Case Reports

Asymptomatic Young Man with Danon Disease

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Danon disease is a rare, codominant X-linked genetic disorder characterized by the triad of left ventricular hypertrophy, mental retardation, and peripheral myopathy. This disease is caused by mutations in the gene that encodes lysosomal associated membrane protein 2 (LAMP2), a deficiency of which results in the accumulation of autophagic granular débris within the vacuoles of muscle cells. This is a report of an asymptomatic 19-year-old man with Danon disease in the absence of mental retardation or clinically significant skeletal myopathy. This case underscores the importance of accurate diagnosis of unexplained left ventricular hypertrophy, in order to establish an appropriate treatment plan and to advise genetic counseling. ***(Tex Heart Inst J 2014;41(3):332-4)***

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Danon disease is a rare genetic disorder characterized by the classic triad of left ventricular (LV) hypertrophy, mental retardation, and peripheral myopathy. We report the case of an apparently healthy young man who, upon emergency-room evaluation of back pain after a motor vehicle accident, was noted to have markedly abnormal routine electrocardiographic results. Further evaluation led to the diagnosis of Danon disease.

Case Report

In August 2011, a 19-year-old man was evaluated in the emergency department for musculoskeletal back pain after a traumatic motor vehicle accident. A routine 12-lead electrocardiogram revealed sinus rhythm with pre-excitation consistent with Wolff-Parkinson-White syndrome and voltage criteria consistent with LV hypertrophy (Fig. 1). He reported no significant cardiovascular symptoms and led an active life. His only limitation was exercise-induced bronchospasm that was well controlled with occasional albuterol use. He was attending community college full time.

The patient was referred for 2-dimensional echocardiography and cardiovascular magnetic resonance imaging (CMR). The echocardiogram showed substantial LV hypertrophy: a maximal thickness in the inferolateral wall of 20 mm and a ventricular septal thickness of 17 mm. Left ventricular systolic function was hyperdynamic (ejection fraction, 0.70), with normal cavity size. Right ventricular (RV) size and function were within normal limits, as were valve structure and function. The CMR revealed morphologic findings similar to those of the echocardiogram, with moderate LV hypertrophy and hyperdynamic LV systolic function. There was also extensive mid-wall late gadolinium enhancement, most prominent in the LV lateral segments (Fig. 2).

Laboratory studies showed a serum creatine kinase level of 1,262 IU/L (normal range, 20–210 IU/L) and a serum aldolase level of 21.5 U/L (normal range, ≤8.1 U/L). The patient was referred for peripheral muscle biopsy, which showed myopathy: intracellular vacuoles containing granular and lipid-rich vacuoles (Fig. 3). These vacuoles had sarcolemmal features, and immunofluorescence revealed an absence of lysosome-associated membrane protein-2 (LAMP2), which is characteristic of Danon disease. Genetic analysis revealed a thymine deletion at position 121 (121 delT) in exon 2 of the LAMP2 gene, thereby confirming the diagnosis of Danon disease.

The patient subsequently underwent electrophysiologic evaluation for ablation of the pre-excitation pathway. During the study, the accessory pathway was localized to the bundle of His, and cryoablation was attempted. After 22 seconds of cryoablation, transient 3rd-degree heart block developed, so cryoablation was aborted and sinus rhythm resumed. Ablation was unsuccessful overall, because of the accessory pathway's proximity to the bundle of His. The patient underwent implantation of a dual-chamber cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death; he

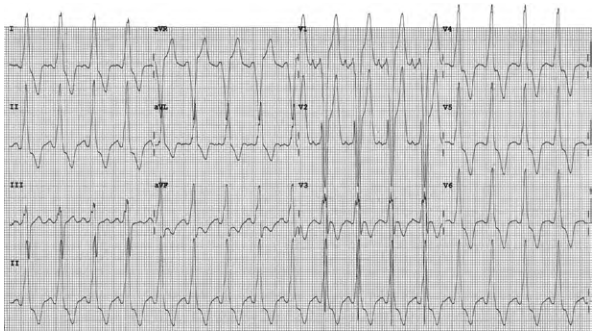

Fig. 1 *Electrocardiogram shows sinus rhythm with ventricular pre-excitation consistent with Wolff-Parkinson-White syndrome and voltage criteria consistent with left ventricular hypertrophy.*

was most recently under evaluation for cardiac transplantation. Approximately one year after the diagnosis of Danon disease, he took leave from college because of his illness and his need for frequent medical appointments. He remained asymptomatic, and, as of our last contact with him, his ICD had detected no untoward cardiac events.

Discussion

Danon disease is a rare genetic disorder caused by mutations in the lysosomal associated membrane protein 2 gene that in turn cause a deficiency of the LAMP2 protein, a component of the lysosomal membrane. The LAMP2 deficiency results in an accumulation of intracellular vacuoles, which contain granular débris and glycogen. The presence of glycogen originally led to the designation of Danon disease as a glycogen storage disease without maltase deficiency (glycogen storage disease type 2B), but the presence of glycogen is now recognized as the result of pseudoglycogenosis (involving, in this instance, the mutation of a membrane protein). The accumulation of intracellular material can lead to myocyte enlargement and cellular death, myocardial scarring,[1,2] and such electrophysiologic abnormalities as Wolff-Parkinson-White syndrome.

The clinical triad of Danon disease includes LV hypertrophy, mental retardation, and peripheral myopathy.[3] However, the phenotypic expression of LAMP2 deficiency varies. Multiple reported cases have shown cardiac involvement but minimal to no cognitive or peripheral muscular impairment.[1,2,4] There is also significant variability between the sexes. Men are affected at an earlier age, with predominantly hypertrophic cardiomyopathy; women are affected at a later age, with equally hypertrophic or dilated cardiomyopathy.[2] Echocardiographic characteristics include marked concentric LV hypertrophy, frequently associated with severe LV systolic dysfunction. An increase in RV wall thickness might also be seen.[4] Subendocardial late gadolinium enhancement in a noncoronary perfusion pattern has been described upon CMR.[5] Our patient, who had no other clinical symptoms related to Danon disease, highlights the variability in phenotypic expression of LAMP2 protein. Although he had marked LV hypertrophy, his LV systolic function was entirely preserved on both echocardiography and CMR. Moreover, he was entirely asymptomatic at the time of his diagnosis, with no active cardiac symptoms. In addition, he had no extracardiac manifestations of Danon disease—evidence neither of cognitive impairment nor of symptomatic peripheral myopathy.

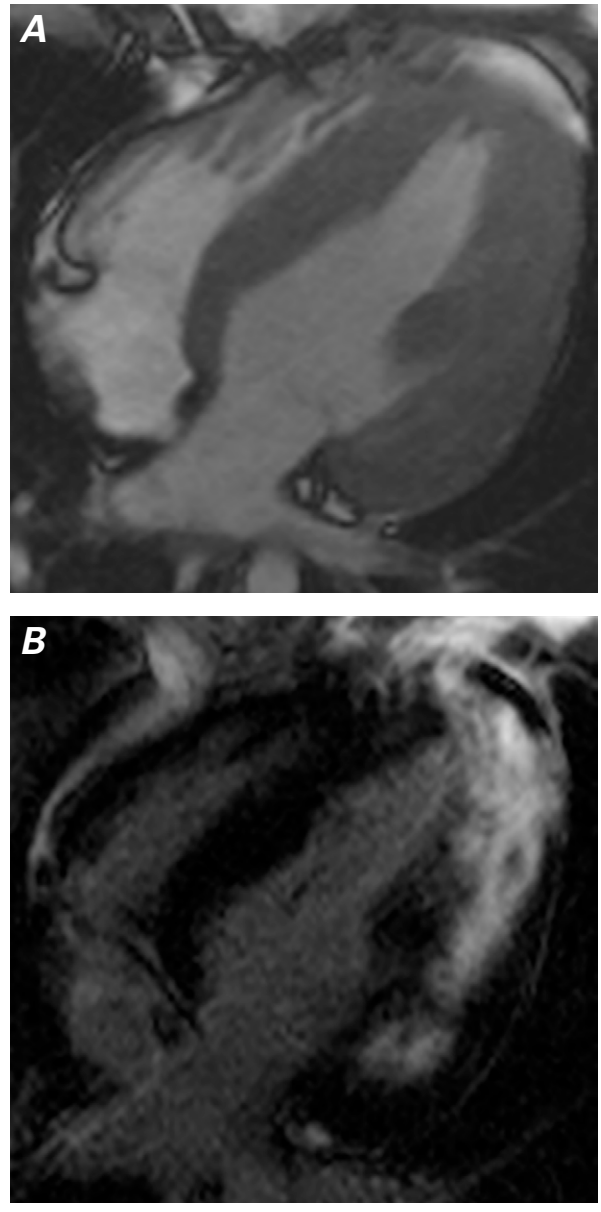

Fig. 2 ***A****) Cardiac magnetic resonance image with horizontal long-axis steady-state free-precession.* ***B****) Inversion recovery image obtained 10 minutes after the administration of gadolinium-based contrast medium. These images show left ventricular hypertrophy and extensive late gadolinium enhancement throughout the lateral wall and apex.*

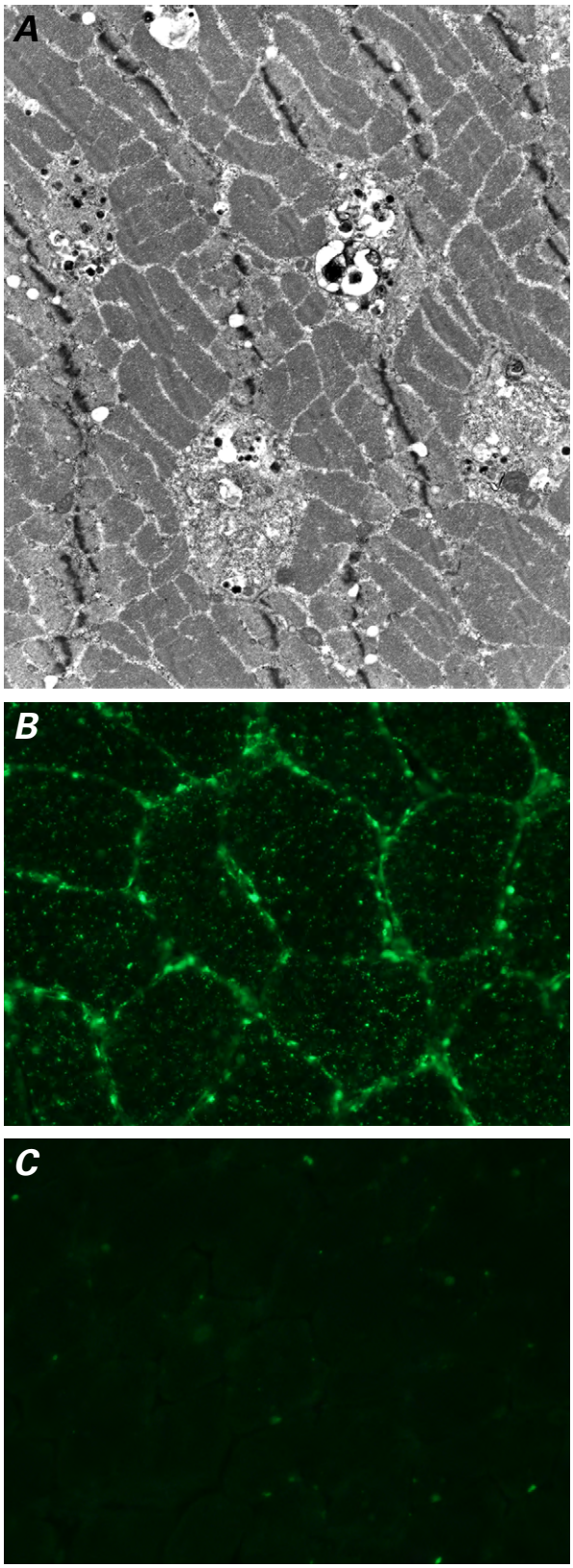

Fig. 3 ***A****) Muscle biopsy section (left biceps) reveals, under electron microscopy (orig. ×5,400), intracellular vacuoles with granular material and sarcolemmal features. Immunofluorescence staining was* ***B****) positive for LAMP2 in a control patient and* ***C****) negative for LAMP2 in our patient (orig. ×20).*

An early diagnosis of Danon disease is crucial, because available data suggest that most patients do not live beyond the 3rd decade of life.[2,3] Affected patients often have an asymptomatic period during childhood, followed by a rapidly symptomatic phase during adolescence, which culminates in death from fulminant heart failure or sudden cardiac death from ventricular tachyarrhythmia in early adulthood.[2,3] Ventricular arrhythmias refractory to defibrillation have been reported in Danon disease.[6] This should not discourage the recommendation of a primary-prevention ICD and emphasizes the need for earlier listing for heart transplantation once a diagnosis has been made. Cardiac transplantation offers the best chance for long-term survival.[7]

Accurate diagnosis of Danon disease is necessary to guide treatment, but determining who will benefit from extensive diagnostic evaluation of unexplained LV hypertrophy presents a clinical challenge. The presence of a pre-excitation pattern on electrocardiograms and of LV hypertrophy and skeletal myopathy should raise the suspicion of lysosomal storage disease.[8] These findings should prompt further investigation, including genetic testing for confirmation, because the most common mutations responsible for storage disease are part of the LV hypertrophy genetic-testing panel. Alternatively, peripheral muscle biopsy can be performed if genetic testing is unavailable or yields uncertain results. Family members of affected patients should also undergo testing.

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