International Journal of Cardiology 286 (2019) 113–114

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Rare X-linked storage heart diseases are tougher on men but not kind to women

Iacopo Olivotto [a,*], Silvia Favilli [b]

[a] Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy
[b] Pediatric Cardiology, Meyer University Hospital, Florence, Italy

ARTICLE INFO

Article history:
Received 26 February 2019
Accepted 4 March 2019
Available online 7 March 2019

Danon disease is a rare X-linked glycogen storage disease caused by deficiency of the lysosome-associated membrane protein 2 (LAMP-2). It classically lies in the domain of pediatric cardiology due to severe cardiac involvement in male children and adolescents, in the form of hypertrophic cardiomyopathy (HCM) associated with ventricular pre-excitation and rapidly progressive course [1,2]. The syndromic context in which the cardiomyopathy occurs, featuring skeletal myopathy, cognitive defects and visual problems, directs clinical suspicion and diagnostic work-up. Cardiologists in adult practice rarely encounter and therefore almost never recognize Danon disease. However, recent evidence shows that they should be aware of its existence. In women, Danon cardiomyopathy may present in the third or fourth decade of life in the absence of extra-cardiac manifestations, indistinguishable from sarcomeric HCM and yet requiring different management including early consideration for heart transplant and aggressive antiarrhythmic prophilaxis.

The paper of Brambatti et al. presented in this issue of the Journal [3] represents a comprehensive review of the existing literature on Danon disease, in the attempt to overcome the sample size limitations of previous studies and provide a broader perspective in both genders. The authors included 146 patients from 83 manuscripts, each comprising small series of patients with definite diagnosis of Danon based on positive gene testing or muscle biopsy. Notably, the vast majority (92%) had evidence of cardiac involvement. Most patients were female, with a ratio of almost 2:1 versus males. Males were typically syndromic, generally exhibiting the triad of cognitive impairment, skeletal myopathy and HCM: only 18% presented with an isolated cardiac phenotype. Male patients showed severe progression and outcome, with a conspicuous 37% reaching the composite outcome of death, heart transplant or ventricular assist devices at a median age of 21 years. On the other hand, women usually presented with isolated cardiac involvement, both in the form of hypertrophic and dilated cardiomyopathy. Unexpectedly, there was occurrence of the combined endpoint in women was high (32%), comparable in absolute figures to that in males albeit with a delay of almost two decades (median age 38 years). While females experienced variable disease onset and clinical course, likely due to variation in X-linked LAMP2 activation, they were not immune from very early onset and rapid clinical deterioration. The authors suggest that LAMP2 haploinsufficiency in females, while generally not sufficient to cause extra-cardiac phenotypes, is severe enough to determine devastating cardiac disease [1].

Gender parity, unfortunately, may exist in X-linked disease [4]. In fact, emphasis on the severity of Danon in women echoes the analogous paradigm shift which occurred over a decade ago in Anderson Fabry disease (AFD), another X-linked storage condition mimicking HCM [5]. Women with AFD have delayed onset of cardiac symptoms and longer life expectancy compared to men, but may present with equally severe cardiomyopathy and suffer life-threatening complications. Based on an increasing wealth of knowledge, heterozygous women with AFD and Danon disease should not be considered mere carriers, a term that may lead to underestimation of early symptoms and delay evaluation and treatment. In both conditions, symptomatic carrier status is the exception rather than the rule. And while today a delay in diagnosis is particularly detrimental in women with AFD, for whom disease-modifying therapies are available [5], this may soon be true for Danon patients as well [6]. Rare disease too often means neglect, a delay of many years from symptom onset to diagnosis, lack of confident response from caregivers and reduced access to appropriate treatment. In the case of X-linked cardiomyopathies, this is even more true for affected women, due to the more insidious and heterogeneous presentation compared to men. There are over a thousand genes on the X chromosome (of which one copy is presumed to be inactivated), versus only a few dozen on the Y chromosome [7]. However, up to 25% of the X chromosome genes may escape or have variable inactivation [8]. This makes X-linked disease in women more diverse, but not necessarily less severe. Thus, the level of attention by all physicians involved must remain high irrespective of gender; to this aim, cultural cross-contamination between pediatric and adult cardiologists should be regarded as a major asset.

Two additional considerations deserve specific attention. The first regards the skewed geographical and racial perspective offered by the

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.01.020.
* Corresponding author at: Azienda Ospedaliera Universitaria Careggi, Largo Brambilla 1, 50134 Firenze, Italy.
E-mail address: iacopo.olivotto@unifi.it (I. Olivotto).

https://doi.org/10.1016/j.ijcard.2019.03.007

existing literature on rare cardiac diseases. As Brambatti et al. appropriately emphasize [3], the overwhelming majority of Danon patients in their report are Caucasians living in Europe and the US. Such limitation appears may seem unavoidable to those who see research directed at rare diseases as a western luxury. But it is not, and we should aim for nothing less than truly global understanding of genetic cardiomyopathies and its ethnic and environmental modifiers [9]. The second issue regards the role of contemporary genetic testing in the diagnosis of rare X-linked disorders. The advent of next generation sequencing (NGS) has revolutionized genetic diagnosis for patients with cardiomyopathies including HCM, allowing scrutiny of a high number of genes at a fraction of the expense and time requirements of traditional Sanger techniques [10]. This has come with a cost: the inclusion of many candidate genes with dubious causative role has considerably increased the background noise of rare variants of unknown significance, leading to major challenges in NGS result interpretation. On the other hand, the increase in firepower has allowed routine inclusion in NGS panels of genes causing metabolic HCM mimics, including Danon and AFD. This represents an important *safety mechanism* preventing neglect of rare diseases. In a recent report by our group [10], among 613 NGS-screened probands presenting with an HCM phenotype, 4 had Danon disease (0.7%) and 4 had Fabry disease (0.8%). Of the Danon patients, 3 were adult women believed to have aggressive HCM in the absence of evident extra-cardiac involvement. Only one had an affected male in the family with typical syndromic features: in the others, a correct diagnosis would have been delayed without NGS testing. Similar considerations hold true for the recently introduced tissue characterization techniques by cardiac magnetic resonance: low T1 mapping values may represent a decisive red flag for unsuspected storage disease in patients with HCM phenotype. As advances in technology are making genetic cardiomyopathies harder to miss, however, clinical awareness remains of the essence: as one only sees what one knows.

Acknowledgments

IO was supported by the European Union's Horizon 2020 - Research and Innovation Framework Programme under Grant Agreement no. 777204: “SILICOFCM - In Silico trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy”; and by the Italian Ministry of Health (Left ventricular hypertrophy in aortic valve disease and hypertrophic cardiomyopathy: genetic basis, biophysical correlates and viral therapy models” (RF-2013-02356787), and NET-2011-02347173 (Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary left ventricular hypertrophy).

Disclosures

None.

References

[1] T.J. Rowland, M.E. Sweet, L. Mestroni, M.R. Taylor, Danon disease - dysregulation of autophagy in a multisystem disorder with cardiomyopathy, J. Cell Sci. 129 (2016) 2135–2143.
[2] R.S. D'souza, C. Levandowski, D. Slavov, et al., Danon disease: clinical features, evaluation, and management, Circ. Heart Fail. 7 (2014) 843–849.
[3] Brambatti M et al. Danon disease: gender differences in presentation and outcomes. Int. J. Cardiol., https://doi.org/10.1016/j.ijcard.2019.01.020.
[4] A.K. Percy, E.M. Kaye, Does gender parity exist in Fabry disease? Neurology. 65 (2005) 508–509.
[5] P.B. Deegan, A.F. Baehner, M.A. Barba Romero, D.A. Hughes, C. Kampmann, M. Beck, European FOS investigators. Natural history of Fabry disease in females in the Fabry outcome survey, J. Med. Genet. 43 (2006) 347–352.
[6] M. Arad, Cardiac Danon disease: insights and challenges, Int. J. Cardiol. 245 (2017) 211–212.
[7] M.T. Ross, D.V. Grafham, A.J. Coffey, et al., The DNA sequence of the human X chromosome, Nature 434 (2) (2005) 325–337.
[8] L. Carrel, H.F. Willard, X-inactivation profile reveals extensive variability in X-linked gene expressi on in females, Nature 434 (2005) 400–404.
[9] Finocchiaro G, Magavern E, Sinagra G, Ashley E, Papadakis M, Tome-Esteban M, Sharma S, Olivotto I. Impact of demographic features, lifestyle, and comorbidities on the clinical expression of hypertrophic cardiomyopathy. J. Am. Heart Assoc. 2017;6(12). pii: e007161, https://doi.org/10.1161/JAHA.117.007161.
[10] F. Mazzarotto, F. Girolami, B. Boschi, F. Barlocco, A. Tomberli, K. Baldini, R. Coppini, I. Tanini, S. Bardi, E. Contini, F. Cecchi, E. Pelo, S.A. Cook, E. Cerbai, C. Poggesi, F. Torricelli, R. Walsh, I. Olivotto, Defining the diagnostic effectiveness of genes for inclusion in panels: the experience of two decades of genetic testing for hypertrophic cardiomyopathy at a single center, Genet. Med. (2018 Jun 6), https://doi.org/10.1038/s41436-018-0046-0.