Clinical Overview of Lysosome-Associated Membrane Protein 2 (LAMP2) Deficiency (Danon Disease) for ICD-10-CM Committee

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Overview of Danon Disease

Definition	A **rare X-linked dominant, genetic metabolic disorder** caused by primary deficiency in Lysosome-associated membrane protein-2 (LAMP2)
Symptoms	**Multi-systemic** with predominant involvement in the: • Heart and skeletal muscles • Central nervous system • Retina Significant clinical differences occur between males and females due to the X-linked inheritance of the disease
Outcomes	• End stage **heart failure and death** in the absence of heart transplant • Average **age of onset is 12 (males) and 28 (females)**[1] • Without a heart transplant, average **age of death is 19 (males) and 35 (females)**[1]
Prevalence	Though exact prevalence not known, a crude estimate is **10,000 – 25,000 cases in the US**[2]

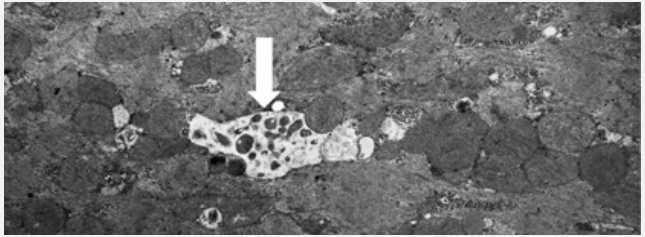
1. Boucek, D., Jirikowic, J., & Taylor, M. (2011). Natural history of Danon disease. *Genetics in Medicine*, 13(6), 563-568.
2. Taylor, M., Adler E. (2020). Danon Disease. GeneReviews. [internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.

Multi-systemic Presentation in Males and Females with Danon Disease

Overview of Clinical Presentation in Males and Females[1]

Factors	Males	Females
Typical age of onset	Childhood to adolescence	Adolescence to adulthood
Cardiac symptoms	Predominantly rapidly progressive hypertrophic cardiomyopathy, Wolff-Parkinson-White Syndrome	Dilated or hypertrophic cardiomyopathy, Wolff-Parkinson-White Syndrome
Neurological symptoms	Mild intellectual disability / learning difficulties	Not frequently reported
Retinal symptoms	Progressive visual impairment	Similar to males, but less severe
Musculoskeletal symptoms	Mild muscle weakness	Not frequently reported

Not all symptoms may be present in all patients; symptoms progress over time



Autophagic vacuole containing glycogen particles in cardiac muscle cells in a Danon patient[2]

1. *Danon Disease - Clinical*. Symptoms of danon disease. (n.d.). Retrieved August 31, 2022, from http://danondisease.org/id2.html
2. Cheng, Z., & Fang, Q. (2012, June 14). *Danon disease: Focusing on heart*. Nature News. Retrieved August 30, 2022, from https://www.nature.com/articles/jhg201272

Diagnosis, Management, and Treatment

Diagnosis	• Established via **pathogenic variant in LAMP2 on genetic testing**[1] • Supportive laboratory findings include elevated creatine kinase, elevated aminotransferase (AST), elevated alanine aminotransferase (ALT), and muscle biopsy demonstrating vacuolar myopathy[1]

Management	• Currently focuses on surveillance and symptom palliation:
	  • **Surveillance** – visits with cardiologist several times yearly, including echocardiograms (ECHOs) and electrocardiograms (EKGs) to monitor cardiac progression
	  • **Symptom palliation** – including physical therapy, beta blockers, and implantable cardioverter-defibrillator (ICD) implants
	• **Heart transplantation** when clinically indicated
	• Patients **may not receive optimal cardiac or multi-systemic management** due to incomplete diagnosis or misdiagnosis
	  • E.g., Patients diagnosed with hypertrophic cardiomyopathy (HCM) may receive alcohol septal ablation, which is not recommended for Danon patients
	  • E.g., Patients with exercise intolerance may be evaluated for heart transplant because skeletal myopathy has not yet been diagnosed

Treatment	No disease-directed or curative treatment currently available[2]

1. Boucek, D., Jirikowic, J., & Taylor, M. (2011). Natural history of Danon disease. *Genetics in Medicine*, 13(6), 563-568.
2. Cheng, Z., Cui, Q., Tian, Z., Xie, H., Chen, L., Fan, L., Zhu, K., Fang, Q. (2011). Danon disease as a cause of concentric left ventricular hypertrophy in patients who underwent endomyocardial biopsy. *European Heart Journal,* 33, 649-656.

Distinction Between Danon and Other Glycogen Storage Diseases (GSDs)

	GSD TYPE	ICD-10 CODE	AFFECTED GENE	INHERITANCE	PREVALENCE/ INCIDENCE	SYMPTOMS	TREATMENT
VON GIERKE	I	E74.01	GSDIA or GSDIB	Autosomal recessive	1:100,000 births	Low blood sugar, enlarged liver and kidney	Diet
POMPE	II	E74.02	GAA	Autosomal recessive	1:40,000 births	Respiratory issues, muscle weakness, HCM	Enzyme replacement
DANON	IIB	N/A	LAMP2	X-linked dominant	1:12,000 – 1:50,000 individuals	Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), musculoskeletal weakness	None; heart transplant
CORI	III	E74.03	PYGL	Autosomal recessive	1:100,000 births	Low blood sugar, enlarged liver	Diet
ANDERSEN	IV	N/A	GBE	Autosomal recessive	1:600,000 – 1:800,000 births	Enlarged liver, fibrosis, cirrhosis	None; liver transplant
MCARDLE	V	E74.04	PYGM	Autosomal recessive	1:100,000 individuals	Cramps and fatigue	Diet and exercise

Danon Disease Summary

- Caused by LAMP2 gene mutation
- Variable presentation in males and females, with males presenting earlier onset and faster progression
- Represents one of most aggressive cardiomyopathies ever characterized, especially for male patients
- Involves heart, skeletal muscles, central nervous system, and retina, although non-cardiac manifestations are most frequently reported in males
- Leads to end-stage heart failure and death, as early as adolescence in males, in absence of heart transplant

Thank You

Questions?