A case report: X-linked dystrophin gene mutation causing severe isolated dilated cardiomyopathy

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Received 30 October 2018; accepted 12 April 2019; online publish-ahead-of-print 3 May 2019

Background
X-linked dilated cardiomyopathy (XLDCM) is a rare but rapidly progressive cardiomyopathy caused by dystrophin gene mutation. Mutations are more often associated with Duchenne and Becker Muscular Dystrophy, which are characterized by skeletal muscle weakness or limb girdle dystrophy. However, patients with isolated XLDCM have normal skeletal muscle but complete dystrophin loss in cardiac muscle resulting in isolated myocardial involvement without overt signs of skeletal myopathy.

Case summary
A previously well 16-year-old boy developed sudden onset dense left-sided weakness and facial droop. Computed tomography (CT) angiography and CT brain showed an occluded right internal carotid artery extending to the right middle cerebral artery. He underwent successful endovascular clot retrieval but developed frank pulmonary oedema and cardiogenic shock requiring inotropic support and intubation. Transthoracic echocardiography demonstrated severe left ventricular (LV) cardiomyopathy and an apical thrombus. Subsequent cardiac magnetic resonance (CMR) imaging confirmed the LV parameters and diffuse late gadolinium enhancement. Despite absence of skeletal manifestations, subsequent genetic testing revealed an X-linked dystrophin gene mutation [c.31+G>T (IVS1G>T)]. He was commenced on empirical heart failure therapy and underwent successful cardiac transplantation.

Discussion
X-linked dilated cardiomyopathy is a rare, rapidly progressing cardiomyopathy. Patients show normal skeletal muscle dystrophin but absent expression in cardiac muscle, resulting fibrosis, and atrophy. About 20% of affected young males have significantly reduced survival and thus the diagnosis must be considered in cases of idiopathic cardiomyopathy with CMR and genetic testing key to the diagnosis. Whilst evidence exists for empirical heart failure medications, cardiac transplantation remains the definitive treatment.

Keywords
Dilated cardiomyopathy • X-linked dystrophin mutation • Cardiac transplantation

Learning points
• X-dystrophin gene mutation with primary muscle phenotype can manifest as rapidly progressing end stage heart failure.
• Cardiac magnetic resonance imaging remains the imaging of choice to establish the extent of damage and fibrosis with characteristic late gadolinium enhancement in the inferolateral left ventricle.
• Cardiac transplantation remains the definitive course of treatment, without which mortality is high.

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Introduction

X-linked dilated cardiomyopathy (XLDCM) is an extremely rare but rapidly progressive cardiomyopathy caused by mutations in the gene that encode for the sarcolemmal protein dystrophin. Typically, mutations of the dystrophin gene results in Duchenne and Becker muscular dystrophy (DMD and BMD) in young males, where there is early loss of skeletal muscle function and the development of cardiomyopathy over time. Rarely, patients may have normal skeletal muscle dystrophin expression and an isolated absence of myocardial dystrophin. In cases of XLDCM, cardiac magnetic resonance (CMR) imaging and genetic testing play an important role in diagnosis. Empirical heart failure therapy and cardiac transplantation are critical in the acute management of these patients. We present such a case of a young male with a dystrophin gene mutation and isolated severe cardiomyopathy without skeletal involvement.

Case presentation

A 16-year-old boy was presented to a peripheral hospital after waking up with left-sided weakness and facial droop. There was no dysphasia or dysarthria. He had a history of a non-productive cough managed without medications. He takes no medications, illicit drugs, or alcohol and had no known allergies. He was fully independent, performing well at school and was captain of his local soccer team.

Imaging with computed tomography (CT) angiography and CT of the brain showed an occluded right internal carotid artery extending to the right middle cerebral artery and a small infarct involving the posterior limb of the right internal capsule. He did not receive thrombolysis due to an uncertain time of symptom onset but transferred to a tertiary centre with endovascular clot retrieval (ECR) capabilities. At our facility the patient was alert, answering questions and following commands. His blood pressure was 90/60 mmHg, heart rate was 100 b.p.m., respiratory rate was 22 breaths per minute, and oxygen saturation was 95% on room air. On cardiovascular examination, his jugular venous pressure was elevated to 7 cm with

Timeline

| Dates          | Relevant past medical history and interventions                                                                 |
|----------------|-----------------------------------------------------------------------------------------------------------------|
| 26 August 2018 | A 16-year-old male with no cardiac history had recent non-productive cough and shortness of breath, for which he was not on any medications |
| 26 August 2018 | Only child, mother died from pancreatic cancer, father remains well                                                |
| 26 August 2018 | Maternal uncle required cardiac transplantation for cardiomyopathy; discovered to have dystrophin gene mutation      |

| Dates          | Summaries from initial and follow-up visits                                                                 |
|----------------|-----------------------------------------------------------------------------------------------------------|
| 26 August 2018 | Presented to peripheral hospital after waking up with left-sided weakness and facial droop (NHSS = 12)       |
| 26 August 2018 | Arrived at tertiary hospital                                                                               |
| 29 August 2018 | Estranged maternal uncle was found to have severe cardiomyopathy managed with cardiac transplantation due to a dystrophin gene mutation |
| 29 August 2018 | Found to have dystrophin gene mutation                                                                       |
| 29 August 2018 | Referred for cardiac transplantation                                                                         |
| 24 September 2018 | Left-sided weakness completely improved with no focal neurological deficit                                |

| Dates          | Diagnostic testing (including dates)                                                                       |
|----------------|-----------------------------------------------------------------------------------------------------------|
| 26 August 2018 | Computed tomography brain, computed tomography angiogram showed right internal carotid artery occlusion extending to the middle cerebral artery |
| 26 August 2018 | Electrocardiogram showed sinus tachycardia at 100 b.p.m.                                                   |
| 26 August 2018 | Two-dimensional transthoracic echocardiography showed bilateral cardiomyopathy with severe left ventricular (LV) function systolic dysfunction and apical thrombi |
| 29 August 2018 | Cardiac magnetic resonance (CMR) confirmed LV parameters and apical thrombi                               |
| 29 August 2018 | Extensive late gadolinium enhancement in mid-antrolateral and inferolateral walls with a mid-myocardial distribution |
| 29 August 2018 | Genetic screen performed including dystrophin gene mutation                                               |
| 29 August 2018 | c.31+G>T (IVS1G>T)                                                                                        |

| Dates          | Interventions                                                                                             |
|----------------|----------------------------------------------------------------------------------------------------------|
| 26 August 2018 | Thrombolysis not indicated due to unknown time of symptom onset. Transferred to tertiary hospital for endovascular clot retrieval (ECR) |
| 26 August 2018 | Successful ECR via the right femoral artery                                                             |
| 29 August 2018 | Heart failure therapy; carvedilol, irbesartan, spironolactone, and frusemide                            |
| 29 August 2018 | Intravenous heparin as a bridge to warfarin therapy                                                      |
| 29 August 2018 | Left-sided weakness completely improved with no focal neurological deficit                             |
| 24 September 2018 | Cardiac transplantation                                                                                   |
an audible S3 but no appreciable murmurs. Air entry was mildly reduced in the left lower zone without inspiratory crackles but he had mild pitting oedema in the lower limbs to the mid shins. On neurological examination, his left upper and lower limbs had increased tone, reduced power (1–2/5), very brisk reflex responses (3+/5), and loss of pin prick sensation. In addition, he had a left facial droop involving his eye and lower half of his face. The remaining cranial nerve examination was normal. His National Institute of Health Stroke Scale (NIHSS) score was 12.

Laboratory workup showed acute kidney injury with elevated creatinine [137 μmol/L (62–115 μmol/L)]; other blood results were within the normal limits. An electrocardiogram showed sinus tachycardia (Figure 1A). Chest X-ray showed left lower-lobe collapse/consolidation and associated pleural effusion with cardiothoracic ratio of 0.76. He underwent successful ECR by the interventional neuroradiology team but unfortunately developed pulmonary oedema and cardiogenic shock requiring inotropic support and intubation. CT of the abdomen showed several infarcts involving both kidneys and the spleen and magnetic resonance imaging of the brain confirmed a hyper-intense signal within the right internal capsule consistent with acute infarction (Figure 1B–F). He had short runs of non-sustained ventricular tachycardia (6–10 beats) but no long-sustained arrhythmias.

On investigation of family history, his mother was adopted and died at 42 years of age from pancreatic cancer and his father had normal cardiac function on 2D TTE. However, an estranged maternal uncle was diagnosed with a dilated cardiomyopathy (DCM) requiring cardiac transplantation at 17 years of age; genetic testing identified an X-linked dystrophin gene mutation. Subsequent genetic testing in our patient also confirmed the same dystrophin gene mutation c.31+G>T (IVS1G>T).

The patient was commenced on carvedilol 6.25 mg twice daily, frusemide 40 mg twice daily, irbesartan 75 mg daily, spirinolactone 12.5 mg daily, and intravenous heparin as a bridge to warfarin. Following a 4-week period of stroke convalescence, the patient had dramatic improvement in neurological function with normal facial symmetry and normal left-sided tone, power (5/5) and reflexes (2+/5). He was referred to the transplant unit and underwent successful cardiac transplantation.

**Discussion**

Although genetic cardiomyopathies represent a small proportion of heart failure overall, in the paediatric and adolescent population, a familial origin is frequently identified (~40%). Dystrophin is a large cytoskeletal protein, which forms a transmembrane link between the sarcomere and the extracellular matrix, glycoproteins, and

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**Figure 1** (A) Twelve-lead electrocardiogram; sinus tachycardia. (B) Axial image of magnetic resonance imaging brain with hyper-intense region within the right internal capsule consistent with acute stroke (yellow arrow). (C, D) b-SSFP images of the left ventricular outflow tract and mid short-axis slice demonstrating ventricular dilatation and mild hyper-trabeculation. (E, F) Post-contrast images of the left ventricular outflow tract and mid-ventricle short-axis slice. Note left ventricular apical thrombus (orange arrow) and late gadolinium enhancement in the mid left ventricle lateral wall indicating focal fibrosis (red arrow). b-SSFP, balanced steady-state free precession.
sarcoglycans. X-linked dystrophin mutations most often cause DMD and BMD with the characteristic skeletal muscle weakness or limb girdle muscular dystrophy. Dystrophin gene mutations are also associated with DCM which have an early onset although the majority of children are relatively asymptomatic until late in the disease course due to their inability to exercise. The incidence of symptomatic DCM increases with age, affecting approximately one-third of patients by age 14 years, half by age 18 years, and in 100% in those >18 years. Interestingly, the severity and the evolution of DCM does not correlate with the type of dystrophin mutation.

The cardiomyopathy secondary to dystrophinopathies has a heterogeneous phenotype and believed to be the result of mechanical stress on a metabolically and structurally abnormal myocardium. Typically, the pathology begins with fibro-fatty infiltration and myocardial atrophy of the LV free wall with associated fibrosis and scar; it remains unclear; however, why the dystrophin mutation results in a segmental distribution of myocardial pathology. Unfortunately, the development of DCM in this population significantly reduces survival in about 20%.

In some patients, the disease process results in a hypertrabeculated LV with or without systolic dysfunction. Studies using CMR have shown that patients with DMD have a high prevalence of LV non-compaction (LVNC), particularly in those with reduced systolic function (up to 28%). The development of hypertrabeculation is believed to be a dynamic process with longitudinal data demonstrating an increase in the non-compacted to compacted myocardial ratio over time. The presence of LVNC in this population is associated with a rapid deterioration in LV function and higher mortality compared to patients without LVNC.

In addition to the classic dystrophinopathies, XLDCM is an extremely rare but rapidly progressive cardiomyopathy. It is a familial myocardial disease with a variable cardiac phenotype that presents with lethal congestive heart failure in young males in their teens or early twenties. Patients with XLDCM have normal dystrophin levels in skeletal muscle but may have no expression in cardiac muscle resulting in isolated myocardial involvement without overt signs of skeletal myopathy. Absence of, or reduction in, dystrophin has been hypothesized to account for the severe dysfunction observed in cardiac compared to skeletal muscle disease. When XLDCM is diagnosed, close monitoring is required due to the often-advanced nature of cardiomyopathy, as in this case, leading to major morbidity and even mortality.

Cardiac magnetic resonance imaging is becoming the modality of choice for the diagnosis and evaluation of dystrophin associated cardiomyopathies given its ability to provide early detection of myocardial damage and fibrosis. Studies have found that the majority of patients have LGE in the postero-basal region of the LV in a subepicardial distribution. This pattern is consistent with the pathological findings from myocardial biopsy of dystrophin-deficient cardiac muscle. Cardiac magnetic resonance imaging with LGE and wall motion analysis has been shown to be superior to 2D TTE and tissue Doppler in early assessment of myocardial damage.

The treatment for dystrophin associated cardiomyopathy is similar to that for other pathologies and should include heart failure specific beta blockers, an angiotensin converting enzyme inhibitor and an aldosterone antagonist. Even with empirical heart failure therapy, cardiac transplantation is the only long-term solution.

**Conclusion**

In individuals with certain DMD gene mutations, isolated DCM can occur without skeletal muscle abnormalities. In such situations, CMR with LGE and genetic testing play an important role in the diagnosis. In addition to empirical heart failure therapy, urgent surgical treatment with cardiac transplantation is necessary for intractable cases.

**Lead author biography**

Dr Geoffrey Lester is a Physician Trainee registrar at Royal Prince Alfred Hospital, Sydney and a Research Fellow at the Aortic and Marfan’s Clinic, Sydney. He is an Honorary Associate Clinical Lecturer and Clinical Teaching Fellow at the University of Sydney and is currently undertaking his MPhil/PhD in Ventricular Function in Aortopathies. His interests include Aortopathy and Aortic Disease and Congenital Valvular and Structural Heart Disease.

**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.

**References**

1. Nakamura A. X-linked dilated cardiomyopathy: a cardiospecific phenotype of dystrophinopathy. Pharmaceuticals (Basel) 2015;8:303–320.
2. Engel AE, Ozawa E. Dystrinopathies. Myology, 3rd edn, (eds. Engel, A.G. and Franzini-Armstrong, C.) New York: McGraw-Hill, 2004, pp. 961–1026.
3. Silva MC, Meira ZMA, Gurgel Giannetti J, da Silva MM, Oliveira Campos AF, de Melo Barbosa M, Filho GMS, de Aguiar Ferreira R, Zatz M, Rochitte CE. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. J Am Coll Cardiol 2007;49:1874–1879.
4. Ferlini A, Sewry C, Melas MA, Mattedu A, Muntoni F. X-linked dilated cardiomyopathy and the dystrophin gene. Neuromuscul Disord 1999;9:339–346.
5. Ishikawa Y, Bach JR, Minami R. Cardioprotection for Duchenne’s muscular dystrophy. Am Heart J 1999;137:895–902.
6. Wu RS, Gupta S, Brown RN, Yancy CW, Wald JW, Kaiser P, Kirklin JP, Patel PC, Markham DW, Drazner MH, Garry DJ, Mammen PPA. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. J Heart Lung Transplant 2010;29:432–438.
7. Cahill TJ, Ashrafian H, Watkins H. Genetic cardiomyopathies causing heart failure. Circ Res 2013;113:660–675.
8. Nigro G, Corin Li, Politano L, Bain RJJ. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. Int J Cardiol 1990;26:271.
9. Ashworth ML, Jacobs IB, Crowe CA, Ashworth RC, Super DM, Bahlir RC. Left ventricular dysfunction in Duchenne muscular dystrophy and genotype. Am J Cardiol 2014;114:284–282.
10. Frankel KA, Rosser RJ. The pathology of the heart in progressive muscular dystrophy: epimyocardial fibrosis. *Hum Pathol* 1976;7:375–386.

11. Shirokova N, Niggli E. Cardiac phenotype of Duchenne Muscular Dystrophy: Insights from cellular studies. *J Mol Cell Cardiol* 2013;58:217–224.

12. Stabile CJ, Taylor MD, Mazar W, Cirpe LH, King E, Pratt J, Benson DW, Hor KN. Left ventricular noncompaction in Duchenne muscular dystrophy. *J Cardiovasc Magn Reson* 2013;15:67.

13. Puchalski MD, Williams RV, Askovich B, Sower CT, Hor KH, Su JT, Pack N, Dibella E, Gottliebson WM. Late gadolinium enhancement: precursor to cardiomyopathy in Duchenne muscular dystrophy. *Int J Cardiovasc Imaging* 2009;25:57–63.

14. Dittrich S, Tuerk M, Haaker G, Greim V, Buchholz A, Burkhardt B, Fijak A, Trollmann R, Schmid A, Schroeder R. Cardiomyopathy in Duchenne muscular dystrophy: current value of clinical, electrophysiological and imaging findings in children and teenagers. *Klin Padiatr* 2015;227:225–231.

15. Wong TC, Pehler K, Punset KS, Moguillansky D, Meier CG, Lacomis JM, Kellman P, Cook SC, Schwartzman DS, Simon MA, Mulukutla SR, Schelbert EB. Effectiveness of late gadolinium enhancement to improve outcomes prediction in patients referred for cardiovascular magnetic resonance after echocardiography. *J Cardiovasc Magn Reson* 2013;15:6.