Screening of LAMP2 expression in peripheral white blood cells by flow cytometry effectively identifies Danon disease among young females with advanced heart failure.

Authors:
M Kubanek¹, J Gurka¹, F Majer², L Píherova², A Krebssová¹, A Chaloupka³, J Krejci³, T Freiburger⁴, D Zakova⁴, T Kalina⁵, J Sikora², V Melenovsky¹, ¹Institute for Clinical and Experimental Medicine (IKEM), Department of Cardiology - Prague - Czechia, ²Charles University of Prague, 1st Medical School, Research Unit for Rare Diseases, Department of Paediatrics - Prague - Czechia, ³Masaryk University, St. Anne’s University Hospital, 1st Internal Cardioangiologic Clinic - Brno - Czechia, ⁴St. Annes University Hospital, Centre of Cardiovascular and Transplant Surgery - Brno - Czechia, ⁵Charles University of Prague, 2nd Medical School, Department of Paediatric Haematology and Oncology - Prague - Czechia,

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Introduction: Danon disease (DD) is a rare X-linked disorder associated with severe heart failure. DD is caused by mutations in the LAMP2 gene. As a result, LAMP2 protein is universally or mosaic absent in the tissues of male and female DD patients, respectively. Contrary to the noticeable phenotype in DD males, presentation in DD females is variable and includes isolated dilated (DCM) or hypertrophic cardiomyopathy (HCM) regularly progressing to advanced heart failure (AHF) between 20-40 years of age. In our study, we aimed to evaluate the prevalence of DD in young females (<40 years) with advanced heart failure due to non-ischemic cardiomyopathy.

Methods: The study cohort comprised of 60 female patients (pts), 47 pts (79%) were heart transplant recipients, 2 pts (3%) were treated by ventricular assist device and 11 pts (18%) were in pre-transplant phase. Median age of disease onset was 22 years, median age at surgery or pre-transplant assessment 28 years, and median age at screening 37 years. DCM was found in 77%, HCM in 15%, and other type of CM in 8% of pts. LAMP2 was detected by flow cytometry (FC) in peripheral leukocytes in 45 females with unexplained aetiology of cardiomyopathy and 2 females with previously diagnosed DD. The remaining 13 pts have already been diagnosed with a different disease at the time of FC screening. Whole exome sequencing and LAMP2 immunohistochemistry (IHC) in explanted myocardial samples were used as independent methods to confirm/exclude the diagnosis of DD.

Results: LAMP2 FC identified DD in 5 patients. In all of them, the diagnosis was confirmed by genetic analyses (and when possible also by IHC). The total DD prevalence in the cohort was 12%. FC detected DD with a sensitivity of 100% and specificity of 90% (p<0.001). Females with DD had more frequently HCM (57% vs. 9%; p=0.011) and delta waves in electrocardiogram (57% vs.0%, p=0.001).

Conclusion: Danon disease is an underdiagnosed cause of advanced heart failure in young females. To facilitate timely diagnosis, treatment and family counselling in these specific patients. LAMP2. FC can be used as an effective screening method.