Original Article

Cardiac MRI in Duchenne and Becker Muscular Dystrophy

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Abstract

Background and Objectives: Cardiovascular magnetic resonance imaging (CMRI) is the noninvasive technique of choice for early detection of cardiac involvement in Duchenne and Becker muscular dystrophy (DMD and BMD, respectively), but is seldom used in routine clinical practice in the Indian context. We sought to determine the prevalence of CMRI abnormalities in patients with DMD and BMD and to compare the CMRI parameters with the phenotypic and genotypic characteristics. **Methods:** A prospective, observational study was conducted on patients genetically diagnosed with DMD and BMD who could complete CMRI between March 2020 and March 2022. Abnormal CMRI was the presence of any late gadolinium enhancement (LGE) that signifies myocardial fibrosis (LGE positivity), regional wall motion abnormality, or reduced left ventricular ejection fraction (LVEF <55%). **Results:** A total of 46 patients were included: 38 patients with DMD and eight with BMD. Cardiac abnormality was seen in 23 (50%) patients. LGE was more common than impaired LVEF in DMD (16, 42.1%), while impaired LVEF was more common in BMD (5, 62.5%). LGE was most frequently found in lateral wall (18/19) followed by inferior (6/19), septal (5/19), anterior (2/19), and apex (1/19). Among the various clinicodemographic parameters, only age ($r = 0.495$, $P = 0.002$) and disease duration ($r = 0.407$, $P = 0.011$) were found to significantly correlate with LGE in patients with DMD. No association was found between the various CMRI parameters and the genotype. **Conclusions:** The current study highlights the differences in myocardial fibrosis and LV dysfunction between DMD and BMD, along with other CMRI parameters. Notably, a genotype–CMRI correlation was not found in the current cohort, which needs to be further explored.

Keywords: Dystrophinopathy, Duchenne muscular dystrophy, Becker muscular dystrophy, cardiomyopathy, cardiac MRI

Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are allelic X-linked recessive disorders manifesting due to out-of-frame and in-frame variations, respectively, among the 79 exons of the dystrophin gene. While DMD and BMD differ in the severity of skeletal muscle involvement, both conditions are unified by the progressive cardiac dysfunction, which can lead to severe dilated cardiomyopathy (DCM). Advances in ventilatory care, use of steroids, and spinal stabilization surgeries have improved survival of patients, and the predominant cause of mortality has shifted from respiratory to cardiac reasons.[1,2] Early detection of cardiac involvement and initiation of angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are recommended to delay development of symptomatic cardiac failure.[3] Over the recent years, cardiac magnetic resonance imaging (CMRI) has proven to be a useful biomarker of cardiac dysfunction in DMD to study cardiac anatomy, functional characteristics, tissue characterization, as well as left ventricle (LV) mechanical properties in DMD patients and has several advantages over echocardiogram (ECHO) and electrocardiogram (ECG).[4–6] Late gadolinium enhancement (LGE) in CMRI also correlates with the extent of myocardial fibrosis; it has been shown to be a prognostic marker in DMD and can be useful marker of disease progression. However, the interrelation between the various CMRI parameters and their association with phenotype–genotype characteristics and treatment effects have been inconsistent across studies pointing to a complex web of association that probably has both genetic and environmental determinants. Besides, studies exploring CMRI in DMD and BMD are limited in the Indian context.[4] In this setting, we explored the CMRI parameters in a cohort of patients with DMD and BMD and attempted to identify the characteristics and predictors of CMRI changes and also to compare between genetically confirmed DMD and BMD.

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Methods

The study was of cross-sectional design and was done after obtaining approval from the Institutional Ethics Committee. Consecutive boys presenting to the neuromuscular clinic with genetically confirmed DMD or BMD irrespective of age were screened after they gave consent. Patients who had contraindication for magnetic resonance imaging (MRI) or who were claustrophobic were excluded. Demographic, clinical, and treatment history was collected and severity was graded based on manual muscle testing and Muscular Dystrophy Functional Rating Scale (MDFRS).

CMRI was performed with a 1.5-T MRI machine (Ingenia CX; Philips Medical Systems, Best, The Netherlands) using a multisequence imaging protocol including dark blood imaging (half-Fourier acquisition single-shot turbo spin echo sequence), bright blood imaging (cine steady-state free precession [SSFP] sequence), contrast-enhanced imaging (phase-sensitive inversion recovery [PSIR] sequence), pre- and post-contrast T1 mapping (modified Look-Locker inversion recovery sequence), and T2 mapping (SSFP). Images were acquired in standard cardiac planes – short-axis and long-axis planes (two-, three-, and four-chambered views) and LV outflow tract views.

Dark blood imaging was used to assess cardiac anatomy. Bright blood imaging was used for functional assessment of heart, including regional wall motion abnormality (RWMA), LV remodeling index (LVRI), LV ejection fraction (LVEF), and LV cardiac output (LVCO). Contrast-enhanced imaging was done 8–10 min after injecting gadolinium-based contrast (Clariscan™, gadoterate meglumine 0.15 mmol/kg body weight) using PSIR sequence, which shows LGE in areas of focal fibrosis.

Cardiac postprocessing was done on either SuiteHEART (NeoSoft, LLC) or IntelliSpace Portal (Philips Medical Systems, Best, The Netherlands). An expert reader segmented epicardial and endocardial contours at these time points, and from these segmentations, the software computes the LV end diastolic volume (LVEDV), LV end systolic volume, LVEF, LV stroke volume, LVCO, and LV mass (LVM).

Cardiac indices derived included 1) LV mass index (LVMI) calculated as LVM divided by body surface area, 2) LVEDV, and 3) LVRI defined as the ratio between LVM and volume. Abnormal CMRI was defined as presence of any LGE that signifies myocardial fibrosis (LGE positivity), RWMA, or reduced LVEF (<55%).

Statistical analysis was done using Statistical Package for the Social Sciences version 26, and results with P value <0.05 were considered statistically significant.

Results

Sixty-five patients were recruited in the study. Nineteen patients could not complete CMRI due to various reasons (poor cooperation and could not complete imaging- 17, lack of consent- 2). Final data was collected from 46 patients, which included 38 patients with DMD and eight patients with BMD. The mean age at evaluation and the duration of symptoms in DMD were 10.79 ± 3.03 and 7.03 ± 3.12 years, respectively, and the values in BMD were 22.0 ± 6.07 and 6.63 ± 2.33 years, respectively. Among patients with DMD, eight were wheelchair-bound at the time of evaluation, while all except one patient were independent for ambulation in the BMD group. Demographic and clinical features are summarized in Table 1.

An abnormal CMRI of LVEF <55% or presence of LGE was detected in 23 (50%) patients: 18 (47.37%) patients in the DMD cohort and five (62.5%) patients in the BMD cohort. In the DMD cohort, impaired LVEF was found in 9/38 (23.7%) patients, while LGE was noted in 16 (42.1%) patients, seven of whom had normal LVEF. However, in the BMD cohort, LGE was noted in three (37.5%) patients, all of whom had impaired LVEF; impaired LVEF in isolation was encountered in two (25%) of the cohort. Lateral wall (18/19) showed LGE more frequently, followed by inferior (6/19), septal (5/19), anterior (2/19), and apex (1/19). Most frequent pattern was both mid-myocardium and subepicardial LGE (8/19), followed by isolated subepicardial (7/19) and isolated mid-myocardium (4/19). None of the patients had subendocardial LGE.

The morphologic indices including LVMI, LVEDV, and LVRI were measured. The median LVMI and LVRI were significantly lower in DMD compared to BMD [Table 2]. RWMA was encountered in two patients each in DMD (5.2%) and BMD (25%). The oldest patient in DMD cohort was 19 years old and that in BMD cohort was 29 years of age. Both had DCM. CMRI of two DMD patients with severe cardiomyopathy is shown in Figures 1 and 2.

The associations of demographic and clinical factors such as age, duration of disease, Medical Research Council (MRC) sum score, and impairment in ambulation with LV morphologic indices LVEF and LGE were examined for both DMD and BMD. The only significant positive correlation was found with LGE for both age (Spearman's rho = 0.495,

Table 1: Demographic and clinical features

	DMD	BMD
Age in years	10.79±3.03	22.00±6.07
Age of disease onset	3.6±1.73	15.38±0.29
Duration of illness, years	7.03±3.12	6.63±2.33
Family history	6/38 (15.8)	2/8 (25)
Lower limb weakness	38/38 (100)	8/8 (100)
Upper limb weakness	34/38 (89.5)	5/8 (62.5)
Facial weakness	24/38 (63.2)	2/8 (25)
Calf hypertrophy	37/38 (97.4)	6/8 (75)
Wheelchair- or bed-bound	8/38 (21.1)	1/8 (12.5)

BMD: Becker muscular dystrophy, DMD: Duchenne muscular dystrophy, SD: standard deviation. All the continuous variables are represented as mean± SD and categorical variables as n (%)

Table 2: CMRI quantitative parameters in patients with DMD and BMD

CMRI parameter	DMD (n=38)		BMD (n=8)		*P* (Mann–Whitney *U* test)
	Mean±SD	Median, Q1–Q3	Mean±SD	Median, Q1–Q3	
LV mass index	33.45±6.6	32.5, 29.75-36.00	38.63±3.16	39, 35.5–41.00	0.009
LV end diastolic volume	73.53±12.27	71.5, 64.00-81.25	75.75±11.17	76, 66.75–83.50	0.540
LV remodeling index	0.46±0.1	0.43, 0.40-0.49	0.55±0.08	0.55, 0.49–0.59	0.002

BMD: Becker muscular dystrophy, CMRI: cardiac magnetic resonance imaging, DMD: Duchenne muscular dystrophy, LV: left ventricle, SD: standard deviation

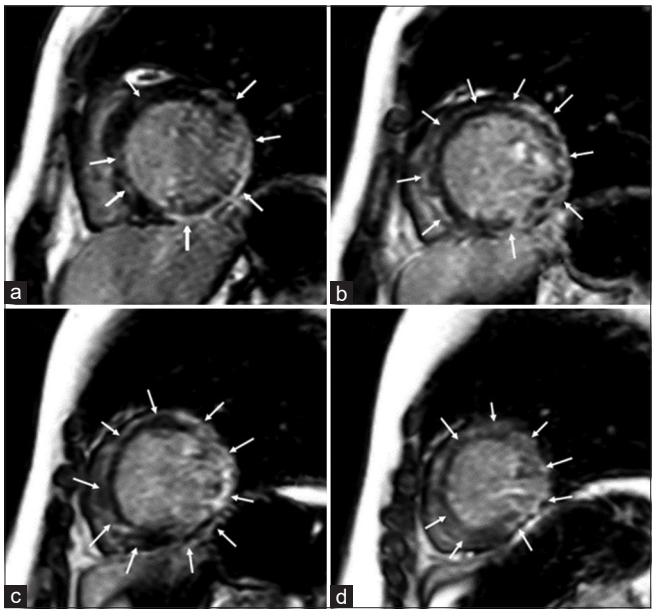

Figure 1: Cardiac MRI (short-axis view) with the phase inversion recovery sequence in short axis view of an 18-year-old with DMD and severe cardiomyopathy (a–d). The images demonstrate extensive late gadolinium enhancement (white arrows) in a nonischemic pattern (subepicardial enhancement in the basal to apical lateral and inferior segments) and mid-wall enhancement in the basal inferoseptal segment and mid to apical septal segments. There is also partial enhancement of both papillary muscles. DMD: Duchenne muscular dystrophy, MRI: magnetic resonance imaging

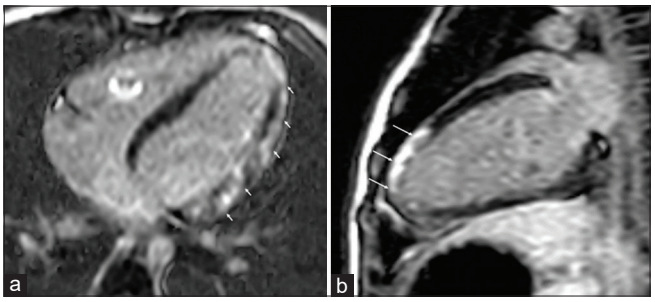

Figure 2: Cardiac MRI with the phase inversion recovery sequence in four-chamber (a) and two-chamber views (b) of an 11-year-old patient with DMD and dilated cardiomyopathy. The images demonstrate late gadolinium enhancement in a nonischemic pattern (subepicardial and mid-wall enhancement, short white arrow) in the basal to apical lateral segments extending into the true apex (a) and subepicardial enhancement in the apical anterior segment (long white arrow) (b). DMD: Duchenne muscular dystrophy, MRI: magnetic resonance imaging

P = 0.002) and disease duration (Spearman's rho = 0.407, P = 0.011), but only in patients with DMD [Figure 3]. Comparison of the severity of muscle weakness by MRC, MDFRS, and use of steroids or ACEIs did not show any significant association.

The genotype profile of our cohort consisted of deletion (40, 86.9%), non-sense mutation (4, 8.7%), duplication (1, 2.2%), and point mutation involving intron (1, 2.2%). No association was found with cardiac involvement or the cardiac morphologic parameters including LGE between the involved dystrophin isoforms [Supplementary Table 1].

The DMD and BMD cohorts included one pair of siblings each, with both having identical genotypes: exons 45–52 deletion and exons 11–43 deletion, respectively. The elder sibling in the DMD cohort had skeletal muscle weakness from 10 years of age and had positive LGE, while the younger sibling of 10 years of age was asymptomatic and had no LGE. Similarly, among the siblings with BMD, the elder sibling who was symptomatic from 26 years of age had impaired LVEF with no LGE and the younger sibling who was symptomatic from 16 years of age had no CMRI changes.

No relation was found between LGE and other CMRI parameters, except with LVEF where a nonlinear negative correlation was found (Spearman's rho = –0.403, P = 0.012) in DMD. A similar nonlinear negative correlation was found between LGE and LVEF in BMD as well (Spearman's rho = –0.671, P = 0.049).

Multivariate analysis showed no correlation between age, duration of symptoms, MDFRS score, steroids, or ACEI with either LVEF or LGE.

Discussion

In this cross-sectional study in a cohort of patients with DMD and BMD, LGE was overwhelmingly more prevalent than LV dysfunction in patients with DMD. However, a higher prevalence of cardiac dysfunction and lesser prevalence of LGE were observed among patients with BMD. Age and duration of symptoms showed a strong correlation with LGE, but only in DMD. Among the cardiac morphologic indices, LVRI and LVMI were lower in DMD compared to BMD. Inferolateral subepicardial region was the most common location for LGE. LGE was the only predictor of LV

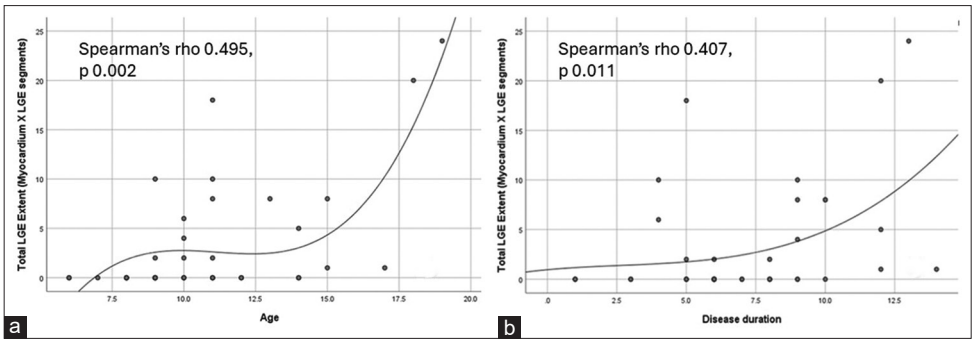

Figure 3: Correlation between age and LGE (a) and duration of disease and LGE (b) in patients with DMD. DMD: Duchenne muscular dystrophy, LGE: late gadolinium enhancement

dysfunction, and age, duration of symptoms, genetic variation, disease severity in terms of muscle weakness, steroids, or ACEI did not independently predict LV dysfunction.

Dystrophin deficiency results in increased mechanical stress-related damage and fibrofatty replacement of the skeletal and cardiac muscles, the latter ultimately resulting in DCM.[7] Unlike idiopathic DCM, the pathology in DMD progresses from the epicardial segment of the posterobasal LV and can be detected by CMRI well before the ECHO changes and clinical manifestations.[8,9] Over the years, several studies have established the role of CMRI LGE as a sensitive marker of both ischemic and nonischemic myocardial fibrosis.[10–12] The pathophysiology behind LGE is the delayed contrast washout due to the decreased capillary density and the increased volume of distribution of the contrast within the fibrosis.[13]

In the current study, LGE was more prevalent than LV dysfunction in DMD, with nearly 25% of the patients who had normal LV function having LGE. However, all the patients with abnormal LVEF had LGE. This is consistent with previous studies substantiating that LGE which denotes myocardial fibrosis is a pre-runner of LV dysfunction in DMD, and that progressive extension of LGE with time correlates strongly with LVEF decline as well as with overall worse prognosis.[14–18] In our cohort as well, among the various clinical factors, it was only age and duration of symptoms that positively correlated with LGE. The evolution of myocardial fibrosis typically starts in the subepicardial location of the inferolateral wall and was also the most frequent location of LGE in the current cohort.[6]

While no relation was noted with LGE and other cardiac morphologic indices, a negative correlation was found between the extent of LGE and LVEF in our cohort both for DMD and BMD. Interestingly, increasing extent of LGE showed a nonlinear correlation with LVEF, whereby an initial decline was followed by brief normalization before further decline [Figure 3]. Without a serial prospective data, the conclusion drawn from this novel observation is limited. However, it may be ventured that the apparent phase of transient normalization of LVEF might coincide with the early phase of compensatory LV remodeling and could be a process unique for dystrophinopathies.[19]

Pertinent differences were noted between the DMD and BMD cohorts with respect to the CMRI findings. First, the prevalence of cardiac dysfunction was comparatively more in the BMD cohort and LVEF was more prevalent than LGE. Notably, the strong correlation of LGE with age and duration of symptoms was not replicated in the BMD cohort. Due to the lesser degree of neuromuscular symptoms, the detection of cardiac involvement in BMD may be delayed until well past the subclinical phase. Moreover, the significantly lesser restriction in physical activities could mean that children with BMD may exert an increased stress and strain on the heart and LV dysfunction may set in even before the myocardial fibrosis evolves to a significant extent. Finally, the role of steroid and early initiation of ACEI, which would be much earlier in children with DMD, could be one of the reasons for the trajectory of cardiomyopathy to differ between DMD and BMD.[15] Other factors such as the distribution and pattern of LGE have been observed to differ between DMD and BMD in previous studies, but this was not observed in the current study.[20]

Multivariate analysis showed neither age, duration of symptoms, genetic variation, disease severity in terms of muscle weakness, steroids, or ACEI correlated with LVEF or LGE. The only factor that independently predicted LV dysfunction was the presence of LGE. It is generally considered that the severity of skeletal muscle involvement does not correlate with cardiac involvement in DMD and BMD.[21–23] Posner et al.[24] found no correlation between muscle strength and cardiac involvement in patients with preserved ambulation, but a correlation was observed between muscle strength and preserved cardiac function in nonambulatory subjects. The disparity or lack of correlation between the skeletal and cardiac muscle involvement in DMD or BMD can be due to the difference in dystrophin isoforms and the dystrophin binding partners expressed at these two sites.[23] But as mentioned previously, the limitations in physical activity or lack thereof, which manifests as differences in the cardiac strain, can be additional contributory factors.

In addition, no association was noted with the genotype profile and CMRI parameters. The genotype–phenotype correlation in terms of cardiac involvement has been inconsistent in

DMD, but assumes tremendous significance, especially with the advent of exon-skipping and antisense oligonucleotide therapies. In a series of 181 patients where cardiac dysfunction was defined by ECHO, mutation between exons 56 and 62 (Dp 116 isoform), was observed to have a survival advantage in terms of cardiac function.[25] Other studies have found contrasting results with mutations involving exons 31–42 associated with cardiac dysfunctions and mutations involving exons 51 or 52 decreasing the risk, while another study found no such association.[26,27] The only study that had employed CMRI for a genotype–phenotype association did not show the association with previously reported exon involvement, but mutations that involved cysteine-rich domain and C-terminal and N-terminal actin-binding domains were protective against LGE and LV dysfunction.[28] These wide variations point to the yet fully unelucidated role of genetic modifiers and nongenetic factors in development of DCM.

There is sufficient evidence in literature confirming CMRI as more sensitive than ECHO for assessing ventricular size, function, and in detecting regional myocardial deformation, and it is the noninvasive imaging modality of choice for cardiac assessment in dystrophinopathies.[29] Treatment initiation with ACEI or ARB is recommended when cardiac dysfunction is noted in MRI, irrespective of age. However, questions have been raised whether an early detection translates to a clinical benefit for the patient. Although treatment that is started on immediate detection of LV dysfunction is beneficial, it has been unable to prevent a long-term decline in LV dysfunction. A Cochrane review examining the effects of intervention to prevent cardiac involvement over a 6-month period revealed questionable benefits with early ACEI and ARB.[30] Nonetheless, ACEI/ARB is well tolerated and is recommended to be initiated as soon as a depressed LVEF, abnormal LV dimensions or LGE is detected, irrespective of age.[29]

Our study was limited by unequal numbers of patients with DMD and BMD, which may undermine generalisability of the comparative data. Advanced CMRI sequences such as T1 mapping and cardiac strain imaging were not obtained in the current series, and comparative data from ECG and ECHO was not included in the current study. Prospective data from the same cohort would provide more information on the nonlinear relation between LGE and LV dysfunction obtained in the current cohort. The lack of relation between the clinical phenotype, steroid and ACEI treatment, and genotypes can be due to several unexplored clinical and nongenetic factors and requires a larger sufficiently powered study to provide definitive answers.

Data availability statement

All basic data including demographic details, lab parameters, electrocardiogram and cardiac magnetic resonance images (CMRIs) will be made available on reasonable request.

Financial support and sponsorship

No funds or grants were obtained for this study. CMRI was done as part of routine evaluation for all patients.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Summary of cohort genotype and cardiac MRI findings

Grouping of cohort of patients with DMD based on dystrophin isoforms[a], n	Normal LV morphologic indices	Abnormal LV morphologic indices	Normal LGE	Abnormal LGE
Dp 427 (exon 1–79), 38	29	9	22	16
Dp260 (exon 30–79), 29	24	5	20	9
Dp140 (exon 45–79), 23	18	5	15	8
Dp116 (exon 56–79), 1	1	-	1	-
Dp71 (exon 63–79), 0	-	-	-	-

[a]Patients with DMD were divided into five groups based on mutations affecting dystrophin isoforms. The Dp427 group included all patients with DMD, whereas the Dp260, Dp140, Dp116, and Dp71 groups included patients with mutations in exons 30–79, 45–79, 56–79, and 63–79, respectively[25].
DMD: Duchenne muscular dystrophy, LGE: late gadolinium enhancement, LV: left ventricle, MRI: magnetic resonance imaging