Lafora Disease is an Inherited Metabolic Cardiomyopathy

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Inherited metabolic storage cardiomyopathies, often clinically misdiagnosed, comprise a small, but important, fraction of patients genotyped with clinical suspicion of hypertrophic cardiomyopathy (HCM, ≤1%). Overall**,** glycogen metabolism disorders affect energy homeostasis primarily in skeletal muscle, heart, liver, and, less frequently, the central nervous system. These rare diseases are quite variable regarding age of onset, symptoms, morbidity and mortality. Typical pathologic vacuoles containing glycogen or intermediary metabolites altering cardiac structure and function are usually described in Pompe's, Danon's and Fabry's diseases as well as in patients with mutations in *PRKAG2*, the regulatory γ subunit of AMP-activated protein kinase. In affected patients, these multisystem disorders may cause left ventricular hypertrophy that could accompany neuromuscular deficits, liver and/or kidney dysfunction and abnormalities of the peripheral central nervous system (1, 2).

Lafora disease (LD) is a rare neurodegenerative disease (<5/1,000,000) mainly present in Mediterranean countries and consanguineous regions, although its exact prevalence is unknown. It manifests during adolescence with neurological symptoms that eventually lead patients to a vegetative state and premature death. There is no treatment available, apart from antiepileptic drugs and palliative support. LD is caused by mutations in laforin (*EPM2A*) or malin (*EPM2B*), which are key regulators of glycogen metabolism. LD patients show abnormal glycogen deposits called Lafora bodies, in brain, skeletal muscle, skin, liver and also in the heart. The accumulation of Lafora bodies as a result of laforin or malin deficiency has recently led some authors to consider Lafora disease as a new member of the family of glycogen storage diseases (3). Although rhythm disturbances and heart failure have been reported in some Lafora disease patients (4), the consequences of laforin or malin loss for cardiac function over time have not been explored.

To address this question, we blindly assessed cardiac function and remodeling in two previously described mouse models of LD, lacking either laforin (*Epm2a*$^{-/-}$) or malin (*Epm2b*$^{-/-}$), which show evident neurological abnormalities beginning at 8-10 months of age (5). Experiments were conducted in accordance with the guidelines of the Institutional Animal Welfare Committee. Echocardiography analysis, performed in two separate groups of mice at 8-10 months of age and at 14-16 months of age under light anesthesia, revealed that laforin and malin knockout mice develop cardiac hypertrophy and marked systolic dysfunction by 14-16 months of age, showed by an increased end-diastolic left ventricle walls thickness and normalized cardiac mass, and a decreased left ventricle ejection fraction (**Table 1**). Histological assessment showed abundant glycogen aggregates inside the cardiomyocytes, including typical Lafora bodies, and increased cardiomyocytes area in both LD mouse lines. In addition, LD mice showed increased normalized cardiac weight (heart weight to tibial length ratio) and BNP expression, confirming the presence of cardiac hypertrophy and dysfunction (**Table 1**).

These pathological features resemble the inherited metabolic cardiomyopathies of human multisystem glycogen-storage disorders caused by mutations in genes regulating glycogen metabolism. Overall, our results strongly suggest that cardiac studies should be systematically performed in patients with LD, that laforin and malin deficiency should be considered part of the genetic spectrum of metabolic HCM, and that HCM patients with an unknown underlying genetic cause might benefit from genetic screening of laforin and malin genes, especially if neurological symptoms are also present.

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Table 1. Cardiac parameters in wild type mice compared to laforin and malin knockout mice.

	8-10 months of age			14-16 months of age		
	WT	***Epm2a*$^{-/-}$**	***Epm2b*$^{-/-}$**	**WT**	***Epm2a*$^{-/-}$**	***Epm2b*$^{-/-}$**
LAX two-dimensional echocardiography data						
LVVold (µl)	68±20	78±12	61±20	70±19	84±16	75±16
LVVols (µL)	28±10	36±9	28±10	30±13	**44±12** *	44±15
LVEF (%)	59±6	53±9	55±6	58±12	**47±7** *	**43±8** **
N	5	6	6	11	12	12
Gravimetric and histological analysis						
HW/TLenth (mg/mm)				0.9±0.0	**1.1±0.1** **	**1.1±0.1** **
BNP expression (fold induction)				1±0.2	**2.33±0.6** ***	**2.28±1.0** ***
Cardiomyocytes area (μm^2)				419±129	**675±255** ***	**521±174** ***
PAS positive				-	+++	+++
N				7	8	8

LVVold, end-diastolic left ventricle volume; LVVols, end-systolic left ventricle volume; LVEF, left ventricle ejection fraction; HW, heart weight; TL, tibial length; PAS, Periodic Acid-Schiff staining in heart sections; N, number of mice. Data are presented as mean±SD. *P<0.05, **P<0.01, ***P<0.001 Epm2a-/- vs WT and Epm2b-/- vs WT; #P<0.05, ##P<0.01, ###P<0.001 Epm2a-/- and Epm2b-/- 8-10m vs Epm2a-/-and Epm2b-/- 14-16m, respectively, using a two-way ANOVA test with Bonferroni correction, or a Student t test for HW/TL, cardiomyocytes area and BNP expression.