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EDITORIAL COMMENT

Early Diagnosis of Cardiac Amyloidosis by Carpal Tunnel Surgery

Is it All in the Wrist?*

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Over the past several years, cardiac amyloidosis has been increasingly recognized by providers, emerging from its characterization as a rare and unusual cause of heart failure. The disease has long enjoyed a "zebra" cachet owing to its confusing nomenclature (AL for light-chain amyloidosis and ATTR for transthyretin disease), challenging diagnostic approach, and perceived rarity. Caused by myocardial deposition of amyloid fibrils composed of misfolded protein, clinicians also learn that cardiac amyloidosis is a disease with no effective treatment. Indeed, the classical teaching was that AL cardiac amyloidosis with concomitant heart failure conferred a median survival of 6 to 12 months (1). Unfortunately, many practicing clinicians adhere to this dogma embracing a mindset of therapeutic nihilism. Why diagnose what you cannot treat? Recent advances have dramatically altered the therapeutic landscape, rendering systemic amyloidosis with cardiac involvement a treatable disease, affording patients an array of therapeutic options (2–5). It is clear that early recognition of amyloidosis is critical because current treatment strategies suppress precursor protein production or stabilize the protein preventing misfolding, but do not directly target existing amyloid deposits.

Historically, diagnosis of cardiac amyloidosis required a cardiac biopsy demonstrating histological evidence of amyloid deposits by Congo Red staining. More recently, cardiac involvement could be diagnosed by a histological identification of amyloidosis from another body site in the context of supportive noninvasive cardiac imaging findings as determined by echocardiography, magnetic resonance imaging, or nuclear scintigraphy (bone avid tracers) (6). Of these noninvasive tests, only nuclear imaging has the capacity to definitively demonstrate ATTR cardiac amyloidosis without a tissue biopsy (7). Although conclusively shown to be highly sensitive and specific among patients with suspected amyloidosis (8), to date, no screening studies using nuclear imaging have been reported. However, ATTR amyloidosis has been demonstrated in up to 13% of patients with heart failure and preserved ejection fraction with increased LV wall thickness (9), 16% of patients with severe aortic stenosis undergoing transcutaneous valve replacement (10), 5% of patients with presumed hypertrophic cardiomyopathy (11), and in 1% to 2% of subjects undergoing bone scintigraphy for noncardiac reasons (12). These observations challenge the conception that ATTR amyloidosis, in particular, is a rare disease.

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Because amyloidosis is a systemic disease with deposition that has also classically been associated with carpal tunnel syndrome (CTS) (13), Sperry et al. (14) in this issue of the *Journal* hypothesized that screening for unsuspected cardiac amyloidosis could be accomplished through histological testing of flexor retinaculum specimens collected during carpal tunnel release surgery. The overall rationale was to characterize the proportion of patients with systemic amyloidosis undergoing carpal tunnel release with the implication that by early identification patients could receive

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treatment at an earlier stage of disease. In this prospective cohort study, a total of 98 patients (mean age 68 years) were recruited from the 319 carpal tunnel release surgeries performed at a single center with broad inclusion criteria of all men >50 years of age and women >60 years of age. Only those with known amyloidosis or CTS related to rheumatoid arthritis or trauma were excluded. Tenosynovium specimens were tested for amyloidosis with Congo Red staining and those that were positive (10 patients or 10.2%) were confirmed by mass spectrometry with further testing by echocardiography, cardiac-specific biomarkers, free light chains/immunofixation electrophoresis, and nuclear imaging to define the presence of cardiac amyloidosis. Of these, 1 case of AL cardiac amyloidosis, 1 case of wild-type ATTR cardiac amyloidosis, and 1 case of hereditary ATTR amyloidosis with polyneuropathy were identified and treated with disease-modifying therapy. Thus, undiagnosed systemic amyloidosis was found in 10% of patients undergoing carpal tunnel release surgery of whom 3 patients were subsequently treated with amyloidosis-specific therapy.

There are a number of additional interesting points raised by this study. First, there is a common conception that bilateral CTS is more common in systemic amyloidosis and can be used as a clinical sign to detect disease. Although the authors did observe that 100% of patients with positive biopsies had bilateral surgeries, so did 83% of the negative biopsies, reducing the specificity of this criteria to identify early systemic amyloidosis. More interestingly, lumbar spinal stenosis was noted in 60% of the positive cohort, which is concordant with other data that demonstrate nearly all subjects undergoing clinically indicated lumbar spine decompression for spinal stenosis have amyloid deposits and almost one-half have evidence of TTR by immunohistochemistry (15). Third, a monoclonal gammopathy was noted in 4 of 7 patients with ATTR amyloidosis, similar to reported data showing that 40% to 50% of subjects with wild-type ATTR have a concomitant monoclonal gammopathy of unknown significance (16). The high coincidence of monoclonal gammopathy underscores the requirement to carefully characterize the precursor protein by tissue biopsy in such subjects and not rely on nuclear scintigraphy alone. Fourth, the authors tested the concentration of native or tetrameric TTR and stability of the TTR protein in the serum of all patients and found that there were no differences either concentration or stability between cases with amyloidosis and controls. As acknowledged by the authors, these analyses may have been confounded as they did not adjust for the concentration of the critical cofactor retinol binding protein 4 (RBP4) that binds TTR, inhibits misfolding, and is lower in ATTR amyloidosis than matched controls (17). Although mechanistically attractive as a means to also identify preclinical disease, it remains to be seen whether measurable instability of circulating TTR associates with fibril formation and subsequent amyloid deposition.

In addition, there a number of caveats to consider when drawing conclusions from these data. Importantly, only those with a positive biopsy went on to further testing, with the assumption that the biopsy of tenosynovium is highly sensitive and specific for identification of systemic amyloidosis. However, the limited tissue sample evaluable for amyloidosis after CTS surgery may be an explanation for the lower yield of amyloidosis (10%) when compared with lumbar spine specimens (15). Thus, we do not know whether some of the patients with negative biopsies may actually also have systemic amyloidosis. Alternatively, as the authors acknowledge, we do not know what proportion of ATTR amyloidosis patients with positive biopsies, but negative nuclear scans, will develop cardiac involvement. Serial imaging studies in this population may address this issue. Interestingly, the authors identified amyloidosis in a similar proportion of men and women, likely as a result of their unbiased recruitment strategy. This finding is discordant from reported referral population studies and current clinical practice, wherein wild-type ATTR cohorts are almost exclusively male (18). These data support the hypothesis that active ascertainment of amyloidosis by screening might show that the true proportion of sex distribution in systemic amyloidosis is closer to even. Finally, as acknowledged by the authors, the proportion of African Americans in study was small (approximately 5%), thus the data here cannot be seen to inform understanding of the association between genotype and the prevalence of amyloid disease in this population.

We commend Sperry et al. (14) for a well-conducted pilot study that should be seen as a justification for larger screening efforts. The advent of contemporary therapies for both AL and ATTR amyloidosis now render the disease treatable, particularly if administered early. It remains to be determined which screening methodology will prove the best approach, but given the emerging nature of amyloidosis, a screening algorithm will likely be incorporated into everyday clinical practice in the near future.

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REFERENCES

1. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997;337:898–909.

2. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22–31.

3. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379:11–21.

4. Muchtar E, Gertz MA, Kumar SK, et al. Improved outcomes for newly diagnosed AL amyloidosis over the years 2000-2014: cracking the glass ceiling of early death. Blood 2017;129:2111–9.

5. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.

6. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018;28:10–21.

7. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404–12.

8. Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol 2016;1:880–9.

9. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36:2585–94.

10. Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879–87.

11. Damy T, Costes B, Hagege AA, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J 2015;37:1826–34.

12. Longhi S, Guidalotti PL, Quarta CC, et al. Identification of TTR-related subclinical amyloidosis with 99mTc-DPD scintigraphy. J Am Coll Cardiol Img 2014;7:531–2.

13. Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid 2016;23:58–63.

14. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. J Am Coll Cardiol 2018;72:2040–50.

15. Westermark P, Westermark GT, Suhr OB, Berg S. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. Ups J Med Sci 2014;119:223–8.

16. Phull P, Sanchorawala V, Connors LH, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid 2018;25:62–7.

17. Arvanitis M, Koch CM, Chan GG, et al. Identification of transthyretin cardiac amyloidosis using serum retinol-binding protein 4 and a clinical prediction model. JAMA Cardiol 2017;2:305–13.

18. Connors LH, Sam F, Skinner M, et al. Heart failure due to age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. Circulation 2016;133:282–90.

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