostic Factors. Methodist Debakey Cardiovasc J. 2022;18(2):17-26. doi: 10.14797/mdcvj.1066.
21. Maraey A, Tarabanis C, Hajduczok AG, Salem M, Said E, Elsharnoby H, et al. Temporal Trends and Sex Differences in Patients With Cardiac Amyloidosis and Heart Failure With Preserved Ejection Fraction: Retrospective Analysis of 22,015 Admissions From the National Inpatient Sample. Curr Probl Cardiol. 2023;48(1):101393. doi: 10.1016/j.cpcardiol.2022.101393.

22. Rapezzi C, Emdin M, Aimo A. Unravelling the Role of Sex in the Pathophysiology, Phenotypic Expression and Diagnosis of Cardiac Amyloidosis. Eur J Heart Fail. 2022;24(12):2364-6. doi: 10.1002/ejhf.2674.

23. Porcari A, Rossi M, Cappelli F, Canepa M, Musumeci B, Cipriani A, et al. Incidence and Risk Factors for Pacemaker Implantation in Light-chain and Transthyretin Cardiac Amyloidosis. Eur J Heart Fail. 2022;24(7):1227-36. doi: 10.1002/ejhf.2533.

24. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. Circulation. 2020;142(1):7-22. doi: 10.1161/CIR.0000000000000792.

25. Mallus MT, Rizzello V. Treatment of Amyloidosis: Present and Future. Eur Heart J Suppl. 2023;25(Suppl B):99-103. doi: 10.1093/eurheartjsupp/suad082.