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RESEARCH ARTICLE

Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies

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Aims We aimed to assess carpal tunnel syndrome (CTS) prevalence in transthyretin (TTR)-related and light-chain amyloidosis (AL), comparing it to the general population, adjusted for age and gender. In TTR-related amyloidosis (ATTR) we investigated (i) CTS prevalence in relation to genotype, cardiac amyloidosis (CA), age and gender; (ii) CTS role as an incremental risk factor for CA; (iii) temporal relationship between CTS and CA; and (iv) CTS prognostic role.

Methods and results Data from 538 subjects (166 hereditary ATTR, 107 wild-type ATTR, 196 AL amyloidosis, and 69 TTR mutation carriers; 64% male, median age 62.4 years), evaluated at our centre (Bologna, Italy), were analysed and compared to a published cohort of 14.9 million people, in which incidence rates of CTS had been estimated. CTS prevalence was highest in ATTR patients with CA (20.3% vs. 4.1% in the general population), while it was comparable to the general population when CA was absent and in AL patients. CTS standardized incidence rates were markedly elevated in ATTR males in the eighth decade of life (13.08 in hereditary ATTR, 15.5 in wild-type ATTR). The risk of developing CA was greater in ATTR patients with CTS; the probability of having CTS was highest 5–9 years prior to CA diagnosis. CTS was an independent mortality risk factor in ATTR.

Conclusions Compared to general population the adjusted prevalence of CTS is higher among elderly men with ATTR; CTS is a prognostic marker in ATTR, independently of cardiac involvement, and precedes CA diagnosis by 5–9 years. The awareness of this association and time delay offers the possibility of an early pre-clinical ATTR-CA diagnosis.

Keywords Transthyretin amyloidosis • Cardiomyopathy • Carpal tunnel syndrome • Orthopaedic surgery

Introduction

Carpal tunnel syndrome (CTS) is the most frequent focal peripheral neuropathy in the general population and carpal tunnel release is one of the most common upper extremity surgical procedures. In a recent study, the lifetime prevalence of carpal tunnel release in the general population was estimated to be as high as 3.1%.[1] The descriptive epidemiology of CTS has constant features over time and across countries, incidence being much higher among females (with a ratio of at least 2:1) and strongly age-related, with a characteristic peak of incidence in females aged between 40 and 60 years.[2,3] CTS arises from a complex pathological process that

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can be determined by both occupational and personal factors. Well known personal determinants of CTS include both modifiable and non-modifiable risk factors and, among them, apart from age and sex, the most studied is obesity. Patients affected by some systemic diseases such as hypothyroidism, diabetes mellitus, and rheumatoid arthritis or subjects presenting specific anthropometric features of the wrist–hand system and pregnant women have also been reported to be at increased risk of CTS.

Amyloidosis is a localized or systemic disease in which proteins with unstable tertiary structures misfold, aggregate and form insoluble fibrils that deposit in different organs and tissues causing morphological and functional alterations.[4] Cardiac involvement, when present, is the most important prognostic factor. Three types of systemic amyloidosis are most frequently associated with cardiac involvement: immunoglobulin light chain (AL) amyloidosis, due to excess monoclonal light chain production by a plasma cell clone, the hereditary form of transthyretin (TTR) amyloidosis (ATTRm), caused by the deposition of mutated TTR and wild-type (non-hereditary) TTR amyloidosis (ATTRwt), that is characterized by an almost exclusive cardiac involvement.[5]

The association between CTS and systemic amyloidosis has been widely described and the main case series report a high prevalence of CTS in ATTR, ranging from 15% to 60%.[5–9] Indeed, TTR-related amyloid deposition has been documented in the transverse carpal ligament of subjects undergoing surgical intervention (with or without associated cardiac involvement).[10–13] However, the real prevalence of CTS in the various tissue types of systemic amyloidosis and in the different TTR genotypes has never been reported in detail and not even adjusted for the potential confounding factors including gender and age. Many other points remain to be clarified including degree and time course of the association with amyloidotic cardiomyopathy and the possible independent prognostic role.

We therefore designed this study to compare the prevalence of CTS requiring surgery – adjusted for age and gender – among patients with AL or ATTR amyloidosis having the general population as a reference. In particular, we planned to assess CTS prevalence in ATTR according to genetic substrate (wild-type vs. mutated form), to investigate the role of CTS as an incremental risk factor for the development of cardiac amyloidosis (CA) and the temporal relationship of this association. Finally, we evaluated the prognostic role of CTS in ATTR patients.

Methods

Study design and study population

We conducted a retrospective study using data extracted from a dedicated prospective local database that includes baseline and follow-up data for subjects evaluated between 1993 and June 2017 at the 'Centre for the Diagnosis and Management of Systemic Amyloidosis' at University of Bologna (Italy). We enrolled all consecutive patients affected by ATTR (both ATTRm and ATTRwt) or AL amyloidosis as well as unaffected TTR mutation carriers. The prevalence of CTS requiring decompression surgery in the study cohort was compared to the general population, stratified by age (5-year classes) and gender. As a refence group we used data from a previously published large cohort of 14.9 million subjects from six Italian regions (Trentino Alto Adige, Piedmont, Emilia-Romagna, Tuscany, Marche and Umbria) in which incidence rates of in-hospital cases of CTS from 1997 to 2002 were estimated (86 641 cases, 79% women).[3] During this period, CTS surgery in Italy was almost invariably conducted in a public or private hospital, and the information for each hospital discharge was recorded in regional databases.

Clinical follow-up was six monthly or earlier if required.

Definitions

The diagnosis of systemic amyloidosis was made by one of the following:

1 Histological documentation of amyloid deposition in at least one involved organ.
2 Known pathogenic TTR mutation and evidence of cardiac and/or neurological involvement.
3 In case of ATTR, echocardiographic evidence of CA and intense cardiac uptake (score 2–3) on 99m technetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy and absence of plasma monoclonal component.[14]

A diagnosis of AL aetiology was made in the presence of a monoclonal protein (identified by serum and urine protein immunofixation plus serum free light chain assay) and histological evidence of amyloid deposition in the myocardial or abdominal fat biopsy with immunohistochemistry or mass spectrometry confirming light chain deposits.

Following a histological or non-invasive diagnosis of ATTR, all patients underwent TTR genetic testing to differentiate between ATTRm and ATTRwt.

Cardiac amyloidosis was defined as left ventricular end-diastolic wall thickness > 12 mm on echocardiography, in absence of any other cause of hypertrophy. Unaffected carriers had a known pathogenic TTR mutation with a normal electrocardiogram (ECG) and echocardiogram as well as no signs of neuropathy.

History of CTS was defined as previous carpal tunnel release surgery.

Electrocardiogram and echocardiography

Electrocardiographic and echocardiographic measures were based on standard definitions.[15]

Genotyping

Genomic DNA was isolated from whole peripheral blood by standard techniques. Exons 2, 3 and 4 of the TTR gene (accession number M11844) were amplified by polymerase chain reaction (Takara ExTaq polymerase) using primers described previously.[16] Amplified DNA fragments were directly sequenced using ABI Prism 3130 automated sequence.

Histology and immunohistochemistry

Patients underwent either cardiac or abdominal fat biopsy. All myocardial samples (five per patient) were microwave fixed/processed, and multiple 2 μm sections were tested for presence of amyloid by Congo-red staining and apple-green birefringence under

Table 1 Characteristics of the study population at first cardiac assessment by history of carpal tunnel syndrome

Characteristics	History of CTS			*P*-value
	No (*n* = 481)	Yes (*n* = 57)	All patients (*n* = 538)	
Sex, *n* (%)				
Females	175 (36.4)	16 (28.1)	191 (35.5)	
Males	306 (63.6)	41 (71.9)	347 (64.5)	0.215*
Age, years, median (IQR)	61.5 (46.8–72.5)	73.3 (60.0–78.3)	62.4 (49.1–74.1)	<0.001**
Aetiology of amyloidosis, *n* (%)				
AL	191 (39.7)	5 (8.8)	196 (36.4)	
ATTRm	210 (43.7)	25 (43.9)	235 (43.7)	
Carrier[a]	67 (13.9)	2 (3.5)	69 (12.8)	
Affected patient[a]	143 (29.7)	23 (40.4)	166 (30.9)	
ATTRwt	80 (16.6)	27 (47.4)	107 (19.9)	<0.001*†
Mutation (ATTRm only), *n* (%)				
Glu89Gln	29 (13.8)	7 (28.0)	36 (15.3)	
Ile68Leu	49 (23.3)	12 (48.0)	61 (26.0)	
Val30Met	50 (23.8)	0 (0.0)	50 (21.3)	
Other	82 (39.1)	6 (24.0)	88 (37.4)	0.001*
Cardiac involvement, *n* (%)				
No	142 (29.5)	5 (8.8)	147 (27.3)	
Yes	339 (70.5)	52 (91.2)	391 (72.7)	0.001*
Wall thickness, mm, median (IQR)[b]	14.0 (11.5–17.0)	15.5 (14.0–18.5)	14.5 (11.5–17.0)	<0.001**
Left atrial diameter, mm, median (IQR)[c]	43 (38–49)	46 (42–52)	44 (38–49)	0.005**
LVEF, %, median (IQR)[b]	60 (50–66)	55 (47–63)	60 (50–66)	0.018**
A-V valve thickening, *n* (%)[b]				
No	281 (59.3)	12 (21.0)	293 (55.2)	
Yes	193 (40.7)	45 (79.0)	238 (44.8)	<0.001*
Restrictive filling pattern, *n* (%)[b]				
No	353 (74.5)	39 (68.4)	392 (73.8)	
Yes	121 (25.5)	18 (31.6)	139 (26.2)	0.326*
Atrial fibrillation, *n* (%)				
No	417 (86.7)	37 (64.9)	454 (84.4)	
Yes	64 (13.3)	20 (35.1)	84 (15.6)	<0.001*
NYHA class, *n* (%)				
I	235 (48.9)	17 (29.8)	252 (46.8)	
II	149 (31.0)	32 (56.1)	181 (33.6)	
III	88 (18.3)	8 (14.0)	96 (17.8)	
IV	9 (1.9)	0 (0.0)	9 (1.7)	0.002*
GFR, mL/min, median (IQR)[d]	64.8 (44.8–85.0)	63.7 (51.4–85.3)	64.6 (46.0–85.0)	0.646**

AL, light-chain amyloidosis; ATTRm, hereditary transthyretin-related amyloidosis; ATTRwt, wild-type transthyretin-related amyloidosis; A-V, atrio-ventricular; CTS, carpal tunnel syndrome; GFR, glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
[a]Distinction between carriers and affected patients is presented only for ATTRm.
[b]Information is missing for 7 patients.
[c]Information is missing for 9 patients.
[d]Information is missing for 173 subjects.
*Pearson's chi-square test.
**Wilcoxon rank-sum test.
†*P*-value refers to the comparison between AL, ATTRm, ATTRwt.

cross-polarized light microscopy. Immunohistochemical analysis was performed using the following monoclonal antibodies: antibodies directed against TTR, lambda and kappa light chain (R.P. Linke, Max Planck Institute of Biochemistry, Martinsried, Germany). Mass spectrometry proteomic analysis was undertaken in selected cases.

Bone tracer scintigraphy

^{99m}Tc-DPD scintigraphy was carried out and cardiac retention was defined as previously described.[17]

Statistical methods

In the descriptive table, continuous variables were expressed as median and interquartile range and compared through Wilcoxon rank-sum test. Categorical variables were summarized as number and percentages and compared using Pearson's chi-square test. The lifetime prevalence rate of CTS was defined as the percentage of subjects who had received surgery for CTS up to the time of amyloidosis diagnosis. Lifetime prevalence in the general population (reference) was calculated assuming the same age and gender distribution observed in each

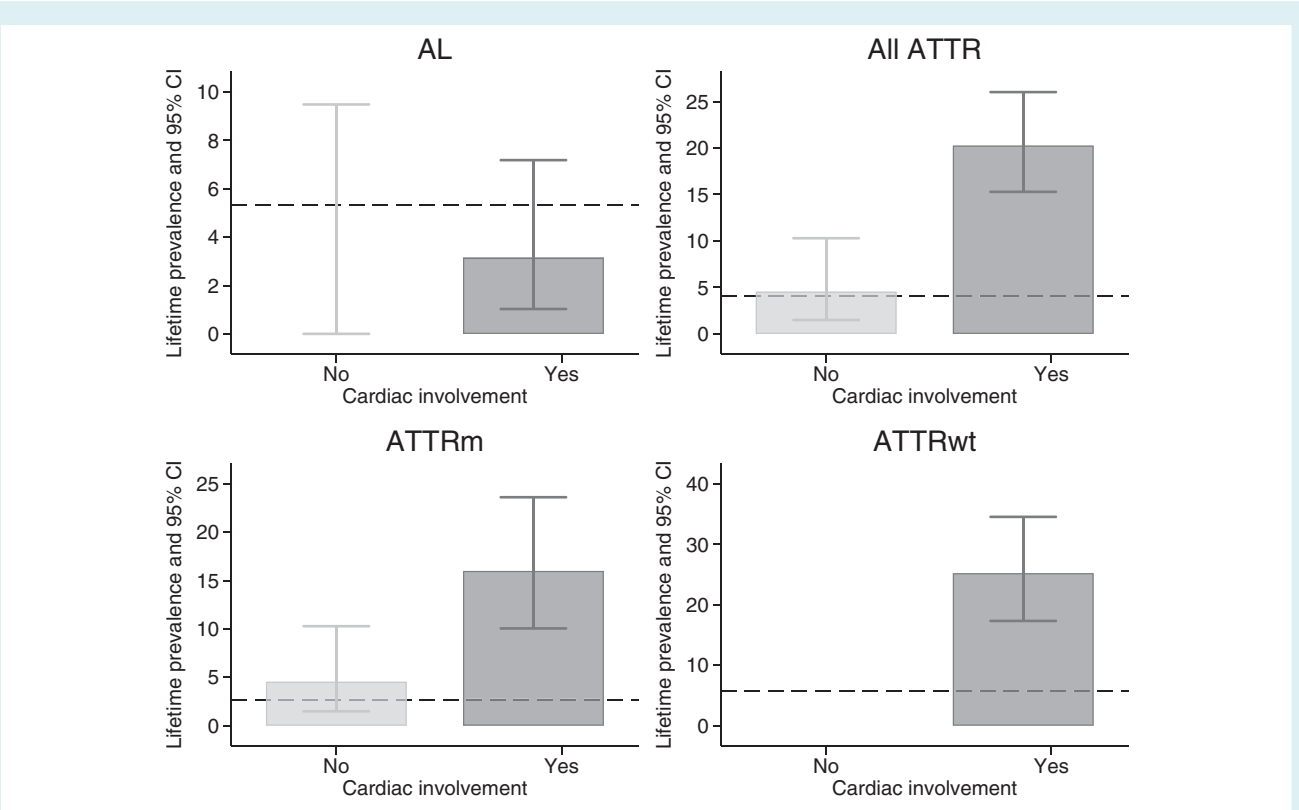

Figure 1 Lifetime prevalence of carpal tunnel syndrome at the time of cardiac assessment, stratified by amyloidosis aetiology and presence of cardiac involvement. The dashed lines represent the lifetime prevalence at reference age (i.e. median age within each aetiology) in the general population, calculated assuming the same gender distribution observed within each specific amyloidosis aetiology. AL, light-chain amyloidosis; ATTR, transthyretin-related amyloidosis; ATTRm, hereditary transthyretin-related amyloidosis; ATTRwt, wild-type transthyretin-related amyloidosis; CI, confidence interval.

group within a specific amyloidosis aetiology. For purposes of external comparison, we calculated age- and gender-standardized incidence rates (SIR) of CTS surgery with exact confidence intervals (CI). Comparison rates for the general Italian population were extracted from Mattioli *et al.*[3] We also estimated the period-specific SIR with reference to the time of the first diagnosis of CA; this analysis was, by definition, restricted to patients with cardiac involvement ($n = 391$). Cumulative hazard functions were plotted using the Nelson–Aalen estimator. Hazard ratios (HR) of cardiac involvement and death were estimated by fitting Cox proportional hazards regression models where age was specified as the main temporal axis. The covariates to be included in the multivariable regression models were selected through a backward stepwise selection strategy (*P*-value for inclusion ≤ 0.1, *P*-value for exclusion > 0.2). We performed statistical analyses using Stata 15.1 MP (Stata Corp., College Station, TX, USA). We defined a two-sided *P*-value < 0.05 as statistically significant.

Results

The characteristics of the study population are reported in *Table 1*. The study cohort consisted of 538 subjects, 64% were male and the median age was 62.4 (interquartile range 49.1–74.1) years. The population included 166 patients with ATTRm (Ile68Leu being the most common mutation, followed by Val30Met and Glu89Gln), 107 with ATTRwt and 196 with AL amyloidosis. Sixty-nine unaffected TTR mutation carriers were also included.

Frequency of carpal tunnel syndrome

A total of 57 patients reported a history of CTS and this was most frequent in ATTRwt patients (25.2%). In ATTRm, it ranged from 0% in Val30Met to 19.7% in Ile68Leu (*Table 1*).

Figure 1 displays the lifetime prevalence of CTS at the time of the first cardiac assessment, according to aetiology, cardiac involvement and compared to the general population. Prevalence of CTS was highest in ATTR patients with cardiac involvement (20.3%, 95% CI 15.3–26.0 vs. 4.1% in the general population), while it was comparable to the general population when cardiac involvement was absent.

In the analysis stratified by gender, the excess prevalence of CTS in ATTR was mainly determined by males (25.6% in ATTRwt male patients vs. 4.2% in the general population; 23.5% in ATTRwt female patients vs. 13.9% in the general population) (online supplementary *Figure S1*). In AL patients, no signs of increased incidence of CTS compared to the general population were observed (*Figure 1* and online supplementary *Figure S1*).

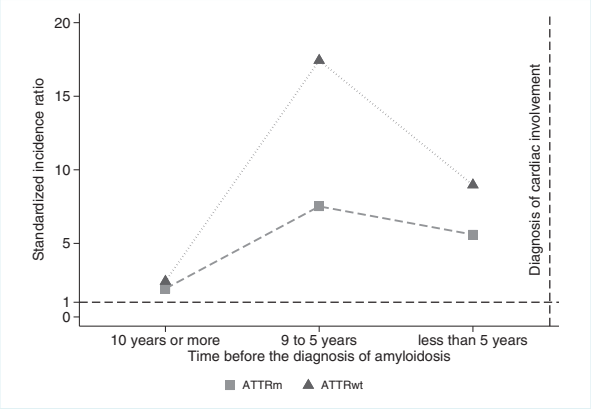

Figure 2 Standardized incidence ratios of carpal tunnel syndrome time before the diagnosis of cardiac amyloidosis. ATTRm, hereditary transthyretin-related amyloidosis; ATTRwt, wild-type transthyretin-related amyloidosis.

All subsequent analyses were limited to ATTR subjects due to the documented low CTS prevalence in AL patients.

Standardized incidence rates of CTS by amyloidosis aetiology are reported in online supplementary *Table S1*. These confirmed an excess of observed CTS in both ATTRm with CA [SIR 4.92 (3.00–7.59)] and ATTRwt [SIR 4.71 (3.10–6.85)]. Again, the estimates were driven by cases in males, and the SIR was extremely elevated for male patients with cardiac involvement due to both ATTRm [SIR 10.1 (5.79–16.4)] and ATTRwt [SIR 6.99 (4.43–10.5)] (online supplementary *Table S2*). Standardized incidence rates stratified by aetiology, gender and age are reported in online supplementary *Table S3*: the highest SIR was observed in males in the seventh and eighth decades, both in ATTRm and in ATTRwt [SIR 13.08 (1.58–47.27) in ATTRm males in the eighth decade; SIR 15.59 (7.78–27.9) in ATTRwt males in the eighth decade].

Association with cardiac amyloidosis and temporal relationship

A history of CTS was very frequent in patients with cardiac involvement (13.3%) (*Table 1*). The probability of having CTS was highest 5 to 9 years prior to the diagnosis of CA (*Figure 2* and online supplementary *Table S4*) and this was more evident in males (*Figure 3*). *Figure 4* shows the Kaplan–Meier curves for the development of cardiac involvement in relation to the presence of CTS. Irrespective of amyloidosis aetiology (ATTRm or ATTRwt), the risk of cardiac involvement was higher in patients with CTS. This persisted after adjusting for gender in a Cox proportional hazards regression model with age specified as the main temporal axis (online supplementary *Table S5*). In the analysis stratified by ATTR variant, no cases of CTS were recorded in Val30Met patients, while CTS was associated with cardiac involvement in all other variants (Glu89Gln, Ile68Leu and other variants grouped together) (online supplementary *Figure S2*).

Among ATTRm patients, the history of CTS surgery was a strong predictor of later cardiac involvement (positive predictive value 92.0%, 95% CI 74.0–99.0%).

Prognostic implication of carpal tunnel syndrome

The results of the multivariable model for survival are reported in *Table 2* (the univariate results are reported in online supplementary

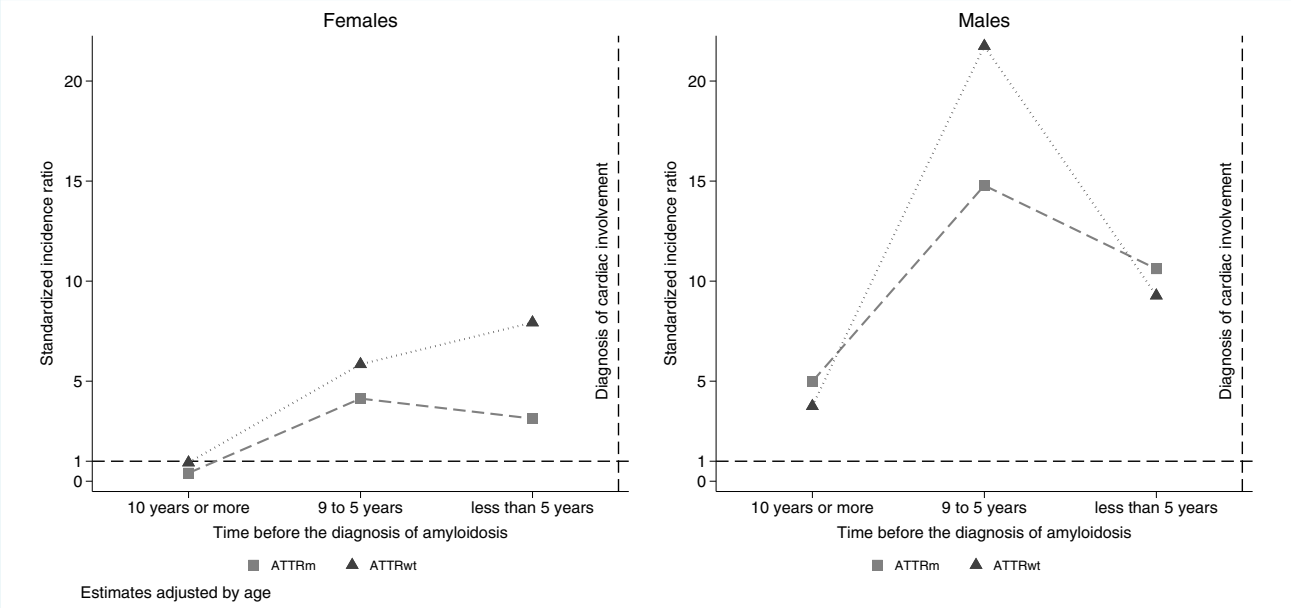

Figure 3 Standardized incidence ratios of carpal tunnel syndrome by time before the diagnosis of cardiac amyloidosis and gender. ATTRm, hereditary transthyretin-related amyloidosis; ATTRwt, wild-type transthyretin-related amyloidosis.

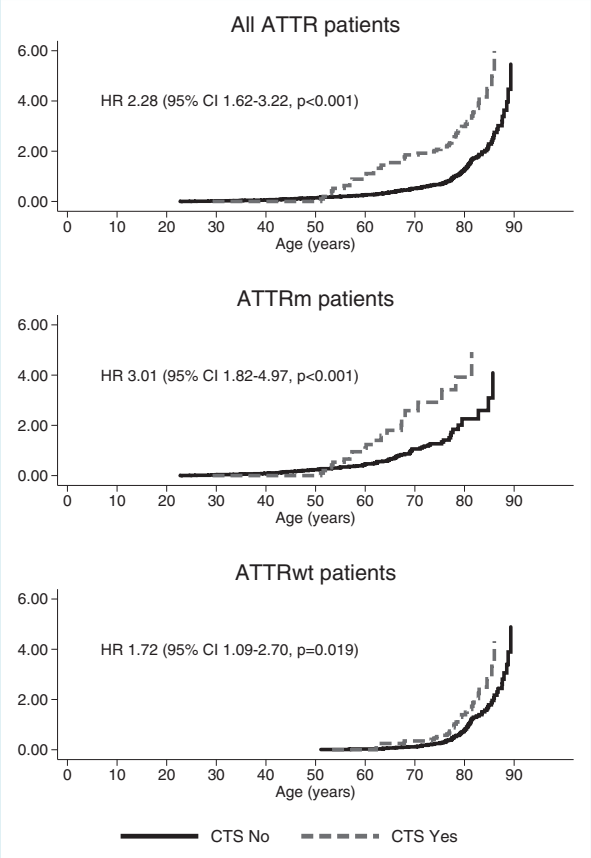

Figure 4 Risk of cardiac involvement by carpal tunnel syndrome (CTS) (time-varying covariate). Cumulative hazard functions (Nelson–Aalen estimator) and hazard ratios (HR) from Cox proportional hazards regression models. ATTR, transthyretin-related amyloidosis; ATTRm, hereditary transthyretin-related amyloidosis; ATTRwt, wild-type transthyretin-related amyloidosis; CI, confidence interval.

Table S6). CTS was associated with an increased risk of death in ATTR patients (HR 2.12, 95% CI 0.99–4.53); this was mainly due to ATTRwt patients (HR 3.63, 95% CI 1.27–10.3).

Discussion

Our study provides a detailed analysis of CTS prevalence in amyloidosis adjusted for the most common potentially confounding variables, and including temporal course, clinical and prognostic implications.

A unique aspect of our study is the availability of unquestionable administrative data generated from the hospital admission for CTS surgery in a population of more than 14 million people with known demographic data and a definite diagnosis of CTS.

Indeed, while a high prevalence of CTS in ATTR is well-known (online supplementary *Table S7*),[5–9,18–25] this is the first study that provides data compared to the general population and adjusted for age and gender. We confirm a higher than expected prevalence only in ATTR patients – reaching 14% in ATTRm and 25% in ATTRwt – with values comparable to the general population in AL. More specifically, four factors were associated with CTS in ATTR: older age, male sex, cardiac involvement and wild-type disease. While the independent role of the first three is clear, it is harder to separate the relationship between ATTRwt aetiology and myocardial involvement, since by definition CA is present in ATTRwt patients. The same applies to genotype correlations in hereditary ATTR, where 'cardiogenic' mutations (e.g. Ile68Leu) were associated with a higher prevalence of CTS. Interestingly, SIR of CTS is 6.4 for ATTRm males aged < 60 years and rises to 13.08 in ATTRm males aged 70 to 79 years, while a comparable increase in SIR is not present in females. Among ATTRwt males, SIR rises from 11.3 to 15.5 considering the seventh and eighth decades of life. In our study, CTS is an incremental risk factor for the development of CA in both ATTRwt and ATTRm with 'cardiogenic' mutations. The phenomenon is clear among Ile68Leu and Glu89Gln, whereas is not evident in the other mutations. Moreover, beyond the correlation with ATTR and cardiogenic TTR mutations, the presence of CTS is associated with a morphologically more advanced form of cardiac involvement, which includes higher mean wall thickness, more enlarged left atrium, slightly lower left ventricular ejection fraction and a higher frequency of atrioventricular valve thickening and atrial fibrillation.

Interestingly, CTS precedes the diagnosis of ATTR-CA by 5–9 years, a finding that is more pronounced in males with wild-type disease. Our observations on this delay are in line with the findings of a large ATTR retrospective cohort study from Aus dem Siepen *et al.*[6] and are also supported by registry data recently published by Fosbøl *et al.*[26]

Furthermore, this temporal association is comparable to that reported by Rubin *et al.*[9] regarding the association of ATTR with orthopaedic surgery. In a series of 313 patients, 172 with ATTR-CA, hip and knee arthroplasty surgery were more frequent than in the general population and – similarly to our findings – preceded the diagnosis of CA by a mean of 7.2 years.

Remarkably, the gender ratio usually observed for CTS (F:M 2:1)[2,3] was not found in our study population and the percentage of men who had received surgery for CTS (11.8%) was actually higher than in females (8.4%). This finding strongly supports the hypothesis that most cases of CTS among ATTR patients are attributable to the disease and are not idiopathic. Moreover, this imbalance in the gender ratio in favour of males in the context of ATTR could be the reason for the low prevalence of CA in a recent prospective study by Zegri-Reiriz *et al.*,[27] that investigated the presence of CA in a mainly female cohort of patients undergoing CTS surgery.

While the epidemiological association between CTS and CA is well established, the underlying mechanisms remain unclear. The reason for these two tissues being exclusively involved, as well as the observed temporal delay between the two remain unexplained, but it has been suggested that a repeated mechanical stimulus on tendons and myocardium could favour fibrillogenesis and/or tissue infiltration.[28] Our retrospective study was not designed to explore the mechanistic relationship between CTS and CA and did not include a histological analysis of the tenosinovial tissue of patients who underwent CTS surgery. The presence of TTR amyloid in the tenosinovium of patients with CTS has been

Table 2 Hazard ratio of death. Estimates from multivariable Cox proportional hazard regression models

Characteristics	All ATTR patients		ATTRm patients		ATTRwt patients	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CTS						
No	–	–	–	–	1.00 (Ref.)	
Yes	2.12 (0.99–4.53)	0.052	–	–	3.62 (1.27–10.3)	0.016
Gender						
Females	1.00 (Ref.)		1.00 (Ref.)		–	–
Males	2.64 (0.86–8.12)	0.090	3.67 (0.84–16.1)	0.084	–	–
Age, years	1.05 (1.01–1.09)	0.006	1.08 (1.02–1.13)	0.008	–	–
Aetiology of amyloidosis						
ATTRm	1.00 (Ref.)		NA	NA	NA	NA
ATTRwt	2.26 (0.98–5.21)	0.056	NA	NA	NA	NA
Mutation (ATTRm only)						
Glu89Gln	NA	NA	2.10 (0.50–8.84)	0.311	NA	NA
Ile68Leu	NA	NA	0.50 (0.11–2.30)	0.370	NA	NA
Val30Met	NA	NA	1.00 (Ref.)		NA	NA
Other	NA	NA	1.62 (0.39–6.73)	0.509	NA	NA
Mean wall thickness, mm	0.90 (0.81–1.01)	0.067	–	–	–	–
Left atrial diameter, mm	–	–	1.08 (1.00–1.17)	0.047		
NYHA class						
I	1.00 (Ref.)		–	–	1.00 (Ref.)	
II	1.66 (0.66–4.16)	0.278	–	–	3.78 (0.48–29.8)	0.206
III/IV	3.93 (1.41–11.0)	0.009	–	–	15.2 (1.73–132)	0.014
GFR, mL/min	0.97 (0.96–0.99)	0.001	0.97 (0.95–0.99)	0.011	0.95 (0.92–0.99)	0.004

ATTR, transthyretin-related amyloidosis; ATTRm, hereditary transthyretin-related amyloidosis; ATTRwt, wild-type transthyretin-related amyloidosis; CI, confidence interval; CTS, carpal tunnel syndrome; GFR, glomerular filtration rate; HR, hazard ratio; NA, not available; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; Ref., reference category. "–" refers to the variables not included in the multivariable regression model.

previously demonstrated (online supplementary *Table S8*),[10–13,29] but the co-existence of CA has been rarely investigated, and when it has, the prevalence was found to be particularly low. In this regard, Sperry *et al.*[10] recently published a prospective study that included 98 patients undergoing CTS surgery and reported a 10% prevalence of TTR amyloid deposits at the time of surgical intervention. Only 2/10 of these patients, however, had signs of CA (2% prevalence). Our findings allow a better interpretation of these data. The delay between CTS and the detection of CA suggest that such a low prevalence of CA at the time of CTS surgery should not discourage the physician from carrying out a cardiac follow-up for the following 5–10 years with the aim of an earlier disease recognition. This peculiar temporal relationship potentially allows a very early diagnosis of ATTR-CA, not only before symptom onset but also prior to the development of a diagnostic cardiac phenotype.

The reason for the association of CTS and CA being limited to ATTR amyloidosis and not being present in AL disease also remains unclear. This could be explained by a different light chain tropism for ligaments and joints as well as difference in disease duration. While ATTR has a long natural history with progressive accumulation of amyloid in tissues over many years, often decades, AL disease has a much faster evolution, often with a grim short-term prognosis, and it is possible that patients do not survive long enough to develop significant articular deposits.

This study also investigated the role of CTS as a prognostic factor in ATTR, independently of other main phenotypic traits. Along with age, New York Heart Association functional class and glomerular filtration rate, CTS was an independent mortality risk factor, particularly in ATTRwt.

Limitations

This is a small, single-centre, retrospective study in which the analysis was based on data obtained from medical records. Due to the frequent absence of data on onset of CTS symptoms and the unavailability of nerve conduction studies, CTS was considered to be present only in patients with a history of specific surgery and this could have led to an underestimation of prevalence in the study cohort, particularly in a subpopulation with severe co-morbidities. No histological data were acquired in the study and therefore there is no direct evidence of amyloid deposition and it can only be supposed that amyloid was the determinant of CTS. N-terminal pro-B-type natriuretic peptide was not systematically recorded, leading to a limitation in the prognostic assessment.

Population rates of surgically treated CTS are not available from national registers or the Italian Census Bureau; thus, the expected number of cases was calculated based on data extracted from a scientific report.[3] The study from Mattioli and colleagues covered a population of almost 15 million inhabitants (including the

Emilia-Romagna region, where our Institution is located), and rates were calculated based on more than 80 000 surgically treated cases. Thus, we are confident that any bias in the calculation of expected number of cases due to uncertainty of the applied population rates should be minimal. SIR for bilateral CTS could not be estimated as rates of bilateral CTS in the general population were unfortunately not available. Of note, 42 out of 57 (74%) surgically treated cases of CTS in our study population reported a history of bilateral symptoms (no major differences were observed between different amyloidosis aetiologies).

Due to the retrospective nature of our study, we could not take into account competing causes of death when estimating the lifetime prevalence of CTS. However, as we observed CTS as an early sign preceding other clinical features (e.g. CA), we do not believe that the absence of information on premature deaths due to causes other than amyloidosis could introduce substantial biases in our analysis.

Clinical implications

Our study has relevant clinical implications. Cardiologists should bear in mind that a clinical history of CTS in an adult or elderly man with cardiomyopathy and hypertrophic phenotype is an important diagnostic 'red flag' useful to foster the suspicion of ATTR-CA and to orient the diagnostic workup. Patients with a clinical history of CTS show a more severe and probably more advanced disease, and CTS is an independent negative prognostic factor. Furthermore, all the different specialists involved in the treatment of CTS, including primary care physicians, general practitioners and orthopaedic surgeons, should be aware of the association between ATTR and CTS and should investigate the possible cardiac involvement in all elderly men undergoing CTS surgery, not only at the time of intervention, but regularly over a 5–10 year follow-up. This could lead to the identification of subjects already affected by the systemic disease (with histology of ligamentum carpale positive for ATTR) but in a very early phase of the cardiac disease, leading to preventive – not therapeutic – treatments of cardiac ATTR.[30]

Conclusions

Compared to the general population, the adjusted prevalence of CTS in ATTR patients is higher, particularly in males. CTS is an incremental risk factor for ATTR-CA, especially in ATTRwt and ATTRm with cardiogenic mutations and precedes the diagnosis of CA by 5–9 years. Moreover, CTS is an independent mortality risk factor in ATTR. These observations have major clinical implications for cardiologists and all physicians involved in CTS treatment, including the general practitioner. Further studies on the natural history of ATTRwt in elderly males who had been diagnosed with CTS are necessary.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Lifetime prevalence of carpal tunnel syndrome at the time of cardiac assessment, stratified by gender, amyloidosis aetiology and presence of cardiac involvement.

Figure S2. Risk of cardiac involvement after carpal tunnel syndrome (time-varying covariate) among patients with acquired transthyretin-related amyloidosis. Analysis stratified by mutation. Cumulative hazard functions (Nelson–Aalen estimator) and hazard ratios from Cox proportional hazards regression models.

Table S1. Age (5-year classes) and sex standardized incidence ratios of carpal tunnel syndrome surgery by amyloidosis aetiology (ATTRm and ATTRwt) and presence of cardiac involvement.

Table S2. Age (5-year classes) standardized incidence ratios of carpal tunnel syndrome surgery by gender, presence of cardiac involvement, and amyloidosis aetiology (ATTRm and ATTRwt).

Table S3. Age (5-year classes) standardized incidence ratios of carpal tunnel syndrome by amyloidosis aetiology, gender, and broad age class.

Table S4. Standardized incidence ratios of carpal tunnel syndrome surgery by amyloidosis aetiology, sex, and time before the diagnosis of amyloidosis.

Table S5. Hazard ratio of cardiac involvement after carpal tunnel syndrome. Estimates from Cox proportional hazards regression models with age as the main temporal axis.

Table S6. Hazard ratio of death. Estimates from univariable Cox proportional hazards regression models.

Table S7. Carpal tunnel syndrome prevalence in patients affected by systemic amyloidosis, according to published data.

Table S8. Prevalence and type of amyloid deposits in tenosinovial tissue of patients undergoing carpal tunnel surgery.

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