Distinct Clinical and Histopathological Presentations of Danon Cardiomyopathy in Young Women

To the Editor: Male patients with Danon disease usually present in adolescence with left ventricular hypertrophy (LVH) and a Wolff-Parkinson-White (WPW) pre-excitation pattern on electrocardiogram (ECG). The typical course involves deterioration to severe ventricular dysfunction with end-stage heart failure or sudden cardiac death. Histopathology of cardiac and skeletal muscle tissue displays vacuolar myopathy and lysosomal glycogen accumulation (1–3).

Characterization of the disease in female patients has been thus far limited. We present 3 families in which an initial diagnosis of Danon disease in a male proband revealed affected female family members who previously presented with a cardiomyopathy as having a dilated cardiomyopathy (DCM) phenotype. Some female members had been previously diagnosed with peri-partum cardiomyopathy (PPCM). Proband 1’s mother developed heart failure at the end of her first pregnancy. She was diagnosed with presumed PPCM (LV enlargement with severely decreased systolic function, estimated EF 20% to 25%). Her clinical status improved shortly after delivery but worsened in a subsequent pregnancy, progressing to severe heart failure and ultimately leading to heart transplantation. The mother of proband 2 was diagnosed with DCM (LVEDD of 66 mm, EF <25%). She deteriorated rapidly, requiring heart transplantation at 19 months after presentation. Neither ECG demonstrated a WPW pattern. Histopathology of both explants showed marked myocyte hypertrophy and extensive interstitial fibrosis. Cytoplasmic vacuolization was present but was heterogeneous in distribution (a representative histology of proband 1’s mother is shown in Fig. 1E). LAMP-2 gene sequencing of proband 1’s mother revealed a LAMP-2 mutation identical to her son’s mutation.

The mother of proband 3 (Fig. 1C, III-3) was diagnosed with presumed HCM at age 14 years (diastolic interventricular septal wall thickness of 15 mm, >9 SDs above the normal mean for body surface area) when a screening echocardiogram was performed because of sudden cardiac death in her maternal half-brother. She has been treated with propranolol for occasional palpitations but has demonstrated neither heart failure nor a WPW pattern on her ECG.

Proband 3’s maternal grandmother (Fig. 1C, II-2) died suddenly during pregnancy at the age of 28 and was diagnosed as PPCM (no further information available). Proband 1’s half sister (Fig. 1A, III-1) was negative, signifying a de novo mutation. Testing of her maternal grandmother (Fig. 1A, I-1) was negative, signifying a de novo mutation in her mother.

Mothers of probands 1 and 2 (Fig. 1A II-2 and 1B II-3, respectively) presented in early adulthood (ages 24 and 34 years, respectively) with heart failure. Proband 1’s mother developed heart failure at the end of her first pregnancy. She was diagnosed with presumed PPCM (LV enlargement with severely decreased systolic function, estimated EF 20% to 25%). Her clinical status improved shortly after delivery but worsened in a subsequent pregnancy, progressing to severe heart failure and ultimately leading to heart transplantation. The mother of proband 2 was diagnosed with DCM (LVEDD of 66 mm, EF <25%). She deteriorated rapidly, requiring heart transplantation at 19 months after presentation. Neither ECG demonstrated a WPW pattern. Histopathology of both explants showed marked myocyte hypertrophy and extensive interstitial fibrosis. Cytoplasmic vacuolization was present but was heterogeneous in distribution (a representative histology of proband 1’s mother is shown in Fig. 1E). LAMP-2 gene sequencing of proband 1’s mother revealed a LAMP-2 mutation identical to her son’s mutation.

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Severe female cases can be attributed to X chromosome inactivation of nonmutated chromosome (unfavorable lyonization), leaving only mutated LAMP-2 protein (1). Random variable X inactivation may account for the differences in phenotypic severity between female members in the same family. A possible caveat is that other untested genetic influences could also have affected the phenotypic expression of the LAMP-2 mutations.

The potential for de novo mutations in the LAMP-2 gene, as demonstrated in proband 1’s family, indicates that Danon cardiomyopathy should be considered even in the absence of a positive family history.

The histopathology of the heart explants of all female family members in this study was characterized by extensive fibrosis, with prominent myocyte vacuolization in the areas of fibrosis. This “end-stage” pathology overlaps and may mask the characteristic vacuolar changes of Danon disease. These findings may be similar to HCM patients who develop a “burned-out” pathology (7,8).

Peri-partum cardiomyopathy is defined as the development of congestive heart failure with a DCM phenotype of unidentified cause, leading to a decreased LVEF (<45%) in the last month of pregnancy or within 5 months after delivery (9). Two female members in these families demonstrate a situation in which Danon cardiomyopathy presented for the first time in the peri-partum period. Thus, these results suggest that some cases of PPCM may be LAMP-2 mutations presenting with a DCM phenotype, either as a coincidence or as the result of the physiologic alterations of pregnancy, triggering the clinical expression of the cardiomyopathy. The absence of pre-excitation in 6 of the 7 female subjects in our study suggests that ECG would not be a reliable screening tool for the presence of Danon cardiomyopathy. These cases emphasize the importance of a detailed family history in the evaluation of young woman presenting with a DCM phenotype in the peri-partum period and consideration of testing for LAMP-2 mutations in this patient population.

*Amir Toib, MD
*Department of Pediatrics
Campus Box 8116-NWT
One Children’s Place
St. Louis, Missouri 63110
E-mail: toiba@kids.wustl.edu

Dorothy K. Grange, MD
Beth A. Kozel, MD, PhD
Gregory A. Ewald, MD
Frances V. White, MD
Charles E. Canter, MD

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REFERENCES
We read with interest a recent review article on the cardiovascular effects of omega-3 fatty acids (ω-3 PUFA) by Lavie et al. (1) and wish to highlight some of the controversial issues in this review. In relation to the role of ω-3 PUFA in primary prevention of coronary artery disease (CAD), the authors quote 3 studies—the DART (Diet And Reinfarction Trial) (2), GISSI Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico—Prevenzione) study (3), and JELIS (Japan EPA Lipid Intervention Study) (4)—as supportive evidence for a beneficial effect. As discussed further in the same review, the DART and GISSI Prevenzione studies are secondary prevention studies, and in the JELIS—which included 14,981 subjects in primary prevention and 3,664 subjects in secondary prevention—major coronary events were indeed significantly reduced in the ω-3 PUFA-treated subjects. However, when the groups with and without previous CAD (i.e., primary and secondary prevention cohorts) were individually analyzed, there was no benefit in the primary prevention group. Therefore, the 3 studies quoted by the authors do not lend any supportive evidence to the claim that ω-3 PUFA are useful in primary prevention of CAD.

In addition, the authors claim that the most significant antiarrhythmic effects of ω-3 PUFA are noted in studies on atrial fibrillation (AF) and quote 2 interventional studies (5,6) in which ω-3 PUFA were shown to be useful in primary prevention of AF. Of note, the study by Mozaffarian et al. (7) exclusively looked at patients ≥65 years of age and could not be extrapolated to the entire population at risk of AF, which would include both young (often lone AF) and old (often with underlying structural heart disease).

The authors have failed to indicate that a recent systematic review by León et al. (10) and a systematic review of the 3 large studies on implantable cardioverter-defibrillator population (11) have reported no benefit with ω-3 PUFA therapy on cardiac arrhythmias. Hence, we believe that the role of ω-3 PUFA on primary prevention of CAD and AF are far from clear as this review seems to suggest.

*Palaniappan Saravanan, MD
Neil C. Davidson, MD
*Cardiovascular Research Group
University of Manchester
46. Grafton Street
Manchester M13 9LT
United Kingdom
E-mail: palaniappan.saravanan@manchester.ac.uk

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