Proposed stages of Fabry disease: insights from multiparametric cardiac MRI and advanced ECG

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Funding Acknowledgements: Type of funding sources: None.

Background: Staging of Fabry disease (FD) cardiomyopathy uses multiparametric cardiac MRI. Advanced disease is characterized by left ventricular hypertrophy (LVH), myocardial inflammation/oedema (high native T2 mapping) and/or fibrosis (late gadolinium enhancement, LGE). Pre-LVH involvement has been described and includes myocardial sphingolipid storage (low native T1 mapping), impaired LV global longitudinal strain (GLS) and microvascular disease/dysfunction (low stress myocardial blood flow, MBF, in perfusion mapping).

We aimed to define (1) the early myocardial phenotype prior to T1 lowering/pre-storage and (2) the stages of cardiac involvement in FD.

Methods: FD patients and age, sex and heart rate matched healthy controls underwent same-day ECG with advanced analysis and multiparametric CMR (cines, GLS, pre-contrast T1 and T2 mapping, adenosine stress perfusion mapping [for MBF] and LGE).

Results: 114 Fabry patients (46 ± 13 years, 61% female, 37% [n = 72] had LVH) and 76 controls (49 ± 15 years, 50% female) were included.

FD with vs without LVH: in brief and as expected, FD with LVH had significantly ($p < 0.05$) lower MBF, GLS and T1, and higher T2 and %LGE.

FD pre-LVH low T1 vs pre-LVH normal T1: low T1 patients (32/72, 44%) had higher LV mass index (67 ± 14 vs 59 ± 10g/m2, P = 0.011), maximum Q wave amplitude (2[1-2] vs 1[1-2]mm, P < 0.001), Sokolow-Lyon index (22[16-28] vs 17[13-23]mm, P = 0.031) and more fractionated QRS complexes (44 vs 18%, P = 0.020).

FD pre-LVH normal T1 vs healthy controls: normal T1 pre-LVH Fabry patients (40/72, 56%) had reduced GLS (-18 ± 2 vs -20 ± 2%, P < 0.001), microvascular impairment (lower MBF 2.5 ± 0.7 vs 3.0 ± 0.8mL/g/min, P = 0.028), subtle T2 elevation (50 ± 4 vs 48 ± 2ms, p = 0.027) and limited LGE (%LGE 0.3 ± 1.1 vs 0%, P = 0.004) when compared to healthy controls; ECG abnormalities included shorter P wave duration (88 ± 12 vs 94 ± 15ms, P = 0.010) and T wave peak time (Tonset–Tpeak; 104 ± 28 vs 115 ± 20ms, P = 0.015), resulting in a more symmetric T wave with lower T wave time ratio (Tonset–Tpeak)/(Tpeak–Tend) (1.5 ± 0.4 vs 1.8 ± 0.4, P < 0.001) compared to controls.

Conclusion: Prior staging of Fabry cardiomyopathy included a pre-LVH stage (accumulation/storage) and two LVH stages (hypertrophy and inflammation; fibrosis and impairment). Here we define an even earlier stage, pre-LVH pre-detectable storage, defined by microvascular dysfunction, impaired GLS and altered atrial depolarization and ventricular repolarization intervals (see Figure).

Abstract Figure. Proposed stages of cardiac involvement