ESC European Society of Cardiology
European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytab145

CASE SERIES
Cardiac imaging

Detection of intracellular histological abnormalities using cardiac magnetic resonance T1 mapping in patients with Danon disease: a case series

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Received 20 August 2020; first decision 26 October 2020; accepted 9 April 2021

Background Danon disease is an X-linked dominant disorder with defects in the lysosome-associated membrane protein 2 (LAMP2) gene and is characterized histologically by intracellular autophagic vacuoles in skeletal and cardiac muscles. Cardiac magnetic resonance (CMR) T1 mapping potentially allows to differentiate intracellular and extracellular cardiac abnormalities with a combination of native T1 value and extracellular volume (ECV) fraction.

Case summary We assessed CMR T1 mapping in two Danon disease patients (a 22-year-old man and his 48-year-old mother), who had a LAMP2 c.864G>A p. Val288Val mutation, and two blood relatives without Danon disease (his 47-year-old maternal aunt and 49-year-old father). The male patient underwent a left ventricular (LV) assist device implantation at 15 months after the image acquisition because he was inotrope dependent (INTERMACS profile 3) and had no noticeable psychological or musculoskeletal symptoms. His mother was in New York Heart Association Class II with mildly reduced LV ejection fraction (46%). The Danon group showed late gadolinium enhancement (LGE) in the anterior and posterolateral LV walls. In the interventricular wall, where evident LGE was not noted, the Danon group had high native T1 value, compared with the T1 value in the non-Danon group, and normal ECV fraction. Cardiac biopsy from the interventricular wall showed intracytoplasmic autophagic vacuoles, which are characteristics of Danon disease.

Discussion This characteristic pattern of high native T1 and normal ECV fraction in the areas without LGE, which may reflect the existence of intracytoplasmic autophagic vacuoles, may support the differential diagnosis of Danon disease from other cardiomyopathies.

Keywords Danon disease • T1 mapping • Native T1 • Extracellular volume fraction • Late gadolinium enhancement • Cardiac magnetic resonance • Case report

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Handling Editor: Matteo Cameli
Peer-reviewers: Hajnalka Vágó and Thomas Schachner
Compliance Editor: Reshma Amin
Supplementary Material Editor: Ross Thomson

Learning points

- Danon disease tends to be misdiagnosed as hypertrophic cardiomyopathy due to clinical heterogeneity, rarity of the disease, and presentation as hypertrophic phenotype.
- Cardiac magnetic resonance of Danon cases showed high native T1 and normal extracellular volume fraction in regions without marked late gadolinium enhancement.
- This characteristic pattern of T1 mapping, which may reflect an existence of intracellular autophagic vacuoles, may be supportive for diagnosis of Danon disease.

Introduction

Danon disease is an X-linked dominant disorder with defects in the lysosome-associated membrane protein 2 (LAMP2) gene and is characterized histologically by the appearance of intracellular autophagic vacuoles in skeletal and cardiac muscles.[1] Because of haploinsufficiency, male patients are more severely affected than female patients and clinically present multiorgan manifestations, including hypertrophic cardiomyopathy (HCM), skeletal muscle weakness, and cognitive disorders.[2] In men, Danon cardiomyopathy initially manifests a hypertrophic phenotype, then progresses to dilated features, and finally develops heart failure (HF), leading to cardiac transplantation in most patients in the second or third decades.[2,3] Diagnosis of Danon disease is based on clinical features (i.e. cardiomyopathy and skeletal muscle weakness), muscle biopsy for the detection of autophagic vacuoles, and evaluation of LAMP2 gene or protein deficiency.[2] However, a non-invasive marker for diagnosis of Danon disease remains to be developed.

Timeline

Cardiac magnetic resonance (CMR) T1 mapping illustrates pixel-wise representations of absolute T1 relaxation times and potentially allows the differentiation of intracellular and extracellular cardiac abnormalities using a combination of native T1 value and extracellular volume (ECV) fraction.[4,5] Native, non-contrasted T1 value is a composite signal of myocytes and extracellular space, and ECV fraction, measured from the non-contrast and contrast-enhanced T1 mapping, estimates the size of the extracellular space.[5]

Herein, we report characteristic findings of CMR T1 mapping in two patients with Danon disease [a 22-year-old man (Case 1) and his 48-year-old mother (Case 2)], who had a previously reported LAMP2 c.864G>A p. Val288Val mutation,[6] in comparison with those in their two blood relatives [his 47-year-old maternal aunt (Case 3) and 49-year-old father (Case 4)] without Danon disease.

Case presentation

Case 1

A 12-year-old boy was admitted to our hospital with a Type I Wenckebach second-degree atrioventricular block, which was found in a regular medical check in his junior high school. His first CMR

Timeline	Events
Case 1 with Danon disease (male)	
Age 12	Electrocardiography showed Type I Wenckebach second-degree atrioventricular block with no symptoms. Cardiac magnetic resonance (CMR) showed mild left ventricular hypertrophy (LVH) and supranormal left ventricular ejection fraction (LVEF) without obvious late gadolinium enhancement (LGE)
Age 19	CMR still showed normal LVEF but evident LVH with LGE
Age 22	LVEF was reduced with enlarged ventricle. Cardiac biopsy showed intracellular autophagic vacuoles. CMR T1 mapping showed high native T1 value and comparable extracellular volume (ECV) fraction in the interventricular wall without evident LGE
Age 23	
Month 0	The patient was hospitalized for his first heart failure (HF) episode and was diagnosed with Danon disease based on the results of genetic analysis
Month 9	The patient was rehospitalized for his second HF episode and underwent a left ventricular assist device implantation
Case 2 with Danon disease (female, the mother of Case 1)	
47 years	CMR T1 mapping and cardiac biopsy showed comparable findings of Case 1
48 years	Implantable cardioverter-defibrillator was inserted for detection of non-sustained ventricular tachycardia
Case 3 without Danon disease (female, the maternal aunt of Case 1)	
46 years	CMR T1 mapping showed normal native T1 value and ECV fraction
Case 4 without Danon disease (male, the father of Case 1)	
49 years	CMR T1 mapping showed low native T1 value and ECV fraction

showed supranormal left ventricular ejection fraction (LVEF) (82%), mild left ventricular hypertrophy (LVH) with mid-interventricular wall thickness of 11 mm, and no obvious late gadolinium enhancement (LGE) (*Figure 1A*). At age 19, the second CMR showed LVH progression (apical interventricular wall thickness of 18 mm) with marked LGE despite normal LVEF (63%) (*Figure 1B*). Carvedilol was started due to a diagnosis of HCM.

At age 22, he underwent T1 mapping in the third CMR, which showed evident LGE in the left ventricular (LV) free wall and right ventricular insertion point, in addition to reduced LVEF (29%) and enlarged left ventricular end-diastolic volume index (LVEDVI) (216 mL/m^2) (*Figure 2A*). The interventricular wall, where LGE was not evident (*Figure 2A*), had a high native T1 value of 1325 ms (reference range: 1250 ± 30ms) (*Figure 2B*) and a normal ECV fraction of 28.2% (reference range: 28 ± 3%) (*Figure 2C*). He was admitted to hospital for cardiac biopsy to perform a histological investigation of these abnormal CMR findings. He was active in everyday life without obvious HF symptoms [New York Heart Association (NYHA) Class I] in spite of elevated brain-natriuretic peptide (BNP) [523.0 pg/mL (normal range: ≤18.4 pg/mL)] and troponin-T [0.136 ng/mL (normal range: ≤0.014 ng/mL)] levels. Physical examination showed normal blood pressure (111/75 mmHg), regular heart rate (52 b.p.m.) without a murmur, rales, or oedema. Electron microscopic examination of cardiac biopsy specimens from the interventricular wall showed intracytoplasmic autophagic vacuoles in myocytes (*Figure 3A*), a characteristic feature of Danon disease.[1] In addition, mild fibrotic changes in the interventricular myocardial tissues were noted microscopically (*Figure 3B*). Perindopril, spironolactone, azosemide, and warfarin were added due to appearance of dilated feature and reduction in LVEF. Perindopril was changed to valsartan because of increased frequency of cough.

At age 23, he was hospitalized for his first HF episode. He was diagnosed with Danon disease based on the detection of LAMP2 c.864G>A p. Val288Val hemizygous mutation. After 9 months, he was rehospitalized and underwent an LV assist device because he

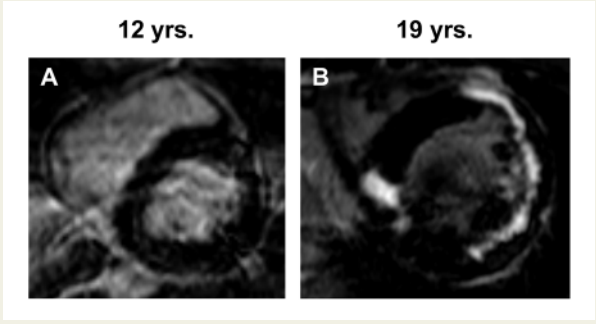

Figure 1 Late gadolinium enhancement of the left ventricle in Case 1 at 12 years (*A*) and 19 years (*B*). The former did not show evident late gadolinium enhancement while an evident late gadolinium enhancement appeared in the latter.

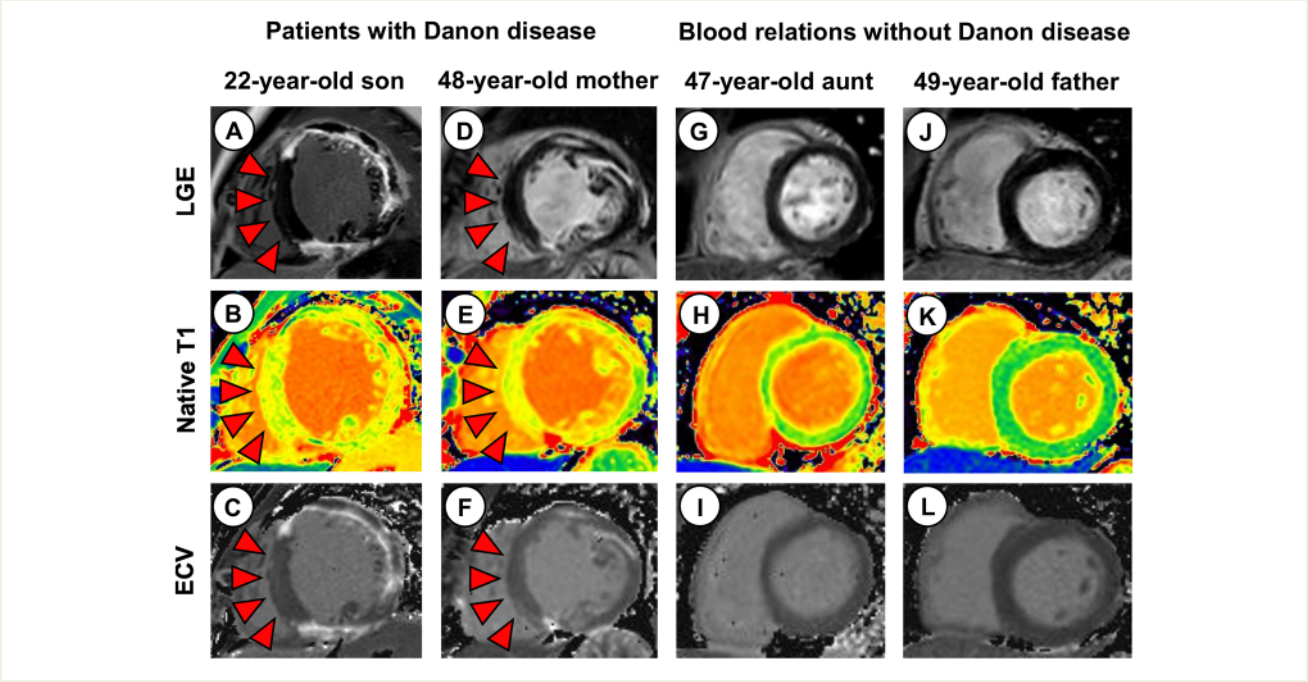

Figure 2 Late gadolinium enhancement, native T1, and extracellular volume fraction of the left ventricle in Cases 1 (*A–C*), 2 (*D–F*), 3 (*G–I*), and 4 (*J–L*). The Danon group showed late gadolinium enhancement in the left ventricular anterior and posterolateral wall (*A* and *D*). In the interventricular wall, where prominent late gadolinium enhancement was not evident (red arrowheads), native T1 value was high in the Danon group [*B* (1325 ms) and *E* (1354 ms)], compared with normal T1 value in the non-Danon group [*H* (1206 ms) and *K* (1163 ms)], and extracellular volume fraction was normal in the two groups [*C* (28.2%), *F* (32.4%), *I* (28.2%), and *L* (21.6%)]. The same colour calibration scale was used in the native T1 images, and the window level and width were the same in the extracellular volume images. ECV, extracellular volume; LGE, late gadolinium enhancement.

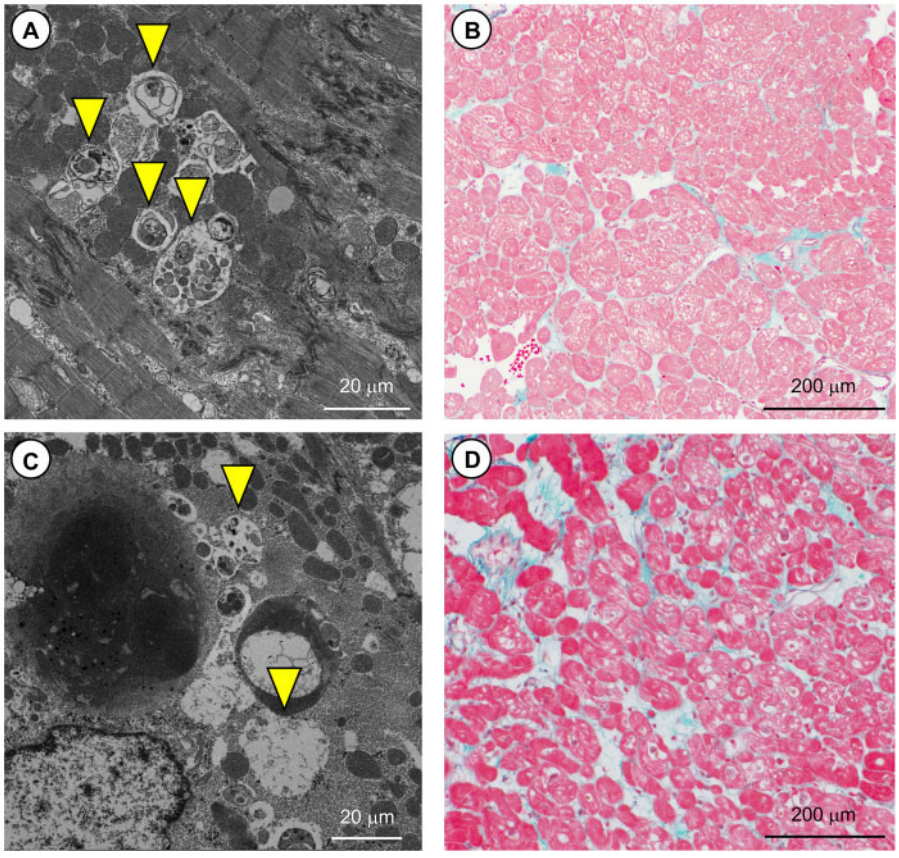

Figure 3 Electromicroscopic picture (*A*) and Elastica-Masson staining (*B*) of the interventricular wall in Case 1, and those in Case 2 (*C* and *D*) showed autophagic vacuoles surrounded by a single membrane in myocytes (yellow arrowheads in *A* and *C*) despite mild fibrotic change (light blue areas in *B* and *D*).

was inotrope dependent (INTERMACS profile 3) and had no evident symptoms of psychological or musculoskeletal disorders. He was discharged home and waited for a heart transplant at age 24.

Case 2

The 47-year-old mother of Case 1 was admitted to hospital because of a concern about the X-linked dominant inheritance of Danon disease. She had noticed exertional dyspnoea for few years (NYHA Class II). She had no medication before and did not receive a thorough cardiac examination although abnormal findings of electrocardiogram, including QS waves in leads V1 to V3 and strain pattern in inferior and posterior leads, were found in regular medical checkups for 10 years. Physical examination showed normal blood pressure (122/88 mmHg), regular heart rate (68 b.p.m.) without a murmur, rales, or oedema. Mildly reduced LVEF (46%) was found on echocardiography with slightly elevated BNP (109.4 pg/mL) and troponin-T (0.018 ng/mL) levels. As in Case 1, the interventricular wall, where evident LGE was not evident (*Figure 2D*), had a high native T1 value of 1354 ms (*Figure 2E*) and a normal ECV fraction of 32.4% (*Figure 2F*). Intracytoplasmic autophagic vacuoles and mild fibrotic changes were also found on cardiac biopsy (*Figure 3C and D*). These comparable imaging and histological phenotypes of Case 1 led her to receive genetic analysis at age 47 and to also be diagnosed with Danon disease based on the detection of the same LAMP2 gene mutation in a heterozygous fashion. Perindopril was started to expect a possible prevention of advancement in cardiac remodelling.

At age 48, she had been suffering from dizziness and lightheadedness. Twenty-four hours Holter monitoring showed non-sustained ventricular tachycardia. Left ventricular ejection fraction was reduced (41%), compared to 1 year before, on echocardiography. Bisoprolol was added and implantable cardioverter-defibrillator was inserted for primary prevention of sudden cardiac death. She was discharged home and had not experienced a major arrhythmic event at age 49.

Cases 3 and 4

The two blood relatives of Case 1 also underwent CMR T1 mapping. They both were in NYHA Class I and had no medication, no previous history of cardiac disease, no remarkable findings of physical examination, normal levels of BNP and troponin-T, and normal LVEF on echocardiography. Case 3 (47-year-old maternal aunt of Case 1) did not have the LAMP2 gene mutation. Her CMR showed normal findings, including no evident LGE (*Figure 2G*), normal native T1 values [*Figure 2H* (1206 ms)], and normal ECV fraction [*Figure 2I* (28.2%)].

Although not receiving genetic analysis, Case 4 (49-year-old father of Case 1) did not have Danon disease because of the X-linked nature of Danon disease and lack of HF symptom around the fifth decades. In spite of the normal LVEF (65%), normal LVEDVI (65 mL/m^2), and no evident LGE (*Figure 2J*), his CMR showed low native T1 value [*Figure 2K* (1163 ms)] and ECV fraction [*Figure 2L* (21.6%)].

Discussion

This case series showed a high native T1 value and normal ECV fraction of the interventricular wall, where LGE was not evident in two patients with Danon disease. Electron microscopy of cardiac tissues of the Danon patients showed intracytoplasmic autophagic vacuoles, which are characteristics of Danon disease.[1] To the best of our knowledge, this is the first report of CMR T1 mapping assessment of Danon patients in comparison with their histological findings.

Major clinical features that suggest Danon disease include an X-linked dominant inheritance pattern, hypertrophied heart in young male patients, muscle weakness, and some degree of cognitive difficulties.[2] However, family history or muscle and cognitive symptoms are not evident in some cases.[7,8] Clinical heterogeneity, disease rarity, and presentation as a hypertrophic phenotype could lead to misdiagnosis of HCM.[8] Moreover, in contrast to predominant hypertrophic phenotype in male patients, female patients show an approximately equal prevalence of dilated cardiomyopathy and HCM.[2] Cardiac or skeletal muscle biopsy and genetic mutation analysis of LAMP2 gene support the diagnosis of Danon disease,[2] which, however, is not easily available. Thus, non-invasive diagnostic tools, such as CMR, are needed for the differential diagnosis of Danon disease from other cardiomyopathies.

Cardiac magnetic resonance has been increasingly used for differential diagnosis of cardiomyopathies, as it can assess myocardial tissue compositions as well as cardiac function and morphology.[5] Late gadolinium enhancement has become a non-invasive standard measure of focal myocardial fibrosis and is helpful especially for differentiating ischaemic cardiomyopathy from non-ischaemic cardiomyopathy based on the location and transmural extent of the scar.[9] As noted in the present two cases, LGE pattern relatively sparing the septum may be a characteristic imaging feature of Danon disease.[10]

In the present two Danon cases, the interventricular wall, where there was no evident LGE, had a high native T1 value and normal ECV fraction. Native T1 value increases with oedema and enlargement of the interstitial space (i.e. fibrosis and amyloid deposition).[5] Extracellular volume fraction estimates the size of the extracellular space and increases with excessive collagen or amyloid deposition.[5] The T1 mapping pattern of the present Danon cases with abnormal T1 values and normal ECV fractions are similar to those of other intracellular storage disorders.[5,11] However, cardiac native T1 value was high in Danon patients, whereas the T1 value was low in Anderson–Fabry disease and iron overload cases.[5,11] This difference may be due to the varying influences of storage contents (autophagic materials vs. lipid or iron) in T1 relaxation. Although future studies with a large number of participants are needed, this unique pattern of T1 mapping may support the differential diagnosis of Danon disease from other cardiomyopathies.

This report has limitations. First, the two Danon cases had the same LAMP2 c.864G>A p. Val288Val mutation. The T1 mapping pattern in this report should be validated in other genetic variants of Danon disease. Second, Case 4 (the father of Case 1) had low native T1 value and ECV fraction. Native T1 value decreases with lipid and/or iron overload and low ECV fraction occurs in thrombus and fat/lipomatous metaplasia.[5] In spite of his unexpected findings of T1 mapping CMR, Case 4 had no HF symptoms with normal LVEF (65%), normal LVEDVI (65 mL/m^2), and no evident LGE. Even if Case 4 were affected by a cardiac disease decreasing T1 value and ECV fraction (e.g. Anderson–Fabry disease), this could be independent of the T1 mapping pattern of Case 1 because of the X-linked nature of Danon disease.

Conclusions

This case series showed high native T1 values and normal ECV fractions in two patients with Danon disease. This unique pattern of T1 mapping, which may reflect intracytoplasmic autophagic vacuoles, potentially support the differential diagnosis of Danon disease from other cardiomyopathies.

Lead author biography

Dr Hideaki Suzuki is a Fellow of the Japanese Society of Internal Medicine and a cardiology specialist qualified in the Japanese Circulation Society. Dr Suzuki is based at Tohoku University and its University Hospital in Sendai, Japan. Dr Suzuki currently works on Advanced Heart Failure and Transplant Cardiology and his research focuses on cardiovascular imaging of the heart and the brain.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

We would like to thank Satoko Sato for her support of electron microscopic examination in Case 2, Hiroto Aota for his assistance of this work, and Editage (www.editage.com) for English language editing.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: This work was supported by the Grants-in-Aid program from the Japan Society for the Promotion of Science [20K07776].

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