Results of Implementation of Amyloidosis Screening for Patients Undergoing Carpal Tunnel Release

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Purpose Many patients with amyloidosis undergo carpal tunnel release (CTR) before amyloidosis diagnosis and before developing cardiac or other serious disease manifestations. The purposes of this study were to examine if our patient population had a similar prevalence of positive amyloidosis diagnoses to that in prior studies and to describe the results of implementing a screening program for amyloidosis.

Methods We retrospectively reviewed the biopsy results and subsequent interventions for all patients who underwent screening tenosynovial biopsy during CTR from March 2020 through December 2021. Amyloid screening was offered to patients who met the criteria for increased risk of disease using an appropriateness screening algorithm.

Results Seventy-five (48%) of 156 patients who underwent CTR met the eligibility criteria for amyloidosis testing. Of the 62 patients who agreed to undergo tenosynovial biopsy, 14 had amyloid-positive biopsy specimens (10 men and 4 women). All patients with positive tenosynovial biopsies had bilateral carpal tunnel syndrome and wild-type transthyretin amyloid subtype. One patient was diagnosed and started treatment for otherwise asymptomatic cardiac amyloidosis.

Conclusions The incidence of amyloid-positive tenosynovial biopsy results from CTR was 22.5% in patients using the criteria from an appropriateness screening algorithm, which was higher than previously reported. Implementation of a screening program for patients undergoing CTR requires a multidisciplinary approach and may result in early diagnosis and lifesaving interventions for patients with amyloidosis. *(J Hand Surg Am. 2024;49(7):675–680.*

Type of study/level of evidence Differential diagnosis/symptom prevalence study, II.

Key words Amyloidosis, carpal tunnel release, carpal tunnel syndrome, screening, tenosynovial.

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CARPAL TUNNEL SYNDROME (CTS) is the most common upper-extremity nerve compression syndrome, with approximately 500,000 carpal tunnel release (CTR) procedures performed annually in the United States.[1] Although most cases of CTS do not have an identifiable etiology, several systemic diseases are associated with CTS, including amyloidosis.[2]

Amyloidosis is a systemic disorder resulting from extracellular aggregation of insoluble amyloid fibrils into soft tissues and organs, including the transverse carpal ligament, flexor tenosynovium, biceps tendon, spinal ligamentum flavum, and myocardium.[3–5] Approximately 30 different proteins can form amyloidosis fibrils. The 2 main types are monoclonal immunoglobulin light chain amyloidosis and transthyretin (ATTR) amyloidosis.[6] Patients often present with CTS 5–10 years before the development of symptomatic systemic amyloidosis.[7,8] The most serious complication of amyloidosis is cardiovascular involvement because amyloid deposition leads to restrictive cardiomyopathy, heart failure, and conduction blockade. Survival is poor after cardiac involvement. In patients with monoclonal immunoglobulin light chain amyloidosis and cardiac involvement, the median survival was <6 months and sudden death occurred in 25% to 30% of patients within 90 days of diagnosis.[9,10] Survival is more favorable with ATTR amyloidosis, with a median survival between 2.6 and 3.6 years.[11,12] Although recent pharmacologic advances appear promising, these treatments function by limiting amyloid production and are, thus, most efficacious early in the course of the disease before widespread amyloid deposition.[13]

Using a screening algorithm, a recent study demonstrated that approximately 10% (10 of 98) of patients with bilateral CTS symptoms who underwent CTR had amyloid-positive tenosynovial biopsy results.[14] In that study, cardiac involvement was present in 2 patients and therapy was started in 3 patients. A second study using the same screening criteria reported amyloid-positive tenosynovial biopsy results in 29% of patients who underwent CTR.[15] An additional retrospective database study including nearly 90,000 patients who underwent CTR from the Veterans Affairs Health System found that 0.3% of patients had a diagnosis of amyloidosis at some point after CTR and that those patients had a significantly increased hazard of heart failure and death.[16] Similarly, a study of Danish health registries identified an increased risk of both amyloidosis and heart failure in patients who underwent CTR compared with that in an age-matched and sex-matched cohort.[17] The discrepancy between the percentage of patients with amyloid-positive biopsy results during CTR (10% or more) and the percentage of patients with a diagnosis of amyloidosis in the aforementioned database studies (0.3%) raises the possibility of underdiagnosis of amyloidosis. Indeed, cardiac amyloidosis is now thought to be an underdiagnosed cause of cardiac conditions, including heart failure.[18] Effective treatment for this progressive, potentially fatal, and systemic disease hinges on early and accurate identification.

Early recognition of amyloidosis in otherwise asymptomatic patients with presumably idiopathic CTS may be efficacious in preventing cardiac complications. The aim of this study was to examine whether our patient population undergoing CTR has a similar prevalence of amyloid-positive biopsy results to that in prior studies and to describe the results of implementing a screening program for amyloidosis in the clinical setting. Our null hypothesis was that no patients would be identified after implementation of a standardized screening algorithm.

MATERIALS AND METHODS

Study design and patient selection

This study was reviewed and approved by our Research Subject Protection Program. This was a retrospective study of patients undergoing CTR by 5 hand surgeons (C.W.) in our health network between March 1, 2020, and December 31, 2021. Beginning in March 2020, we offered amyloid testing to patients undergoing CTR who met the appropriateness screening criteria proposed by Sperry et al.[14,19] Surgeons completed an eligibility form, documenting whether patients met the criteria for testing and whether the patient agreed to undergo a biopsy. Patients who met the criteria for biopsy received an information sheet discussing amyloidosis, the purpose of screening, and the subsequent steps in the case of a positive test result. A tenosynovial biopsy specimen was obtained at the time of CTR from patients who agreed to undergo testing. Samples were sent to pathology in formalin for Congo red staining. Positive biopsy samples (apple-green birefringence in polarized light) were sent for subtype analysis via mass spectrometry. Patients with ATTR-type amyloid present on biopsy specimens were referred to cardiology and hematology for further evaluation and provided with the option for referral to a genetics counselor.

All patients with a completed eligibility form who subsequently underwent an amyloid biopsy were

included in the study. All patients underwent open CTR using wide awake local anesthetic no tourniquet techniques in an office-based procedure room. Demographics, including patient age, sex, and biopsy results (positive or negative for amyloid, amyloid subtype), were obtained from their medical records. In addition, we documented whether the patient underwent additional cardiac or hematologic testing or had treatment initiated for amyloidosis as a result of their subsequent evaluation.

RESULTS

A total of 156 patients who underwent CTR had completed eligibility forms for amyloidosis screening (Table 1). Of those, 75 (47.8%) patients met the criteria for biopsy and amyloid testing. Sixty-four (85.3%) patients met the tier 1 screening criteria, and 11 (14.7%) patients met the tier 2 screening criteria. Thirteen (17.3%) patients declined to undergo a biopsy, 10 (76.9%) patients from tier 1 and 3 (23.1%) patients from tier 2. The final biopsy cohort included 62 (38.5%) patients with completed eligibility forms. Thirty-three (53.2%) patients were men, and the average age was 65.4 years (range, 36−86 years). The most common risk factors identified on initial screening were men aged ≥50 years and bilateral CTS or prior CTR.

Fourteen (22.5%) patients had an amyloid-positive tenosynovial biopsy result (Table 2). Ten (71.4%) patients were men, and the average age was 69.6 years (range, 52−86 years). Amyloid-positive test results were much more common in men than in women (30% of men vs 13% of women). All patients had wild-type ATTR. Four patients elected to see a genetics counselor, 12 patients elected to see a cardiologist, and 9 patients saw both a hematologist and a cardiologist. Seven patients underwent cardiac nuclear medicine testing, with 1 patient having a positive test result. Four patients underwent cardiac magnetic resonance imaging, with 1 patient having a positive test result. The same patient tested positive on both imaging modalities and was ultimately diagnosed with cardiac amyloidosis and later started on oral amyloid-specific therapy (tafamidis). One patient had an electrical heart block, and all patients had normal cardiac ejection fractions. All 14 patients with amyloid-positive biopsy results met the tier 1 testing criteria, with the most common risk factors being men aged ≥50 years and bilateral CTS or prior CTR.

TABLE 1. Diagnostic Criteria and Screening Results*

Tier 1	No. of Patients	Tier 2	No. of Patients
Men aged ≥50 years	40	Spinal stenosis	10
Women aged ≥60 years	34	Distal biceps tendon rupture	0
Bilateral CTS or prior CTR	67	Atrial fibrillation or flutter	3
		Pacemaker	1
		Congestive heart failure	0
		Family history of amyloidosis	0

*Biopsy recommended: 2 tier-1 characteristics or 1 tier-1 and 1 tier-2 characteristic.

DISCUSSION

Emerging evidence suggests that cardiac amyloidosis is an underdiagnosed cause of morbidity and mortality.[20] In several retrospective studies, CTR preceded the diagnosis of cardiac amyloidosis by 5−9 years.[8,16,21] Tenosynovial biopsy during CTR allows the identification of patients with amyloidosis before developing systemic symptoms.

We found a higher prevalence of amyloid-positive biopsy results (22.5%) in our patient sample than reported previously by Sperry et al[14] (10.2%) after implementing a similar screening program. Our results are similar to those of DiBenedetto et al,[15] who identified amyloid-positive biopsy results in 54 of 185 (29%) patients, with a higher incidence of positive biopsy results in men. Others have also noted a higher incidence of amyloid-positive biopsy results in male patients who underwent CTR.[8,16] In our study, 14% of women (4 of 29 patients) and 30% of men (10 of 33 patients) who underwent biopsy had positive results for amyloidosis, further confirming that male sex is a risk factor for amyloidosis. In both our study and that by Sperry et al,[14] all patients who tested positive for amyloidosis had bilateral CTS. Donnelly et al[19] have further suggested that a bilateral CTS diagnosis should be considered a red flag in this population, which would be supported by our data.

The value of amyloid screening during CTR in preventing cardiac disease and death remains to be seen. The incidence of a positive amyloid biopsy result in our patient sample is much higher than the incidence of pathologic findings with other accepted screening tests, such as colonoscopy (0.5% incidence

TABLE 2. Positive Amyloid Tenosynovial Biopsy Patient Demographics*

	Age (y)	Sex	Race	Men Aged ≥50 y	Women Aged ≥60 y	Bilateral CTS, Prior Release	Spinal Stenosis	Subtype	Genetics Counselor	Cardiology Evaluation	Hematology Evaluation	Heart Block	Ejection Fraction	NucPYP
1	75	Female	White	0	1	1	0	wtATTR	0	1	1	None	64%	Negative
2	56	Male	White	1	0	1	0	wtATTR	1	0	1	None	61%	Negative
3	74	Male	White	1	0	0	1					None	60%	-
4	73	Male	White	1	0	1	0	wtATTR	1	1	1	None	62%	Positive
5	82	Female	Hispanic	0	1	1	0	wtATTR	0	1	1	-	-	-
6	64	Male	White	1	0	1	0	wtATTR	0	0	1	RBBB	60%	Negative
7	67	Male	White	1	0	1	0	wtATTR	0	1	1	None	66%	-
8	62	Male	White	1	0	1	0	wtATTR	0	1	1	None	68%	-
9	75	Male	White	1	0	1	1	wtATTR	0	1	1	None	65%	-
10	86	Female	White	0	1	1	0	wtATTR	1	1	0	None	60%	-
11	74	Female	White	0	1	1	0	wtATTR	0	1	1	None	65%	Negative
12	65	Male	White	1	0	1	1	wtATTR	0	1	1	None	-	-
13	52	Male	White	1	0	1	0	wtATTR	0	1	1	None	56%	Negative
14	70	Male	White	1	0	1	0	wtATTR	1	1	0	None	57%	Negative

NucPYP, technetium pyrophosphate nuclear scintigraphy; RBBB, right bundle branch block; wtATTR, wild-type transthyretin amyloidosis.
*No patient had a history of distal biceps tendon rupture, atrial fibrillation/flutter, pacemaker, congestive heart failure, or family history of amyloidosis.

of identifying colon cancer and 8% positive for advanced adenoma).[22] However, although colon cancer screening has been shown to decrease mortality from colon cancer, we do not have comparable data for amyloidosis screening. In terms of the potential to reduce mortality, the incidence of intervention for fatal disease resulting from tenosynovial biopsy during CTR (1 of 75, 1.3% in this study; 3 of 98, 3% from Sperry et al[14]) compares favorably to that for colonoscopy (0.5%).

To date, the relationship between amyloidosis and heart failure has been established on retrospective data, and no data exist regarding how many asymptomatic patients identified by biopsy during CTR will go on to develop cardiac amyloidosis.[7,16] In our study, only 1 patient started treatment for amyloidosis (7%, 1 of 14); whereas, in the study by Sperry et al,[14] 3 patients started treatment (30%, 3 of 10). The remaining 7 in their cohort underwent continued surveillance, similar to the recommended annual cardiac surveillance within our health network. We may find that standardized amyloid screening yields many patients who undergo additional cardiac testing without ever initiating treatment; however, evidence suggests that early diagnosis of amyloidosis is key to successful intervention. Screening via tenosynovial biopsy during CTR has lower morbidity than that of delayed diagnosis of cardiac amyloidosis. Tafamidis, which is approved by the US Food and Drug Administration for the treatment of cardiac amyloidosis, was found to be most effective at reducing hospitalization and death when initiated earlier in the disease process.[23] With this in mind, we hope that amyloid screening during CTR allows early identification of patients who may otherwise go undiagnosed until their prognosis is poor.

Currently, the relative costs of screening and subsequent testing compared to potential cost savings from the prevention of other amyloidosis manifestations are not known. At our institution, the billed cost of the pathology services for the tenosynovial biopsy was approximately $170, with additional subtyping analysis costing more than $1,000. Additional cardiac and other testing adds to these expenses. Although insurance typically covers these costs, patients with high deductible plans may encounter substantial out-of-pocket costs.

In our study, all patients had ATTR amyloidosis, with all 14 having the wild-type subtype. A recently developed blood test is available for diagnosing hereditary ATTR. Given the preponderance of ATTR in our patient sample, we considered whether the genetic blood test for ATTR would be a reasonable choice for screening rather than biopsy. Unfortunately, the genetic test would most likely not have detected amyloidosis in our patients because of the preponderance of wild-type ATTR. At this time, tenosynovial biopsy during CTR remains a low-morbidity screening tool for amyloidosis that provides the needed information about amyloid subtype, which cannot be obtained by other screening modalities, such as a blood test.

Because of the relatively infrequent diagnosis of amyloidosis historically, we found partnering with a cardiology team interested in amyloidosis to be essential. The first few patients diagnosed through our screening program underwent variable courses of evaluation and testing after referral to hematology and/or cardiology, in part, because of care disruption from the coronavirus disease 2019 pandemic. However, we refined the pathway over time so that patients with positive amyloid biopsy results were referred directly to the amyloidosis specialist within cardiology, and the cardiology team contacted the patient to arrange appropriate cardiac tests before that clinic visit and referrals to other specialists as needed.

This study has limitations. The inherent weaknesses of a single-center retrospective review, including the inability to control for selection bias in treatment decision-making, are present. We did not collect extensive demographic data to risk-stratify outcomes. The criteria for screening described by Sperry et al[14] used at our institution are straightforward and easy to implement but may not include all patients with amyloidosis. After the initiation of amyloid screening at our institution, Sood et al[16] created a more complex risk nomogram based on retrospective data from the Veterans Affairs Health System. Age, male sex, and Black or African American race were identified as major contributors to the risk of amyloidosis. Other factors, such as bilateral CTS, rheumatoid arthritis, monoclonal gammopathy of unknown significance, spinal stenosis, and atrial fibrillation, increased the likelihood of amyloidosis diagnosis to a lesser degree. Because of the use of the more simplistic criteria by Sperry et al,[14] we may have missed patients who had an increased risk of amyloidosis. For example, a 35-year-old Black man would meet the criteria for screening by the nomogram created by Sood et al[16] but not by the criteria by Sperry et al.[14] Both the proposed screening guidelines are based on retrospective data, and further refinement of the screening criteria is necessary. In an additional retrospective analysis of VA patients, Sood et al[24] also identified trigger finger release surgery as a potential risk factor

for amyloidosis. Additional research, most optimally with registry data or well-controlled prospective multicenter trials, is required to better elucidate red-flag symptoms and risk factors and outcomes of patients with a diagnosis of amyloidosis during CTR. Such an effort will allow for improved characterization of longitudinal outcomes in this population and efficacy of screening.

The present experience illustrates the realities of implementing a screening program. Similar to colonoscopies or mammograms, screening requires the physician to commit time to discuss testing with the patient and a mechanism for managing results. Although all surgeons in our group agreed to offer amyloid screening, several surgeons were vigilant about patient inclusion, and others did few or no biopsies. Because surgeons became more comfortable discussing screening with patients and the pathway for managing results was clearly defined, the number of patients offered screening increased substantially. Our health system is in the process of expanding this offering to other sites. Patient acceptance represents an additional barrier to screening because 17% of patients who met the eligibility criteria declined testing. Although we did not formally collect data on reasons for declining biopsy, several patients mentioned concerns about cost. Implementing the screening program required contributions from hand surgeons, pathologists, cardiologists, and hematologists for the successful care of included patients.

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