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Utility of Retinol Binding Protein 4 (RBP4) concentration for screening of V122I transthyretin cardiac amyloidosis

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INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR) is likely an under-recognized case of heart failure (HF) in the elderly,[1] owing to misattribution of clinical features to other common co-morbidities such as hypertension. The V122I TTR polymorphism is carried by 3–4% of African Americans in the United States, and may represent a significant contributor to HF.[2] Given available treatment options, there is now an urgent clinical need to simplify diagnostic algorithms that identify ATTR to permit widespread screening and diagnosis. Retinol binding protein 4 (RBP4) is an endogenous ligand that stabilizes TTR and prevents misfolding and aggregation.[3] Preliminary data from our Center suggest that RBP4 concentration can differentiate ATTR from other causes of cardiomyopathy, however utility in V122I ATTR remains undefined.

MATERIAL & METHODS

We prospectively recruited and genotyped n = 49 elderly (age > 60 years) self reported African American patients with diagnosis of heart failure (HF) and echocardiographic septal diameter (IVSd) of > 12 mm. Genotype identified n = 47 with wild-type TTR comprising non-amyloid controls and n = 2 patients with newly identified V122I ATTR (prevalence 4.2%). Circulating RBP4, TTR, B-type natriuretic peptide (BNP), and troponin I (TNI) concentrations, echocardiography, and clinical characteristics were assessed and compared with findings from n = 25 previously identified patients with known V122I ATTR. Data were compared by means testing, receiver operating characteristic (ROC) analysis to identify

optimal thresholds for V122I ATTR identification, and logistic regression to assess relationships between V122I ATTR and RBP4 concentration.

RESULTS

Age, gender and race were not significantly different between V122I ATTR patients and controls. Left ventricular ejection fraction was lower in V122I ATTR (42% *vs.* 58%, p<0.001), while IVSd was higher (16 *vs.* 14 mm, p<0.001), and creatinine was similar (1.47 vs 1.80 mg/dl, p=0.8). Plasma RBP4 levels were significantly lower in patients with V122I ATTR compared to controls (31.7 *vs.* 49.4 ug/mL, p < 0.001) and the difference persisted after controlling for age, gender, body mass index and echocardiographic parameters. ROC analysis identified RBP4 as a valuable tool in the diagnosis of V122I ATTR cardiomyopathy (AUC 0.77). For the purposes of screening, a cut-off value of < 49.5 ug/mL achieved high sensitivity (100% with 95% CI, 100–100%) but low specificity of (38% with 95% CI, 26–53%) for V122I ATTR, with values above this threshold yielding a negative predictive value (NPV) of 100% in a population with 36% prevalence of the disease. Importantly, 38% of the non-amyloid control cohort had RBP4 values above this threshold.

DISCUSSION & CONCLUSIONS

Circulating RBP4 concentration is a robust discriminator of V122I ATTR cardiomyopathy from non-amyloid HF in an age, gender, and race matched cohort. RBP4 concentration may be useful as a first step in a screening algorithm.

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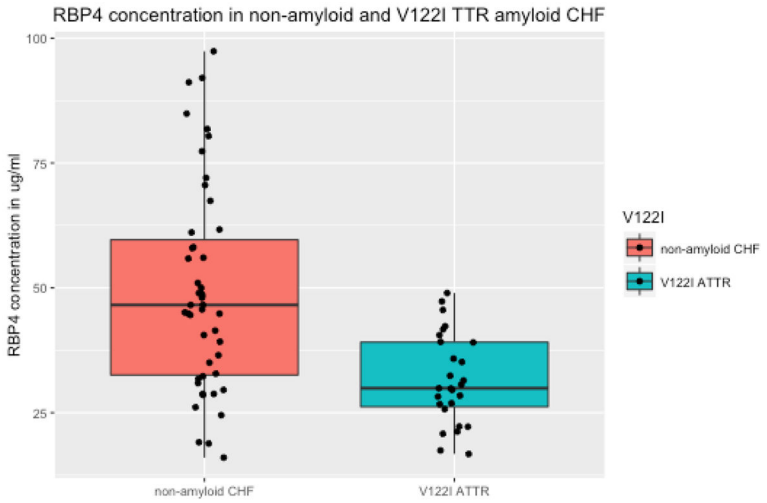

Fig. 1.

Boxplot showing the median RBP4 concentrations along with their corresponding 95% confidence intervals for patients with V122I ATTR compared to controls with non-amyloid cardiomyopathy.