ISSN 2666-0873

Letters

RESEARCH LETTER

Prospective Screening for Transthyretin Cardiac Amyloidosis in Spinal Stenosis Surgery Patients

Results of the CASS Study

Symptomatic lumbar spinal stenosis (SS) related to ligamentum flavum (LF) hypertrophy has been associated with transthyretin amyloid (ATTR) deposition.[1] Moreover, SS precedes a diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) in up to 40% on average 5 to 15 years prior.[2] Yet, prospective data on systematic screening for concomitant ATTR-CM in patients undergoing SS surgery are scarce. Studies have reported an ATTR-CM prevalence of 0% to 10% of patients with ATTR amyloid positive LF biopsy during SS surgery, but they were mostly retrospective nonsystematic analyses in highly select patient groups.[1,3,4] Optimal ATTR-CM screening strategies in patients presenting with diagnostic red flags represent an unmet clinical need because early treatment initiation offers the best opportunity to improve morbidity and mortality in ATTR-CM, both in age-related degenerative (wild-type) and hereditary (variant-type) forms.[5]

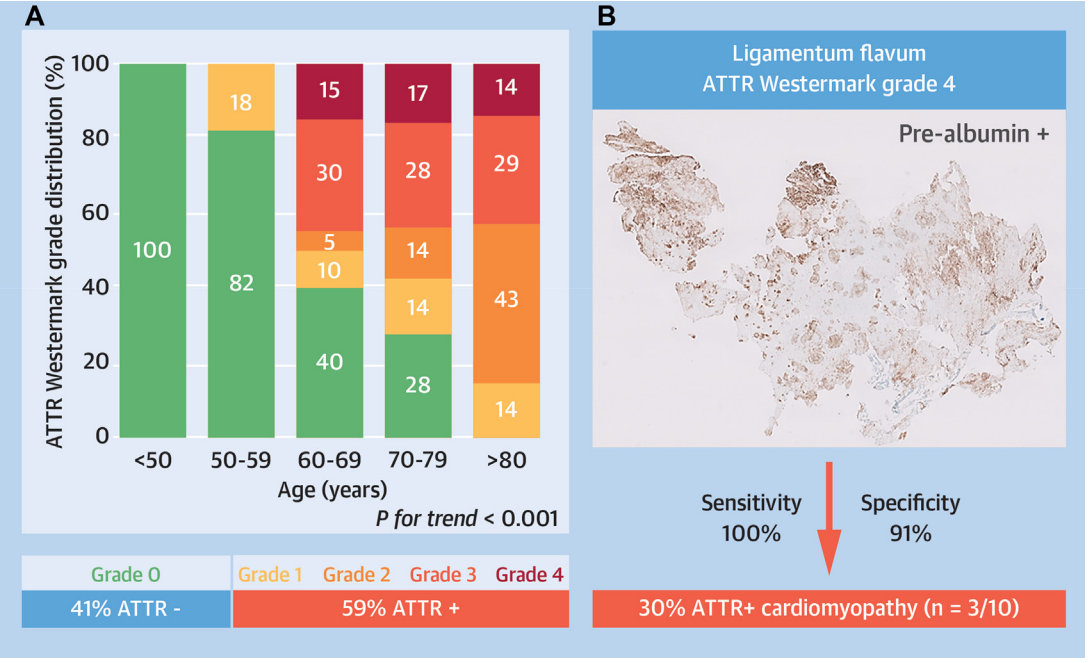
The CASS (Cardiac Amyloidosis in Spinal Stenosis; NCT04653675) mandated technetium-99m hydroxymethylene diphosphonate bone scintigraphy and monoclonal protein assessment to rule out ATTR-CM in patients undergoing symptomatic SS surgery, including those with ATTR amyloid detected on LF biopsy, defined by both Congo red and prealbumin positive staining. All patients provided written informed consent. The study was approved by the institutional ethics committee (EC 2674) and conducted in accordance with the Declaration of Helsinki. The current report focuses on patients with ATTR amyloid on LF biopsy.

A total of 82 unselected, consecutive participants (48% male, mean age 68 ± 9 years, age range 46-84 years) were prospectively enrolled. LF biopsy revealed a high prevalence of ATTR amyloid deposits in 59% (n = 48/82) of the study population (**Figure 1A**). The age range of patients with ATTR amyloid positive biopsy was 56 to 85 years, with 21% of patients (n = 10) <65 years of age. All patients >80 years of age had ATTR amyloid deposits on LF. LF ATTR amyloid-positive vs -negative patients were older (age 72 ± 7 years vs 62 ± 9 years; $P < 0.01$) but had similar sex distribution (46% vs 50% males; $P = 0.71$), respectively. Atrial fibrillation (19% vs 3%), bilateral carpal tunnel history (27% vs 9%), worse renal function (estimated glomerular filtration rate 72 ± 19 mL/1.73 m^2 vs 81 ± 18 mL/1.73 m^2), and higher left ventricular wall thickness (11 ± 2 mm vs 10 ± 2 mm) were more prevalent in LF ATTR amyloid-positive vs -negative patients, respectively (all $P < 0.05$). However, multivariable regression analysis showed age to be the only independent predictor of LF ATTR amyloid positivity (OR: 1.15; 95% CI: 1.07-1.22; $P < 0.01$).

The burden of ATTR amyloid deposition in LF biopsy was assessed by semiquantitative visual grading on ATTR amyloid-positive fragments, adapted with permission from Eldhagen et al,[1] as grade 0 (no ATTR), 1 (few small scattered deposits), 2 (scattered nonconfluent or single large deposits, 1%-5% of fragments), 3 (widely spread moderately large deposits or large confluent deposits, 5%-10% of fragments), or 4 (widely spread large confluent deposits, >10% of fragments).[1] ATTR amyloid burden on LF biopsy increased gradually with age ($P < 0.01$) (**Figure 1A**). High ATTR amyloid burden (Westermark grade 4) was detected only in subjects >60 years of age and present in 21% (n = 10/48) of ATTR amyloid-positive subjects but was found in similar proportions across different age categories. No clinical, demographic, laboratory, or echocardiographic markers differed between Westermark grade 4 vs lower grade 1 to 3 burden patients (all $P > 0.05$).

De novo wild-type ATTR-CM was identified in 6.3% of subjects with ATTR amyloid deposition on LF biopsy (n = 3/48), all National Amyloidosis Centre Stage I. One 81-year-old woman and one 73-year-old man showed both Perugini grade 1 myocardial uptake with confirmatory endomyocardial biopsy and N-terminal pro-B-type natriuretic peptide levels of 2,120 pg/mL and 108 pg/mL, respectively, but an elevated high-sensitivity troponin I of 58 ng/L was present in the female subject only. One 74-year-old man showed Perugini grade 2 myocardial tracer uptake with an

FIGURE 1 Presence, Burden, and Relevance of ATTR Amyloid Deposition in Ligamentum Flavum Biopsy



(A) Transthyretin amyloid presence and burden according to age category. Age was an independent predictor of ATTR amyloid presence; however, high burden (Westermark grade 4) was similarly distributed among age categories, starting from age onset of >60 years old. (B) Relevance of high ATTR amyloid burden. Concomitant ATTR cardiomyopathy was found only in patients with Westermark grade 4 deposition, present in 21% of subjects with ATTR amyloid-positive ligamentum flavum biopsy.

N-terminal pro-B-type natriuretic peptide level of 89 pg/mL and slightly increased high-sensitivity troponin I of 25 ng/L. Importantly, all 3 de novo ATTR-CM patients had high ATTR amyloid burden on LF biopsy, translating into a prevalence and positive predictive value of 30% (n = 3/10) for ATTR-CM in Westermark grade 4 patients (**Figure 1B**).

Based on these current findings, systematic screening for the presence of ATTR amyloid on LF in patients >60 years of age undergoing SS surgery could be considered, and further evaluation of ATTR-CM should be performed when ATTR amyloid deposition is high. Prospective multicenter validation of such an ATTR-CM screening strategy is warranted. In addition, further study is needed to identify which patients may progress to cardiac involvement and should be screened serially.

***Philippe Debonnaire, MD, PhD**
Mathias Claeys, MD, PhD
Pascale De Paepe, MD, PhD
Emma Christiaen, MSc, PhD
Bert Geerts, MD
Frank De Geeter, MD
Sander Trenson, MD, PhD
Davy Hoste, MD
Jan Van Droogenbroeck, MD
Kristof Verhoeven, MD
Nikolaas Vantomme, MD
René Tavernier, MD, PhD

*Sint-Jan Hospital Bruges
Ruddershove 10
8000 Bruges, Belgium
E-mail: philippe.debonnaire@azsintjan.be

https://doi.org/10.1016/j.jaccao.2023.05.012

Dr Debonnaire has received consultancy and speaker fees from Alnylam and Pfizer on the topic of cardiac amyloidosis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors are indebted to our study nurses and secretarial teams for their continued and valuable clinical and administrative support.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Eldhagen P, Berg S, Lund LH, et al. Transthyretin amyloid deposits in lumbar spinal stenosis and assessment of signs of systemic amyloidosis. *J Intern Med*. 2021;289:895-905.

JACC: CARDIOONCOLOGY, VOL. 5, NO. 6, 2023
DECEMBER 2023:836–838

2. Debonnaire P, Claeys M, De Smet M, et al. Trends in diagnosis, referral, red flag onset, patient profiles and natural outcome of de novo cardiac amyloidosis and their multidisciplinary implications. *Acta Cardiol*. 2022;77(9):791–804.

3. Maurer MS, Smiley D, Simsolo E, et al. Analysis of lumbar spine stenosis specimens for identification of amyloid. *J Am Geriatr Soc*. 2022;70:3538–3548.

4. Godara A, Riesenburger RI, Zhang DX, et al. Association between spinal stenosis and wild-type ATTR amyloidosis. *Amyloid*. 2021;28:226–233.

5. Griffin JM, Rosenthal JL, Grodin JL, et al. ATTR amyloidosis: current and emerging management strategies: *JACC: CardioOncology* State-of-the-Art Review. *J Am Coll Cardiol CardioOnc*. 2021;3:488–505.