MANIFESTATIONS OF RARE MUTATIONS

Multimodality Imaging of Danon Disease in a Patient with a Novel LAMP2 Mutation

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INTRODUCTION

Danon disease is a rare X-linked genetic disorder presenting typically as a triad of mental retardation, skeletal myopathy, and hypertrophic cardiomyopathy (HCM). Mutations of the lysosome-associated membrane protein 2 (LAMP2) gene lead to impaired lysosomal functioning and the accumulation of intracellular glycogen. Similarly to Pompe disease (glycogen storage disease type II), with which it was initially confused, Danon disease is seen as a glycogen storage disorder, but is not related to α-glucosidase enzyme deficiency. Instead, Danon disease results from an LAMP2-associated impairment of lysosomal membrane integrity.

Cardiac involvement is a prominent clinical feature of Danon disease, in which young, often adolescent patients present with apparent left ventricular hypertrophy (LVH) and arrhythmias. Danon disease is commonly mistaken for sarcomeric HCM, despite being a lysosomal storage disease. The distinction between these two disorders is important because Danon disease has a more rapid disease progression and higher mortality. Here we describe the importance of multimodality imaging of Danon disease in a patient with a novel LAMP2 mutation.

CASE PRESENTATION

A 15-year-old Caucasian boy presented with dyspnea on exertion. Since the age of 5 years, he had been noted to have exercise limitation and mild cognitive delay. There was not a family history of cardiomyopathies, arrhythmias, or sudden cardiac death. On physical examination, he appeared well developed and there were no dysmorphic facial features. On cardiac auscultation, a grade 3/6 harsh systolic ejection murmur along the left middle sternal border was appreciated. There were no signs of skeletal myopathy, mental retardation, and cardiomyopathy.

His past medical history included exercise limitation. He had not yet been considered for a heart transplantation.

Antiarrhythmic agents were being titrated with the hope of controlling symptoms. The patient had not yet been considered for a heart transplantation.

DISCUSSION

Danon disease was first described by Moris Jak Danon and colleagues at the University of Illinois as a distinct form of lysosomal glycogen storage disease in two unrelated 16-year-old boys with mental retardation, cardiomegaly, and proximal skeletal myopathy.1 It was subsequently shown to be a result of LAMP2 gene mutations, leading to deposition of intracytoplasmic vacuoles and organ pathology. This rare genetic condition has been traditionally defined as a clinical triad of skeletal myopathy, mental retardation, and cardiomyopathy. However, on the basis of multiple clinical reports, including our case, the central nervous and skeletal myopathic symptoms are usually mild or clinically silent, with the cardiac symptoms consistently presenting as the dominant clinical feature.2,3

Phenotypically, the cardiomyopathy associated with LAMP2 mutation can mimic the HCM caused by sarcomere protein gene mutations. However, it is distinguished by a high incidence of electrophysiologic patterns of preexcitation and has been noted as one of the most lethal cardiomyopathies in young patients. The clinical coupling of HCM and conduction abnormalities, including preexcitation, has also been described in the literature as a result of adenosine monophosphate-activated protein kinase disease.4,5

Mutations of the adenosine monophosphate-activated protein kinase gene γ2 subunit, PRKAG2, is associated with altered cellular metabolism, and the affected myocytes have been observed to have glycogen deposition on histologic review.6 However, the electrocardiographic pattern of
WPW is more frequently observed with Danon disease, and the pairing with both developmental delay and skeletal myopathy has not been described in adenosine monophosphate-activated protein kinase disease. Ultimately, it is of upmost importance to learn from cases of LAMP2 mutation–associated cardiomyopathy to detail the clinical characteristics and diagnostic evaluation of this rare condition and avoid misdiagnosis and delays in management.

As our case demonstrates, the presentation of isolated ventricular hypertrophy in a young patient with Danon disease can often lead to an erroneous diagnosis of a sarcomeric HCM. The diagnosis of HCM is clinically defined as an unexplained left ventricular wall thickness ≥ 15 mm on cardiac imaging, a measurement criterion adopted from studies involving adults and children as young as 7 years of age. Mutations of sarcomere proteins remain the most common cause of HCM in genetic studies, with more than 200 mutations identified thus far. Stopping at this presumed diagnosis can result in rare cases of Danon disease going unrecognized. However, a young patient presenting with an impressive degree of LVH and ventricular preexcitation should prompt consideration for a LAMP2 mutation.

In a genetic analysis of 75 unrelated subjects with unexplained

![Figure 1](image1.png) **Figure 1** Twelve-lead electrocardiogram demonstrating WPW syndrome and voltage criteria for LVH.

![Figure 2](image2.png) **Figure 2** Transthoracic echocardiogram in four standard views at end-diastole demonstrates extremely severe LVH.
LVH, only 9.3% had LAMP2 mutations, but the measurements of maximal left ventricular wall thickness for sarcomere protein gene mutations compared with LAMP2 mutations were 24 ± 10 and 35 ± 15 mm, respectively. This same study subsequently evaluated an additional cohort of 24 subjects with unexplained LVH and electrocardiograms suggesting ventricular preexcitation, and the incidence of LAMP2 mutations had increased to 16.6%.9

According to ClinVar archives of human genetic variations and phenotypes, hosted by the National Center for Biotechnology Information, there have been >500 genetic variants described of the LAMP2 gene, but <20% of those are deemed pathologic.10 The genetic sequencing in our patient revealed a novel frameshift variant in the LAMP2 gene (Xq24), denoted p.Leu141ValfsX9. This genetic variant causes a shift in the reading frame, changing a leucine to a valine followed by a premature stop codon. The genetic analysis of this novel frameshift variant will be detailed in a separate publication.

By nature of an X-linked inheritance, young men with LAMP2 deficiency are more affected than women and present with more advanced disease at an earlier age. The average age of disease onset is 12.1 years for male patients and 27.9 years for women.2 Cardiac symptoms typical of HCM, including of chest pain, palpitations, and syncope, are the dominant clinical features at diagnosis. Conversely, there have been reported cases in which an isolated increase in creatinine kinase or abnormal electrocardiographic findings prompted the cardiac evaluation.11 Mental retardation or overt neurologic or musculoskeletal abnormalities tend to be minimal or absent in most documented cases.12

Danon disease is characterized by an adverse clinical course, despite treatment strategies. A longitudinal study by Maron et al.3 detailed the phenotype and clinical outcomes of a cohort of adolescent patients with HCM and identified LAMP2 mutations. The seven patients, with a median age of 14 years, were followed for mean of 8.6 years; all patients developed systolic dysfunction with ejection fractions of 20% to 35% (mean, 25%), and left ventricular wall thickness ranged from 29 to 65 mm. Five patients experienced lethal ventricular arrhythmias, and despite receiving implantable cardioverter-defibrillators, four died of progressive heart failure and one underwent heart transplantation.3

Multimodality imaging is a key to a successful diagnosis of Danon disease, as demonstrated by our patient’s case. A combination of WPW syndrome on electrocardiography and severe LVH on imaging, such as echocardiography, should immediately raise suspicion for Danon disease. Thereafter, positron emission tomography demonstrating glucose hypermetabolism in the myocardium further strengthens a diagnosis of Danon disease. The ultimate diagnosis requires genetic confirmation.

CONCLUSION

Danon disease is commonly mistaken for sarcomeric HCM. Because Danon disease has been associated with a more rapid disease progression and higher mortality, accurate diagnosis is essential and requires multimodality imaging. The combination of WPW syndrome on
electrocardiography, massive LVH on echocardiography or other imaging modality, and glucose hypermetabolism on positron emission tomography is indicative of Danon disease. The ultimate diagnosis requires genetic confirmation.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2019.04.007.

REFERENCES