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DIFFUSE FIBROSIS IN ALSTRöM SYNDROME: A MARKER OF DISEASE PROGRESSION

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Background Alström syndrome (ALMS) is a rare autosomal recessive genetic disorder with progressive multi-system involvement including; endocrine disarray, sensorineural deficit, cardiac, renal,

and hepatic abnormalities. Idiopathic dilated cardiomyopathy (CM) is a major cause of morbidity and mortality. It is observed acutely in infancy in approximately 45% of individuals with high rates of recurrence and new cases in adulthood. Myocardial fibrosis has been demonstrated at post-mortem and on MRI with patchy diffuse late gadolinium enhancement (LE) in an older cohort of ALMS patients. We hypothesise that subclinical diffuse fibrosis in young patients with ALMS precedes any change in conventional parameters of ventricular function or overt scarring on LE.

Methods Ten patients with ALMS (mean age 30±11 years, 70% male, 24 h ABPM 135±13/84±9 mm Hg) were compared to 10 newly diagnosed borderline hypertensive patients (mean age 42 years, 70% male, 24 h ABPM 134±8/84±8 mm Hg) and 10 gender matched healthy volunteers. All subjects underwent cardiac MRI (1.5T). Myocardial extracellular volume (ECV) was assessed using T1-mapping pre and 15 min post gadolinium (0.1 mmol/kg) using a modified look-locker inversion recovery sequence (MOLLI). Late gadolinium images were acquired 5–7 min after contrast. Myocardial T1 was assessed by manual contouring of the basal and mid interventricular septum, avoiding areas of LE from a four chamber view.

Results Females in all three groups had significantly increased septal myocardial ECV compared with males (0.29±0.03 vs 0.25 ±0.03, $p<0.01$). Septal myocardial ECV was higher in ALMS than hypertensive and controls (0.28±0.02 vs 0.25±0.03 vs 0.24±0.03, $p<0.05$). Three male older ALMS patients (mean 43±5 years vs 27 ±10 years) without a history of infantile CM had patchy diffuse LE in non-coronary artery territories with an increased ECV compared to remote 'normal' myocardium (ECV 0.41±0.08 vs 0.27 ±0.03, $p<0.05$). MAPSE was reduced in patients with ALMS and hypertension compared to controls (13±2 cm/s vs 12±3 cm/s vs 17±2 cm/s, $p<0.01$. There were no differences in LV ejection fraction, LV mass or LA volumes. Septal myocardial ECV was negatively correlated with a MAPSE in patients with ALMS ($r=-0.64$, $p<0.05$). NT-BNP was not correlated with septal ECV but was increased in patients with LGE (median 178 pmol/l vs 44 pmol/l).

Conclusions Patients with ALMS have increased septal myocardial fibrosis and reduced longitudinal systolic function which appears independent of blood pressure and left ventricular hypertrophy. Monitoring left ventricular ECV as an imaging biomarker may be a target for early modification of pharmacological therapy in this cohort at high cardiovascular risk.

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