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REVIEW

Musculoskeletal co-morbidities in patients with transthyretin amyloid cardiomyopathy: a systematic review

Francesc Formiga*, Laia Saumell Baeza, David Chivite and Sergi Yun

Geriatric Unit, Internal Medicine Department, Hospital Universitari de Bellvitge, Systemic Diseases and Ageing Group, Cardiovascular, Respiratory and Systemic Diseases and Cellular Aging Program, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de LLobregat, Barcelona, Spain

Abstract

The prevalence of transthyretin-associated amyloidosis cardiomyopathy (ATTR-CM) has grown because of newer non-invasive diagnosis tools. Detecting the presence of extra-cardiac ATTR manifestations such as musculoskeletal pathologies considered 'red flags', when there is minimal or non-cardiac clinical involvement is primordial to carry out an early diagnosis. The aim of this systematic review is to examine the prevalence of musculoskeletal, ATTR-deposition-related co-morbidities in patients already diagnosed with ATTR-CM, specifically carpal tunnel syndrome, ruptured biceps tendon, spinal stenosis, and trigger finger. We performed a systematic review using PRISMA guidelines. Inclusion criteria were all studies in English and Spanish language and participants had to be patients diagnosed with ATTR-CM, by any diagnostic method, with the musculoskeletal co-morbidities subject of this review. The quality of the studies was based on the Risk of Bias Tool. This systematic review included 22 studies for final analysis. Carpal tunnel syndrome is reported in 21 studies, brachial biceps tendon rupture is reported in three, and spinal stenosis in eight studies. No articles that accomplished all the inclusion criteria for trigger finger were found. Regarding to the quality of the studies, all of them were categorized as being of high and moderate quality. The frequent association between ATTR-CM and carpal tunnel syndrome, ruptured biceps tendon, and lumbar spinal is confirmed, and the onset of these co-morbidities usually precedes the diagnosis of by years. This association defines them as red flags that should be search proactively due to the current treatment possibilities and the severity of the presentation of cardiac amyloidosis.

Keywords Amyloid transthyretin; Biceps tendon; Cardiac amyloidosis; Carpal tunnel syndrome; Musculoskeletal co-morbidities; Spinal stenosis

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**Correspondence to:*
Francesc Formiga, Geriatric Unit, Internal Medicine Department, Hospital Universitari de Bellvitge, Systemic Diseases and Ageing Group, Cardiovascular, Respiratory and Systemic Diseases and Cellular Aging Program, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de LLobregat, Barcelona, Spain. Email: fformiga@bellvitgehospital.cat

Introduction

The interest of the medical community in transthyretin-associated amyloidosis (ATTR)-cardiomyopathy (CM) has increased in recent years, due to the availability of both newer non-invasive diagnosis tools such as 99mTC-DPD scintigraphy[1] and therapies.[2] Non-invasive diagnosis has translated into better detection of ATTR-CM and therefore a growing prevalence, especially that of wild-type ATTR (ATTRwt). This scenario has been compared with the emergence of the tip of an iceberg previously unaware.[3–5]

Early diagnosis of ATTR-CM is crucial to improve the outcome of these patients, as most of the therapeutic options available to treat this disease target the deposition of additional amyloid in the affected organs, but do not attenuate or reverse the organ dysfunction caused by the deposits already present.[3] ATTR-CM is still being diagnosed in late stages, when the deposit-related signs and symptoms of

heart disease are evident, and the clinical suspicion is raised. The delay between the first cardiological symptoms and the diagnosis of ATTR-CM has been estimated to be as long as 4 years in 42% of cases.[6] Therefore, a high index of suspicion of the disease is essential for an early diagnosis.[7–8]

In the last years, efforts have been focused on the non-cardiac manifestations of the disease that precede the onset of cardiac symptoms. If detected, extra-cardiac, early ATTR-related disease might trigger suspicion of the presence of ATTR-CM at a sub-clinical level, when symptoms are still not present. Most of these early, extra-cardiac manifestations are related to the deposition of amyloid fibres in regions of the musculoskeletal system.[9]

The extra-cardiac deposit of ATTRwt is less prevalent than that of hereditary ATTR (ATTRv) and mostly limited to musculoskeletal manifestations. Patients with ATTRwt-related musculoskeletal involvement usually present with carpal tunnel syndrome (CTS), stenosis of the lumbar canal, non-traumatic rupture of the biceps tendon (which is diagnosed by the detection of the 'Popeye's sign' in the affected arm)[10] and, to a lesser extent, trigger finger and rotator cuff tear.

Detecting the presence of extra-cardiac ATTR manifestations, when there is minimal or non-cardiac clinical involvement, might therefore be a powerful clinical tool, allowing for an early diagnosis of ATTR-CM. Patients could therefore derive an earlier benefit from an advanced prescription of the current therapies for ATTR. The aim of this systematic review is to examine the prevalence of musculoskeletal, ATTR-deposition related co-morbidities in patients already diagnosed with ATTR-CM. This information might help in the purpose of an earlier diagnosis for these patients.

Methods

Searching strategy and selection criteria

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Metanalyses (PRISMA) guidelines.[11] Medical literature was systematically examined searching for studies reporting the prevalence of musculoskeletal (osteoarticular) co-morbidities in patients with ATTR-CM, specifically CTS, brachial biceps tendon rupture (BBTR), spinal stenosis (SS), and/or trigger finger. The study is registered with PROSPERO (ID CRD42022364866).

Screening was performed by three independent reviewers (LS, FF, and SY). The data search was performed using the PubMed and Scopus databases, since their inceptions until 21 November 2022. PubMed was used in first place, by using the terms ('TTR' OR 'cardiac amyloidosis') AND ('trigger finger', 'spinal stenosis', 'carpal tunnel syndrome', 'biceps tendon') appearing either in the 'title' or 'abstract' fields. Each musculoskeletal co-morbidity was searched independently. Subsequently, the search was reproduced in the Scopus database. All article duplicates were removed prior to screening.

Eligibility criteria for including studies as follows:

- *Types of studies*: all studies in English and Spanish language were accepted except for reviews, systematic reviews, case reports and letters to the editor.
- *Types of participants*: patients diagnosed with ATTR-CM, by any diagnostic method, with the musculoskeletal co-morbidities subject of this review (carpal tunnel syndrome, ruptured biceps tendon, spinal stenosis and/or trigger finger).

This article is based on previously reported studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data extraction

Data were extracted by a single reviewer (LSB) using a bespoke extraction grid and checked by a second and a third reviewers (FF and SY). Any disagreements at the end of each step were settled by discussion between the reviewers. In all cases, a consensus was reached. For each study, data were extracted: year of publication, country, study design, total of subjects (*n*), mean age and/or age onset (where possible, if reported by the study), sex (%female), ATTR subtype and musculoskeletal pathology and its prevalence.

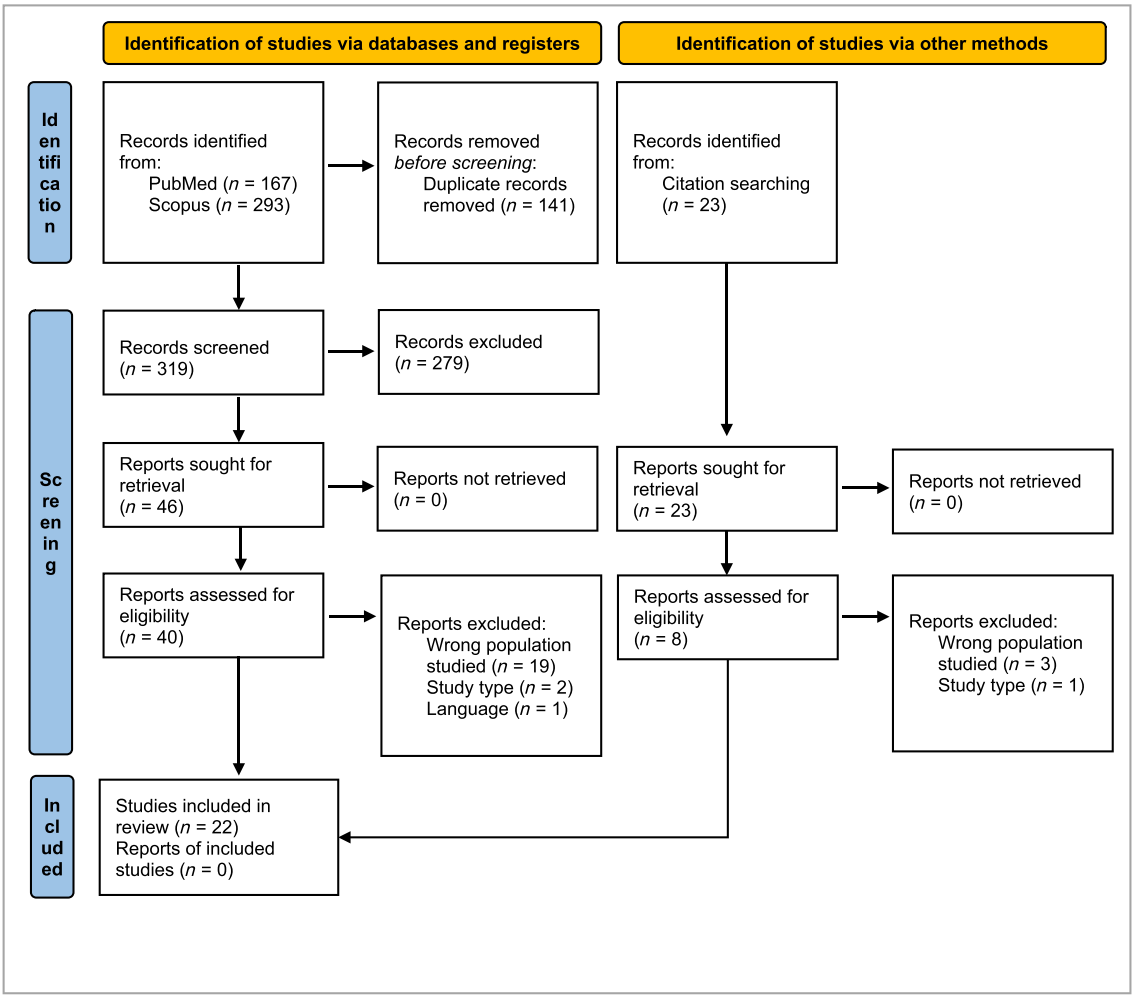
Quality of the studies

The quality of the studies was based on the Risk of Bias Tool for prevalence studies (based on the Leboeuf-Yde and Lauritsen tool) developed by Hoy et al. in 2012.[12] According to the quality assessment checklist, which consists of 10 items (*Table S1*), the studies are classified as 'high' (9–10 points), 'moderate' (6–8 points), or 'low' quality (0–5 points). Items 1 to 4 assess the external validity of the study and items 5 to 10 assess the internal validity. These assessments were performed by one author (LSB) and independently checked by another author (Dch).

Results

A flow diagram of the selection process is shown in *Figure 1*. In total, 460 studies were identified from the PubMed and Scopus searches. After removing the duplicates, 319 studies remained. Out of these, 40 were considered eligible based on the title and abstract and full-text review found 18 of them to meet all the inclusion criteria. Of the 22 excluded articles 19 were excluded due to the characteristics of the population evaluated (patients diagnosed with ATTR but not

Figure 1 The PRISMA search strategy flow chart.



specifically ATTR-CM: screening amyloidosis in the resected tissue, which was obtained at surgery for SLB, or trigger finger), two were reviews and one used a non-included language (German). In the additional search through reference lists and citations of the 18 included studies, four additional studies fulfilling the selection criteria were additionally found. As a result, a total of 22 studies were included in the final analysis. Their details are provided in *Table 1*.

With respect to the geographic area where the studies were performed: three studies collected data in North America,[13–15] seven in Asia,[16–22] and 12 in Europe.[23–24] Regarding the musculoskeletal manifestation assessed: 21 publications reported data for CTS (depending on the study was defined by surgical reports, electromyography diagnosis or typical symptomatology),[8,13,14,16–31,33,34] eight for SS (depending on the study was defined by surgical reports or magnetic resonance imaging [RM]) diagnosis),[17,20,24,25,27,30,31,33] three for BBTR (all of them defined it by the presence of the Popeye sign)[15,25,26]; none was found for only trigger finger. Some of them recorded data for more than one these musculoskeletal conditions. All of them were retrospective descriptive studies, except for two which were case–control studies (a prospective one and a cross sectional one) and two others which were prospective observational studies. Regarding the type of ATTR-CM, four studies only collected data for ATTRv, five collected data for ATTRwt, 10 both and three did not specify which subtype was studied.

Included subjects were predominantly male in both ATTR subtypes. The gender gap was particularly huge for ATTRwt population (97.3–77% male vs. 2.7–23% female),[12,21,23,25,27] but more variable for ATTRv, above all depending on the TTR mutation involved (93.1–54.5%).[14,16,20,23] According to the totality subjects' age, the mean range was very wide from 53 to 75.9 years old at symptom onset and from 56 to 80 years old at diagnosis. If data is analysed separately based on ATTR subtype, patients with ATTRwt were between 53

Table 1 Summary of key elements of assessed studies

Authors, year	Country	Quality grade*	Study design	Total subjects** (*n*)	Age (years)***	Female sex (%)	ATTR subtype	Orthopaedic pathology and prevalence
Auer-Grumbach et al., 2020	Austria	8	Prospective observational study	18	66.9/63.5/61.7	45.5	ATTRv, 100%	CTS, 55%
aus dem Siepen et al., 2019	Germany	9	Retrospective descriptive study	389	ATTRwt, 74/-/- ATTRv, 59/-/-	ATTRwt, 8 ATTRv, 30	ATTRwt, 65% ATTRv, 35%	CTS, ATTRwt, 60% CTS, ATTRv, 57% SS, ATTRwt, 14% SS, ATTRv, 5%
Barge-Caballero et al., 2022	Spain	9	Prospective observational study	128	81/-/-	23.8	ATTRwt, 89.9% ATTRv, 1.6% Unknown, 8.6%	CTS, 28.1% BBTR, 38.3% SS, 18.8%
Bishop et al., 2018	USA	8	Retrospective descriptive study	52	-/73.4/-	19	Non specified	CTS, 51.9%
Cappelli et al., 2020	Italy	9	Prospective case–control study	168	77.9/-/-	10	ATTRwt, 83.9% ATTRv, 16.1%	CTS, 73% BBTR, 44%
Chen et al., 2021	Singapore	8	Retrospective descriptive study	29	-/-/57	41.4	ATTRv 100%	CTS, 58.6%
Debonnaire et al., 2021	Belgium	9	Retrospective descriptive study	114	-/80/-	24	ATTRwt, 96.4% ATTRv, 3.6%	Bilateral CTS, 43% SS, 40%
Gagliardi et al., 2018	Italy	9	Retrospective descriptive study	149	ATTRwt, -/78/- ATTRv, -/71/-	ATTRwt, 11 ATTRv, 22	ATTRwt, 55% ATTRv, 45%	CTS, ATTRwt, 37% CTS, ATTRv, 43%
Galat et al., 2016	France	8	Retrospective descriptive study	16	79/-/-	19	ATTRwt,81% ATTRv, 6% Unknown, 12%	CTS, 31%
Geller et al., 2017	USA	9	Cross sectional case–control study	111	74.9/-/-	2.7	ATTRwt,100%	BBTR, 33.33%
Itzhaki Ben Zadok et al., 2020	Israel	9	Retrospective descriptive study	26	-/68/-	40	ATTRwt, 76.9% ATTRv, 23.1%	CTS, 62%
Karam et al., 2019	USA	7	Retrospective descriptive study	23	-/61/53	26	ATTRv, 100%	CTS, 73%
López-Sainz et al., 2021	Spain	8	Retrospective descriptive study	116	-/79.4/-	ATTRwt, 23 ATTRv, 56	ATTRwt, 84.5% ATTRv, 15.5%	CTS, 41.4% SS, 9.5%
Milandri et al., 2020	Italy	9	Retrospective descriptive study	273	61.5	36.9	ATTRwt, 39.2%[a] ATTRv, 60.8%[a]	CTS, ATTRwt, 25.2% CTS, ATTRv, 13.9%
Nakagawa et al., 2016	Japan	9	Retrospective descriptive study	31	-/74.5/69.8	22.6	ATTRwt, 100%	CTS, 68% SS, 13%
Papagianni et al., 2021	Germany	9	Retrospective descriptive study	30	ATTRwt, 76/-/- ATTRv, 65/-/-	ATTRwt, 8.7 ATTRv, 42.8	ATTRwt, 23.3% ATTRv, 76.7%	CTS, ATTRwt, 87% SS, ATTRwt, 30.4%
Rapezzi et al., 2009	Italy	8	Retrospective descriptive study	76	ATTRwt, 75.5/-/- ATTRv, 51.5/-/-	ATTRwt, 7 ATTRv, 20	ATTRwt, 19,7% ATTRv, 80,3%	CTS, ATTRwt, 13% CTS, ATTRV, 38%
Takashio et al., 2022 a	Japan	8	Retrospective descriptive study	174	-/80/-	19	Non specified	CTS (*n* = 172) 36%

(*Continues*)

Table 1 (continued)

Authors, year	Country	Quality grade*	Study design	Total subjects** (*n*)	Age (years)***	Female sex (%)	ATTR subtype	Orthopaedic pathology and prevalence
Takashio et al., 2022 b	Japan	8	Retrospective descriptive study	199	-/77.9/75.9	15	ATTRwt, 100%	CTS (*n* = 199) 57%
Wang et al., 2022	China	7	Retrospective descriptive study	29	-/56/53	6.9	ATTRv, 100%	CTS, 20.7% SS, 3.4%
Westin et al., 2021	Denmark	9	Case–control study	619	70/69.9/68.2	37	Non specified	CTS, 10,6% SS, 7,3%
Yamada et al., 2020	Japan	8	Retrospective descriptive study	129	-/78.5/74.3	15	ATTRwt, 100%	CTS, 54%

ATTRwt, wild-type ATTR; ATTRv, variant ATTR; BBTR, brachial biceps tendon rupture; CTS, carpal tunnel syndrome; SS, Spinal stenosis.
*Quality grade: High quality: score >8; Moderate quality: score 6–8; Low quality: score 0–5 (Source: Hoy et al.).
**Total subjects: only considered those with ATTR.
***Age: Where possible, if reported by the study is registered as age at baseline/ age at diagnosis/age at first manifestation or onset. If the study reported the duration from onset of symptom to diagnosis it has been calculated.
[a]This information has been calculated from the study characteristics which accomplished all the inclusion criteria, patients who are carriers have been excluded.

and 61.7 years old at first manifestation and ATTRv population was between 69.8 and 75.9 years old. Referring to the age at diagnosis, ATTRwt population was 74.5–78.5 in contrast with ATTRv population that was 56–71 years old.

Study methodological quality was assessed using the Risk of Bias Tool.[12] There were no low-quality studies as it is shown on *Table 2*. In all studies, except for Westin et al.,[33] the possibility of external validity was low as the target population was not nationally representative of the country. However, all studies have been categorized as being of high and moderate quality, which is the equivalent of low and moderate risk of bias, hence they have been included in the review.

Carpal tunnel syndrome

Twenty-one publications reported data for CTS, becoming the most studied orthopaedic pathology related with ATTR amyloidosis. Some publications recollected data from history of CTS and specified if it was unilateral or bilateral,[23,24,26,27] but the majority did not.

The prevalence of CTS in ATTRwt patients in those publications that only studied this subtype was 68%, 57%, and 54%.[17,19,21] Concerning the articles, which studied both subtypes but distinguished between the results, the prevalence of CTS in ATTRwt subjects was 60%, 37%, 25.2%, 87%, and 13%.[24,28,31,32,34] In terms of ATTRv, the prevalence of CTS was 55%, 73%, 20.7%, and 31% in the publications which only considered ATTRv subtype[14,16,20,23] and 57%, 43%, 13.9%, and 38% in those which studied both subtypes but differentiated the results.[8,24,28,34]

Nine publications did not specify the prevalence of each ATTR subtype. The prevalence of CTS ranged from 10.6–75%, with a huge variation between them.[13,18,22,25–27,29,30,33]

From those studies that evaluated bilateral CTS, its prevalence was between 19% and 60% according to the series and the amyloidosis subtype.[23,24,26,27] Only two studies differentiated between the ATTR subtype. Auer-Grumbach et al.[23] studied ATTRv and showed that the prevalence of bilateral CTS was 50% while Aus dem Siepen et al.[24] studied both subtypes and reported that 19% of patients with ATTRv had bilateral CTS and 25% of those with ATTRwt presented it. The other two studies did not distinguish between subtypes and the prevalence of bilateral CTS were 60% and 43%.[26–27]

Regarding the initial manifestation in ATTRwt patients, Takashio et al.[19] observed that the most common was heart failure (44% in male patients and 52% in female patients), followed by CTS (38% in male patients and 38% in female patients). Yamada T et al[21] found the same results, heart failure was the first manifestation in 49% of patients and peripheral neuropathy was the initial symptom in 31% of subjects, being CTS in most cases (39 of 40 cases). Conversely, Nakagawa et al.[17] observed that the most common initial symptom was CTS (*n* = 17, 55%), followed by heart failure symptoms (*n* = 14, 45%).

Table 2 Quality assessment of the 22 included studies

	External validity				Internal validity							
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	TS	QG
Auer-Grumbach, 2020	0	1	1	1	1	1	0	1	1	1	**8**	Moderate
aus dem Siepen, 2019	0	1	1	1	1	1	1	1	1	1	**9**	High
Barge-Caballero, 2022	0	1	1	1	1	1	1	1	1	1	**9**	High
Bishop, 2018	0	1	1	1	1	0	1	1	1	1	**8**	Moderate
Cappelli, 2020	0	1	1	1	1	1	1	1	1	1	**9**	High
Chen, 2021	0	0	1	1	1	1	1	1	1	1	**8**	Moderate
Debonnaire, 2021	0	1	1	1	1	1	1	1	1	1	**9**	High
Gagliardi, 2018	0	1	1	1	1	1	1	1	1	1	**9**	High
Galat, 2016	0	1	1	1	1	0	1	1	1	1	**8**	Moderate
Geller, 2017	0	1	1	1	1	1	1	1	1	1	**9**	High
Itzhaki Ben Zadok, 2020	0	1	1	1	1	1	1	1	1	1	**9**	High
Karam, 2019	0	1	1	1	1	0	0	1	1	1	**7**	Moderate
López-Sainz, 2021	0	1	1	1	1	0	1	1	1	1	**8**	Moderate
Milandri, 2020	0	1	1	1	1	1	1	1	1	1	**9**	High
Nakagawa, 2016	0	1	1	1	1	1	1	1	1	1	**9**	High
Papagianni, 2021	0	1	1	1	1	1	1	1	1	1	**9**	High
Rapezzi, 2009	0	1	1	1	1	0	1	1	1	1	**8**	Moderate
Takashio, 2022a	0	1	1	1	1	0	1	1	1	1	**8**	Moderate
Takashio, 2022b	0	1	1	1	1	0	1	1	1	1	**8**	Moderate
Wang, 2022	0	1	1	1	1	0	1	1	1	0	**7**	Moderate
Westin, 2021	1	1	1	1	1	0	1	1	1	1	**9**	High
Yamada, 2020	0	1	1	1	1	0	1	1	1	1	**8**	Moderate

TS = total score; QG = quality grade.
Methodological quality: High quality: score >8; Moderate quality: score 6–8; Low quality: score 0–5 (Source: Hoy et al.).

Spinal stenosis

Eight studies questioned and reported data of spinal stenosis but just four publications distinguished the results between ATTR subtypes. Nakagawa et al.[17] and Papagianni et al.[31] reported that the prevalence of SS in ATTRwt was 13% and 30.4%. Wang et al.,[20] who studied ATTRv, reported that the SS prevalence in that population was 3.4%. Finally, Aus dem Siepen et al.[24] studied both subtypes and differenced its results and concluded that the prevalence of SS in ATTRwt population was 15% and in ATTRv patients it was 5%.

The prevalence of SS in those studies which did not specify ATTR subtype ranged from 7.3 to 40%.[25,27,30,33]

Brachial biceps tendon rupture

Only three studies reported information about brachial biceps tendon rupture[15,25,26] and in all of them, the presence of tendon rupture was defined by the presence of the Popeye sign upon flexion of each arm against gentle resistance. The prevalence of BBTR in ATTR patients ranged from 33.3% to 44%.

Geller et al.[15] studied the prevalence of BBTR in patients with ATTRwt and reported that it was observed in 33.3% of the patients and was bilateral in the 24.3%. Of those with BBRT, 37.8% were unaware of the onset or existence of tendon rupture. Cappelli et al.[26] also noticed that 20% of the patients with BBRT were not aware of ligament lesion and was diagnosed as a spontaneous rupture during physical examination. Without specifying ATTR subtype, in this study the prevalence of BBRT was 44%, being 15% bilateral,[26] and in the third, one,[25] the prevalence of BBRT was 38.3%.

Trigger finger

No articles that accomplished all the inclusion criteria were found.

Discussion

In this systematic review, extra-cardiac ATTR manifestations, specifically musculoskeletal co-morbidities, are analysed. These manifestations are caused by the amyloid infiltration of connective tissue such as the carpal transverse ligament, the synovial sheaths of the flexor tendons or the ligamentum flavum, which CTS and SS respectively.[25] It is important to note that the most prevalent extra-cardiac manifestation of ATTR is CTS, with a wide range of presentation. Its prevalence ranges substantially from 10.6 to 68%, depending on the series. Due to progressive amyloid infiltration into tendon structures, ATTR-related CTS diagnosis usually precedes the cardiac disease by a long period of time (5 to 10 years).[14,17,27,34] Interestingly, latency between CTS surgery and onset heart failure is significantly longer in ATTRwt (117 months) compared with ATTRv (66 months), owing to the lowest progression claimed to ATTRwt.[24] This temporal discrepancy is repeated for SS, it is diagnosed at a mean of 7 years before CA diagnose.[27] The delay between CTS/SS and detection of ATTR-CM should encourage the physician to perform a cardiac follow-up over the next 5–10 years with the aim of earlier recognition of the disease, opening up the possibility of early diagnosis.

In addition to CTS, it is consistently more prevalent among patients with ATTRwt with cardiac involvement; for patients with ATTRv the prevalence is more variable, depending on the mutation. While no cases of CTS were recorded in patients with the Val30Met mutation (a variant without cardiac involvement),[16–34] it was described in the 19.7% of those with the Ile68Leu mutation.[34]

With reference to the prognostic implication of CTS, Milandri et al.[34] showed that CTS might be an independent risk factor for mortality in patients with ATTR, especially when secondary to deposits of the ATTRwt form (HR 3.36, 95% CI 1.27–10.3). However, this one is not the only mortality risk factor: age, New York Heart Association functional class and glomerular filtration rate are also taken into account.[34]

A CTS diagnosis, especially when carpal involvement is bilateral, should therefore raise suspicion for carpal ATTR infiltration. In the presence of bilateral CTS, the positive predictive values were 96% in the whole population and 98% in the hypertrophic phenotype subgroup in the study performed by Cappelli et al.[26] It is in this sense that bilateral manifestations should always raise suspicion for amyloidosis. For instance, bilateral BBTR has a 100% positive predictive value for ATTR-CM versus hypertrophic cardiomyopathy in patients with a hypertrophic phenotype.[26]

Likewise, the combination of systemic symptoms without a common alternative explanation and CTS should raise concern about amyloidosis, how Karam et al.[14] explain. For example, amyloidosis should be though as a diagnosis in men who have erectile dysfunction and CTS in the absence of diabetes. However, other nonspecific symptoms as GI disturbance, exercise intolerance, and burning pain in the feet must be contemplated in association with CTS to reach and early diagnosis.

Regarding BBTR, 20–37.8% of the patients who presented it were unaware of its existence,[15,26] reflecting the importance for physician to actively look for it on physical examination in suspicious subjects. Cappelli et al.,[26] who studied CTS and BBRT, reported that 82% of the ATTR-CM population had at least one of the two features and 34% had both. They also demonstrated that the presence of any upper limb complication (CTS, BBTR or both) was associated with a 24-fold independent increase in likelihood of ATTR-CM in the overall population. Becoming a 41-fold increase when the analysis was limited to cardiac patients with a hypertrophic phenotype.[26]

In terms of SS, the lumbar spinal canal stenosis is the correlated with ATTR-CM. Several studies only looked for SS in the lumbar section,[20,25,30,31] some others did not specify where the stenosis was located[24,27,33] and just Nakagawa et al.[17] studied all the spinal sections. They observed four patients with SS in their series, two of them had lumbar spinal canal stenosis, and the other two had cervical spinal canal stenosis. However, they reported that pathological examination of the ligamentum flavum was not performed.[17] We think that it is important to understand that not only the lumbar spine can be affected but also other parts of the spine.

Aus dem Siepen et al.[24] specify that 12% of patients with ATTRwt had history of CTS and SS and 2% of ATTRv has history of both conditions. Furthermore, analysing only spinal canal stenosis cases, in the majority of them (81%), it appeared in combination with CTS. In front of this combination, is crucial to consider amyloidosis as the aetiology to, as it has been mentioned before, perform an accurate follow-up for early diagnosis.

One aspect to reflect on is the fact that the presence of musculoskeletal manifestations seems to be much more prevalent in ATTRwt compared with ATTRv, although differences have not always been reported. There are several theories in this sense, such as the deleterious effect of age (acting as a possible confounding factor) among others, but more studies are needed.

All the included studies have been categorized as high and moderate quality, so they are considered to be at low and moderate risk of bias with tool created by Hoy et al.[12] There are two items, which are the most compromised by most of the articles. The first one has to do with external validity, and it asks: 'Was the study's target population a close representation of the national population in relation to relevant variables, for example, age, sex, and occupation?'. For this item just for Westin et al.[33] could be answered: Yes. The second item that was most compromised has to do with internal validity asking: 'Was an acceptable case definition used in the study?'. In this case, several studies did not precisely define the included population and/or did not expose the musculoskeletal pathologies' definitions used. Even though these two items were answered No, the articles accomplished moderate quality, explaining the results.

Limitations

There are some limitations in the collection process of some studies. Firstly, the definitions used by the included articles were different and therefore some were more restrictive than others were. As mentioned before, some studies used surgical reports as inclusion criteria for CTS.[23,24,33,34] In contrast, others were laxer and defined it by electromyography diagnosis or typical symptomatology.[14,16–18,22,25–28,31,32] In any case, some did not even specify which inclusion criteria was used.[13,19–21,29,30] This lack of information was detrimental to their internal validation score.[12] The same problem was seen regarding to SS. Some articles just included those patients who had surgical reports,[24,33] and others recorded SS if diagnosed on computed tomography or RMI.[17,25,27,31]

Therefore, Milandri et al.,[34] who determine that the prevalence was 25.5% in ATTRwt population and 13.9% in ATTRv population, explain that CTS was considered present only in patients with a history of specific surgery because of the absence of data on onset of CTS symptoms and the unavailability of nerve conduction studies. These criteria could have led

to an underestimation of prevalence in the study, explaining the difference with the other results. The prevalence of CTS in the ATTRwt subtype in the Rapezzi et al.[32] publication is also lower (13%) than the expected. They do not explain the criteria to determine this pathology and the total of ATTRwt subjects is only 15. This low number of participants could explain the results and at the same time, it would be interesting knowing if their criteria contemplate symptoms or just previous surgery.

Secondly, in the present systematic review the inclusion criteria defined patients diagnosed with ATTR-CM, probably due to the lack of articles focusing on this specific population, some of those included also reported information on other types of amyloidosis. For instance, the group of Westin et al.[33] studied the CTS and SS prevalence in those patients with cardiac amyloidosis but without specifying the aetiology (AL amyloidosis was also included). Their findings of CTS and SS prevalence are significantly lower, presumably owing to the mixed aetiology and the criteria of only including those with surgical reports. However, they demonstrated that the prevalence of CTS surgery compared with the control subjects was higher (10.6% vs. 1.8%) and the prevalence of SS surgery also compared with control was higher and statistically significant (7.3% vs. 2.3%; $P < 0{,}001$).

Thirdly, medical history records of CTS were infrequent in the regional hospital cohorts probably due to the difficulty recording medical history among very elderly patients and the retrospective nature of the study as it happened to Takashio et al.[18] However, the prevalence of CTS in their publication was not as low as to spotlight (36%), but they explain that as a limitation that could explain an underestimated prevalence. This limitation is probably in more than one article even though it was not specified.

Fourth, despite the fact that this review only contemplated articles about CTS, BBTR, and SS because no one studying trigger finger accomplished the inclusion criteria, there are other orthopaedic manifestations that could be related with ATTR-CM due to the deposition of transthyretin in the soft tissues and joints. For example, shoulder pathologies as Basdavanos et al. study,[35] as well as other joints.

Finally, we do not include articles after the date of publication of the protocol in Prospero (November 2022), nor do we evaluate and to investigate the temporal association between the onset of musculoskeletal manifestations and ATTR amyloidosis diagnosis, as does Aldinc et al[36] in a very interesting systematic review evaluating studies up to November 2021. They conclude that the exact prevalence of different musculoskeletal manifestations in patients with ATTR amyloidosis remains unclear, and therefore our review will help in improve this knowledge.

Conclusions

In summary, the results of our systematic review confirm the frequent association of osteoarticular symptoms in patients with cardiac amyloidosis, frequently preceding it. Many are retrospective studies and not specifically designed to answer the question of the frequency of this association. Given the severity of the presentation of cardiac amyloidosis, and the current treatment possibilities,[37] it would be advisable to conduct proactive studies and increase attention to the red flags of amyloidosis.

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Conflict of interest

The authors declare no competing interests.

Supporting information

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

Table S1. Quality appraisal checklist for prevalence studies from Hoy et al. [12].

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