

Early Cardiac Sympathetic Denervation in Hereditary Transthyretin Amyloidosis (ATTRv): A Multimodal Evaluation with ¹²³I-mIBG Scintigraphy and Peripheral Biomarkers

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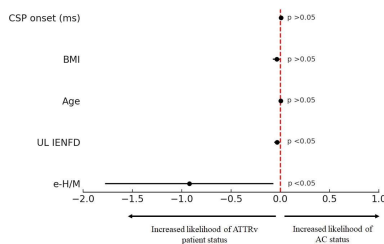
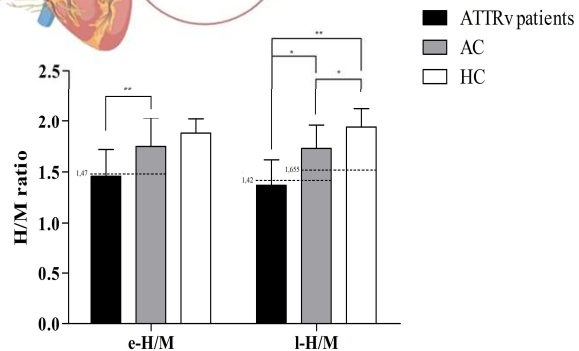
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Background: Hereditary transthyretin amyloidosis (ATTRv) is a multisystem disorder caused by misfolded TTR deposition, leading to neuropathy and cardiomyopathy. Early detection of subclinical involvement remains challenging. This study aimed to evaluate cardiac sympathetic innervation and small fiber neuropathy in symptomatic ATTRv patients and asymptomatic carriers (AC) using ¹²³I-metaiodobenzylguanidine (¹²³I-mIBG) scintigraphy, skin biopsy, and cutaneous silent period (CSP).

Methods: We conducted a cross-sectional study including 14 symptomatic ATTRv patients, 18 AC, and 32 healthy controls (HC). ¹²³I-mIBG planar and tomographic imaging assessed early and late heart-to-mediastinum ratios (e-H/M, l-H/M) and summed scores (ESS, LSS). Skin biopsies quantified intraepidermal nerve fiber density (IENFD) and pilomotor nerve fiber density (PMNFD) from upper (UL) and lower (LL) limbs. CSP evaluated A-δ fiber function from UL. Correlations between ¹²³I-mIBG parameters and years from disease onset (delta-PADO) were analyzed.

Results: l-H/M was reduced in AC versus HC (1.73±0.23 vs 1.94±0.19; p<0.05< best threshold: 1.655, sensitivity 93.8%, specificity 50.0) and further decreased in symptomatic patients (1.37±0.25; p<0.01; best threshold compared to AC: 1.42, sensitivity 94.4%, specificity 78.6%). e-H/M was also reduced in ATTRv patients vs AC (1.46±0.26 vs 1.75 ± 0.28; best threshold: 1.47, sensitivity 94.4%, specificity 78.6%). Delta-PADO correlated with e-H/M, ESS, and LSS, indicating progressive denervation. LL IENFD was reduced in 50% of AC and in ATTRv patients correlated with higher NIS and resting heart rate. CSP onset and end latencies were increased in symptomatic patients, with complete absence observed only in advanced stages. Univariate GLM identified e-H/M and UL IENFD as independent predictors of symptomatic status.



Conclusion: Cardiac sympathetic denervation, detectable by reduced l-H/M, occurs in AC before both clinical symptoms and conventional instrumental markers of disease, representing an early biomarker of ATTRv. Skin biopsy confirms progressive small fiber involvement, while CSP abnormalities emerge later, restricted to advanced disease. ¹²³I-mIBG parameters correlate with predicted age of onset, highlighting their potential for early risk stratification.

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