A phenocopy of sarcomeric hypertrophic cardiomyopathy: LAMP2 cardiomyopathy (Danon disease) from China

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This editorial refers to ‘Danon disease as a cause of concentric left ventricular hypertrophy in patients who underwent endomyocardial biopsy’, by Z. Cheng et al., on page 649

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease characterized by otherwise unexplained left ventricular (LV) hypertrophy, and caused by a multitude of mutations in genes encoding proteins of the cardiac sarcomere.1–3 Notably, HCM is heterogeneous in terms of phenotypic expression, clinical presentation and course, as well as management strategies, i.e. with severe disease consequences in some patients but a benign course and normal life expectancy in many others.2,3 Recently, there has been increasing recognition that other uncommon inherited diseases may mimic the phenotypic and clinical features of sarcomeric HCM, but are caused by distinctly different gene mutations.4–7 These conditions include most prominently Fabry disease (X-linked α-galactosidase deficiency with glycosphingolipid deposition), PRKAG2 (regulatory subunit of adenosine monophosphate-activated protein kinase), and LAMP2 (a lysosomal storage disease, also known as Danon disease) (Figure 1).4–7

LAMP2 cardiomyopathy is an X-linked primary deficiency in lysosome-associated membrane protein-2 caused by several ‘private’ (i.e. reported in only a single patient or family) radical mutations in the LAMP2 gene, including frameshifts, splicing sites, deletions, and insertions.5–7 Although apparently rare, the geographic distribution of LAMP2 mutations is wide, i.e. reported from the USA, Italy, Australia, Sweden, the UK, and Japan,5–9 and now recognized in China.10 Most of the current knowledge of LAMP2 is based on case reports and small series, although a registry consisting of 82 patients has been assembled since 2006.7

This ‘new’ disease is the subject of a report by Cheng and associates from Beijing.10 These investigators studied 50 consecutive and unselected patients with a concentric pattern of LV hypertrophy (using ventricular septal to posterior wall thickness ratio of <1.3). After diagnosing and excluding 14 patients with cardiac amyloidosis, genetic testing for mutations in the LAMP2 gene was performed in the remaining 36; unfortunately, the clinical cardiac diagnoses in these latter patients are not specified. Nevertheless, in 3 of these 36 patients with concentric hypertrophy novel LAMP2 frameshift mutations were identified (6% of the overall study cohort).

Cheng et al.10 recognize that the distinction of LAMP2 cardiomyopathy from ‘typical’ sarcomeric HCM is not an academic exercise, but rather a key differential diagnosis that is likely to be unreliable based on clinical criteria alone (Figure 1), and is resolvable only with contemporary genetic testing. Indeed, an accurate and reliable LAMP2 molecular diagnosis is crucial, given that the natural history and complications attributable to these two conditions are very different. LAMP2 is an almost uniformly severe and unfortunate clinical entity (particularly in affected males) characterized by early morbidity and limited life expectancy, with survival beyond 25 years uncommon. The Danon Registry10 reports the following disease landmarks on average: first symptoms, 12 years; transplant, 18 years; death, without transplant, 19 years. While the three Chinese patients reported here are currently asymptomatic, they are still young (14–16 years old), with the future potential risk of clinical deterioration.

Such dire consequences of LAMP2 mutations result from the profound structural abnormalities evident in the histopathology of LV myocardium characterized by extensive replacement scarring, with autophagic and vacuolated myocytes presumably containing degraded lysosomal material (Figure 2). Indeed, and perhaps not unexpectedly, this greatly distorted myocardium has proved refractory to effective and reliable termination of potentially life-threatening ventricular tachyarrhythmias by implantable cardioverter-defibrillators (ICDs) (Figure 2), as occurred in five of...
our seven LAMP2 patients. Therefore, the only primary treatment intervention to preserve life in LAMP2 cardiomyopathy is heart transplantation, usually performed in young patients out of necessity.

In addition to complications related to the cardiomyopathy, the most common manifestations of LAMP2 are relatively mild cognitive and intellectual disability (consistent with the report of Cheng et al.\textsuperscript{10}) and muscle weakness, although the disease process may involve the liver, retina, and lungs.\textsuperscript{7} Also, in LAMP2, distinct differences in disease expression are evident according to gender; females are considered less severely affected, presenting clinically $\sim 15$ years later than males,\textsuperscript{7–9} although we have observed striking exceptions to this generalization\textsuperscript{6} (Figure 2).

As the study of Cheng et al.\textsuperscript{10} underscores, the challenge of LAMP2 lies in the ability to identify those patients among general cardiac populations or subspecialty HCM clinics. In this regard, the authors have implied that concentric hypertrophy is characteristic of LAMP2, although phenotypic expression is in fact quite variable in this disease, with asymmetric patterns of LV hypertrophy without dilatation reported (identical to sarcomeric HCM),\textsuperscript{5} as well as an end-stage dilated form with LV wall thinning\textsuperscript{6} (Figure 2).

Molecular DNA diagnosis for HCM was first introduced > 20 years ago,\textsuperscript{1} and in the last 5 years has become available from commercial laboratories in the USA and Europe on a fee-for-service basis. In the USA, there are four such companies offering testing panels that consist of the major HCM sarcomere genes, as well as its phenocopies (including LAMP2). Therefore, the tools necessary to diagnose LAMP2 are readily available. However, the other ingredient necessary for this clinical diagnosis is a high index of suspicion.

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\includegraphics[width=\textwidth]{figure1.png}
\caption{Sarcomere and non-sarcomere mutations responsible for hypertrophic cardiomyopathy and its phenocopies. LVH, left ventricular hypertrophy.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Diverse morphological forms of LAMP2 cardiomyopathy (Danon disease). (A) Gross heart at autopsy from an asymptomatic patient with LAMP2 cardiomyopathy initially diagnosed as sarcomeric hypertrophic cardiomyopathy, who died suddenly at 12 years of age refractory to cardioverter-defibrillator intervention (see below; B). Evident is asymmetric massive hypertrophy of the ventricular septum (VS), 65 mm in thickness, and small cavity size. Ao, aorta; LA, left atrium. From Maron et al.,\textsuperscript{5} reproduced with permission of JAMA. (C) Clusters of myocytes with vacuolated sarcoplasm (stained red) embedded in an area of scarring (stained blue); Masson trichrome; original magnification $\times 100$. (D) High power photomicrograph of the area in the box in C showing a large empty myocyte surrounded by smaller vesicles and replacement fibrosis (Masson trichrome). (E and F) Explanted heart from a 24-year-old woman with LAMP2 cardiomyopathy and successful transplant. (E) Cross-section of the left ventricle (LV) at the mitral valve level. (F) Distal cross-section of the LV at the papillary muscle level. In contrast to the patient shown in A–D, substantial remodelling is present with cavity dilatation and marked LV wall thinning (only 3, 6, and 9 mm thickness evident in some areas), due to extensive and diffuse transmural and subepicardial scarring of the ventricular septum (VS); LV free wall, and right ventricle (RV). From Maron et al.,\textsuperscript{6} reproduced with permission of Elsevier.}
\end{figure}
clinical suspicion, since genetic testing is not routine in the evaluation of HCM patients. Genetic testing can be triggered by disease features common in LAMP2 patients, such as distinctive electrocardiographic patterns with Wolff–Parkinson–White and/or extraordinary increases in pre-cordial voltages with T-wave inversion, or massive LV hypertrophy (wall thickness $\geq$ 30 mm) (Figure 2), such as reported by Cheng et al.\(^{10}\) Indeed, the two most hypertrophied hearts in our experience were caused by mutations in the LAMP2 gene with septal thickness of 60–65 mm (heart weight up to 1425 g).\(^{4,5}\)

In conclusion, LAMP2 (Danon disease) is an important clinical entity recognized only recently in cardiovascular practice which will undoubtedly prove to be more common than it appears at this early juncture, given the rapidly increasing application of genetic testing to cardiomyopathies. However, with the present rarity of LAMP2, most cardiologists, even those in specialized centres, are not familiar with this disease. Reports such as that of Cheng et al.\(^{10}\) not only serve to increase awareness of LAMP2 throughout the world, and increase penetration of this disease into the consciousness of the cardiovascular community, but also promote life-saving therapeutic interventions and the potential diagnostic power of genetic testing for heart muscle diseases.

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**References**