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Carpal Tunnel Syndrome: A Marker for Amyloidosis

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Abstract

Introduction: Amyloidosis are systemic conditions and carpal tunnel syndrome (CTS) precedes the principal systemic complications and can be used as an early marker. Our objective was to determine the frequency of amyloid deposition in idiopathic CTS and its systemic impact. **Methods**: We retrospectively evaluated patients with CTS between September 2019 to January 2020. Samples from the anterior carpal ligament were pathologically evaluated and amyloid deposition was confirmed by apple-green birefringence on polarized light using Congo red stain. When amyloid was detected we performed genetic testing for transthyretin variants (ATTRv), immunofixation electrophoresis in serum and urine for light chains and multidisciplinary evaluation. **Results**: Thirty consecutive patients were included, 19 women, 11 men, mean age 70 years old (range 42 - 89 years). We identified 3 patients (10%) with amyloid deposits (mean age: 78.6 years, 2 men, 1 woman). Genetic testing for ATTRv and light chains studies were negative. During follow-up: The first patient required aortic valve replacement. The second patient developed progressive cardiac failure with syncopal episodes, atrioventricular block and atrial fibrillation and required a pacemaker and anticoagulation. The third patient had unexplained chronic edemas. The cardiac evaluation in all 3 patients revealed left ventricular hypertrophy and myocardial uptake (Perugini Score > 2) in their nuclear bone scintigraphies with technetium pyrophosphate. Two patients were treated with tafamidis and one patient died due to refractory cardiac insufficiency. **Discussion**: Our findings underline the importance of investigating amyloidosis in idiopathic CTS. The identification of deposits allows early diagnosis of cardiac amyloidosis leading

to timely intervention and treatment.

Keywords

Carpal Tunnel, Amyloid, Transthyretin, Amyloid Cardiac, Transthyretin Variants, Light Chains

1. Introduction

Carpal Tunnel Syndrome (CTS) is recognized as the most frequent entrapment neuropathy with a peak incidence at 40 - 60 years of age [1]. Females could be twice more likely affected than males. [2] The carpal tunnel is located between the carpal bones and the flexor retinaculum and contains the median nerve, the four tendons of the flexor digitorum superficialis, the four tendons of the flexor digitorum profundus and the flexor pollicis longus. The small volume of the tunnel creates a susceptible environment for median nerve compression affecting neural transmission.

Symptoms typically include numbness, paresthesias, and pain along the median nerve distribution. [1]

Amyloidosis is the generic term for a group of diseases in which different previously healthy soluble proteins misfold and precipitate as fibrous deposits (amyloid fibrils) in different tissues disrupting the normal function of these organs through either compression or toxic effects. [3]

Musculoskeletal complications in amyloidosis may manifest as CTS which often precede the systemic symptoms by 5 - 9 years indicating that screening around the time of CTS surgery may identify patients at an early disease stage [4]. Amyloid deposition has been reported within the flexor retinaculum, synovial tissue, flexor tendon sheath, fascia, and vessel walls of capillaries, small arteries, and veins and within endoneurial fibers of the median nerve. [5]

Although CTS is a common manifestation of transtiretin amyloidosis (ATTR), it has not been well recognized by most hand surgeons or cardiologists in clinical practice. [6] [7]

Recent advances have dramatically altered the therapeutic management of ATTR [8] for this reason early recognition of amyloid in CTS surgery may allow early diagnosis and treatment of these deadly disorders.

The principal aim of this study was to determine the frequency and type of amyloid deposition in patients with idiopathic CTS, and to evaluate its systemic impact in a multidisciplinary evaluation.

2. Material and Methods

We evaluated retrospectively 30 consecutive patients who underwent CTS surgery (from September 2019 to January 2020) and whose samples of the transverse carpal ligament were pathologically evaluated in the search for amyloid deposits. Clinical and electromyographic criteria were used in the diagnosis of CTS. [9]

Patients with known familial history of inherited neuropathy, diabetes mellitus, symptomatic thyroid disease, rheumatoid arthritis or other connective tissue diseases, amyloidosis, CTS secondary to trauma or pregnancy were excluded.

The surgical procedure included the opening of carpal tunnel and the extraction of samples from the transverse carpal ligaments were sent for pathological evaluation. Samples were fixed in buffer formol 10% and paraffin, with hematoxylin eosin stain. Amyloid deposition was confirmed by the presence of apple-green birefringence on polarized light microscopy using Congo red stain.

In the patients in whom amyloid was detected, we performed genetic testing for ATTRv, and immunofixation electrophoresis in blood and urine in search of monoclonal light chains. Moreover, in patients with amyloid deposits, we also performed a multidisciplinary evaluation including neurological examination, nerve conduction studies (NCS). Ophthalmological evaluation including slit lamp examination, and cardiological studies including electrocardiogram (ECG), transthoracic echocardiogram and nuclear bone scintigraphy with technetium pyrophosphate (99^{m}TC PYP). The last study was interpreted according to Perugini Score. [10]

The Institutional Review Board of the Hospital Británico approved the study.

3. Results

Thirty consecutive patients were included, 19 women, 11 men, mean age 70 years (range 42 - 89 years). Sixty percent of them had bilateral CTS.

We identified 3 patients (10%) with amyloid deposits (mean age: 78.6 years, 2 men, 1 woman). All of them were born in Argentina. None had had diagnosis of amyloidosis before CTS surgery.

Genetic testing for ATTRv and light chains studies were negative in all of them.

Patient 1 (**Table 1**) had a family history of bilateral CTS and required aortic valve replacement after a follow-up of 18 months. Patient 2 (**Table 1**, **Figure 1**) had had an antecedent of spontaneous left biceps tendon rupture 20 years before CTS surgery and after 24 months of follow-up developed progressive cardiac failure with syncopal episodes. ECG revealed atrioventricular block and atrial fibrillation that required permanent pacemaker as well as oral anticoagulation. Patient 3 (**Table 1**) had a history of breast cancer and unexplained chronic edemas in her lower limbs.

The cardiac evaluation in all 3 patients revealed left ventricular hypertrophy (LVH) and interventricular septum (IVS) > 12 mm, and myocardial uptake (Perugini Score >2) in their nuclear bone scintigraphies 99^{m}TC PYP. (**Table 1**)

We found evidence of subclinical sensory neuropathy in lower limbs in one patient (patient 3 **Table 1**) and none had ocular abnormalities associated with amyloidosis.

Patients 1 and 3 (**Table 1**) are receiving tafamidis. Patient 2 (**Table 1**) died due to refractory cardiac insufficiency.

Table 1. Characteristics of the patients with confirmed amyloidosis.

	Patient 1	Patient 2	Patient 3
Age	80	74	82
Sex	Male	Male	Female
Familial history CTS	Yes	No	No
Neuropathy	No	No	Bilateral sural involvement
Ocular abnormalities	No	No	No
Cardiac complications	Aortic stenosis	Cardiac pacemaker/atrial fibrillation	Edemas in lower limbs
Other antec.	No	Biceps tendon rupture	Breast cancer
Light chains	Negative	Negative	Negative
ATTRv genetic testing	Negative	Negative	Negative
Echocardiographic findings	LVH 13 mm, IVS 14 mm	LVH 14 mm, IVS 14.5 mm	LVH 13.6 mm, IVS 14 mm
Nuclear bone scintigraphy 99^{m}TC PYP	Abnormal uptake (Perugini 2)	Abnormal uptake (Perugini 3)	Abnormal uptake (Perugini 2)

References: CTS: Carpal Tunnel Syndrome, ATTRv: Amyloidosis Transthyretin variants, 99^{m}TC PYP: technetium pyrophosphate, LVH: left ventricular hypertrophy, IVS: interventricular septum.

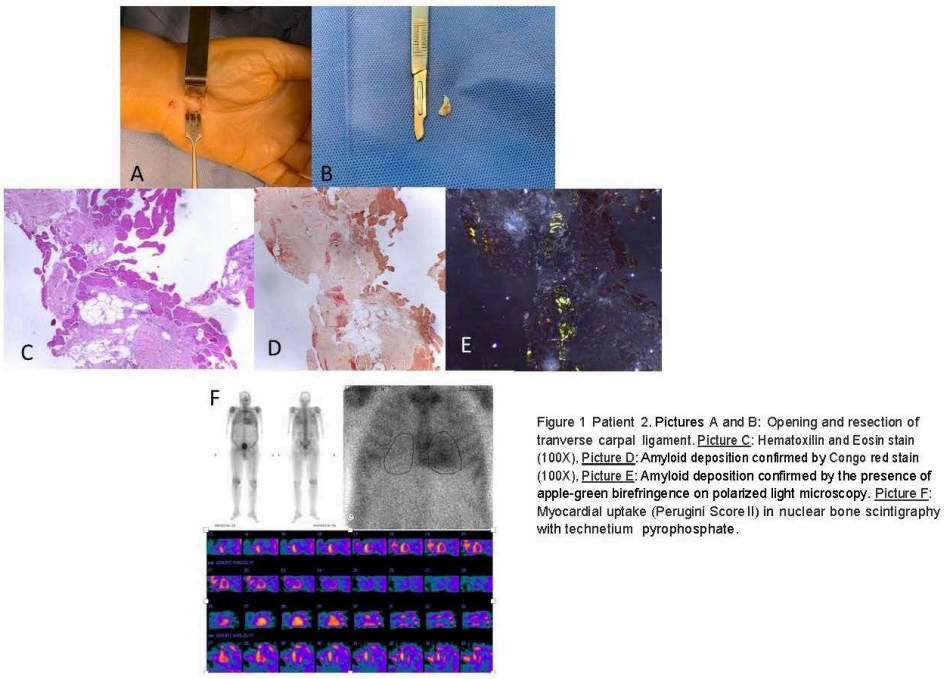

Figure 1. Findings from an affected patient with CTS and amyloid in our serie.

4. Discussion

In our study, the first finding was that 10% percent of elderly patients with idiopathic CTS had amyloid deposits in their biopsies.

The absence of light chain monoclonal gammopathy in addition to lack of pathogenic variants in the transthyretin gene, and the abnormalities in the nuclear bone scintigraphies 99^{m}TC PYP indicated that the amyloid deposits of our patients likely represent wild type ATTR (ATTRwt) and it is the most common amyloid identified in CTS. [11] [12]

Mass spectrometry was not used in this study because this technique is not still available in Argentina.

Across all CTS-focused publications, CTS symptoms onset preceded a diagnosis of ATTR amyloidosis (ATTRv and ATTRwt inclusive) by up to 12 years. [13]-[15]

The frequency reported varied from 1.4% to 34% in previous published studies usually affecting the more frequently elderly males (**Table 2**). [4] [16]-[25] Nevertheless, in many of these studies there is no information available regarding other clinical manifestations of the patients with ATTR. Our three patients were studied by searching amyloids in other parts of the body for example presence of neuropathy and ocular deposition.

Table 2. Frequency of amyloid deposits in patients undergoing CTS surgery from selected publications.

Author	Year	Study	N pat.	CTS uni/bilat	Freq amyloid dep. (%)	Type of prot.	Subtype ATTR	Other complic.
Kyle *et al.* [16]	1992	Retros	35	Bilat	100%	9 AL, 26 ATTR	Wild T	Cardiop
Takei *et al.* [17]	2002	Retros	1	Bilat	NA	ATTR	Wild T	No
Tojo *et al.* [18]	2010	Retros	2	Bilat	NA	ATTR	Variant	Neurop
Sekijima *et al.* [19]	2011	Prosp	123	NA	34	ATTR	Wild T	NA
Uchiyama *et al.* [20]	2014	Prosp	100	NA	13	ATTR	Wild T	NA
Nakagawa *et al.* [21]	2016	Prosp	31	Bilat	14	ATTR	Wild T	Cardiop
Sperry *et al.* [22]	2018	Prosp	98	Bilat	10	7 ATTR, 3 AL	2 variants, 5 Wild T	Cardiop Neurop
Scott *et al.* [23]	2019	Retros	35	Bilat	26	7 ATTR, 1 AL	7 Wild T	NA
Milandri *et al.* [24]	2020	Retros	583	NA	20.3	342 ATTR, 196 AL	235 variants, 107 Wild T	Cardiop
Bäcker *et al.* [25]	2022	Retros	699	NA	1.4%	NA	NA	NA
Ladefoged *et al.* [4]	2023	Prosp	120	Bilat	8.3	ATTR	Wild T	Cardiop

References: Pat: patients, CTS: Carpal Tunnel Syndrome, Uni: unilateral, Bilat: bilateral, Freq: frequency, Dep: deposits, Prot: protein, Complic: complications, Retros: retrospective, Prosp: prospective, NA: not available, ATTR: amyloid transthyretin, Wild T: wild type, AL: amyloidosis light chain, Cardio: cardiopathy, Neurop: neuropathy.

In early studies among patients with amyloid deposition in the carpal tunnel, the majority were of the ATTR type, but rarely systemic disease was also identified. More recently Sperry identified concomitant cardiomyopathy in 2/10 patients with amyloid in the tenosynovium biopsy. [22]

Therefore, a second clinically important finding of our study was that the 3 patients with amyloid deposition in their transverse carpal ligament, developed ATTR cardiopathy during follow-up evaluation.

Amyloid cardiopathy (AC) is an under-recognized etiology of heart failure with preserved ejection fraction. AC associated with ATTR deposition has a prevalence as low as 1.2% when CTS is absent and increases to 5.5% when CTS is present. [26] [27]

Similar to our study Boyle et al identified that overall, 10.2% of men older than 50 years of age, and women older than 60 years of age had amyloid identified on tenosynovial biopsies following carpal tunnel release. Out of these, 20% showed cardiac involvement. [28]

A different, more complex and expensive approach, was used in a recent study which included 120 patients aged ≥60 years at the time of CTS surgery who were invited for screening. Red flags were defined as elevated biomarker levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) or as cardiac troponin, an electrocardiogram pattern associated with ATTRwt, LVH, and impaired longitudinal strain with apical sparring. All patients with a red flag were referred for diagnostic scintigraphy. They identified that 10 patients (8.3%) had ATTRwt. [5]

The same as in our patient with valvulopathy (Patient 1 **Table 1**) ATTR could be found in patients with aortic stenosis with a prevalence of 6% to 8% and 16% in those evaluated for transcatheter aortic valve replacement. [29]

The identification of amyloid deposition in the transverse carpal ligament months or even years ahead of the beginning of AC can lead to a significant improvement in the care of these patients, and it is of utmost clinical importance considering that 44% of patients with ATTR visited 3 or more different physicians before receiving a correct diagnosis [24] with a mean delay of 34 months. [6] Furthermore, diagnostic delays of greater than 1 year in these patients were associated with poorer cardiac outcomes, including higher levels of NT-proBNP and a higher prevalence of atrial fibrillation. [6]

ATTR deposits may involve other soft tissues including the ligamentum flavum of the lumbar canal resulting in lumbar spinal stenosis, the biceps and quadriceps tendons leading to a traumatic tendon rupture and hand tendons with subsequent Dupuytren's contracture. [30]

Therefore, amyloid deposition in the tenosynovium particularly in the elderly, may be an early indication of systemic amyloidosis especially when the patients present LVH in the absence of hypertension, CTS, lumbar stenosis or a history of biceps tendon rupture. [4]

Different from previous publications our study included a multidisciplinary evaluation of patients with amyloid deposition in the transverse ligament. We did not find ocular abnormalities related to amyloid deposits, and only 1 patient

(Patient 3 Table 1) presented subclinical bilateral sural nerve involvement. It is unclear whether this finding represented an age-related finding or was an early subclinical manifestation of ATTRwt peripheral neuropathy. Distal symmetric, predominantly sensory polyneuropathy is a common neurological manifestation of ATTRv. Compared to hereditary ATTR, the severity of polyneuropathy in ATTRwt is milder and without relevant motor involvement. [31]

We did not have a relapse of symptoms of CTS in our patients (Patient 1 and 3 Table 1), but some patients could relapse after CTS surgery if they have a non-treated systemic condition**.** The reduction of amyloid associated with ATTR could have occurred with the use of new treatments. These have as objective to reduce TTR protein synthesis using gene silencers drugs for example: patisiran, vutrisiran, inotersen, eplontersen [32] and in the future gene editing therapies with CRISPR-Cas9. [33] Another possibility is using the approved drug tafamidis a kinetic stabilizer of TTR tetramer in patients with clinical neuropathy [34] and cardiomyopathy [35].

We recognized the small size of our sample and the retrospective nature or our study as part of our limitations. However, we would like to mention that it was the first study evaluating CTS as a marker for systemic amyloidosis in Argentina with clinical implications for the diagnosis of an underlying myocardiopathy. Probably the inclusion criteria limited to older adults, may reduce the chances of identifying younger patients with amyloid deposits who may be more likely to have AL.

5. Conclusion

Our findings underline the importance of investigating amyloidosis in idiopathic CTS, and incorporating transverse carpal ligament or tenosynovial tissue biopsy as a standard procedure, making hand surgeons aware of the importance of considering these tissues, particularly in patients at a higher risk of cardiac amyloidosis allowing for timely intervention and treatment.

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Conflicts of Interest

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

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