Carpal Tunnel Syndrome: A Potential Early, Red-Flag Sign of Amyloidosis

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Learning Objectives

Upon completion of this CME activity, the learner should achieve an understanding of:

- The red-flag symptoms and indications for biopsy and amyloid testing in patients undergoing carpal tunnel release
- The 2 major subtypes of systemic amyloidosis that affect the heart and the associated implications
- The importance of referral to the appropriate specialist when there is diagnosis of amyloidosis based on biopsy during carpal tunnel release

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Carpal tunnel syndrome (CTS) can be caused by the deposition and accumulation of misfolded proteins called amyloid and is often an early manifestation of systemic amyloidosis. In patients undergoing surgery for idiopathic CTS, a recent study identified amyloidosis by tenosynovial biopsy in 10.2% of men older than 50 years and women older than 60 years; all positive patients had bilateral symptoms. These findings have led to a renewed interest in

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amyloidosis as an etiology of CTS. The 2 most common systemic amyloidoses, immunoglobulin light chain and transthyretin amyloidosis, affect the heart, nerves, and other organ systems throughout the body including the soft tissues. Patients with cardiac involvement of amyloidosis have an especially poor prognosis if the disease remains unrecognized and untreated. Early diagnosis is paramount, and patients classically present with cardiac disease several years after being operated on by a hand surgeon for carpal tunnel release. Herein, we present a review of amyloidosis as it pertains to CTS and an algorithm for the detection of amyloidosis in patients undergoing carpal tunnel release. Implementation of this straightforward algorithm will allow for early diagnosis of amyloidosis, a group of progressive and lethal diseases. *(J Hand Surg Am. 2019;44(10):868−876.*

Key words Amyloid, amyloidosis, carpal tunnel syndrome, light chain, transthyretin.

FOR MORE THAN 60 YEARS, HAND surgeons and other physicians have noted the presence of amyloid, a tough and grayish-white substance composed of misfolded protein, in patients undergoing carpal tunnel release.[1] A recent study has described a 10.2% rate of amyloid deposits found in the tenosynovium in a prospective cohort of men aged 50 years and older and women 60 years and older undergoing surgery for idiopathic carpal tunnel syndrome (CTS); all amyloid-positive patients presented with bilateral symptoms.[2] General lack of appreciation for the causative link between CTS and amyloidosis in the wider community may result from the fact that patients typically present with systemic symptoms of amyloidosis several years after their encounter with the hand surgeon or the fact that the diagnosis had been challenging and treatment options limited.

In recent years, great advances in the diagnosis and treatment of the most common forms of systemic amyloidosis have changed the outlooks for these diseases. Existing and emerging treatments demonstrating a mortality benefit make it critical to recognize, diagnose, and manage amyloidosis as early as possible.[3] The prognosis is poor in patients with late disease, especially those with cardiac involvement due to amyloid deposition in the heart. Current therapies for amyloidosis are designed to slow or stop disease progression by preventing further amyloid deposition rather than promoting degradation of existing amyloid fibrils and are, thus, more effective in earlier stages of disease.[4] Furthermore, some types of amyloidosis can be hereditary or associated with plasma cell dyscrasias including multiple myeloma, highlighting the importance of a timely diagnosis.

In this review, we begin by providing an overview of amyloidosis and a primer on 2 of the most common types of systemic amyloidosis, light chain (AL) and transthyretin (ATTR) amyloidosis. We highlight red-flag symptoms of bilateral CTS, biceps tendon rupture, and spinal stenosis in patients older than 50 years that suggest a high clinical suspicion for amyloidosis. We present a straightforward algorithm using carpal tunnel release biopsy samples of the tenosynovium, transverse carpal ligament (TCL), or fascia to test for amyloid deposition and underscore the importance of referral to the appropriate specialist to screen for organ involvement.

AMYLOIDOSIS TYPES

Innumerable proteins in the body are able to function normally owing to a unique preserved 3-dimensional structure. However, more than 30 proteins are known to pathologically misfold and subsequently aggregate into amyloid fibrils, which can deposit in various tissues throughout the body.[4] These amyloid diseases can be acquired or hereditary (owing to mutations in the gene encoding the amyloid precursor protein). The 2 major types of systemic amyloidosis that affect the heart are AL and ATTR.

Light chain amyloidosis

This type results from excess production and misfolding of immunoglobulin light chain proteins (kappa or lambda) that are produced by plasma cells in the bone marrow and secreted into the bloodstream.[4] Multiple myeloma, a related disease, overlaps with amyloidosis in about 20% of cases.[5] A recent analysis using U.S. health insurance claims data estimated the 2015 prevalence of AL as 50.1 cases per million (rate age-adjusted based on 2010 U.S. census data).[6] This translates to a U.S. prevalence of approximately 12,000 cases of AL as of 2015. An epidemiological study based on 2015 U.S.

census data estimated an incidence of nearly 4,000 new cases of AL in the United States every year.[7]

Transthyretin amyloidosis

This type results from the misfolding of the transthyretin (TTR) protein, a transporter of retinol and thyroxine. Transthyretin is produced primarily in the liver and secreted into the bloodstream but is also synthesized locally in the eye and choroid plexus.[8]

Transthyretin amyloidosis is further categorized into 2 subtypes, hereditary or variant ATTR (ATTRv) and wild-type ATTR (ATTRwt) amyloidosis. The ATTRv results from *TTR* gene mutations, of which more than 100 are known, that decrease the stability of the TTR protein.[9] The estimated worldwide prevalence of ATTRv amyloidosis is less clear, with an estimated prevalence of amyloid polyneuropathy of 10,000 to 40,000 cases, some of which are concentrated in endemic areas.[10] The ATTRwt, conversely, results from misfolding of the nonmutated or wild-type TTR protein; at one point, it was called senile cardiac amyloidosis because of its manifestation in the aged population. The true prevalence of ATTRwt is unknown, but it is thought to be greatly underdiagnosed. A Finnish autopsy study found wild-type TTR amyloid deposits in the heart of 25% of subjects aged 85 years and older, with severe deposition in 11% of these cases.[11] In addition, 13% of elderly patients admitted for heart failure with preserved ejection fraction[12] and 16% of elderly patients undergoing transcatheter aortic valve replacement for severe calcific aortic stenosis[13] have been diagnosed with ATTRwt.

CLINICAL PRESENTATION OF SYSTEMIC AMYLOIDOSIS

Immunoglobulin light chains and TTR both deposit systemically and within many of the same organs. However, patterns of amyloid deposition vary depending on the amyloid precursor protein, largely for unknown reasons. There is considerable heterogeneity in the systems and organs affected, even among patients with the same type of amyloidosis. Mechanistically, extracellular deposition of amyloid in tissues can affect function by altering anatomic structure and/or through direct cytotoxic effects.[14]

Both AL and ATTR amyloid can deposit extracellularly in the heart, peripheral and autonomic nerves, gastrointestinal tract, and soft tissues.[4] The AL amyloid also accumulates in the kidneys and the liver,[4] and selected mutations of ATTRv can lead to deposition in the vitreous humor of the eye and leptomeninges of the brain, thought to be due to local TTR synthesis.[8]

Cardiac amyloid deposition leads to heart failure, often with preserved ejection fraction and, sometimes, atrial fibrillation. Bundle branch block on electrocardiogram occurs more commonly in ATTR than in AL, and patients may require pacemaker implantation.[4] In ATTRwt, amyloid deposition in the heart is typically the only clinical manifestation of the disease, whereas different mutations of ATTRv lead to variable amounts of cardiac and neuropathic symptoms.[4] Cardiac involvement leads to an especially poor prognosis, particularly in patients with AL not treated in a timely fashion.[4] The median survival of untreated patients with cardiac involvement ranges from less than 6 months (patients with AL who present with heart failure) to approximately 4 years (patients with ATTRwt).[4,5]

Amyloid deposition within peripheral and autonomic nerves can occur in both AL and ATTR and cause a wide range of clinical manifestations, including peripheral and autonomic neuropathies.[4,9] Peripheral neuropathy is often small fiber and typically affects the hands and feet first. Autonomic neuropathy may result in hypotension, orthostatic hypotension, and gastrointestinal motility issues with constipation and/or diarrhea. Both AL and ATTRv are more likely to have neuropathic manifestations, whereas in ATTRwt, these are less common.

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY OF AMYLOID DEPOSITION IN MUSCULOSKELETAL CONNECTIVE TISSUE (FIG. 1)

Carpal tunnel syndrome

A history of bilateral symptoms or multiple carpal tunnel release surgeries is common in patients with AL and ATTR and should be considered a red-flag symptom. In a recent study that included men older than 50 and women older than 60, all patients with amyloid deposits in the carpal tunnel had either bilateral symptoms or a history of a prior contralateral carpal tunnel release.[2] Thus, bilaterality should be considered a red flag in this population. Data from future, multicenter studies may well expand the target population in which to consider bilaterality a red-flag symptom of amyloidosis. A study of patients in the United States with cardiac amyloidosis due to AL or ATTR demonstrated that CTS was the presenting symptom in 16% of patients and occurred in 40% overall.[15]

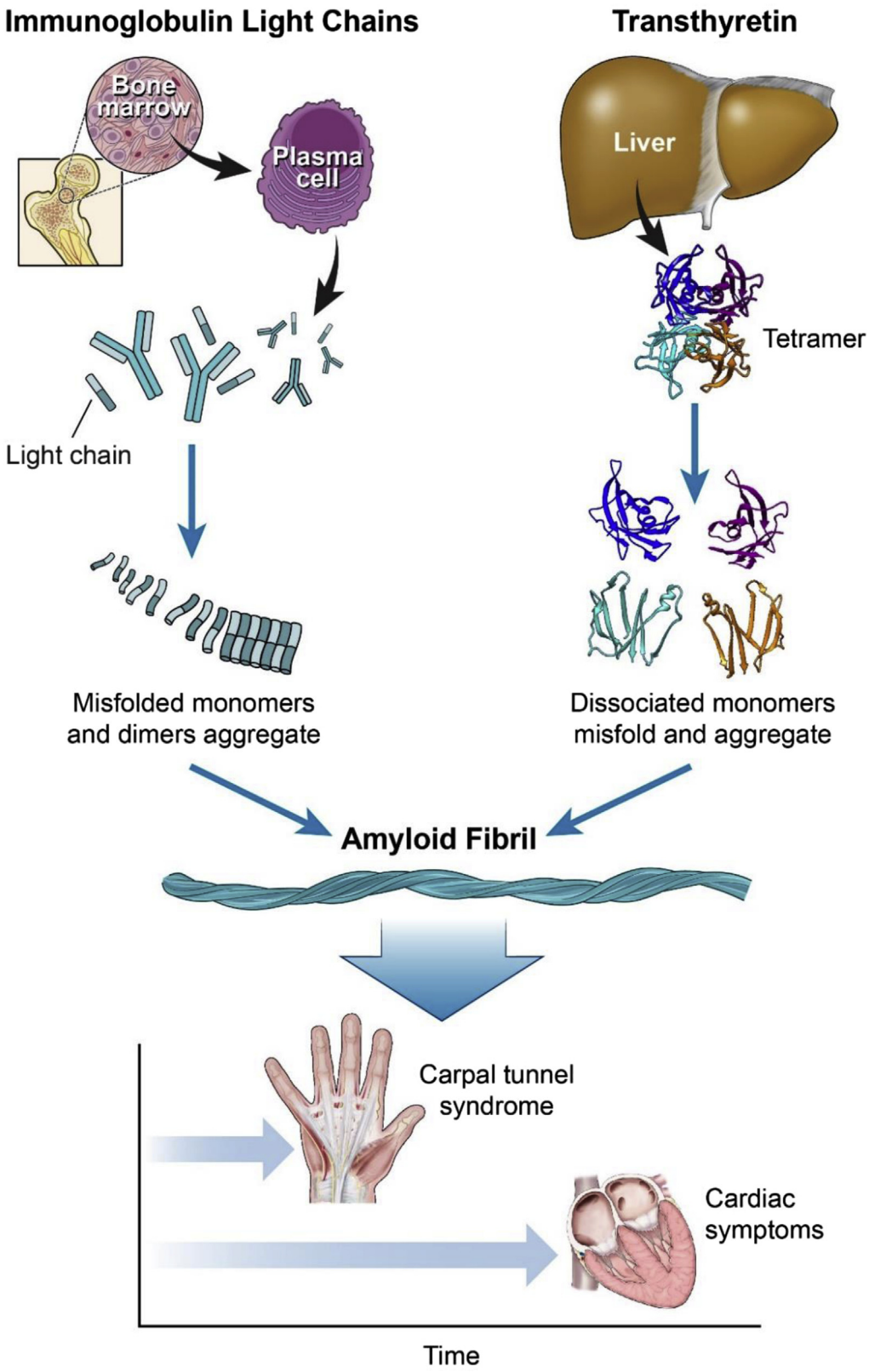

FIGURE 1: Pathophysiology of AL and ATTR amyloidosis and timeline to development of CTS and cardiac symptoms. (Reproduced from Sperry et al, with permission from *Journal of the American College of Cardiology*.[2])

Several amyloid precursor proteins have been identified from carpal tunnel biopsies, including AL, ATTR, amyloid A, and amyloid β^2-microglobulin.[16] Amyloid deposition has been reported on or within the TCL/flexor retinaculum, synovial tissue, flexor tendon sheath, fascia, and vessel walls of capillaries, small arteries, and veins.[1,16,17] Endoneurial amyloid deposits in the median nerve are also thought to contribute to CTS, at least in patients with ATTRv.[18]

Whether CTS is caused by amyloid deposition in connective tissue, within the median nerve, or both remains an open question. Cases have been reported in which carpal tunnel release did not relieve symptoms.[19] Nerve conduction studies in patients with ATTRv have demonstrated abnormalities in the median nerve, signifying that CTS may not be just a simple entrapment injury.[20]

In general, CTS is relatively less common in AL than in ATTR, but it is still experienced by a substantial number of patients. Studies and surveys of patients with AL have reported that CTS occurs in nearly 30% of patients and is bilateral in many cases.[21] Importantly, CTS often precedes diagnosis by several years. In 1 survey, the delay between CTS and AL diagnosis was at least 2 years in 71% of patients (Lousada et al, poster presented at the European Hematology Association 22nd Annual Congress, 2017).

The prevalence of CTS in patients with ATTR depends on the presence of a hereditary mutation, but it generally ranges between 29% and 68%.[22,23] In 1 study of patients with ATTRwt, CTS was the most common initial symptom in about half of patients (55%), preceding cardiac symptoms by a mean of 6.1 years, and preceding diagnosis by a mean of 6.9 years.[23] Similarly, in a cohort of patients with cardiac amyloidosis due to either ATTRwt or ATTRv, CTS was the most common noncardiac manifestation and was associated with the longest time to diagnosis (median, 4.4 years; mean, 5.7 years).[24] Although CTS is a common manifestation of ATTR, it has not been well recognized by most hand surgeons or cardiologists in clinical practice.[15,22,23]

Trigger finger (stenosing flexor tenosynovitis)

Trigger finger is thought to occur when movement of the flexor tendon is restricted because of thickening of the A1 pulley. The pathophysiological mechanisms of CTS and trigger finger in patients with amyloidosis are likely similar. Amyloid deposits have been identified in connective tissue beneath the synovial lining of the flexor tendon sheath in patients with idiopathic trigger finger.[25]

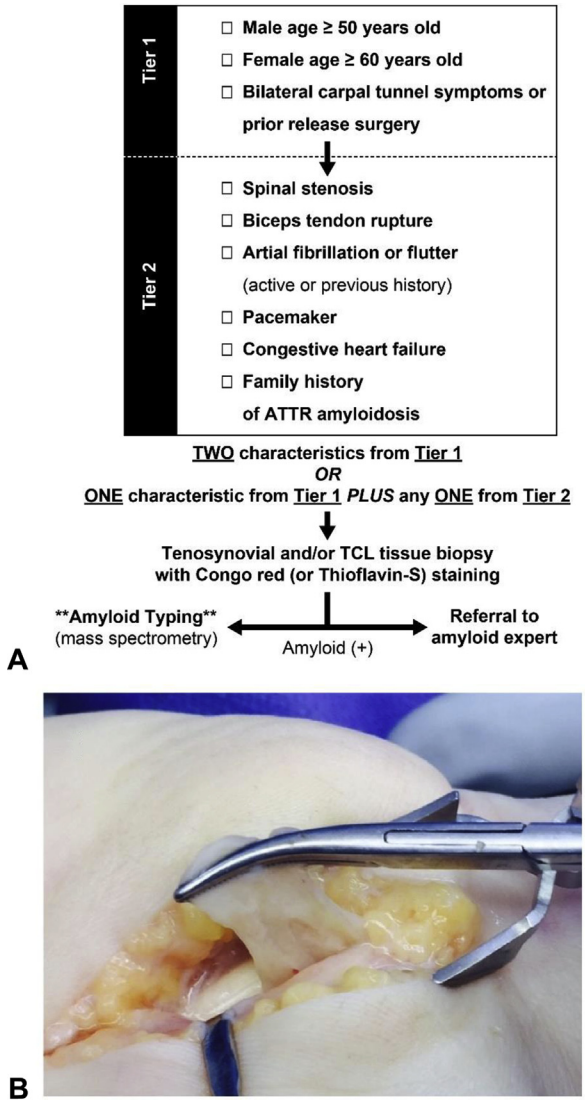

FIGURE 2: A Diagnostic algorithm for amyloidosis based on carpal tunnel release biopsy samples. **B** Image of tenosynovial biopsy. (Adapted from Sperry et al, with permission from *Journal of the American College of Cardiology*.[2])

In the general population, there seems to be a link between CTS and trigger finger, with concomitant occurrence in 16% to 61% of patients.[26] An association between CTS and trigger finger may be underappreciated in patients with amyloidosis. Although reports are limited, Uotani et al[27] described the coexistence of trigger finger and CTS in 3 members of a Japanese family with ATTRv. A recent study found that 60% (6 of 10) of patients with CTS and either AL or ATTR also had a history of intervention for trigger finger.[2]

Spontaneous rupture of the distal biceps tendon

Amyloid infiltration has been implicated in the rupture of a distal biceps tendon. In a cohort of

TABLE 1. Selected Pathology Studies That Identified Amyloid in Carpal Tunnel Biopsy Specimens

Year Published	Type of Study	Patients (n)	Amyloid-Positive Patients (n)	Amyloid-Positive* (%)	Source of Study Samples (Time Period)	Reference
1965	Retrospective (CTS)	177	12	6.8	Mayo Clinic, U.S. (1930–1960)	Yamaguchi et al[34]
1974	Retrospective (CTS)	87	2	2.3	Duke University, U.S. (1960–1969)	Bastian[17]
1987	Retrospective (CTS)	45	2	4.4	North Staffordshire Medical Centre, U.K.	Neal et al[35]
1987	Retrospective (CTS)	108	23 (severe in 5)	21.3 (severe in 4.6)	University of Mainz, Germany (1975–1986)	Stein et al[16]
1989	Retrospective (CTS) with follow-up	1500	152	10.1	Mayo Clinic, U.S. (1968–1977)	Kyle et al[36]
1996	Retrospective (CTS) with follow-up	108	10 (severe in 2)	9.3 (severe in 1.9)	Toranomon Hospital, Japan	Nakamichi and Tachibana[37]
2001	Retrospective (trigger finger)	47	11	23.4	Nuffield Orthopaedic Centre, U.K.	Cordiner-Lawrie et al[25]
2011	Prospective (CTS)	100	34 (severe in 15)	34 (severe in 15)	Nagano Prefecture, Japan (2008–2010)	Sekijima et al[38]
2017	Prospective (CTS)	147	29	19.7	Hospital Universitario de León, Spain (2006–2007)	Fernandez Fuertes et al[39]
2018	Retrospective (CTS)	4990	582	11.7	Amyloid Registry Kiel, Germany (2010–2018)	Hahn et al[33]
2018	Prospective (CTS) with follow-up	98	10	10.2†	Cleveland Clinic, U.S. (2016–2017)	Sperry et al[2]

*Note that the proportion of patients with CTS found to have amyloid deposits in these studies varies widely, from 2.3% to 34%. It is important to note the many differences among these studies, including the patient populations studied and whether or how the extent of amyloid deposition was graded. In studies that further categorized infiltration in amyloid-positive biopsies as severe, the proportion of patients with substantial amounts of amyloid decreased to 1.9% to 15%.

†Twelve percent of patients with bilateral carpal tunnel symptoms or previous contralateral release surgery.

patients with cardiac ATTRwt, a ruptured biceps tendon was present in 33% (37 of 111), more than 10 times that seen in patients with heart failure due to nonamyloid causes (2.5%).[28] Similar to CTS, a ruptured biceps tendon can be an early sign of amyloidosis, occurring a median of 5 years before heart failure diagnosis.[28] A distal biceps tendon rupture in patients older than 50 years should raise a red flag to consider amyloidosis.

Other sites of amyloid deposition in connective tissue: spine, hip, knee, elbow, shoulder

Spinal stenosis, both lumbar and cervical, is seen in AL and ATTR patients. Deposition of ATTR in the ligamentum flavum has been linked to the pathogenesis of lumbar spinal stenosis,[29] and a Japanese study found the comorbidity present in 22% of patients with ATTRwt.[30] Amyloid deposits have also been found in histologically examined rotator cuff tendon specimens following rotator cuff repair.[31]

DIAGNOSIS

Both AL and ATTR are complex diseases with varied presentations. The hand surgeon can contribute to earlier disease recognition by incorporating a tenosynovial, TCL, or fascial biopsy into the perioperative workflow for carpal tunnel release. A proposed diagnostic algorithm is provided in Figure 2.[2] Open carpal tunnel release readily provides access for biopsy of the tenosynovium,[32] but endoscopic techniques may still be used to obtain a diagnostic tissue sample from the surrounding fascia. It is important to note that the tenosynovium does not need to appear grossly thickened for there to be amyloid deposits. Criteria in tier 1 of the diagnostic algorithm were selected based on a higher prevalence of amyloidosis in older individuals and the observation that CTS is typically bilateral and can recur in patients with amyloidosis, requiring multiple surgical interventions.[2,33] Tier 2 includes other red-flag symptoms or common characteristics of patients with AL or ATTR.

The carpal tunnel tissue biopsy should be sent to pathology in standard formalin for Congo red staining, which allows identification of amyloid by its characteristic apple-green birefringence under polarized light microscopy but does not provide any information on the amyloid type. Thioflavin staining for amyloid fibrils may also be used. If Congo red or thioflavin staining is positive, then immunohistochemistry or mass spectrometry must be ordered to define the subtype. If AL or ATTR amyloid is detected, patients should promptly be referred to a provider with experience evaluating and managing amyloidosis. Subsequent work-up depends on which type of amyloid is found, as discussed later.

There is precedent in the literature (Table 1)[2,16,17,25,33-39] for identifying amyloidosis using the approach suggested in Figure 2. Earlier studies (from the 1950s through the 1980s) simply identified the presence of amyloid using Congo red staining, and later studies (beginning around the late 1980s) typed the protein source of amyloid using immunohistochemistry. Current studies often use mass spectrometry, an improved method and gold standard for protein identification.

Many of the studies evaluating carpal tunnel biopsies for the presence of amyloid deposits advocate for screening older patients with idiopathic CTS for amyloid.[2,33] Recently, CTS was identified as a strong predictor of delayed diagnosis in patients with cardiac amyloidosis.[15] Diagnostic delays of greater than 1 year in these patients were associated with poorer cardiac outcomes, including higher levels of *N*-terminal prohormone of b-type natriuretic peptide (NT-proBNP) and a higher prevalence of atrial fibrillation.[15] This highlights the need for increased suspicion of amyloidosis in patients with idiopathic CTS.

Testing for systemic amyloidosis

Identification of 1 of the most common amyloid types, AL or ATTR, in the carpal tunnel biopsy should trigger cardiac testing with electrocardiography and echocardiography.[5] Patients with AL kappa or lambda deposition in the carpal tunnel biopsy should be referred to a hematologist specializing in amyloidosis. There, testing for a plasma cell dyscrasia with free kappa and lambda levels, serum immunofixation, and urine immunofixation should be ordered. A bone marrow biopsy is often done to evaluate for amyloid involvement or multiple myeloma.[4] In patients with ATTR deposition in the carpal tunnel, referral to a cardiologist or neurologist specializing in amyloidosis is recommended. In addition to an electrocardiogram and an echocardiogram, we recommend technetium-99m pyrophosphate (^{99m}Tc-PYP) nuclear scintigraphy,[40] a highly sensitive noninvasive study, to evaluate for cardiac amyloid involvement. Genetic testing should be performed to differentiate between ATTRv and ATTRwt.[4]

Until recently, no prior investigators had examined systemic involvement in patients found to have amyloid deposition in tenosynovial tissue. However, our recent prospective study of patients with

idiopathic CTS found that 10 patients (10.2%, all with bilateral symptoms) tested positive for amyloid, and 3 of them (3%) already had existing systemic manifestations of amyloidosis.[2] Of these, 2 had concomitant cardiac amyloidosis (1 AL, 1 ATTRwt) and 1 had polyneuropathy due to ATTRv. All 3 patients received appropriate disease-modifying therapy, and the patient with AL achieved a complete hematological response and regression of cardiac symptoms after 5 months of therapy.[2] The remaining 7 patients whose carpal tunnel biopsies tested positive for amyloid in this study are being carefully monitored longitudinally for the onset of systemic signs and symptoms.

TREATMENT AND MANAGEMENT

Therapies for AL amyloidosis

Clonal immunoglobulin light chains are treated using anti−plasma cell chemotherapy regimens, thereby eradicating the source of amyloid production. The recommended first-line treatment is typically a combination of cyclophosphamide (an alkylating agent), bortezomib (a proteasome inhibitor), and dexamethasone (a steroid).[41] Patients with cardiac AL treated with this 3-drug regimen showed significantly improved survival compared with other chemotherapeutic regimens or no treatment.[41] A CD38 monoclonal antibody, daratumumab, is currently being studied in patients with refractory or relapsed disease (NCT03201965).[4] Bone marrow transplantation can induce a complete hematological response in patients and is considered in patients without severe cardiac involvement.

Therapies for ATTR amyloidosis

Two drugs that decrease production of the amyloidogenic TTR protein by the liver, inotersen and patisiran, have recently been approved by the U.S. Food and Drug Administration for patients with ATTRv with polyneuropathy following the publication of the landmark randomized clinical trials in the *New England Journal of Medicine*.[42,43] Both work by slightly different mechanisms to promote degradation of the *TTR* mRNA in liver cells. A second approach to treating ATTR is to stabilize the TTR protein in its tetrameric form, thereby preventing its dissociation into monomers and eventually amyloid fibrils. Two drugs in this class, tafamidis and diflunisal, have been tested in phase 3 clinical trials (tafamidis in cardiomyopathy and diflunisal in polyneuropathy),[3,44] and another, AG10, is currently being studied in a phase 3 trial for cardiomyopathy (NCT03860935). Tafamidis has been shown to decrease mortality and improve quality of life and functional capacity in patients with ATTR cardiac amyloidosis.[3]

Importance of early diagnosis and treatment

Although clinical trial results have been encouraging, these therapies have been shown to slow disease progression as opposed to reverse it. There are currently no therapies for amyloidosis that reliably reverse the damage that has already been done by deposited amyloid fibrils. Therefore, early identification and initiation of treatment are essential to limiting the clinical impact of amyloidosis.

DISCUSSION

Carpal tunnel syndrome is an early red-flag symptom of both AL and ATTR amyloidosis and is present in 10.2% of men aged 50 years and older and women aged 60 years old and older undergoing surgery for idiopathic CTS. Carpal tunnel syndrome classically presents bilaterally, years before cardiac and multisystem involvement. Prognosis is poor once cardiac symptoms develop and is measured on the order of months to years. A simple biopsy of the tenosynovium, TCL, or fascia during carpal tunnel release surgery may allow for early recognition of this disease. Early diagnosis is essential because the therapies available for both AL and ATTR are most effective in earlier stages of the disease. The hand surgeon who makes the connection between CTS and amyloidosis creates an opportunity for timely intervention and can positively impact a patient's life, long after surgical intervention.

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