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ORIGINAL PAPER

Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy?

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Abstract

Background Carpal tunnel syndrome (CTS) and spinal canal stenosis can be frequently observed in the medical history of patients with transthyretin amyloidosis (ATTR), both in the hereditary (mt-ATTR) and wild-type (wt-ATTR) form. The aim of this retrospective single-center analysis was to determine the prevalence of these findings, delay to diagnosis of systemic amyloidosis and the prognostic value in a large cohort of patients with wt-ATTR and mt-ATTR amyloidosis.

Methods Medical records of 253 patients diagnosed with wt-ATTR, 136 patients with mt-ATTR and 77 asymptomatic gene carriers were screened for history of CTS and spinal canal stenosis and laboratory analysis, electrocardiography and echocardiographic results, respectively. Clinical follow-up was performed by phone assessment.

Results History of CTS was present in 77 patients (56%) with mt-ATTR, in 152 patients (60%) with wt-ATTR and even in 10 of the asymptomatic gene carriers (13%). Latency between carpal tunnel surgery and first diagnosis of systemic amyloidosis was significantly longer in wt-ATTR compared to mt-ATTR (117 ± 179 months vs. 66 ± 73 months; $p=0.02$). In total, 36 patients (14%) with wt-ATTR and 7 patients (5%) with mt-ATTR had a history of clinically significant spinal canal stenosis. In the subgroup of mt-ATTR, patients with CTS had thicker IVS (19 ± 5 mm vs. 16 ± 5 mm, $p<0.05$), higher LV mass index (225 ± 78 g vs. 193 ± 98 g, $p<0.05$), lower Karnofsky index (78 ± 15% vs. 83 ± 17%, $p<0.05$), and lower mitral annular plane systolic excursion (MAPSE; 9 ± 4 mm vs. 11 ± 5 mm, $p<0.05$) compared to patients without CTS, whereas in wt-ATTR no significant differences could be observed. No significant difference in survival was observed between patients with and without CTS (wt-ATTR: 67 vs. 63 months, $p=0.45$; mt-ATTR: 74 vs. 63 months, $p=0.60$). A combination of CTS and spinal stenosis was present in 32 wt-ATTR patients (12%) and 3 mt-ATTR patients (2.2%).

Conclusions The prevalence of CTS is high and the latency between CTS surgery and diagnosis of amyloidosis is long among patients with wt-ATTR and mt-ATTR. CTS might be predictive for future occurrence of systemic (predominantly cardiac) ATTR amyloidosis.

Keywords Amyloidosis · Carpal tunnel syndrome · Spinal canal stenosis · Heart failure

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Introduction

Transthyretin (TTR) amyloidosis is a rare systemic disease, caused by the deposition of fibrillar proteins in the interstitial space. More than 120 different mutations in the *TTR* gene are known to result in different phenotypes of mutant-ATTR amyloidosis (mt-ATTR). Depending on the underlying mutation, patients with mt-ATTR predominantly develop bilateral senso-motoric as well as autonomic polyneuropathy and/or hypertrophic cardiomyopathy. Due to the amyloidogenic character of the monomeric form of the wild-type TTR protein, ATTR amyloidosis can also occur despite lack of any mutation, named wild-type ATTR amyloidosis

(wt-ATTR). This subtype is characterized mainly by cardiac manifestation in elderly men with higher prevalence in more advanced age.

Carpal tunnel syndrome (CTS) is the most common compressive neuropathy of the upper extremity defined by symptomatic compression of the median nerve in the carpal tunnel. Prevalence in the general population ranges from 2.7 to 5% [1, 2]. A pathological analysis of an unselected cohort of tissues obtained from German patients without any endemic background of hereditary ATTR amyloidosis removed during carpal ligaments surgery reports on a prevalence of ATTR amyloid of 7% [3].

Spinal stenosis results in compression of the spinal cord due to thickening of the ligamentum flavum, finally causing neurological symptoms. The prevalence of acquired spinal stenosis ranges from 1.7 to 13.1% in the general population [4–6] and amyloid is frequently present in material obtained from surgery. Furthermore, recent studies demonstrated that amyloid deposition was frequently observed in different joints and ligaments [7–12]. Interestingly, symptomatic CTS and spinal stenosis seem to occur before cardiac manifestation of ATTR amyloidosis [13] and, therefore, appears to be an inaugural symptom.

The aim of this retrospective analysis was to determine the prevalence of CTS and spinal canal stenosis in patients with ATTR amyloidosis, characterization of latency between surgery for CTS/spinal canal stenosis and diagnosis of cardiac amyloidosis, as well as definition of the clinical impact of CTS regarding severity of cardiac manifestation and outcome.

Methods

Study population

Records of all patients evaluated at the Heidelberg Amyloidosis Center between 2005 and 2016 were screened. Patients with mt-ATTR or wt-ATTR amyloidosis as well as asymptomatic gene carriers were selected for the present analysis. The local ethics committee approved this retrospective study and all patients gave written informed consent to use their acquired clinical data for research purposes.

Overall, complete datasets of 253 patients with wt-ATTR, 136 patients with mt-ATTR and 77 asymptomatic gene carriers were identified. Diagnosis of ATTR amyloidosis was confirmed by endomyocardial biopsy or ^{99m}Tc-DPD scintigraphy [14]. Amyloid proteins were analyzed by Congo-red and immunohistochemical staining. All patients were screened for amyloidogenetic *TTR* variants by sequencing of genomic DNA and monoclonal gammopathy by free light-chain assay and serum electrophoresis including immunofixation.

Results of clinical examination, echocardiography, 12-lead electrocardiogram (ECG) and laboratory results were recorded. Additionally, primary physicians were contacted to obtain surgical reports regarding carpal tunnel surgery and surgery for spinal canal stenosis. Clinical follow-up was performed by phone assessment.

Laboratory testing

Blood analyses included cardiac biomarkers. NT-proBNP was measured by Elecsys®proBNP, troponin T by Elecsys®2010 (Roche Diagnostics, Mannheim, Germany).

Echocardiography

Transthoracic echocardiography was done on commercially available ultrasound diagnostic systems (Vivid S5, GE Healthcare, Milwaukee, WI, USA) and were analyzed offline on a commercially available workstation (Centricity Cardiology CA1000 2.0, GE Medical Systems, Milwaukee, WI, USA). Thickness of interventricular septum (IVS) and posterior wall was measured in late diastole; left ventricular (LV) cavity diameter was scaled in end-diastole and end-systole. Longitudinal myocardial function was quantified by excursion of mitral (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) obtained from the apical four-chamber view using M-mode imaging.

Statistical analysis

Statistical analysis was performed using SPSS version 22 (IBM, Armonk, United States). The Kolmogorov–Smirnov test was used to test for normal distributions. Categorical data are expressed as percentages and continuous variables as mean ± standard deviation. For comparison of two parametric variables the *t* test was used, for comparison of two categorical variables the Chi-squared test was used. For analysis of survival we used Kaplan–Meier plots and the Log-rank test. A p value of less than 0.05 was considered as statistically significant.

Results

Prevalence of carpal tunnel syndrome and spinal stenosis

Baseline characteristics of all study patients divided by individual subtypes (mt-ATTR, wt-ATTR, asymptomatic carriers of TTR gene mutation) are given in Table 1. The most common mutations in mt-ATTR patients were p.Val50Met (32%), p.Val40Ile (20%) and p.Leu78His (4%). All patients had cardiac or mixed phenotypes. CTS was present in 77

Table 1 Baseline characteristics and frequency of carpal tunnel syndrome/spinal canal stenosis

	Asymptomatic gene carriers ($n=77$)	mt-ATTR ($n=136$)	wt-ATTR ($n=253$)	p value (ANOVA/χ^2)
Male gender (n, %)	17 (49%)	124 (70%)	232 (92%)	<0.001
Age (years)	38 ± 11	59 ± 12	74 ± 6	<0.001
Height (cm)	174 ± 10	173 ± 8	175 ± 8	0.04
Weight (kg)	81 ± 19	76 ± 16	81 ± 19	0.03
mBMI	1206 ± 237	1098 ± 246	1120 ± 180	0.02
Karnofsky index (%)	97 ± 9	80 ± 16	82 ± 9	ns
Carpal tunnel syndrome (n, %)	10 (13%)	77 (57%)	152 (60%)	<0.001
Unilateral	10 (13%)	51 (38%)	90 (36%)	
Bilateral	0 (0%)	26 (19%)	62 (25%)	
Latency between carpal tunnel surgery and diagnosis of cardiac amyloidosis (months)	–	66 ± 73	117 ± 179	0.02
Spinal canal stenosis (n, %)	0 (0%)	7 (5%)	36 (14%)	<0.001

Data are mean ± standard deviation or absolute numbers (percentage)

mt-ATTR mutant transthyretin amyloidosis, *wt-ATTR* wild-type transthyretin amyloidosis, *BMI* body mass index, *mBMI* metabolic BMI

patients (57%) with mt-ATTR without any significant differences between the individual mutations, in 152 patients (60%) with wt-ATTR and finally in 10 of the asymptomatic gene carriers (13%). Prevalence of CTS increased with age. Bilateral CTS was more frequent with wt-ATTR ($n=62$; 25%) as compared to mt-ATTR ($n=26$; 19%). Latency between surgery for carpal tunnel syndrome and diagnosis of systemic amyloidosis was significantly longer in wt-ATTR compared to mt-ATTR (117 ± 179 months vs. 66 ± 73 months; $p=0.02$).

36 patients (14%) with wt-ATTR and 7 patients (5%) with mt-ATTR had a history of symptomatic spinal canal stenosis. A history of both conditions, CTS and spinal stenosis, was present in 32 patients with wt-ATTR (12%) and 3 patients with mt-ATTR (2%). No significant differences could be observed in this subgroup compared to patients with CTS only.

Clinical parameters and laboratory results

Patients with CTS were older (70 ± 10 years vs. 65 ± 14 years, $p<0.001$), had a lower Karnofsky index (80 ± 11% vs. 83 ± 14%, $p<0.05$) as well as significantly higher values for IVS (19 ± 4 mm vs. 17 ± 4 mm, $p<0.001$) compared to patients without CTS. Dividing the cohort according to the amyloid type (Table 2), mt-ATTR patients with CTS had a higher age (62 ± 10 years vs. 55 ± 13 years, $p<0.01$), higher values for IVS (19 ± 5 mm vs. 16 ± 5 mm, $p<0.05$) and LV mass index (225 ± 78 g/m^2 vs. 193 ± 98 g/m^2, $p<0.05$), a lower Karnofsky index (78 ± 15% vs. 83 ± 17%, $p<0.05$)

Table 2 Comparison between patients with and without carpal tunnel syndrome at the time of first diagnosis of amyloid cardiomyopathy in the subgroups wild-type-ATTR (wt-ATTR) and mutant-ATTR (mt-ATTR)

	mt-ATTR ($n=136$)			wt-ATTR ($n=253$)		
	With CTS ($n=77$)	Without CTS ($n=59$)	p Value	With CTS ($n=152$)	Without CTS ($n=101$)	p Value
Age (years)	62 ± 10	55 ± 13	<0.01	74 ± 6	74 ± 7	ns
Karnofsky index (%)	78 ± 15	83 ± 17	0.04	81 ± 8	78 ± 11	ns
IVS (mm)	19 ± 5	16 ± 5	0.001	19 ± 4	19 ± 3	ns
LV mass index (g/m^2)	225 ± 78	193 ± 98	0.02	227 ± 66	233 ± 62	ns
LVEF (%)	47 ± 16	47 ± 16	ns	46 ± 15	41 ± 16	<0.01
MAPSE (mm)	9 ± 4	11 ± 5	0.047	9 ± 3	4 ± 4	ns
TAPSE (mm)	16 ± 5	16 ± 6	ns	14 ± 5	14 ± 5	ns
eGFR (ml/min)	95 ± 37	87 ± 35	ns	70 ± 22	65 ± 25	0.013

IVS interventricular septum thickness, *LVEF* left ventricular ejection fraction, *MAPSE* mitral annulus plain systolic excursion, *TAPSE* tricuspidal annulus plain systolic excursion, *eGFR* estimated glomerular filtration rate

and a severe reduced MAPSE (9 ± 4 mm vs. 11 ± 5 mm, $p < 0.05$) compared to patients without CTS. In the subgroup of wt-ATTR patients, significantly higher values for estimated glomerular filtration rate (70 ± 22 ml/min vs. 65 ± 25 ml/min; $p < 0.05$) and LVEF were observed in patients with CTS compared to patients without CTS. No significant differences could be observed in blood pressure, NT-proBNP, Troponin-T and NYHA class.

In a subgroup analysis, patients with latency longer than 2 years were compared to patients with shorter latency (Table 3). Intraventricular septum thickness was significantly higher in patients with longer latency. In the mt-ATTR group, patients with longer latency presented with significantly higher Troponin-T levels, and finally, tended to higher LV mass index. No significant differences could be observed in blood pressure, NT-proBNP, Troponin-T, eGFR, Karnofsky index, LVEF, MAPSE, TAPSE and NYHA class.

Survival

Mean follow-up was 29 ± 29 months (mt-ATTR 33 ± 37 months, wt-ATTR 25 ± 23 months). During this period, 46 (26%) patients with mt-ATTR died, 12 (7%) patients underwent heart transplantation, and 66 (26%) patients died in the cohort of wt-ATTR. The causes of death in the cohort were heart failure, sudden cardiac death or other cardiovascular causes. Kaplan–Meier analysis revealed differences in survival among the alternate mutations: median survival was 85 months in patients with p.Val50Met, 56 months in patients with p.Val40Ile and 50 months in patients with other mutations. However, survival did not differ between patients with or without CTS in wt-ATTR (median survival 67 vs. 63 months, $p = 0.45$, Fig. 1a) as well as mt-ATTR (median survival 74 vs. 63 months, $p = 0.60$, Fig. 1b). No significant differences between patients with or without CTS could be observed in the subgroups of different mutations or in the subgroup of patients with both, CTS and spinal stenosis. No events occurred in the subgroup of asymptomatic mutation carriers.

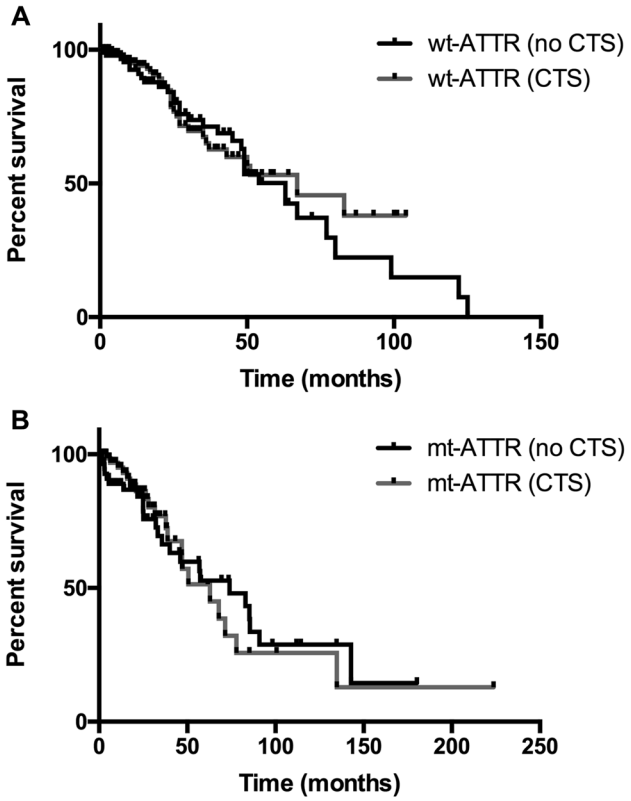

Fig. 1 Kaplan–Meier analysis of patients with and without CTS for the subgroup of wt-ATTR (**a**) and the subgroup of mt-ATTR (**b**)

Discussion

In this retrospective analysis a high prevalence of CTS among patients with wt-ATTR and mt-ATTR was demonstrated. Interestingly, in most of the patients, CTS surgery was performed several years before diagnosis of systemic amyloidosis with longest latency in wt-ATTR. Furthermore, in the mt-ATTR group, patients with CTS presented with more severe cardiac disease at the time of first diagnosis compared to patients without CTS, as demonstrated by

Table 3 Comparison between patients with short and long latency between CTS surgery and diagnosis of systemic amyloidosis in the subgroups of wild-type-ATTR (wt-ATTR) and mutant-ATTR (mt-ATTR)

	mt-ATTR with CTS ($n = 77$)			wt-ATTR with CTS ($n = 152$)		
	Latency < 2 years ($n = 37$)	Latency > 2 years ($n = 40$)	p Value	Latency < 2 years ($n = 47$)	Latency > 2 years ($n = 105$)	p Value
Age (years)	60 ± 11	64 ± 9	ns	75 ± 6	74 ± 6	ns
IVS (mm)	17 ± 5	20 ± 4	0.03	18 ± 4	10 ± 4	0.03
LV mass index (g/m^2)	209 ± 82	241 ± 14	ns (0.06)	218 ± 67	232 ± 66	ns
hs-TnT (pg/ml) cut-off < 14 pg/ml	40 ± 29	55 ± 27	0.02	55 ± 33	68 ± 74	ns

IVS interventricular septum thickness

higher values for IVS thickness and myocardial mass index, as well as worse longitudinal function and lower Karnofsky index. However, only morphological, but no functional or biochemical differences, e.g., NYHA or NT-proBNP were observed. Prevalence of spinal canal stenosis was less common than CTS in both groups, but in the wt-ATTR cohort with 14% more frequent than in the general population with 1.7–13.1% [4–6]. In the majority of cases (81%), spinal canal stenosis appeared in combination with CTS, the value of isolated spinal canal stenosis, therefore, remains uncertain.

Carpal tunnel syndrome may be triggered by mechanical stress and is more frequent in females. Compared to the general population, prevalence of CTS among ATTR patients is higher, the age of onset is later and the gender ratio is shifted towards males [13]. Amyloid fibrils in the carpal ligament might contribute to the development of a symptomatic compression of the median nerve, even if typical risk factors, e.g., trauma, exposure to vibrations or repetitive motions of the hands, are absent. The clinical improvement after CTS surgery and deposition of amyloid in the retinaculum flexorum suggests that even in ATTR patients, CTS has to be considered as a compressive disease and not as a symptom of amyloid polyneuropathy. Interestingly, latency between CTS surgery and onset of heart failure is longer in patients with wt-ATTR, which is claimed to be less progressive than mutant-type TTR.

The association of amyloid deposition in individual ligaments and occurrence of systemic amyloid deposition is poorly studied. In a first prospective study by Fernandez et al., samples from CTS surgery were evaluated for amyloid deposition. In approximately 20% of the specimen amyloid was detected and 3% of the patients developed events attributable to systemic amyloidosis within 3 years after surgery [15]. A link between CTS and ATTR amyloidosis is also endorsed by a retrospective study, demonstrating a prevalence of ATTR amyloid in 7% of the specimens among a non-selected cohort of german patients [3].

There are several differences in clinical presentation between mt-ATTR and wt-ATTR amyloid cardiomyopathy. Depending on the underlying TTR-mutation, mt-ATTR patients may develop either sole cardiac involvement (FAC), e.g., patients with the p.Val142Ile [16, 17] or the p.Val40Ile [18] mutation, or a mixed type with predominantly polyneuropathy (FAP) and additional cardiomyopathy. Patients with wt-ATTR are older, predominantly male [19] and usually no other organs than the heart are affected [20]. Heart failure is typically less severe and disease progression is slower, despite morphological similarities by echocardiography [21] and magnetic resonance imaging [22]. Thus wild-type TTR may be less toxic to the tissue than mutant-type TTR resulting in earlier and more severe organ manifestation. This might also be an explanation, why the latency between CTS operation and occurrence of heart failure is significant longer in wt-ATTR. Previous studies demonstrated a median survival of 25–36 months in mt-ATTR and 24–66 months in wt-ATTR [16, 19, 21, 23, 24].

Treatment options for both, mt-ATTR and wt-ATTR, are limited. Positive effects could be demonstrated for the non-steroidal anti-inflammatory drug (NSAID) diflunisal in FAP patients [25, 26], epigallocatechingallat (EGCG), the most abundant catechin in green tea [27–31], the combination of doxycycline and tauroursodeoxycholic acid (TUDCA) [32] and Tafamidis [33], a selective stabilizer of the transthyretin tetramer. A novel approach to prevent amyloid deposition is RNA interference (RNAi) with small interfering RNAs or antisense oligonucleotides to achieve a serum TTR knockdown, the drugs Inotersen [34] and Patisiran [35] are approved for patients with stage 1–2 hereditary amyloid polyneuropathy since October 2018.

So far, therapeutic strategies target a reduction of the amyloid precursor protein to slow disease progression. Thus, early diagnosis and initiation of treatment is still essential to preserve organ function. Therefore, identification of individuals at risk and the identification of early predictors for systemic amyloidosis are crucial. The present data suggest that compression diseases such as CTS and spinal canal stenosis might be predictive for the future occurrence of systemic amyloid diseases.

In conclusion, prospective studies are needed to investigate the relationship of amyloid deposition in the carpal ligament and future occurrence of systemic ATTR.

Conclusion

The high prevalence of CTS and the long latency between CTS surgery and diagnosis of systemic amyloidosis among patients with wt-ATTR and mt-ATTR suggest that CTS might be predictive for future occurrence of systemic amyloidosis, especially ATTR cardiomyopathy. Moreover, CTS appears to be a predictor of more severe cardiac disease in mt-ATTR. Further prospective studies are mandatory to evaluate the relationship between amyloid deposition in different ligaments and occurrence of an early systemic amyloid disease.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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