Dilated cardiomyopathy in a patient with newly diagnosed Becker muscular dystrophy: more than meets the eye

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Dear Sir,

A 20-year-old Indian man presented with exercise-induced myalgia. He is the only child of non-consanguineous parents and had no family history of neuromuscular diseases. Growing up, his developmental milestones were noted to be normal. His parents, however, observed that he had difficulties performing prolonged exercise, 'tiring out' more easily than his peers and preferring indoor activities. He had frequent exertional leg cramps requiring analgesics. In addition, he struggled to pass fitness tests in school.

On clinical examination, no muscle fasciculations were observed and sensation was intact. Power was relatively preserved. He had a markedly elevated creatine kinase level at 13,223 U/L (normal range 30–350 U/L). Nerve conduction studies and electromyography were normal. He underwent left vastus lateralis muscle biopsy, which demonstrated rounded fibres with significant fibre size variability and the presence of myopathic grouping. There was no endomysial fibrosis on biopsy. Furthermore, a reduction of dystrophin-N staining raised the possibility of dystrophinopathy. Subsequent genetic tests confirmed a pathogenic in-frame deletion in the *DMD* gene at Exon 10–18. He was diagnosed with Becker muscular dystrophy (BMD).

This patient was subsequently referred to the cardiology clinic to be screened for associated cardiomyopathy. On questioning, he did not report any heart failure symptoms such as worsening effort tolerance, orthopnoea, paroxysmal nocturnal dyspnoea or lower limb swelling. He also did not have a history of unexplained syncope. Cardiovascular examination was unremarkable. He was normotensive and had normal heart rate at rest. Jugular venous pressure was not elevated and heart sounds were dual with no murmurs. Lung fields were clear and there was no evidence of lower limb oedema.

Electrocardiography (ECG) showed sinus rhythm with normal conduction intervals (Fig. 1). However, a subsequent transthoracic echocardiogram incidentally revealed a left ventricular ejection fraction (LVEF) of 30% and dilated left heart chambers. He was diagnosed with dilated cardiomyopathy and stage B heart failure. In view of the structural abnormalities seen on imaging, he was promptly started on neuro-hormonal cardiac therapies with perindopril, an angiotensin-converting enzyme inhibitor (ACE-I).

Cardiac magnetic resonance imaging (CMR) was performed 12 weeks after the initiation of perindopril. CMR demonstrated improvement in LVEF to 44% and normal right ventricular ejection fraction. The previously noted left heart chamber dilatation had also resolved. Upon administration of gadolinium, there was linear sub-epicardial late gadolinium enhancement (LGE) along the basal to apical lateral and inferior walls. Mid-myocardial LGE of the mid-ventricular septum was also noted (Fig. 2).

The patient has had no new symptoms since his diagnosis of dilated cardiomyopathy. Low blood pressure following the initiation of perindopril prevented the up-titration of perindopril or the addition of other heart failure therapies, specifically beta-blockers or eplerenone. After weighing the pros and cons of long-term steroid use in a young patient, a decision was made not to start the patient on corticosteroids due to the relative absence of muscle weakness,. A repeat CMR was planned one year later to assess LVEF and progression of myocardial fibrosis.

Dystrophin is a protein encoded by the *DMD* gene. It is a component of the dystroglycan complex, which is present in skeletal muscle and myocardial cells. This complex provides mechanical support to the plasma membrane during muscular contraction.[1] Complete absence of dystrophin results in Duchenne muscular dystrophy (DMD), a severe neuromuscular disorder, while a partial deficiency in dystrophin manifests as BMD, a milder form of the disease. Collectively, these conditions are termed dystrophinopathies.

BMD is an X-linked inherited disorder that was first described in 1955.[2] BMD mutations occur in-frame, resulting in misfolded dystrophin rather than a total absence of dystrophin, thus its milder muscular phenotype compared to DMD. Over 70% of patients with BMD develop cardiomyopathy, which is the leading cause of death in BMD. Dystrophin-deficient cardiomyopathies tend to present late, with its severity dissociated from the skeletal muscle symptoms. Our patient had cardiomyopathy diagnosed at a young age, immediately after the diagnosis of BMD. This is due to proactive screening for cardiomyopathy using cardiac imaging, despite the patient being asymptomatic and having a normal ECG. In the absence of active cardiac screening, BMD patients are likely to be diagnosed with cardiac involvement only when they present with heart failure symptoms at an older age.

Histologically, there is fibrous or fatty replacement of dysfunctional cardiomyocytes.[3] As seen in our patient, this change is typically distributed in the sub-epicardial layer and initially starts in the postero-basal left ventricular free wall, eventually spreading throughout all the myocardium, leading to dilated cardiomyopathy.[4]

CMR with LGE is the best non-invasive tool for early identification of this fibrotic change. Its advantages over echocardiography are clear, including the ability to detect early fibrosis, accuracy in imaging technique and reproducibility. These are of paramount importance for longitudinal monitoring of cardiomyopathy progression or response to treatment. Serial CMR will allow us to look for extension of myocardial fibrosis, worsening of ventricular functions or progressive dilatation of cardiac chambers, which will confer a poorer prognosis from the cardiomyopathy point of view.

Medical therapy remains the best treatment to halt the progression of fibrosis. ACE-I is the standard of care in the treatment of severe cardiomyopathies and heart failure. The benefits of ACE-I are also seen in dystrophin-deficient cardiomyopathy. In a study by Duboc et al, 28 participants were randomised to ACE-I versus placebo for three years.[5] At ten years, 93% of

the ACE-I group were alive vs. 66% of the placebo group. This study also showed that early initiation of treatment with ACE-I conferred 27% of absolute risk reduction in all-cause mortality.

For beta-blockers, Kajimoto et al studied the use of a combination therapy of ACE-I with carvedilol in a broad range of neuromuscular disorders, including BMD.[6] The dual therapy group had increased left ventricular fractional shortening and decreased left ventricular dimensions when compared to the ACE-I only group. Furthermore, the study found that the earlier the treatment was initiated, the better the outcome. Ogata et al studied DMD patients with asymptomatic vs. symptomatic heart failure.[7] The asymptomatic group who were initiated on treatment had a ten-year survival rate of 72% compared to 0% for those treated after the onset of symptoms. Lastly, eplerenone was also studied in a cohort of 40 DMD patients. The addition of eplerenone to the standard therapy of ACE-I or angiotensin receptor blockers in this cohort of DMD patients with preserved LVEF was associated with attenuation of decline in LVEF at 12 months as compared to placebo.[8]

We have seen how early detection and early initiation of therapy are the key strategies in the management of patients with dystrophin-deficient cardiomyopathies. However, screening should not stop there. In a European cohort of 130 female dystrophinopathy carriers, up to 14% of these subjects were found to have abnormal cardiac findings on echocardiogram.[9] In a Japanese cohort of female dystrophinopathy carriers, dilated cardiomyopathy was diagnosed using echocardiography in 15 out of the 28 subjects studied.[10] Out of these 15 individuals diagnosed with cardiomyopathy, six underwent further CMR evaluation and LGE was detected in five of them. It is, therefore, important to also screen female carriers of the dystrophin gene mutation for cardiomyopathy. CMR is the preferred imaging modality in these patients.[11] In the long run, they will also benefit from close follow-up and initiation of early cardiac therapies.

In summary, this case serves to highlight classical CMR imaging findings in dystrophin-deficient cardiomyopathy, reinforcing the importance of cardiac screening in this patient population and female dystrophinopathy carriers. It is important to initiate early treatment of heart failure therapies even before symptoms appear, as this leads to improved cardiac outcomes.

Yours sincerely,

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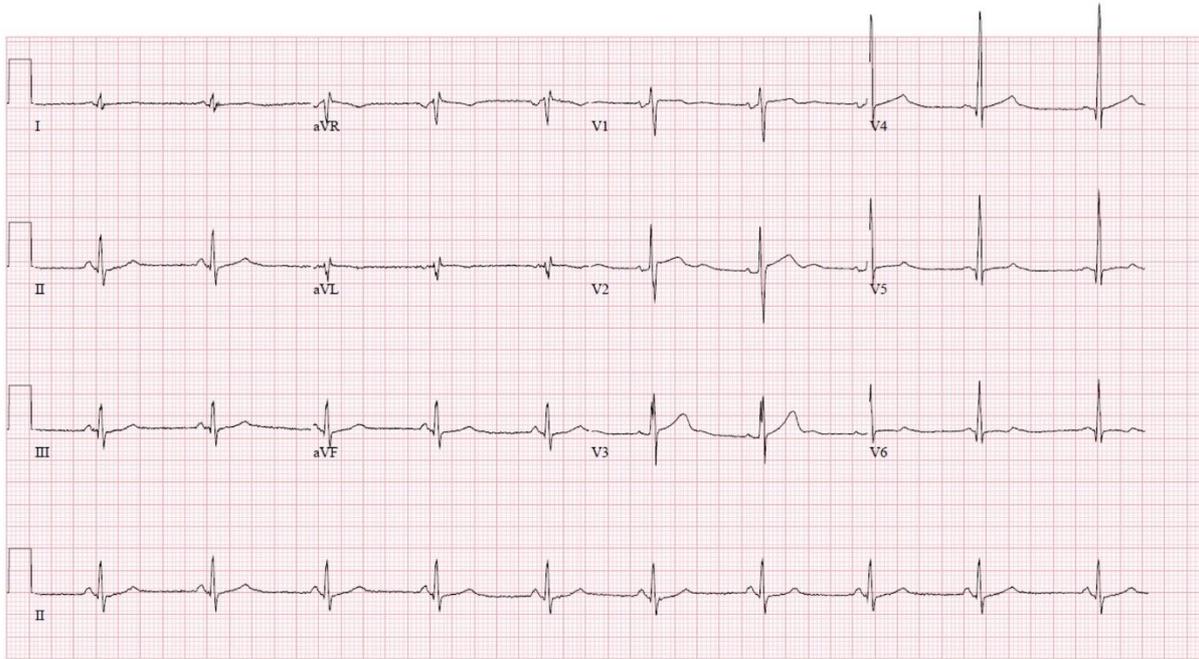
Fig. 1 ECG shows sinus rhythm with normal PR and QRS intervals.

Fig. 2 Cardiac magnetic resonance images. (a) 3-chamber view shows sub-epicardial late gadolinium enhancement (LGE) in the inferolateral wall of the left ventricle (LV) (white arrowheads); (b) 4-chamber view shows sub-epicardial LGE in the anterolateral wall (white arrowheads) and mid-wall LGE in the inferior septum (black arrowheads); (c) Short-axis view shows sub-epicardial LGE of lateral/inferior LV walls (white arrowheads) and mid-wall LGE in the inter-ventricular septum (black arrowheads).