

Abstract

Introduction

Danon disease is a rare X-linked lysosomal storage disorder caused by pathogenic variants of the *LAMP2* gene, leading at the cellular level to impaired autophagy and subsequent apoptosis.

Clinically, it manifests primarily as cardiac involvement with a risk of early progression to advanced heart failure.

In hemizygous males, presentation is usually early and conspicuous; however, in heterozygous females, the clinical presentation is variable, often without prominent extracardiac manifestations, and diagnosis is therefore more difficult. In both sexes, a characteristic ophthalmologic phenotype of pigmentary retinopathy can be observed.

In clinical practice, the disease in women may remain unrecognized for a long time despite its serious prognosis. This dissertation focuses on the pathophysiological and clinical aspects of Danon disease in women, with particular emphasis on screening, diagnosis, and phenotypic characterization.

Hypothesis

Danon disease is an underdiagnosed cause of advanced heart failure in young women with non-ischemic cardiomyopathy. Clinical signs alone are insufficient for reliable disease identification. Flow cytometry with *LAMP2* detection in peripheral leukocytes may represent an effective screening tool.

Aims

1. To describe the prevalence and phenotype of Danon disease in young women with non-ischemic cardiomyopathy and manifestations of advanced heart failure.
2. To improve the diagnosis of Danon disease in women with non-ischemic heart failure using *LAMP2* flow cytometry in peripheral leukocytes.
3. To investigate the genetic architecture of Danon disease in the Czech population and to evaluate the contribution of X-inactivation of the *LAMP2* allele in affected tissues.

Methods

The dissertation is based on four studies. The first study evaluated a cohort of young women with advanced heart failure due to non-ischemic cardiomyopathy and applied targeted screening for Danon disease using flow cytometry of peripheral leukocytes. The second study provided a detailed description of a patient with a complex *de novo* rearrangement of the *Xq24* region and a heterozygous contiguous deletion involving *LAMP2* and neighboring genes. The third study focused on the ophthalmologic phenotype of Danon disease using modern imaging methods. The fourth study evaluated pregnancy outcomes in women with cardiomyopathy of various etiologies (including Danon disease) and in women after orthotopic heart transplantation.

Results

In the cohort of young women with advanced heart failure, a relatively high prevalence of Danon disease (12%) was found. Clinically, a hypertrophic cardiomyopathy phenotype and ECG pre-excitation were more frequent in affected women; however, the sensitivity of these signs was low. LAMP2 flow cytometry in peripheral leukocytes demonstrated very good diagnostic yield and identified two new cases in our cohort. Genetic analysis confirmed heterogeneous findings, including a deletion in the *Xq24* region affecting the *CUL4B*, *LAMP2*, *ATP1B4*, *TMEM255A*, and *ZBTB33* genes. Ophthalmic examination showed pigmentary retinopathy with autofluorescence abnormalities and structural alterations of the outer retinal layers despite relatively preserved central visual acuity, including in an otherwise clinically asymptomatic carrier of a pathogenic *LAMP2* variant. During pregnancy in a patient with Danon disease, progression of heart failure was described, requiring early heart transplantation. The course of four pregnancies in women after heart transplantation was predominantly favorable.

Conclusion

Danon disease is a significant yet underdiagnosed cause of advanced heart failure in young women with non-ischemic cardiomyopathy. Flow cytometry with LAMP2 detection in peripheral leukocytes is a rapid and practical tool that may substantially improve early diagnosis, especially in cases of inconclusive genetic findings. Integration of cardiologic, ophthalmologic, genetic, and cytometric findings enables more accurate diagnosis and thereby supports timely therapeutic decision-making, genetic counseling, and targeted follow-up of affected families.

Keywords

Danon disease, *LAMP2*, cardiomyopathy, heart failure, flow cytometry, X-inactivation, pigmentary retinopathy, pregnancy, heart transplantation.