CASE REPORT

Subclinical Cardiomyopathy in Miyoshi Myopathy Detected by Late Gadolinium Enhancement Cardiac Magnetic Resonance Imaging
A Case for Routine Cardiac Screening?

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Summary
Dysferlin is a sarcolemmal protein present in muscle cells; it is important for muscle membrane repair. Mutations in the dysferlin gene (DYSF) located on chromosome 2p13 lead to reduce or absent expression of dysferlin. This has been termed “dysferlinopathy,” which can have different clinical manifestations. The main clinical phenotypes of dysferlinopathies are limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi myopathy (MM). Both phenotypes are characterized by autosomal recessive inheritance, early adulthood onset of muscle weakness, and massively elevated serum creatine kinase levels. However, they are clinically distinct as they show preferential involvement for different muscle groups at disease onset. LGMD2B initially involves proximal limb-girdle muscles, while MM predominantly involves distal lower limb muscles.

MM is a distal dysferlinopathy that was first described in Japan by Miyoshi, et al. in 1967 and subsequently in 1986.1-4 The incidence and prevalence of dysferlinopathies worldwide are unknown. However, it has been reported in other geographical regions including Italy, Spain, India, and Middle Eastern countries.5 Majority of patients with the MM phenotype present in their late teens and early adulthood, with good muscle strength prior to symptom onset (Table I). Initially, selective weakness of muscles in the posterior compartment of the lower limb, specifically the gastrocnemius and soleus muscles, leads to difficulty walking on tiptoes and going down stairs. Disease progression is usually slow, and weakness of anterior compartment muscles of the distal lower extremities eventually occurs. As the disease progresses, proximal leg and arm muscles may be involved to varying extents. Serum CK levels are characteristically elevated in early disease or before symptom onset in some cases.5

In many neuromuscular disorders, cardiac involvement is common and carries prognostic significance.6 However, cardiac involvement is not a common feature of the dysferlinopathies.7,8 Only a few studies have observed abnormalities, including dilated cardiomyopathy (DCM), left ventricular (LV) hypertrophy, repolarization abnormalities, and myocardial fibrosis, in patients with dysferlinopathies.9-14 We present a case of cardiac involvement...
Table 1. Clinical Characteristics of Miyoshi Myopathy

| Features                                                                 |
|--------------------------------------------------------------------------|
| Inheritance pattern                                                      | Autosomal recessive                                           |
| Age of onset                                                             | 15–30 years (mean: 19 years)                                  |
| Major muscle involvement                                                | Posterior compartment muscles of distal extremities: gastrocnemius and soleus muscles |
| Clinical course and prognosis                                            | Slow disease progression:                                     |
|                                                                          | Most patients able to walk in their 30s and 40s                |
|                                                                          | 10%–20% become wheelchair-dependent (within 15 years onset)    |
| Laboratory findings                                                     | Serum creatine kinase levels: 10- to 100-fold increase         |
|                                                                          | Muscle immunohistochemical staining: absent or reduced staining of dysferlin protein |

Information from Fanin, et al.25 and Urtizberea, et al.53

Figure 1. Electrocardiogram (ECG) of patient taken during first presentation in 2014, showing sinus rhythm with normal intracardiac conduction. There was left ventricular hypertrophy (LVH) by voltage criteria, with related T-wave inversions in the lateral precordial leads suggestive of LVH with strain.

in dysferlinopathy in a patient diagnosed with MM.

Case Report

A 35-year-old Chinese lady first presented to our institution with hypertensive crisis, complicated by acute pulmonary edema in December 2014. Her hypertension was subsequently found to be secondary to primary hyperaldosteronism. Following that diagnosis, she was started on targeted antihypertensive therapy with eplerenone and long-acting nifedipine, achieving good blood pressure control thereafter. During that same admission, she was incidentally noted to have persistently elevated serum CK levels (1110-1900 U/L; normal range: 20-300 U/L).

This patient is the only child to non-consanguineous parents, with no personal or family history of neuromuscular or cardiovascular diseases. There was no recent history of falls, strenuous activity, muscle trauma, or infections. Neurological examination revealed mild weakness of her foot dorsiflexors. There was no muscle atrophy, tenderness, or joint contractures. Electrocardiogram (ECG) then showed sinus rhythm and LV hypertrophy (LVH) by voltage criteria. There was no evidence of atroventricular (AV) nodal block, and the QRS complexes were narrow, with no evidence of bundle branch block. There were T-wave inversions in the lateral leads, likely secondary to LVH (Figure 1). Renal function, electrolytes, antinuclear antibody (ANA), and extractable nuclear antigen antibody (anti-ENA) panels were normal. Thyroid-stimulating hormone levels were elevated (5.43 mIU/L; normal: 0.45-4.50 mIU/L), while free thyroxine levels were normal. As the patient had subclinical hypothyroidism, she was started on short-term levothyroxine 50 mcg for one month. Hypothyroid myopathy, as a complication of hypothyroidism, was considered as a differential for elevated serum CK. However, serum CK levels remained elevated on follow-up despite normalization of thyroid function tests, and the patient did not have characteristic proximal myopathy and generalized myalgia.15

Nerve conduction study was normal, while electromyography demonstrated evidence of a mildly irritable distal myopathy in the gastrocnemius and tibialis anterior muscles bilaterally. Subsequent muscle biopsy of her right deltoid muscle showed minimal variability in muscle fiber size, with no evidence of necrotic or regenerating fibers or inflammatory infiltrate. Immunohistochemical staining revealed the absence of dysferlin immunoreexpression in all muscle fibers, but positive staining for other dystrophin-
related proteins (e.g., dystrophin, desmin, alpha-sarcoglycan, beta-sarcoglycan, gamma-sarcoglycan, delta-sarcoglycan, merosin, caveolin-3, emerin, telethonin) (Figure 2). The combined findings of absent dysferlin expression on immunohistochemistry and massively elevated CK levels suggested dysferlinopathy. Furthermore, distal muscle involvement on examination and electromyography raised the clinical suspicion of MM.

Four years later in May 2019, the patient presented with a fall, on a background of progressively worsening distal muscle weakness in a pattern consistent with the MM phenotype. She had difficulty walking on tiptoes and had been falling over more frequently. Neurological examination was significant for atrophy of her bilateral tibialis anterior and gastrocnemius muscles, with worsening foot drop. Medical Research Council Scale for Muscle Strength was 3/5 for foot dorsiflexion and plantar flexion bilaterally. Proximal muscle strength was still relatively preserved. Sensation and proprioception of upper and lower limbs were intact. Significant laboratory findings included elevated CK levels (2254 U/L) and negative testing for myositis-specific and myositis-associated antibodies. A subsequent genetic analysis identified two heterozygous mutations in her DYSF gene. She was heterozygous for two pathogenic variants in the DYSF gene, c.5668-7 G > A (Intronic) and c.1667T > C (p.Leu556Pro). Although parental testing to determine if the genetic mutations were in cis or trans was declined, we felt that these were plausible mutations explaining her clinical and pathological findings.

At this time, the patient was referred for cardiac evaluation. There was no complaint of chest pain or shortness of breath on exertion or presence of any cardiac failure symptoms. The only significant finding on cardiovascular examination was elevation of the jugular venous pulse, which measured 12 cm with the patient lying at a 45-degree incline, suggestive of increased cardiac filling pressures. A repeat ECG revealed that the patient remained in sinus rhythm. Previously noted LVH by voltage criteria was no longer seen, given adequate management of hypertension. There were nonspecific T-wave changes in the lateral precordial leads, but no evidence of conduction delays (Figure 3). Transthoracic echocardiography revealed normal chamber sizes and LV ejection fraction (LVEF) of 60%. There was no evidence of LVH on echocardiography.

Cardiac magnetic resonance (CMR) imaging was performed to further evaluate the myocardium. CMR showed normal biventricular volumes and ejection fractions. There was no myocardial edema seen. However, mid-wall fibrosis was seen in the basal to mid-inferoseptum and basal inferolateral segments of the LV myocardium (Figure 4), which led to the suspicion of an underlying cardiomyopathy possibly related to MM. In view of preserved LVEF, normal ventricular volumes, and lack of symptoms, the patient was not started on any cardiac medications. She has been scheduled for a repeat CMR in 18 months to look for progression of the fibrosis.

**Discussion**

Dysferlinopathies were previously believed to spare the heart. However, increasing evidence suggests that dysferlin deficiency has impact on cardiomyocytes. Dysferlin has been found to be abundantly expressed in cardiac muscle cells and may be involved in cardiomyocyte membrane repair. Han, et al. demonstrated that aged dysferlin-null mice developed DCM, with evidence of cardiac fibrosis and elevated serum troponin levels. Stress exercise in dysferlin-null mice also induced systolic dys-
Figure 3. Repeat ECG performed in 2019. There was resolution of LVH, with LV strain pattern that was less prominent compared to 2014 ECG, attributable to good control of blood pressure. Intracardiac conduction remained normal.

Figure 4. A: Short-axis view on cardiac magnetic resonance (CMR) at the level of the basal myocardium. Mid-wall late gadolinium enhancement (LGE) was seen in the basal inferoseptal and inferior segments of the left ventricular myocardium (white arrowheads). B: Two-chamber view on CMR showing mid-wall LGE at the basal inferior wall (white arrowheads).

function and pathologic chamber dilation alongside myocardial necrosis. Dysferlin deficiency may thus lead to defective cardiomyocyte membrane repair and compromised muscle membrane integrity, especially in the presence of mechanical stress.

Several cases of cardiac involvement in dysferlinopathies have been reported (Table II). In one case, a 57-year-old Japanese woman with LGMD2B was diagnosed with DCM, with ventricular dilation and diffuse hypokinesia on echocardiography, after more than 20 years of disease onset. DCM was similarly observed in two out of a series of seven patients with LGMD2B, manifesting as shortness of breath, LV dilatation, and reduced LVEF. Other studies have reported associated ECG abnormalities, including arrhythmias, intraventricular conduction delay, LVH, and repolarization abnormalities. These ECG changes may represent structural or functional changes in the cardiac conduction system, potentially related to dysferlinopathies. Moreover, histopathological data from two endomyocardial biopsies and one autopsy revealed deficient dysferlin expression in cardiomyocytes, accompanied by myocardial disarray and fibrosis. Collectively, these findings indicate that dysferlin deficiency may lead to cardiac dysfunction.

Identifying cardiac involvement in dysferlinopathies is challenging, as it may be subclinical in initial stages.
Table II. Overview of Studies Observing Cardiac Involvement in Dysferlinopathy

| Year published | Author, et al. | Study type | Population | Cardiac modality | Findings |
|----------------|---------------|------------|------------|------------------|----------|
| 2004           | Kuru, et al.  | Case report | 1 LGMD2B   | Echocardiogram   | 57-year-old Japanese lady with dysferlinopathy (onset at 34 years) associated with DCM |
|                |               |            |            |                  | Echocardiogram: ventricular enlargement, diffuse hypokinesia |
| 2007           | Wenzel, et al. | Observational study | 7 LGMD2B | ECG Echocardiogram Cardiac catheterization Endomyocardial biopsy | 2/7 patients: symptomatic DCM ECG: repolarization abnormalities Echocardiogram: LVEF < 45%; LV dilatation Cardiac catheterization: global LV hypokinesia, coronary artery disease excluded |
|                |               |            |            |                  | Endomyocardial biopsy: absence of sarcotendinous dysferlin expression |
| 2007           | Choi, et al.  | Observational study | 5 MM | ECG Echocardiogram with 2D strain CMR | All patients had preserved LVEF, but subclinical cardiac involvement: ECG: LVH (2/5 patients) Echocardiogram: decreased segmental peak systolic longitudinal strain, in same distribution as LGE (3/5 patients) CMR: LGE showing fibrosis of mid anterior and anterolateral wall; basal to mid anterolateral wall; inferior area and basal anteroseptal wall; septal side of LV (4/5 patients) |
| 2011           | Rosales, et al. | Observational study | 9 LGMD2B 7 LGMD2I | CMR | 15/16 patients: normal LVEF with mean 60% ± 7% (9 patients with LGMD2B; 6 patients with LGMD2I) 7/16 patients: LGE on CMR showing focal epicardial or mid-wall fibrosis (4 patients with LGMD2I, 3 patients with LGMD2B) |
| 2012           | Suzuki, et al. | Case report | 1 LGMD | ECG Echocardiogram Autopsy | 78-year-old lady with LGMD (onset at 22 years) who died of respiratory failure ECG: PSVT, T-wave inversion in aVL and ST elevation in H, III, AVF Echocardiogram: hypertrophic cardiomyopathy Autopsy and cardiac histology: variation in muscle fiber size, disarrayed appearance, fibrosis; deficient sarcotendinous dysferlin expression in cardiac muscle |
| 2016           | Nishikawa, et al. | Retrospective study | 22 LGMD2B 26 MM | ECG Echocardiogram Autopsy | ECG: prolonged QRS duration (19/46 patients) Echocardiogram: normal LVEF with mean 68.0% ± 8.3% (23/23 patients) Autopsy and cardiac histology: endomyocardial fibrosis, scattered adipose infiltration; absent cardiac sarcotendinous dysferlin expression in cardiac muscle (2/48 patients) |
| 2016           | Harris, et al. | Observational study | 193 dysferlinopathy patients | ECG Echocardiogram CMR (if abnormal echocardiogram) | Echocardiogram: impaired LVEF < 55% (7/193 patients; for further evaluation by CMR) Longitudinal data collection for this cohort is ongoing |

CMR indicates cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECG, electrocardiogram; LGE, late gadolinium enhancement; LGMD2B, limb girdle muscular dystrophy type 2B; LGMD2I, limb girdle muscular dystrophy type 2I; LVEF, left ventricular ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; MM, Miyoshi myopathy; and PSVT, paroxysmal supraventricular tachycardia.

and difficult to elucidate. This is even more challenging, given patient limitations in physical activity due to neuromuscular weakness. Furthermore, routine screening methods such as ECG and echocardiography may not reveal early abnormalities. Thus, studies assessing cardiac function using routine methods or clinical assessment alone may underestimate the actual occurrence of cardiac involvement in dysferlinopathies. CMR imaging is a more sensitive method for recognizing early cardiac involvement. It is the gold standard for noninvasively assessing cardiac volumes and mass, LVEF, and myocardial fibrosis, given its high reproducibility and spatial resolution. Most importantly, CMR can detect myocardial fibrosis through late gadolinium enhancement (LGE), which has been shown to precede LV dysfunction and clinically overt cardiac involvement in other muscular dystrophies.

Despite its promising role in cardiac evaluation, CMR imaging is still not commonly employed for cardiac screening in dysferlinopathies. In two CMR studies by Choi, et al. and Rosales, et al., myocardial fibrosis was present in four out of five MM and three out of nine patients with LGMD2B, respectively. Interestingly, these patients had no cardiac symptoms nor abnormalities on ECG or echocardiography. CMR was thus able to identify cardiac involvement before clinically overt disease developed. More recently, an ongoing international multi-
center study identified impaired LVEF in 7 out of 193 patients with dysferlinopathy. These patients will be further evaluated with CMR. As LVEF may be preserved in initial stages, the number of patients with cardiac involvement may be underrepresented in the study. So far, the study obtained CMR in five out of seven of these patients. These showed abnormalities in three patients, specifically segmental cardiomyopathy, hypertrophic cardiomyopathy, and impaired LV function.20

On screening CMR for our patient, mid-wall myocardial fibrosis was detected, consistent with findings from previously reported cases of myocardial involvement in dysferlinopathies.12,13) CMR with LGE can potentially discriminate between ischemic and non-ischemic cardiomyopathies, based on different distribution patterns and locations of LGE. Characteristically, ischemic etiologies cause subendocardial enhancement or fibrosis, while non-ischemic etiologies cause mid-wall myocardial fibrosis.21 In this case, the mid-wall pattern of myocardial fibrosis likely reflects non-ischemic pathology, which is in stark contrast to the subendocardial fibrosis pattern seen in ischemic heart disease. Furthermore, the absence of previous anginal symptoms and normal coronary angiogram during her first admission make ischemic pathology unlikely. Another important differential diagnosis is hypertensive cardiomyopathy, since our patient first presented with hypertensive crisis and pulmonary edema. However, her blood pressure has been well controlled since the index admission 4 years ago. Furthermore, cardiac chamber sizes and LV wall thickness were all normal on echocardiography and CMR. While we cannot completely exclude hypertensive cardiomyopathy as a potential contributor to LGE, these aforementioned factors make the diagnosis of hypertensive cardiomyopathy less likely.

Early recognition of myocardial fibrosis provides the opportunity to identify and risk stratify dysferlinopathy patients at increased risk of adverse cardiac outcomes. Myocardial fibrosis is of prognostic relevance, given its association with re-entrant arrhythmias, ventricular dilatation, and remodeling, which may predispose to heart failure and sudden cardiac death.25 Timely initiation of cardioprotective therapies is therefore important, as it may help prevent cardiac complications.25 There are currently no recommendations or consensus for managing cardiac involvement in dysferlinopathies. However, early treatment has been advocated for cardiomyopathy in other muscular dystrophies, with dystrophin-deficient myopathies being the best studied. In patients with Duchenne (DMD) and Becker muscular dystrophy with preserved LVEF and myocardial fibrosis, ACE inhibitors (ACEIs) slowed the progression of myocardial fibrosis in these patients with early cardiomyopathy.25 In a separate study, epelone none added to background ACEIs or angiotensin II receptor blockers further delayed LVEF decline in DMD patients with myocardial fibrosis.26 Myocardial fibrosis around the region of the AV node can also alert cardiologists to the possibility of conduction system involvement. In the presence of any degree of AV block, a permanent pacemaker can be considered in patients with dysferlinopathy.25 Additionally, the extent of myocardial fibrosis burden, evaluated by LGE on CMR, is a known independent predictor for ventricular arrhythmias. The presence and extent LGE on CMR may therefore help to guide and optimize the timing of implantable cardioverter-defibrillator insertion, which could help prevent life-threatening ventricular arrhythmias.20

In summary, current evidence suggests that cardiomyopathies can be seen in dysferlinopathies.4,14,19) In this case, we identified a non-ischemic pattern of myocardial fibrosis in a patient with MM through LGE-CMR, which we believe was associated with her underlying dysferlinopathy. The limitation, however, is that LGE is not disease-specific. We are ultimately unable to categorically rule out other causes of cardiomyopathy without endocardial biopsy. Larger-scale longitudinal studies and systematic reviews will therefore be needed to further strengthen the association between cardiac involvement and dysferlinopathies, as well as determine its natural history. Follow-up studies should also ascertain the prognostic value of myocardial fibrosis detected by LGE-CMR, along with its optimal management in patients with dysferlinopathies. This case ultimately highlights the importance of cardiac surveillance in patients with dysferlinopathies despite the lack of cardiac symptoms. As CMR is a reliable method for evaluating cardiac function, it should ideally be used for cardiac screening and follow-up. Given its ability to recognize subclinical myocardial fibrosis, systematic CMR screening may help to identify patients with dysferlinopathy who may benefit from early cardioprotective treatment.

Disclosure

Authors’ contributions: Sarah Ming Li Tan contributed in literature review, acquisition of data, data interpretation, and manuscript drafting. Drs. Ching Ching Ong, Kong Bing Tan, Hui-Lin Chin, Prakash R Paliwal, and Kay Wei Png Ng contributed in literature review, acquisition of data, data interpretation, and manuscript revisions. Dr. Weiqin Lin contributed in the conception of paper, literature review, acquisition of data, data interpretation, and manuscript drafting and revisions. This manuscript has been read by and approved for submission by all authors.

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