Association between carpal tunnel syndrome and amyloid heart disease may assist with early detection and reduced morbidity and mortality

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Abstract

Carpal tunnel syndrome may help identify more systemic issues than previously thought. Multiple research studies establish an association between carpal tunnel syndrome and heart disease, most specifically cardiac amyloidosis. This link is of importance as it requires alternative treatment choices to extend life expectancy for those diagnosed with the disease. Based on this analysis of multiple studies, there may be an indication for a screening criterion in those with carpal tunnel syndrome to identify a previously illusive disease before it progresses.

Key points

- Carpal tunnel syndrome and ATTR amyloidosis show positive correlation with one another.[1,3–7,11,16–18]
- ATTR is managed differently than other forms of heart failure and ATTR specific treatments have proven effective in clinical trials.[9]
- Certain presentations such as bilateral CTS, or CTS that returns following release surgery, are more likely to be associated with ATTR.[4,5,7]

Carpal Tunnel Syndrome (CTS)

CTS is the most common entrapment neuropathy which up to 6% of the general population may experience at some point in their life.[7] It is characterized by numbness or tingling due to median nerve compression in the carpal tunnel of the wrist.[10] It is caused by thickening of the lining from irritated tendons or other swelling.[11] Carpal tunnel release surgery is often a secondary step when less invasive treatments do not resolve symptoms.[10]

ATTR Amyloidosis

Amyloidosis is a disease caused by proteins with an unstable tertiary structure that misfold and aggregate as amyloid fibrils in tissues. Cardiac amyloidosis is the condition of primary interstitial protein deposition that occurs in the extracellular space of the heart.[13,14] There are 27 identified proteins that can form amyloid fibrils and are associated with human disease.[15] Primary systemic and transthyretin are two causes for almost all clinical cases of cardiac amyloidosis.[8]

Transthyretin amyloidosis is a fatal disorder which is characterized by progressive neuropathy and cardiomyopathy.[13] Transthyretin is a normal protein that is synthesized in the liver that plays an important role in behavior, cognition, nerve regeneration, and axonal growth. These proteins can abnormally aggregate and deposit into tissues causing amyloidosis.[13] It occurs in the mutant form with autosomal dominant inheritance (TTRm) and as wild-type form (TTRwt).[13] Wild-type TTR is sporadic, with no known biomarkers for its diagnosis, and is more common.[13]

The TTR amyloid deposition causes reduced diastolic relaxation leading to poor filling and low-end diastolic volume.[13] Thus, it is typically seen with findings of right-sided heart failure with preserved ejection fraction. The symptoms include edema of the lower extremities, ascites, hepatomegaly, dyspnea, and increased jugular venous pressure.[13] Due to neurological involvement, it is associated with a high incidence of CTS.[13]

Association between CTS & amyloid heart disease

Multiple studies have established an association between CTS and transthyretin amyloidosis through methods such as comparative chart reviews and tissue biopsy during carpal tunnel release surgery.[1,3–7,11,16–18] Patients with cardiac amyloidosis often have CTS that precedes cardiac manifestations by several years.[1,3–7,11,16–18] In many cases, patients whose biopsies were positive for amyloid protein had either bilateral CTS or had a history of contralateral carpal tunnel release surgery.[5] Although recurrence of CTS following surgery is rare, many patients that underwent CTS release surgery and were later diagnosed with ATTR-CM did not experience relief of symptoms following surgery.[4,7,10] Both phenomena are of note when considering possible criteria for screening for ATTR in patients who present with CTS.

Discussion

Concerning symptoms → Biopsy on release surgery → If positive, may warrant systemic screening such as echocardiogram

- The link between a systemic disorder with significant morbidity and mortality and another that is common and easy to assess makes early detection a beneficial possibility.[1,3–7,11,16–18]
- Knowledge of this association prompts development of criteria for screening of at-risk individuals.
- Criteria may include patients with bilateral carpal tunnel syndrome and/or lack relief of symptoms following carpal tunnel release surgery.[4,5,7]
- There still remains a question on if the increase in amyloid protein found on carpal biopsy may be due to greater than expected prevalence of amyloid protein in general.[5,6,7]

Figure

	PREVALENCE AND DEMOGRAPHICS	CLINICAL PHENOTYPE	PROGNOSIS	TREATMENT
Primary systemic amyloidosis (AL)	8.9 cases per million persons per year Male predominance Presents in fifth to seventh decade	Restrictive cardiomyopathy with additional acute toxicity from light chains Multiorgan disease	Untreated median survival ~6 months from onset of heart failure	Supportive for heart failure Chemotherapy to eliminate the abnormal plasma cell population Stem cell transplant in selected group of patients
Transthyretin Amyloidosis – Wild Type (ATTRwt)	High in some groups (elderly with severe AS/hypertrophy/or heart failure): prevalence 10%-16% Sporadic point mutation Male predominance	Restrictive cardiomyopathy Other clinical involvement rare, apart from carpal tunnel syndrome	Untreated median survival ~6 years from onset of heart failure	Supportive for heart failure Pacemaker for advanced AV block TTR stabilizer agents
Transthyretin Amyloidosis – Mutant form (ATTRm)	0.4 cases per million per year Autosomal dominant point mutation 3.4% African American Male predominance	Variable phenotype Restrictive cardiomyopathy Peripheral/autonomic neuropathy Autonomic dysfunction Renal involvement Eye involvement	Dependent on mutation with cardiac involvement	Supportive for heart failure Pacemaker for advanced AV block Liver transplantation in selected group of patients TTR stabilizer agents

Conclusion

- Carpal tunnel syndrome may act as a red flag, warning clinicians of possible danger of amyloidosis down the road.[4,5,7,10]
- Cardiomyopathy due to amyloidosis is rare but requires different treatment regiments than other more common forms of cardiomyopathy.[9,13, 15]
- Early detection and treatment of cardiac amyloidosis, in any form, can reduce morbidity and mortality.[8,9, 12]
- Unless the presence of other symptoms are considered, or additional assessments are conducted, ATTR is easily confused with other forms of heart failure.[8]

Sources

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