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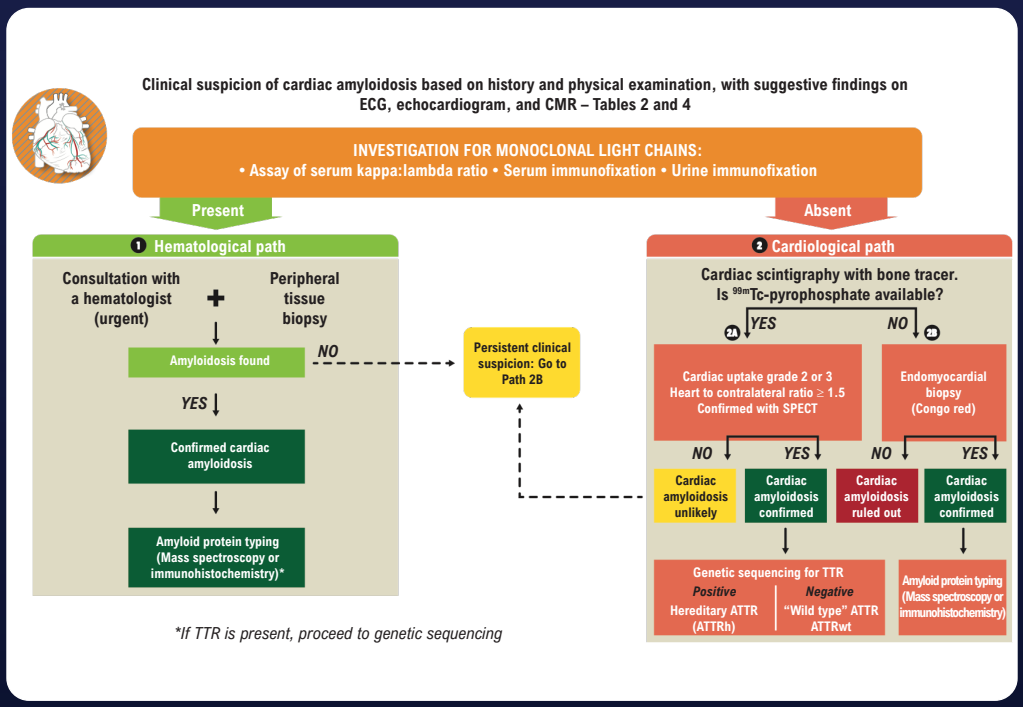

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ABPAR and the Needs of Patients with Amyloidosis in Brazil

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The Brazilian Paramyloidosis Association (ABPAR)[1] was founded on November 17, 1989 at the in the Convention Room of Hotel Rio Copa, in the city of Rio de Janeiro. In December of that year, it became a legal entity following registration at the notary's office and publication in the Brazilian Official Gazette.

Starting then, members began the fight against the countless obstacles in the dissemination and prevention of familial amyloidotic polyneuropathy, also known as hereditary transthyretin amyloidosis. Due to lack of information, the Brazilian population, all too often, would not seek assistance and, when people did so, public agencies would not provide it, refusing to invest material and funds in this serious and fatal health problem.

In addition to monitoring medical-scientific research in the search for solutions for people who carry hereditary transthyretin amyloidosis, the ABPAR also understands the great importance of an educational focus, offering lectures and regional events that include patients, family members, and doctors from the diverse areas related to providing care for this disease.

The ABPAR, through the functions highlighted in its Mission Statement, seeks an alliance with science to improve the relationship of patients and family members who deal with this reality, in order to promote greater awareness and acceptance of the disease and to increase the capacity to react in the search for treatment and quality of life.

When Glaide Mara's father passed away, in March 2008, the association went on hiatus until the year 2011.

Revival of the ABPAR in 2011

The first reunion took place at Glaide Mara's residence, on May 14, 2011, and a commitment was made to start promoting the association and aggregating new members. Several meetings were scheduled, raising contributions to begin with the revival of the association.

On September 18, 2011, the fifth meeting took place, according to the publication in the newspaper O Dia, the new board members of the ABPAR were elected, maintaining Roberto Beltrami as president, and Glaide was elected vice president. The bylaws of the ABPAR were registered in accordance with the new civil code.

Subsequently, faced with a situation where all proposals vanished and the members became increasingly sick, meetings became more and more difficult; judicial barriers accumulated, and the group lost its strength. Once more, the ABPAR went on hiatus.

In 2014, a new group of patients got together, following conversations on the theme of amyloidosis in social networks, and they decided, once again, to revive the association, with Fabio Almeida as president until September 2020. In September 2020, I was elected to head the current management.

To explain a little about hereditary transthyretin amyloidosis, we can say that Brazil is an endemic country due to its history of colonization; for this reason, the vast majority of patients have the Portuguese VAL50MET and African ILE142 genetic mutation variants, in addition to many others from other peoples, with diverse origins, who came to this country. Hereditary transthyretin amyloidosis may present cardiac, neuropathic, or mixed phenotypes, depending on the mutation. Due to this diversity, the age of onset of the disease may vary substantially, starting at 20 years. Life expectancy after the first symptoms is 10 years for those with the untreated neuropathy phenotype and 5 years for those with the cardiac phenotype, for whom there is still no therapeutic option available through the Brazilian Unified Health System.

Today, I have taken up this commitment with the goal of maintaining the institution and, above all, continuing the work of spreading awareness about the disease, which is essential so that we will have access to treatments that already exist, but which still require approval and distribution in Brazil's national health system.

The work of the ABPAR is also aimed at seeking information to guide patients and their families regarding where they can seek specialized care and which treatments are available, in addition to attempts to create more referral centers that can facilitate patient access to locations that are closer to their homes.

Furthermore, ABPAR is mobilizing so that new treatments will be approved by the responsible organs, by means of reunions involving specialist doctors and patients, forwarding official communications and letters to government representatives who work for the cause and to the organs that make decisions regarding the adaptation and distribution of these new treatments, in addition to campaigns on social networks, awareness movements, and petitions. We currently have an open petition, which already has more than 35,000 signatures, asking for the pricing and inclusion of two newer medications for the most serious stages of the disease, the Inoteresen and the Patisiran. During the conference period of this article, we had information from the Ministry of Health

Keywords

Amyloidosis; Hereditary Amyloidosis; Hereditary Amyloidosis TTP; Hereditary Amyloidosis associated with TTR - PAF - CAF; Amyloidotic Cardiomyopathy; Amyloidotic Neuropathy; ABPAR; Rare Diseases.

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Editorial

that this issue was resolved and both drugs were priced and approved as category 1, which refers to innovative treatment.

In order to meet the needs of patients with transthyretin amyloidosis in Brazil, our work is thus essentially focused on seeking and forming support networks that offer multidisciplinary diagnosis and treatment, because, in both the neuropathic and cardiac forms, the disease affects several organs. This work is very difficult, given that all of the therapeutic forms have yet to be made available to everyone, be it due to the fact that they have not yet been offered through the Brazilian Unified Health System, due to very high costs that make them impossible to purchase privately, or due to difficulty in finding doctors who are familiar with the disease and who know what to do for patients.

Today, our greatest challenge lies precisely in these three situations: early diagnosis, creation of more referral centers, and access to treatments for all forms and stages of transthyretin amyloidosis. This is not an easy task, but it is my understanding that we all have the right to life, and it is our duty to seek treatment, given that it does exist.

Reference

1. Associação Brasileira de Paramiloidose [Internet]. São Paulo: ABPAR; c2021 [cited 2021 Sep 26]. Available from: www.abpar.org.br.

Amyloidosis: Rare or Underdiagnosed Disease?

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Amyloidosis is the general term for a clinical condition caused when one of more than 30 different precursor proteins with unstable tertiary structure misfolds and aggregates as insoluble amyloid fibrils which deposit in the extracellular space of organs and soft tissue. Classification of amyloidosis is based upon the type of precursor protein.[1, 2]

Specifically, cardiac amyloidosis (CA) is a type of restrictive cardiomyopathy, in which the infiltration of amyloid fibrils into myocardial tissue results in progressive ventricular stiffness, wall thickening, and diastolic dysfunction due to restrictive physiology, which typically manifests as heart failure with preserved ejection fraction (HFpEF). When the disease is advanced, systolic dysfunction might also be seen.[3, 4]

CA can clinically simulate other cardiovascular diseases; therefore, it is believed to be underdiagnosed, and the true prevalence and incidence are uncertain.[2]

Among the many types of amyloidosis, nearly all cases of clinical CA (> 95%) are caused by transthyretin amyloidosis (ATTR) or light chain amyloidosis (AL).

Transthyretin amyloidosis

Transthyretin amyloidosis (ATTR) is caused by the deposition of transthyretin (TTR), a protein synthesized by the liver, which has a stable tetrameric structure and whose function is the transport of thyroid hormones and retinol. TTR can dissociate into monomers and oligomers and then be deposited as amyloid fibrils, in a natural (wtATTR or "wild type", previously known as senile systemic amyloidosis) or genetic manner (hATTR or "hereditary").[4]

The number of patients diagnosed with ATTR has increased over the years, and it has come to be considered that it may be more prevalent than AL.

According to different studies, ATTR deposits have been identified in 25% of autopsies in patients older than 80 years; using non-invasive imaging methods, it has been estimated that ATTR represents 13% of patients with HFpEF and 16% of those who undergo transcutaneous aortic valve replacement for severe low-flow, low-gradient aortic stenosis with preserved ejection fraction (paradoxical).[5]

If the instability of the tetrameric structure of TTR is due to a genetic mutation, a predominantly neurological or cardiac condition will occur. hATTR is considered a rare disease, with a prevalence of less than 1 per 100,000 inhabitants. Currently there are more than 120 mutations that can cause ATTR, and the most frequent mutation worldwide is *Val30Met*, which is endemic in Portugal, Sweden, Japan, Brazil, and Spain. This mutation can cause a symmetric and ascending sensorimotor polyneuropathy, dysautonomia, and in 43% of cases cardiac involvement.[5]

Immunoglobulin light chain amyloidosis

Immunoglobulin light chain amyloidosis (AL) is caused by multisystem deposition of immunoglobulin light chains, as a consequence of plasma cell dyscrasia. The currently reported incidence is 1 in 100,000 people, being more frequent in those over 40 years of age, compromising the liver, lungs, kidneys, spleen, and the autonomic and peripheral nervous systems. Cardiac involvement, which occurs in 50% to 70% of cases, is considered a prognostic factor, because light chains have greater cardiotoxicity than TTR, and, consequently, a lower response to heart failure treatment.[6]

It is important to clinically differentiate between ATTR and AL, as they have different clinical courses.

In general, ATTR presents slowly progressive development, and it is more frequent in older male adults. AL generally has a rapidly progressive course, presenting at younger ages with less male predominance.[4]

Diagnosis and management

AC should be suspected when the patient presents symptoms and signs of HFpEF with unexplained increased left ventricular wall thickness (> 12 mm) and 1 or more clinical manifestations.[5,7,8] (Table 1)

Clinical signs of CA with echocardiography, cardiac magnetic resonance, elevated biomarkers, and grade 2-3 uptake with 99mTc-PYP (pyrophosphate) in scintigraphy, with the exclusion of a monoclonal protein that could cause AL by the light chain test in serum and urine, confer a positive predictive value of 100% for the diagnosis of ATTR.[8] (Table 2)

In these cases, biopsy is not required, and genetic testing should be performed to distinguish a "hereditary" from "wild" variant. When AL is suspected, biopsy of bone marrow and other tissues (fat pad, salivary, or endomyocardial) is

Keywords

Amyloidosis; Heart Failure; Restrictive Cardiomyopathy.

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Editorial

Table 1 – Extra-cardiac manifestations of common subtypes of cardiac amyloidosis

Extra-cardiac manifestations	AL	hATTR	wtATTR
Renal	Renal insufficiency Nephrotic syndrome	Milder renal insufficiency (mainly due to heart failure)	
Autonomic		Orthostatic hypotension Gastroparesis Sexual dysfunction	
Neurologic		Peripheral sensorimotor neuropathy (predominant in hATTR) Carpal tunnel syndrome (bilateral) Spinal stenosis (predominantly lumbar)	
Musculoskeletal	Pseudohypertrophy (macroglossia)	Muscle weakness Arthropathy Fatigue Cachexia	Biceps tendon rupture
Gastrointestinal	Nausea, constipation, early satiety, abdominal bloating	Elevated liver enzymes	
Hematologic	Bleeding and periorbital bruising		
Ocular manifestations		Vitreous opacities	

AL: light chain amyloidosis; hATTR: hereditary transthyretin amyloidosis; wtATTR: wild type transthyretin amyloidosis
Adapted from Fine M, Davis M, Anderson K, Delgado D, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis. CJCA. 2020; 20:322-334

Table 2 – Main findings in cardiac amyloidosis

Electrocardiography	Echocardiography	Biomarkers	Cardiac magnetic resonance
-Low voltage QRS (disproportional to LV wall thickness) -Poor R-wave progression (pseudoinfarction pattern) abnormalities -Left bundle branch block -Atrial fibrillation -AV block	-Unexplained LV hypertrophy -Biatrial dilatation -RV free wall hypertrophy -Speckled appearance of the myocardium -Diastolic LV dysfunction -Low flow, low gradient aortic stenosis -Abnormal GLS with apical sparing ("cherry on top" pattern -Apical strain/average of mid and basal >1.0 -Moderate pulmonary Hypertension -Small pericardial and pleural effusions	-Unexplained persistent low-level cTn elevation -Significant BNP or NT-proBNP elevation -BNP and troponin are higher in AL.	-Diffuse subendocardial LGE -Later transmural LGE -Native myocardial T1 increased -High extracellular volume

AL: light chain amyloidosis; AV: atrioventricular; BNP: brain natriuretic peptide; cTN: cardiac troponin; GLS: global longitudinal strain; LGE: late gadolinium enhancement; LV: left ventricular; NT-proBNP: N-terminal proBNP; RV: right ventricle
Adapted from Papinglotis G, Basmpana L, Farmakis D. Cardiac Amyloidosis: epidemiology, diagnosis and therapy. ESC. 2021; 19:19-21

indicated. The microscopic examination will show apple green birefringence with Congo red.[5,8] (Figure 1)

In patients with heart failure due to amyloidosis, the maintenance of euvolemia will be essential, through fluid restriction and diuretics. There is no evidence for the use of beta blockers, neprilysin, angiotensin, or aldosterone receptor inhibitors . On the contrary, they can produce hypotension, exposing an autonomic neuropathy.[5]

The first and only medication indicated to reduce cardiovascular mortality and cardiovascular hospitalization in adults with hATTR or wtATTR is tafamidis, in a daily dose of 80 mg, which stabilizes the TTR tetramer and reduces the formation of TTR.[8,9]

Heart transplantation plays a small role due to the multiorgan nature of amyloidosis. Patients with AL have significant non-cardiac amyloidosis and are not suitable candidates for heart transplantation, except when they have autologous stem cell transplantation or high-dose chemotherapy. Patients with wtATTR have the disease clinically isolated to the heart and would, thus, appear to be more suitable candidates. However, most patients are diagnosed in their seventh or eighth decade of life and are excluded based on their age. Patients with hATTR are younger and may be candidates if amyloid neuropathy is absent or mild.[6,8]

Other mechanisms of therapies continue to be investigated, such as the suppression of the TTR protein, through liver transplantation or genetic silencers, and the elimination of deposits by doxycycline and epigallocatechin-3-gallate.[1,8]

In summary, CA is an entity that is being diagnosed more frequently. The use of non-invasive techniques, such as scintigraphy with 99mTc-PYP, cardiac magnetic resonance, and light chains in blood and urine allow early identification and treatment of this disease, whose incidence and prevalence are still uncertain.

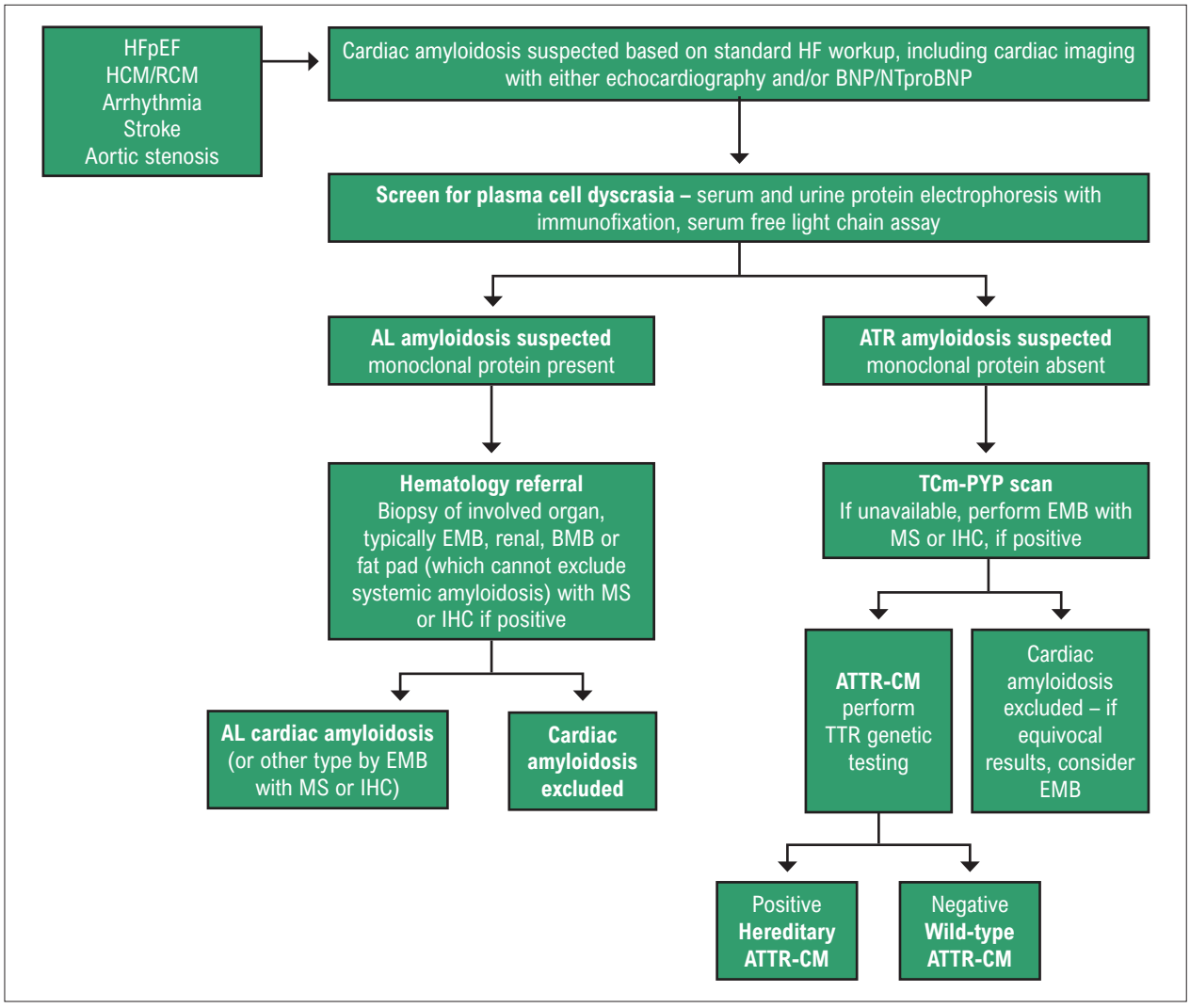

Figure 1 – *Diagnostic algorithm for evaluating suspected cardiac amyloidosis AL: Light chain amyloidosis; ATTR: transthyretin amyloidosis; ATTR-CM: transthyretin amyloid cardiomyopathy; BMB: bone marrow biopsy; BNP: b-type natriuretic peptide; CMR: cardiac magnetic resonance imaging; EMB: endomyocardial biopsy; HCM: hypertrophic cardiomyopathy; HF: heart failure; HFpEF: heart failure preserved ejection fraction; IHC: immunohistochemistry; MS: mass spectrometry; PYP: pyrophosphate; RCM: restrictive cardiomyopathy. Adapted from Fine M, Davis M, Anderson K, Delgado D, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis. CJCA. 2020; 20:322-334*

References

1. García-Pavía P, Tomé-Esteban MT, Rapezzi C. Amiloidosis. También una Enfermedad del Corazón. Rev Esp Cardiol. 2011;64(9):797-808. doi: 10.1016/j.recesp.2011.05.003.
2. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, et al. Cardiac Amyloidosis: The Great Pretender. Heart Fail Rev. 2015;20(2):117-24. doi: 10.1007/s10741-015-9480-0.
3. Fontana M, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. JACC Cardiovasc Imaging. 2019;12(11):2345-56. doi: 10.1016/j.jcmg.2019.06.023.
4. González-López E, Gallego-Delgado M, Guzzo-Merello G, Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-Type Transthyretin Amyloidosis as a Cause of Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2015;36(38):2585-94. doi: 10.1093/eurheartj/ehv338.
5. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, et al. J Am Coll Cardiol. 2015;66(21):2451-66. doi: 10.1016/j.jacc.2015.09.075.
6. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. J Am Coll Cardiol. 2016;68(12):1323-41. doi: 10.1016/j.jacc.2016.06.053.
7. Sipe JD, Benson MD, Buxbaum JN, Ikeda SI, Merlini G, Saraiva MJ, et al. Amyloid Fibril Proteins and Amyloidosis: Chemical Identification and Clinical Classification International Society of Amyloidosis 2016 Nomenclature Guidelines. Amyloid. 2016;23(4):209-13. doi: 10.1080/13506129.2016.1257986.
8. Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis. Can J Cardiol. 2020;36(3):322-34. doi: 10.1016/j.cjca.2019.12.034.
9. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

Editorial

The Importance of the DEIC/GEMIC/SBC 2021 Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis to Clinical Practice

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The latest edition of *Arquivos Brasileiros de Cardiologia* has brought us the publication of the Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis by the DEIC/GEMIC/SBC. This document was the result of the collaborative efforts of many experts in the area, exponents of cardiology in Brazil, but it also included other specialists, such as neurologists, hematologists and nuclear physicians.

The need to bring together this group of collaborators reflects a fundamental aspect of amyloidosis, namely, a complex and multifaceted disease that affects multiple organs and requires the assistance of several specialties for comprehensive management. This was, in fact, a positive aspect of the document: its scope and multidisciplinary character.

It is here appropriate to state the reasons that led the DEIC/GEMIC/SBC to produce this document, fulfilling the mission of producing documents that contribute to updating science and medical education, offering the signposts that are necessary to guide the practice of cardiology based on scientific evidence. The sense of urgency for this action was the clear perception of the recent and profound reformulation of concepts regarding cardiac amyloidosis (CA), including evidence that it is a more prevalent disease than previously imagined, the significant advance in imaging methods that has made non-invasive diagnosis possible, and the emergence of new specific treatments that can change the natural history of the disease (Figure 1).

Cardiac amyloidosis is a frequent cause of heart failure with preserved ejection fraction

The main cardiological phenotype of CA is that of an infiltrative restrictive cardiomyopathy, whose more general aspects of symptoms, increased thickness of the ventricular walls, and concentric remodeling of the left ventricle, overlap with those of heart failure with preserved ejection fraction (HFpEF), produced by risk factors such as high blood pressure, obesity, diabetes, and aging. Thus, CA should be considered as a differential diagnosis in patients who exhibit HFpEF.[1]

Keywords

Amyloidosis; Cardiomyopathy; Diagnostic Methods; Treatment.

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It is worth remembering that, among the different amyloidogenic proteins that can be deposited in the myocardium and cause CA, the wild type transthyretin form (ATTR-CAwt), which is closely linked to aging, is the most frequently reported in several series of specialized medical literature. This has been repeated both in large reference centers and in real world registers.[2] Accordingly, a recent article has shown a very significant increase in CA as a cause of hospitalizations due to heart failure in several regions of the United States, between 2000 and 2012, exceeding the rate of 65 cases per 100,000 people/year, indicating that CA is not a rare disease according to the current criteria of the World Health Organization (Figure 2).[3]

It is important to remember that there are no similar statistics in our country to confirm the higher prevalence of CA in the Brazilian population. This is a gap that we hope will be filled in the near future.

Non-invasive diagnosis using bone tracer scintigraphy

Of all the advances in the clinical scenario of CA, the one with the greatest impact has been the development of the bases for non-invasive diagnosis of ATTR-CA, dispensing the use of endomyocardial biopsy. In the celebrated study published by Perugini et al. in 2005, it was well demonstrated that patients with ATTR-CA exhibited intense and anomalous myocardial accumulation of some bisphosphonate agents used for bone scintigraphy. In this seminal study, only patients with ATTR-CA exhibited ^{99m}Tc-DPD (3,3-diphosphono-1,2-propanedicarboxylic acid) uptake equivalent or superior to costal arch uptake (grades 2 or 3), while none of the patients with AC linked to light chains (AL form) showed the same behavior.[4]

It was subsequently identified that a certain percentage (20% to 30%) of patients with AL-CA could also exhibit expressive uptake of bone markers, making it essential to rule out the presence of immunoglobulin light chains for diagnostic confirmation of ATTR-CA in patients with positive cardiac scintigraphy using bone markers. In the fundamental study by Gillmore et al., this set of results (cardiac scintigraphy with grade 2 or 3 bone marker uptake + light chain exclusion) had 100% specificity and predictive value, thus defining the non-invasive criteria for diagnosis of ATTR-CA, which have gone on to become a standard of conduct worldwide.[5]

These fundamental aspects have guided the choices made by the panel of experts who created the flowchart for the diagnosis of CA in our Position Statement, which is reproduced in Figure 3. This alone is the most important item of the entire document, and we hope that it will be able to guide the diagnostic flow of CA in routine cardiology practice.

Editorial

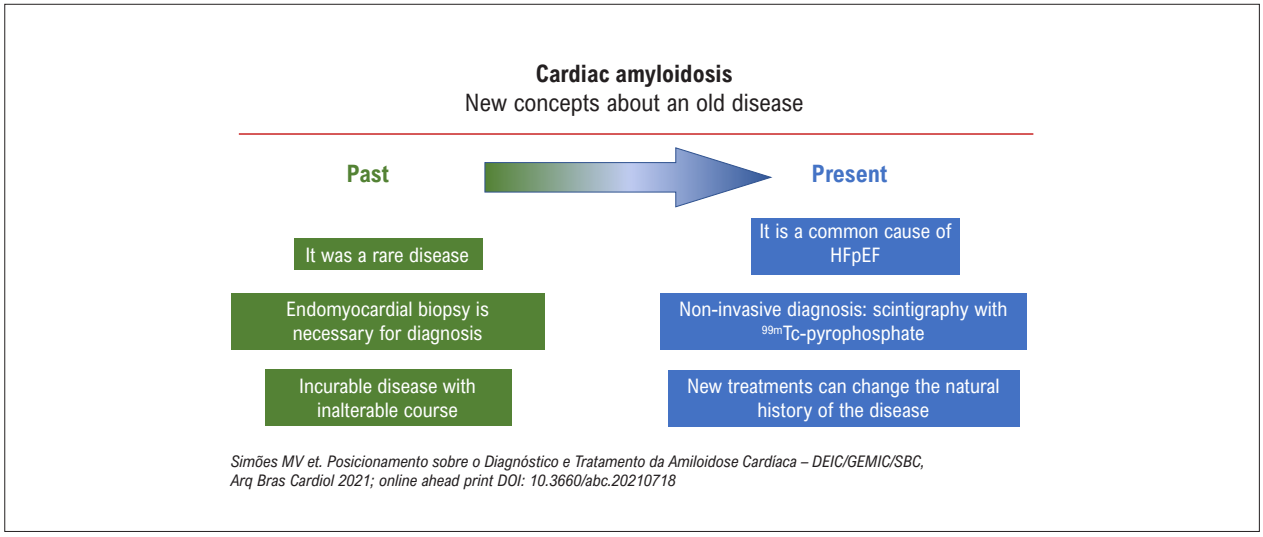

Figure 1 – *Illustration outlining the aspects involved in the profound reformulation of concepts regarding cardiac amyloidosis that have expanded in recent years. HFpEF: heart failure with preserved ejection fraction.*

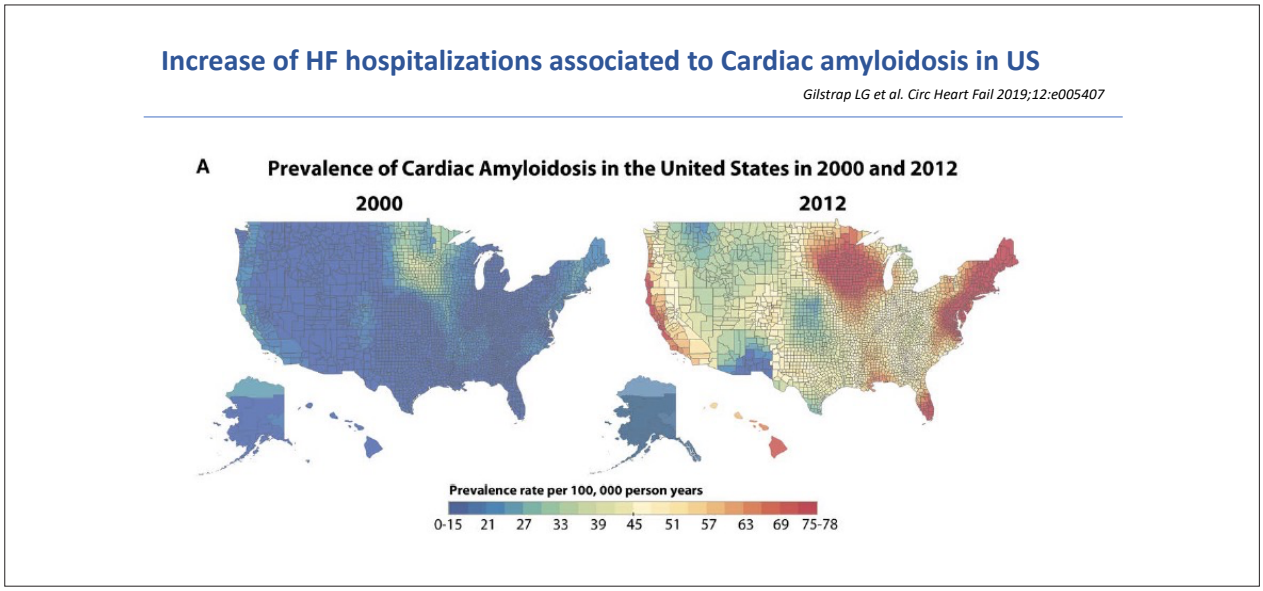

Figure 2 – *Heat map showing the increased prevalence of cardiac amyloidosis as a cause associated with hospitalizations due to heart failure in the United States, between 2000 and 2012. Reproduced from (Gilstrap et al., 2019).*

New specific treatments

There is no doubt that any efforts made to improve our ability to diagnose a given condition are only fully valid and compensated when we are able link this finding to the use of specific treatments capable of alleviating symptoms and prolonging our patients' lives. The emergence of new therapies specific to CA has been the fundamental spring that has fueled research and initiatives to raise the level of care for more accurate and earlier diagnosis of CA.

The transthyretin tetramer stabilizer tafamidis was the first drug for specific treatment of ATTR-CA to be tested in a multicenter, randomized, blinded study, the ATTRACT study.[6] The main results of ATTRACT have shown that the use of tafamidis was associated with a significant reduction in all-cause mortality by 30% (HR = 0.70, 95% CI: 0.51 to 0.96) and a reduction in hospitalizations/year of around 32% (HR = 0.68%; 95% CI: 0.56 to 0.81). In this manner, tafamidis is the first specific treatment for ATTR-CA capable of changing the natural history of the disease, and it has received approval from the Brazilian Health Regulatory Agency for the treatment of ATTR-CA in Brazil.

Other very promising molecules are currently being developed and tested in phase 3 multicenter trials, including

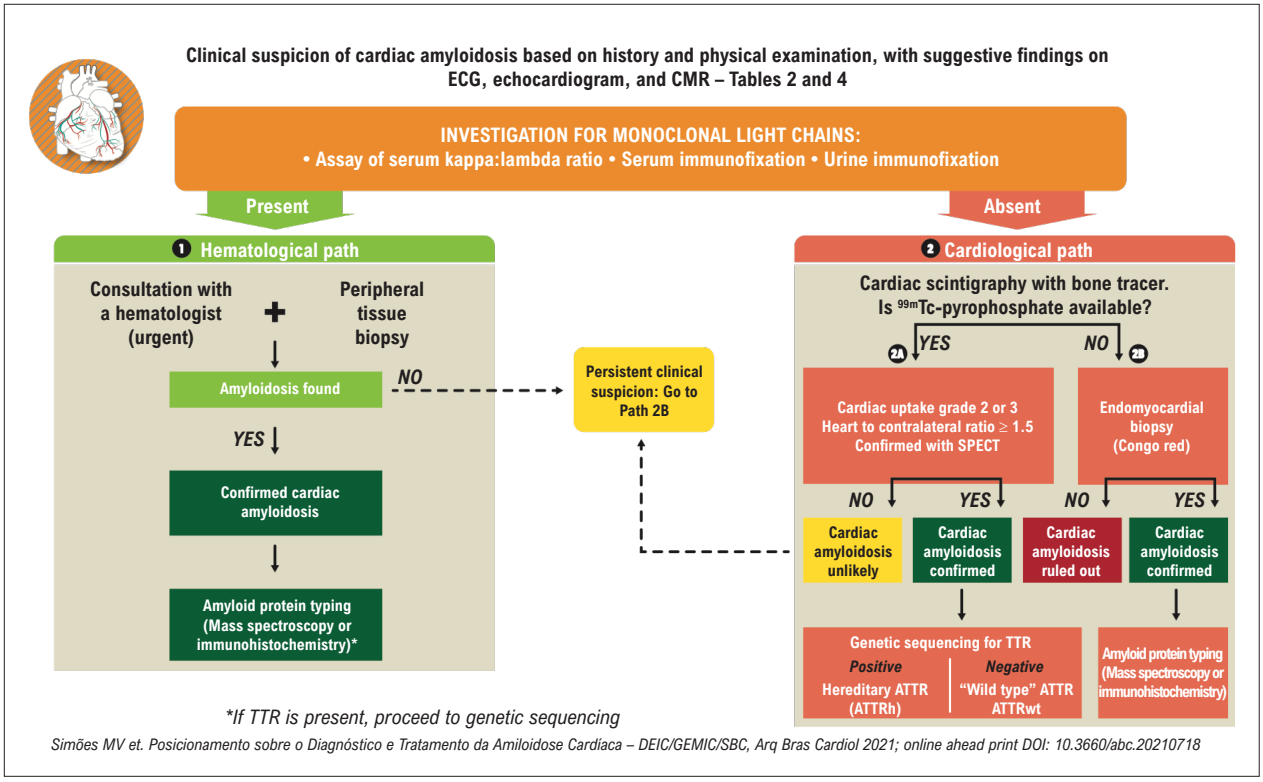

Figure 3 – *Flowchart for diagnosis of CA*

strategies for silencing the gene expression of TTR production through "small interference RNA" (patisiran) and "anti-sense" oligonucleotide (eplontersen) platforms.

It is important to remember that we have recently witnessed the incorporation of significant advances in the treatment of AL-CA, using monoclonal antibodies and autologous bone marrow transplantation, which are associated with a surprising positive impact on mortality due to AL-CA, provided that patients are referred during earlier stages of disease evolution, which highlights the need for more accurate and quicker diagnosis of this disease.[7]

Final comments

As reviewed here, there is strong evidence to suggest that CA is a relatively prevalent but broadly underdiagnosed condition. The emergence of new therapies capable of changing the natural history of this serious disease has brought about the need for earlier and safer diagnosis. The publication of the DEIC/GEMIC/SBC 2021 Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis takes on fundamental importance at this moment by contributing to the incorporation of these new concepts in clinical practice and providing signposts based on the most recent scientific evidence.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Simões MV, Fernandes F.

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References

1. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, et al. Cardiac Amyloidosis: The Great Pretender. Heart Fail Rev. 2015;20(2):117-24. doi: 10.1007/s10741-015-9480-0.
2. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. Circulation. 2019;140(1):16-26. doi: 10.1161/CIRCULATIONAHA.118.038169.
3. Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF, et al. Epidemiology of Cardiac Amyloidosis-Associated Heart Failure Hospitalizations Among Fee-for-Service Medicare Beneficiaries in the United States. Circ Heart Fail. 2019;12(6):e005407. doi: 10.1161/CIRCHEARTFAILURE.118.005407.
4. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis using 99mTc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy. J Am Coll Cardiol. 2005;46(6):1076-84. doi: 10.1016/j.jacc.2005.05.073.
5. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12. doi: 10.1161/CIRCULATIONAHA.116.021612.
6. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.
7. Gertz MA, Dispenzieri A. Systemic Amyloidosis Recognition, Prognosis, and Therapy: A Systematic Review. JAMA. 2020;324(1):79-89. doi: 10.1001/jama.2020.5493.

ATTRv: a Multisystemic Disease Requires a Multiprofessional Approach

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Pathogenic variants of the transtiretin gene (TTRv) result in the production of amyloidogenic fibrils that deposit in the extracellular space of many tissues, resulting in amyloidogenic multisystemic disease (ATTRv). Several tissues may be affected in different combinations, including the peripheral nerves and the cardiac system, which are usually the main targets, but also the kidneys, eyes, gastrointestinal system, central nervous system and musculoskeletal structures.[1]

ATTRv is a progressive disease[2] that results in death around 8 to 15 years after the onset of the disease, even more rapidly when the cardiac system is involved early.[3] However, the natural history of the disease has changed with the introduction of treatments that, by different mechanisms, decrease the production of amyloid fibrils.[4]

Such a complex disease demands coordinated multiprofessional interaction in order to provide the best care for patients. Considering medical specialties, well trained cardiologists, neurologists, ophthalmologists, gastroenterologists, nephrologists and geneticists should work in close collaboration both to treat patients who have already manifested the disease and to follow asymptomatic carriers, in order to detect the disease onset, when treatment is much more effective. For the best care, however, in addition to professionals who are trained in the field of amyloidosis, it is necessary that an institution is able to provide a complex set of prepared investigations, including neurophysiology (including small fiber evaluation), skin biopsy, other types of biopsy, magnetic resonance imagine, and scintigraphy.

For these reasons, we believe these patients should be followed in tertiary reference centers that should interact closely with local physicians, in order to offer the best care at the best time to patients with this complex disease.

Keywords

Cardiomyopathy; Polyneuropathy; Transthyretin; TTR.

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References

1. Koike H, Katsuno M. Transthyretin Amyloidosis: Update on the Clinical Spectrum, Pathogenesis, and Disease-Modifying Therapies. Neurol Ther. 2020;9(2):317-33. doi: 10.1007/s40120-020-00210-7.
2. Adams D, Coelho T, Obici L, Merlini G, Mincheva Z, Suanprasert N, et al. Rapid Progression of Familial Amyloidotic Polyneuropathy: A Multinational Natural History Study. Neurology. 2015;85(8):675-82. doi: 10.1212/WNL.0000000000001870.
3. Adams D, Ando Y, Beirão JM, Coelho T, Gertz MA, Gillmore JD, et al. Expert Consensus Recommendations to Improve Diagnosis of ATTR Amyloidosis with Polyneuropathy. J Neurol. 2021;268(6):2109-22. doi: 10.1007/s00415-019-09688-0.
4. Russo M, Gentile L, Toscano A, Aguennouz M, Vita G, Mazzeo A. Advances in Treatment of ATTRv Amyloidosis: State of the Art and Future Prospects. Brain Sci. 2020 Dec 9;10(12):952. doi: 10.3390/brainsci10120952.

Registry of Transthyretin Amyloidosis in the State of São Paulo (REACT-SP)

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Abstract

Background: Amyloidosis is a systemic disease that involves multiple organs, characterized by the deposition of amyloid fibrils. Knowledge regarding the epidemiological, clinical, and genetic profile of the population affected by amyloidosis throughout the country is of fundamental importance for establishing diagnostic and therapeutic strategies.

Objective: To evaluate the epidemiological, clinical, laboratory, imaging, and treatment variables of patients with TTR cardiac amyloidosis.

Methods: A multicenter, retrospective, prospective, and observational study based on collection of data on the natural history of patients with TTR amyloidosis, followed in the state of São Paulo.

Results: To make it possible to map the regional distribution of the disease, increasing knowledge about the disease among clinicians and specialists in different areas. To evaluate patients with hereditary and wild-type TTR amyloidosis, in addition to following individuals with positive genotype and negative phenotype.

Conclusion: The information collected may show greater awareness of the disease, development of new diagnostic and treatment flowcharts with a direct impact on knowledge of the natural history of the disease and patient prognosis.

Keywords: Amyloidosis; Ventricular Hypertrophy; Heart Failure.

Introduction

Amyloidosis is characterized by the deposition of amyloid fibrils in the extracellular space of several organs, such as the heart, peripheral nerves, and gastrointestinal tract.[1,2] The 2 most common types of amyloidosis are those caused by monoclonal proteins (AL) and those caused by hepatic transthyretin (TTR) proteins. The TTR form can be further divided into 2 types: hereditary, when there is a known genetic mutation that causes the disease (ATTRh) and the wild type (ATTRwt, previously known as senile amyloidosis).[3]

TTR protein disorders cause it to dissociate into monomers, which aggregate to form amyloid fibrils and infiltrate the extracellular matrix. The consequences in the heart are increased ventricular wall thickness and myocardial stiffness, in addition to valvular and interatrial septum thickening. Patients present a phenotype of hypertrophic cardiomyopathy, evolving to restrictive cardiomyopathy associated with heart failure syndrome, with poor prognosis.[4]

Mutations related to TTR amyloidosis may be associated with specific phenotypes, with a tendency toward cardiac or neurological involvement, for example.[5] However, several other factors may also influence phenotype and prognosis, including age, sex, environmental factors, and maternal genetics.[6] Amyloid heart disease is commonly associated with

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the Val122Ile mutation, whereas familial TTR amyloidotic polyneuropathy is more related to the Val30Met mutation

ATTR amyloidosis was considered a rare cause of heart failure, but it was perhaps only underdiagnosed. Technetium bone scintigraphy as a diagnostic technique, associated with advances in therapeutic possibilities, has led to changes in the disease prevalence.[7,8] The nonspecific symptomatology of this disease and its heterogeneous phenotype make this a challenging task, but identifying patients at an early stage is essential for the use of disease-modifying medications and a better opportunity to impact patients' clinical course.

It could be extremely useful to know the epidemiological, clinical, and genetic profile of the population affected by amyloidosis in the state of São Paulo, as well as patients' age and time to diagnosis, exams conducted, medical specialty consulted, evolution of the clinical condition, and the treatment used. This information is lacking in Brazil, and it may make it possible to adopt public policies in order to raise awareness of the disease, target investments, and create new diagnosis and treatment flowcharts with a direct impact on knowledge of the disease's natural history and patients' prognosis.

Objectives

Primary

To describe the population affected by TTR-associated amyloidosis, evaluating the epidemiological and clinical variables, complementary laboratory and imaging methods, and treatment types of patients in the state of São Paulo.

Methods

Study design and population

This is a multicenter, retrospective, prospective, and observational study. It will include patients of both sexes, with a minimum age of 18 years, who are followed for TTR-associated amyloidosis, including both the hereditary and wild-type disease, including polyneuropathy and cardiomyopathy, as well as participants with TTR mutations who have not been diagnosed with ATTR, in the state of Sao Paulo.

Data will be collected from patients' medical records at the service of origin, after the last follow-up visit, and data collection must be carried out using the online platform (REDCap). Data from all patient consultations will be recorded and entered into the data registry/electronic database. This study will include an estimated 600 patients.

The following research centers will participate: Instituto do Coração-HC FMUSP, Instituto Dante Pazzanese de Cardiologia, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Centro Universitário de Saúde ABC, Associação Paulista para o Desenvolvimento da Medicina Hospital São Paulo, Instituto de Pesquisa e Inovação Tecnológica da Santa Casa de São Paulo, Hospital Universitário São Francisco na Providência de Deus, Clinicor Clínica Cardiológica, and Hospital Israelita Albert Einstein. Centers with volumes of patients with forms of ATTR may be selected. New centers may be included, if they include at least 10 patients with ATTR.

In order to participate in REACT, each research unit must obtain approval from the local Research Ethics Committee before beginning to enroll patients. The study will only be conducted in units where approval has been obtained from the Research Ethics Committee. It is the responsibility of investigators to obtain future approval of the study protocol.

Patients will be enrolled in the study based on the results of genotyping, which will be conducted prior to the last visit, in accordance with the units' standard practices. TTR genotyping is required to confirm patient eligibility. For patients with a documented TTR mutation, the mutation(s) will be entered into the their medical records.

All tests necessary to confirm diagnosis of ATTR will be conducted prior to the last visit.

Inclusion criteria

- **Patients and disease characteristics**

1. Male or female sex ≥ 18 years.

2. TTR mutation confirmed by genotyping, with or without diagnosis of ATTR or wild-type TTR amyloidosis. Confirmation of wild-type TTR amyloidosis will be determined by genotyping, confirming that the patient does not have a known mutation in the TTR gene (i.e., only a carrier of the wild-type allele), by means of genetic testing and one of the following criteria (A, B or C):

a. Evidence of cardiac involvement on echocardiography, as defined by mean left ventricular wall thickness > 12 mm and presence of amyloids in cardiac tissue on biopsy confirmed as TTR amyloid by mass spectrometry or immunohistochemistry; or

b. Evidence of cardiac involvement on echocardiography, as defined by mean left ventricular wall thickness > 12 mm and presence of amyloids in non-cardiac tissue on biopsy confirmed as TTR amyloid by mass spectrometry or immunohistochemistry; or

c. Evidence of cardiac involvement on echocardiography, as defined by mean left ventricular wall thickness > 12 mm, without evidence of primary (light chain) amyloidosis and presence of amyloid in cardiac tissue, indirectly confirmed by scintigraphy with a bone tracer, for example, 99mTC-DPD (99mTC-3,3-diphosphono-1,2-propane-dicarboxylic acid), 99mTC-PYP (pyrophosphate), or 99mTC-HMDP (hydroxymethylene diphosphonate), with Perugini grade ≥ 2.

Exclusion criteria

- **Patients with primary or secondary amyloidosis.**

Statistical analysis

Analysis of clinical outcomes will be performed for all enrolled patients whose data are available. Results will be examined for the entire patient group, as well as by stratifying important variables that may affect outcomes (including, but not limited to TTR variant, age, race, gender, country of origin, and transplant recipient status).

Data for continuous variables will be presented as statistics of position and scale (mean and standard deviation and/or median and interquartile range). Categorical variables will be presented as absolute and relative frequencies. Comparisons between cohorts and subgroups will be made using the chi-square test for categorical variables. Student's t test will be used for paired and unpaired comparisons, when appropriate. Nonparametric tests (Wilcoxon rank-sum test) will be used when data are not normally distributed.

Limitations to the research methods

The observational nature of this study may potentially introduce selection or verification bias. The study population could be more heterogeneous. Confounding factors lead to biased estimates of associations of risk factors or treatments with the result and, therefore, affect the validity of study conclusions. Analytical methods (such as multivariate, corresponding regression) should be used to control for the occurrence of confounding factors. Other potential limitations to study validity include missing data.

Chronogram of the Project

Step	Planned date
Beginning of data collection (first subject first visit [FSFV])	15 October 2021
End of data collection (last subject last visit [LSLV])	15 December 2022
Study progress reports	Study progress reports should be sent in May 2022
Final study report	23 December 2022

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References

1. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving Landscape in the Management of Transthyretin Amyloidosis. Ann Med. 2015;47(8):625-38. doi: 10.3109/07853890.2015.1068949.
2. Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. Circulation. 2012;126(10):1286-300. doi: 10.1161/CIRCULATIONAHA.111.078915.
3. Buxbaum JN, Tagoe CE. The Genetics of the Amyloidoses. Annu Rev Med. 2000;51:543-69. doi: 10.1146/annurev.med.51.1.543.
4. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the Cardiomyopathies: A Position Statement From the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270-6. doi: 10.1093/eurheartj/ehm342.
5. Carr AS, Pelayo-Negro AL, Evans MR, Laurà M, Blake J, Stancanelli C, et al. A Study of the Neuropathy Associated With Transthyretin Amyloidosis (ATTR) in the UK. J Neurol Neurosurg Psychiatry. 2016;87(6):620-7. doi: 10.1136/jnnp-2015-310907.
6. Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, et al. Transthyretin-Related Amyloidoses and the Heart: A Clinical Overview. Nat Rev Cardiol. 2010;7(7):398-408. doi: 10.1038/nrcardio.2010.67.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12. doi: 10.1161/CIRCULATIONAHA.116.021612.
8. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31. doi: 10.1056/NEJMoa1716793.

Original Article

Review Article

Cardiac Amyloidosis and Aortic Stenosis: When to Consider it and How to Treat it?

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Abstract

Aortic stenosis is the most prevalent valve disease in clinical practice. The wild form of transthyretin amyloidosis has an increased incidence in elderly individuals, usually over 70 years of age. Amyloidosis and aortic stenosis are 2 diseases that affect similar populations; therefore, they may coexist in the same patient.

Patients with amyloidosis and aortic stenosis have disproportionately higher serum levels of troponin and NT-proBNP compared to patients with pure severe aortic stenosis in addition to greater ventricular hypertrophy. Therapeutic decisions for these patients must be individualized and promptly discussed by the heart team. In this article, we discuss this association and possible valve therapies, in addition to the possibility of specific treatment for amyloidosis.

Clinical case

J.P.S., a 73-year-old, male patient who was born and raised in Bahia, had prior diagnosis of systemic arterial hypertension, benign prostatic hyperplasia, and bilateral glaucoma. Regarding family history, his father had died due to Chagas disease, and his mother had died of an acute myocardial infarction. He was using losartan 50 mg, acetylsalicylic acid 100 mg, and finasteride/doxazosin.

He sought outpatient care, reporting that, 2 months prior, he had started to experience progressive dyspnea upon moderate exertion, orthopnea, and tachycardic palpitations. On physical examination, the presence of a rough midsystolic ejection murmur 3+/6 radiating to the carotids and a blowing protodiastolic murmur 3+/6, both in aortic focus, stood out. There were no signs of significant edema or turgescent jugular veins. At that time, the syndromic diagnosis of heart failure was suggested, with anatomical and etiological diagnosis of double degenerative aortic lesion. Furosemide 40 mg was prescribed and additional tests were requested.

He returned 2 months later with dyspnea upon minimal exertion, as well as the following additional exams:

Keywords

Aortic Stenosis; Amyloidosis; Heart failure; preserved ejection fraction

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- 12-lead electrocardiogram: sinus bradycardia and left chamber overload.

- Two-dimensional echocardiography: important fibrocalcification in the aortic valve, with reduced valve mobility, maximum jet velocity of 4.9 m/s, and mean systolic gradient of 50 mmHg (Velocities > 4 m/s and mean gradient > 40 mmHg indicate important stenosis); mild to moderate aortic regurgitation and pulmonary artery systolic pressure estimated at 50 mmHg. Biventricular systolic function was preserved; he had grade I diastolic dysfunction and moderate atrial enlargement.

Based on this new information, aortic valve replacement with a biological prosthesis was indicated, and preoperative tests were requested. Coronary cineangiography did not demonstrate any obstructive lesions. Euroscore II was 1.45%.

Three years after the first evaluation, the patient was submitted to aortic valve replacement with a 23 mm biological prosthesis, and myectomy was performed due to the intraoperative finding of subvalvular aortic membrane. The surgery occurred without complications.

During anatomopathological study of the myectomy, morphological and immunohistochemical alterations consistent with transthyretin cardiac amyloidosis were observed. Subsequently, monoclocal gammopathy was ruled out by means of serum and urinary immunofixation and kappa and lambda immunoglobulin assay. The patient underwent pyrophosphate scintigraphy, demonstrating Perugini grade III uptake (Figure 1), and genetic testing showed no variants that would justify the clinical condition. This case illustrates the concomitant association of wild-type transthyretin systemic amyloidosis (ATTRwt) with cardiac involvement and aortic stenosis, with difficult clinical diagnosis.

Introduction

Aortic stenosis is the most prevalent valve disease in clinical practice, with an estimated prevalence of 0.2% in people over 50 years of age and a prevalence of up to 10% in octogenarians. This condition is characterized by aortic valve degeneration and calcification causing a fixed obstruction in the left ventricular outflow tract. Due to the pressure overload caused by aortic stenosis, the heart is affected by concentric remodeling, characterized by left ventricular wall hypertrophy and increased left ventricular filling pressures.[1]

Amyloidosis is characterized by the deposition of amyloid fibrils in the extracellular space of several organs, such as the heart, peripheral nerves, and gastrointestinal tract. The 2 most common types of amyloidosis are those caused by monoclonal proteins (AL) and those caused by hepatic transthyretin (TTR)

proteins. The TTR form can be further divided into 2 types: hereditary, when there is a known genetic mutation that causes the disease (ATTRh) and the wild type (ATTRwt, previously known as senile amyloidosis) (2). ATTR amyloidosis was considered a rare cause of heart failure, but it was perhaps only underdiagnosed. ATTRwt has an increased incidence in elderly individuals, usually over 70 years of age. On the other hand, necropsy studies have shown a prevalence of up to 25% of amyloidosis in patients over 80 years of age.[2,3]

ATTR and aortic stenosis are 2 diseases that affect similar populations; therefore, they may coexist in the same patient.

The prevalence of concomitant amyloidosis and aortic stenosis ranges from 4% to 16%. The smallest sample occurred in patients who underwent aortic valve replacement surgery and biopsy during the procedure.[4] In a systematic study in 2 centers from the United States that used myocardial scintigraphy with technetium in all patients with aortic stenosis who underwent transcatheter aortic valve implantation (TAVI), a prevalence of 13% was described.[5] On the other hand, the National Amyloidosis Centre in the United Kingdom, in a cohort of 1240 patients with amyloidosis, performed echocardiography and found severe aortic stenosis in 1.8%.[6]

In the vast majority of cases where aortic stenosis and amyloidosis coexist, the amyloid form is, generally, ATTRwt, and fewer than 5% of cases are the AL form.[7]

Given that both diseases are prevalent in the elderly population and that they cause similar structural changes in the heart (disproportionate hypertrophy, increased filling pressures, early change in global longitudinal strain), it is difficult to differentiate between patients with aortic stenosis who have amyloidosis and those who do not.

Establishing diagnosis of amyloidosis requires a high degree of clinical suspicion. Correct and accurate diagnosis is necessary, because conventional therapy for heart failure is not always well tolerated in cardiac amyloidosis. Prognosis is different from other etiologies of heart failure, and evolution and clinical management are different from other cardiomyopathies with a hypertrophic phenotype. Furthermore, the current specific therapeutic possibilities can modify the natural history of the disease.

In some studies,[8] average time from onset of symptoms to establishment of diagnosis is up to 4 years in ATTRwt. In the case reported, it is possible to observe the patient's long journey, 36 months, to receive definitive diagnosis. In this context, imaging exams, especially echocardiography, scintigraphy, and cardiac magnetic resonance, have increasingly contributed to recognition of cardiac amyloidosis. The most important aspect, however, is to consider the disease.

Diagnosis

There are some red flags that have been described in the literature, which may help differentiate patients with aortic stenosis who may have concomitant amyloidosis. Patients with amyloidosis and aortic stenosis have disproportionately higher serum levels of troponin and NT-proBNP compared to patients with pure severe aortic stenosis; they may have greater ventricular thickness, and they may have more typical changes in the strain echocardiogram, such as the apical sparing pattern.[9,10] We must take into account, however, that patients with severe aortic stenosis typically show early changes in global longitudinal strain; this fact that can interfere with the appearance of apical sparing caused by amyloidosis. In a study that evaluated the echocardiography pattern of mean S wave velocity, measurement < 6 cm/s was considered the best independent predictor of amyloidotic cardiomyopathy, with 100% sensitivity.[9]

Another condition that may be related to cardiac amyloidosis is low-flow, low-gradient aortic stenosis, both in cases of reduced left ventricular ejection fraction (LVEF), where the patient's mean systolic gradient in the aortic valve is > 40 mmHg but valve area is ≤ 1.0 cm^2, and in cases of paradoxical aortic stenosis, where the patient has small cavities due to extreme concentric remodeling, generating low-flow, low-gradient aortic stenosis with normal ejection fraction, mean systolic gradient < 40 mmHg, valve area ≤ 1.0 cm^2 and normal LVEF.

Although they have been described in the literature, no study has found red flags that were adequate for giving rise to suspicion of cardiac amyloidosis in patients with aortic stenosis, given that cardiac remodeling caused by both diseases has similar, confounding characteristics.

A study by Sperry et al. outlining factors that demonstrated this association drew attention to the presence of carpal tunnel syndrome and a mismatch between low voltage and ventricular mass on electrocardiogram.[11] Nitsche et al. developed the RAISE score, which takes ventricular remodeling, age, troponin, systemic involvement, and electrocardiographic changes into account; it showed good specificity and sensitivity for suspected amyloidosis in patients with severe aortic stenosis.[12] A score greater than or equal to 2 had a sensitivity of 84%, and a score greater than or equal to 3 had a specificity of 94% for detection of cardiac amyloidosis. Thus, a score greater than or equal to 2 is already a good milestone to begin confirmatory investigation of cardiac amyloidosis, but this score requires further studies for validation (Table 1).

Patients who undergo TAVI also undergo tomography for preoperative evaluation; currently, this method allows assessment of the extravascular space, which is enlarged in amyloidosis.[13] Accordingly, this could be yet another exam to aid in screening these 2 conditions.

Treatment

Both diseases have poor prognosis if they are not identified and treated. Treatment of aortic stenosis consists of aortic valve intervention to reverse the structural disease. In elderly patients, TAVI has been shown to be the procedure of choice in all patient profiles, due to its safety and efficacy.[14,15]

The central question would be whether symptoms are due to a hemodynamic valve problem or to the myocardial disease that results from amyloid deposits. In relation to this, several studies have evaluated the effectiveness of treatment of aortic stenosis in patients with TTR cardiac amyloidosis.

Table 1 – Table 1 Multiple parameters applied by Nitsche et al. (2021)

Age > 85 years	1 point
Carpal tunnel syndrome	3 points
Right bundle branch block	2 points
Sokolow-Lyon index < 1.9 mV	1 point
High sensitivity troponin > 29 ng/mL	1 point
E/A > 1.4	1 point

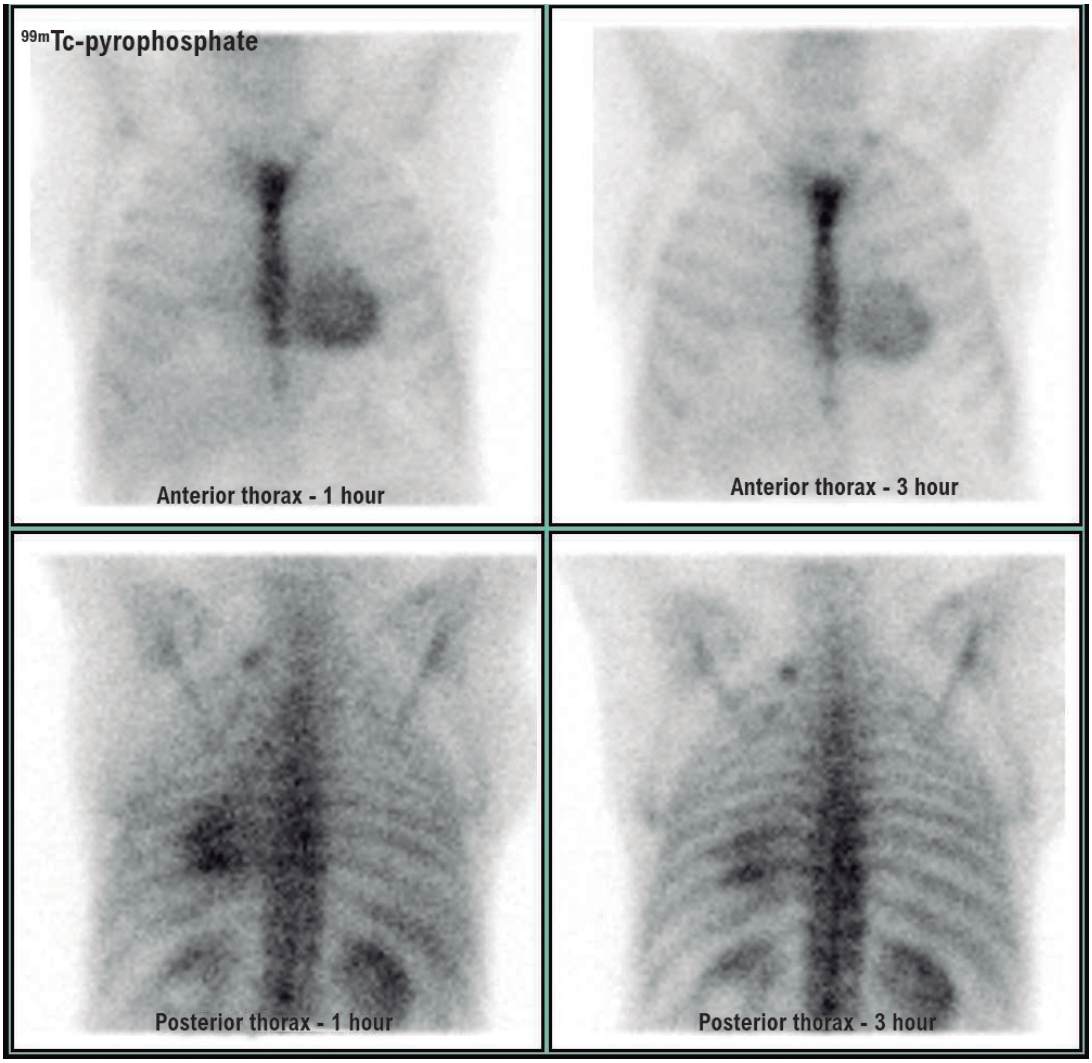

Figure 1 – *Technetium pyrophosphate bone scintigraphy showing Perugini grade III uptake, 1 and 3 hours*

In contrast to the initial study by Cavalcante et al., which provided evidence of higher mortality in patients with amyloidosis who underwent TAVI in comparison with patients with pure aortic stenosis,[16] the most recently published studies that have used pyrophosphate scintigraphy to screen for amyloidosis in patients with aortic stenosis showed evidence that the patients who were submitted to aortic valve intervention benefit from the procedure, regardless of cardiac amyloidosis.[12,16]

With respect to defining which valve intervention to choose for patients with cardiac amyloidosis, Treibel et al. identified amyloid protein deposits in 6% of patients who underwent endomyocardial biopsy during aortic valve replacement surgery, and the presence of amyloidosis was a predictor of

negative outcomes in the patients evaluated.[4] Rosenblum et al. identified 13% of cases of cardiac amyloidosis in patients who underwent TAVI, and, in this population, the presence of amyloidosis was not identified as an outcome predictor.[5] In spite of all these studies, we still do not have any randomized clinical trials that demonstrate the best intervention for aortic stenosis in patients with cardiac amyloidosis.

As amyloidosis induces a fragile state in patients, it predisposes them to arrhythmias and atrioventricular blocks, and TAVI has been shown to be safe in this population. We consider that, when possible, TAVI should be the procedure of choice for elderly patients with aortic stenosis and concomitant amyloidosis. Specific treatment for amyloid heart disease with transthyretin stabilizing drugs may impact the clinical course of patients.

The use of tafamidis was tested in the Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy (ATTR-ACT) study. This was a multicenter clinical randomized, placebo-controlled trial, involving 441 patients with cardiac amyloidosis, 264 of whom received the drug in doses of 20 mg or 80 mg daily. The main results showed that the use of tafamidis was associated with a 30% reduction in the primary outcome of all-cause mortality (RR = 0.70 [95% CI: 0.51 – 0.96]); moreover, it reduced cardiovascular hospitalizations by 32% (RR = 0.68 [95% CI: 0.56 – 0.81]) and reduced worsening of functional capacity and quality of life. In Brazil, these results provided the bases for the Brazilian Health Regulatory Agency to approve the use of this medication for treatment of TTR cardiac amyloidosis at a dose of 80 mg/day.[17]

To date, no published studies have evaluated the role of tafamidis specifically in patients with aortic stenosis; we may, however, infer that the medication remains effective, given that the pathophysiology of TTR cardiac amyloidosis does not differ in the context of aortic stenosis.

Conclusion

Aortic stenosis and TTR cardiac amyloidosis are 2 diseases that are very frequently associated, and the importance of their association has yet to be well understood. Both diseases are prevalent in the elderly, and their prognosis is poor if they are not promptly identified and treated. Therapeutic decisions for these patients must be individualized and promptly discussed by the heart team for the patient's benefit. It is very important to identify which patients with aortic stenosis we should screen in order to avoid underdiagnosis of cardiac amyloidosis in this population and to offer the best treatment to all patients.

Author contributions

Conception and design of the research: Fernandes F, Kirschbaum M, Kalil Filho R, Tarasoutchi F. Acquisition of data: Kirschbaum M, Alencar Neto AC, Rosa VEE, Ramires FJA. Analysis and interpretation of the data: Fernandes F, Tarasoutchi F, Brito Junior FS, Brito Junior FS. Writing of the manuscript: Fernandes F, Kirschbaum M, Kalil Filho R, Tarasoutchi F, Alencar Neto AC. Critical revision of the manuscript for intellectual content: Fernandes F, Kirschbaum M, Kalil Filho R, Tarasoutchi F, Alencar Neto AC, Rosa VEE, Ramires FJA, Brito Junior FS, Abizaid AAC. Supervision / as the major investigador: Fernandes F, Kirschbaum M, Tarasoutchi F.

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References

1. Otto CM, Prendergast B. Aortic-Valve Stenosis – From Patients at Risk to Severe Valve Obstruction. N Engl J Med. 2014 A;371(8):744-56. doi: 10.1056/NEJMra1313875.
2. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
3. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, et al. Senile Systemic Amyloidosis Affects 25% of the Very Aged and Associates with Genetic Variation in Alpha2-Macroglobulin and Tau: A Population-Based Autopsy Study. Ann Med. 2008;40(3):232-9. doi: 10.1080/07853890701842988.
4. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, et al. Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement. Circ Cardiovasc Imaging. 2016;9(8):e005066. doi: 10.1161/CIRCIMAGING.116.005066.
5. Rosenblum H, Masri A, Narotsky DL, Goldsmith J, Hamid N, Hahn RT, et al. Unveiling Outcomes in Coexisting Severe Aortic Stenosis and Transthyretin Cardiac Amyloidosis. Eur J Heart Fail. 2021;23(2):250-8. doi: 10.1002/ejhf.1974.
6. Chacko L, Martone R, Bandera F, Lane T, Martinez-Naharro A, Boldrini M, et al. Echocardiographic Phenotype and Prognosis in Transthyretin Cardiac Amyloidosis. Eur Heart J. 2020;41(14):1439-47. doi: 10.1093/eurheartj/ehz905.
7. Rapezzi C, Giannini F, Campo G. Aortic Stenosis, Transcatheter Aortic Valve Replacement and Transthyretin Cardiac Amyloidosis: Are We Progressively Unraveling the Tangle? Eur J Heart Fail. 2021;23(2):259-63. doi: 10.1002/ejhf.2057.
8. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, et al. Guideline of Transthyretin-Related Hereditary Amyloidosis for Clinicians. Orphanet J Rare Dis. 2013;8:31. doi: 10.1186/1750-1172-8-31.

9. Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, et al. Prevalence and Outcome of Dual Aortic Stenosis and Cardiac Amyloid Pathology in Patients Referred for Transcatheter Aortic Valve Implantation. Eur Heart J. 2020;41(29):2759-67. doi: 10.1093/eurheartj/ehaa170.

10. Peskó G, Jenei Z, Varga G, Apor A, Vágó H, Czibor S, et al. Coexistence of Aortic Valve Stenosis and Cardiac Amyloidosis: Echocardiographic and Clinical Significance. Cardiovasc Ultrasound. 2019;17(1):32. doi: 10.1186/s12947-019-0182-y.

11. Milandri A, Farioli A, Gagliardi C, Longhi S, Salvi F, Curti S, et al. Carpal Tunnel Syndrome in Cardiac Amyloidosis: Implications for Early Diagnosis and Prognostic Role Across the Spectrum of Aetiologies. Eur J Heart Fail. 2020;22(3):507-15. doi: 10.1002/ejhf.1742.

12. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, et al. Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. J Am Coll Cardiol. 2021;77(2):128-39. doi: 10.1016/j.jacc.2020.11.006.

13. Oda S, Takashio S, Nagamatsu S, Yamashita T, Uchimura R, Kidoh M, et al. Myocardial Extracellular Volume Quantification Using CT for the Identification of Occult Cardiac Amyloidosis in Patients with Severe Aortic Stenosis Referred for Transcatheter Aortic Valve Replacement. Amyloid. 2019;26(2):97-8. doi: 10.1080/13506129.2019.1597701.

14. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1706-15. doi: 10.1056/NEJMoa1816885.

15. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019;380(18):1695-705. doi: 10.1056/NEJMoa1814052.

16. Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, et al. Cardiac Amyloidosis is Prevalent in Older Patients with Aortic Stenosis and Carries Worse Prognosis. J Cardiovasc Magn Reson. 2017;19(1):98. doi: 10.1186/s12968-017-0415-x.

17. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

Review Article

How to Treat Heart Failure in Patients with Cardiac Amyloidosis

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Abstract

Amyloidosis is a multisystem disease characterized by deposition of fibrillar proteins in different tissues, the heart being one of the sites of amyloid deposition. Cardiac amyloidosis may present as a restrictive syndrome with symptoms of heart failure (HF). Treatment includes prognosis-modifying medications in HF; their optimization, however, is a challenge due to the frequent adverse effects in this population. Renin-angiotensin-aldosterone system blockade should be carried out using low doses because, due to autonomic dysfunction, these drugs may cause hypotension and fatigue. The use of diuretics is necessary to maintain euvolemic status and optimized preload; however, due to the ventricular restriction present in cardiac amyloidosis, these medications should be used with caution. In patients with amyloidosis who progress to advanced HF, there are particularities in relation to indications for heart transplantation or long-term ventricular assist devices. The objective of this article is to review the treatment alternatives for HF in patients with cardiac amyloidosis.

Amyloidosis is a multisystem disease characterized by the deposition of fibrillar proteins with specific structural characteristics and a beta-pleated shape. The deposition of these proteins in the heart and the involvement of the autonomic nervous system make it challenging to manage heart failure (HF) in these patients. Given this scenario, This article aims to demonstrate how to manage HF in patients with cardiac amyloidosis.

Approach to treatment of heart failure in patients with cardiac amyloidosis

Data on HF treatment in patients with amyloidosis is lacking in randomized clinical trials. Therapeutic recommendations are based on expert opinions and experiences.

The deposition of fibrillar proteins in the myocardium leads to a reduction in the ventricular cavity, with consequent restricted filling, initially culminating in HF with preserved ejection fraction and finally HF with reduced ejection fraction. This condition partially explains the difficulty in optimizing classic HF treatment.[1]

Orthostatic hypotension is frequently seen in AL amyloidosis due to involvement of the autonomic nervous system. It complicates neurohormonal blockade, which has already been established in HF treatment. Medications such as corticosteroids with greater mineralocorticoid action (fludrocortisone), anticholinergics, and alpha-adrenergic agonists (midodrine) can be used to minimize postural hypotension.[1] In addition, when autonomic polyneuropathy develops, the presence of hypotension can make it difficult to use diuretics due to labile preload.[2]

The main goal is to maintain euvolemia, which is a great challenge, because these patients may present themselves hypervolemia, euvolemia, and hypovolemia. The main drugs used for pulmonary and systemic decongestion are loop diuretics, which may be associated with mineralocorticoid receptor antagonists and even thiazide diuretics in situations of resistance to loop diuretics. It is important to underscore that hypervolemia may result in worsening of renal function as a consequence of cardiorenal syndrome due to renal venous congestion, and hypovolemia may lead to renal hypoperfusion due to reduced systolic volume, precipitating pre-renal acute kidney injury.[2-3]

The use of prognosis-modifying medications in HF is also a challenge due to the autonomic dysfunction that these patients very often develop Beta-blockers and renin-angiotensin-aldosterone system blockers are used sometimes, at low doses, given that these drugs can cause hypotension and fatigue. In other words, there is underutilization of medications that have been proven to promote reverse remodeling.[4]

Angiotensin II converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid antagonists can be used safely, with gradual dose adjustment, in cases where there are no contraindications. Recently described drugs for treating HF, such as neprilysin inhibitors, angiotensin II receptor antagonists, and SGLT2 inhibitors have not yet been tested, and there is no scientific evidence to support their use in patients with cardiac amyloidosis.[2]

The use of beta-blockers and non-dihydropyridine calcium channel blockers are usually not well tolerated, because, due to the low systolic ejection volume, these patients need heart rate to maintain cardiac output. In addition, the use of non-dihydropyridine calcium channel blockers in AL amyloidosis should be avoided, as they bind to amyloid fibrillar proteins, which can lead to advanced conduction disorders and even cardiogenic shock.[2]

Digitalis medications may be used cautiously to control heart rate and to improve cardiac performance with relative safety in cases of transthyretin and AL amyloidosis. However, it is important to underscore that the binding

Keywords

Therapeutics; Heart Failure; Amyloidosis.

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of these drugs with amyloid proteins increases the risk of digitalis toxicity. Thus, it is essential to monitor frequently by means of electrocardiogram and measurement of serum digoxin level.[5-6]

Specific treatment of AL amyloidosis with chemotherapy drugs may worsen preexisting cardiac dysfunction due to type I or type II cardiotoxicity. These drugs include cyclophosphamide, tyrosine kinase inhibitors, proteasome inhibitors, and checkpoint inhibitors. In view of this scenario, it is indispensable to monitor with cardiac markers, such as troponin and natriuretic peptides, which are already elevated in amyloidosis, as well as with Doppler echocardiography, preferably with assessment of global longitudinal strain, in order to early detect myocardial dysfunction due to cardiotoxicity[7]

In patients with amyloidosis who progress to advanced HF, there are particularities in relation to indications for heart transplantation or long-term ventricular assist devices.

The reduced size of the left ventricular cavity and the frequent involvement of the right ventricle may be limitations to the indication of long-term ventricular assist devices.[8-9]

In relation to heart transplantation, patients with advanced HF should be evaluated for combined heart-liver transplantation, given that the amyloid protein in transthyretin amyloidosis originates in the liver, and there are clinical reports of progression of cardiomyopathy and neuropathy in these patients, especially in those with the ValMet30 mutation.[10]

In patients with AL amyloidosis who progress to advanced HF, heart transplantation may be indicated, provided that there is remission of the monoclonal gammopathy by means of chemotherapy drugs or bone marrow transplantation.[11]

The Figure 1 shows the difficulties and special care in the use of guideline directed medical treatment for HFrEF to patients with cardiac amyloidosis.

Conclusion

The treatment that has already been well established for HF in patients with cardiac amyloidosis is challenging. It must be adapted to the structural and pathophysiological characteristics of the disease. It is important to highlight that, in addition to treating HF, specific treatment of amyloidosis is indispensable to increasing survival and quality of life in these patients.

Author contributions

Conception and design of the research: Marcondes-Braga F, Aragão CAS. Acquisition of data:Aragão CAS. Analysis and interpretation of the data: Marcondes-Braga F, Aragão CAS. Writing of the manuscript: Marcondes-Braga F, Aragão CAS. Critical revision of the manuscript for intellectual content: Marcondes-Braga F. Supervision / as the major investigador: Marcondes-Braga F.

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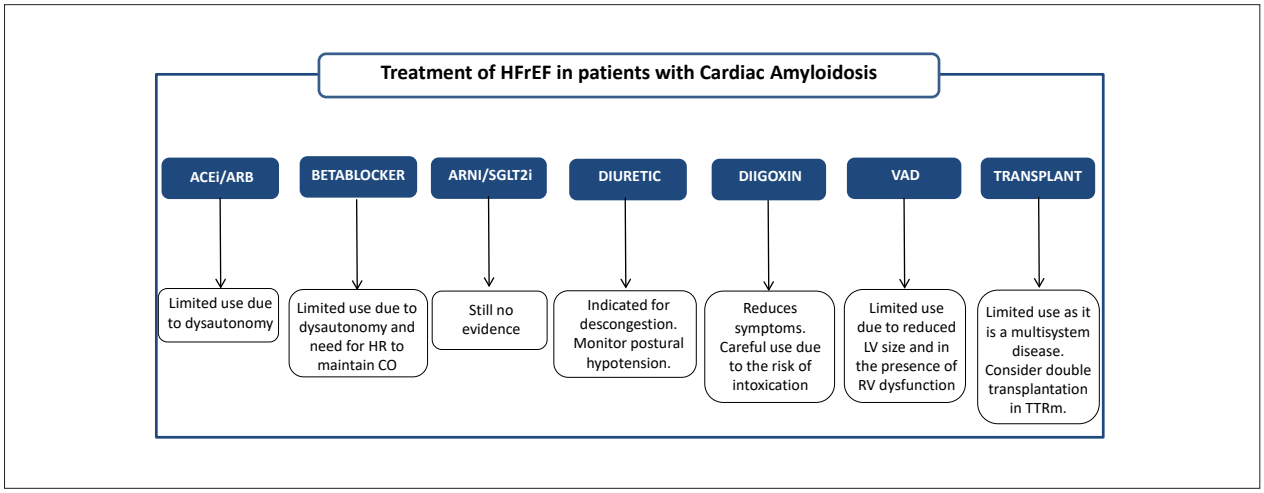

Figure 1 – *Treatment of HFrEF in patients with Cardiac Amyloidosis. HFrEF: heart failure with reduced ejection fraction; ACEi: angiotensin conversor enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor and neprilisin inhibitor; SGLT2i: SGLT2 inhibitor; VAD: ventricular assist device; CO: cardiac output; RV: rigth ventricule; TTR: transtiretin.*

References

1. Ritts AJ, Cornell RF, Swiger K, Singh J, Goodman S, Lenihan DJ. Current Concepts of Cardiac Amyloidosis: Diagnosis, Clinical Management, and the Need for Collaboration. Heart Fail Clin. 2017;13(2):409-16. doi: 10.1016/j.hfc.2016.12.003.
2. Pollak A, Falk RH. Left Ventricular Systolic Dysfunction Precipitated by Verapamil in Cardiac Amyloidosis. Chest. 1993;104(2):618-20. doi: 10.1378/chest.104.2.618.
3. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, et al. Cardiac Amyloidosis: Updates in Diagnosis and Management. Arch Cardiovasc Dis. 2013;106(10):528-40. doi: 10.1016/j.acvd.2013.06.051.
4. Shin SC, Robinson-Papp J. Amyloid Neuropathies. Mt Sinai J Med. 2012;79(6):733-48. doi: 10.1002/msj.21352.
5. Donnelly JP, Sperry BW, Gabrovsek A, Ikram A, Tang WHW, Estep J, et al. Digoxin Use in Cardiac Amyloidosis. Am J Cardiol. 2020;133:134-38. doi: 10.1016/j.amjcard.2020.07.034.
6. Donnelly JP, Gabrovsek A, Sperry BW, Young L, Estep J, Tang WW, et al. Digoxin Use in Cardiac Amyloidosis. J. Card. Fail. 2019;25(8):25-6. doi: 10.1016/j.cardfail.2019.07.070.
7. Sperry BW, Ikram A, Hachamovitch R, Valent J, Vranian MN, Phelan D, et al. Efficacy of Chemotherapy for Light-Chain Amyloidosis in Patients Presenting with Symptomatic Heart Failure. J Am Coll Cardiol. 2016;67(25):2941-8. doi: 10.1016/j.jacc.2016.03.593.
8. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, et al. Left Ventricular Assist Device Therapy in Patients with Restrictive and Hypertrophic Cardiomyopathy. Circ Heart Fail. 2011;4(3):266-75. doi: 10.1161/CIRCHEARTFAILURE.110.959288.
9. Grupper A, Park SJ, Pereira NL, Schettle SD, Gerber Y, Topilsky Y, et al. Role of Ventricular Assist Therapy for Patients with Heart Failure and Restrictive Physiology: Improving Outcomes for a Lethal Disease. J Heart Lung Transplant. 2015;34(8):1042-9. doi: 10.1016/j.healun.2015.03.012.
10. Suhr OB, Herlenius G, Friman S, Ericzon BG. Liver Transplantation for Hereditary Transthyretin Amyloidosis. Liver Transpl. 2000;6(3):263-76. doi: 10.1053/lv.2000.6145.
11. Hasserjian RP, Goodman HJ, Lachmann HJ, Muzikansky A, Hawkins PN. Bone Marrow Findings Correlate with Clinical Outcome in Systemic AL Amyloidosis Patients. Histopathology. 2007;50(5):567-73. doi: 10.1111/j.1365-2559.2007.02658.x.

Review Article

Heart Failure with Preserved Ejection Fraction and Cardiac Amyloidosis: Implications for Treatment

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a syndrome with multiple etiologies and varied phenotypic manifestations. Amyloidosis is a systemic disease that frequently affects the myocardium, and it may represent a specific etiology of HFpEF. The treatment of HFpEF associated with amyloidosis is not based on specific evidence, and the risk of hypotension as an adverse effect of pharmacological management is always a concern. In this context, this review addresses some strategies for controlling circulatory congestion, arrhythmias, cardiac conduction disorders, valvular heart diseases, and treatment of the specific type of amyloidosis based on available evidence as well as the latest recommendations and guidelines for managing cardiac amyloidosis.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a syndrome with a potentially underestimated prevalence, and it accounts more than half of the population with heart failure (HF), when assessed in primary health care units.[1] HFpEF is induced by multiple coexisting morbidities, mainly of non-cardiac origin, leading to systemic inflammation, increased oxidative stress, endothelial dysfunction, and biochemical signaling that determines hypertrophy and decreased elasticity of the cardiac myocyte, in addition to some degree of interstitial fibrosis. The functional result is an increase in ventricular filling pressures, especially during exertion, culminating in symptoms and signs of HF.[2] Some systemic diseases can specifically alter the cardiac extracellular matrix, which is the case of cardiac amyloidosis (CA). This infiltrative cardiomyopathy most strongly impacts myocardial stiffening due to tissue deposition of insoluble fibrillary proteins in different tissues, including the myocardium, valves, and cardiac conduction tissue. The following amyloidogenic proteins may affect the heart: immunoglobulin heavy chain proteins; immunoglobulin light chain proteins (AL); and those related to transthyretin (ATTR), to amyloid A, and to apolipoprotein A1. In practice, pathophysiological models due to the AL and ATTR types represent more than 90% of cases of CA.[3]

The clinical condition of HF arises from an inadequate cardiac response to the need for increased cardiac output, linked to depressed systolic volume due to inadequate left ventricular pressure-volume ratio, to the chronotropic response compromised by sinus frequency, or to atrioventricular conduction blocks. Arrhythmic complications, which are related mainly to atrial fibrillation and to the potential thromboembolic impairment in this condition, but also to ventricular arrhythmias, occur in the more advanced stages of the disease, when systolic dysfunction is already installed. Parallel to myocardial changes, postural hypotension and syncope may occur due to dysautonomia related to neuronal amyloid infiltration, while aortic valve stenosis secondary to amyoloidosis may severely compromise a condition of HFpEF or represent a clinical syndrome of severe aortic stenosis. [4,5]

The bases of treatment for HFpEF associated with cardiac amyloidosis

Recommendations for treatment of HFpEF in patients with CA are not based on data from randomized clinical trials (RCT), but on observational studies with few participants, involving more traditional drugs, such as beta-blockers, digitalis, diuretics, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB). Medications more recently introduced as options for managing HFpEF, such as angiotensin receptor-neprilysin inhibitors, and sodium-glucose cotransporter 2 inhibitors have not yet been studied in combined HFpEF and CA. Arrhythmic complications, in terms of both atrial fibrillation and atrioventricular blocks must also be addressed, because, from the pathological point of view, patients with CA, even without loss of left ventricular ejection fraction (LVEF), have difficulty maintaining cardiac output or increasing it during exercise, and conventional HF treatment strategies that have an impact on reduced heart rate, preload, and afterload, can cause symptomatic hypoperfusion.[6] Appropriate treatment of amyloidosis should be guided according to diagnosis of the two important phenotypic groups, AL or ATTR amyloidosis (Figure 1).

Diuretics

Diuretic treatment for all HF phenotypes is based on principles of clinical plausibility, rather than on placebo-controlled RCTs, for obvious reasons. One piece of evidence available for management of patients with HFpEF, although

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it was not designed for patients with CA exclusively, comes from the Hong Kong study.[7] That trial tested treatment with diuretics (loop or thiazide) alone or associated with ACEI or ARB in relation to outcomes of quality of life, functional capacity, and rates of cardiac function in a population of 150 participants with HF, in New York Heart Association (NYHA) class II to IV, and LVEF > 45%. The study was not placebo controlled. They evaluated the outcomes of HF symptoms and the Minnesota quality of life score (−46%, $p < 0.01$) in the comparison between 0 and 52 weeks of follow-up. Association with ramipril or irbesartan did not add additional clinical benefits.

The effect of the diuretic can also be verified when its use is guided by the degree of circulatory congestion with invasive pulmonary pressure devices. The CHAMPION study,[8] using a pressure-sensing device implanted in the pulmonary artery, tested its effectiveness as a guide for the use of diuretics. The population was not specifically composed of patients with HFpEF and CA, but 23% of participants had LVEF ≥ 40%. Patients with device-guided diuretic treatment had 28% lower hospital admission rates for HF (RR: 0.72, 95% CI: 0.60 to 0.85, $p = 0.0002$), demonstrating not only the potential usefulness of this type of device, but also the clinical benefit of effective decongestion.

The 2021 Update to the Brazilian Guidelines on Heart Failure[9] classifies diuretic therapy as a class I recommendation with level of evidence B for patients with HFpEF with evidence of clinical congestion, but these drugs should be used cautiously due to the possibility of hypotension,[10] especially in patients with neurological dysfunction due to polyneuropathy, whose diuretic doses must be appropriately adjusted to avoid syncope.

Mineralocorticoid-receptor antagonists

This is one of the most investigated drug classes in populations with HFpEF. The TOPCAT study[11] allocated a population of 3,445 patients with HF and LVEF ≥ 45%, randomized to spironolactone versus placebo.[11] A reduction in the primary endpoint composed of total cardiovascular mortality, sudden death, or hospitalization due to HF was not achieved, but the isolated secondary endpoint of HF hospitalization was reduced by 14%. Nevertheless, spironolactone appears to have a more consistent effect in the most congested patients, as a post hoc analysis testing the population with elevated natriuretic peptides found a 35% reduction in the primary composite endpoint. In patients with CA, there are no specific studies, and, even if this class of drugs has reached a class IIa recommendation, according to the current Brazilian Guidelines on Heart Failure,[12] these drugs should be used sparingly, on account of the potential hypotensive effect due to relative hypovolemia in this group. In a recent position statement by the Brazilian Society of Cardiology, mineralocorticoid-

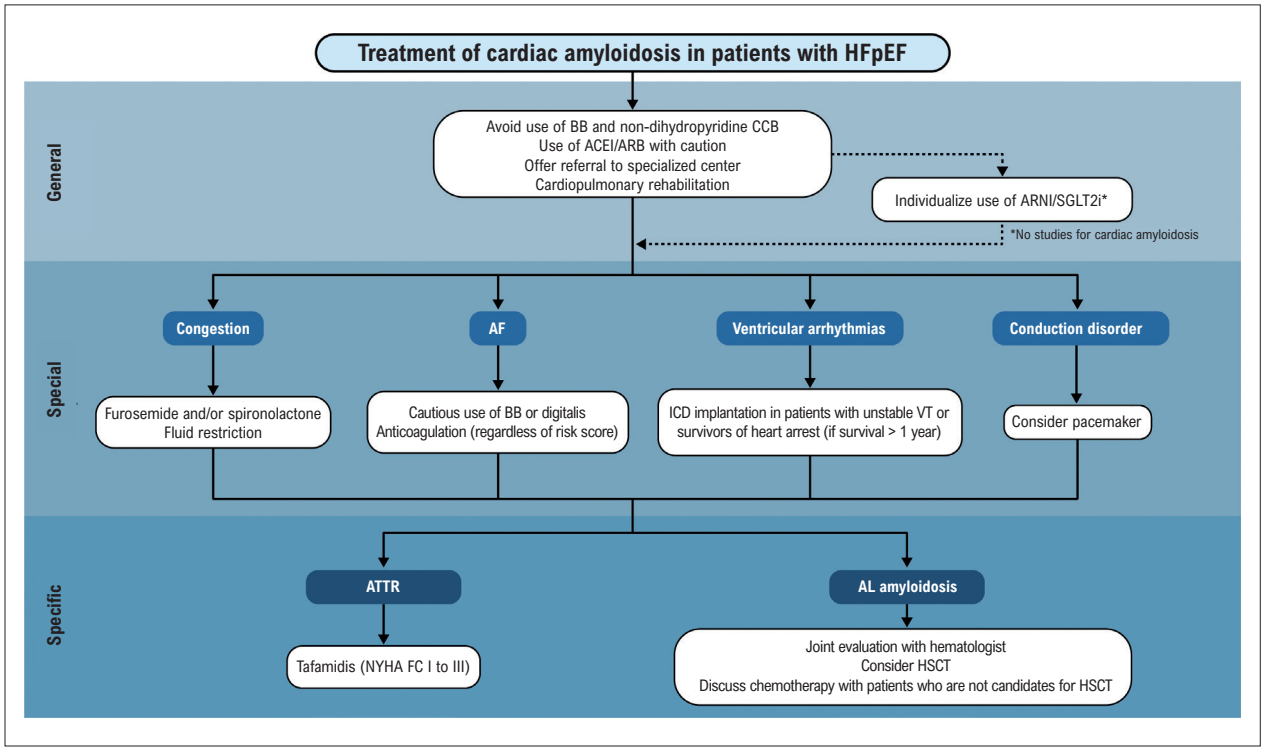

Figure 1 – *Treatment of cardiac amyloidosis in patients with HFpEF. ACEI: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; AL: light-chain; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; ATTR: transthyretin amyloidosis; BB: beta-blockers; CCB: calcium channel blockers; HFpEF: heart failure with preserved ejection fraction; HSCT: hematopoietic stem cell transplantation; ICD: implantable cardioverter-defibrillator; NYHA FC: New York Heart Association functional class; SGLT2i: sodium-glucose cotransporter 2 inhibitors; VT: ventricular tachycardia*

receptor antagonists have been recommended for patients with congestion, HFpEF, and CA, provided that there is monitoring for eventual hypotensive manifestations.[13]

Angiotensin II receptor blockers

The CHARM-Preserved Trial allocated participants with HF, functional class II and III, and LVEF > 40%, testing candesartan versus placebo. The results demonstrated a reduction in the number of hospitalizations due to HF. In the Brazilian Guidelines on Heart Failure,[12] ARB in HFpEF is a class IIb recommendation with level of evidence B; however, this does not consider cases of amyloidosis. In relation to ACEI, strictly speaking, there have not been any RCTs that have demonstrated benefit versus placebo in patients with HFpEF, and the guidelines do not include recommendations regarding this drug class for this group of patients.[14] A recent position paper on CA by the European Society of Cardiology[15] recommends avoiding ARB and ACEI, due to their hypotensive potential in cases of HF, in general. However, this recommendation should be viewed with caution, as many patients with HFpEF and amyloidosis may present with hypertension.

Sacubitril/valsartan

The best evidence for the use of this medication in HFpEF comes from the PARAGON-HF Trial,[16] which included 4,796 participants with LVEF ≥ 45%, elevated natriuretic peptides, and NYHA functional class II to IV. The results showed no benefits in terms of cardiovascular mortality and/or hospitalization for HF. However, in a pre-specified analysis, a reduction in this composite outcome was observed in female participants and in those of both sexes who had LVEF < 57%. These results suggest that sacubitril-valsartan could be an alternative for populations with HFpEF, symptoms that are difficult to control, and LVEF below 57%. The use of this drug has not been tested in the context of CA, and it is necessary to be very cautious regarding the potential reduction of left ventricular preload and postload and eventual hypotensive effects. This medication is currently only recommended for patients with HF with slightly reduced LVEF, in the 2021 Update to the Brazilian Guidelines on Heart Failure.[9]

Sodium-glucose cotransporter inhibitors

The SOLOIST-WHF RCT recruited a population of patients with type 2 diabetes who had recently been hospitalized due to HF, testing sotagliflozin versus placebo, finding a significant reduction in the outcome of cardiovascular death and hospitalization due to worsening HF in patients with both reduced LVEF and preserved LVEF (RR = 0.67, 95% CI, 0.52 to 0.85, p < 0.001). The EMPEROR Preserved placebo-controlled RCT [17] allocated 5,988 participants with signs and symptoms of HF, with patterns of heart failure with slightly reduced ejection fraction and HFpEF (LVEF > 40%) and high serum levels of natriuretic peptides. The results of the study demonstrated a 25% reduction in the relative risk for the combined primary endpoint of cardiovascular death and hospitalization due to HF, making it the first study to demonstrate a reduction in the primary endpoint in populations with HF with LVEF > 40%. This class of drugs represents a potential therapeutic resource in HFpEF associated with CA, as it does not promote hypovolemia, bradycardia, or exacerbated hypotension; however, patients' volume status and blood pressure should be monitored during use.

Beta-adrenergic blockers and calcium channel blockers

Regarding patients with HFpEF, beta-blockers are only recommended for the treatment of angina pectoris in patients with HFpEF associated with the ischemic phenotype or for heart rate control in the event of atrial fibrillation.[12] In the context of CA, beta-blockers and non-dihydropyridine calcium channel blockers are generally not well tolerated, due to their negative influence on chronotropism. Furthermore, non-dihydropyridine calcium channel blockers should be avoided in patients with AL-CA as they bind to amyloid fibrils, which can result in advanced heart blocks.[18]

Digoxin

In patients with atrial fibrillation and high ventricular response, digoxin is always remembered as a therapeutic alternative. However, an in vitro study has demonstrated that isolated amyloid fibrils bind to digoxin with an important degree of affinity.[19] This interaction may play some role in the sensitivity to digoxin observed in some patients with CA, and this selective binding of digoxin to amyloid fibrils may increase the severity of myocardial disorders previously attributed to fibrillar amyloid deposits. In general, therefore, great caution is recommended when administering digoxin to patients with CA.

Atrial fibrillation and prevention of embolic phenomena

The management of atrial fibrillation by heart rate control should be carried out with monitoring of possible excessive bradycardia by commonly used agents, due to the aforementioned reasons. Radioablation for this arrhythmia seems to be feasible, and it may be an interesting alternative when performed early in CA.[20,21]

Anticoagulation has been indicated for CA with atrial fibrillation regardless of the risk score for thromboembolism, given that atrial amyloid infiltration significantly reduces atrial contractility and increases the possible appearance of thrombi, especially in AL-CA.[13] Anticoagulation in patients in sinus rhythm has not been well established, but it can be considered in specific cases of decreased contractility or cardiac deformation, especially in cases of AL-CA.

Ventricular arrhythmias

Non-sustained tachycardia is the most frequently detected ventricular arrhythmia on electrocardiographic monitoring, in cases of AL-CA,[22] and, in this context, an implanted defibrillator may be an option, even without systolic ventricular dysfunction. However, implanting these devices for primary prevention per se can be ineffective, given that most events have pulseless electrical activity.[23]

Thus, the best evidence is in favor of early detection, when it is possible to identify arrhythmias that can potentially be treated by devices.[24]

Cardiac conduction blocks

Blockages, especially atrioventricular blocks, are frequent in amyloidosis. Implantation of artificial stimulation is effective and in following with the contemporary recommendations for the disease.[25]

Specific treatment of amyloidosis

Treatment should follow diagnosis of the phenotype of CA. Once AL-CA has been diagnosed, it becomes urgent to activate the hematology team in order to initiate treatment with antineoplastic agents and/or autologous stem cell transplantation.[13]

Treatment of ATTR-CA

The following potential treatments exist for CA caused by TTR: a- TTR tetramer stabilizers; b- inhibitors of hepatic TTR synthesis; c- degradation and resorption of deposited amyloid fibrils, and d- liver transplantation.[13]

Tafamidis is a tetramer stabilizer and the only drug that has been tested in a multicenter RCT, the ATTR-ACT study.[26] Patients were not selected by ejection fraction, but rather by NYHA functional class between I and III and high BNP. The groups that received tafamidis 80 and 20 mg were analyzed together, and the results indicated a statistically significant 30% reduction in the relative risk of all-cause mortality (RR = 0.70 [95% CI: 0.51 to 0, 96]), as well as a 32% reduction in cardiovascular hospitalizations (RR = 0.68 [95% CI: 0.56 to 0.81]). Subsequently, a long-term extension of the same study demonstrated that the sample that received 80 mg of tafamidis had an additional 30% decrease in relative risk of the outcome of mortality (RR = 0.70, 95% CI: 0.5 to 0.97, p = 0.037).[27]

Final considerations

The association of HFpEF and CA is based on the plausibility of treating circulatory congestion, heart rhythm, and associated morbidities, but, above all, treating amyloidosis itself. Potentially hypotensive drugs must be used very cautiously and bradycardia-causing agents must be avoided.

Author contributions

Conception and design of the research:Danzmann LC. Acquisition of data: Danzmann LC, Tscheika AP, Zimmer JRC. Analysis and interpretation of the data:Danzmann LC, Tscheika AP, Zimmer JRC. Writing of the manuscript:Danzmann LC, Tscheika AP. Critical revision of the manuscript for intellectual content: Danzmann LC. Supervision / as the major investigador: Danzmann LC.

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References

1. Jorge AL, Rosa ML, Martins WA, Correia DM, Fernandes LC, Costa JA, et al. The Prevalence of Stages of Heart Failure in Primary Care: A Population-Based Study. J Card Fail. 2016;22(2):153-7. doi: 10.1016/j.cardfail.2015.10.017.
2. Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol. 2013;62(4):263-71. doi: 10.1016/j.jacc.2013.02.092 1.
3. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. J Am Coll Cardiol. 2016;68(12):1323-41. doi: 10.1016/j.jacc.2016.06.053.
4. González-López E, Gallego-Delgado M, Guzzo-Merello G, Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-Type Transthyretin Amyloidosis as a Cause of Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2015;36(38):2585-94. doi: 10.1093/eurheartj/ehv338.
5. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, et al. Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice. JACC Heart Fail. 2019;7(8):709-16. doi: 10.1016/j.jchf.2019.04.010.
6. Castaño A, Drachman BM, Judge D, Maurer MS. Natural History and Therapy of TTR-Cardiac Amyloidosis: Emerging Disease-Modifying Therapies from Organ Transplantation to Stabilizer and Silencer Drugs. Heart Fail Rev. 2015;20(2):163-78. doi: 10.1007/s10741-014-9462-7.
7. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, et al. The Hong Kong Diastolic Heart Failure Study: A Randomised Controlled Trial of Diuretics, Irbesartan and Ramipril on Quality of Life, Exercise Capacity, Left Ventricular Global and Regional Function in Heart Failure with a Normal Ejection Fraction. Heart. 2008;94(5):573-80. doi: 10.1136/hrt.2007.117978.
8. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless Pulmonary Artery Haemodynamic Monitoring in Chronic Heart Failure: A Randomised Controlled Trial. Lancet. 2011;377(9766):658-66. doi: 10.1016/S0140-6736(11)60101-3.
9. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.

10. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and Treatment of Cardiac Amyloidosis. Nat Rev Cardiol. 2015;12(2):91-102. doi: 10.1038/nrcardio.2014.165.

11. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014;370(15):1383-92. doi: 10.1056/NEJMoa1313731.

12. Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539. doi: 10.5935/abc.20180190.

13. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis - 2021. Arq Bras Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.

14. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.

15. 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 European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail. 2021;23(4):512-26. doi: 10.1002/ejhf.2140.

16. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20. doi: 10.1056/NEJMoa1908655.

17. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.

18. Pollak A, Falk RH. Left Ventricular Systolic Dysfunction Precipitated by Verapamil in Cardiac Amyloidosis. Chest. 1993;104(2):618-20. doi: 10.1378/chest.104.2.618.

19. Rubinow A, Skinner M, Cohen AS. Digoxin Sensitivity in Amyloid Cardiomyopathy. Circulation. 1981;63(6):1285-8. doi: 10.1161/01.cir.63.6.1285.

20. Mints YY, Doros G, Berk JL, Connors LH, Ruberg FL. Features of Atrial Fibrillation in Wild-type Transthyretin Cardiac Amyloidosis: A Systematic Review and Clinical Experience. ESC Heart Fail. 2018;5(5):772-9. doi: 10.1002/ehf2.12308.

21. Donnellan E, Wazni O, Kanj M, Elshazly MB, Hussein A, Baranowski B, et al. Atrial Fibrillation Ablation in Patients with Transthyretin Cardiac Amyloidosis. Europace. 2020;22(2):259-64. doi: 10.1093/europace/euz314.

22. Palladini G, Malamani G, Cò F, Pistorio A, Recusani F, Anesi E, et al. Holter Monitoring in AL Amyloidosis: Prognostic Implications. Pacing Clin Electrophysiol. 2001;24(8):1228-33. doi: 10.1046/j.1460-9592.2001.01228.x.

23. Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HJ, Fontana M, et al. A Study of Implanted Cardiac Rhythm Recorders in Advanced Cardiac AL Amyloidosis. Eur Heart J. 2015;36(18):1098-105. doi: 10.1093/eurheartj/ehu506.

24. Giancaterino S, Urey MA, Darden D, Hsu JC. Management of Arrhythmias in Cardiac Amyloidosis. JACC Clin Electrophysiol. 2020;6(4):351-61. doi: 10.1016/j.jacep.2020.01.004.

25. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, et al. Left Ventricular Assist Device Therapy in Patients with Restrictive and Hypertrophic Cardiomyopathy. Circ Heart Fail. 2011;4(3):266-75. doi: 10.1161/CIRCHEARTFAILURE.110.959288.

26. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

27. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, et al. Efficacy and Safety of Tafamidis Doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and Long-Term Extension Study. Eur J Heart Fail. 2021;23(2):277-85. doi: 10.1002/ejhf.2027.

Review Article

Ventricular Arrythmias in Cardiac Amyloidosis: It is Possible to Prevent Sudden Death?

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Abstract

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that occurs secondary to deposition of misfolded protein in the myocardium. The two most common subtypes are amyloid light chain amyloidosis and amyloid transthyretin amyloidosis. CA frequently results in congestive cardiac failure and arrhythmias, due to a disruption in cardiac substrate with subsequent electromechanical remodeling. Disease progression is usually demonstrated by development of progressive pump failure, which may be seen with a high arrhythmic burden, usually portending a poor prognosis. Arrhythmias are common, and many commonly used pharmacological therapies may be poorly tolerated and lead to clinical decompensation in this population, adding complexity to the co-management of these conditions. Studies are required to assess the risks and benefits of catheter ablation for ventricular tachycardia, with no current data showing a mortality benefit. The role of implantable cardioverter-defibrillator therapy is controversial, with benefits seen predominantly in early phases of the disease process. High-quality evidence and guideline recommendations are limited with regard to the management of arrhythmias. Providers are often left to clinical experience and expert consensus to aid in decision-making. This review summarizes both historical and contemporary data and describes evidence-based strategies for managing ventricular arrhythmias and their sequelae in patients with CA.

Introduction

Amyloidosis is a systemic disease characterized by the extracellular deposition of pathological insoluble fibrillar protein, known as amyloid, within various organs (mainly the heart and kidneys).[1] The leading cause of morbidity and mortality in these patients is from development of restrictive cardiomyopathy with progressive congestive cardiac failure (CCF).[2] Approximately 95% of cases of cardiac amyloidosis (CA) are misfolded transthyretin (ATTR) or immunoglobulin light-chain (AL) types.[3] The ATTR group is characterized by misfolding of transthyretin, a protein made mainly in the liver. Both wild-type ATTR cardiomyopathy (wtATTR-CM) and hereditary ATTR cardiomyopathy (hATTR-CM) have been described. The prevalence of wtATTR-CM is estimated to be between 5.5% and 16.0% of people > 80 years of age. Recent trends have revealed a significant increase in the number of new diagnoses of ATTR-CM over the past 10 years, suggesting that estimates of disease burden underestimate the true prevalence amyloid cardiomyopathy.[3] AL amyloidosis is a clonal plasma cell proliferative disorder characterized by production of abnormal protein fibrils in the bone marrow. The estimated prevalence of AL amyloidosis in the United States ranges from 15.5 to 40.5 cases per million.[1-3]

CA should be suspected particularly in patients with heart failure with preserved left ventricular ejection fraction presenting "red flag" signs such as (1) either symmetrical or asymmetrical unexplained left and right ventricular hypertrophy with concomitant diastolic dysfunction and reduced left ventricular global longitudinal strain (LV GLS) with an "apical sparing" pattern in echocardiography, (2) discrepancy between the left ventricular (LV) wall thickness and QRS voltage and the presence of pseudo-infarct pattern in electrocardiography, especially if associated with increased levels of N-terminal pro B-type natriuretic peptide (NT-proBNP).[4]

Although novel treatment vastly improved survival in AL and ATTR CA, cardiovascular events account for more than two thirds of fatal casualties in both groups.[5] Moreover, sudden cardiac death (SCD) accounts for up to 50% of all cardiac deaths.[6] Electromechanical dissociation is thought to be the most common cause of SCD in patients with CA; however, ventricular arrhythmias (VA) and conduction abnormalities are also common.[7] To date, little is known about risk factors for ventricular tachyarrhythmias as a cause of SCD in patients with amyloidosis and cardiac involvement. Therefore, identification of patients with CA who may be eligible for implantable cardioverter-defibrillator (ICD) is challenging.

While both forms of amyloid subtypes have a predilection to the development of amyloid cardiomyopathy, the underlying electrical burden and arrhythmogenic substrate vary between them, with distinct clinical implications.[8] The resultant disruption of the cardiac conduction system in patients with CA predisposes to arrhythmias, with the most frequent identified as atrial fibrillation (45% to 65%) and, less frequently, atrioventricular conduction delays (3.5%) and ventricular tachyarrhythmias (ventricular tachycardia

Keywords

Amyloidosis; Tachycardia, Ventricular; Death, Sudden, Cardiac; Defibrillators, Implantable.

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9.9% and ventricular fibrillation 0.7%, respectively).[9,10] wATTR appears to carry the highest risk of atrial fibrillation, and commonly used cardiovascular therapeutics such as beta-blockers, calcium-channel blockers, and digoxin may be poorly tolerated and lead to clinical decompensation in CA, adding further complexity to the co-management of these conditions. The literature currently states that patients with AL CA have a higher propensity to develop VA.[11] The historically reported survival of < 12 months in patients with cardiac AL has represented a contraindication to ICD. However, recently, the evolution of treatment options has improved overall survival, opening new perspectives in terms of cardiac protection and calling for further understanding of the arrhythmic profile and SCD prevention in patients with AL.

Epidemiology of Ventricular Arrhythmias

The prevalence of nonsustained ventricular tachycardia (NSVT) in AL amyloidosis ranges from 5% to 27% with routine monitoring,[11-13] and 100% during the stem cell transplant period.[14] The prevalence of ventricular tachycardia (VT) in the ATTR population is less frequently reported, but small studies suggest a prevalence of approximately 17%.[15] Additionally, as AL amyloidosis is more likely to cause end-stage CCF when compared to ATTR, there is a higher preponderance to development of VA. The clinical significance of VA is varied, with some studies suggesting a prognostic role[11-14] and other studies reporting no such correlation.[16]

Pathophysiology of Ventricular Arrhythmias

There are a variety of mechanisms that form the fundamental pathogenesis for VA in CA. Firstly, amyloid fibril deposition with a resultant inflammatory response and oxidative stress leads to a separation of myocytes resulting in remodeling and LV fibrosis, which progressively develops arrhythmogenic potential.[1,2-4] Secondly, amyloid fibril deposition in the conduction system can potentiate arrhythmias.[17] Thirdly, micro- and macrovascular myocardial ischemia from amyloid deposition can be demonstrated by regional myocardial dysfunction, as assessed by cardiac magnetic resonance (CMR).[18] The cause and mechanisms of VA in CA, however, are poorly understood and are likely to be multifactorial.

Prognosis

Cardiac involvement is the determinant of prognosis in amyloidosis. Risk of death in patients with AL amyloidosis can be stratified using the revised Mayo staging models, including cardiac biomarkers: cardiac troponin T (cTnT ≥ 0.025 ng/mL), NT-proBNP (≥ 1,800 pg/mL) and serum immunoglobulin free light chain difference ≥ 18 mg/dL.[19] Similar to AL amyloidosis, a staging system including markers of increased myocardial stress, such as NT-proBNP and high sensitivity cTnT, has been proposed for ATTR amyloidosis. Patients with both cTnT > 0.05 ng/mL and NT-proBNP > 3,000 pg/mL had the worst prognosis, with median survival of only 20 months.[20] Additional to elevated cardiac biomarkers, renal dysfunction was also identified as a significant risk factor of worse prognosis. In the recently proposed prognostic system for staging ATTR amyloidosis, patients with decreased estimated glomerular filtation rate < 45 mL/min/1.73 m^2 and NT- proBNP > 3,000 pg/mL had significantly worse survival compared to those not meeting these cut-off values.[21] However, the mentioned staging models only predict overall mortality. There is no significant correlation between cardiac biomarkers levels and the risk of VA.[22]

It is crucial to understand the pathophysiology of VA in CA in order to predict the risk of death. Amyloid in the extracellular spaces distorts the myocardial cells, and it can also infiltrate cardiac conduction system and coronary arteries. Besides infiltration, amyloidogenic light chains in AL amyloidosis may directly impair cardiomyocyte function through an increase in cellular oxidant stress. It appears that myocardial scarring and fibrosis that are typical of chronic ischemic or non-ischemic cardiomyopathies are less common in CA. It is well known that patients with structural heart disease have a lower threshold in developing arrhythmias, and this may be the case for patients with CA, specifically the AL subtype.[23] Several echocardiographic correlates of structural heart disease are known to result in VT, for example evidence of elevated LV systolic diameter, impaired left ventricular ejection fraction (LVEF < 30%), widened QRS (> 125 msec), age > 65 years, prior history of CCF, and active diuretic therapy, when compared to patients without VT.[23,24] These specific clinical and echocardiographic findings are frequently seen in patients with CA, and, therefore, these high-risk populations should undergo frequent monitoring.[24] Similarly, a study by Falk et al. has shown that, in patients with CA who present with high-grade VA, there is more likely to be a history of CCF and an abnormal echocardiogram, when compared to patients without arrhythmias.[25] These findings highlight the relationship between structural heart disease, heart failure, and VT. Therefore, structural assessment in these patients may provide prognostic value and allow for more appropriate medical therapy. In some patients, the qualification for primary ICD implantation is based on the standard LV systolic dysfunction with LVEF ≤ 35%. However, in the majority of patients with CA, the decline of LV systolic function is a late manifestation; therefore, other echocardiographic parameters are needed to assess LV function (even in those with preserved LVEF). Harmon et al. showed that VA was more common in patients with reduced two-dimensional LV GLS (≥ −15%) assessed by speckle-tracking echocardiography.[26]

CMR not only plays an important role in the diagnosis of CA; it also provides important prognostic information. In amyloidosis, CMR enables myocardial tissue characterization by means of T1- and T2-weighted imaging sequences, T1 mapping (pre- and post-contrast), late gadolinium enhancement (LGE), and extracellular volume (ECV) imaging. Global subendocardial or transmural pattern of LGE and, to a lesser degree, focal patchy LGE are all features of CA. The extent of LGE may also serve as a surrogate of arrhythmogenic substrate for the occurrence of VA.[27] Two-year survival in patients with CA without LGE was 92%, whereas it was significantly lower in those who showed subendocardial or transmural LGE (81% and 45%, respectively).[28] Both in AL and ATTR CA, the presence of transmural LGE has been shown to be an independent predictor of worse survival.[28] However, the limitation of LGE is that it is difficult to quantify, making it

difficult to track changes in CA, for example, due to treatment. Post-contrast T1 mapping following gadolinium administration enables estimation of ECV. ECV values are significantly elevated in CA, and ECV is a robust prognostic marker in CA. Moreover, the assessment of ECV as well as native T1 values makes it possible to track the disease and response to therapy over time. Additionally, T2 mapping provides data on T2 relaxation times which represent myocardial edema and active inflammation and are potentially linked with arrhythmogenic potential. In a recent study,[29] the presence of myocardial edema was shown in CA, as indicated by increased T2 relaxation times in patients with amyloidosis compared to control subjects, as well as in untreated AL amyloidosis compared with treated AL and ATTR amyloidosis. In this study, T2 was a prognostic predictor in AL amyloidosis, which may suggest mechanisms additional to amyloid infiltration contributing to mortality in this disease.[23,30]

There have also been studies assessing the relationship between cardiac monitoring findings and VT in CA. In a recent study of 239 patients with AL CA, while the presence of NSVT conferred worse survival prior to stem cell transplant, cardiac monitoring only detected its presence in approximately 25% of patients.[31] In a prospective series of 20 patients with syncope in the context of severe CA by Sayed et al., only 1 episode of VT was documented, with a total of 13 deaths. The remaining arrhythmias detected were either atrial arrhythmias or atrioventricular conduction block.[12] NSVT is a common finding among patients with CA, and its role in predicting SCD in this population is debated, as it appears to have little discriminative value to identify those who die from VA.[26,32] In the meta-analysis by Halawa et al., despite high prevalence of NSVT (in 51% of patients with CA), only 18% received appropriate ICD therapy.[33] Nevertheless, NSVT in the early stage of AL amyloidosis can be considered an indication for ICD implantation in primary prevention (class IIb).[34]

To better understand the underlying pathophysiology, Orini et al. combined the assessment of the electrophysiological and structural ventricular substrate from 21 patients with CA (11 AL and 10 ATTR).[35] The authors used a special electrocardiographic system with 256 electrodes for non-invasive epicardial mapping of ventricular potentials and CMR imaging. When compared with healthy volunteers, patients with CA had significantly lower epicardial signal amplitude, slower heterogeneous intraventricular conduction, and prolonged and more spatially dispersed repolarization. Moreover, epicardial signal fractionation and average repolarization time increased with ECV calculated in CMR. A strong inverse correlation was found between epicardial signal amplitude and native T1 in CMR. Both epicardial conduction and repolarization abnormalities were more notable in patients with AL amyloidosis compared with ATTR. Spatial conduction-repolarization heterogeneity is thought to be a marker of increased propensity to VA and sudden arrhythmic death in patients with heart failure and may contribute to higher mortality in AL amyloidosis.[36] This study also suggests a link between conduction-repolarization delay and increased extracellular deposition.

Invasive electrophysiological study is infrequently performed in patients with CA. Reisinger at al. demonstrated a prolongation of the His-ventricular (HV) interval > 55 ms in the majority of the examined population (23 of 25 patients with biopsy-confirmed AL amyloidosis), which indicated disease of the distal His-Purkinje system.[6] Markedly prolonged HV interval (≥ 80 ms) was the only independent predictor for SCD in the multivariate analysis. The authors concluded that prolongation of the HV interval not only indicates a risk of complete atrioventricular block due to conduction system infiltration with amyloid fibrils and bradyarrhythmia as a potential cause of death; it may also indicate severe myocardial infiltration and serve as a marker of the propensity for lethal VA or acute electromechanical dissociation. Interestingly, in this study, monomorphic VT was induced in only 4 patients during programmed ventricular stimulation, and, similarly to other non-ischemic cardiomyopathies, VT non-inducibility showed little prognostic value.

Amyloid infiltration is more severe in ATTR when compared to AL amyloidosis, which ultimately results in greater LV mass and higher rates of CCF.[2] In spite of these phenotypic differences, AL amyloidosis confers worse prognosis with high rates of SCD (approximately 33% of patients) in the first 3 months of diagnosis.[12] This may be secondary to higher spatial heterogenous conduction and repolarization, which is a marker of arrhythmogenesis and overall worse prognosis, as shown by Orini et al.[35]

Management

The management of VA in CA requires a different approach to standard VA guidelines in the context of heart failure or conventional cardiomyopathies. The treatment of VT can be subdivided into cardiac antiarrhythmic medications, procedural-based therapy, and surgical modalities. Patients presenting with VT frequently undergo extensive investigation, including CMR imaging to evaluate myocardial LGE or scarring, as it provides prognostic information and may identify a site of origin of VT that can then be effectively targeted by catheter ablation.[37] This work-up may be beneficial in patients with CA presenting with VA. Conventional pharmacotherapies that are used in treatment of VT include oral antiarrhythmic agents and beta-blockade. Beta-blockers, while used widely in the suppression of VT with beta-adrenergic antagonist activity, may be detrimental with a resultant loss in cardiac output, in patients with CA.[9] Amiodarone, another commonly used and effective therapy for VT, may result in complications when treating patients with CA, namely complete heart block when compared to patients without CA, as shown in a study (43.8% versus 30.0%, $P < 0.0001$).[38] These findings indicate poorer overall outcomes with conventional pharmacological therapy for VT, when used in patients with CA.

Chemotherapy for AL amyloidosis is mainly based on regimens used for the treatment of myeloma and not specifically approved for AL cardiac involvement. Most of these drugs have established cardiotoxic potential, with increased risk of heart failure and arrhythmic events. A study by Le Bras et al. demonstrated that dexamethasone as an induction agent for treatment of patients with AL CA may potentiate fluid retention and promote arrhythmias, hence resulting in an arrhythmogenic ventricular substrate.[39] Similarly, high dose chemotherapy, specifically cyclophosphamide and bortezomib,

in AL amyloidosis can be cardiotoxic in nature and result in VT due to myocardial dysfunction.[40,41]

While the role of catheter ablation for treatment of atrial arrhythmias is evolving, with the current literature showing potential benefits in terms of recurrence rate and overall survival, there is a lack of data on its use in VA.[42,43] Other than case reports of successful radiofrequency VT ablation, there have been no large-scale studies assessing the role of VT or ventricular fibrillation ablation in CA.[44,45] Catheter ablation of VT has been shown to have some utility in patients with other infiltrative cardiomyopathies, such as cardiac sarcoidosis, and it may, therefore, be a viable option for patients with CA.[46] Further large-scale studies are required to assess the risk and benefits of catheter ablation for VT in CA, with no current data showing a mortality benefit.

The development of refractory heart failure is usually seen with incessant VT and portends a poor prognosis. Epicardial mapping and catheter ablation are also options for management of incessant VT.[47] The definitive surgical therapy for treatment of end-stage heart failure, which may be seen with recurrent VA, is orthotopic cardiac transplantation, an option in the setting of failed medical management.[48] Heart transplantation is an effective therapy for end-stage CA with good follow-up survival rates.[49]

The advent of disease modifying therapies for ATTR has revolutionized management protocols. Tafamidis, a transthyretin stabiliser, prevents overall tetramer dissociation and amyloidogenesis; therefore, it has been shown to reduce all-cause mortality and cardiovascular hospitalizations.[50] Similarly, diflusinal is a non-steroidal drug that also stabilizes the transthyretin tetramer and has been shown to stabilize LV mass, indicating a halt in progression of cardiac amyloidogenesis.[51] By effectively preventing amyloidogenesis, these therapies may result in reduced incidence of SCD with the potential to mitigate VA in the population with ATTR.

Device Therapy

Whether there is a selected population of patients with CA at risk of arrhythmic SCD (versus SCD due to electromechanical dissociation) who would benefit from ICD placement is still a matter of debate.[52] Currently, there is no consensus on the absolute benefit that ICDs can confer patients with CA. While its potential to eliminate fatal VA is supported by select and anecdotal cases, the overall effectiveness of ICDs and their safety remains unclear.[52] Most decisions made regarding ICD insertions are largely patient-centered and based upon local expertise.

Studies have shown that up to one half of patients with CA die suddenly; however, ICD placement for both primary and secondary prevention in CA has not been strongly supported by expert guidelines. Reasons for this include the following: 1) the most common cause of sudden death has been historically thought to be secondary to electromechanical dissociation resulting in pulseless electrical activity rather than a lethal VA; 2) suggestion by some that CA carries a higher defibrillation threshold that may be refractory to ICD therapy; and 3) a historically poor prognosis and life expectancy in this population.[12,16]

The 2015 European Society of Cardiology (ESC) Guidelines for management of VA and prevention of SCD state that "there are insufficient data to provide recommendations" for the use of ICDs for primary prevention of SCD in patients with CA.[53] The ESC gives class IIa, level of evidence C, for ICD implantation in secondary prevention, recommending consideration for those with either AL or hATTR CA and "ventricular arrhythmia causing hemodynamic instability who are expected to survive > 1 year with good functional status." The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for management of patients with VA and prevention of SCD recommends individualized decision-making for both primary and secondary prevention ICD placement in CA, as data remain too limited to allow formal recommendations.[54] According to the Heart Rhythm Society consensus statement from 2019, a prophylactic ICD may be considered in patients with NSVT in the course of AL and expected survival more than 1 year.[35] However, it is only a class IIb recommendation. Both the ESC and American Heart Association guidelines are consistent in recommending against placement of ICD for primary or secondary prevention in patients with heart failure and expected meaningful survival of < 1 year, including in those with medication-refractory New York Heart Association functional class IV heart failure who are not also candidates for cardiac resynchronization therapy, cardiac transplantation, or LV assist devices.

Retrospective analyses (Table 1) of outcomes in patients with CA implanted with ICD for primary and secondary prevention have shown that almost one quarter of patients received appropriate ICD therapy, and the incidence of inappropriate ICD interventions was low (7%). However, only one quarter of patients who received appropriate ICD therapy survived the follow-up, and in almost two thirds of patients the ICD probably had no effect on their survival. Kristen et al.[55] found that only 11% of 19 patients with AL CA implanted with ICD for primary prevention received appropriate ICD therapies for sustained ventricular tachyarrhythmias. Lin et al.[32] from the Mayo Clinic found that 28% of 53 patients received appropriate ICD shocks at 1 year. Patients with AL CA comprised most of those who received appropriate shocks (12 of 15 patients), and those who were shocked more often had received an ICD for secondary prevention. ICD therapy was not associated with improved mortality in follow-up. Varr et al.[22] from Stanford University found that 26% of 19 patients received appropriate shocks in follow-up. In this study, not a single patient who received an ICD for primary prevention received appropriate successful ICD therapy. There are multiple limitations to these studies. First, all of the studies included in this review were retrospective with various sample sizes. Second, the reports included patients with a variety of CA etiologies, including AL and ATTR, while each has a different clinical presentation, natural history, prognosis, and treatment. Regarding prognosis, Harmon et al. indicated in multivariate analysis that AL amyloidosis was an independent predictor of high mortality in patients with CA.[26] Third, the majority of ICDs were implanted in primary prevention for patients who had LVEF < 35%. Qualification was mostly based on arbitrarily adopted criteria, which included the presence of different types of VA (such as NSVT or frequent premature ventricular beats) and/or non-postural syncope. Although the detection of NSVTs and reports of syncope should prompt immediate clinical concerns, the predictive value for primary SCD prevention

is controversial. Unexplained syncope is a common and non-specific symptom in CA population, and it can result from other causes than conduction disturbances or VA, such as orthostatic hypotension, autonomic dysfunction, or the use of diuretics or vasodilating drugs.[16]

There is an increasing awareness that the primary driver of mortality in these patients is electromechanical dissociation, as opposed to VT.[56,57] Electromechanical dissociation is likely a manifestation of progressive deterioration in heart failure not amenable to ICD therapy.[55] CA is often diagnosed late in various stages of amyloidosis, and overall mortality is higher in advanced stages of the disease. It is noteworthy that patients with greater cardiac involvement, manifested as higher NT-proBNP concentration and lower LVEF, may be at higher risk of death from electromechanical dissociation.[22] Therefore, ICD implantation can be more beneficial in patients with cardiac involvement but with lower NT-proBNP level and preserved LVEF.[32]

It is known that the risk of ventricular tachyarrhythmias and SCD varies with the type of CA and is significantly greater in patients with AL amyloidosis.[52] Based on the current state of knowledge, there are no robust guidelines for the decision to implant an ICD for primary prevention in CA. When NSVT and syncope are captured and documented, ICD implantation for prevention of SCD in CA is most likely a reasonable approach.[57] Specifically, this would be most appropriate for patients with AL amyloidosis, where ICD implantation is associated with a high rate of appropriate discharges for VA. An algorithm for ICD implantation could be proposed in patients with AL amyloidosis and LVEF > 35% (Figure 1). ICD should be considered in patients with registered NSVT and in early stages of the disease with less impairment in cardiac function, as indicated by minimally to moderately elevated cardiac biomarkers. As NSVT has been documented to be a poor predictor of SCD in AL amyloidosis, the incidence of syncope, decreased LV GLS in echocardiography, and the presence of transmural LGE in CMR can further improve stratification. Finally, specifically for AL amyloidosis, ICD implantation for primary prevention may also be reasonable for patients awaiting heart transplantation or a mechanical LV assist device, either as destination therapy or bridge-to-transplantation. This is reasonable only if perceived survival is meaningful (greater than 1 year), NT-pro BNP is less than 8,500 ng/L and NYHA functional class is less than IV.[58]

Conduction disease is highly prevalent in CA, and atrioventricular conduction delay involving the His-Purkinje system appears to be more common than pure sinus node disease.[6,59] HV interval prolongation with relatively narrow QRS duration may suggest frequent widespread involvement of both right and left bundle branches in patients with CA. Permanent pacemakers are commonly indicated for patients with CA and significant conduction disease, most often in wtATTR.[3] Donnellan et al.[60] from the Cleveland Clinic found that routine use of cardiac resynchronization therapy was associated with improvements in mitral regurgitation severity (67% of patients), New York Heart Association functional class (67% of patients), and LVEF (78% of patients) in patients with ATTR CA and an indication for permanent pacemaker.

Future Directions

Novel medical therapies for both AL and ATTR CA are leading to increased survival. These management paradigms are aimed at reducing overall arrhythmogenic burden in this population group.[61,62] As patients with CA are living longer, future studies on arrhythmia management in this population are needed. Questions that need answering include the following: 1)What clinical factors predict lethal VA in this population? 2) What is the appropriate patient

Table 1 – Studies reporting on treatment with implantable cardioverter-defibrillator and survival in patients with cardiac amyloidosis

Study/Year Published	CA Patients with ICD (n)	AL Amyloidosis	ICD in Primary Prevention (n/%)	Criteria for ICD Implantation in Primary Prevention	Appropriate ICD Therapy (n/%)	Overall Survival (n/%)
Kristen et al. (2008) [55]	19	19/19 (100%)	19 (100%)	Syncope and/or frequent PVBs	2 (11%)	1/2(50%)
Lin et al. (2013) [32]	53	33/53 (62%)	41 (77%)	LVEF ≤35% or syncope or NSVT	15 (28%)	21/53(40%)
Varr et al. (2014) [22]	19	15/19 (79%)	15 (79%)	Not specified	5 (26%)	UN
Harmon et al. (2016) [26]	45	12/45 (27%)	38 (84%)	LVEF ≤35% or pacing indication and LV GLS ≥–15% and/or NSVT/ frequent PVBs with syncope or planned HTX	12 (27%)	27/45 (60%)
Chuzi et al. (2018)	31	14/31 (45%)	25 (80%)	Not specified	2 (6%)	19/31 (61%)
Rezc et al. (2018)	15	15/15 (100%)	14 (93%)	NSVT and syncope/presyncope	4 (27%)	13/15 (87%)
Kim et al. (2019) [62]	23	7/23 (30%)	23 (100%)	LVEF ≤35% or NSVT and/or syncope	6 (26%)	14/23 (61%)
Donellan et al. (2019) [60]	38	0/38 (0%)	35 (92%)	Not specified	8 (21%)	UN

AL: Immunoglobulin light chain; CA: cardiac amyloidosis; HTX: heart transplantation; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; LV GLS: left ventricular global longitudinal strain; NSVT: nonsustained ventricular tachycardia; PVBs: premature ventricular beats; UN: unknown.

selection and, importantly, is there a mortality benefit for ICD placement?

Conclusion

CA carries a high risk of SCD. However, ICD implantation for primary prevention of SCD remains controversial, and it is not clear whether ICDs improve survival in CA. Few data are available on arrhythmic SCD risk stratification, and the usual approach in these patients is secondary prevention or extrapolation of risk factors due to other cardiomyopathies, for example, impaired LV systolic dysfunction or NSVT, with or without syncope. However, their overall mortality is still high, particularly in patients in advanced stages of the disease, and they are, thus, at increased risk of death due to electromechanical dissociation. Therefore, the challenge is to identify at-risk patients in the early stage of the disease when VA risk predominates and to identify who may benefit from ICD therapy, mainly in the AL subtype. Accurate identification of patients who are more likely to die of an arrhythmia and less likely to die of other causes is required to ensure improvement in outcomes and wise use of resources. Incorporating methods that identify patients at particularly high risks of death from competing causes, who are unlikely to benefit from ICD therapy, will form an important part of this process. Further prospective studies are needed to understand the pathophysiology of cardiac arrhythmias in patients with CA, including electrophysiological study with endocardial mapping and modern CMR imaging, to indicate predictors of arrhythmic SCD and, finally, define the role of ICD in this group of patients.

Author contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Dumont CA, Sosa Liprandi MI.

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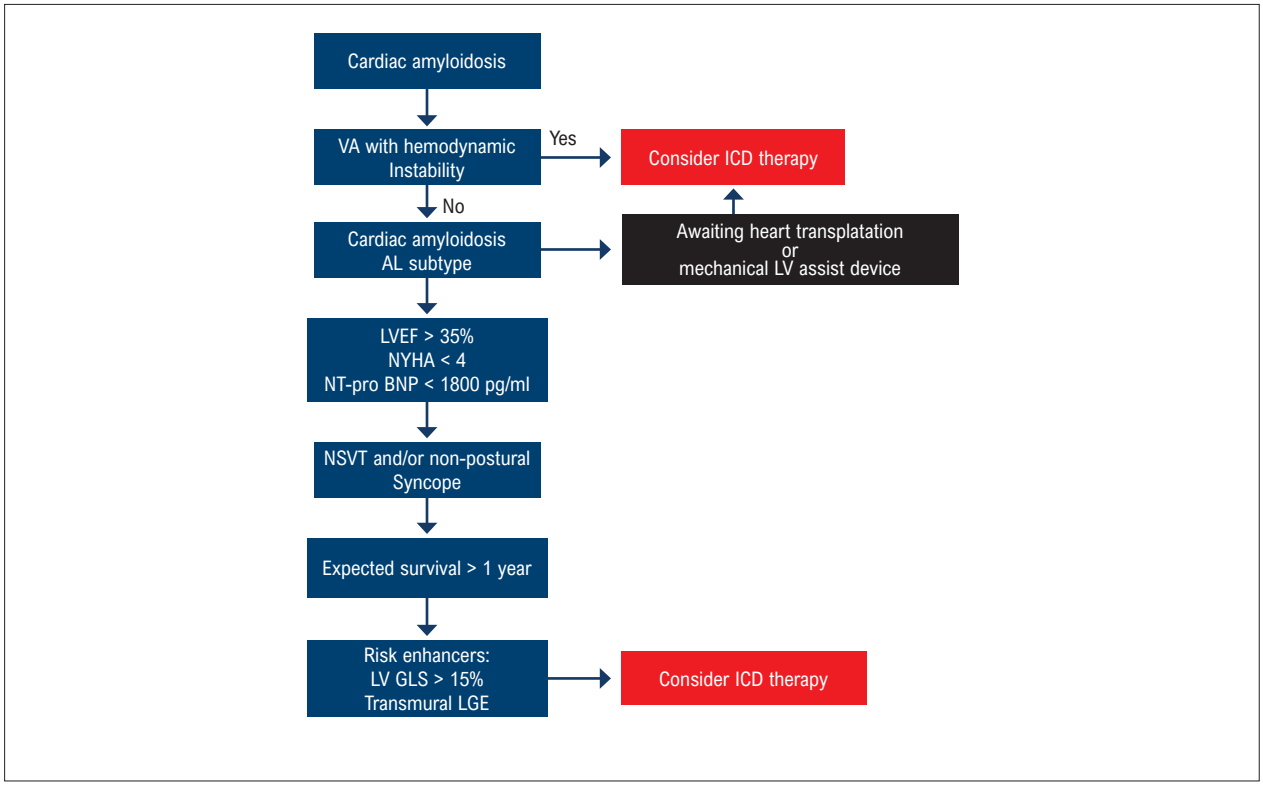

Figure 1 – *Proposed algorithm for qualifying patients with cardiac amyloidosis for ICD implantation. AL: immunoglobulin light chain; ICD: implantable cardioverter-defibrillator; LGE: late gadolinium enhancement in cardiac magnetic resonance imaging; LV: left ventricular; LVEF: left ventricular ejection fraction; LV GLS: left ventricular global longitudinal strain assessed by speckle-tracking echocardiography; NT-proBNP: N-terminal B-type natriuretic peptide; NYHA: New York Heart Association; NSVT: nonsustained ventricular tachycardia; VA: ventricular arrhythmia.*

References

1. Falk RH. Diagnosis and Management of the Cardiac Amyloidoses. Circulation. 2005;112(13):2047-60. doi: 10.1161/CIRCULATIONAHA.104.489187.
2. Dubrey SW, Hawkins PN, Falk RH. Amyloid Diseases of the Heart: Assessment, Diagnosis, and Referral. Heart. 2011;97(1):75-84. doi: 10.1136/hrt.2009.190405.
3. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac Amyloidosis. Clin Med (Lond). 2018;18(Suppl 2):30-5. doi: 10.7861/clinmedicine.18-2-s30.
4. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural History, Quality of Life, and Outcome in Cardiac Transthyretin Amyloidosis. Circulation. 2019;140(1):16-26. doi: 10.1161/CIRCULATIONAHA.118.038169.
5. Escher F, Senoner M, Doerler J, Zaruba MM, Messner M, Mussner-Seeber C, et al. When and How do Patients with Cardiac Amyloidosis Die? Clin Res Cardiol. 2020;109(1):78-88. doi: 10.1007/s00392-019-01490-2.
6. Reisinger J, Dubrey SW, Lavalley M, Skinner M, Falk RH. Electrophysiologic Abnormalities in AL (Primary) Amyloidosis with Cardiac Involvement. J Am Coll Cardiol. 1997;30(4):1046-51. doi: 10.1016/s0735-1097(97)00267-2.
7. D'Errico S, Mazzanti A, Baldari B, Maiese A, Frati P, Fineschi V. Sudden Death in Lambda Light Chain AL Cardiac Amyloidosis: A Review of Literature and Update for Clinicians and Pathologists. Int J Clin Exp Pathol. 2020;13(7):1474-82.
8. Cappelli F, Vignini E, Martone R, Perlini S, Mussinelli R, Sabena A, et al. Baseline ECG Features and Arrhythmic Profile in Transthyretin Versus Light Chain Cardiac Amyloidosis. Circ Heart Fail. 2020;13(3):e006619. doi: 10.1161/CIRCHEARTFAILURE.119.006619.
9. Rochlani YM, Nishi SN, Hakeem A, Bhatti S. Burden of Arrhythmias in Patients Hospitalized with Cardiac Amyloidosis. Circulation. 2015;132(Suppl 3):A20097.
10. Sanchis K, Cariou E, Colombat M, Ribes D, Huart A, Cintas P, et al. Atrial Fibrillation and Subtype of Atrial Fibrillation in Cardiac Amyloidosis: Clinical and Echocardiographic Features, Impact on Mortality. Amyloid. 2019;26(3):128-38. doi: 10.1080/13506129.2019.1620724.
11. Palladini G, Malamani G, Cò F, Pistorio A, Recusani F, Anesi E, et al. Holter Monitoring in AL Amyloidosis: Prognostic Implications. Pacing Clin Electrophysiol. 2001;24(8):1228-33. doi: 10.1046/j.1460-9592.2001.01228.x.
12. Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HJ, Fontana M, et al. A Study of Implanted Cardiac Rhythm Recorders in Advanced Cardiac AL Amyloidosis. Eur Heart J. 2015;36(18):1098-105. doi: 10.1093/eurheartj/ehu506.
13. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic Findings in Primary Systemic Amyloidosis and Biopsy-Proven Cardiac Involvement. Am J Cardiol. 2005;95(4):535-7. doi: 10.1016/j.amjcard.2004.10.028.
14. Goldsmith YB, Liu J, Chou J, Hoffman J, Comenzo RL, Steingart RM. Frequencies and Types of Arrhythmias in Patients with Systemic Light-Chain Amyloidosis with Cardiac Involvement Undergoing Stem Cell Transplantation on Telemetry monitoring. Am J Cardiol. 2009;104(7):990-4. doi: 10.1016/j.amjcard.2009.05.040.
15. Hörnsten R, Wiklund U, Olofsson BO, Jensen SM, Suhr OB. Liver Transplantation Does not Prevent the Development of Life-Threatening Arrhythmia in Familial Amyloidotic Polyneuropathy, Portuguese-Type (ATTR Val30Met) Patients. Transplantation. 2004;78(1):112-6. doi: 10.1097/01.tp.0000133517.20972.27.
16. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, Falk RH. The Clinical Features of Immunoglobulin Light-Chain (AL) Amyloidosis with Heart Involvement. QJM. 1998;91(2):141-57. doi: 10.1093/qjmed/91.2.141.
17. Ridolfi RL, Bulkley BH, Hutchins GM. The Conduction System in Cardiac Amyloidosis. Clinical and Pathologic Features of 23 Patients. Am J Med. 1977;62(5):677-86. doi: 10.1016/0002-9343(77)90870-1.
18. Li R, Yang ZG, Wen LY, Liu X, Xu HY, Zhang Q, et al. Regional Myocardial Microvascular Dysfunction in Cardiac Amyloid Light-Chain Amyloidosis: Assessment with 3T Cardiovascular Magnetic Resonance. J Cardiovasc Magn Reson. 2016;18:16. doi: 10.1186/s12968-016-0240-7.
19. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements. J Clin Oncol. 2012;30(9):989-95. doi: 10.1200/JCO.2011.38.5724.
20. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol. 2016;68(10):1014-20. doi: 10.1016/j.jacc.2016.06.033.
21. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A New Staging System for Cardiac Transthyretin Amyloidosis. Eur Heart J. 2018;39(30):2799-806. doi: 10.1093/eurheartj/ehx589.
22. Varr BC, Zarafshar S, Coakley T, Liedtke M, Lafayette RA, Arai S, et al. Implantable Cardioverter-Defibrillator Placement in Patients with Cardiac Amyloidosis. Heart Rhythm. 2014;11(1):158-62. doi: 10.1016/j.hrthm.2013.10.026.
23. Ashraf I, Peck MM, Maram R, Mohamed A, Crespo DO, Kaur G, et al. Association of Arrhythmias in Cardiac Amyloidosis and Cardiac Sarcoidosis. Cureus. 2020;12(8):e9842. doi: 10.7759/cureus.9842.
24. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017;10(3):e005588. doi: 10.1161/CIRCIMAGING.116.005588.
25. Falk RH, Rubinow A, Cohen AS. Cardiac Arrhythmias in Systemic Amyloidosis: Correlation with Echocardiographic Abnormalities. J Am Coll Cardiol. 1984;3(1):107-13. doi: 10.1016/s0735-1097(84)80436-2.
26. Hamon D, Algalarrondo V, Gandjbakhch E, Extramiana F, Marijon E, Elbaz N, et al. Outcome and Incidence of Appropriate Implantable Cardioverter-Defibrillator Therapy in Patients with Cardiac Amyloidosis. Int J Cardiol. 2016;222:562-8. doi: 10.1016/j.ijcard.2016.07.254.
27. Fluechter S, Kuschyk J, Wolpert C, Doesch C, Veltmann C, Haghi D, et al. Extent of Late Gadolinium Enhancement Detected by Cardiovascular Magnetic Resonance Correlates with the Inducibility of Ventricular Tachyarrhythmia in Hypertrophic Cardiomyopathy. J Cardiovasc Magn Reson. 2010;12(1):30. doi: 10.1186/1532-429X-12-30.
28. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation. 2015;132(16):1570-9. doi: 10.1161/CIRCULATIONAHA.115.016567.
29. Kotecha T, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, et al. Myocardial Edema and Prognosis in Amyloidosis. J Am Coll Cardiol. 2018;71(25):2919-31. doi: 10.1016/j.jacc.2018.03.536.
30. John RM. Arrhythmias in Cardiac Amyloidosis. J Innov Card Rhythm Manag. 2018;9(3):3051-7. doi: 10.19102/icrm.2018.090301.
31. Sidana S, Tandon N, Brady PA, Grogan M, Gertz MA, Dispenzieri A, et al. Prognostic Significance of Holter Monitor Findings in Patients with Light Chain Amyloidosis. Mayo Clin Proc. 2019;94(3):455-64. doi: 10.1016/j.mayocp.2018.08.039.
32. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable Cardioverter Defibrillators in Patients with Cardiac Amyloidosis. J Cardiovasc Electrophysiol. 2013;24(7):793-8. doi: 10.1111/jce.12123.
33. Halawa A, Woldu HG, Kacey KG, Alpert MA. Effect of ICD Implantation on Cardiovascular Outcomes in Patients with Cardiac Amyloidosis: A Systematic Review and Meta-Anaylsis. J Cardiovasc Electrophysiol. 2020;31(7):1749-58. doi: 10.1111/jce.14541.

34. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy. Heart Rhythm. 2019;16(11):301-72. doi: 10.1016/j.hrthm.2019.05.007.

35. Orini M, Graham AJ, Martinez-Naharro A, Andrews CM, de Marvao A, Statton B, Cook SA, O'Regan DP, Hawkins PN, Rudy Y, Fontana M, Lambiase PD. Noninvasive Mapping of the Electrophysiological Substrate in Cardiac Amyloidosis and Its Relationship to Structural Abnormalities. J Am Heart Assoc. 2019;8(18):e012097. doi: 10.1161/JAHA.119.012097.

36. Ramírez J, Orini M, Mincholé A, Monasterio V, Cygankiewicz I, Luna AB, et al. T-Wave Morphology Restitution Predicts Sudden Cardiac Death in Patients with Chronic Heart Failure. J Am Heart Assoc. 2017;6(5):e005310. doi: 10.1161/JAHA.116.005310.

37. Tilz RR, Lenarczyk R, Scherr D, Haugaa KH, Iliodromitis K, Pürerfellner H, et al. Management of Ventricular Tachycardia in the Ablation Era: Results of the European Heart Rhythm Association Survey. Europace. 2018;20(1):209-13. doi: 10.1093/europace/eux332.

38. Alkindi S, Almasoud A, Younes A, Elamm C, Benatti R, Oliveira G, et al. Increased Risk of Heart Block in Patients with Cardiac Amyloidosis on Amiodarone. J Card Fail. 2015;21(8):125. doi: https://doi.org/10.1016/j.cardfail.2015.06.359.

39. Le Bras F, Molinier-Frenkel V, Guellich A, Dupuis J, Belhadj K, Guendouz S, et al. Sequential Cyclophosphamide-Bortezomib-Dexamethasone Unmasks the Harmful Cardiac Effect of Dexamethasone in Primary Light-Chain Cardiac Amyloidosis. Eur J Cancer. 2017;76:183-7. doi: 10.1016/j.ejca.2017.02.004.

40. Goldberg MA, Antin JH, Guinan EC, Rappeport JM. Cyclophosphamide Cardiotoxicity: An Analysis of Dosing as a Risk Factor. Blood. 1986;68(5):1114-8.

41. Xiao Y, Yin J, Wei J, Shang Z. Incidence and Risk of Cardiotoxicity Associated with Bortezomib in the Treatment of Cancer: A Systematic Review and Meta-Analysis. PLoS One. 2014;9(1):e87671. doi: 10.1371/journal.pone.0087671.

42. Tan NY, Mohsin Y, Hodge DO, Lacy MQ, Packer DL, Dispenzieri A, et al. Catheter Ablation for Atrial Arrhythmias in Patients with Cardiac Amyloidosis. J Cardiovasc Electrophysiol. 2016;27(10):1167-73. doi: 10.1111/jce.13046.

43. Donnellan E, Wazni O, Kanj M, Elshazly MB, Hussein A, Baranowski B, et al. Atrial Fibrillation Ablation in Patients with Transthyretin Cardiac Amyloidosis. Europace. 2020;22(2):259-64. doi: 10.1093/europace/euz314.

44. Chung FP, Lin YJ, Kuo L, Chen SA. Catheter Ablation of Ventricular Tachycardia/Fibrillation in a Patient with Right Ventricular Amyloidosis with Initial Manifestations Mimicking Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. Korean Circ J. 2017;47(2):282-5. doi: 10.4070/kcj.2016.0328.

45. Mlcochova H, Saliba WI, Burkhardt DJ, Rodriguez RE, Cummings JE, Lakkireddy D, et al. Catheter Ablation of Ventricular Fibrillation Storm in Patients with Infiltrative Amyloidosis of the Heart. J Cardiovasc Electrophysiol. 2006;17(4):426-30. doi: 10.1111/j.1540-8167.2005.00321.x.

46. Muser D, Santangeli P, Pathak RK, Castro SA, Liang JJ, Magnani S, et al. Long-Term Outcomes of Catheter Ablation of Ventricular Tachycardia in Patients with Cardiac Sarcoidosis. Circ Arrhythm Electrophysiol. 2016;9(8):e004333. doi: 10.1161/CIRCEP.116.004333.

47. Shumway SJ, Johnson EM, Svendsen CA, Kriett JM, Ring WS. Surgical Management of Ventricular Tachycardia. Ann Thorac Surg. 1997;63(6):1589-91. doi: 10.1016/s0003-4975(97)00358-5.

48. Estep JD, Bhimaraj A, Cordero-Reyes AM, Bruckner B, Loebe M, Torre-Amione G. Heart Transplantation and End-Stage Cardiac Amyloidosis: A Review and Approach to Evaluation and Management. Methodist Debakey Cardiovasc J. 2012;8(3):8-16. doi: 10.14797/mdcj-8-3-8.

49. Donnelly J, Soltesz E, Tong MZ, Hall SA, Kale P, Estep JD, et al. Heart Transplantation in Cardiac Amyloidosis: A Ten Year Experience. J Heart Lung Transplant. 2019;38(4):389. doi: https://doi.org/10.1016/j.healun.2019.01.989.

50. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

51. Castaño A, Helmke S, Alvarez J, Delisle S, Maurer MS. Diflunisal for ATTR Cardiac Amyloidosis. Congest Heart Fail. 2012;18(6):315-9. doi: 10.1111/j.1751-7133.2012.00303.x.

52. Khanna S, Lo P, Cho K, Subbiah R. Ventricular Arrhythmias in Cardiac Amyloidosis: A Review of Current Literature. Clin Med Insights Cardiol. 2020;14:1179546820963055. doi: 10.1177/1179546820963055.

53. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Europace. 2015;17(11):1601-87. doi: 10.1093/europace/euv319.

54. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;138(13):210-e71. doi: 10.1161/CIR.0000000000000548.

55. Kristen AV, Dengler TJ, Hegenbart U, Schonland SO, Goldschmidt H, Sack FU, et al. Prophylactic Implantation of Cardioverter-Defibrillator in Patients with Severe Cardiac Amyloidosis and High Risk for Sudden Cardiac Death. Heart Rhythm. 2008;5(2):235-40. doi: 10.1016/j.hrthm.2007.10.016.

56. Cheung CC, Roston TM, Andrade JG, Bennett MT, Davis MK. Arrhythmias in Cardiac Amyloidosis: Challenges in Risk Stratification and Treatment. Can J Cardiol. 2020;36(3):416-23. doi: 10.1016/j.cjca.2019.11.039.

57. Bart NK, Thomas L, Korczyk D, Atherton JJ, Stewart GJ, Fatkin D. Amyloid Cardiomyopathy. Heart Lung Circ. 2020;29(4):575-83. doi: 10.1016/j.hlc.2019.11.019.

58. John RM, Stern DL. Use of Implantable Electronic Devices in Patients with Cardiac Amyloidosis. Can J Cardiol. 2020;36(3):408-15. doi: 10.1016/j.cjca.2019.12.002.

59. Boldrini M, Salinaro F, Mussinelli R, Raimondi A, Alogna A, Musca F, et al. Prevalence and Prognostic Value of Conduction Disturbances at the Time of Diagnosis of Cardiac AL Amyloidosis. Ann Noninvasive Electrocardiol. 2013;18(4):327-35. doi: 10.1111/anec.12032.

60. Donnellan E, Wazni OM, Saliba WI, Baranowski B, Hanna M, Martyn M, et al. Cardiac Devices in Patients with Transthyretin Amyloidosis: Impact on Functional Class, Left Ventricular Function, Mitral Regurgitation, and Mortality. J Cardiovasc Electrophysiol. 2019;30(11):2427-32. doi: 10.1111/jce.14180.

61. 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.

62. Kim EJ, Holmes B, Huang S, Lugo R, Al Aboud A, Richardson T, et al. Does an Implantable Defibrillator Alter Outcomes in Patients with Cardiac Amyloidosis? J Am Coll Cardiol. 2019;73(9):837. doi: 10.1016/S0735-1097(19)31444-5.

Review Article

New Paradigms in Cardiac Amyloidosis: The Current Experience of the Northeast Region of Brazil

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Cardiac amyloidosis (CA) is a severe and progressive infiltrative disease caused by the deposition of amyloid fibrils, with poor prognosis and limited therapeutic options. It can occur due to rare genetic variants or as a consequence of acquired conditions. Thanks to advances in imaging techniques and the possibility of obtaining non-invasive diagnosis, we now know that CA would perhaps be better classified as an underdiagnosed disease rather than as a rare one.[1-3]

González-Lopez et al. demonstrated that, in a series of 120 patients with preserved ejection fraction heart failure, 13.3% had a diagnosis of transthyretin-associated amyloid cardiomyopathy (ATTR-CM).[4] In patients with aortic stenosis, we found a prevalence of around 15% of ATTR-CM,[5] and, in necropsy studies, amyloid protein deposition was found in 25% of patients over 85 years old, which shows the importance of this diagnosis in the spectrum of myocardial diseases.[6]

Bone scintigraphy with PYP-^{99m}Tc is being increasingly used in the diagnosis of ATTR-CM.[7] Thus, it is expected that the number of patients diagnosed with ATTR-CM will continue to increase. New therapies reduce the progressive morbidity and mortality associated with ATTR-CM, contributing to improve the journey of these patients. The importance of early recognition of ATTR-CM is essential, as the prompt initiation of appropriate treatment is essential to maximize its therapeutic potential and improve patients' quality of life.[8]

As it presents heterogeneous clinical manifestations that may involve different medical specialties, the creation of groups dedicated to the identification and monitoring of these patients is of great value.[2,9] In Brazil, Centers of Excellence (CEs) in amyloidosis have already been created, offering extensive care based on the team's experience with ATTR-CM, multidisciplinary approach, advanced diagnostics, and time dedicated to patient care and education.

Keywords

Amyloidosis; Prealbumin; Brazil.

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Raising awareness of best practices in amyloidosis centers among health professionals can reinforce the benefits of early referral and comprehensive care for patients with ATTR-CM.[10,11] However, as Brazil is a continent-sized country with many disparities related to public and private health systems, the different geographic regions have progressed separately in the creation of these centers. Recently, we brought together specialists from the Northeast Region of Brazil to share best practices and define the best flow for identification and management of ATTR-CM in institutions from different states. Here, we share our learning, difficulties faced (Table 1), and general point of view regarding the current scenario in our region.

One of the main difficulties in the setting of the Brazilian Unified Health System (SUS) is the structure to adequately complete the flowchart for non-invasive diagnosis of CA. The first obstacle we face, regardless of region, is the need to exclude immunoglobulin light-chain amyloidosis. Specific laboratory tests (immunofixation of proteins and kappa and lambda chain assays) are not covered by the SUS or even by some private health plans. Also regarding the setting of the SUS, pyrophosphate scintigraphy, echocardiography with myocardial strain analysis, and cardiac resonance are not performed in most tertiary cardiac care units in the Northeast Region. When we are with a patient who has been diagnosed with ATTR, it is necessary to distinguish whether it is the variant or senile form, and we then need to turn to genotyping, which can often only be done through partnerships with laboratories.

Before carrying out the genetic study and, subsequently, due to the size of the result, adequate genetic counseling is required,

Table 1 – Main difficulties faced, in different centers in the Northeast, in the search for specialized care for ATTR-CM

1.1 - Structural limitations to achieving diagnosis in a non-invasive manner;
1.2 - Lack of basic medical education dedicated to the subject;
1.3 - Difficulties in connecting specialties to discuss the same case;
1.4 - Restricted access to genetic tests and interaction with geneticists;
1.5 - Difficulty in using the specific drug (tafamidis) that has been approved in Brazil, as well as others that have not yet been approved by the Brazilian Ministry of Health;
1.6 - Overload of public services, making it difficult to monitor diagnosed patients' family members.

and it is at this point that the absence of a geneticist becomes evident. In supplementary medicine, we find fewer difficulties in this flow, which leads to a much faster diagnostic process, but the paths are no less tortuous, as the scarcity of geneticists and the high cost of genetic testing, in addition to the fact that they are not covered by supplementary health plans also hinder this diagnosis. The lack of interaction between specialists from different areas and the lack of basic and continuing education about ATTR-CM are also other important obstacles. It is noteworthy that, in the Northeast Region, there are already reference cardiology centers that have become CEs, with clinical support from an ophthalmologist, nephrologist, neurologist, and geneticist, but this number is still very small given the importance and increasing incidence of CA. The few people who have been involved in this area are, in a selfless and dedicated way, growing together and trying to develop diagnosis, in addition to spreading knowledge, but there is still a lot to be done. For example, there is still no widespread diffusion of the red flags that suggest diagnosis (Table 2), which would greatly facilitate the journey of these patients to their final diagnosis.

Despite all the barriers found, our region has stood out due to the growing number of diagnoses of this disease, making it possible for more patients to benefit from specific therapy. CEs in the region have been gaining expertise in the treatment of these patients, highlighting the symptomatic benefit of diuretic therapy and the poor tolerance of beta-blockers and renin-angiotensin-aldosterone system blockers, confirming what has already been seen in other centers around the world. The use of direct anticoagulants in FA + cardiac amyloidosis has also been part of our practice, with good results, in terms of both efficacy and safety

The use of tafamidis, a drug that stabilizes the transthyretin protein, has been shown to reduce in mortality in patients with ATTR-CM, but its extremely high cost and its availability through the SUS is perhaps currently the biggest obstacle for the treatment of these patients. Once again, this is not a problem exclusive to the Northeast Region, but rather to the whole of Brazil and even in the most developed countries. Its use, via the SUS, is only authorized in association with family amyloidotic polyneuropathy (FAP), which, to a certain extent, restricts its administration. Furthermore, when doses of tafamidis versus placebo were evaluated in the ATTR-ACT[12] and ATTR-ACT extension[13] studies, it was possible to verify that the highest dose (80 mg) brought better results in worse outcomes. This posology, which is already on the medication package insert, is 4 times higher than that approved for the treatment of FAP and released by the SUS, which can bring major limitations in relation to therapy in ATTR-CM. The cost of tafamidis is undoubtedly a major limiting factor to its use; however, when we analyze the cost-effectiveness ratio, keeping in mind that the denominator is the main determinant in this ratio, we realize that the use of this drug is much more than indicated.[12,13] Despite all these obstacles, we have been able to use the drug, and it appears to be safe, with good results so far. We also remember that new drugs, such as patisiran and inotersen, must reach the market and can be approved by the SUS and that solving the problems of access to tafamidis will also help with greater accessibility to these drugs, when available.

Amyloidosis is potentially severe and progressive, and its incidence increases as we seek to further diagnose it. We, from the CEs in the Northeast Region, seek to offer the best and most up-to-date care to our patients with CA, and, despite the limitations, obstacles, and difficulties, we can say that in recent years, we have seen much more progress than setbacks, and this is precisely what encourages us to continue. The union of CEs, which are already centers of excellence in cardiology, is only the first step towards joint technical and scientific development, in order to overcome the difficulties intrinsic to our health system and also the disease itself, reaching the final goal, namely, the best care for our patients.

We have no doubt that many of the difficulties faced by CEs in our region are also shared by colleagues throughout Brazil, and it is through further discussion and approaches to the topic, as we are doing through this publication, that we will ensure that more people are diagnosed early, that genetic counseling (when indicated) is done, and that patients are treated in accordance with international recommendations.[3]

Table 2 – "Red flags"

When we should think about cardiac amyloidosis:
1 - Patients over 60 years old with heart failure with preserved ejection fraction
2 - LVH of unclear etiology
3 - Intolerance or refractoriness to conventional treatment for heart failure
4 - History of carpal tunnel syndrome, mainly if bilateral
5 - Patients with polyneuropathy or family history of polyneuropathy
6 - Orthostatic hypotension and renal dysfunction with proteinuria

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Writing of the manuscript: Silva T, Montenegro CEL, Melo MDT, Ritt L, Almeida ALC.Critical revision of the manuscript for intellectual content: Silva T, Montenegro CEL, Melo MDT, Ritt L, Almeida ALC.

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References

1. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation. 2017;135(14):1357-77. doi: 10.1161/CIRCULATIONAHA.116.024438.

2. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-91. doi: 10.1016/j.jacc.2019.04.003.

3. 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.

4. González-López E, Gallego-Delgado M, Guzzo-Merello G, Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-Type Transthyretin Amyloidosis as a Cause of Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2015;36(38):2585-94. doi: 10.1093/eurheartj/ehv338.

5. Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, et al. Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2018;71(4):463-4. doi: 10.1016/j.jacc.2017.11.037.

6. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, et al. Senile Systemic Amyloidosis Affects 25% of the Very Aged and Associates with Genetic Variation in Alpha2-Macroglobulin and Tau: A Population-Based Autopsy Study. Ann Med. 2008;40(3):232-9. doi: 10.1080/07853890701842988.

7. Rezk T, Fontana M, Gillmore JD. A Review of the Criteria for Non-Invasive Diagnosis of Cardiac Transthyretin Amyloidosis. Expert Opin Orphan Drug. 2021;9(3):87-94. doi: 10.1080/21678707.2021.1898371.

8. Lindmark K, Pilebro B, Sundström T, Lindqvist P. Prevalence of Wild Type Transtyrethin Cardiac Amyloidosis in a Heart Failure Clinic. ESC Heart Fail. 2021;8(1):745-9. doi: 10.1002/ehf2.13110.

9. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, et al. Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice. JACC Heart Fail. 2019;7(8):709-16. doi: 10.1016/j.jchf.2019.04.010.

10. Nativi-Nicolau J, Sarswat N, Fajardo J, Finkel M, Abdulsattar Y, Castaño A, et al. Best Practices in Specialized Amyloidosis Centers in the United States: A Survey of Cardiologists, Nurses, Patients, and Patient Advocates. J Clin Res Pediatr Endocrinol. 2021;13(2):124-35. doi: 10.1177/11795468211015230.

11. Dang D, Fournier P, Cariou E, Huart A, Ribes D, Cintas P, et al. Gateway and Journey of Patients with Cardiac amyloidosis. ESC Heart Fail. 2020;7(5):2418-30. doi: 10.1002/ehf2.12793.

12. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

13. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, et al. Efficacy and Safety of Tafamidis Doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and Long-Term Extension Study. Eur J Heart Fail. 2021;23(2):277-85. doi: 10.1002/ejhf.2027.

Cardiac Magnetic Resonance and Amyloidosis: How can it Assist Clinical Reasoning?

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The real incidence of cardiac amyloidosis (CA) is still unknown, and this is, at least in part, due to difficulties in confirming diagnosis. Currently, however, different imaging exams and genetic tests can, in association with clinical presentation, confirm diagnosis. Cardiac magnetic resonance (CMR) can contribute to confirmation of diagnosis and, more recently, to the screening of family members of carriers of hereditary forms of CA.[1,2] In this article, we will review the contributions of CMR in relation to clinical suspicion or screening for CA, initiating with a review of the information that the exam offers and, subsequently, discussing clinical scenarios in which CMR can be most useful.

Evaluation of cardiac morphology

CA leads to changes in cardiac structure. In the atria, dilatation and increased thickness of the septum usually occur, while, in more advanced phases, there may be slow flow and thrombi, which, when arrhythmias are present, may be difficult to identify via CMR.[3]

The ventricular myocardium usually shows increased thickness, typically at levels higher than those observed in patients with arterial hypertension; the levels are typically greater in forms of transthyretin amyloidosis than in light chain amyloidosis, and they may involve both ventricles.[4,5]

It is, moreover, not uncommon to find pericardial or pleural effusion, which are characteristics that can be easily seen on CMR.[4,5]

Analysis of ventricular function

CMR is considered the gold standard for analysis of global and regional ventricular contractility of both ventricles.[6] Nevertheless, in clinical practice, analysis of ventricular contractility parameters is conducted, with good quality, using echocardiography, and resonance is reserved for conditions where there are doubts or conflicting echocardiograms.[1] It is important to remember that ventricular contractility can be preserved for long periods and that regional contractile analysis, especially based on strain analysis, can be more sensitive in detecting abnormalities in early stages of CA.[1,4,5]

Examples of morphological alterations in patients who are carriers of CA are displayed in Figure 1.

Characterization of the myocardium – late enhancement techniques

CMR with late enhancement (LE) is a well-established means of non-invasively investigating the existence of myocardial necrosis, inflammation, or fibrosis. Thanks to the dynamics of the material used as a contrast agent, a metal known as gadolinium, it is possible to identify the regions of the heart where it is retained and to quantify and define the morphological patterns of these regions. As these areas turn white and shiny, 7 to 12 minutes after the injection of the paramagnetic agent, this finding is called LE, which offers 2 types of information.[5,6] The first is diagnostic in nature, given that different heart diseases tend to exhibit distinct LE patterns (Figure 2). In cases of CA, the most common pattern shows diffuse LE, often affecting the subendocardium or the entire transmural thickness of the heart walls, but different morphologies can arise, including involvement of the mesocardial segment and the pattern of focal enhancement.[5,7]

Characteristics of LE do not play a prominent role in defining the type of CA that patients present, but the presence and, in particular, the extent of LE are related to prognosis, and they add value to the markers that are classically used in clinical practice. Analyzing 250 patients, Fontana et al. demonstrated that LE quantification was an independent predictor of mortality, even considering variables such as pro-BNP, ejection fraction, and ventricular systolic volume index, diastolic function, and ventricular mass index.[3,5]

These elements make LE analysis a fundamental step in the evaluation of patients with clinical suspicion of CA.

Characterization of the myocardium – T1 mapping

Mapping, a more recently introduced form of characterizing the myocardium, comprises series based on changes that occur in T1, one of the parameters used to compose the CMR image. The data are presented in the form of quantifiable parametric maps, and they are able to reveal disease processes, even in conditions where LE is not observed, thus making them an important tool to complement diagnostic investigation of different heart diseases, including CA.[4,5,8]

Measurement of native T1 is conducted without the injection of contrast medium, which makes it an interesting alternative to examine patients who have contraindications

Keywords

Amyloidosis; Heart Failure; Ventricular Function.

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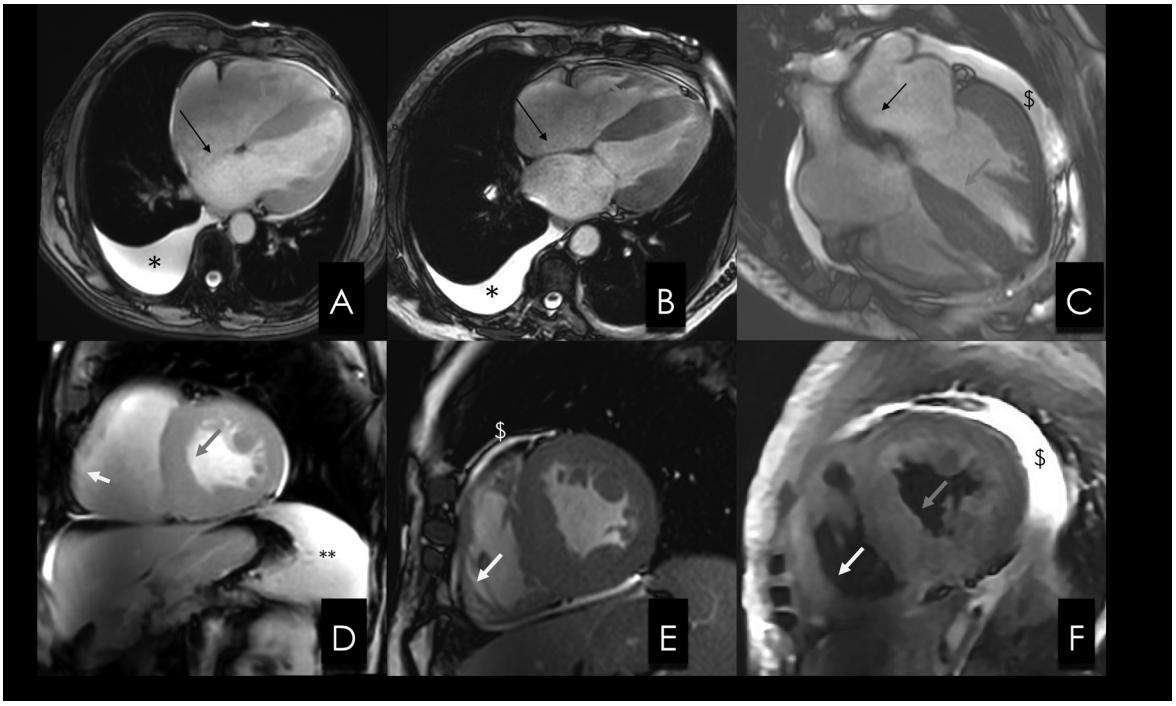

Figure 1 – *CA can present different morphological patterns, depending on the degree of involvement and the duration of disease evolution. There is usually dilation of the atria (1A, 1B, and 1C), while the thickness of the interatrial septum may be normal, slightly increased, or significantly increased, which is most characteristic (1A, 1B, and 1C, respectively, black arrows). The thickness of the interventricular septum (red arrows) is usually increased, but the degree of involvement varies, as does the relationship between the measurements of the interventricular septum and the free wall. Right ventricle thickness may be preserved (yellow arrow, 1D), slightly enlarged (yellow arrow, 1E), or significantly enlarged (yellow arrow, 1F). Often, there are pericardial effusion (1C and 1F = $), pleural effusion (1A and 1B =*), and even ascites (1D = **).*

to the use of gadolinium, such as severe renal failure, or patients on a dialysis program.[4,5,8] Diagnostic efficacy also increases in cases where the extracellular space is quantified; in this condition, a contrast agent is applied, and it reveals changes when there are processes that lead to expansion of the interstitium, which is the case with CA.[4,5,8]

The usefulness of this approach has been proven in a meta-analysis by Pan et al., who documented that the presence of elevated T1 mapping and extracellular space measurement led to improved diagnostic performance, compared to LE (odds ratio: 4.27; 95% confidence interval: 2.87 – 6.37 vs. odds ratio: 2.60; 95% confidence interval: 1.90 – 3.56; p = 0.03). However, the authors underscore that there may be cases where T1 mapping and the measurement of extracellular space do not confirm the diagnosis, and it may be necessary to evaluate the.[8]

Contribution of resonance in different clinical scenarios

Screening family members for hereditary forms of CA

Morphological and functional changes that result from CA may be useful for confirming diagnosis, but, as with LE, they may only appear later. What is expected in this scenario is that the diagnosis should be made earlier. The use of T1 mapping can be useful in this context, especially because, if this parameter is within the normal limits, it is very safe to rule out diagnosis of CA.[4,5,8] Even though this approach is not widely used, it has shown great clinical potential.

Differential diagnosis of myocardium with increased thickness

Different heart diseases can cause increased thickness in the ventricular walls, and these conditions are often difficult to differentiate clinically.[1,2,6,9] CMR can assist in the characterization of the etiology by identifying cases that are secondary to hypertension, cases of hypertrophic cardiomyopathy, Fabry disease, and CA. In this scenario, it is important to use all the tools that the exam provides, especially because both LE patterns and T1 mapping values vary according to etiology, and they can provide information that is essential to diagnosis. In the event that CA is confirmed, CMR results will make it possible to proceed to define the type of alteration and establish appropriate treatment as quickly as possible.[1,2,6,9]

Evaluation of patients with heart failure with preserved ejection fraction

In our experience, there have been cases of CA that have manifested as heart failure with preserved ejection fraction, even before there were significant increases in myocardial thickness.

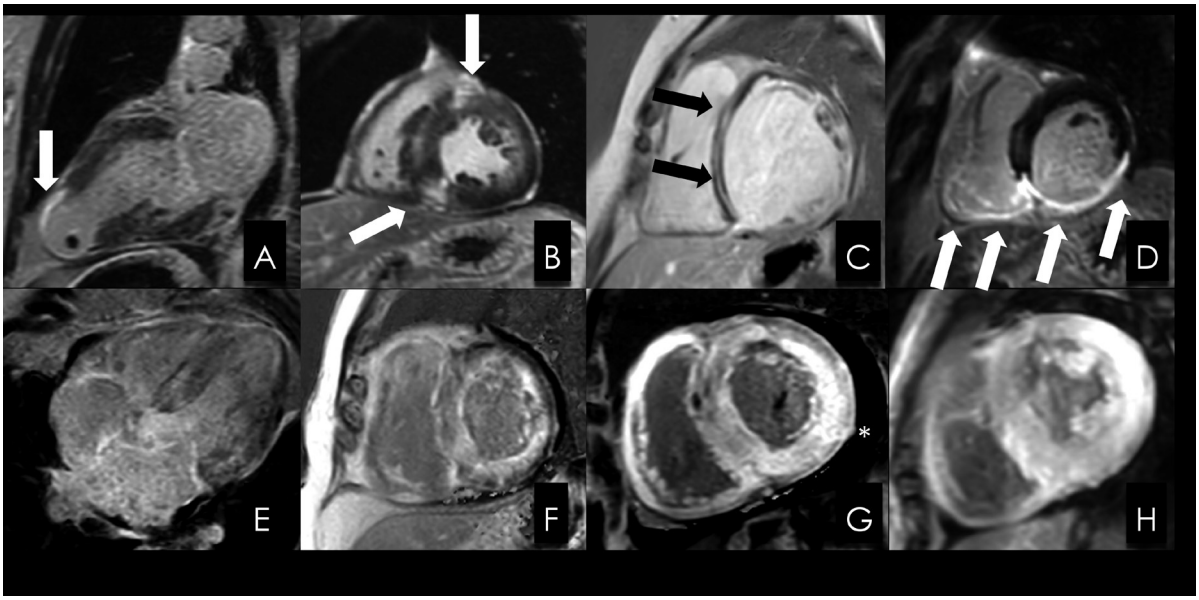

Figure 2 – *LE patterns (arrows, 2A, 2B, 2C, and 2D) can help in diagnosis and provide prognostic data. Cases of Chagas disease show apical enhancement, at times accompanied by filling failure, as in 2A; the presence of increased mural thickness with LE in the mesocardium at the meeting points of the right and left ventricles is characteristic of hypertrophic cardiomyopathy (2B). Cases of dilated cardiomyopathy often show areas of mesocardial LE in the interventricular septum (2C), and cases of coronary disease usually show enhancement in areas that are irrigated by only one coronary artery and have a "wave" morphology involving subendocardial to transmural regions. In cases of CA, LE is usually diffuse, and it is more relevant to the subendocardial region (2E and 2F). In more advanced cases of the disease, the involvement becomes transmural (2G and 2H). Due to difficulties in adjusting parameters that define LE, it can be difficult to visualize alterations, such as pericardial effusion (2G =*), in these series. Studies have shown that cases of diffuse, transmural, extensive LE are associated with worse prognosis (2H) (3)*

In this scenario as well, CMR can assist in identifying CA as the cause of the alterations and guide treatment.[1,6]

Diagnostic uncertainty on other exams

Due to the reduced intra- and interobserver variability and the superior capacity for myocardial characterization, CMR can be useful for defining diagnosis in cases where there are doubts after other forms of analysis, such as echocardiography, have been carried out.[1,2,10]

In elderly patients with aortic stenosis

The incidence of both aortic stenosis and CA increase as age advances, and this association is not rare; there are reports that both coexist in 13.9% to 16% of cases of aortic stenosis that will undergo percutaneous treatment.[11] CMR is recommended to clarify whether or not CA is present, especially if there is a disproportionate increase in myocardial thickness. LE techniques can identify myocardial injury and differentiate whether it is the consequence of valve damage or infiltrative disease.[12] Furthermore, T1 mapping and increased extracellular space also favor diagnosis of infiltrative cardiomyopathy, and they may assist in the diagnostic strategy.

Prognosis and treatment monitoring

In addition to aiding in diagnosis of CA, CMR can also be useful in estimating the prognosis of patients with CA. Although the applications of T1 mapping and estimation of extracellular space have the potential to contribute to this area, the main information regarding evolution is provided by LE. Fontana et al. demonstrated that the presence of LE is associated with worse evolution and that cases with transmural LE show more adverse events than cases with subendocardial LE.[3] These data can help define the severity of the case and the treatment planning.

T1 mapping and extracellular space, on the other hand, have shown potential to monitor the therapeutic response in patients with specific treatments and, thus, assist in guiding the management strategy.[4,5,8]

Table 1 summarizes the potential contributions of CMR in different clinical scenarios.

Conclusion

CMR is highly useful in the evaluation of CA, and its application can have a positive impact on the management of these patients.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Pinto IMF.

Table 1 – Contribution of CMR to different clinical situations of patients with CA

Clinical scenario	Contribution of CMR
Screening family members for hereditary forms of CA	Early diagnosis of heart disease, preceding installation of structural heart disease, especially with use of T1 mapping
Differential diagnosis of myocardium with increased thickness	Differential diagnosis based on use of T1 mapping and LE patterns, contributing to early diagnosis and treatment
Evaluation of patients with heart failure with preserved ejection fraction	Confirming diagnosis of CA and guiding correct treatment
Diagnostic uncertainty on other exams	Confirming diagnosis and facilitating treatment
In elderly patients with aortic stenosis	Identification of cases of CA, based on analysis of T1 mapping and LE pattern
Prognosis and treatment monitoring	The characteristics and extent of LE have an important prognostic impact. T1 mapping is useful for evaluating the efficacy of specific treatment.

CA: cardiac amyloidosis; CMR: cardiac magnetic resonance; LE: late enhancement

Potential Conflict of Interest

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Study Association

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Ethics approval and consent to participate

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

References

1. 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.
2. Wang TKM, Abou Hassan OK, Jaber W, Xu B. Multi-Modality Imaging of Cardiac Amyloidosis: Contemporary Update. World J Radiol. 2020;12(6):87-100. doi: 10.4329/wjr.v12.i6.87.
3. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation. 2015;132(16):1570-9. doi: 10.1161/CIRCULATIONAHA.115.016567.
4. Baggiano A, Boldrini M, Martinez-Naharro A, Kotecha T, Petrie A, Rezk T, et al. Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2020;13(1):69-80. doi: 10.1016/j.jcmg.2019.03.026.
5. Jurcuţ R, Onciul S, Adam R, Stan C, Coriu D, Rapezzi C, et al. Multimodality Imaging in Cardiac Amyloidosis: A Primer for Cardiologists. Eur Heart J Cardiovasc Imaging. 2020;21(8):833-44. doi: 10.1093/ehjci/jeaa063.
6. Sara L, Szarf G, Tachibana A, Shiozaki AA, Villa AV, Oliveira AC, et al. II Diretriz de Ressonância Magnética e Tomografia Computadorizada Cardiovascular da Sociedade Brasileira de Cardiologia e do Colégio Brasileiro de Radiologia. Arq Bras Cardiol. 2014;103(6 Suppl 3):1-86. doi: 10.5935/abc.2014S006.
7. Zhao L, Tian Z, Fang Q. Diagnostic Accuracy of Cardiovascular Magnetic Resonance for Patients with Suspected Cardiac Amyloidosis: A Systematic Review and Meta-Analysis. BMC Cardiovasc Disord. 2016;16:129. doi: 10.1186/s12872-016-0311-6.
8. Pan JA, Kerwin MJ, Salerno M. Native T1 Mapping, Extracellular Volume Mapping, and Late Gadolinium Enhancement in Cardiac Amyloidosis: A Meta-Analysis. JACC Cardiovasc Imaging. 2020;13(6):1299-310. doi: 10.1016/j.jcmg.2020.03.010.
9. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017;70(4):466-77. doi: 10.1016/j.jacc.2017.05.053.
10. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019;12(9):e006075. doi: 10.1161/CIRCHEARTFAILURE.119.006075.
11. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling Transthyretin Cardiac Amyloidosis and its Predictors Among Elderly Patients with Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. Eur Heart J. 2017;38(38):2879-87. doi: 10.1093/eurheartj/ehx350.
12. Bohbot Y, Renard C, Manrique A, Levy F, Maréchaux S, Gerber BL, et al. Usefulness of Cardiac Magnetic Resonance Imaging in Aortic Stenosis. Circ Cardiovasc Imaging. 2020;13(5):e010356. doi: 10.1161/CIRCIMAGING.119.010356.

Viewpoint

Comprehensive Echocardiogram: What is it? For which Patients?

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Amyloidosis occurs due to the gradual deposition of protein aggregates, which may infiltrate more than one organ, progressively evolving to organ dysfunction. Prognosis is determined by the organ involved and by the involvement of the heart; cardiac amyloidosis (CA) leads to the worst evolution. CA may be due to myocardial deposition of the protein transthyretin, which is derived from liver tissue; this condition is known as ATTR. The other form of myocardial deposition is secondary to immunoglobulin light chain proteins, which are derived from a clone of plasma cells; this is known as the systemic form or AL amyloidosis.[1] The ATTR and AL forms need to be differentiated, because they have different treatments.

CA is a common cause of restrictive cardiomyopathy, and it should always be considered in the context of patients with heart failure with preserved ejection fraction (HFpEF). Symptoms encompass reduced effort threshold, fatigue, and edema of the lower limbs. It is common for the conduction system to be involved, and reduced voltage of the QRS complex on electrocardiogram (ECG) is one of the diagnostic clues. Evolution with arrhythmias and atrioventricular block is also characteristic.[2-4]

The gold standard for diagnosis of CA is myocardial biopsy. This procedure, however, in addition to being invasive, can be inaccurate if we remove a fragment of tissue that is not affected by the disease. With the evolution of imaging methods, we are currently moving towards a non-invasive diagnostic algorithm. The use of nuclear medicine with pyrophosphate scintigraphy, combined with hematological tests for light chain immunoglobulins, makes it possible not only to diagnose but also, in many cases, to differentiate between the ATTR and AL forms.[5] This algorithm is initiated following clinical suspicion, combining ECG with an imaging method, such as echocardiogram or magnetic resonance imaging.

And where does the importance of comprehensive echocardiogram come from? Due to the peculiar characteristics provided by each of the imaging methods in relation to the pathogenesis of CA, most patients will need more than one method for complete evaluation. Due to its wide availability and low cost, echocardiogram is usually the first diagnostic tool in patients with clinical suspicion of heart failure, and it should always be performed in the investigation of CA.[6] The initial alteration that should draw the attention of the echocardiographer is increased left ventricular (LV) wall thickness, usually above 12 mm. This finding, especially when it is associated with left atrial enlargement (or even biatrial enlargement) and preserved systolic function, raises the possibility of CA. Other associated findings that may be present include thickening of the atrioventricular valves and functional regurgitation (mitral and tricuspid valves without organic alterations). We may detect elevated pulmonary artery systolic pressure (a common finding in patients with HFpEF), and infiltration of the interatrial septum is also a very suggestive sign. The presence of pleural and/or pericardial effusion is very common. Although it is subjective in appearance, we can observe an image of granular infiltration of the ventricular walls (granular sparkling). The right ventricle may also be involved. These findings can be observed in Figure 1.

Nevertheless, typical alterations are more evident in the advanced stage of the disease, and they may go unnoticed at earlier stages, even when the patient is already in heart failure. Thus, a high degree of suspicion is necessary. It is through detailed study of diastole that we will be able to add information to our initial suspicion. As this is a muscular infiltration, reduced early diastolic filling velocities, detected by tissue Doppler (e' velocities in the septal and lateral mitral annulus), are very common. As the condition worsens, we will observe progressive diastolic dysfunction, with reduced atrial compliance and increased mean pressure of the left atrium. We will go from grade I diastolic dysfunction to a pseudonormal pattern and, subsequently, a restrictive pattern (e/a ratio > 2 on pulse Doppler and increased e/e' ratio), as exemplified in Figures 2 and 3.

CA is an example of a restrictive heart disease where LV ejection fraction may remain unchanged until the more advanced stages of the disease, but longitudinal contractile function is reduced in an early manner.[7] With examination of myocardial deformation, known as global strain, we have yet another tool that can be explored via echocardiogram. In particular, LV longitudinal global strain is significantly altered in CA, in an early manner, before the drop in ejection fraction.[8-10] Although it is a non-specific pattern, more than reduced global strain, the apical sparing pattern (colloquially known as "cherry on the cake," visualized as a bull's eye) is a characteristic that can be present in CA, as exemplified in Figure 4.

It is worth remembering other pathologies with which CA may be associated. A very common scenario, especially with greater population longevity, is the detection of aortic stenosis. LV hypertrophy secondary to valve restriction is very common, but valve stenosis is not always the only diagnosis. The association of these two pathologies, aortic stenosis and amyloidosis, has been described in

Keywords

Amyloidosis; Echocardiogram; Comprehensive.

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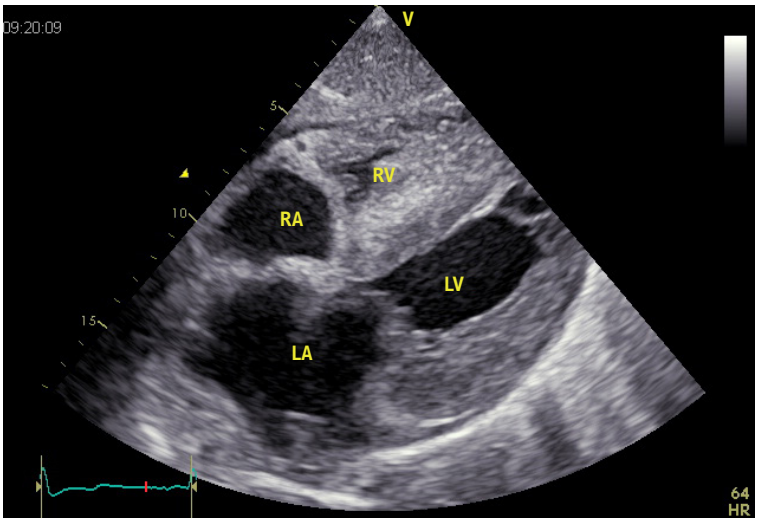

Figure 1 – *Subcostal window. Important thickening of the left ventricular and right ventricular walls, the interatrial septum, and the mitral and tricuspid valves. Granular aspect of the left ventricular walls (granular sparkling). LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle. Source: personal archive.*

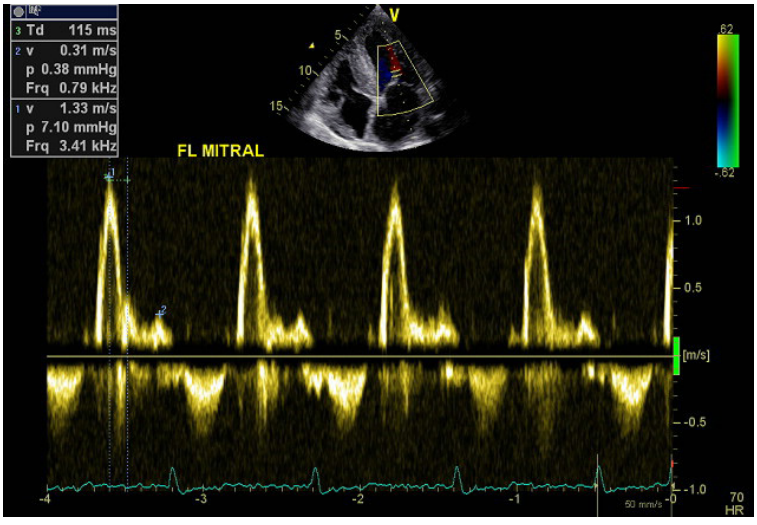

Figure 2 – *Mitral flow on pulse Doppler with e wave velocity = 1.33 m/s, low atrial contribution (a wave = 0.31 m/s), reduced acceleration time (115 ms), and e/a ratio = 4.29, denoting a restrictive pattern. Source: personal archive.*

up to 13% of patients referred to the hemodynamic laboratory for percutaneous implantation of aortic prostheses.[11] Low-gradient aortic stenosis may be a form of presentation, with LV ejection fraction > 50%, indexed systolic volume < 35 ml/m², peak systolic velocity < 4 m/s, and mean LV-Ao gradient < 40 mmHg.

Amyloid deposits may also coexist among hypertrophic cardiomyopathies or even hypertensive cardiomyopathies. In these cases, longitudinal global strain may be the only echocardiographic marker that is altered.[12] Only by conducting detailed examination, with the echocardiographer considering the possibility of amyloidosis, will we proceed with the appropriate diagnostic investigation.

In summary, CA is frequently underdiagnosed, and the echocardiographer's role is fundamental. More than

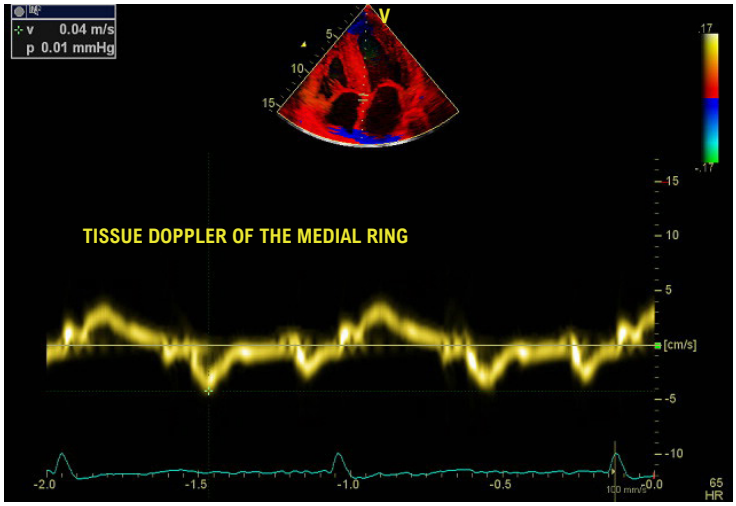

Figure 3 – *Important reduction in e' wave velocity of the septal mitral annulus (0.04 m/s); e/e' ratio = 33.2 (1.33 m/s divided by 0.04 m/s), denoting a large increase in the mean pressure of the left atrium.*
Source: personal archive.

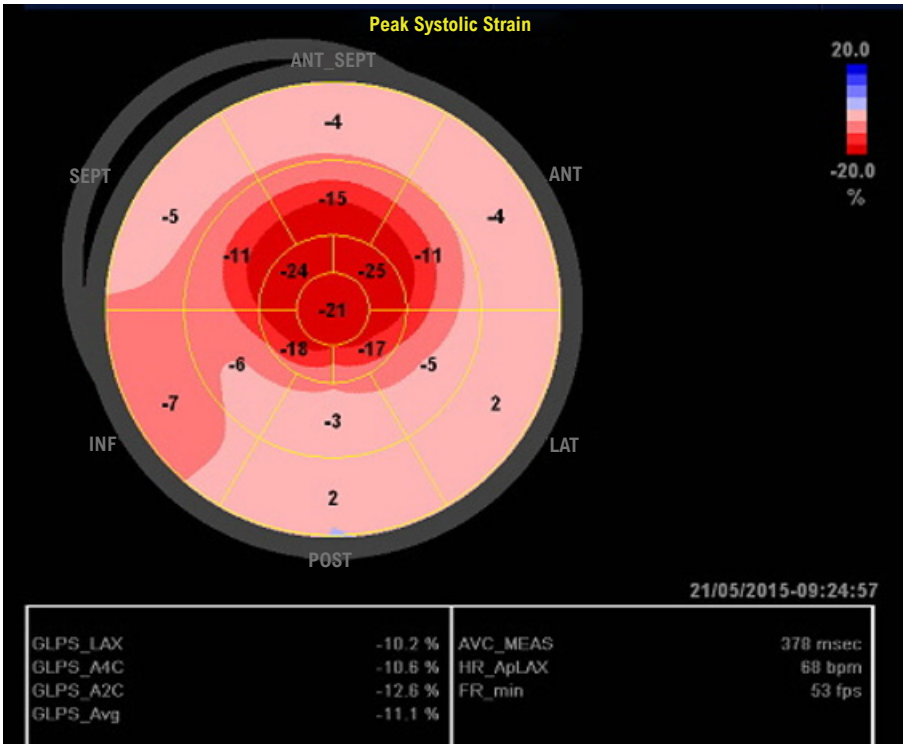

Figure 4 – *Important reduction in left ventricular global longitudinal strain (–11.1%), sparing the apical segments, which appear in red. Apical sparing, resembling a "cherry on the cake," is demonstrated by the bull's eye.*
Source: personal archive.

using the name "comprehensive" echocardiogram, it is necessary to establish an examination routine, using all the tools that are available today. Think of all the situations in our daily routine where we find ventricular thickness > 12 mm! They are countless! It is through a good echocardiogram, combined with good interaction with the clinician, that suspicion will be more sharpened. The diagnostic algorithm will only be implemented if we raise the hypothesis. There is no point in using the exams in an isolated manner, given that the diagnostic sequence is only valid when used correctly.

Author contributions

Writing of the manuscript: Garcia MI.

Potential Conflict of Interest

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Ethics approval and consent to participate

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References

1. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2-Evidence Base and Standardized Methods of Imaging. J Nucl Cardiol. 2019;26(6):2065-123. doi: 10.1007/s12350-019-01760-6.
2. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and Treatment of Cardiac Amyloidosis. Nat Rev Cardiol. 2015;12(2):91-102. doi: 10.1038/nrcardio.2014.165.
3. Grogan M, Dispenzieri A. Natural History and Therapy of AL Cardiac Amyloidosis. Heart Fail Rev. 2015;20(2):155-62. doi: 10.1007/s10741-014-9464-5.
4, Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, et al. Cardiac Amyloidosis: Updates in Diagnosis and Management. Arch Cardiovasc Dis. 2013;106(10):528-40. doi: 10.1016/j.acvd.2013.06.051.
5. 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. European Heart Journal. 2021;42(16):1554-68. doi: 10.1093/eurheartj/ehab072.
6. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis - 2021. Arq Bras Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
7. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019;32(1):1-64. doi: 10.1016/j.echo.2018.06.004.
8. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a Common Standard for 2D Speckle Tracking Echocardiography: Consensus Document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. J Am Soc Echocardiogr. 2015;28(2):183-93. doi: 10.1016/j.echo.2014.11.003.
9. Collier P, Phelan D, Klein A. A Test in Context: Myocardial Strain Measured by Speckle-Tracking Echocardiography. J Am Coll Cardiol. 2017;69(8):1043-56. doi: 10.1016/j.jacc.2016.12.012.
10. Pagourelias ED, Vassilikos VP, Voigt JU. Left Ventricular Pressure Strain-Derived Myocardial Work at Rest and during Exercise in Patients with Cardiac Amyloidosis. J Am Soc Echocardiogr. 2020;33(10):1295-6. doi: 10.1016/j.echo.2020.06.001.
11. Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, et al. Prevalence and Outcome of Dual Aortic Stenosis and Cardiac Amyloid Pathology in Patients Referred for Transcatheter Aortic Valve Implantation. Eur Heart J. 2020;41(29):2759-67. doi: 10.1093/eurheartj/ehaa170.
12. Sattar Y, Maya TR, Zafrullah F, Patel NB, Latchana S. Diagnosis and Management of a Cardiac Amyloidosis Case Mimicking Hypertrophic Cardiomyopathy. Cureus. 2018;10(12):e3749. doi: 10.7759/cureus.3749.

What is the Importance of Clinical Clues, and How can we Avoid Mistakes in Following Them?

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Approximately half of patients with heart failure (HF) have preserved ejection fraction (EF),[1] and approximately half of these patients have increased left ventricular (LV) wall thickness[2]. This increase in LV wall thickness is usually attributed to left ventricular hypertrophy induced by arterial hypertension (AH). However, cardiac amyloid fibril infiltration also increases ventricular wall thickness, and it can lead to a clinical syndrome of HF with preserved EF (HFpEF).[3]

Light chain amyloidosis (AL) cardiomyopathy occurs in patients with AL or primary amyloidosis, which is a hematologic disease with specific hematologic treatment. Both hereditary transthyretin (hATTR) and wild-type (ATTRwt) amyloidosis can cause transthyretin amyloid cardiomyopathy (ATTR-CM).[3]

The identification of ATTR-CM, among the broad spectrum of the population with HFpEF, is particularly important, because there is currently a specific, effective treatment for these clinical forms of HFpEF.[4] These findings and clinical observations are extremely important, and they alert us that we are possibly facing a patient with cardiac amyloidosis.

What is the prevalence of ATTR-CM in the population with HFpEF with a thickened ventricular wall?

In a recently published prospective cohort study[5] involving 1235 consecutive patients with validated diagnosis of HF and increased risk of ATTR-CM due to age, HFpEF, and increased LV thickness, the prevalence by clinical recognition was only 1.3%, but it was approximately six times higher (6.3%) in the sample of 286 patients who had signed informed consent for additional tests for systematic screening of ATTR-CM. This evaluation consisted of technetium 99m pyrophosphate scintigraphy and appropriate laboratory exams for ruling out AL amyloidosis.

Several clinical parameters help us consider amyloidosis; Table 1 systematizes the usual clinical clues.[6]

The prevalence is usually higher in men (80%), and it increases with age. History of carpal tunnel syndrome (37%) and spinal stenosis (31%) are common.[5] These extra-cardiac alterations may precede the development of cardiac amyloidosis by many years. The recognition of these signs as part of the clinical picture of amyloidosis is essential, and it may lead to earlier diagnosis and prevent the progression of heart disease through the implementation of specific treatment.

In cases where peripheral neuropathy affects the most distal segments of the limbs, especially the lower limbs, and progresses to involve the proximal and upper limbs, this is a clinical clue that should lead us to consider amyloidosis.[6]

Eelectrocardiogram is usually the first exam that is requested for evaluation of a possible heart disease. In AL cardiac amyloidosis, low voltage of the QRS complex calls our attention, especially if we have already conducted an echocardiogram showing significant left ventricular hypertrophy. In the ATTR form, this finding is less common, occurring in approximately 30% of cases. Therefore, this discrepancy between the magnitude of hypertrophy on the echocardiogram and the QRS amplitude on the electrocardiogram is a clinical clue that should be emphasized in considering diagnosis of cardiac amyloidosis. The rhythm of atrial fibrillation is frequent, due to the large atrial volumes caused by the elevated LV end-diastolic pressure (restrictive cardiomyopathy).[7]

Echocardiography is one of the most important tests to raise suspicion of cardiac amyloidosis. We should consider the hypothesis of amyloidosis when we find LV wall thickening (greater than 12 mm) in the absence of AH, in elderly patients (> 65 years), and in patients with biatrial enlargement that is disproportionate to the size of the ventricles. Also noteworthy is the thickening of the atrioventricular valves and the interatrial septum, as well as increased echogenicity of the myocardium with a granular appearance, which are alterations that are due to the deposition of amyloid filaments in these structures[7] (Table 2 and Figure 1).

It is in these "combined clues" that our greatest likelihood of diagnosing cardiac amyloidosis lies. When we are faced with an elderly patient, with clinical picture of HF, non-dilated LV, preserved EF, and thickened LV walls, without AH, this hypothesis is imposed. Another interesting clue that needs to be taken into account is when the patient presents with a diagnosis of late-onset hypertrophic cardiomyopathy, after 60 years of age. This is unusual, and it should lead us to remember cardiac amyloidosis.[7]

Another clinical situation is that of a patient with aortic stenosis, with thickening of the right ventricular walls, particularly in paradoxical cases with low flow and low gradient.

Therefore, when faced with diagnosis of HFpEF, with symptoms of dysfunction in another organ (peripheral sensorimotor neuropathy, gastrointestinal and central nervous system manifestations, carpal tunnel syndrome,

Keywords

Heart Failure; Amyloidosis; Restrictive Cardiomyopathy.

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Table 1 – Clues related to history and physical examination

HFpEF, especially in elderly men (> 65 years)
Intolerance to ACEI/ARB/ARNI/BB
Bilateral carpal tunnel syndrome
Biceps tendon rupture
Peripheral polyneuropathy and/or autonomic dysfunction
Periorbital ecchymosis
Macroglossia

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BB: betablockers; HFpEF: heart failure with preserved ejection fraction.

Table 2 – Clues related to routine imaging exams

Concentric thickening of the LV walls with reduced QRS amplitude
Echocardiogram showing hypertrophy of the septum and LVPW, biventricular hypertrophy, valve thickening, pericardial effusion, or interatrial septal thickening; myocardial hyperrefringence
Reduced longitudinal strain that spares the apical region (apical sparing)
Restrictive pattern of LV filling with thickening of the RV walls
Delayed enhancement on CMR with diffuse subendocardial or transmural pattern or increased extracellular volume

CMR: cardiac magnetic resonance; LV: left ventricle; LVPW: left ventricular posterior wall; QRS: QRS complex on electrocardiogram; RV: right ventricle.

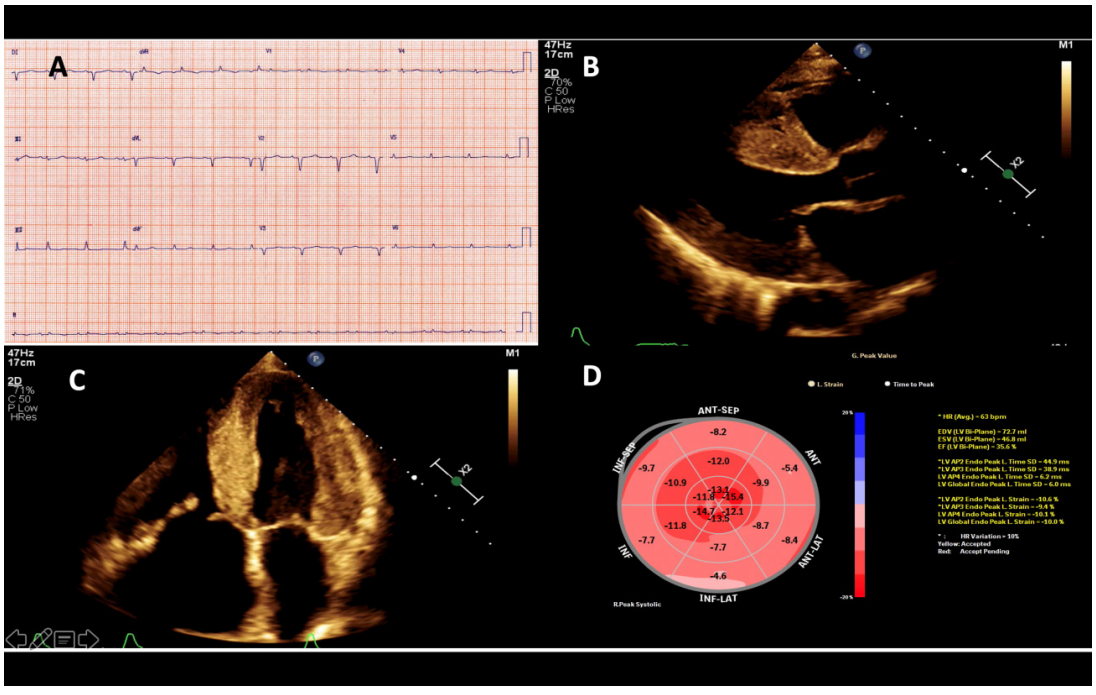

Figure 1 – *Illustrative image shows electrocardiogram (A) with low QRS voltage. Transthoracic echocardiogram demonstrates, through the parasternal long axis (B) and apical 4-chamber (C) views, increased myocardial thickness with a shiny, granular appearance, thickening of the atrioventricular valve cusps, and significant dilation of both atria. In the parametric representation of longitudinal systolic strain (D), it is possible to observe reduced global longitudinal strain with a characteristic apical sparing pattern (images from the authors' personal archives).*

Table 3 – Combined clues

HF with non-dilated LV and septum > 12 mm, in patients without AH
Clinical presentation of late-onset HCM (> 60 years)
AoS with thickening of the RV walls, especially in paradoxical cases with low flow and low gradient

AH: arterial hypertension; AoS: aortic stenosis; HCM: hypertrophic cardiomyopathy; HF: heart failure; LV: left ventricle; RV: right ventricle.

and autonomic neuropathy, mainly) in a patient over 65 years of age, who is also unresponsive to the usual treatment for HF, we must consider the possibility of cardiac amyloidosis.[8]

The implementation of this systematic evaluation can increase the diagnosis of ATTR-CM and make appropriate treatment possible for this HFpEF phenotype.

Author contributions

Conception and design of the research: Rassi S, Rassi DC, Freitas AF. Acquisition of data: Rassi S, Rassi DC, Freitas AF. Analysis and interpretation of the data: Rassi S, Rassi DC, Freitas AF. Statistical analysis:Rassi S. Writing of the manuscript:Rassi S, Rassi DC, Freitas AF. Critical revision of the manuscript for intellectual content:Rassi S.

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References

1. Redfield MM. Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2017;376(9):897. doi: 10.1056/NEJMc1615918.
2. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, et al. Comorbidity and Ventricular and Vascular Structure and Function in Heart Failure with Preserved Ejection Fraction: A Community-Based Study. Circ Heart Fail. 2012;5(6):710-9. doi: 10.1161/CIRCHEARTFAILURE.112.968594.
3. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-91. doi: 10.1016/j.jacc.2019.04.003.
4. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.
5. AbouEzzeddine OF, Davies DR, Scott CG, Fayyaz AU, Askew JW, McKie PM, et al. Prevalence of Transthyretin Amyloid Cardiomyopathy in Heart Failure with Preserved Ejection Fraction. JAMA Cardiol. 2021:e213070. doi: 10.1001/jamacardio.2021.3070.
6. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
7. Simões MV, Alves SMM, Fernandes F, Coelho Filho OR, Mangini S. Emerging Topics in Heart Failure: New Paradigms in Cardiac Amyloidosis. Arq Bras Cardiol. 2020;115(5):945-8. doi: 10.36660/abc.20201126.
8. Gertz MA. Hereditary ATTR Amyloidosis: Burden of Illness and Diagnostic Challenges. Am J Manag Care. 2017;23(7):107-12.

Cardiac Scintigraphy with Bone Markers in Clinical Practice: When to Solicit the Exam? How to Interpret the Results?

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One of the greatest and most recent advances in clinical management of cardiac amyloidosis (CA), which has completely reshaped clinical practice, took place in the field of diagnosis, based on the possibility of using molecular scintigraphy images for non-invasive detection of amyloid deposits in the myocardium, making endomyocardial biopsy unnecessary to conclude diagnosis.[1]

There are some fundamental aspects that clinicians need to know in order to apply this powerful tool in their practice, choosing wisely the best time to request it and how to interpret the results.

Preliminarily, it is important for us to review the main studies that have offered signposts for the application of scintigraphy with bone markers for diagnosis of CA.

In one of the first studies to demonstrate this application, Wizenberg et al. evaluated 10 consecutive patients with biopsy-confirmed CA, having observed that all patients exhibited intense and diffuse anomalous myocardial uptake on cardiac scintigraphy with ^{99m}Tc-pyrophosphate.[2] However, later studies showed variable yield of these images in patients with different forms of CA, underscoring CA associated with immunoglobulin light chains (AL-CA), in addition to transthyretin-associated CA (ATTR-CA). The mechanisms by which bone radiotracers are accumulated in tissue deposits of amyloid protein probably involve the presence of microcalcifications in these protein aggregates, as these radiotracers are highly avid for calcium deposits. It is this aspect that also makes it possible for us to detect accumulation of these radiotracers in the hearts of patients with ischemic heart disease with recent acute myocardial infarction, and this was, historically, the first clinical application of this type of image.

The progress of knowledge with respect to the clinical applicability of cardiac scintigraphy images with bone radiotracers for diagnosis of CA occurred with the seminal study by Enrica Perugini et al., who investigated 10 patients with ATTR-CA and 15 patients with AL-CA, in addition to 10 control patients who were not affected by CA.[3] In this study, by means of visual analysis of planar chest images, complemented by analysis of SPECT images, all patients with ATTR-CA exhibited intense anomalous radiotracer uptake in the myocardium at a comparative intensity equivalent to (grade 2) or higher than (grade 3) that seen in the costal arches. In contrast, all patients with AL-CA and all controls exhibited absence of cardiac uptake (grade 0). Thus, visual analysis of Perugini cardiac uptake grade was shown to be useful for differentiating between the main forms of CA (ATTR and AL), suggesting that positive myocardial uptake could indicate the presence of ATTR-CA.

Nevertheless, it was later identified that a significant proportion, approximately 20%, of patients with AL-CA could also exhibit grade 2 or 3 of cardiac uptake of bone markers, making it essential to rule out the presence of immunoglobulin light chains in order to confirm diagnosis of ATTR-CA in patients with positive cardiac scintigraphy using bone markers.[4]

In another fundamental study, Gillmore et al. tested the diagnostic application of scintigraphy with bone markers, compared to the result of endomyocardial biopsy, in an expressive sample of 374 patients, seeking to identify those with ATTR-CA.[5] The general results showed a high sensitivity for scintigraphy, above 99%, but a reduced specificity of 86%, for diagnosis of ATTR-CA. The false positives observed in this study were almost entirely due to the presence of uptake in patients with AL-CA. Thus, analysis of the results based on the double criteria (scintigraphy with grade 2 or 3 uptake, in addition to the absence of light chains), obtained 100% specificity and predictive value, thus defining the non-invasive criteria for diagnosis of ATTR-CA, which have gone on to become a standard of conduct worldwide (Figure 1).[5] Sensitivity for diagnosing ATTR-CA, according to these criteria, was 70%.[5]

When to solicit cardiac scintigraphy with bone markers?

In view of the aspects mentioned above, it is important for investigation of the specific form of ATTR-CA, using bone marker scintigraphy, to begin after 2 key preliminary steps: 1. establishing high clinical suspicion of the presence of CA and 2. ruling out the presence of immunoglobulin light chains, which would lead us to diagnosis of AL-CA.

It is fundamental to establish high clinical suspicion, given that negative scintigraphy does not rule out the presence of CA in its various forms, particularly the AL form. In other words, in a significant percentage of cases with high clinical suspicion and negative scintigraphy, investigation should continue with tissue biopsy, including endomyocardial biopsy, in order to conclude diagnosis. It is clear that endomyocardial biopsy should only be performed in cases of high clinical suspicion, as it is an invasive method with risks that, although low, are inherent to the procedure.

On the other hand, it is fundamental to rule out the presence of light chains previously, so that a positive scintigraphy result is not taken as evidence of ATTR-CA. This

Keywords

Amyloidosis; Scintigraphy; Diagnostic Methods.

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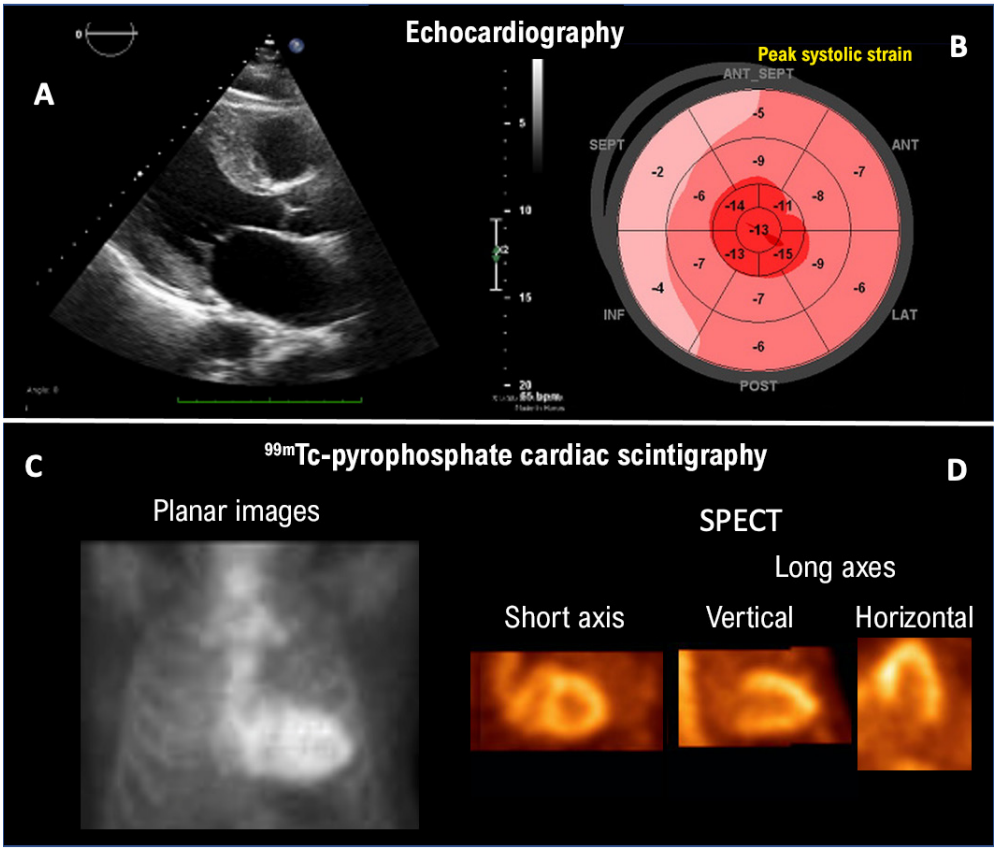

Figure 1 – *Illustrative images of a 73-year-old male patient with symptoms of heart failure with preserved ejection fraction, showing changes compatible with ATTR-CA, after laboratory tests showing absence of immunoglobulin light chains: (A) structural alterations on echocardiogram and increased left ventricular wall thickness (interventricular septum = 14 mm); (B) images of global longitudinal strain on a polar map showing the sign of apical sparing; (C) planar 99mTc-pyrophosphate cardiac scintigraphy images, showing intense radiotracer uptake over the heart (Perugini grade 3, greater than that of the costal arches), which were confirmed in the myocardial walls of the left and right ventricles on SPECT images. (D) Genetic analysis was negative for transthyretin gene mutations, characterizing diagnosis of wild type ATTR-CA.*

misdiagnosis could delay or exclude patients with AL-CA from chemotherapy/bone marrow transplantation, which could save the patient's life. On the other hand, it is worth remembering that AL-CA has very poor prognosis, with a median survival of 6 to 8 months in cases with heart failure and late diagnosis, which highlights the urgent need to rule out this diagnosis during the initial moments of investigation of suspected cases of CA.

The hypothesis that scintigraphy with bone markers could be used as a screening tool in elderly men with heart failure with preserved ejection fraction who exhibit the warning signs for CA has been tested in several clinical studies, but the value of this strategy has yet to be defined.[6]

How to interpret the results?

When interpreting cardiac scintigraphy images with bone markers in patients with suspected ATTR-CA, it is important that we keep 2 essential aspects in mind:

1. Positive images for ATTR-CA should have triple confirmation: 1. Perugini grade 2 or 3 cardiac uptake, 2. heart to contralateral ratio > 1.5 on imaging 1 hour after radiotracer injection, and 3. confirmation of radiopharmaceutical concentration in the ventricular myocardium in the SPECT images, as illustrated in Figure 1.

2. There are common conditions in clinical practice that lead to false positive cases for ATTR-CA, including acute myocardial infarction, AL-CA, and uptake restricted to the blood pool in planar images, which can be misinterpreted as a positive exam.

The most frequent cause of diagnostic error, with "false positive" scintigraphy exam for ATTR-CA, is AL-CA. In fact, these cases are "scintigraphically positive," but they should be interpreted in light of the knowledge that 20% to 30% of patients with AL-CA may have grade 2 or 3 positive scintigraphy. In this manner, preliminary exclusion of the presence of light chains is fundamental in order to avoid this "false positive."

Another false positive, which results from the interpretation of planar scintigraphy images, without confirmation from SPECT images, is increased uptake in the cardiac area in planar images associated with radioactivity present in the blood pool, not located in the myocardium.[1] If we consider that the application of this imaging method for this purpose is still recent in Brazil, a careful review of positive tests performed by the nuclear physician together with the requesting clinician is desirable, in order to safely rule out this type of false positive test, not losing sight of the fundamental importance of these exam results to non-invasive diagnosis of ATTR-CA.

It is worth remembering here that ischemic heart disease, corresponding to cases with more severe myocardial ischemia, acute myocardial infarction, or recurrent ischemia at rest, may exhibit significant accumulation of the bone radiotracer. It is, therefore, essential to rule out severe coronary artery disease in patients with risk factors, ischemic changes on electrocardiogram, or angina pectoris, as an essential initial diagnostic step in these cases.

Finally, it is necessary to remember that there are false negatives of bone marker scintigraphy in patients with confirmed ATTR-CA. This can occur in patients with hereditary ATTR with mutations that are known not to capture bone markers, such as early-onset V50M and P64L. Accordingly, cases with high clinical suspicion of CA in which the presence of light chains has been ruled out and which exhibit negative bone marker scintigraphy, may proceed to endomyocardial biopsy to confirm/reject diagnosis of the disease.

Author contributions

Conception and design of the research: Simões MV. Acquisition of data: Simões MV. Analysis and interpretation of the data: Simões MV. Statistical analysis: Simões MV. Obtaining financing: Simões MV. Writing of the manuscript: Simões MV. Critical revision of the manuscript for intellectual content: Simões MV. Supervision / as the major investigador: Simões MV.

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References

1. Hanna M, Ruberg FL, Maurer MS, Dispenzieri A, Dorbala S, Falk RH, et al. Cardiac Scintigraphy with Technetium-99m-Labeled Bone-Seeking Tracers for Suspected Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2020;75(22):2851-62. doi: 10.1016/j.jacc.2020.04.022.
2. Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM. Value of Positive Myocardial Technetium-99m-Pyrophosphate Scintigraphy in the Noninvasive Diagnosis of Cardiac Amyloidosis. Am Heart J. 1982;103(4):468-73. doi: 10.1016/0002-8703(82)90331-3.
3. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using 99mTc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy. J Am Coll Cardiol. 2005;46(6):1076-84. doi: 10.1016/j.jacc.2005.05.073.
4. Quarta CC, Zheng J, Hutt D, Grigore SF, Manwani R, Sachchithanantham S, et al. 99mTc-DPD Scintigraphy in Immunoglobulin Light Chain (AL) Cardiac Amyloidosis. Eur Heart J Cardiovasc Imaging. 2021:jeab095. doi: 10.1093/ehjci/jeab095.
5. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12. doi: 10.1161/CIRCULATIONAHA.116.021612.
6. González-López E, Gallego-Delgado M, Guzzo-Merello G, Haro-Del Moral FJ, Cobo-Marcos M, Robles C, et al. Wild-Type Transthyretin Amyloidosis as a Cause of Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2015;36(38):2585-94. doi: 10.1093/eurheartj/ehv338.

Genetic Testing in Amyloidosis: For Whom?

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Over the past years, the recognition of cardiac involvement due to deposition of amyloid substances has received greater emphasis. Cardiac amyloidosis (CA), as it is known, has been shown to be a more prevalent cause of heart failure with preserved ejection fraction than in previous decades, although diagnosis remains a constant challenge.

With advances in pathophysiological knowledge of this disease, as well as relevant advances in diagnostic methods, particularly in the field of cardiovascular imaging, there has been a significant contribution to earlier identification of CA, as well as a consistent change in the natural course of the disease, given that we are witnessing the emergence of therapies that are capable of prolonging these patients' survival.

As part of this diagnostic evolution, we have also witnessed an expressive increase in knowledge in the genetic field, which has become a powerful tool in the clinical arsenal for diagnosis of CA. To better understand the role of genetic testing in CA, it is worth detailing the main forms of cardiac alterations in amyloidosis.

Among the forms of amyloidosis that may affect the heart, the following 5 different types of amyloidogenic proteins stand out: heavy and light immunoglobulin chains, transthyretin (TTR), amyloid A, and apo A1. Two of these are responsible for about 95% of cases of AC: immunoglobulin light chain deposits (AL form) and transthyretin (ATTR form).[1-3]

In the AL form, amyloid light chain proteins originate from plasma cells or from anomalous B lymphocytes, configuring a clonal or neoplastic hematological disease.[4]

Another typical presentation of AC occurs through accumulation and deposition of an amyloid protein called TTR. TTR is a protein composed of four monomers, which circulate as a tetramer[5] and which, under physiological conditions, function as a transporter of thyroxine (T4) and retinol (vitamin E). The limiting step in the rate of amyloid fibril formation by TTR is the dissociation of the tetramer into monomers, which possibly involves proteolysis. Subsequently, the partial denaturation of the monomer can lead to incorrect assembly of this protein in various aggregate structures.[6]

Keywords

Amyloidosis; Genetic Testing; Prealbumin.

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When this inappropriate assembly is caused by a mutation in the TTR gene, changing the amino acid sequence, it is known as variant or hereditary TTR amyloidosis (ATTRv). This mutation has an autosomal dominant character; its gene is located on chromosome 18, and several types of mutations have been described.[7]

Furthermore, there also exists an acquired form of TTR accumulation, known as the wild type, where the amino acid sequence is normal. The process through which this wild protein becomes unstable and aggregates into amyloid fibrils, causing wild-type TTR amyloidosis (ATTRwt) is not entirely clear.[7]

It is precisely in this scenario of differentiating between ATTRv (the hereditary form) and ATTRwt (the acquired form) that diagnostic genetic testing becomes strongest and is most highly indicated. In accordance with the "Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis"[6] of the Brazilian Society of Cardiology, it has been given a class I recommendation with level of evidence B, based on the findings of the Spanish study that estimated the prevalence of allelic variants in the TTR gene through analysis of large-scale sequencing data.[8]

Among genetic aspects, another important point that has been increasingly underscored is the screening of pre-symptomatic patients. This category includes relatives of people who are known to be affected by the inherited form of ATTRv.

Unlike genetic diagnostic testing, screening of pre-symptomatic patients should only be conducted if patient expressly state that this is their will and if they are considered psychologically prepared. For this purpose, the test must be conducted by trained professionals, and there must be a psychological support team. In addition to the mandatory inclusion of a pre-diagnostic preparation phase, in this scenario, genetic testing must also provide a post-result support phase.[9]

Given that all forms of hereditary amyloidosis begin in adulthood, genetic testing of minors is discouraged. Genetic testing may be offered during young adulthood if the genetic information would be useful to guiding career choices or reproductive planning. As age at onset, penetrance, and disease progression depend on the genetic variant, assessment of penetrance in carriers of the allele is generally recommended starting 10 years before the age of disease onset in affected family members (or other individuals with the same mutation), or as soon as symptoms that are compatible with amyloidosis develop.[10]

In addition to the aforementioned recommendations, genetic testing allows us to infer some correlations between mutations and possible phenotypes of amyloidosis involvement. More than 140 different types of mutations have been identified, and not all of them are pathological.[11]

Although the genotypic and phenotypic correlation is not strict, it is possible to mention some pathogenic

mutations with greater tendency toward neurological (TTRv V30Met) and cardiac (TTRv V122I) involvement, as well as some that occur with both neuropathy and heart disease (Leu58Hist).[12]

We therefore conclude that genetic testing in amyloidosis has a precise recommendation for distinguishing the hereditary TTR form (ATTRv) from the acquired TTR form (ATTRwt), as well as in screening of pre-symptomatic patients (relatives of people who are known to be affected by ATTRv), provided that they express this wish.

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References

1. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. J Am Coll Cardiol. 2016;68(12):1323-41. doi: 10.1016/j.jacc.2016.06.053.
2. Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. Circulation. 2012;126(10):1286-300. doi: 10.1161/CIRCULATIONAHA.111.078915.
3. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and TREATMENT OF Cardiac Amyloidosis. Nat Rev Cardiol. 2015;12(2):91-102. doi: 10.1038/nrcardio.2014.165.
4. Mankad AK, Sesay I, Shah KB. Light-Chain Cardiac Amyloidosis. Curr Probl Cancer. 2017;41(2):144-56. doi: 10.1016/j.currproblcancer.2016.11.004.
5. Koike H, Katsuno M. Ultrastructure in Transthyretin Amyloidosis: From Pathophysiology to Therapeutic Insights. Biomedicines. 2019;7(1):11. doi: 10.3390/biomedicines7010011.
6. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
7. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-91. doi: 10.1016/j.jacc.2019.04.003.
8. Pueyo CL, Arregui MÁA, Gutierrez AG, Juana EB, Guillén SM. Estimating the Prevalence of Allelic Variants in the Transthyretin Gene by Analysing Large-Scale Sequencing Data. Eur J Hum Genet. 2019;27(5):783-91. doi: 10.1038/s41431-019-0337-1.
9. Obici L, Kuks JB, Buades J, Adams D, Suhr OB, Coelho T, et al. Recommendations for Presymptomatic Genetic Testing and Management of Individuals at Risk for Hereditary Transthyretin Amyloidosis. Curr Opin Neurol. 2016;29(Suppl 1):27-35. doi: 10.1097/WCO.0000000000000290.
10. Conceição I, Coelho T, Rapezzi C, Parman Y, Obici L, Galán L, et al. Assessment of Patients with Hereditary Transthyretin Amyloidosis - Understanding the Impact of Management and Disease Progression. Amyloid. 2019;26(3):103-11. doi: 10.1080/13506129.2019.1627312.
11. Park GY, Jamerlan A, Shim KH, An SSA. Diagnostic and Treatment Approaches Involving Transthyretin in Amyloidogenic Diseases. Int J Mol Sci. 2019;20(12):2982. doi: 10.3390/ijms20122982.
12. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019;12(9):e006075. doi: 10.1161/CIRCHEARTFAILURE.119.006075.

A Practical Approach to Differential Diagnosis of Cardiomyopathies with Infiltrative Phenotypes

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Introduction

Heart failure (HF) affects approximately 2% of the world population; heart failure with preserved ejection fraction (HFpEF) is responsible for approximately 50% of cases, and it has shown a progressive increase in prevalence with the aging of the population.[1]

HFpEF is associated with high morbidity and mortality, and it is responsible for frequent hospitalizations, especially in the most elderly population. It has a complex pathophysiology and a diversified group of risk factors and etiologies. To date, few therapies have been shown to be effective in reducing cardiovascular outcomes in HFpEF; however, for specific etiologies, the possibility of disease-modifying therapeutic strategies exists.[2-4]

Restrictive cardiomyopathies (RCM) represent a small yet significant portion of patients with HFpEF, and they are characterized by diastolic dysfunction secondary to myocardial infiltration or primary dysfunction due to ventricular hypertrophy. RCM can result from hereditary or acquired diseases or a combination of both. Depending on their etiology, RCM are classified as infiltrative, non-infiltrative, storage diseases, and endomyocardial, and they may vary by age group. Some are more prevalent in certain regions (Table 1).[5]

The most common phenotypic characteristic of infiltrative RCM is increased ventricular wall thickness; amyloidosis and storage diseases are the main etiologies, and situations of hypertrophy (hypertensive cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, and their phenocopies) are differential diagnoses (Figure 1). Due to the heterogeneous nature and variable phenotypic expression of RCM, diagnosis is a challenge; however, it plays a prognostic and therapeutic role. Early recognition remains a fundamental barrier to having an impact on survival in these cases.[5-7] The objective of this publication is to assist clinicians in reasoning by means of a practical approach to differential diagnosis of RCM with infiltrative phenotypes.

Pathophysiology

Ventricular walls evolve with increased stiffness and reduced relaxation, resulting in impaired filling and consequent increase in pressure while resting and, more intensely, during exertion; this severe diastolic dysfunction results in limited increases in end-diastolic volume of one or both ventricles. In addition, non-compliant ventricles inhibit rapid venous return, resulting in limited increases in stroke volume. Biatrial enlargement is characteristic; systolic function is generally preserved or slightly reduced, as is the size of the ventricular chambers, until advanced stages of the disease occur.[5,7]

RCM do not have a uniformly accepted diagnostic criterion; additionally, the classic pattern of restriction can be found in other diseases that affect the heart. In a simultaneous hemodynamic study of the ventricles, initial diastolic pressure declines and rises rapidly, with a tendency to equalize end-diastolic pressures of both ventricles. This restrictive physiology has been attributed to a reduction in ventricular compliance secondary to fibrosis or an infiltrative process in the subendocardium and/or myocardium. In RCM, right atrial pressure usually exceeds 15 mmHg, and there should be a difference of at least 5 mmHg between right atrial pressure and pulmonary capillary pressure, as well as between the end-diastolic pressures of the left and right ventricles, due to the unequal involvement and compliance of both ventricles, unlike what is found in constrictive pericarditis, where equalization of ventricular filling pressures occurs.[8]

Clinical characteristics

HF is a common initial manifestation, and intolerance to physical exertion is a common complaint. Arrhythmias and conduction disturbances are often found due to progressive biatrial enlargement. Physical examination may reveal findings of pulmonary congestion and, especially, systemic congestion, including jugular stasis, hepatomegaly, ascites, lower limb edema, and the presence of B3 and B4; Kussmaul's sign is usually absent. Mitral and tricuspid regurgitation may be present.[9] Thromboembolic complications, with or without concomitant atrial fibrillation, are not uncommon due to marked biatrial enlargement and low atrial contractility.[10] The clinical phenotype of HF due to systemic diseases that affect the heart is very similar; however, extracardiac manifestations are varied, and they increase diagnostic suspicion of specific etiologies, in addition to family history of heart disease (Table 2).

Diagnostic investigation (Figure 2)

Laboratory exams

Troponin and NT-proBNP may be elevated, and they have prognostic value. Renal function can be altered when there is renal infiltration or in patients with advanced HF. When amyloidosis is suspected, free light chain assay and serum and urinary immunofixation have high sensitivity for diagnosing light chain amyloidosis (AL).

Keywords

Amyloidosis; Heart Failure; Cardiomyopathy, Restrictive

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Table 1 – Classification of restrictive cardiomyopathies

Involvement of the myocardium	< 30 years	Age 30 to 65 years	> 65 years	Genetic
Non-infiltrative	Idiopathic	Idiopathic	Idiopathic	Acquired
	Scleroderma	Scleroderma		Acquired
		Elastic pseudoxanthoma		ABCC6
			Diabetic cardiomyopathy	Acquired
Infiltrative				
		ATTR Sarcoidosis		TTR gene variants*
			ATTR-WT**	Acquired
			AL amyloidosis	Acquired
	Sarcoidosis	Sarcoidosis		Acquired
Storage diseases				
	Hemochromatosis			HAMP, HFE, HFE2, HJV, PNPLA3, SLC40A1, TfR2
	Fabry disease			GLA
	Gaucher disease			GBA
	Hurler disease			IDUA
	Glycogen deposition***			Due to a specific type
		Iron overload	Iron overload	Acquired
Endomyocardial				
	Endomyocardial fibrosis			Acquired
	Eosinophilic syndrome	Eosinophilic syndrome	Eosinophilic syndrome	Acquired
		Carcinoid disease		Acquired
			Metastatic tumor	Acquired
			Radiation	Acquired
		Medication-related	Medication-related	Acquired

AL: light chain; ATTR: transthyretin amyloidosis; ATTR-WT: wild-type transthyretin amyloidosis
**V122I; I68L; L111M; T60A; S23N; P24S; W41L; V30M; V20I; APOA1*
**** PRKAG2 gene disease, Danon disease (LAMP2)*

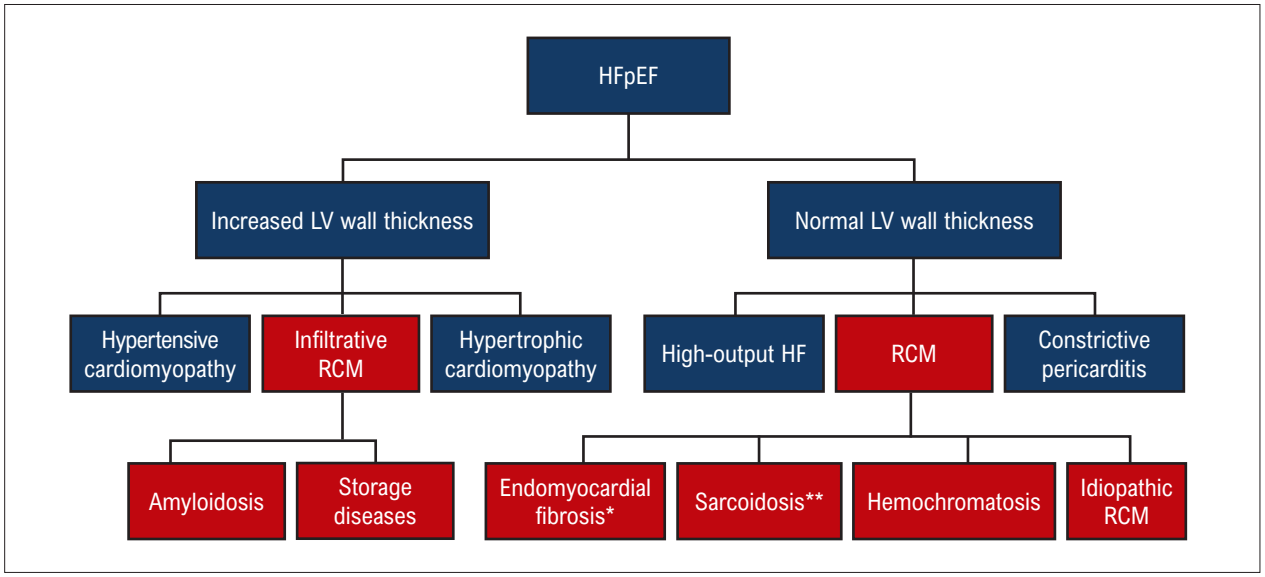

Figure 1 – *Differential diagnoses of heart failure with preserved ejection fraction. * Thickening of the left ventricular inferobasal wall and apical obliteration are frequent. ** Abnormal septal thickness (thickening or thinning). HF: heart failure; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle; RCM: restrictive cardiomyopathy. Adapted from Pereira, N.L. et al. J AM Coll Cardiol. 2018; 71 (10)1130-48.*

Table 2 – Specific characteristics and treatment of restrictive cardiomyopathies

Etiology	Clinical history	Extracardiac manifestations	ECG	Echo	NMR	Other methods	Treatment
Infiltrative restrictive cardiomyopathies							
Cardiac amyloidosis More than 30 proteins can lead to amyloidosis, 5 of which can lead to cardiac involvement; 95% are related to AL and TTR (mutation or WT)	Symptoms of HF Positive family history In TTR due to mutation, autosomal dominant inheritance	TTR: bilateral carpal tunnel syndrome, dysautonomia, Gastrointestinal tract alteration, peripheral neuropathy, sexual dysfunction WT: bilateral carpal tunnel syndrome AL: macroglossia, periorbital erythema	Normal to QRS complexes with low voltage, Anteroseptal/inferior pseudoinfarction	Hyperrefringence, biatrial enlargement, symmetric hypertrophy, preserved EF, apical sparing strain pattern	Diffuse or focal late enhancement may be subendocardial or transmural Increased ECV	AL: free light chain assay, serum and urinary immunofixation, if positive bone marrow and tissue biopsy (abdominal fat, endomyocardial) TTR: pyrophosphate scintigraphy in ATTR: presence of grade 2 or 3 or heart/contralateral ratio > 1.5 TTR: genetic testing Endomyocardial biopsy: Congo red and mass spectrometry	AL: chemotherapy, bone marrow transplant, consider heart transplant TTR: acting on RNA, blocking protein synthesis (patisiran and inotersen), stabilization of monomers (tafamidis, diflusisal, and AG10) and acting to remove already formed fibrils (doxycycline). Consider double transplantation (liver-heart) in TTR due to mutation and cardiac transplant in WT
Fabry disease X-linked recessive inheritance Alpha-galactosidase A deficiency, globotriaosylceramide accumulation	Symptoms of HF Positive family history	Neuropathic pain, heat intolerance, presence of angiokeratoma in the skin and/or mucous membranes, kidney injury, cornea verticillata, central nervous system injury	QRS with normal or extended amplitude, altered PR interval.	Symmetrical hypertrophy of the LV and RV wall, normal EF	Focal involvement, middle wall, inferolateral wall, normal or reduced ECV	Enzyme testing Genetic testing	Enzyme replacement therapy to control symptoms
Danon disease Dominant X-linked inheritance, caused by mutation of lysosomal-linked membrane protein 2 (LAMP2)	Symptoms of HF, ventricular arrhythmias	Skeletal myopathy, cognitive deficit	QRS with increased amplitude; short PR with delta wave	Major LV hypertrophy with possible outflow tract obstruction	Subendocardial late enhancement sparing the septum; normal or reduced ECV	Genetic testing	No specific treatment
Restrictive cardiomyopathies							
Sarcoidosis	Symptoms of HF, presyncope, syncope, arrhythmias, sudden death	Most frequently presents pulmonary involvement. It may present hepatic, spleen, ocular, lymphatic, cutaneous, nervous system, and renal involvement.	Arrhythmias, AVB, nonspecific repolarization changes	Thinning of the basal region of the interventricular septum, septal hypertrophy and aneurysms	Multi-focal myocardial involvement, sparing the edge of the endocardium; "mid-ventricular and subepicardial."	PET/CT with 18F FDG for detection of the inflammatory process. Endomyocardial biopsy	Immunosuppression with a corticosteroid. In refractory cases, methotrexate, azathioprine, and myocofenalate mofetil Implantable defibrillator

Continuation

Hemochromatosis	Symptoms of HF Positive family history	Weakness, arthralgia, skin hyperpigmentation, diabetes, liver cirrhosis, hypogonadism, hypothyroidism	Supraventricular arrhythmia	Presents restrictive diastolic dysfunction that progresses to dilation and systolic dysfunction	T2*	Ferritin assay, transthyretin saturation Genetic testing	Therapeutic phlebotomy iron chelators
Endomiocardial fibrosis	Symptoms of HF, massive ascites disproportionate to lower limb edema, giant V wave		Arrhythmias (AF, AVB), low voltage QRS complexes	Normal EF. Thickening of the LV inferobasal wall, apical obliteration, and thrombi adherent to the endocardial surface. Pericardial effusion. Mitral and tricuspid regurgitation.	Late enhancement identified as a hyperintense linear image representing endocardial fibrosis or the double V sign	Angiography can be seen with left and right ventriculography show chamber distortion due to fibrosis and apical obliteration. Endomyocardial biopsy	Consider myocardial resection surgery with ventricular reconstruction and valve replacement

AF: atrial fibrillation; AL: light chain; AVB: atrioventricular block; ECG: electrocardiogram; echo: echocardiography; EF: ejection fraction; HF: heart failure; LV: left ventricle; NMR: nuclear magnetic resonance; RV: right ventricle; TTR: transthyretin

Electrocardiogram

Electrocardiogram (ECG) is very important to initiate diagnostic reasoning. Infiltrative disorders generate abnormal accumulations of substances in myocytes or in the interstitium of the myocardium, which are responsible for increased wall thickness; therefore, the voltage of the QRS complex may be reduced or incompatible with the degree of thickening in the presence of infiltration between myocardial fibers (a common finding in amyloidosis); on the other hand, when myocardial fibers are involved, we can observe an increase in QRS amplitude on ECG (Fabry disease, for example), with differential diagnoses of diseases related to increased afterload (arterial hypertension and aortic stenosis) and hypertrophic cardiomyopathy.[11] Although low voltage favors clinical reasoning of cardiac amyloidosis, it is present in only 20% of patients with the TTR form (transthyretin) and is more frequent in the AL form (50% of cases). The most common finding related to cardiac amyloidosis is the mismatch between increased ventricular thickness on echocardiogram and the amplitude of the QRS complex; another common finding is the presence of electrically inactive areas in the absence of obstructive coronary artery disease (pseudoinfarction).[7,12] In Fabry disease, ECG abnormalities may include short PR interval, right bundle branch block, left ventricular hypertrophy, and giant negative T waves.[13]

In infiltrative RCM, sinus rhythm with biatrial overload may be observed. Atrial fibrillation, however, is not uncommon. Bundle branch blocks and atrioventricular blocks can also be a presentation of infiltrative diseases. Ventricular arrhythmias are also common.[7]

Echocardiography

Transthoracic echocardiography typically demonstrates normal ejection fraction, normal chamber volumes with biatrial enlargement, and restrictive diastolic filling parameters. Infiltrative RCM progresses with concentric increase in left ventricular wall and septum thickness; in amyloidosis, we may observe thickening of the right ventricle and interatrial septum. Assessment of left ventricular thickening on transthoracic echocardiography, especially when correlated with ECG, contributes to differential diagnoses in HFpEF (Figure 1). Diastolic compliance is abnormal, and it shows increased early diastolic filling velocity (E wave), reflecting elevated left atrial pressure, decreased atrial filling velocity (A wave) due to high ventricular diastolic pressures (E/A > 1.5), shortening of mitral deceleration time (< 120 ms), and decreased isovolumetric relaxation time. Tissue Doppler imaging reveals reduced initial diastolic longitudinal axis or mitral annular velocities (e') and increased E/e' ratio (> 15).

An aspect of myocardial hyperrefringence is often characteristic of amyloid infiltrate. Using the speckle tracking technique, the longitudinal strain pattern can help differentiate between cardiac amyloidosis and hypertrophic cardiomyopathy due to the characteristic of restricted basal movement compared to apical movement in amyloidosis (apical sparing).[14-16]

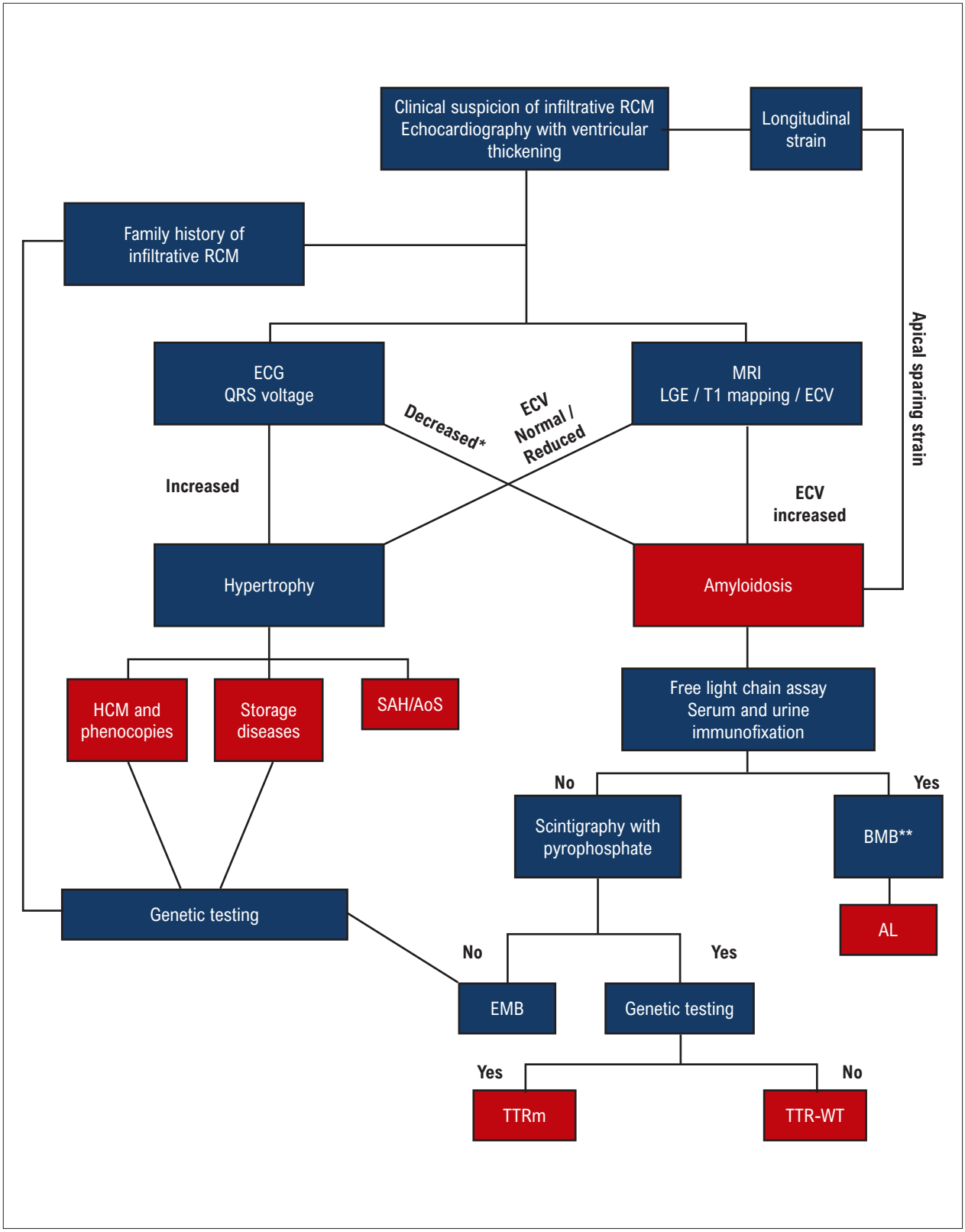

Figure 2 – *Flowchart for investigation of restrictive cardiomyopathies with infiltrative phenotypes. * Reduced or normal QRS complex with mismatch between left ventricular wall thickness on echocardiography and QRS complex on electrocardiogram. ** Bone marrow and tissue biopsy of any affected organ (e.g. abdominal fat, endomyocardial). AL: light chain; AoS: aortic stenosis; BMB: bone marrow biopsy; ECG: electrocardiogram; ECV: extracellular volume; EMB: endomyocardial biospy; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; MRI: magnetic resonance imaging; SAH: systemic arterial hypertension; TTRm: transthyretin mutation; TTR-WT: transthyretin, wild-type.*

Cardiac resonance

Cardiac magnetic resonance imaging, with a combination of native and contrast images, allows for accurate anatomical and functional assessment, as well as tissue characterization, indisputably assisting the assessment of RCM.[17]

Late gadolinium enhancement plays an established role in assisting differential diagnosis of cardiomyopathies, including restrictive ones. Diffuse subendocardial late enhancement is indicative of fibrosis, and it is observed in approximately one third of all cases of RCM; however, it is limited to patients with creatinine clearance above 30 mL/min. Gadolinium is an extracellular contrast agent, and, under normal conditions, it is not retained in the myocardium after administration. Amyloid infiltration results in volume expansion and contrast retention.

One of the greatest advantages of cardiac magnetic resonance imaging is tissue characterization of various structures and cardiac diseases. Recently, this characterization went from being merely qualitative to measuring objectively by means of T1 and T2 parametric maps, with the additional advantage of not requiring contrast. T1 mapping has made it possible to objectively measure areas of edema, inflammation, and fibrosis, reflecting systemic changes that occur in the extracellular space. Another advantage of the technique is that it allows measurement of extracellular volume (ECV), with contrast infusion, assisting in differential diagnosis of the restrictive infiltrative cause, given that, in amyloidosis, there is an increase in ECV. On the other hand, in diseases that occur with hypertrophy, there is a more reduced pattern of ECV.[18,19]

Bone tracer scintigraphy

For suspected amyloidosis, this technique has demonstrated a sensitivity of 99% and specificity of 86% for diagnosis of cardiac involvement due to TTR cardiac amyloidosis, whether wild-type or due to a mutation, once the light chain form has been excluded. Radiopharmaceutical uptake is classified by the semi-quantitative visual score of cardiac retention in relation to the sternum; the presence of grade 2 or 3 is highly suggestive of TTR in the absence of monoclonal proteins. Furthermore, quantitative analysis of cardiac retention in ratio to the contralateral chest wall greater than 1.5 is consistent for diagnosis of the TTR form.[20]

Endomyocardial biopsy

The evolution of imaging methods has reduced the need for endomyocardial biopsy in diagnosis, but it may still play a fundamental role in the diagnostic evaluation of patients with restrictive disease. Diagnoses of systemic diseases with cardiac involvement, such as amyloidosis and hemochromatosis, can be definitively established by biopsy of the right ventricle. Endomyocardial biopsy can be used when clinical, laboratory, and imaging data are not sufficient to establish diagnosis. It is worth underscoring that a recent study observed that right ventricular biopsy was effective in only 29% of patients with unexplained RCM.[20]

Genetic assessment

The genetic etiology of RCM is strongly suspected, due to its familial occurrence. Clinical and imaging presentations in infiltrative RCM are similar, and they may be difficult to differentiate when the extracardiac clinical expression is not as pronounced; correct genetic diagnosis implies prognostic assessment and specific therapeutic possibilities. In TTR amyloidosis, genetic analysis is essential to differentiate between mutation and wild-type; furthermore, mutational TTR is associated with the phenotypic expression of neuropathy and/or heart disease. It is also important in the differential diagnosis of hypertrophy, including hypertrophic RCM, its phenocopies, and storage diseases.[21-23]

Treatment

Treatment of RCM must be individualized according to etiology (Table 2). Management of HF is a challenge, given that few pharmacological therapies have been associated with favorable outcomes in this scenario. Patients poorly tolerate antihypertensives and betablockers; digoxin should be avoided due to the risk of intoxication. Diuretic therapy and volume management is the most used strategy. Oral anticoagulation should be considered in the presence of atrial fibrillation, regardless of risk scores, due to the associated high thromboembolic risk. Pacemakers considered in blocks and symptomatic bradycardias and defibrillators are controversial.[23-26]

Conclusion

HFpEF is currently a great challenge for clinicians, as it represents a phenotype with many possibilities and, in general, limited therapeutic strategies; however, the search for etiologies should not be neglected, as it makes it possible to establish prognosis and specific therapeutic strategies that can modify the evolution of patients. For this purpose, all available workup should be taken into account, from clinical history and detailed physical examination, family history, and involvement of other systems, combined with adequate diagnostic procedures, including ECG, echocardiogram, laboratory tests, nuclear medicine, coronary and hemodynamic assessment, magnetic resonance, and, in specific situations, endomyocardial biopsy and genetic analysis. To paraphrase Claude Bernard, "If you do not know what you are looking for, you will not know how to interpret what you find." Therefore, we must not neglect considering and seeking differential diagnoses of HFpEF, including in RCM with infiltrative phenotypes.

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References

1. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart Failure with Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol. 2017;70(20):2476-86. doi: 10.1016/j.jacc.2017.08.074.
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):146-603. doi: 10.1161/CIR.0000000000000485.
3. Madan N, Kalra D. Clinical Evaluation of Infiltrative Cardiomyopathies Resulting in Heart Failure with Preserved Ejection Fraction. Rev Cardiovasc Med. 2020;21(2):181-90. doi: 10.31083/j.rcm.2020.02.65.
4. Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Phenotype Mapping of Heart Failure with Preserved Ejection Fraction. Int.J. Cardiovasc. Sci. 2018;31(6):652-61. doi: 10.5935/2359-4802.20180047.
5. Pereira NL, Grogan M, Dec GW. Spectrum of Restrictive and Infiltrative Cardiomyopathies: Part 1 of a 2-Part Series. J Am Coll Cardiol. 2018;71(10):1130-48. doi: 10.1016/j.jacc.2018.01.016.
6. Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ Res. 2017;121(7):819-37. doi: 10.1161/CIRCRESAHA.117.310982.
7. Seward JB, Casaclang-Verzosa G. Infiltrative Cardiovascular Diseases: Cardiomyopathies That Look Alike. J Am Coll Cardiol. 2010;55(17):1769-79. doi: 10.1016/j.jacc.2009.12.040.
8. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical Profile and Outcome of Idiopathic Restrictive Cardiomyopathy. Circulation. 2000;101(21):2490-6. doi: 10.1161/01.cir.101.21.2490.
9. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure with Preserved Ejection Fraction In Perspective. Circ Res. 2019;124(11):1598-617. doi: 10.1161/CIRCRESAHA.119.313572.
10. Hausfater P, Costedoat-Chalumeau N, Amoura Z, Cacoub P, Papo T, Grateau G, et al. AL Cardiac Amyloidosis and Arterial Thromboembolic Events. Scand J Rheumatol. 2005;34(4):315-9. doi: 10.1080/03009740510015203.
11. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation. 2017;135(14):1357-77. doi: 10.1161/CIRCULATIONAHA.116.024438.
12. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and Prognostic Significance of Low QRS Voltage Among the Three Main Types of Cardiac Amyloidosis. Am J Cardiol. 2014;114(7):1089-93. doi: 10.1016/j.amjcard.2014.07.026.
13. Weidemann F, Reiser M. Fabry Disease: Cardiomyopathy Staging. JACC Cardiovasc Imaging. 2019;12(8):1684-5. doi: 10.1016/j.jcmg.2018.05.029.
14. Stricagnoli M, Cameli M, Incampo E, Lunghetti S, Mondillo S. Speckle Tracking Echocardiography in Cardiac Amyloidosis. Heart Fail Rev. 2019;24(5):701-7. doi: 10.1007/s10741-019-09796-z.
15. Bellavia D, Pellikka PA, Al-Zahrani GB, Abraham TP, Dispenzieri A, Miyazaki C, et al. Independent Predictors of Survival in Primary Systemic (Al) Amyloidosis, Including Cardiac Biomarkers and Left Ventricular Strain Imaging: An Observational Cohort Study. J Am Soc Echocardiogr. 2010;23(6):643-52. doi: 10.1016/j.echo.2010.03.027.
16. Koyama J, Falk RH. Prognostic Significance of Strain Doppler Imaging in Light-Chain Amyloidosis. JACC Cardiovasc Imaging. 2010;3(4):333-42. doi: 10.1016/j.jcmg.2009.11.013.
17. Galea N, Polizzi G, Gatti M, Cundari G, Figuera M, Faletti R. Cardiovascular Magnetic Resonance (CMR) in Restrictive Cardiomyopathies. Radiol Med. 2020;125(11):1072-86. doi: 10.1007/s11547-020-01287-8.
18. Abulizi M, Sifaoui I, Wuliya-Gariepy M, Kharoubi M, Israël JM, Emsen B, et al. 18F-Sodium Fluoride PET/MRI Myocardial Imaging in Patients with Suspected Cardiac Amyloidosis. J Nucl Cardiol. 2021;28(4):1586-95. doi: 10.1007/s12350-019-01885-8.
19. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017;70(4):466-77. doi: 10.1016/j.jacc.2017.05.053.
20. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12. doi: 10.1161/CIRCULATIONAHA.116.021612.
21. Chung WK. Predictive Genetic Testing for Cardiomyopathies. Prog Pediatr Cardiol. 2007;23(1):33-8. doi: 10.1016/j.ppedcard.2007.05.002.
22. Colombo MG, Botto N, Vittorini S, Paradossi U, Andreassi MG. Clinical Utility of Genetic Tests for Inherited Hypertrophic and Dilated Cardiomyopathies. Cardiovasc Ultrasound. 2008;6:62. doi: 10.1186/1476-7120-6-62.
23. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. 2018;24(5):281-302. doi: 10.1016/j.cardfail.2018.03.004.
24. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.
25. Ribeiro Neto ML, Jellis CL, Joyce E, Callahan TD, Hachamovitch R, Culver DA. Update in Cardiac Sarcoidosis. Ann Am Thorac Soc. 2019;16(11):1341-50. doi: 10.1513/AnnalsATS.201902-119CME.
26. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Sousa N, Cunha D. Fabry Disease Therapy: State-of-the-Art and Current Challenges. Int J Mol Sci. 2020;22(1):206. doi: 10.3390/ijms22010206.

Algorithms for Cardiac Amyloidosis Diagnosis: How to apply them in practice?

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Cardiac amyloidosis has long been an entity neglected by most doctors, being considered a rare disease with limited treatment options. Recent diagnostic and therapeutic advances have brought a renewed vision in the evaluation strategies of the different forms of amyloidosis that potentially affect the heart.[1,2] In this article we carry out a critical reflection on the importance of early diagnostic suspicion and use of contemporary algorithms to instrumentalize the cardiologist for clinical practice.

Diagnostic suspicion

The main obstacle to rapid and proper diagnosis of cardiac amyloidosis is the absence of early suspicion in patients who have clinical hints (red flags) that could – or should – trigger an investigation. This phenomenon becomes even more clear when it is documented that before the definitive diagnosis of amyloidosis or cardiac involvement due to amyloid deposition, investigation may take several months or years, usually involving many doctors from different specialties. In a study by the University of Toulouse, the average delay between the onset of symptoms and the diagnosis of amyloidosis was 8, 10 and 18 months, respectively,

for light chain amyloidosis (AL), wild-type transthyretin amyloidosis and hereditary transthyretin amyloidosis.[3] Similarly, the number of health professionals that each patient needs to consult on their "journey" for the correct diagnosis may vary substantially. In interviews with family members and patients with amyloidosis, predominantly due to deposition

of light chains, the diagnosis was not established during the first year after symptom onset in more than 1/3 of cases and the diagnosis was made only after consulting with 5 different doctors in 32%.[4]

It is critical to emphasize that for a disease characterized by continued myocardial deposition, but at a heterogeneous rate, the delay in diagnosis can have significant implications from a therapeutic and prognostic point of view. The cardiologist must continuously look for clues that should increase clinical suspicion.[5-8] In practice, these are warning signs that suggest amyloid deposition in the bone-tendon-muscular system (carpal tunnel syndrome, particularly bilateral; lumbar canal stenosis or biceps tendon rupture) and peripheral neuropathic involvement (sensory and motor), particularly if associated with autonomic dysfunction (postural hypotension, gastroparesis and changes in bowel habits). The resting electrocardiogram – a simple, inexpensive, but fundamental test – can provide relevant clues if it identifies the presence of conduction system disturbances, the appearance of pseudo Q waves or low voltage in a patient with signs of increased wall thickness in other imaging exams. The scenario of heart failure with preserved ejection fraction, particularly in males, in patients with advanced age and with manifestations of biventricular involvement, should increase the suspicion index for cardiac amyloidosis. Finally, proteinuria on the common urine test, loss of renal function, macroglossia, and the diagnosis of "low-flow and low-gradient" aortic stenosis – particularly of the paradoxical type – may also be suggestive of cardiac amyloidosis.

Initial Cardiac Imaging Exams

Cardiac imaging as an initial assessment is mandatory, but which exam should be requested is not consensual, and transthoracic echocardiography and/or cardiac magnetic resonance with evaluation of delayed enhancement are often recommended. Suggestive echocardiographic signs are thickening of the walls of both ventricles, which are usually not dilated, valve thickening, and pericardial effusion. An important warning sign on cardiac magnetic resonance, in addition to the respective findings identified on echocardiography, is the presence of diffuse subendocardial delayed enhancement. The assessment of left ventricular global longitudinal strain on the echocardiogram and the identification of relative preservation of the apical deformation (apical sparing) is a suggestive finding of cardiac amyloidosis, but not pathognomonic. Likewise, the multiparametric evaluation on cardiac resonance identifying an increase in native T1 time and extracellular volume may be strongly suggestive of cardiac amyloidosis.[9]

Diagnostic Algorithms and Flowcharts

Once the clinical suspicion of cardiac amyloidosis is established, the cardiologist – or responsible physician

Keywords

Amyloidosis; Heart Failure.

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– must launch a rational investigation strategy. Several algorithms and diagnostic flowcharts have been proposed with this objective. None of the proposed regimens will be perfect for all patients, since there is a wide variety of initial clinical presentations, depending on the type of amyloidosis in question (due to light chain, mutant or wild-type transthyretin deposition). Many algorithms (Figures 1 and 2) suggest that all suspected patients should be initially screened only for plasma dyscrasias (presence of monoclonal proteins). The European Society of Cardiology (Figure 3) proposes that concomitant myocardial scintigraphy with a bone radiotracer (99mTc-DPP/PYP/HMDP) should be requested and the diagnostic definitions be based on the combination of results. The recent position statement on the diagnosis and treatment of cardiac amyloidosis (Figure 4) clearly separates the hematological route and the cardiology route of investigation, emphasizing that the suspicion of light chain amyloidosis (LA) should be considered a medical emergency, and that the cardiologist should act together with the hematologist for accelerated referral of diagnostic and therapeutic procedures. Our position statement also recommends performing an endomyocardial biopsy in doubtful cases and, according to finding of cardiac amyloid deposition (positive congo red staining), indicates protein typing by mass spectroscopy or immunohistochemistry.

Regardless of the recommended or chosen algorithm, some facts, and scenarios in the investigation of cardiac amyloidosis are central, deserve attention and appear in almost all flowcharts. These can be summarized into 10 cardinal rules described below:

1. Evaluation of monoclonal proteins. We should simultaneously order three tests to increase the accuracy in identifying monoclonal proteins: (1) serum kappa and lambda free chain ratio, (2) serum protein immunofixation, and (3) urinary protein immunofixation.

2. Hematological route. The presence of abnormal monoclonal proteins in hematological screening in individuals suspected of having cardiac deposition suggests the presence of light chain amyloidosis (LA) and the patient should quickly proceed with the investigation with tissue biopsies aimed at clinical presentation, which may include collection of bone marrow, renal and myocardial tissue. The hematologist must be involved in the investigation process early on.

3. Abdominal fat biopsy. Abdominal fat biopsy, a test frequently used for the diagnosis of systemic amyloidosis, has an inadequate negative predictive value to rule out the diagnosis.

4. Diagnosis of amyloidosis without the need for biopsy. The diagnosis of cardiac amyloidosis due to transthyretin deposition, without the need for tissue biopsy, can be achieved

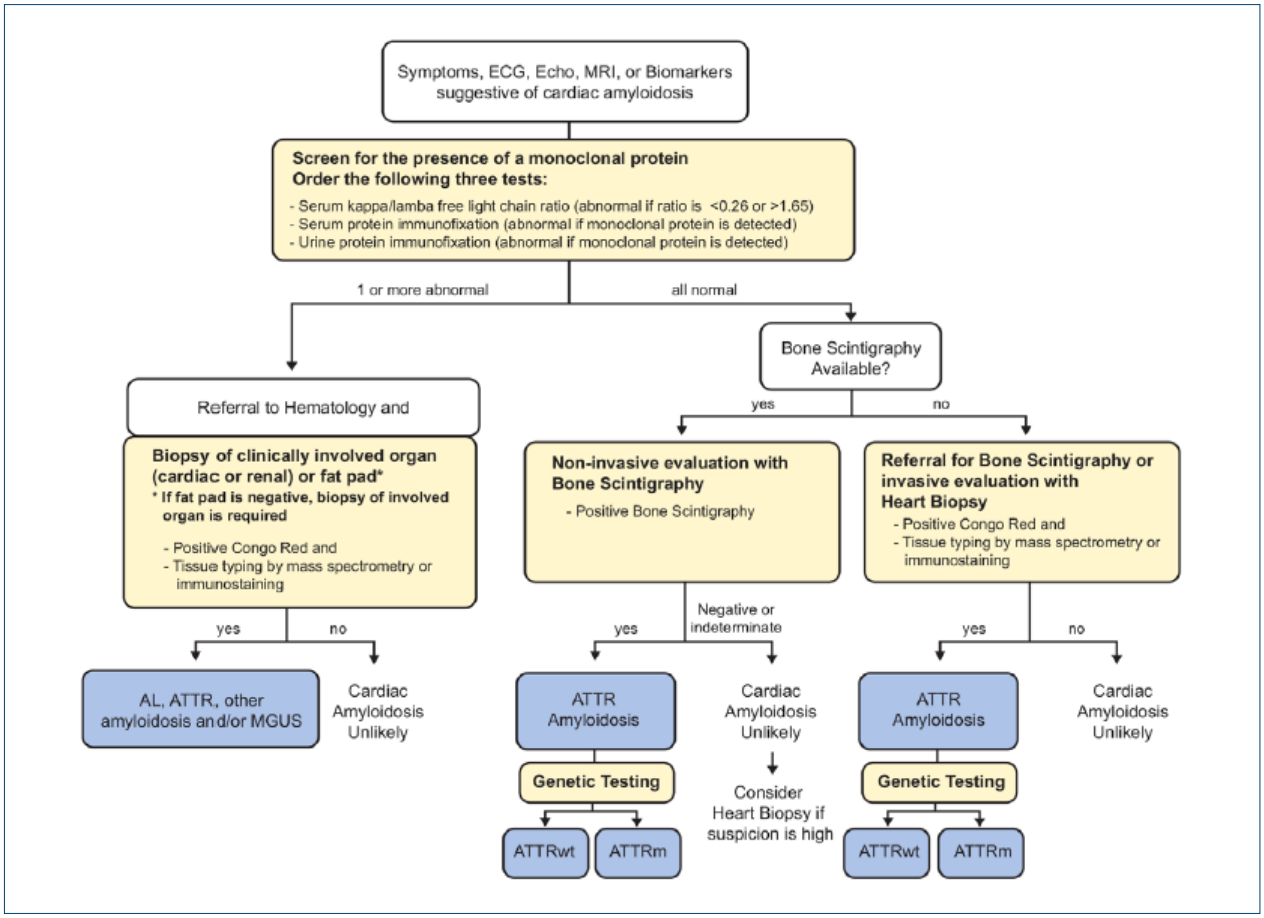

Figure 1 – *International Expert Panel diagnostic algorithm (2019)*[5]

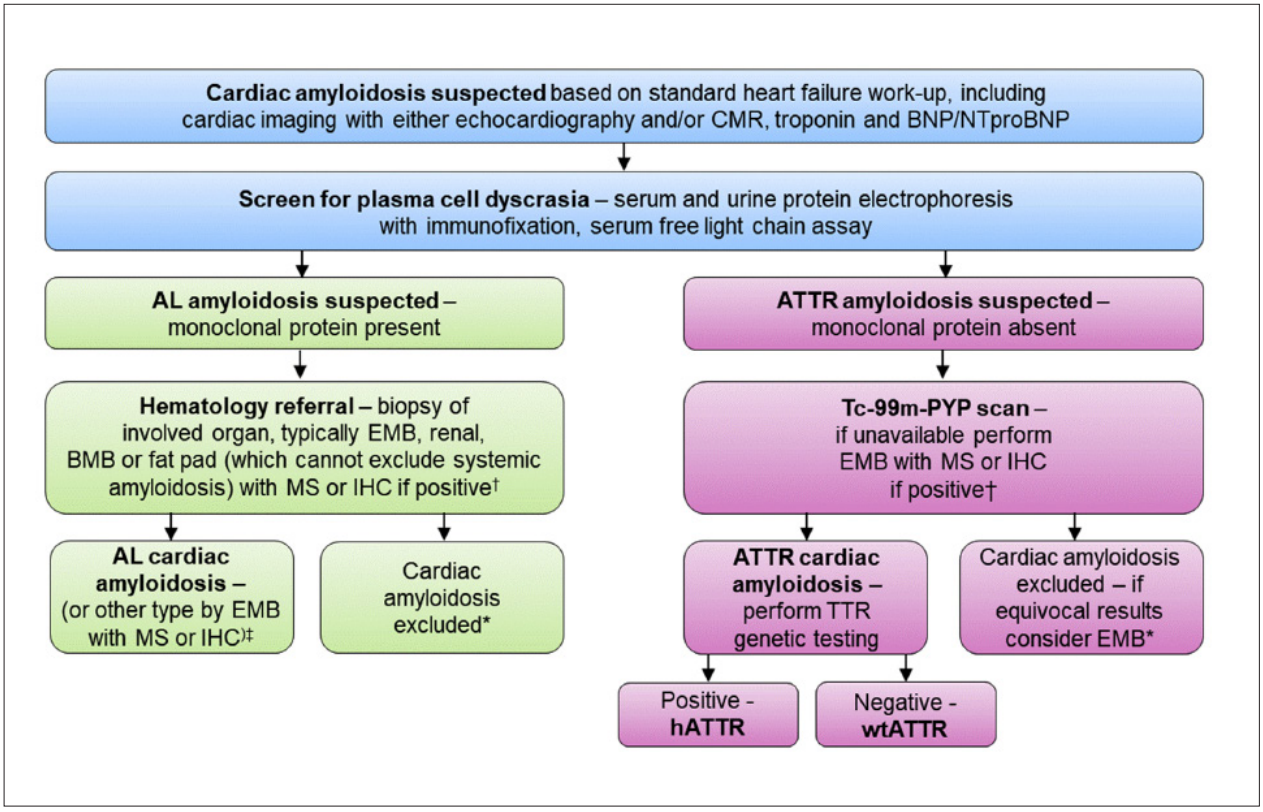

Figure 2 – *Canadian societies diagnostic algorithm (2020)*[6]

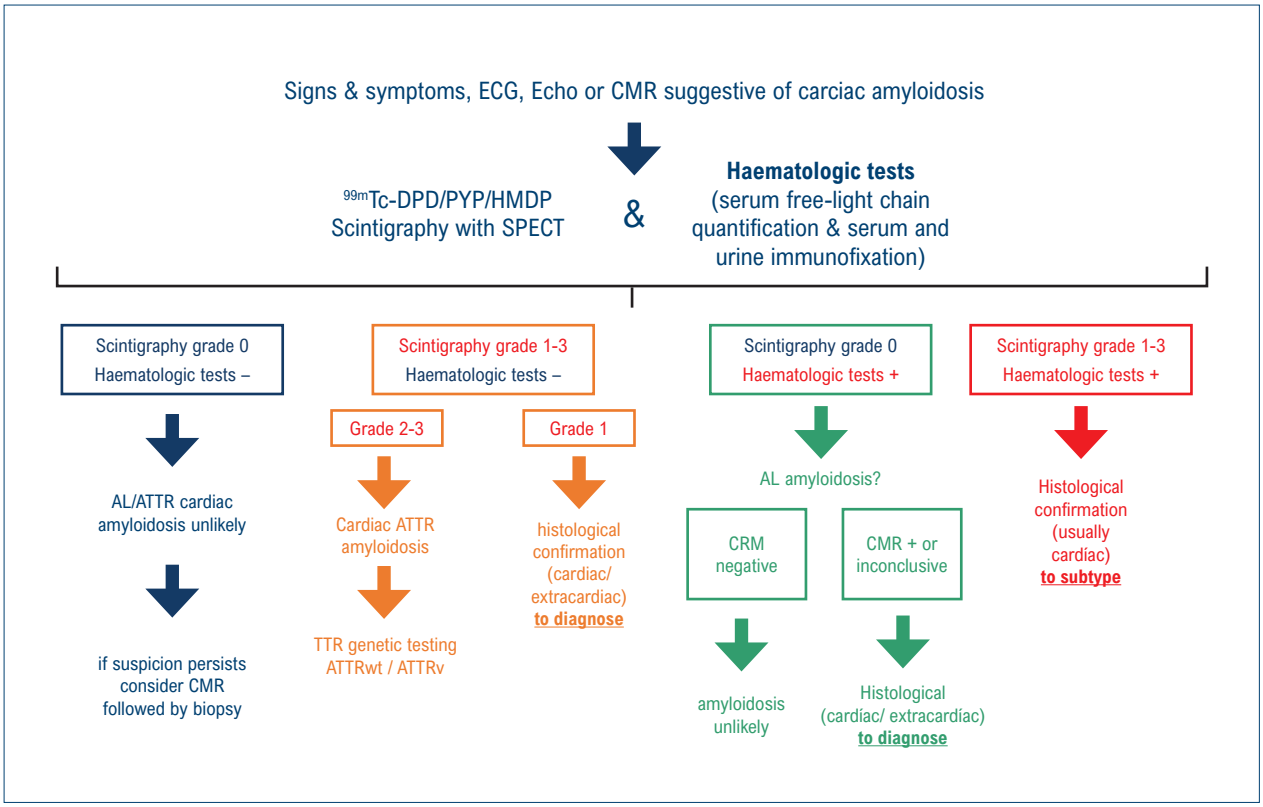

Figure 3 – *Diagnostic algorithm of the European Society of Cardiology Working Group (2021)*[7]

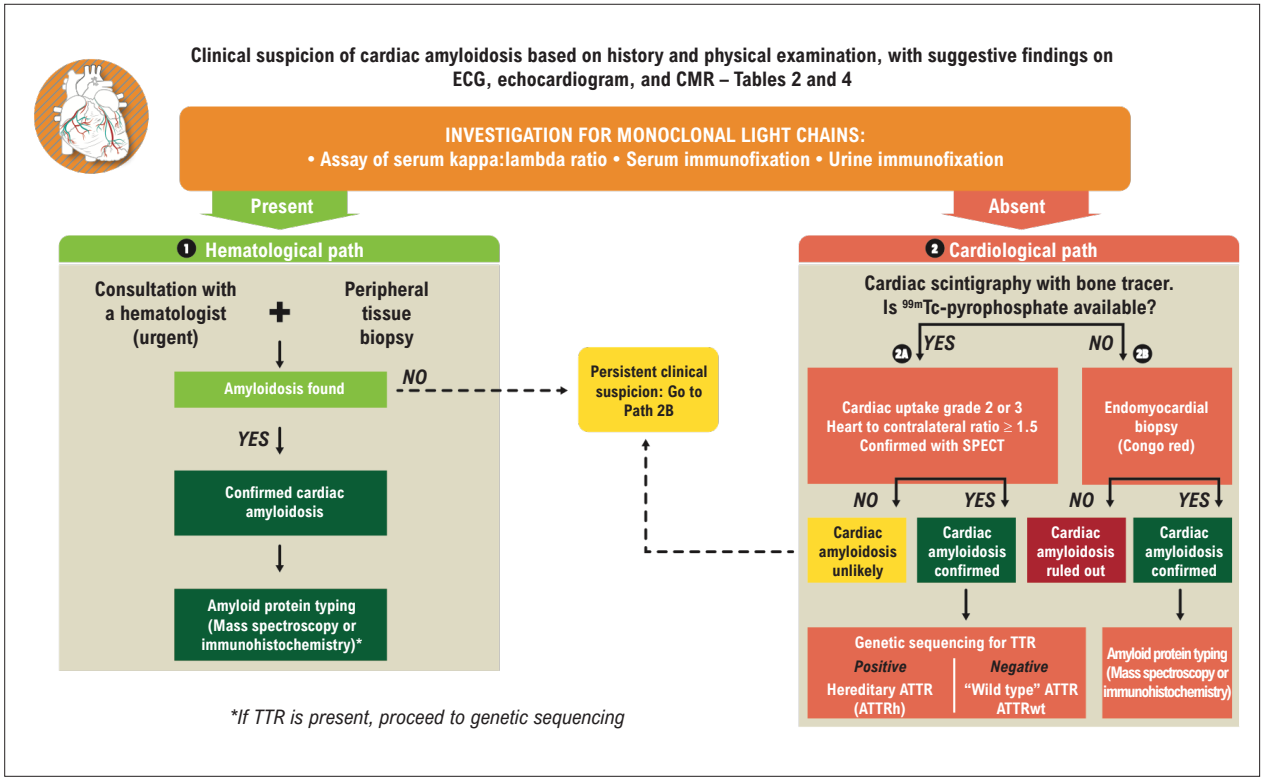

Figure 4 – *Diagnostic algorithm of the Heart Failure Department of the Brazilian Society of Cardiology (2021)[8] ATTR: transthyretin amyloidosis; CMR: cardiac magnetic resonance; ECG: electrocardiogram; TTR: transthyretin.*

with the use of myocardial scintigraphy with a bone radiotracer (the marker available in Brazil is 99mTc pyrophosphate). For this purpose, marker uptake must be moderately or markedly positive (grade 2 or 3 and/or cardiac versus contralateral uptake > 1.5) and the 3 hematological screening tests must demonstrate the absence of monoclonal proteins.

5. Transthyretin gene mutations. Genetic tests for evaluation of mutations related to specific phenotypes (neurological, cardiac, or mixed) are indicated for patients diagnosed with cardiac amyloidosis due to transthyretin deposition. The results of this assessment have implications for family counseling and genetic counseling.

6. Altered scintigraphy & presence of monoclonal proteins. A small but not negligible percentage of patients with amyloidosis due to light chain deposition may simultaneously have positive bone radiotracer uptake in myocardial scintigraphy with hematological tests that identify the presence of monoclonal proteins.

7. Monoclonal gammopathy of uncertain significance. On the other hand, the identification of a monoclonal protein is not diagnostic of light chain amyloidosis (AL). In addition, monoclonal gammopathy of undetermined significance may also coexist with wild-type transthyretin deposition amyloidosis, especially in elderly patients.

8. Endomyocardial biopsy. Direct analysis of myocardial tissue may be essential in scenarios where clinical suspicion is high and other tests are inconsistent, or when myocardial scintigraphy with a bone radiotracer is not available.

9. Mass spectroscopy and/or immunohistochemistry. Tissue analysis by mass spectrometry and/or immunohistochemistry are not readily available for most patients but should be used in doubtful scenarios or with conflicting findings during the investigation, as they allow a definitive diagnosis and can differentiate the type of amyloid deposits.

10. Clinical suspicion, the cornerstone. Diagnostic clues can appear separated from other signs/symptoms and at different time frames in the natural history of the disease, affecting apparently unrelated bodily systems. The cardiologist should place amyloidosis within the scope of their differential diagnoses, because without an initial clinical suspicion no flowchart or algorithm will work.

Conclusion

Amyloidosis, an underdiagnosed, life-threatening entity, has long been considered untreatable. However, the recent availability of disease course-modifying therapies has renewed efforts to raise awareness about the initial symptoms of the disease and the assessments that are available to confirm its diagnosis.[10] Clinical clues (red flags) must be remembered and involve manifestations of cardiac, renal, tendon or neurological involvement. The use of diagnostic flowcharts is recommended to assist the physician in investigating suspected cases in a systematic, rational, and orderly manner. These algorithms, however, are not infallible, since the disease has a very large spectrum of clinical presentations, which can vary substantially according to the phase and system in which amyloid deposition occurs.

Author contributions

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References

1. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.
2. Hanna M, Ruberg FL, Maurer MS, Dispenzieri A, Dorbala S, Falk RH, et al. Cardiac Scintigraphy with Technetium-99m-Labeled Bone-Seeking Tracers for Suspected Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2020;75(22):2851-62. doi: 10.1016/j.jacc.2020.04.022.
3. Dang D, Fournier P, Cariou E, Huart A, Ribes D, Cintas P, et al. Gateway and Journey of Patients with Cardiac Amyloidosis. ESC Heart Fail. 2020;7(5):2418-30. doi: 10.1002/ehf2.12793.
4. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. Adv Ther. 2015;32(10):920-8. doi: 10.1007/s12325-015-0250-0.
5. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019;12(9):e006075. doi: 10.1161/CIRCHEARTFAILURE.119.006075.
6. Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients with Cardiac Amyloidosis. Can J Cardiol. 2020;36(3):322-34. doi: 10.1016/j.cjca.2019.12.034.
7. 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.
8. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
9. Banypersad SM, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A, et al. T1 Mapping and Survival in Systemic Light-Chain Amyloidosis. Eur Heart J. 2015;36(4):244-51. doi: 10.1093/eurheartj/ehu444.
10. Gertz M, Adams D, Ando Y, Beirão JM, Bokhari S, Coelho T, et al. Avoiding Misdiagnosis: Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Amyloidosis for the General Practitioner. BMC Fam Pract. 2020;21(1):198. doi: 10.1186/s12875-020-01252-4.

Disease Modifying Therapies for Transthyretin Amyloid Cardiomyopathy

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Transthyretin (TTR) is a tetrameric protein synthesized essentially by the liver. TTR molecules may misfold and store as amyloid fibrils in the heart and other organs, leading to TTR-related amyloidosis (ATTR)[1]. ATTR can follow the deposition of either variant ATTR (ATTRv), which was previously known as mutant ATTR, or wild-type ATTR (ATTRwt).[1] ATTR is an underdiagnosed disease, as well as a crucial determinant of morbidity and mortality.[2] Cardiac involvement is common in ATTR, leading to transthyretin cardiomyopathy (ATTR-CA). ATTR-CA is a progressive disorder, and patients ultimately develop heart failure, arrhythmias, and cardiac conduction disturbances, resulting in decreased functional capacity, diminished quality of life, and death.[3] Until recently, treatment of ATTR-CA was limited to treating symptoms and complications; however, the development of new specific therapies that delay or stop the progress of the cardiomyopathy has positively modified the outcomes[4]. These specific treatments work by targeting the inhibition of TTR synthesis (inotersen or patisiran); tetramer stabilization (diflunisal, tafamidis, or acoramidis [AG10]); inhibition of oligomer aggregation and disruption (epigallocatechin-3-gallate); and degradation and reabsorption of amyloid fibers (doxycycline-tauroursodeoxycholic acid [TUDCA] or doxycycline-ursodeoxycholic acid [UDCA]).4

In patients with ATTR-CA, either ATTRv or ATTRwt, tafamidis is considered the agent of choice due to the proven clinical benefit in cardiovascular outcomes.[5] Tafamidis is a kinetic TTR stabilizer that binds to the unoccupied thyroxine binding sites of tetrameric TTR and blocks the amyloidogenic cascade.[6] It was first adopted for treatment of symptomatic ATTRv polyneuropathy, and it is the only therapy approved with effectiveness to treat ATTR-CA.[5] This recommendation is essentially based on the results of a large, well-designed phase III randomized clinical trial (RCT), ATTR-ACT.[7] In this study, tafamidis (20 and 80 mg, pooled) showed a decline in all-cause mortality and cardiovascular-related hospitalization, decreased decline in 6-minute walk test, slower deterioration in quality of life, and a minor increase of NT-proBNP in patients with biopsy-proven ATTRwt or ATTRv CA with heart failure and NYHA class I to III at 30 months. The safety profile was similar to placebo, and individuals with NYHA classes I and II reached the most meaningful benefit.[7] ATTR-ACT was not designed to assess a specific dose; therefore, further analysis from ATTR-ACT and its long-term extension study support tafamidis 80 mg as the optimal dose to be used in clinical practice.[8]

Other drugs with the capacity to stabilization of TTR have been tested, but, differently from tafamidis, they have not been approved for ATTR-CA treatment yet.[5] Diflunisal is a nonsteroidal anti-inflammatory (NSAID) drug with TTR-stabilizing attributes. Studies on diflunisal are all noncomparative, small non-RCTs, including almost exclusively patients with ATTRv, with exploratory cardiovascular endpoints limited to cardiovascular biomarkers and echocardiographic parameters.[9] Although these potential beneficial effects have been described, adverse events associated with NSAIDs may impede their use in patients with heart failure.[3]

AG10 is a highly selective, small-molecule TTR stabilizer. Phase I and II studies exhibited a good toxicity profile and stabilization of both types of TTR.[10] AG10 cannot be supported at present for ATTR-CA, as the only study of AG10 had a short duration of 1 month, and the cardiovascular endpoints are only exploratory and restricted to cardiac biomarkers.[10] A phase III study to evaluate AG10 compared with placebo in subjects with symptomatic ATTR-CA is ongoing. The ATTRIBUTE-CM study evaluates AG10 in patients with ATTRwt or ATTRv CA, and the primary endpoints are 6-minute walk test change from baseline at 12 months and all-cause mortality and cardiovascular hospitalizations at 30 months (ClinicalTrials.gov Identifier: NCT03860935).

Lately, agents able to silence the TTR gene and considerably reduce the concentration of circulating TTR have joined clinical practice.[3] They specifically degrade TTR mRNA at the nucleus (inotersen) or cytoplasm (patisiran).[11,12]

Both agents have been accepted for the therapy of ATTRv polyneuropathy after proof of their effectiveness in neurologic RCTs. Patisiran is a promising drug for patients with ATTR-CA based on a subgroup analysis of a phase III double-blind RCT, APOLLO,[11,13,14] which suggested that therapy with patisiran was associated with a decline in mortality and hospitalization, as well as a decrease in NT-proBNP and left ventricular wall thickness, without significant adverse events. By contrast, inotersen failed to demonstrate significant differences in echocardiographic variables compared with placebo in patients with ATTRv and cardiac disease in the neurological trial.[12] However, a small, open-label study showed stabilization

Keywords

Amyloidosis; Cardiac amyloidosis; Treatment; TTR; Transthyretin

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of cardiac parameters in most patients with ATTRv or ATTRwt followed for up to 3 years.[15,16]

The possible benefit of patisiran in patients with ATTR-CA is currently under research in the APOLLO-B phase III RCT. APOLLO B (ClinicalTrials.gov Identifier: NCT03997383) is assessing patisiran in patients with ATTR-CA (ATTRwt or ATTRv), considering a 6-minute walk test as the primary endpoint and death and hospitalization outcomes as secondary endpoints at 12 months. Phase III trials with new gene silencing molecules are ongoing. The HELIOS-B (ClinicalTrials.gov Identifier: NCT04153149) study evaluates the RNA interference agent, vutrisiran, with the convenience of a subcutaneous administration every 3 months in patients with either ATTRwt or ATTRv CA. The primary endpoint is the composite outcome of all-cause mortality and recurrent cardiovascular hospitalizations at 30 months. The CARDIO-TTRansform trial (ClinicalTrials.gov Identifier: NCT04136171) evaluates different antisense oligonucleotides, AKCEA-TTR-LRX, with the comfort of a lower frequency of administration (every 4 weeks). This study will also include patients with ATTRwt or ATTRv CA, and the primary endpoint is cardiovascular mortality and clinical events at 120 weeks.

Another potential alternative to mRNA targeting-based gene silencing is use of the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) system to achieve in vivo gene editing. NTLA-2001 is a new CRISPR-Cas9–based in vivo gene-editing therapy, administered by intravenous infusion, that is intended to edit *TTR* in hepatocytes, leading to a decrease in the production of both wild-type and mutant TTR after a single administration.[17] In patients with ATTRv with polyneuropathy, treatment with NTLA-2001 was associated with sustained reductions in the serum TTR protein concentration at day 28 (87% in the group that received a dose of 0.3 mg per kilogram).[17]

Additional molecules are under examination to inhibit oligomer aggregation and disruption (epigallocatechin-3-gallate), accelerate clearance, and eliminate existing cardiac deposits (TUDCA). Although a small, but significant benefit was found on cardiac magnetic resonance parameters such as left ventricular mass and native T1 in patients with ATTR-CA treated with epigallocatechin-3-gallate (green tea extract), these effects should be assessed thoroughly, as they are based on noncomparative single-arm small non-RCTs.[18-20]

The compound of doxycycline and tauroursodeoxycholic bile acid (TUDCA) has been investigated in phase II trials, with variable outcomes and an adverse side-effect profile.[21,22] At this stage, the absence of evidence and the presence of side-effects do not allow its utilization in clinical practice. A phase III clinical trial evaluating doxycycline and TUDCA in ATTR-CM is also ongoing and will shed light on their utility (ClinicalTrials.gov Identifier: NCT03481972).

Finally, other early-phase investigations are ongoing with monoclonal antibodies that promote the removal of deposits (ClinicalTrials.gov Identifiers: NCT03336580 and NCT04360434).

Notwithstanding the tremendous ongoing investigation, there is still a data gap concerning subsets of patients who have been excluded from the studies, such as patients manifesting ATTR-CA after liver transplantation, patients with ATTR-CA with advanced heart failure (NYHA class IV), and patients with ATTR over 90 years of age. Furthermore, it is necessary to assess whether the association of treatments with distinct mechanisms of action could improve the outcome of ATTR-CA.[5]

As demonstrated, this is a growing research field with many RCTs currently ongoing, and their results will likely shift the paradigm of treatment of ATTR-CA. Our main goal continues to be finding the best therapy or combination of therapies for each patient with ATTR-CA by optimizing the efficacy and minimizing the side effects.

Author contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript: Macedo AVS, Fernandes F, Lopes RD. Critical revision of the manuscript for intellectual content: Macedo AVS, Fernandes F, Lopes RD.

Potential Conflict of Interest

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References

1. Saelices L, Johnson LM, Liang WY, Sawaya MR, Cascio D, Ruchala P, et al. Uncovering the Mechanism of Aggregation of Human Transthyretin. J Biol Chem. 2015;290(48):28932-43. doi: 10.1074/jbc.M115.659912.

2. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019;12(9):e006075. doi: 10.1161/CIRCHEARTFAILURE.119.006075.

3. 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.

4. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.

5. Marques N, Azevedo O, Almeida AR, Bento D, Cruz I, Correia E, et al. Specific Therapy for Transthyretin Cardiac Amyloidosis: A Systematic Literature Review and Evidence-Based Recommendations. J Am Heart Assoc. 2020;9(19):e016614. doi: 10.1161/JAHA.120.016614.

6. Miroy GJ, Lai Z, Lashuel HA, Peterson SA, Strang C, Kelly JW. Inhibiting Transthyretin Amyloid Fibril Formation via Protein Stabilization. Proc Natl Acad Sci U S A. 1996;93(26):15051-6. doi: 10.1073/pnas.93.26.15051.

7. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

8. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, et al. Efficacy and Safety of Tafamidis Doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and Long-Term Extension Study. Eur J Heart Fail. 2021;23(2):277-85. doi: 10.1002/ejhf.2027.

9. Sekijima Y, Tojo K, Morita H, Koyama J, Ikeda S. Safety and Efficacy of Long-Term Diflunisal Administration in Hereditary Transthyretin (ATTR) Amyloidosis. Amyloid. 2015;22(2):79-83. doi: 10.3109/13506129.2014.997872.

10. Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, et al. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2019;74(3):285-95. doi: 10.1016/j.jacc.2019.03.012.

11. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):11-21. doi: 10.1056/NEJMoa1716153.

12. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31. doi: 10.1056/NEJMoa1716793.

13. Solomon SD, Adams D, Kristen A, Grogan M, González-Duarte A, Maurer MS, et al. Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis. Circulation. 2019;139(4):431-43. doi: 10.1161/CIRCULATIONAHA.118.035831.

14. Minamisawa M, Claggett B, Adams D, Kristen AV, Merlini G, Slama MS, et al. Association of Patisiran, an RNA Interference Therapeutic, With Regional Left Ventricular Myocardial Strain in Hereditary Transthyretin Amyloidosis: The APOLLO Study. JAMA Cardiol. 2019;4(5):466-72. doi: 10.1001/jamacardio.2019.0849.

15. Benson MD, Dasgupta NR, Rissing SM, Smith J, Feigenbaum H. Safety and Efficacy of a TTR Specific Antisense Oligonucleotide in Patients with Transthyretin Amyloid Cardiomyopathy. Amyloid. 2017;24(4):219-25. doi: 10.1080/13506129.2017.1374946.

16. Dasgupta NR, Rissing SM, Smith J, Jung J, Benson MD. Inotersen Therapy of Transthyretin Amyloid Cardiomyopathy. Amyloid. 2020;27(1):52-8. doi: 10.1080/13506129.2019.1685487.

17. Gillmore JD, Gane E, Taubel J, Kao J, Fontana M, Maitland ML, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med. 2021;385(6):493-502. doi: 10.1056/NEJMoa2107454.

18. Kristen AV, Lehrke S, Buss S, Mereles D, Steen H, Ehlermann P, et al. Green Tea Halts Progression of Cardiac Transthyretin Amyloidosis: An Observational Report. Clin Res Cardiol. 2012;101(10):805-13. doi: 10.1007/s00392-012-0463-z.

19. Aus Dem Siepen F, Buss SJ, Andre F, Seitz S, Giannitsis E, Steen H, et al. Extracellular Remodeling in Patients with Wild-Type Amyloidosis Consuming Epigallocatechin-3-Gallate: Preliminary Results of T1 Mapping by Cardiac Magnetic Resonance Imaging in a Small Single Center Study. Clin Res Cardiol. 2015;104(8):640-7. doi: 10.1007/s00392-015-0826-3.

20. Aus Dem Siepen F, Bauer R, Aurich M, Buss SJ, Steen H, Altland K, et al. Green Tea Extract as a Treatment for Patients with Wild-Type Transthyretin Amyloidosis: An Observational Study. Drug Des Devel Ther. 2015;9:6319-25. doi: 10.2147/DDDT.S96893.

21. Obici L, Cortese A, Lozza A, Lucchetti J, Gobbi M, Palladini G, et al. Doxycycline Plus Tauroursodeoxycholic Acid for Transthyretin Amyloidosis: A Phase II Study. Amyloid. 2012;19(Suppl 1):34-6. doi: 10.3109/13506129.2012.678508.

22. Wixner J, Pilebro B, Lundgren HE, Olsson M, Anan I. Effect of Doxycycline and Ursodeoxycholic Acid on Transthyretin Amyloidosis. Amyloid. 2017;24(Suppl 1):78-9. doi: 10.1080/13506129.2016.1269739.

Indications for Anticoagulation in Cardiac Amyloidosis

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In cardiac amyloidosis, amyloid infiltrate at the atrial level promotes atrial dilation and contractile dysfunction as well as a higher prevalence of atrial fibrillation which, when associated with ventricular diastolic and systolic dysfunction, favors blood stasis and the consequent development of intracardiac thrombosis (ICT) and cardioembolic events.

In a study of 116 autopsies of patients with cardiac amyloidosis, conducted at the Mayo Clinic, the presence of ICT was demonstrated in 33% of hearts, with a significantly higher prevalence in patients with the AL form of amyloidosis than in those with other forms (56% versus 16%, $p < 0.001$).[1]

When evaluating 324 patients with cardiac amyloidosis using cardiac magnetic resonance, we found an ICT prevalence of 6.2%, with 90% located in the atrial appendage. Among the patients, 70% had atrial fibrillation, and 30% had sinus rhythm, with a similar prevalence of ICT in the AL (5.2%) and ATTR forms (7.2%).[2,3]

Morphological and functional changes caused by atrial amyloid infiltrate favor the development of atrial fibrillation, with a prevalence ranging from 29% to 60%, depending on the population, and it is more prevalent in the ATTR form, given that it affects an older population. The presence of atrial fibrillation poses a high risk for the development of ICT and stroke, especially in patients with AL amyloidosis.[4]

Approximately 20% to 30% of patients who have ICT, as well as 27% of patients with cerebral ischemic events are in sinus rhythm.[3,5]

The probable mechanism responsible for the development of thrombotic events and thromboembolism in patients in sinus rhythm would be the presence of atrial myopathy due to amyloid infiltrate and high ventricular filling pressures, which induce atrial contractile dysfunction and favor blood stasis and ICT formation.[5-7]

By means of logistic regression analysis, several factors have been identified that are related to greater predisposition to ICT and thromboembolic events, such as biventricular systolic dysfunction, restrictive pattern of diastolic dysfunction, atrial dilatation, degree of atrial amyloid infiltration, and high NT-proBNP levels. In the presence of these factors, we must carry out a specific evaluation as to the possible benefit of anticoagulation for preventing cardioembolic events.[2]

In patients with cardiac amyloidosis who have ICT or atrial fibrillation, anticoagulation treatment is absolutely indicated, due to the benefits in reducing thromboembolic events and improving survival.[8]

New anticoagulants and coumarin are similar in terms of benefits in reducing stroke and increasing survival, as well as in terms of increasing the incidence of bleeding events. Approximately 55% to 68% of patients taking coumarin have difficulties reaching the stable therapeutic target of the international normalized ratio, especially in the elderly population, which we must take into account when making decisions regarding the choice of new anticoagulants as an alternative for anticoagulation.[9-11]

Even though anticoagulation in patients with amyloidosis has been associated with an increased risk of bleeding events due to amyloid angiopathy, especially in patients with the ATTR form, who are at risk of intracranial hemorrhage, this risk does not outweigh the benefits of preventing thromboembolic events; therefore, anticoagulation should be carried out when it is indicated.[12-13]

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References

1. Cannistraro RJ, Meschia JF. The Clinical Dilemma of Anticoagulation Use in Patients with Cerebral Amyloid Angiopathy and Atrial Fibrillation. Curr Cardiol Rep. 2018;20(11):106. doi: 10.1007/s11886-018-1052-1.
2. Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, Mirelis JG, Baksi AJ, Moon JC, et al. High Prevalence of Intracardiac Thrombi in Cardiac Amyloidosis. J Am Coll Cardiol. 2019;73(13):1733-4. doi: 10.1016/j.jacc.2019.01.035.
3. Feng D, Edwards WD, Oh JK, Chandrasekaran K, Grogan M, Martinez MW, et al. Intracardiac Thrombosis and Embolism in Patients with Cardiac Amyloidosis. Circulation. 2007;116(21):2420-6. doi: 10.1161/CIRCULATIONAHA.107.6977636.
4. Zubkov AY, Rabinstein AA, Dispenzieri A, Wijdicks EF. Primary Systemic Amyloidosis with Ischemic Stroke as a Presenting Complication. Neurology. 2007;69(11):1136-41. doi: 10.1212/01.wnl.0000276951.39112.2b.
5. Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G, et al. Arterial Thrombo-Embolic Events in Cardiac Amyloidosis: A Look Beyond Atrial Fibrillation. Amyloid. 2021;28(1):12-8. doi: 10.1080/13506129.2020.1798922.
6. Dubrey S, Pollak A, Skinner M, Falk RH. Atrial Thrombi Occurring During Sinus Rhythm in Cardiac Amyloidosis: Evidence for Atrial Electromechanical Dissociation. Br Heart J. 1995;74(5):541-4. doi: 10.1136/hrt.74.5.541.
7. Roudaut R, Pepin C, Marazanof M, Bonnet J. Systemic embolism and thrombosis of the left atrium in a patient in sinus rhythm with cardiac amyloidosis. Ann Cardiol Angeiol. 1996;45(3):119-21.
8. Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, et al. Intracardiac Thrombosis and Anticoagulation Therapy in Cardiac Amyloidosis. Circulation. 2009;119(18):2490-7. doi: 10.1161/CIRCULATIONAHA.108.785014.
9. Mitrani LR, Santos J, Driggin E, Kogan R, Helmke S, Goldsmith J, et al. Anticoagulation with Warfarin Compared to Novel Oral Anticoagulants for Atrial Fibrillation in Adults with Transthyretin Cardiac Amyloidosis: Comparison of Thromboembolic Events and Major Bleeding. Amyloid. 2021;28(1):30-4. doi: 10.1080/13506129.2020.1810010.
10. Rohla M, Weiss TW, Pecen L, Patti G, Siller-Matula JM, Schnabel RB, et al. Risk Factors for Thromboembolic and Bleeding Events in Anticoagulated Patients with Atrial Fibrillation: The Prospective, Multicentre Observational Prevention of Thromboembolic Events - European Registry in Atrial Fibrillation (PREFER in AF). BMJ Open. 2019;9(3):e022478. doi: 10.1136/bmjopen-2018-022478.
11. Agarwal S, Hachamovitch R, Menon V. Current Trial-Associated Outcomes with Warfarin in Prevention of Stroke in Patients with Nonvalvular Atrial Fibrillation: A Meta-Analysis. Arch Intern Med. 2012;172(8):623-31. doi: 10.1001/archinternmed.2012.121.
12. Adam SS, McDuffie JR, Ortel TL, Williams JW Jr. Comparative Effectiveness of Warfarin and New Oral Anticoagulants for the Management of Atrial Fibrillation and Venous Thromboembolism: A Systematic Review. Ann Intern Med. 2012;157(11):796-807. doi: 10.7326/0003-4819-157-10-201211200-00532.
13. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Stroke. 2012;43(12):3298-304. doi: 10.1161/STROKEAHA.112.673558.

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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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)

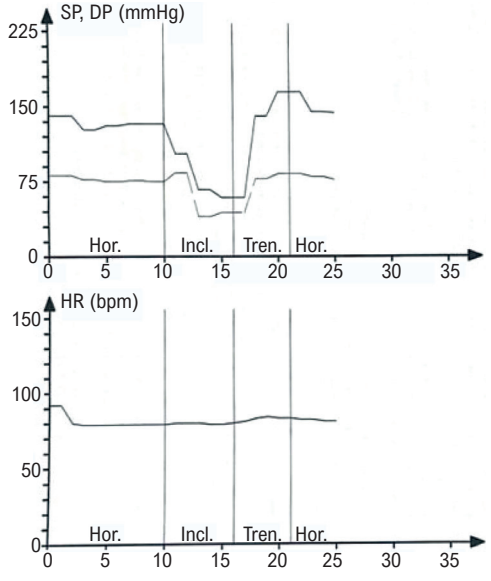
Discussion

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.



Time (min)	Phase	HR (bpm)	SP (mmHg)	DP (mmHg)
8	Hor.	79		
9	Hor.	79	133	75
10	Incl.	80	103	84
11	Incl.	80		
12	Incl.	80	67	40
13	Incl.	79		
14	Incl.	79	59	44
15	Hor.	80	76	56
16	Tren.	81		
17	Tren.	83	141	78
18	Tren.	84		
19	Tren.	84		
20	Tren.	83	165	83

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.*

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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Special thanks to the Cardiomyopathy Sector and the Amyloidosis Center of Dante Pazzanese Cardiology Institute for providing medical services to the community and contributing to the development of research in this area of neglected diseases in Brazilian health. Thanks to the hospital management and the medical teams in the sectors, for working together on behalf of patients. Special thanks to the patients who place their trust in the hospital's multidisciplinary team to care for their health.

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Potential Conflict of Interest

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References

1. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy. Heart Rhythm. 2019;16(11):301-72. doi: 10.1016/j.hrthm.2019.05.007.
2. 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.
3. Yilmaz A, Bauersachs J, Bengel F, Büchel R, Kindermann I, Klingel K, et al. Diagnosis and Treatment of Cardiac Amyloidosis: Position Statement of the German Cardiac Society (DGK). Clin Res Cardiol. 2021;110(4):479-506. doi: 10.1007/s00392-020-01799-3.
4. Castaño A, Drachman BM, Judge D, Maurer MS. Natural History and Therapy of TTR-Cardiac Amyloidosis: Emerging Disease-Modifying Therapies from Organ Transplantation to Stabilizer and Silencer Drugs. Heart Fail Rev. 2015;20(2):163-78. doi: 10.1007/s10741-014-9462-7.
5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.

Sustained Ventricular Tachycardia as an Isolated Presentation of Transthyretin Amyloidosis Cardiomyopathy - Val50Met

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Introduction

Amyloidosis is characterized by extracellular deposition of insoluble proteins (amyloid deposition) in multiple organs and progressive organ dysfunction. It is classified by the type of protein that is deposited, including transthyretin amyloidosis (ATTR), which can occur due to a genetic variant and aging.[1] Approximately 120 genetic variants have been recognized to cause ATTR; one of the most common is Val50Met. The phenotypic presentation of ATTR due to the Val50Met mutation is mostly neurological, known as familial amyloidotic polyneuropathy (FAP), but cardiac involvement is being increasingly recognized.[2] Sporadic cases with strictly cardiac manifestation, causing ventricular wall hypertrophy, dysfunction diastolic, and conduction disturbances have already been described in the literature.[3]

In this article, we report a case of ATTR due to the Val50Met mutation, with the phenotypic expression of cardiac involvement, with sustained ventricular tachycardia as an isolated presentation.

Case Report

A 61-year-old Brazilian man with hypertension, whose parents were Portuguese, complained of chest pain, followed by palpitations 1 hour before arriving at the emergency room. He presented with intense sweating, elevated heart rate (196 beats per minute) and resting blood pressure of 130/80 mmHg. Electrocardiogram revealed sustained ventricular tachycardia (Figure 1). He was promptly submitted to successful electrical cardioversion, and, 2 days later, an internal cardiac defibrillator (ICD) was implanted. During etiological investigation, several tests were performed, as described subsequently. Myocardial necrosis markers were shown to be elevated, in an ascending curve (peak CK-MB: 31.3 ug/L and ultra-sensitive troponin: 19,400 ng/ml); coronary cineangiography revealed a 30% lesion in the circumflex artery and a luminal area of 8.6 mm^2 (intracoronary ultrasound); echocardiogram showed ejection fraction of 66%, increased wall thickness (septum 19 mm and posterior wall 15 mm), increased thickness of the right ventricle (RV) and interatrial septum, left ventricle (LV) with 52/33 mm, moderate atrial enlargement (indexed left atrial volume of 45 ml/m^2) , severe diastolic dysfunction (grade III), and pulmonary artery systolic pressure (PASP) of 45 mmHg. In spite of the normal ejection fraction, global longitudinal strain showed impairment of the LV systolic function of −9 (reference value: −18), sparing the apical portion.

Magnetic resonance imaging showed the greatest thickness in the middle inferoseptal wall of the left ventricle (22 mm), diffuse late enhancement with non-ischemic, circumferential gadolinium pattern, and myocardial edema (Figure 2). The investigation of light chains, kappa:lambda ratio, serum and urinary immunofixation were negative, and pyrophosphate scintigraphy showed intense uptake of pyrophosphate labeled with symmetrical technetium in the LV walls and light intensity in the RV, with a left hemithorax to contralateral hemithorax count ratio of 2.3 (positive study > 1.5). Genetic testing revealed a mutation in the p.Val50Met transthyretin gene.

The patient evolved with weight loss, bilateral carpal tunnel syndrome, and a slight decrease in the distal strength of the lower limbs; these symptoms are compatible with impairment of the peripheral and autonomic nervous systems. He started treatment with tafamidis in November 2019. One year later, he showed symptoms of dyspnea upon exertion; upon physical examination, hepatomegaly and jugular swelling were observed. He was given a low dose of a diuretic for 3 days, and his implantable defibrillator heart rate was increased to 80 bpm, which resolved the symptoms. During evolution, he showed appropriate ICD therapy for ventricular tachycardia.

The patient evolved to become asymptomatic, reporting only that his steps slowed when climbing steep slopes. The echocardiogram was repeated 1.5 years after starting the use of tafamidis, revealing ejection fraction of 56%, septal thickness of 18 mm, posterior wall of 16 mm, increased RV and interatrial septum thickness, VE 51/36 mm, moderate atrial volume (indexed left atrial volume 42 ml/m^2), grade II diastolic dysfunction, PASP of 23 mmHg, and global longitudinal strain of –7.7.

Discussion

Ventricular tachyarrhythmia in an elderly patient with curved elevation of troponin levels is highly indicative of acute coronary syndrome.[4] In the present case, this was the first diagnostic hypothesis considered; however, coronary cineangiography ruled out this possibility. The echocardiogram, by demonstrating the presence of a significant increase in thickness in both the septum and the lateral wall, guides us

Keywords

Familial Amyloidosis; Restrictive Cardiomyopathy; Ventricular Tachycardia.

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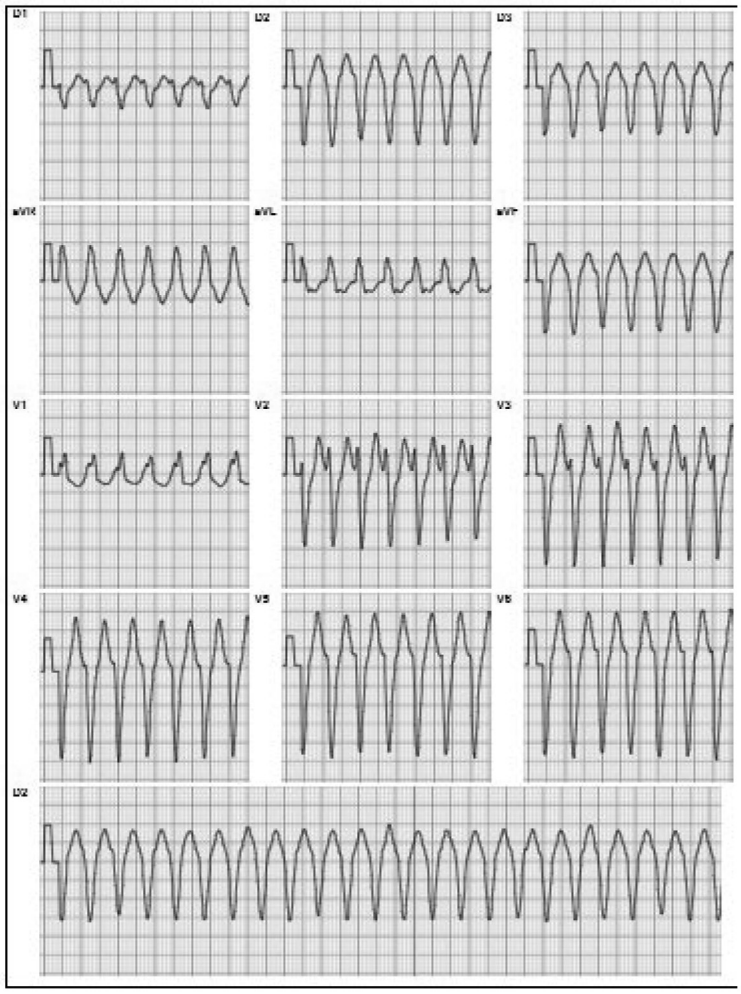

Figure 1 – *Electrocardiogram showing sustained ventricular tachycardia.*

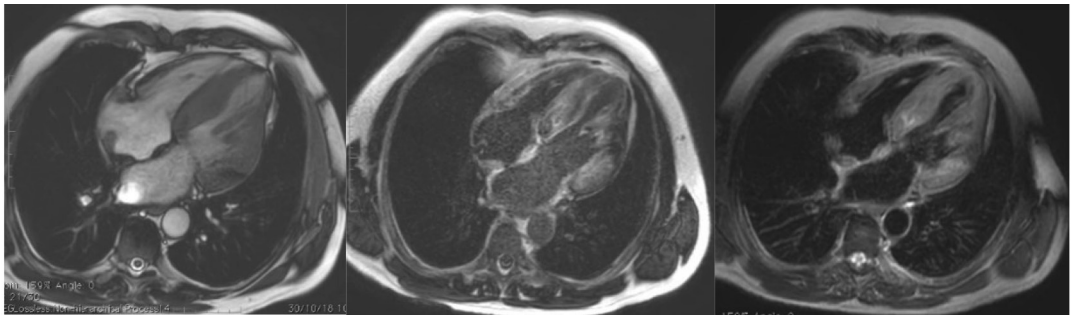

Image 1 Image 2 Image 3

Figure 2 – *Cardiac magnetic resonance showing evidence, in image 1: 4-chamber cine; image 2: 4-chamber late enhancement; image 3: Tripple BB edema.*

away from the diagnosis of inflammatory conditions due to the magnitude of hypertrophy and leads us toward diagnosis of a group of diseases that present with increased wall thickness, such as hypertrophic cardiomyopathy, which is the most prevalent after hypertensive cardiomyopathy, Fabry disease, and cardiac amyloidosis.[5] Increased wall thickness, associated with other findings on echocardiography, such as severe diastolic dysfunction, apical sparing, and significantly reduced longitudinal strain, which are typical of amyloidosis, point us toward this diagnosis. Cardiac resonance, in addition to confirming these findings, added more information that is characteristic of this disease, namely, circumferential delayed enhancement and myocardial edema. The finding of myocardial edema has been related to the acute disease; it is more common in light chain amyloidosis, and it is associated with the occurrence of severe complications.[6] In this case, the occurrence of ventricular tachycardia can be related to this structural substrate.

ICD implantation in patients with amyloidosis has conflicting indications in studies conducted before the start of specific therapy, which modifies survival. The progressive character of the disease, with progressive loss of ventricular function, may explain why the benefit of the implantation has not been demonstrated. However, currently, with the introduction of specific treatment, especially if the patient is at an earlier stage of disease evolution, in NYHA functional class I/II, it is likely that this recommendation will be modified in the guidelines, given that it is possible to expect reasonable survival.[1]

Conclusion

Val50Met is a pathogenic mutation that is characterized, mainly, as being clinically expressed by FAP. Cardiomyopathy, nephropathy, and vitreous humor opacity may be present, but PAF is the main presentation. When cardiomyopathy is present, the main presentation is generally heart failure, but without ventricular arrhythmia. In the patient whose case has been described, ventricular arrhythmia was the only manifestation, and amyloidosis was not even considered in the differential diagnosis, until magnetic resonance was performed. This case highlights the risk of sudden cardiac death in patients with hereditary ATTR. Although the association between hereditary ATTR and sudden death has been well recognized, studies have not shown any survival benefit from defibrillator implantation, perhaps due to delayed diagnosis. Hereditary ATTR should thus be considered as a cause of sustained ventricular tachycardia.

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Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Correia EB, Bruscky LVR; Acquisition of data: Correia EB, Bruscky LVR, Silva LML, Murta ACS; Analysis and interpretation of the data: Correia EB, Bruscky LVR, Chen K, Quagliato PC; Writing of the manuscript: Correia EB, Bruscky LVR, Francisco YA, Silva LML.

Ethics approval and consent to participate

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References

1. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
2. Yilmaz A, Bauersachs J, Bengel F, Büchel R, Kindermann I, Klingel K, et al. Diagnosis and Treatment of Cardiac Amyloidosis: Position Statement of the German Cardiac Society (DGK). Clin Res Cardiol. 2021;110(4):479-506. doi: 10.1007/s00392-020-01799-3.
3. Cordeiro CP, Pozzatti RR, Ferreira SG, Freitas MS, Rocha AM, Ribeiro ML, et al. Cardiomyopathy Related to Transthyretin Val30met Mutation in Hereditary Systemic Amyloidosis. Arq Bras Cardiol. 2015;28(2):104-8. doi: 10.5935/2318-8219.20150012.
4. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy. Heart Rhythm. 2019;16(11):301-72. doi: 10.1016/j.hrthm.2019.05.007.
5. Bruscky LVR, Murta ACS, Albrecht FC, Magalhães MJL, Borges Filho R, Francisco YA. Differential Diagnosis among Cardiomyopathies that evolve with ventricular hypertrophy. Rev Soc Cardiol Estado de São Paulo. 2021;31(2):171-80. doi: http://dx.doi.org/10.29381/0103-8559/20213102171-80.
6. Fontana M, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. JACC Cardiovasc Imaging. 2019;12(11):2345-56. doi: 10.1016/j.jcmg.2019.06.023.

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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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/mm^3; hemaglobin, 14.6/mm^3; platelet count 202/mm^3; 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

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]

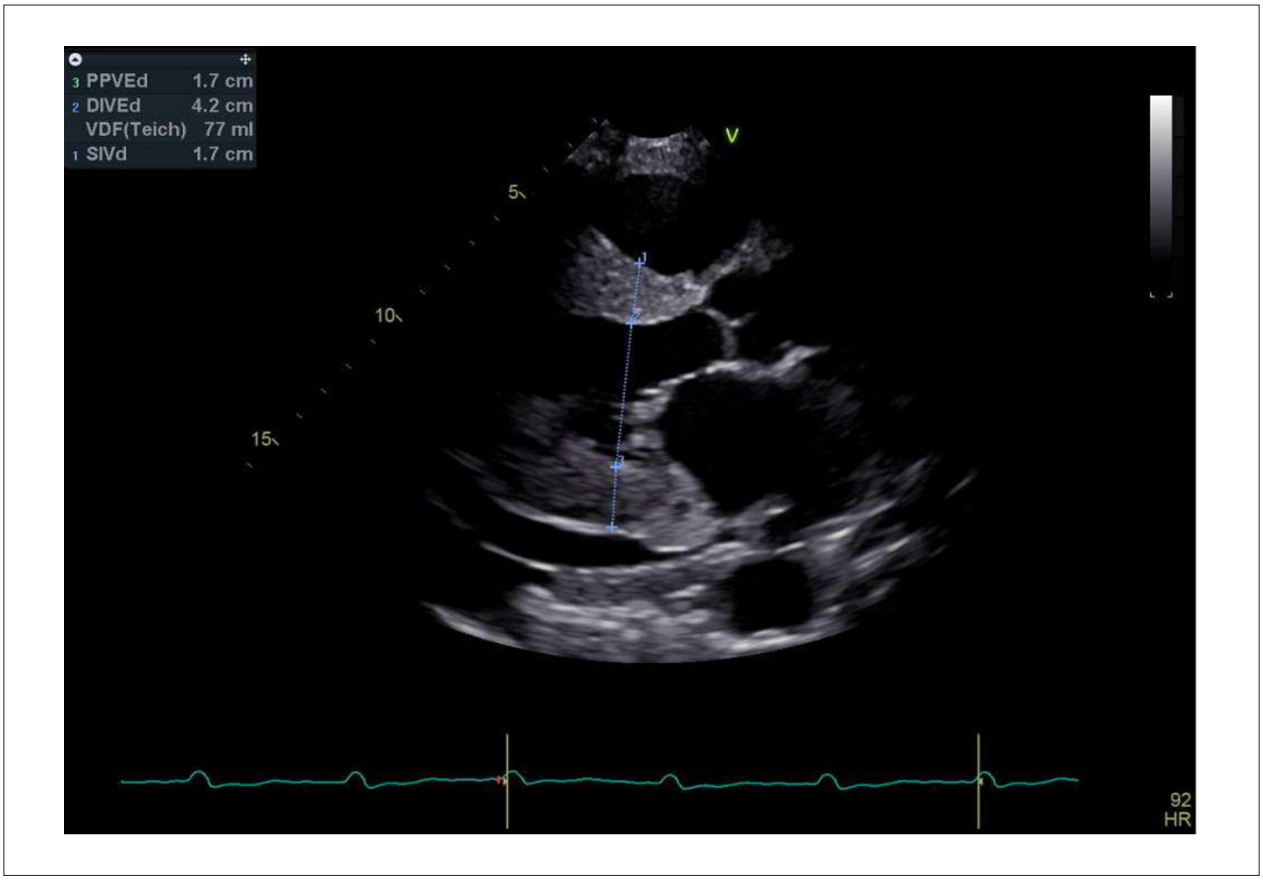

Figure 1 – *Echocardiogram showing increased thickness of the septal and inferior lateral walls, increased thickness of the interatrial septum and mitral and aortic valves, and pericardial effusion.*

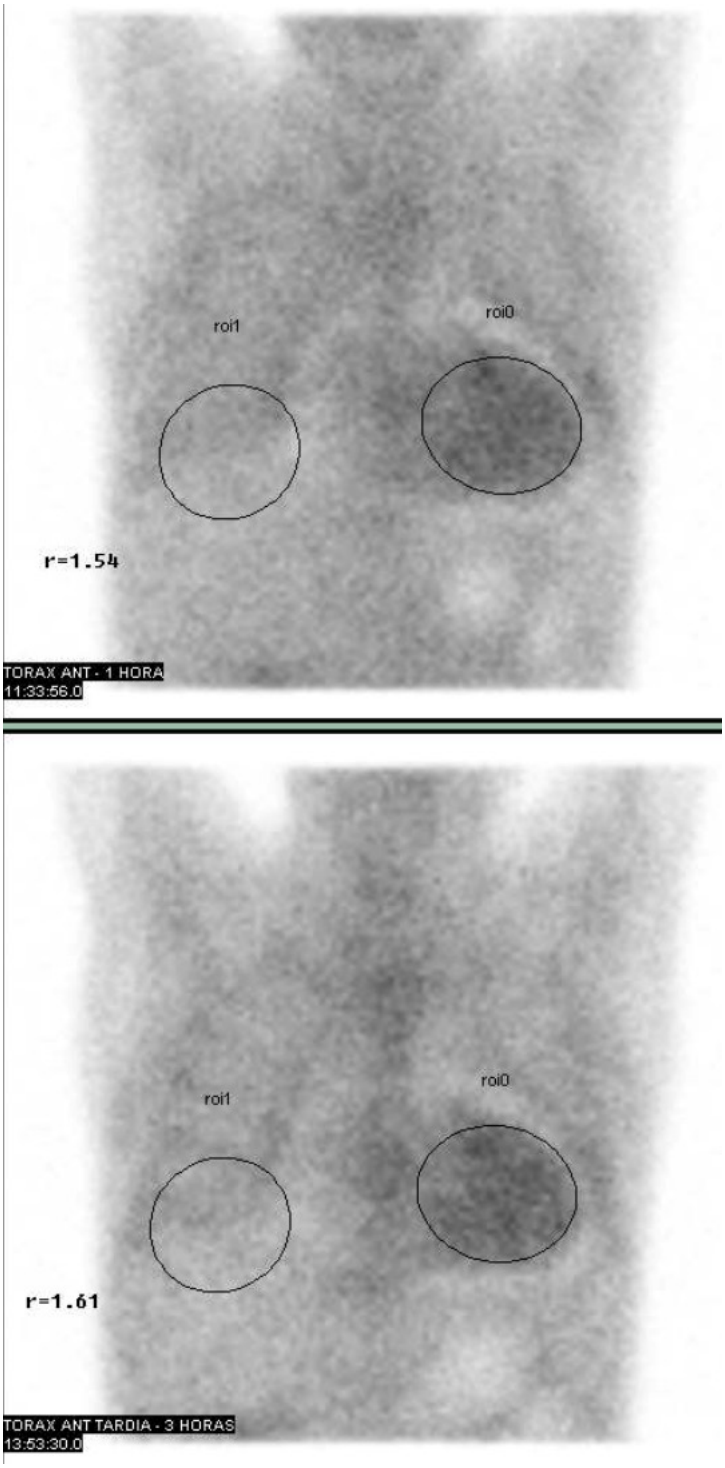

Figure 2 – *Cardiac pyrophosphate scintigraphy at 1 hour and 3 hours, showing grade 3 cardiac uptake.*

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

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References

1. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic Amyloidosis. Lancet. 2016;387(10038):2641-54. doi: 10.1016/S0140-6736(15)01274-X.
2. Buxbaum JN, Tagoe CE. The Genetics of the Amyloidoses. Annu Rev Med. 2000;51:543-69. doi: 10.1146/annurev.med.51.1.543.
3. Gorevic PD, Prelli FC, Wright J, Pras M, Frangione B. Systemic Senile Amyloidosis. Identification of a New Prealbumin (transthyretin) Variant in Cardiac Tissue: Immunologic and Biochemical Similarity to One Form of Familial Amyloidotic Polyneuropathy. J Clin Invest. 1989;83(3):836-43. doi: 10.1172/JCI113966.
4. Dungu JN, Papadopoulou SA, Wykes K, Mahmood I, Marshall J, Valencia O, et al. Afro-Caribbean Heart Failure in the United Kingdom: Cause, Outcomes, and ATTR V122I Cardiac Amyloidosis. Circ Heart Fail. 2016;9(9):e003352. doi: 10.1161/CIRCHEARTFAILURE.116.003352.
5. Connors LH, Prokaeva T, Lim A, Théberge R, Falk RH, Doros G, et al. Cardiac Amyloidosis in African Americans: Comparison of Clinical and Laboratory Features of Transthyretin V122I Amyloidosis and Immunoglobulin Light Chain Amyloidosis. Am Heart J. 2009;158(4):607-14. doi: 10.1016/j.ahj.2009.08.006.
6. Reddi HV, Jenkins S, Theis J, Thomas BC, Connors LH, Van Rhee F, et al. Homozygosity for the V122I Mutation in Transthyretin is Associated with Earlier Onset of Cardiac AMYLOIDOSIS in the African American population in the Seventh Decade of Life. J Mol Diagn. 2014;16(1):68-74. doi: 10.1016/j.jmoldx.2013.08.001.
7. Negrín NM, Gil JMM, Cruz MLG, Cabrera FJ. Transthyretin Cardiac Amyloidosis Due to Homozygous Val122Ile Mutation in a Caucasian Man. Rev Esp Cardiol (Engl Ed). 2019;72(12):1086-8. doi: 10.1016/j.rec.2019.06.007.
8. Westermark P, Westermark GT, Suhr OB, Berg S. Transthyretin-Derived Amyloidosis: Probably a Common Cause of Lumbar Spinal Stenosis. Ups J Med Sci. 2014;119(3):223-8. doi: 10.3109/03009734.2014.895786.
9. Maetani Y, Agari D, Nomura E, Ueda M, Ando Y, Yamawaki T. Familial amyloid polyneuropathy involving a homozygous Val30Met mutation in the amyloidogenic transthyretin gene presenting with superficial siderosis: a case report. Rinsho Shinkeigaku. 2016;56(6):430-4. doi: 10.5692/clinicalneurol.cn-000869.
10. Dubrey SW, Burke MM, Khaghani A, Hawkins PN, Yacoub MH, Banner NR. Long Term Results of Heart Transplantation in Patients with Amyloid Heart Disease. Heart. 2001;85(2):202-7. doi: 10.1136/heart.85.2.202.
11. Hamour IM, Lachmann HJ, Goodman HJ, Petrou M, Burke MM, Hawkins PN, et al. Heart Transplantation for Homozygous Familial Transthyretin (TTR) V122I Cardiac Amyloidosis. Am J Transplant. 2008;8(5):1056-9. doi: 10.1111/j.1600-6143.2008.02162.x.

Heart Failure Due to Cardiac Transthyretin Amyloidosis

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Abstract

A 90-year-old male patient presented with complaints and physical examination compatible with decompensated heart failure. Electrocardiogram showed atrial fibrillation and low voltage in limb leads, and echocardiogram identified biatrial dilatation, in addition to mild increases in ventricular wall thickness and diameter. Magnetic resonance imaging confirmed suspicion of cardiac amyloidosis. With negative serum and urinary protein electrophoresis and positive pyrophosphate cardiac scintigraphy, diagnosis of transthyretin cardiac amyloidosis was confirmed. Transthyretin gene mutations were not identified on sequencing, characterizing wild-type transthyretin cardiac amyloidosis.

Case Report

A 90-year-old man sought emergency assistance at a hospital complaining of dyspnea on mild exertion, orthopnea, paroxysmal nocturnal dyspnea, and lower limb edema for 3 weeks. Until 4 months before presentation, he had been able to walk close to his residence without any major limitations and climb 2 flights of stairs. Since then, he had had a decline in functional capacity, with progressive dyspnea on exertion. He did not complain of chest pain, palpitations, or syncope.

Previously, he had been diagnosed with glaucoma, benign prostatic hyperplasia, and depression, for which he was receiving treatment with timolol and travoprost eye drops, finasteride 5 mg daily, doxazosin 2 mg in the evening, and escitalopram 10 mg daily. In the past, he had undergone inguinal hernioplasty and appendectomy, as well as transurethral resection of the prostate. He denied tobacco or alcohol use. After the death of his wife, which had occurred 3 months before hospitalization, he lived with his daughter. He had not traveled recently, and he had no history of allergies.

On physical examination upon arrival at the hospital, he was in regular general state, with well hydrated and colored mucous membranes; he was anicteric, acyanotic, alert, oriented, and cooperative. Blood pressure was 107/62 mmHg; heart rate was 110 bpm, and respiratory rate 24 breaths per minute. He was afebrile, and peripheral oxygen saturation was 93%, while breathing spontaneously with an O2 nasal catheter at 3 L/min. He showed jugular turgescence at 45°, irregular cardiac auscultation, with 2 sounds, and normal heart sounds, without murmurs. Pulmonary auscultation revealed abolished vesicular murmur at the right base, with crackling rales up to the middle thirds bilaterally. Palpation of the upper right quadrant of the abdomen was painful, and he had edema with Godet's sign in the lower limbs extending to the area below the knees. Extremities were warm, and capillary refill time was adequate.

Anteroposterior chest radiograph was conducted, showing bilateral pleural effusion, which was greater on the right, and extensive interstitial infiltrate, predominantly in bases, compatible with the clinical hypothesis of decompensated heart failure. Electrocardiogram on arrival showed atrial fibrillation rhythm with frequent monomorphic ventricular extrasystoles, left bundle branch block, and low voltage in limb leads (Figure 1a). Laboratory tests demonstrated ultrasensitive troponin I of 59.1 pg/mL (reference value 0 to 34.2 pg/mL) and brain natriuretic peptide of 1243.2 pg/mL (reference value 0 to 100 pg/mL).

Transthoracic echocardiogram revealed dilation of both atria, slightly increased ventricular diameters, septal thickness of 13 mm, and posterior wall thickness of 11 mm, with left ventricular ejection fraction of 35% (Figure 1b). The right ventricle was normal, and there was moderate tricuspid regurgitation, with no signs of significant pulmonary hypertension. The other echocardiographic parameters are displayed in Table 1.

The clinical, electrocardiography, and echocardiography findings led to suspicion of cardiac amyloidosis. In order to define diagnosis, cardiac magnetic resonance and electrophoresis of blood and urine proteins with immunofixation were initially performed. Cardiac magnetic resonance showed partial nulling of the myocardial signal with extensive late enhancement of mesocardial and endocardial non-ischemic aspect, with circumferential involvement, predominantly in the basal portions, and additional involvement of the right ventricle and atria. These characteristics and distribution are associated with amyloidosis (Figure 2). Electrophoresis did not identify any monoclonal paraproteinemia.

The patient was treated for decompensated heart failure with a diuretic, which resolved the congestion; functional limitation persisted, compatible with New York Heart Association functional class III. Moreover, anticoagulation with rivaroxaban was initiated in order to prevent thromboembolic phenomena secondary to atrial fibrillation.

When the patient was discharged, exams for transthyretin (TTR) gene mutation and myocardial scintigraphy with pyrophosphate were forwarded. Thirty days later, when he returned to the outpatient clinic, he showed clinical

Palavras-chave

Heart Failure; Amyloidosis; Prealbumin.

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Figure 1a

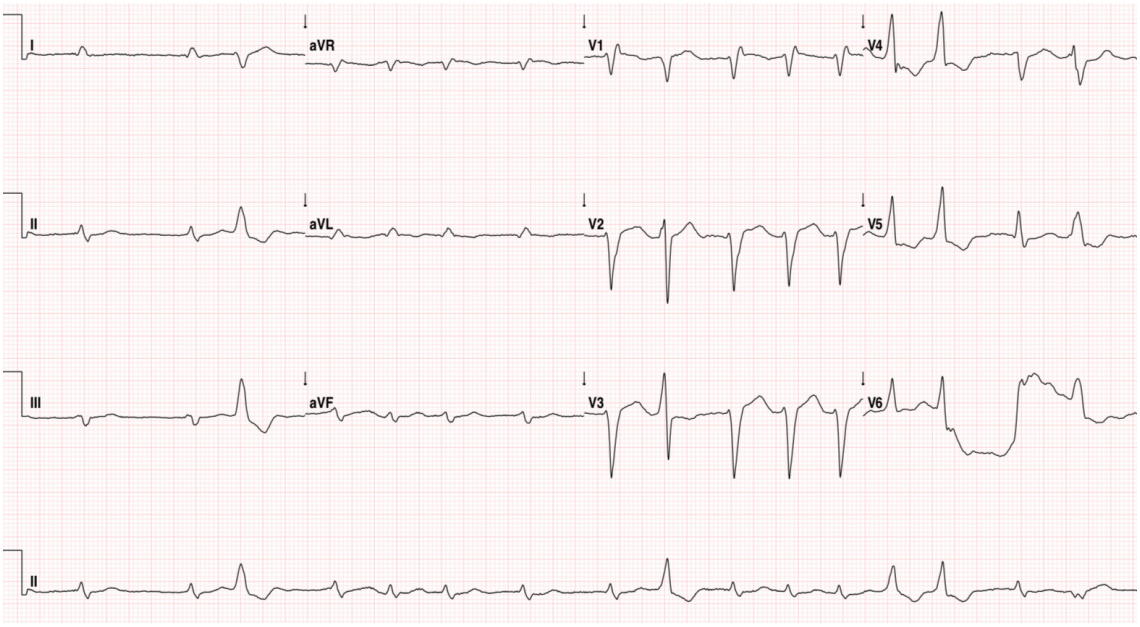

Figure 1b

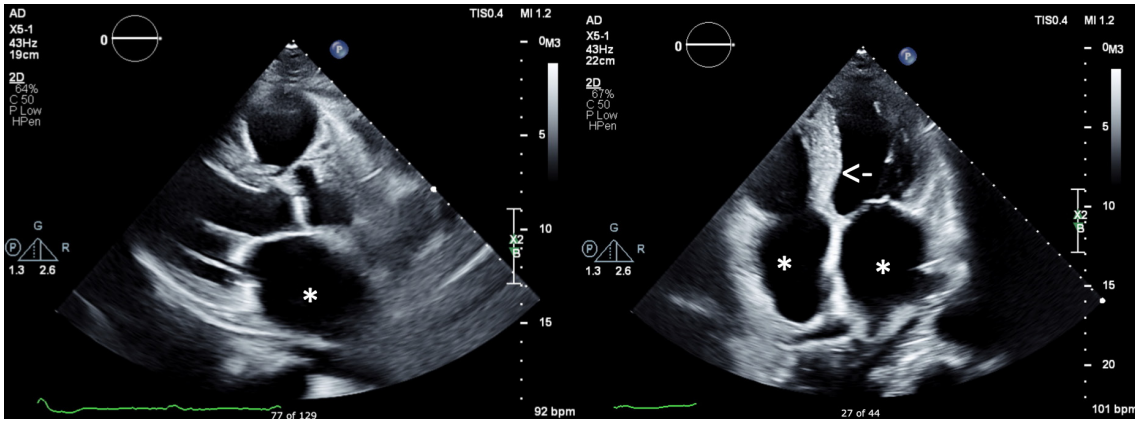

Figure 1 – *1a. Electrocardiogram demonstrating atrial fibrillation with frequent ventricular extrasystoles, left bundle branch block, and low voltage in limb leads. 1b. Transthoracic echocardiogram with biatrial dilatation (*) and increased thickness of the interventricular septum (<-).*

Table 1 – Transthoracic echocardiogram

Echocardiography measurements		Reference values
Aortic root	37 mm	up to 39 mm
Left atrial diameter	58 mm	up to 40
Left atrial indexed volume	72 mL/m2	up to 34 mL/m2
Systolic left ventricle	53 mm	up to 59 mm
Diastolic left ventricle	44 mm	up to 40 mm
Septal thickness	13 mm	up to 11 mm
Posterior wall thickness	11 mm	up to 11 mm
Left ventricular ejection fraction	35%	> 50%
Basal right ventricle	40 mm	up to 41 mm

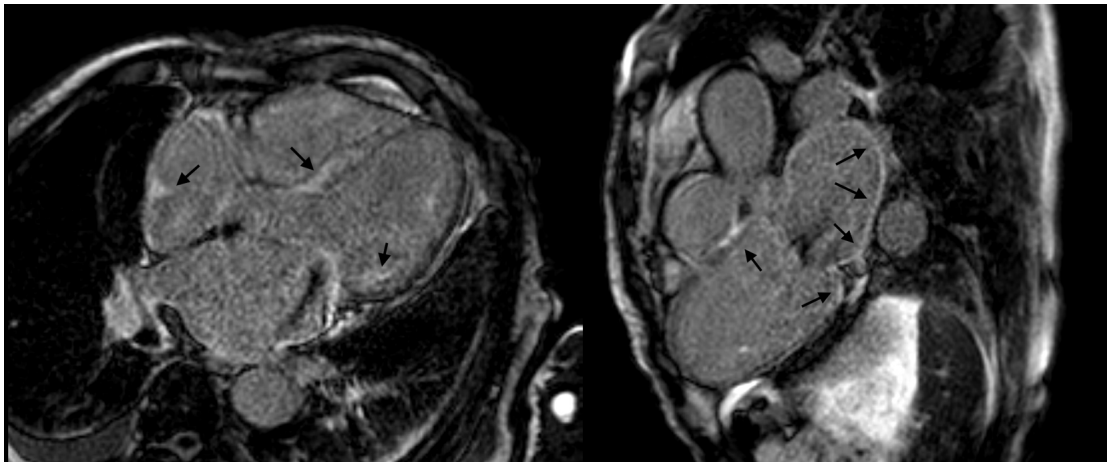

Figure 2 – *Cardiac magnetic resonance imaging with delayed enhancement of non-ischemic appearance, predominantly in the basal portions of the left ventricle, right ventricle, and atria (arrows).*

improvement, and he was able to take short walks, without orthopnea or clinical signs of pulmonary congestion. Investigation of mutations of the transthyretin gene was negative, and scintigraphy showed grade 2 myocardial uptake (Figure 3). These findings, in the absence of evidence of plasma cell dyscrasia, are compatible with the diagnosis of wild-type TTR amyloidosis. Thus, treatment with tafamidis 80 mg a day was prescribed, and outpatient follow-up was maintained. The patient is waiting for the medication to be provided.

Discussion

Amyloidosis is a systemic or localized disease characterized by tissue deposition of insoluble fibrillar proteins that are resistant to proteolysis and that have lost their conformation, which can lead to organic dysfunction, including the heart. More than 30 types of proteins with amyloidogenic potential have been described. However, about 95% of cases of cardiac amyloidosis are related to 2 types of deposition: light chain immunoglobulins (AL) or transthyretin (ATTR); the latter may be secondary to mutation (ATTRm) or wild (ATTRwt), usually induced by changes related to aging.[1] Although it is one of the most rapidly progressive heart diseases and one of the ones with the worst prognosis, with average untreated survival of less than 6 months for the AL form and between 3 and 5 years for ATTR, diagnosis often goes unnoticed or is delayed. It is estimated that the prevalence of AL amyloidosis is around 8 to 12 cases per million, and 30% to 50% of these individuals will develop some cardiac symptom. The estimated prevalence of the ATTR form is more uncertain, with recent data suggesting underdiagnosis, especially in the elderly. Autopsy studies have shown amyloid TTR deposits in the myocardium of 25% of individuals over 80 years of age.[1,2]

Heart failure with preserved ejection fraction, especially in elderly men, is an early manifestation characteristic of cardiac amyloidosis, most often accompanied by echocardiographic changes (concentric hypertrophy, diastolic dysfunction, and septal thickening).[2] Atrial fibrillation or flutter or conduction system abnormalities are also common findings.[3] Bilateral carpal tunnel syndrome manifests approximately 5 to 10 years before diagnosis of ATTRwt amyloidosis in up to 70% of patients, and it may indicate an initial manifestation of transthyretin deposits. Sensory and autonomic neuropathy, orthostatic hypotension, biceps tendon rupture, spinal stenosis, and digestive disorders are also among the multisystem manifestations that may raise suspicion of ATTR. Therefore, with patients who complain of progressive exercise intolerance associated with any of these conditions and cardiac imaging suggestive of concentric thickening of the left ventricle, with an infiltrative phenotype or a restrictive pattern, it is necessary to be alert to the possibility of cardiac amyloidosis. [2,3]

Given that it is a disease with complex diagnosis, high clinical suspicion is fundamental. As highlighted in the recent Position Statement of the Brazilian Society of Cardiology[4], there are some warning signs, also known as clinical clues, that should lead to further investigation. In the reported case, there was a considerable mismatch between the left ventricular concentric hypertrophy and the electrocardiographic manifestations, most notably in the limb leads.

When facing clinical suspicion of cardiac amyloidosis, careful analysis of cardiovascular tests is essential. Resting electrocardiograms may show suggestive changes, such as low voltage, absence of R-wave progression in precordial leads, or changes in heart rhythm. On echocardiography, we may identify characteristics of restrictive infiltrative cardiomyopathy, with diastolic dysfunction, thickening of the walls and septum, increased filling pressures, and biatrial dilatation. Ejection fraction usually remains preserved until later stages of the disease. Cardiac magnetic resonance imaging makes it possible to accurately assess changes in myocardial tissue, such as increased ventricular thickness, as well as the presence of delayed enhancement, which have a sensitivity of 85% and a specificity of 92% for diagnosing cardiac amyloidosis.

In order to differentiate between the AL and ATTR forms, a search for monoclonal light chains must be carried out, requiring the measurement of the serum kappa:lambda ratio and serum

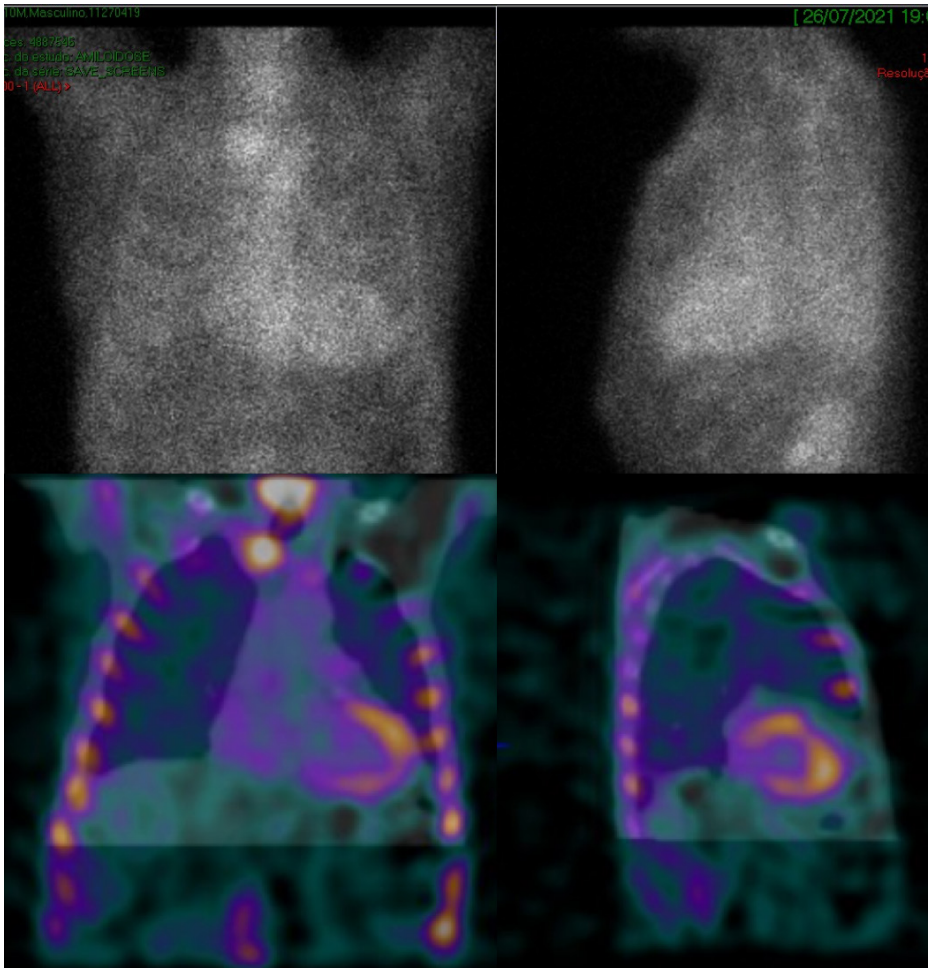

Figure 3 – *Myocardial pyrophosphate scintigraphy with planar images (upper quadrants) and SPECT (lower quadrants), showing increased cardiac uptake in relation to the contralateral chest, with similar intensity to that of the costal arches (grade 2).*

and urinary immunofixation. In the event that one of these tests is positive, a hematologist should be consulted, and a biopsy of peripheral tissues should be obtained for analysis and confirmation of diagnosis, as well as typing of the amyloid protein.

In the absence of monoclonal proteins, the cardiological path of the Brazilian Position Statement on Amyloidosis should be followed[4] (Figure 4). Cardiac scintigraphy with pyrophosphate is the exam of choice for confirming diagnosis, given that it can have 99% sensitivity and 86% specificity in diagnosing the ATTR form. Gene sequencing is recommended to differentiate between wild and hereditary forms.

Treatment of ATTR involves treating the clinical syndrome and specific approaches that interfere with the formation and deposition of amyloid fibrils. Liver transplantation was once the preferred option, but, currently, the use of TTR stabilizers, inhibitors of liver synthesis of TTR, and degradation and reabsorption of TTR fibrils has gained prominence. Among these strategies, tafamidis, a molecule that effectively inhibits the cascade of amyloid fibril formation, is the only drug that has been proven to prolong survival in patients with ATTR.[5] Among therapies in the experimental phase, the following stand out: patisiran[6] (microRNA that inhibits expression of genes that encode the liver production of TTR), compounds that stabilize TTR, and compounds that induce TTR degradation and reabsorption.

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Author contributions

Conception and design of the research: Motta HB, Biolo A. Acquisition of data: Motta HB, Costa GOM, Biolo A. Writing of the manuscript: Motta HB, Costa GOM, Biolo A. Critical revision of the manuscript for intellectual content: Motta HB, Biolo A.

Case Report

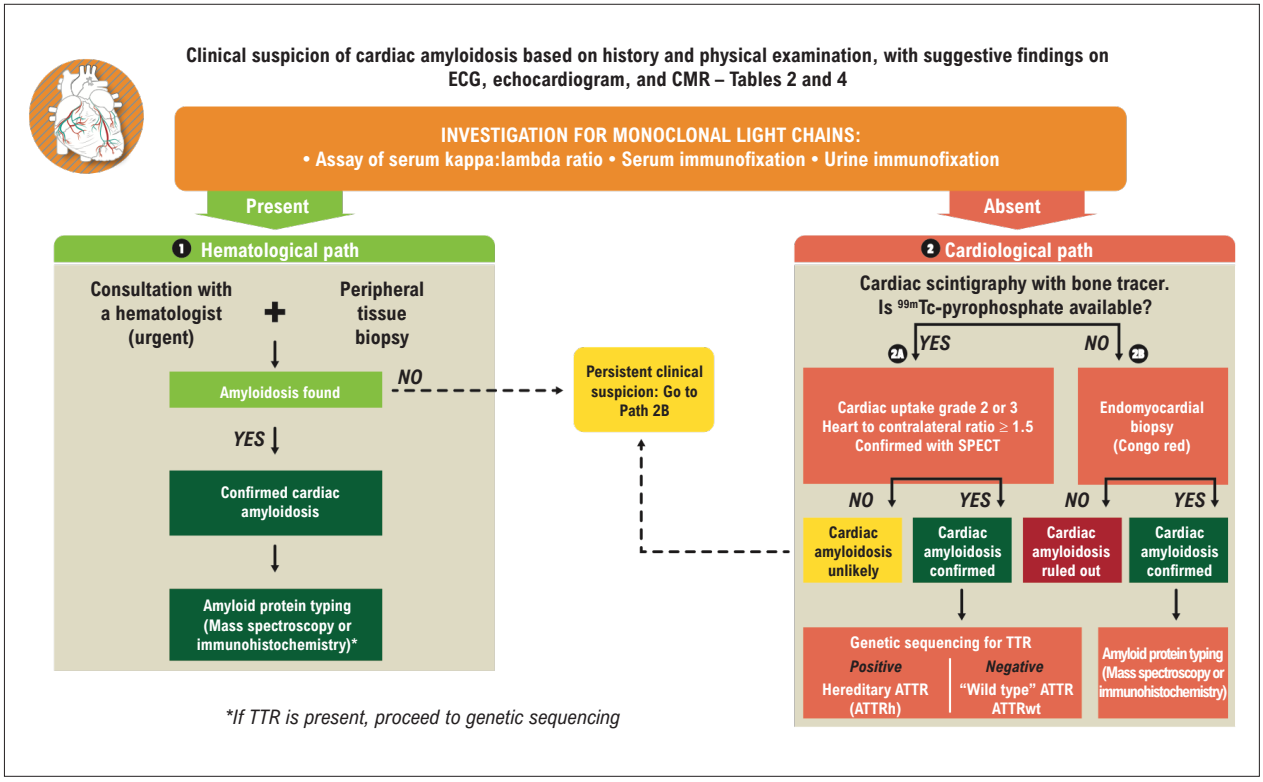

Figure 4 – *Flowchart for diagnostic investigation of cardiac amyloidosis, according to the Position Statement of the Brazilian Society of Cardiology. ATTR: transthyretin amyloidosis; CMR: cardiac magnetic resonance; ECG: electrocardiogram; TTR: transthyretin*

Potential Conflict of Interest

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

Sources of Funding

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References

1. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation. 2017;135(14):1357-77. doi: 10.1161/CIRCULATIONAHA.116.024438.
2. Dorbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis: A Practical Approach. JACC Cardiovasc Imaging. 2020;13(6):1368-83. doi: 10.1016/j.jcmg.2019.07.015.
3. Muchtar E, Dispenzieri A, Magen H, Grogan M, Mauermann M, McPhail ED, et al. Systemic Amyloidosis from A (AA) to T (ATTR): A Review. J Intern Med. 2021;289(3):268-92. doi: 10.1111/joim.13169.
4. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. doi: 10.1056/NEJMoa1805689.
6. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):11-21. doi: 10.1056/NEJMoa1716153.

First Combined Heart-Liver Transplant in Amyloidosis Due to Transthyretin Mutation in Brazil: Impact of the Liver on Reducing anti-HLA Antibodies

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Introduction

Cardiac amyloidosis is characterized by the presence of deposits of amyloid material between myocardial fibers, leading to impaired function. In 95% of cases, it can be secondary to excessive production of abnormal light chain immunoglobulins or changes in transthyretin (TTR), either due to mutation or wild type. TTR is a protein produced mainly by the liver, and it is responsible for transporting retinol and thyroid hormone. Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant genetic disease due to mutation in the TTR gene, and it has high morbidity and mortality, especially when there is cardiac involvement. More than 130 mutations have been described, and they determine phenotypes of neurological and/or cardiac predominance. Historically, liver transplantation was the standard treatment to reduce progression of FAP; in the presence of heart disease with advanced heart failure (HF), heart transplantation may be considered. Combined heart-liver transplant (CHLT), although uncommon, is a well-established indication for transthyretin amyloidosis (ATTR), with good outcomes; furthermore, the presence of the liver seems to minimize the risks of cellular or antibody-mediated rejection, which could be of interest for patients with high immunological risks, especially those with human leukocyte antigen (HLA) hypersensitivity.

Objective

To report the first CHLT in Brazil, performed in a patient with ATTR with a mixed phenotype, in the context of cardiogenic shock, who, as an additional risk factor, had HLA hypersensitivity.

Case Report

"RGP," a 50-year-old female patient, who worked as a housewife and had 2 children, began to have a condition of HF associated with sensory motor polyneuropathy, orthostatic hypotension, and diarrhea, in 2013; regarding family history, she reported that her father and brother had died of undefined heart disease at the age of 50; in 2015, she had signs and symptoms of HF requiring frequent hospitalizations. Electrocardiogram revealed an anteroseptal electrically inactive area and low voltage in the frontal plane; echocardiogram revealed thickening of the septum and posterior wall of 13 mm, left ventricular diameters 54 × 43 mm, left ventricular ejection fraction 32%, and severe diastolic dysfunction (restrictive pattern). Magnetic resonance imaging revealed diffuse late enhancement with a non-coronary pattern, suggesting deposition disease. In this context, she underwent endomyocardial biopsy, which was positive for Congo red, defining diagnosis of cardiac amyloidosis. Electroneuromyography showed sensory-motor pattern of upper and lower limbs. She was referred to the liver transplant unit at the Hospital Israelita Albert Einstein, and light chain amyloidosis was ruled out (free light chain, negative serum and urinary immunofixation); heterozygous Glu89Lys mutation in the TTR gene was confirmed, and an evaluation of the heart transplant group was requested. Due to the recurrent hospitalizations due to decompensated HF and difficult clinical management, pre-transplant evaluation tests were requested, including immunological evaluation through the collection of lymphocyte panel reactive antibody (PRA), and the presence of anti-HLA antibodies was identified in 51% of class I and was negative in class II.

The patient was hospitalized in cardiogenic shock and maintained compensated with inotropic agents and intravenous diuretics; 3 months after admission, on October 17, 2017, she underwent simultaneous CHLT, as a priority recipient, due to inotropic dependence; there was positive virtual crossmatch (donor HLA A 11.23, B 07.35, DR 03.04 and presence of antiB35-MFI 2094) and real crossmatch due to negative complement-dependent cytotoxicity. She received induction with basiliximab. Collection of PRA in the pre-reperfusion portal vein and the post-reperfusion vena cava demonstrated an immediate antibody-reducing effect after the passage of blood through the transplanted liver. The explanted heart and liver were Congo red positive. Time zero liver biopsy showed grade 1 preservation-reperfusion injury. Maintenance immunosuppression was initiated with corticosteroid, tacrolimus, and mycophenolate. On postoperative day 3 after the transplant, she presented an episode of severe abdominal pain, characterized by acute abdomen secondary to extensive intramural hematoma of the ascending colon, and she underwent right hemicolectomy

Keywords

Amyloidosis; Double heart-liver transplant

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and colostomy. She required hemodialysis due to acute renal failure (urea 104 mg/dl and creatinine 1.4 mg/dl the day before the transplant) and remained dependent on vasopressor drugs for a prolonged period, requiring the association of fludrocortisone and venlafaxine for weaning from noradrenaline. Due to intense diarrhea and abdominal pain, she did not tolerate the use of mycophenolate, and immunosuppression was maintained with corticosteroids and tacrolimus. Serial endomyocardial biopsies showed no cell rejection (0R); moreover, there were no histological or immunohistological signs (c4d and CD68) of antibody-mediated rejection (pAMR0). She showed good hepatic progression, in relation to function and integrity, without requiring biopsy. She was discharged on January 11, 2018, on postoperative day 86, receiving tacrolimus and prednisone, on intermittent hemodialysis.

The patient underwent intestinal transit reconstruction 6 months after hemicolectomy (April 2018). On account of recurrent episodes of urinary tract infection, in addition to the context of dysautonomia and risk of renal graft loss due to hypotension, kidney transplantation was not indicated. Serially collected PRA demonstrated a fluctuation in the levels of anti-HLA antibodies; however, they were always negative to the specific donor antibody (B35) (Table 1). Endomyocardial biopsies did not show rejection (Table 2), and non-invasive coronary disease evaluations were negative. Over time, there were episodes of hospitalization due to long-term hemodialysis catheter infection and, in the last year, need for surgery to treat a tibial fracture due to a fall. The patient was stable from the point of view of symptoms of polyneuropathy. She maintains outpatient follow-up, with no symptoms of HF; cardiac and liver grafts show no signs of dysfunction, and the patient maintains intermittent hemodialysis. One of the children and niece 30 years old have the same mutation; they have incipient polyneuropathy and heart disease, and they began use of tafamidis after diagnosis.

Discussion

To the best of our knowledge, this is the first CHLT performed in Brazil; in addition to the fact that it was unprecedented in our country, the presence of HLA hypersensitization, where liver transplantation promoted an immediate reduction of antibodies, was a further interesting characteristic.

CHLT may be indicated for patients with heart diseases that lead to cardiac cirrhosis, especially congenital diseases, patients with liver cirrhosis and concomitant heart disease, and patients with FAP and cardiomyopathy. According to the ISHLT registry, CHLT was responsible for less than 1% of heart transplants performed in 2019, and FAP was the most common cause, accounting for more than half of cases. It may be performed simultaneously (heart transplant immediately followed by liver transplant, from the same donor) or sequentially (heart transplant preceded or followed by liver transplant, from different donors); in cases of FAP, simultaneous transplantation has been more frequent. Another interesting aspect is the possibility of using the liver of a patient with FAP (domino transplant), in spite of the risk of inducing FAP in the recipients.

In the literature and in Brazil, the Val30Met mutation appears to be the most common, and its relationship with

Table 1 – Evolution of lymphocyte panel reactive antibody

Date (DD/MM/YYYY)		Class I	Class II	DSA/MFI
04/03/2016	Pre-transplant	51%	Negative	B35 3753
17/10/2017	Pre-transplant	46.7%	Negative	B35 2094
17/10/2017	Pre-reperfusion portal	18.1%	Negative	B35 1044
17/10/2017	Post-reperfusion cava	2.6%	Negative	B35 979
07/11/2017	Post-transplant	73.1%	Negative	Absent
13/11/2017	Post-transplant	73.8%	Negative	Absent
11/12/2017	Post-transplant	61%	Negative	Absent
29/01/2018	Post-transplant	61%	Negative	Absent
14/03/2018	Post-transplant	30.3%	Negative	Absent
22/05/2018	Post-transplant	62.3%	Negative	Absent
31/07/2018	Post-transplant	35.4%	Negative	Absent
29/10/2018	Post-transplant	0%	Negative	Absent
06/08/2019	Post-transplant	0%	Negative	Absent
21/09/2020	Post-transplant	6.6%	Negative	Absent
15/12/2020	Post-transplant	6.6%	Negative	Absent
19/04/2021	Post-transplant	6.6%	Negative	Absent

Donor HLA: A 11,23 / B 07,35 / DR 03,04; DSA: donor specific antibody; MFI: median fluorescence intensity.

Table 2 – Endomyocardial biopsies

Date (DD/MM/YYYY)	Cellular rejection	Humoral rejection	Congo red
01/11/2017	0R	pAMR 0	negative
07/12/2017	0R	pAMR 0	negative
15/02/2018	0R	pAMR 0	negative
06/11/2018	0R	pAMR 0	negative
08/04/2021	0R	pAMR 0	negative

pAMR: pathology antibody mediated rejection

the development of advanced cardiomyopathy is less frequent and generally occurs later, with good outcomes by means of isolated liver transplant. On the other hand, the Val122Ile mutation, which is present in 4% of African Americans has shown a predominantly cardiac phenotype, affecting patients over 60 years of age, and it is a differential diagnosis for wild-type ATTR; due to the older age of onset and the inherent risk of combined transplant in this age group, some reports have shown good evolution involving heart transplant alone. Other mutations may have mixed characteristics of involvement, and many of them have already been described in case series, including Glu89Lys, as an indication for CHLT. There appear to be better results with combined transplant compared to isolated liver transplant; however, each case must be evaluated in an individualized manner, considering the mutation and the phenotype/manifestation of the disease at the moment of evaluation. With the development of therapeutic strategies that act in different phases of the evolution of ATTR, it is likely that liver and heart transplants related to FAP become even less frequent; however, in our case, due to advanced cardiomyopathy, including the need for inotropic agents, the indication of simultaneous CHLT was unquestionable. Due to the reduced size of the left ventricular cavity and the frequent involvement of the right ventricle, there may be limitations to the use of long-term mechanical circulatory assist devices.[1]

From an immunological point of view, CHLT shows a lower incidence of rejection, whether cellular or antibody-mediated.[3,4] Many mechanisms have been proposed to explain the tolerance properties of the liver which may possibly act simultaneously to reduce risk of rejection; among them, we can highlight the ability to secrete soluble class I HLA antigens, allied to the great capacity for absorption and neutralization of alloantibodies directed against HLA antigens. In our case, it was possible to demonstrate the ability to reduce anti-HLA antibodies in the first passage of blood through the transplanted liver; in spite of positive virtual crossmatch, there was a progressive reduction in specific antibody titers against the donor, until negativization; moreover, serial biopsies never demonstrated cellular or antibody-mediated rejection.

Notwithstanding the excellent survival to date, as well as the normal cardiac and liver graft function, multiple complications occurred throughout the reported transplant, including acute abdomen and need for colectomy and transit reconstruction, multiple infections, fracture, and chronic renal failure on dialysis, thus demonstrating the complexity and challenges inherent to CHLT in the population of patients with FAP.

Conclusion

Patients with FAP and cardiac involvement can benefit from CHLT, as demonstrated in this first Brazilian case report. Notwithstanding the presence of HLA hypersensitivity and specific antibodies against the donor, there was a reduction in titers in the first passage of blood through the liver and the case has progressed without rejection to date, reinforcing the concept of hepatic protection in the context of CHLT.

Author contributions

Conception and design of the research: Mangini S, Sabbion BC, Poffo R, Meira Filho SP, Almeida MD, Bacal F. Writing of the manuscript: Mangini S, Sabbion BC. Critical revision of the manuscript for intellectual content: Mangini S, Sabbion BC, Bacal F.

Potential Conflict of Interest

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Ethics approval and consent to participate

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

References

1. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Posicionamento sobre Diagnóstico e Tratamento da Amiloidose Cardíaca – 2021. Arq. Bras. Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
2. Sousa M, Monohan G, Rajagopalan N, Grigorian A, Guglin M. Heart Transplantation in Cardiac Amyloidosis. Heart Fail Rev. 2017;22(3):317-27. doi: 10.1007/s10741-017-9601-z.
3. Gong T, Hall S. Considerations and Experience Driving Expansion of Combined Heart-Liver Transplantation. Curr Opin Organ Transplant. 2020;25(5):496-500. doi: 10.1097/MOT.0000000000000804.
4. Rizvi SSA, Challapalli J, Maynes EJ, Weber MP, Choi JH, O'Malley TJ, et al. Indications and Outcomes of Combined Heart-Liver Transplant: A Systematic Review and Met-Analysis. Transplant Rev. 2020;34(2):100517. doi: 10.1016/j.trre.2019.100517.
5. Vollmar J, Schmid JC, Hoppe-Lotichius M, Barreiros AP, Azizi M, Emrich T, et al. Progression of transthyretin (TTR) amyloidosis in Donors and Recipients After Domino Liver Transplantation-A Prospective Single-Center Cohort Study. Transpl Int. 2018;31(11):1207-15. doi: 10.1111/tri.13326.
6. Okumura K, Yamashita T, Masuda T, Misumi Y, Ueda A, Ueda M, et al. Long-Term Outcome of Patients with Hereditary Transthyretin V30M Amyloidosis with Polyneuropathy After Liver Transplantation. Amyloid. 2016;23(1):39-45. doi: 10.3109/13506129.2015.1123149.
7. Thenappan T, Fedson S, Rich J, Murks C, Husain A, Pogoriler J, et al. Isolated Heart Transplantation for Familial Transthyretin (TTR) V122I Cardiac Amyloidosis. Amyloid. 2014;21(2):120-3. doi: 10.3109/13506129.2013.853660.
8. Suhr OB, Larsson M, Ericzon BG, Wilczek HE. Survival After Transplantation in Patients with Mutations Other Than Val30Met: Extracts From the FAP World Transplant Registry. Transplantation. 2016;100(2):373-81. doi: 10.1097/TP.0000000000001021.
9. Chou AS, Habertheuer A, Chin AL, Sultan I, Vallabhajosyula P. Heart-Kidney and Heart-Liver Transplantation Provide Immunoprotection to the Cardiac Allograft. Ann Thorac Surg. 2019;108(2):458-66. doi: 10.1016/j.athoracsur.2019.02.012.
10. Cheng EY. The Role of Humoral Alloreactivity in Liver Transplantation: Lessons Learned and New Perspectives. J Immunol Res. 2017;2017:3234906. doi: 10.1155/2017/3234906.