

# A rare case report of severe cardiomyopathy associated with myotonic dystrophy type 2

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## Background

Myotonic dystrophies (DM) are multi-systemic diseases characterized by muscle weakness and myotonia. Despite a growing appreciation for the cardiovascular manifestations in myotonic dystrophy type 1 (DM1), cardiac involvement in myotonic dystrophy type 2 (DM2) has been less well characterized. In patients with DM2, cardiomyopathy has rarely been described.

## Case summary

This case report describes a rare case of DM2 associated cardiomyopathy. A 56-year-old male with DM2 who presented with palpitations and fatigue. Cardiac magnetic resonance (CMR) imaging confirmed a severely enlarged left ventricular cavity with a left ventricular ejection fraction of 28% consistent with severely reduced global systolic function. The lateral wall epicardium exhibited late gadolinium enhancement in a pattern seen in myotonic dystrophy-related cardiomyopathy.

## Discussion

This case highlights the potential for significant cardiovascular involvement in DM2, as well as the importance of screening, including CMR imaging, and therapy in the myotonic dystrophy patient population.

## Keywords

Case report • Cardiac magnetic resonance • Cardiomyopathy • Chronic heart failure • Genetic disorders • Myotonic dystrophy • Reduced ejection fraction

## ESC Curriculum

2.3 Cardiac magnetic resonance • 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy

## Learning points

- Myotonic dystrophy type 2 can have significant cardiovascular involvement including severe cardiomyopathy.
- Patients with myotonic dystrophy should be referred for cardiovascular screening to identify possible cardiovascular involvement.
- Other causes of cardiomyopathy should be excluded based on history, exam, and diagnostic testing in patients with myotonic dystrophy.

## Introduction

Myotonic dystrophy type 2 (DM2, proximal myotonic myopathy, or PROMM) is an autosomal dominant multi-systemic disorder caused by a microsatellite repeat expansion within intron 1 of the zinc finger

protein 9 (*ZNF9*; also known as *CNBP*) gene. Myotonic dystrophy type 2 results in myotonia, muscle weakness, cataracts, and diabetes, and it is generally characterized by a less severe phenotype than myotonic dystrophy type 1 (DM1).<sup>1</sup> Myotonic dystrophy type 2 is prevalent in Europe, especially within the Finnish population.<sup>2</sup> The

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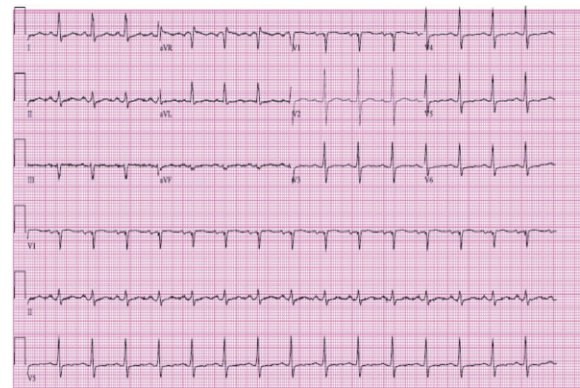
prevalence is thought to be largely underestimated, and DM2 may in fact be the most common inherited muscle disease in the European populations.<sup>2</sup> Cardiovascular involvement is increasingly being identified in other inherited muscular dystrophies.<sup>3,4</sup> In DM1, cardiac conduction disturbances, arrhythmias, and cardiomyopathy are well-recognized cardiac manifestations, and the primary cause of death is cardiac in 20–29% of patients.<sup>5,6</sup> In DM2, cardiovascular involvement has been less well characterized, but conduction defects, systolic dysfunction, and supraventricular arrhythmias have been reported.<sup>7</sup> This case report describes a rare case of severe DM2 associated cardiomyopathy, highlighting the potential for significant cardiovascular involvement in DM2 and successful medical management.

## Timeline

Month 0	Patient was referred to neurology for possible myotonic dystrophy type 2 based on clinical symptoms and family history. Weakness noted particularly in hip flexors, shoulder abductors, and handgrip. Electromyography consistent with myotonic dystrophy.
Month 2	Initial cardiology consultation. Brain natriuretic peptide was mildly elevated. Creatine kinase was elevated consistent with muscular dystrophy.
Month 4	Cardiac magnetic resonance imaging (MRI) showed non-ischaemic, severe cardiomyopathy with enlargement of the left ventricular cavity with left ventricular ejection fraction (LVEF) of 28%, global hypokinesis, and normal right ventricular size and function. Late gadolinium enhancement showed mid-lateral epicardial wall enhancement in a pattern suggestive of muscular dystrophy-related cardiomyopathy. No ischaemia based on regadenoson stress perfusion.
Month 6	Lisinopril, metoprolol, and Sprionolactone were initiated and uptitrated gradually.
Month 18	Cardiac MRI showed LVEF of 34%. No change in the ventricular function or fibrosis.
Month 19	Dual-chamber implantable cardioverter-defibrillator was placed for primary prevention.
Month 27	Cardiac MRI demonstrated no change in LVEF and no increase in late gadolinium enhancement.
Month 35	Sacubitril-valsartan and dapagliflozin initiated and patient's symptoms are improving.

## Case presentation

A 56-year-old Caucasian man presented to cardiology clinic with several months of fatigue, reduced exercise tolerance, palpitations, atypical chest pain, and lower extremity oedema.



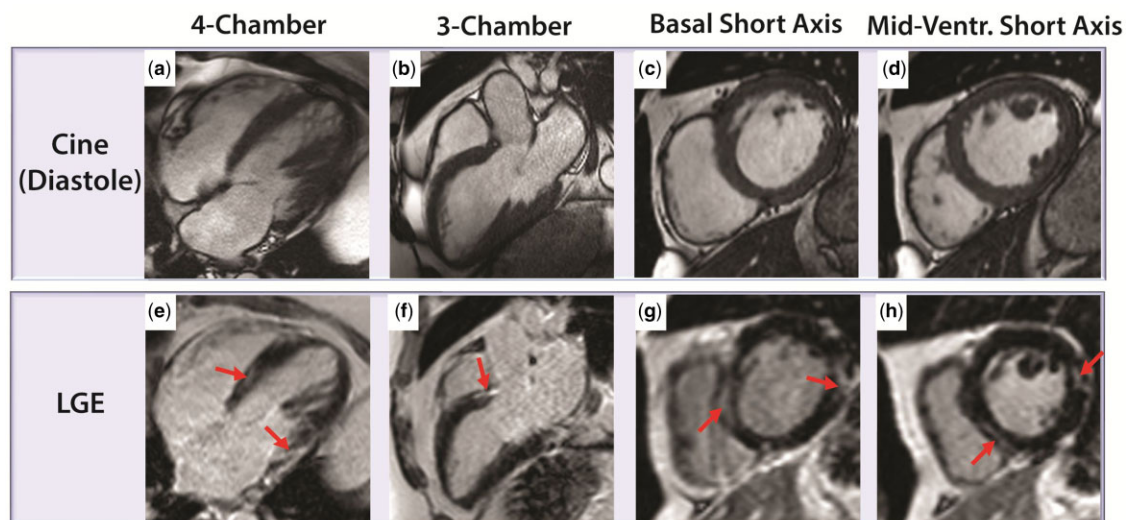
**Figure 1** Patient electrocardiogram on admission. Electrocardiogram shows a sinus rate of 83 b.p.m., inverted T wave in V4, and flat T waves V5–6. ECG, electrocardiogram.

He had a history of hypertension, well-controlled diabetes mellitus type 2, dyslipidaemia, obesity, and prior 15-pack year tobacco use. Additionally, he had progressive muscle weakness and a family history of genetically confirmed DM2 due to ZFN9 mutation in his brother and daughter. Based on his symptoms and family history, he had an electromyogram that was consistent with myotonic dystrophy, but he did not have genetic testing performed due to the cost. He had no history of significant alcohol or illicit substance use, malignancy, HIV, family history of cardiomyopathy or premature coronary disease, or personal history of cardiovascular disease including myocardial infarction or myocarditis.

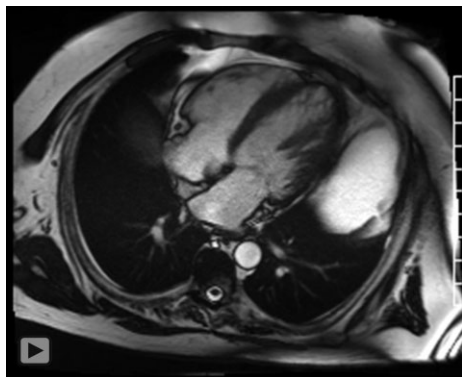
Medications at that time included the following: lisinopril (10 mg daily), ezetimibe (statin intolerance), insulin, and metformin.

Physical exam showed normal vital signs, no jugular venous distention, clear lungs, regular heart rate and rhythm without murmurs, presence of peripheral oedema, and mild proximal muscle weakness.

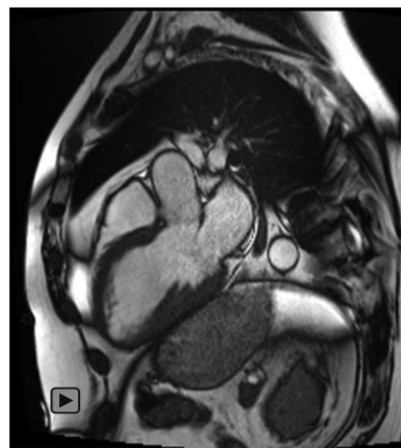
Laboratory testing revealed an elevated creatine kinase of 495 U/L (ref range 30–300 U/L), elevated N-terminal prohormone of brain natriuretic peptide of 384 pg/mL (ref range 0–125 pg/mL), but normal Troponin I. Other labs including electrolytes, renal and liver function, and complete blood count were normal. An electrocardiogram (ECG) demonstrated normal sinus rhythm with inverted T waves in V4 and flat T waves in V5–6 (Figure 1). A 72-h ambulatory cardiac monitor recorded sinus rhythm with short runs of non-sustained ventricular tachycardia but no atrioventricular conduction issues. Given his history of DM2, suspicion for heart failure, atypical chest pain, and coronary artery disease (CAD) risk factors, we pursued a cardiac magnetic resonance (CMR) imaging with contrast and regadenoson stress to assess for function, scar, and perfusion. Cardiac magnetic resonance revealed a left ventricular ejection fraction (LVEF) of 28%, global hypokinesis, and a severely enlarged (6.9 cm) LV cavity (Figure 2A–D; Videos 1 and 2). Regadenoson stress perfusion imaging showed no ischaemia. Late gadolinium enhancement (LGE) imaging showed mid-myocardial enhancement in the basal and mid-septal and lateral segments with a total scar burden of 12% (Figure 2E–H,



**Figure 2** Cardiovascular magnetic resonance with late gadolinium enhancement imaging. Cardiovascular magnetic resonance cine imaging shown in diastole (A–D) and with LGE (E–H) in four-chamber (A, E), three-chamber (B, F), basal short-axis (C, G), and mid-ventricular short-axis (D, H) views. The left ventricular cavity was severely enlarged with normal wall thickness. There was global hypokinesia and severely reduced systolic function with a left ventricular ejection fraction of 28%. Late gadolinium enhancement (E–H) showed mid-myocardial enhancement in the basal and mid-septal and lateral segments (E–H, red arrows), consistent with fibrosis from myotonic dystrophy type 2-associated cardiomyopathy. Total myocardial scar burden was estimated at 12% via semi-quantitative scar assessment. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction.



**Video 1** CMR 4-chamber cine showing a severely enlarged LV cavity with severely reduced systolic function and global hypokinesia. (CMR: Cardiac magnetic resonance imaging, LV: Left ventricular).



**Video 2** CMR 3-chamber cine showing a severely enlarged LV cavity with severely reduced systolic function and global hypokinesia. (CMR: Cardiac magnetic resonance imaging, LV: Left ventricular).

red arrows). This was consistent with non-*ischaemic* scar seen in muscular dystrophies, and other causes of non-*ischaemic* systolic heart failure including alcohol, toxic, viral, and chemotherapy-induced cardiomyopathy were excluded based on history.

Our investigations demonstrated severe LV dysfunction and LGE pattern consistent with DM2 associated cardiomyopathy. We initiated goal-directed medical therapy for heart failure including lisinopril, metoprolol succinate, and spironolactone with titration to maximally tolerated doses. After 1 year, his LVEF remained <35%

and he received a primary prevention implantable cardioverter-defibrillator (ICD). Now 3 years later, his LVEF has not decreased, his scar burden on CMR has not increased, and his symptoms have improved. Additionally, we have changed lisinopril to sacubitril-valsartan and also added dapagliflozin based on current heart failure guidelines.

## Discussion

Myotonic dystrophy type 2 has been regarded as less severe with less cardiac involvement than type 1 (DM1). However, a study examining cardiovascular involvement in the DM2 patients identified a similar risk of cardiac involvement in DM2 and DM1 patients, with a tendency towards more frequent atrial fibrillation and LV dysfunction in DM2 patients.<sup>7</sup> Only two of the 38 DM2 patients (5%) in this study had LVEF <35% by echocardiography and lacked CMR data including LGE,<sup>7</sup> which may have underestimated cardiovascular involvement. While we are still understanding the nature of cardiac involvement in DM2, the importance of cardiovascular screening and management is becoming increasingly clear. In this case, we highlight the successful management of a DM2 patient with severe symptomatic DM2 associated cardiomyopathy.

Diagnosis of DM2 associated cardiomyopathy in this case was made based on symptoms, clinical suspicion given his DM2, and CMR findings. Given his CAD risk factors and atypical chest pain, we obtained stress imaging and excluded ischaemic cardiomyopathy. Other non-ischaemic aetiologies were excluded based on history and findings, though a causal link cannot be made between DM2 and cardiomyopathy in this isolated case. Ambulatory ECG excluded significant arrhythmias contributing to cardiomyopathy and was also important for evaluating for conduction disturbances which have been reported in 17–36% of DM2 patients.<sup>8</sup> This highlights the importance of excluding other aetiologies of cardiomyopathy in the setting of a neuromuscular disorder.

Cardiac magnetic resonance imaging with gadolinium was utilized to assess myocardial fibrosis frequently associated with muscular dystrophies.<sup>4</sup> Cardiac magnetic resonance imaging is a more sensitive modality than echocardiography for assessing early cardiovascular involvement in neuromuscular cardiomyopathies, since fibrosis often precedes systolic dysfunction.<sup>4,8–10</sup> In a study of 27 patients with DM2 with a preserved ejection fraction who underwent CMR, they identified that 22% of patients had LGE.<sup>8</sup> Early identification of fibrosis presents a potential opportunity to modify the disease course.<sup>11</sup> In this case, LGE was identified in the basal and mid-septal and lateral segments; however, variable patterns of LGE in myotonic dystrophy have been reported.<sup>12</sup>

While cardiac involvement has been described in Duchenne muscular dystrophy, there have been relatively few cases of severe cardiomyopathy associated with DM2. In one case, a 61-year-old man with DM2 was identified to have an LVEF <20% with antero-septal LGE by CMR and LV non-compaction which is often associated with neuromuscular cardiomyopathies.<sup>13</sup> A second group reported a case of severe cardiomyopathy in a 65-year-old female DM2 patient with an LVEF of 20–25% and severely reduced cardiac output.<sup>14</sup> Thus, patients with DM2 can have severe cardiomyopathy, which has high morbidity and mortality.

The potential for early cardiac involvement in the DM2 population, including the possibility of severe cardiomyopathy, suggests that patients with DM2 should undergo systematic cardiac investigations.<sup>15</sup> This is particularly important in the European population given the increased prevalence of DM2.<sup>2</sup> Current guidelines for patients with muscular dystrophies recommend cardiology evaluation at the time of DM diagnosis, regardless of symptoms, with ECG, ambulatory ECG, and cardiac imaging to assess for cardiomyopathy, arrhythmias, and

conduction disturbances.<sup>10,15</sup> While these guidelines are largely focused on other muscular dystrophies and DM1, there is increasing evidence of cardiovascular manifestations in DM2. Enhanced screening in the DM2 population may uncover greater cardiac involvement. Recognizing cardiovascular involvement early in DM2 is important because there are therapies that are disease modifying.<sup>11</sup> As were implemented in this case, neurohormonal antagonists including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers are recommended for all neuromuscular disease patients with LVEF <50% given their propensity to develop worsening heart failure.<sup>10,15</sup> Mineralocorticoid receptor antagonists are effective in systolic heart failure and should be considered in neuromuscular heart failure.<sup>3,11,15</sup> In this patient, neurohormonal therapy did not result in an improvement in cardiac function necessitating an ICD; however, the disease progression was attenuated as demonstrated by no further change in LVEF or scar burden on serial CMRs. Further studies assessing the impact of neurohormonal therapies in DM2 including early introduction are needed.

## Conclusion

In summary, this case highlights the potential for significant cardiomyopathy in DM2, and the importance of aggressive cardiovascular screening and treatment by a specialized cardiovascular team to modify the disease course.

## Lead author biography



Dr Anja Touma began the MD/PhD (MSTP) dual degree program at the University of Minnesota in Minneapolis, Minnesota (USA) in 2015. She earned her Ph.D. in biochemistry, molecular biology, and biophysics in 2021. Her research is focused on the molecular basis for genetic cardiomyopathies. She is supported by the National Heart, Lung, and Blood Institute (NHLBI) at

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## Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

**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 image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** None declared.

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## References

- Gatchel JR, Zoghbi HY. Diseases of unstable repeat expansion: mechanisms and common principles. *Nat Rev Genet* 2005;**6**:743–755.
- Suominen T, Bachinski LL, Auvinen S, Hackman P, Baggerly KA, Angelini C et al. Population frequency of myotonic dystrophy: higher than expected frequency of myotonic dystrophy type 2 (DM2) mutation in Finland. *Eur J Hum Genet* 2011;**19**:776–782.
- McNally EM, Mann DL, Pinto Y, Bhakta D, Tomaselli G, Nazarian S et al. Clinical care recommendations for cardiologists treating adults with myotonic dystrophy. *J Am Heart Assoc* 2020;**9**:e014006.
- Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. *J Am Coll Cardiol* 2016;**67**:2533–46.
- Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *N Engl J Med* 2008;**358**:2688–2697.
- Bhakta D, Lowe MR, Groh WJ. Prevalence of structural cardiac abnormalities in patients with myotonic dystrophy type 1. *Am Heart J* 2004;**147**:224–227.
- Wahbi K, Meune C, Bécane HM, Laforêt P, Bassez G, Lazarus A et al. Left ventricular dysfunction and cardiac arrhythmias are frequent in type 2 myotonic dystrophy: a case control study. *Neuromuscul Disord* 2009;**19**:468–472.
- Schmacht L, Traber J, Grieben U, Utz W, Dieringer MA, Kellman P et al. Cardiac involvement in myotonic dystrophy type 2 patients with preserved ejection fraction: detection by cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2016;**9**:e004615.
- Lamacie MM, Warman-Chardon J, Crean AM, Florian A, Wahbi K. The added value of cardiac magnetic resonance in muscular dystrophies. *J Neuromuscul Dis* 2019;**6**:389–399.
- McNally EM, Sparano D. Mechanisms and management of the heart in myotonic dystrophy. *Heart* 2011;**97**:1094–1100.
- Raman SV, Hor KN, Mazur W, Halnon NJ, Kissel JT, He X et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015;**14**:153–161.
- Petri H, Ahtarovski KA, Vejstrup N, Vissing J, Witting N, Køber L et al. Myocardial fibrosis in patients with myotonic dystrophy type 1: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2014;**16**:10.
- Wahbi K, Meune C, Bassez G, Laforêt P, Vignaux O, Marmursztejn J et al. Left ventricular non-compaction in a patient with myotonic dystrophy type 2. *Neuromuscul Disord* 2008;**18**:331–333.
- Lee TM, Maurer MS, Karbassi I, Braastad C, Batish SD, Chung WK. Severe dilated cardiomyopathy in a patient with myotonic dystrophy type 2 and homozygous repeat expansion in ZNF9. *Congest Hear Fail* 2012;**18**:183–186.
- Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL et al. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. *Circulation* 2017;**136**:e200–e231.