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Early Tissue Clues of Transthyretin Cardiac Amyloidosis: Musculoskeletal Manifestations as Preclinical Indicators

Gustavo Alberto Gutiérrez-Barros[1,2], María Victoria Morales-Morales[3], Gabriela María Morales-Donado[1], Sharon Nicole Rueda-Cogollo[1], Daniela Valentina Britton-Sierra[1], Frank David Palomino-Hooker[1], María José Serrano-Monterrosa[1], Daniela Valentina Fontalvo-Bustamante[1], Mario Andrés Mendoza-Castillo[1], Juan Camilo Rodríguez Gale[1], Victoria Barros-Lorduy[1], Antonio Joaquin Pumarejo-Insignares[1], María Camila Martínez-Morales[1], Miguel Elías de Jesús Babilonia-Morelo[1], Laurent María Redondo-Athias[1]

[1]Research Group in Medicine and Surgery, Universidad Libre, Barranquilla, Colombia
[2]Universidad Libre, Barranquilla, Colombia
[3]Universidad Simón Bolívar, Barranquilla, Colombia
Email: gustavoa-gutierrezb@unilibre.edu.co, Vicky.mvmm@gmail.com, gabrielam-moralesd@unilibre.edu.co, sharonn-ruedac@unilibre.edu.co, danielav-brittons@unilibre.edu.co, Frankpalominohooker@gmail.com, mariaj-serranom@unilibre.edu.co, danielav-fontalvob@unilibre.edu.co, Mario.mencas31@gamil.com, Juancamilogale@hotmail.com, victoriabarrosl31@gmail.com, antoniopumajero@hotmail.com, mcamimar@hotmail.com, migueleliasb89@gmail.com, laurent.m1195@gmail.com

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Abstract

Transthyretin cardiac amyloidosis is an important cause of chronic heart failure with preserved ejection fraction in the adult population; however, it remains underdiagnosed due to a lack of clinical suspicion, and current diagnostic screening methods identify cardiac involvement at stages in which structural and functional myocardial changes have already been established. Therefore, the identification of extracardiac manifestations that precede cardiac amyloid deposition is of particular importance. We review the main musculoskeletal clinical manifestations associated with cardiac amyloidosis, such as bilateral carpal tunnel syndrome, spinal stenosis, biceps tendon rupture, and a history of orthopedic surgeries, addressing the prevalence of amyloid deposits identified in biopsies of these tissues and their temporal relationship with the diagnosis of cardiac involvement. We conclude that these musculoskeletal manifestations constitute early tissue clues of an evolving systemic disease and represent warning signs that may facilitate the timely recognition of transthyretin cardiac amyloidosis, allowing therapeutic intervention at ear-

lier stages of the disease.

Keywords

Transthyretin Cardiac Amyloidosis, Musculoskeletal Manifestations Carpal Tunnel Syndrome, Tenosynovial Amyloid Deposition

1. Introduction

Amyloidosis is a systemic disease characterized by the interstitial deposition of misfolded proteins in organs and peripheral tissues, leading to alterations in their structure and function [1]. There are two major subtypes of amyloidosis that are differentiated according to the protein involved: light-chain amyloidosis (AL), which is associated with monoclonal gammopathies, and transthyretin amyloidosis (ATTR), the latter being the leading cause of amyloid cardiomyopathy [2] [3]. Although noninvasive diagnostic methods with greater accessibility have been validated, this disease remains underdiagnosed worldwide [4], mainly due to a lack of clinical suspicion and the absence of screening strategies to identify early stages of myocardial infiltration, resulting in an estimated diagnostic delay of five years from the onset of signs and symptoms of heart failure [5]-[7], with worse clinical outcomes and prognosis for patients. Unfortunately, currently approved pharmacological therapies limit disease progression by stabilizing or inhibiting the synthesis of misfolded transthyretin, thereby preventing de novo amyloidogenesis, but they do not act directly on previously formed deposits, establishing a profile of non-reversibility of organ damage once treatment is initiated at advanced stages [8]-[10]. To improve patient prognosis, it is essential to establish screening strategies aimed at identifying individuals at early stages of myocardial infiltration or at high risk of developing cardiac amyloidosis, considering that multiple musculoskeletal manifestations precede the clinical expression of cardiac disease by several years [11]. The objective of this article is to review the current evidence on the deposition of transthyretin-derived amyloid fibrils in musculoskeletal structures, as well as their clinical correlation with the subsequent development of cardiac amyloidosis and their value as early warning signs that may allow a more timely diagnosis of the disease.

2. Transthyretin Amyloidosis

Transthyretin is a tetrameric protein with a molecular weight of 55 kDa, encoded by the TTR gene located on chromosome 18. It is synthesized mainly in the liver and participates in the transport of thyroxine and retinol [12]. Transthyretin amyloidosis (ATTR) may be caused by genetic alterations (variant/hereditary ATTR) or may occur in the absence of identified genetic abnormalities (wild-type ATTR, previously referred to as senile amyloidosis) [13]. Variant ATTR is caused by a single nucleotide polymorphism (SNP) that alters the amino acid sequence and

protein structure, leading to misfolding and deposition as amyloid fibrils [14]. More than 130 polymorphisms associated with the TTR gene have been identified, and the clinical phenotype depends on the specific variant described. Some variants show a greater predominance of neurological involvement (peripheral polyneuropathy); however, the most frequent variant worldwide, Val122Ile (substitution of valine by isoleucine at position 122), shows a greater predominance of cardiac involvement [15]. This variant is observed almost exclusively in individuals of African descent, with an estimated prevalence of approximately 3% - 4% in African American populations in the United States, as well as in individuals from the Caribbean and regions of West Africa. Despite its high population frequency, clinical penetrance is incomplete and age-dependent, with manifestations typically appearing from the sixth or seventh decades of life, and with a clear male predominance. In this demographic group, the Val122Ile variant is predominantly associated with isolated cardiac involvement, characterized by progressive heart failure and conduction disturbances, with minimal or no neurological expression [16].

Wild-type ATTR represents the most frequent subtype of transthyretin-related amyloidosis. It is caused by age-related instability of transthyretin tetramers, leading to progressive dissociation into monomers and aggregation into amyloid fibrils. Its clinical presentation is mainly characterized by cardiac involvement with a low expression of neurological manifestations, and it predominantly affects men older than 70 years [17] [18].

Transthyretin-related amyloid cardiomyopathy (ATTR-CM) is caused by myocardial infiltration with amyloid fibrils, resulting in a restrictive pattern of ventricular filling associated with concentric left ventricular hypertrophy and diastolic dysfunction [19]. Consequently, it presents clinically as heart failure with preserved ejection fraction and predominantly affects elderly individuals, in whom the high prevalence of cardiovascular comorbidities such as arterial hypertension may justify the previously described structural cardiac alterations and contribute to the underdiagnosis of this disease [20]. Transthyretin deposition may also involve the cardiac conduction system and be associated with the development of arrhythmias such as atrial fibrillation, ventricular tachycardias, or atrioventricular blocks [21]. Infiltration of the valvular annulus or aortic valve leaflets leads to chronic inflammation and accelerated calcification, resulting in the development of aortic stenosis with a requirement for aortic valve replacement in 10% - 15% of patients during follow-up [22]. Although disease-modifying therapies currently exist that prevent disease progression, such as transthyretin stabilizers including tafamidis and acoramidis, and transthyretin messenger RNA silencers such as vutrisiran, these agents have not demonstrated reversal of myocardial infiltrates formed prior to treatment initiation. Therefore, establishing the diagnosis at stages with low myocardial infiltration is fundamental for improving patient prognosis [23].

The gold standard for the diagnosis of ATTR-CM remains endomyocardial biopsy; however, the risk of procedure-related complications has driven the devel-

opment of noninvasive diagnostic methods such as imaging techniques [24]. Nuclear scintigraphy using bone-avid radiotracers is a method validated by current clinical practice guidelines for establishing the diagnosis of cardiac amyloidosis. Nevertheless, uptake of these radiotracers does not differentiate whether amyloid deposition is secondary to transthyretin or to light chains derived from monoclonal plasma cell disorders; therefore, measurement of serum free light chains with assessment of the kappa/lambda ratio, serum protein electrophoresis with immunofixation, and urine protein electrophoresis with immunofixation are required to exclude this etiology, achieving a sensitivity of 99% [25]-[27]. In the absence of circulating light chains, bone scintigraphy using radiotracers with affinity for amyloid tissue, such as technetium-99m pyrophosphate, should demonstrate myocardial uptake of grade 2 or 3 according to the Perugini classification, where grade 2 corresponds to cardiac uptake equal to or greater than bone uptake, and grade 3 corresponds to intense cardiac uptake with suppression or minimal visualization of the skeleton. The presence of grade 0 or 1 uptake is not sufficient to establish the diagnosis of ATTR-CM [28].

The utility of biopsies from non-cardiac tissues has also been proposed, using Congo red staining as a method to detect the presence of amyloid fibrils based on their beta-pleated sheet conformation, with apple-green birefringence observed under polarized light microscopy (an optical phenomenon produced by the binding of the dye to amyloid fibrils) [29]. Abdominal fat pad biopsy is used in cases of suspected AL amyloidosis; however, it shows low sensitivity in cases of ATTR [30]. Dasari *et al*. evaluated the frequency of amyloid deposits in non-cardiac biopsies from an anatomic pathology database, demonstrating amyloid fibrils in 75% of musculoskeletal tissue samples (tendon-synovium), 38% in the urinary bladder, and 33% in the prostate, highlighting the relevance of further analyzing the strong correlation between amyloid deposition in musculoskeletal tissues as potential predictors of ATTR and its cardiac involvement [31]. From a practical standpoint, obtaining musculoskeletal samples with a higher likelihood of diagnostic success requires targeted tissue selection and careful surgical technique, given that amyloid deposition is often focal, patchy, and of low burden in early stages. Pathological evidence supports prioritizing fragments of tendon, synovium, or ligament with a macroscopically thickened, fibrotic, or hyalinized appearance. Thermal damage during sample acquisition should be minimized by avoiding direct use of electrocautery on tissue intended for histological evaluation, as alteration of the fibrillar architecture may compromise identification of amyloid material.

In histopathological processing, Congo red staining remains the reference method for the initial detection of amyloid; however, its interpretation requires expertise and optimal technical conditions, as birefringence may vary in intensity and color, particularly in collagen-rich samples such as musculoskeletal tissue. Therefore, it is recommended to complement the analysis with additional stains such as Azan-Mallory, which facilitate differentiation between collagen and amy-

loid deposits, as well as with targeted immunohistochemical techniques and, when available, proteomics based on mass spectrometry for precise fibril precursor typing. Systematic acquisition of musculoskeletal tissue during orthopedic surgeries in patients with red flags constitutes a high diagnostic-yield strategy that may facilitate early identification of transthyretin amyloidosis and its correlation with underlying cardiac involvement [32] [33].

3. Bilateral Carpal Tunnel Syndrome

Bilateral carpal tunnel syndrome is the most frequent musculoskeletal manifestation associated with ATTR, preceding the diagnosis of ATTR-CM by an average of 5 to 10 years [34]. It is caused by interstitial deposition of amyloid fibrils in the transverse carpal ligament and peritendinous connective tissue, leading to thickening of these structures and chronic compression of the median nerve [35] [36]. Although its prevalence is low in the general population, it affects 40% - 60% of adults diagnosed with wild-type ATTR, whereas in the hereditary form its frequency varies according to the underlying genetic polymorphism [37]. An association between carpal tunnel syndrome and amyloidosis should be suspected when its presentation is bilateral, recurrent, with late onset, and without mechanical risk factors that would explain the development of the condition in older adults [36].

In a cross-sectional study, the prevalence of cardiac amyloidosis was evaluated in patients who required orthopedic surgery for bilateral carpal tunnel syndrome, identifying that 4.8% of participants had previously undiagnosed wild-type ATTR, predominantly men older than 70 years without signs or symptoms of heart failure, allowing identification of these patients at early stages of cardiac involvement [38]. Sperry *et al*. conducted a cross-sectional study in men older than 50 years and women older than 60 years undergoing carpal tunnel release surgery; tissue samples were collected intraoperatively from 98 patients, identifying the presence of amyloid fibrils by Congo red staining, and finding that 10% of participants had amyloid fibril deposits, and within this cohort, 20% had previously undiagnosed cardiac amyloidosis [39]. Consistent with these findings, Saade *et al*. identified the presence of amyloid fibrils in 29% of a cohort of 54 adult patients older than 50 years without mechanical risk factors for the development of carpal tunnel syndrome; when referred for cardiology evaluation, no significant electrocardiographic abnormalities were identified; however, cardiac amyloidosis was detected in 18% of participants [40].

Zhang *et al*. developed a score to estimate the probability of identifying amyloid fibril deposition in patients undergoing carpal tunnel release surgery. The variables included in the score were age range, sex, and a history of trigger finger; a score greater than or equal to 4 demonstrated a sensitivity of 69% and a specificity of 80% for detecting tenosynovial amyloidosis [41]. All these findings support the importance of obtaining biopsies in patients undergoing carpal tunnel release surgery to identify cardiac amyloidosis at early stages; however, this practice remains infrequent among hand surgeons. In a recently published study, a survey was con-

ducted among active members of the American Society for Surgery of the Hand regarding the frequency of biopsy collection during carpal tunnel release surgery in patients with high-risk clinical criteria. Approximately 40% of the surgeons who responded to the survey reported never performing biopsies in these patients; additionally, considerable heterogeneity was observed in amyloid subtyping and subsequent referral to cardiology. The findings of this survey reinforce the need for standardized protocols that integrate carpal tunnel release surgery into early screening strategies for ATTR-CM [42].

4. Spinal Stenosis

Spinal stenosis is the second most frequent musculoskeletal manifestation in patients with ATTR. It is caused by amyloid fibril deposition in the ligamentum flavum of the spine, with ligament hypertrophy leading to the progressive development of stenosis. It mainly affects the lumbar spine and is estimated to precede the onset of cardiac amyloidosis by an average of 5 to 10 years. However, the high prevalence of concomitant degenerative causes in the adult population makes it difficult to identify patients who truly present ATTR-related spinal stenosis [43].

Therefore, Negreira-Camacho *et al.* evaluated the presence of red flags to suspect cardiac amyloidosis in patients with spinal stenosis. In a cohort of 103 adults older than 65 years with ligamentum flavum hypertrophy (ligament thickness greater than 4 mm on magnetic resonance imaging), clinical suspicion of cardiac amyloidosis was defined as the presence of left ventricular hypertrophy plus at least one red flag (heart failure with preserved ejection fraction, hypotension or poor tolerance to antihypertensive therapy such as beta-blockers, peripheral neuropathy, low-voltage electrocardiogram, or cardiac conduction abnormalities). At least one red flag was identified in 89.3% of the evaluated individuals; the median number of red flags per patient was 2, and 11.6% presented four or more. Overall, 57.3% of patients met criteria for clinical suspicion of cardiac amyloidosis, demonstrating that more than half of patients evaluated for spinal stenosis share a clinical phenotype suggestive of cardiac amyloidosis [44].

To determine the prevalence of amyloid deposits in patients undergoing surgery for spinal stenosis, Eldhagen *et al.* conducted a cross-sectional study including 250 adults aged between 50 and 89 years. Biopsy samples of the ligamentum flavum were obtained during surgery, and Congo red staining demonstrated the presence of amyloid fibrils in 88.4% of patients, identifying type A amyloid fibrils (associated with the development of cardiomyopathy) in 18% of these individuals. Although no cases of cardiac amyloidosis were identified using noninvasive cardiac imaging studies, the presence of transthyretin was demonstrated in adipose tissue and vascular walls, supporting the hypothesis that the ligamentum flavum may represent one of the tissues affected at early stages prior to the development of overt cardiac disease [45].

Although the most frequent location is the lumbar spine, cases involving other vertebral levels have been described. MacLennan and Le Roux reported a case of a

71-year-old patient with cervical spinal stenosis and severe spinal cord involvement associated with ATTR, whose medical history was notable for the presence of other musculoskeletal manifestations, including prior carpal tunnel release surgery [46].

5. Biceps Tendon Rupture

Spontaneous rupture of the long head of the biceps brachii tendon is a characteristic musculoskeletal manifestation in patients with ATTR and precedes the diagnosis of ATTR-CM by approximately five years. It is caused by amyloid deposition in the peritendinous connective tissue, with loss of elasticity and tensile strength, leading to tendon rupture under every day or minimal mechanical loads. Clinically, it is characterized by the presence of the Popeye sign; pain is mild in most cases, with low rates of hospital consultation for this reason, and it has high specificity and low sensitivity for the diagnosis of ATTR [47]. Geller *et al*. identified a higher prevalence of spontaneous rupture of the long head of the biceps tendon in patients with a diagnosis of wild-type ATTR and cardiomyopathy established by biopsy or cardiac scintigraphy, compared with patients with heart failure due to other etiologies, at 33% versus 2.5%, respectively [48]. Griffin *et al*. evaluated the prevalence of amyloid deposition in patients with brachial biceps tendon rupture who required surgical repair. Intraoperative biopsies were obtained, identifying transthyretin amyloid fibrils in 10% of individuals, of whom 20% had other musculoskeletal manifestations such as carpal tunnel syndrome, without evidence of established cardiac disease [49].

6. Other Musculoskeletal Manifestations

The presence of transthyretin amyloid fibrils has been described in osteotendinous structures other than the carpal tunnel, the biceps brachii tendon, and the spine. However, their correlation with the development of cardiac amyloidosis is less frequent. Rotator cuff rupture has been studied as an extracardiac manifestation of amyloidosis; nevertheless, available studies do not provide clear evidence to support routine biopsy during shoulder surgery [50]. Yamada *et al*. followed two groups of patients requiring orthopedic surgery. The first group consisted of 41 patients with rotator cuff rupture who underwent shoulder surgery with tissue biopsy, identifying amyloids in 7.3% of individuals, none of whom were associated with cardiac amyloidosis. In contrast, the second group consisted of 33 patients who underwent carpal tunnel release surgery, in whom amyloid deposition was identified in 36.4% of patients, and among these, 28.6% were associated with the presence of cardiac amyloidosis. These findings demonstrate the limited value of shoulder biopsy as a predictor of cardiac amyloidosis [51].

Sperry *et al*. expanded the search for musculoskeletal tissues with amyloid deposition by following a cohort of 100 patients older than 50 years who underwent surgery for idiopathic trigger finger, identifying the presence of amyloid fibrils in 2% of patients, without correlation with cardiac amyloidosis [52]. Within the population of patients diagnosed with ATTR-CM, a retrospective history of orthopedic

interventions such as knee or hip arthroplasty has been documented, with a higher prevalence compared with the general population, and an estimated mean interval of 7.2 years prior to the diagnosis of cardiac amyloidosis. Additionally, evidence suggests that these less frequent orthopedic manifestations increase the subsequent risk of ATTR-CM when more than one musculoskeletal alteration is present and in patients requiring multiple recurrent orthopedic interventions [53].

7. Conclusions

The available evidence supports that musculoskeletal clinical manifestations may represent early expressions of systemic deposition of transthyretin-derived amyloid fibrils, preceding in many cases the development of clinically overt cardiac involvement. Considering that ATTR-CM continues to be frequently diagnosed at advanced stages, recognition of these musculoskeletal alterations offers a window of opportunity for early suspicion of the disease.

The systematic integration of clinical histories such as bilateral carpal tunnel syndrome, lumbar spinal stenosis, spontaneous rupture of the biceps tendon, and a history of orthopedic surgeries may contribute to identifying a clinical profile at higher risk for ATTR-CM. In this context, obtaining tenosynovial tissue biopsies during surgical procedures indicated for these conditions could be considered a complementary screening strategy in selected patients.

Finally, these findings reinforce the need to promote greater interdisciplinary awareness among orthopedic surgeons, cardiologists, and primary care physicians, to facilitate an integrated diagnostic approach that may reduce diagnostic delay and potentially improve the prognosis of patients with transthyretin cardiac amyloidosis.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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