Cardiac Involvement in Patients With Muscular Dystrophies: Magnetic Resonance Imaging Phenotype and Genotypic Considerations

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Muscular dystrophy (MD) connotes a heterogeneous group of inherited disorders characterized by progressive wasting and weakness of the skeletal muscles. In several forms of MD, cardiac dysfunction occurs, and cardiac disease may even be the predominant manifestation of the underlying genetic myopathy. Cardiologists may be unfamiliar with these diseases owing to their low incidence; also, significant advances in respiratory care have only recently unmasked cardiomyopathy as a significant cause of death in MD.1

Early detection of MD-associated cardiomyopathy is important, because institution of cardioprotective medical therapies may slow adverse cardiac remodeling and attenuate heart failure symptoms in these patients.2–4 Although ECG and echocardiography are typically advocated for screening,5–8 cardiovascular magnetic resonance (CMR) has shown promise in revealing early cardiac involvement when standard cardiac evaluation is unremarkable.9,10

This review will focus on 4 groups of skeletal muscle disease most commonly associated with cardiac complications (the Table): (1) dystrophin-associated diseases such as Duchenne and Becker MD (DMD and BMD, respectively), (2) Emery-Dreifuss MD (EDMD), (3) limb-girdle MD (LGMD), and (4) myotonic dystrophy (DM).

Dystrophin-Associated MDs

Molecular and Genetic Features

DMD and BMD are X-linked disorders affecting the synthesis of dystrophin, a large, sarcolemmal protein that is absent in DMD11 and reduced in amount or abnormal in size in BMD patients.12 Dystrophin provides the connection between a large, multimeric complex of glycoproteins in the muscle cell membrane (termed the dystrophin-glycoprotein complex) and intracellular actin filaments (Figure 1), thereby transmitting forces generated by sarcomere contraction to the extracellular matrix.13,14 Correlations between dystrophin mutations and the onset of cardiomyopathy have been noted15; some mutations result in only cardiomyopathy without skeletal myopathy.16 Other proteins not shown in Figure 1 that are particularly involved in both inside-out and outside-in transmission between the myocyte and the extracellular matrix include vinculin and talin; ongoing investigations are further defining their role in cardiomyopathies, particularly those associated with MDs.

Dystrophin has an important role in stabilizing the cell membrane of both skeletal and cardiac myocytes,17,18 and its absence produces sarcolemmal fragility and muscle cell degeneration. Dystrophin deficiency may also lead to conformational changes in stretch-activated calcium channels, resulting in pathologic leakage of calcium in the muscle cytosol.19 Intracellular calcium accumulation then leads to protease activation, increased reactive oxygen species production, and cell death.20,21 Finally, impaired vasoregulation occurs via marked reduction in membrane-associated neuronal nitric oxide synthase (Figure 1) in both cardiac and skeletal muscle.22 Without dystrophin, neuronal nitric oxide synthase mislocalizes to the cytosol; this greater distance between neuronal nitric oxide synthase and the sarcolemma may impair NO diffusion through the myocyte membrane to the microvasculature. As a consequence, insufficient NO release follows muscle contraction, resulting in muscle ischemia.23 Unopposed vasoconstriction may, therefore, explain the necrosis observed in skeletal and cardiac muscle of dystrophinopathy patients. Microvasculature abnormalities have also been shown to result primarily from the absence of dystrophin or sarcoglycan components of the dystrophin-glycoprotein complex in cardiomyocytes.24,25

X inactivation, the random process by which 1 of the 2 X chromosomes in female cells becomes transcriptionally inactive, may result in cardiomyocytes with an active X chromosome containing the normal dystrophin gene. The X chromosome containing the normal dystrophin gene may become inactivated in cardiac muscle to a greater degree than in skeletal muscle, causing female carriers to develop dystrophinopathic cardiomyopathy. The exact prevalence and severity of such in the carrier population are uncertain.26–29

Cardiac Disease and Imaging Phenotype

Almost all DMD patients who survive to the third decade of life display cardiomyopathy.30 Recognition may be delayed...
by relative physical inactivity obscuring symptomatology. This most common and severe form of childhood MDs is associated with an increased R-to-S ratio in the right precordial ECG leads, deep Q waves in the lateral leads, conduction abnormalities, and arrhythmias (mainly supraventricular but also ventricular).

BMD patients, whose skeletal myopathy occurs later and progresses more slowly, experience worse cardiomyopathy
than do DMD patients: up to 70% have left ventricular (LV)
dysfunction on echocardiography. Perhaps because of less
skeletal muscle weakness, these patients can perform more
strenuous exercise with dystrophin-deficient myocardial
muscle fibers and have earlier manifestations of myocardial
disease.31

Most CMR data in MDs currently exist for patients with
DMD and BMD. The pathology of cardiomyopathy in
patients with dystrophinopathy classically produces sub-
epicardial fibrosis of the inferolateral wall,32 remarkably
similar to the pattern observed in some patients with viral
myocarditis (Figures 2 and 3; movie files 1 and 2 in the
online-only Data Supplement). Myocardial damage in
DMD/BMD has been postulated to result from mechanical
stress imposed on a metabolically and structurally abnor-
mal myocardium, although it remains unclear how a
genetic abnormality presumably affecting the heart in a
diffuse manner may result in a segmental distribution.

Figure 1. Proteins implicated in the MDs. Dystrophin is located inside the cell and is bound to actin at its N-terminus and to a
large oligomeric complex of membrane glycoproteins at its C-terminus. This complex, referred to as the dystrophin-glycoprotein
complex, consists of dystrophin, sarcoglycans (α, β, γ, and δ subunits), α- and β-dystroglycan, sarcospan, and syntrophins.
Mutations in the dystrophin gene lead to BMD and DMD. Mutations in the sarcoglycan subunits cause LGMD. LGMD2I is a
distinct form of LGMD caused by a mutation in the FKRP gene, encoding a Golgi apparatus protein. FKRP is involved in the glycosyl-
ation of α-dystroglycan, necessary for its binding to laminin-α2, and the extracellular matrix. Mutations in the genes encoding
emerin and lamin A/C cause a spectrum of “nuclear envelopathies,” X-linked and AD EDMD belong to this group of diseases and
are both characterized by skeletal muscle wasting, cardiac conduction defects, and cardiomyopathy. Distinct LMNA gene muta-
tions have also been associated with AD LGMD (LGMD1B) and with isolated cardio-
myopathy and conduction-system disease (lamin A/C cardiomyopathy). nNOS indicates neuronal nitric oxide synthase.

Figure 2. CMR findings in DMD in patients with different degrees of cardiac involvement. End-diastolic (A) and end-systolic (B) frames
from a 3-chamber, long-axis cine acquisition (supplemental movie 1) show preserved LV systolic function in this 28-year-old man with
DMD. LGE images (C, 3-chamber view; D, midventricular short-axis view) in the same patient show that despite preserved global LV
systolic function, myocardial injury is evident as subepicardial fibrosis of the inferolateral wall (arrowheads). E, LGE in a 14-year-old boy
with DMD shows more advanced cardiomyopathy with profound LV dilatation and systolic dysfunction (supplemental movie 2) and
more extensive subepicardial scarring as well as septal fibrosis (arrowheads). Whether the inferolateral wall is more vulnerable owing to
regional molecular changes caused by the mutation or whether this regional susceptibility results from exposure
to higher mechanical stress remains to be elucidated.31 Of
note, enterovirus infection has been shown to produce
myocardial damage via cleavage of dystrophin33; this
mechanism may help to explain the similarity in the late
gadolinium enhancement (LGE) pattern between myocar-
ditis and dystrophin-associated cardiomyopathy.

The rationale to perform CMR in BMD/DMD patients in
addition to the current standard of care (monitoring by
echocardiography and ECG) is based on 2 sets of observa-
tions. First, studies have shown that early initiation of
standard heart failure therapy can delay the onset and pro-
gression of LV systolic dysfunction and potentially even lead
to reverse remodeling in patients with X-linked dystrophi-
opathy2–6. Second, it has been shown that myocardial
fibrosis detected by LGE imaging may be observed even
when findings by echocardiography are still normal\textsuperscript{9,10} (Figure 2). CMR can therefore serve as a more sensitive means to detect early cardiac involvement and help clinicians decide when cardioprotective treatment should be instituted. In addition to LGE, CMR also provides accurate and reproducible quantification of LV volumes, making this modality well suited for monitoring response to both standard therapy and novel treatment strategies.

Cardiac screening has been recommended for female DMD/BMD mutation carriers, particularly beginning after the teenage years, as these individuals are known to be at risk for developing cardiomyopathy.\textsuperscript{28} Interestingly, CMR has revealed a pattern of myocardial fibrosis in mutation carriers similar to that seen in DMD patients (Figure 4).\textsuperscript{34} Because myocardial damage in carriers has been observed even in the absence of clinically apparent muscular weakness, cardiac screening should be considered in female relatives of DMD/BMD patients.

**Emery-Dreifuss MDs**

**Clinical and Genetic Features**

The nuclear envelope is composed of a double lipid bilayer that separates the contents of the nucleus from the cytoplasm. Within the inner nuclear membrane are a variety of integral proteins. EDMD is a form of MD caused by mutations in these nuclear membrane proteins. One of these proteins, emerin (Figure 1), is almost completely absent in the X-linked form of EDMD owing to a mutation in the \textit{EMD} gene.\textsuperscript{35} The exact function of emerin is unclear; it binds to a variety of other nuclear factors involved in gene regulation, mRNA splicing, ordering of chromatin structure, and nuclear assembly.\textsuperscript{36} EDMD can also occur as an autosomal dominant (AD) or recessive disorder resulting from mutations in the \textit{LMNA} gene that encodes lamins A and C.\textsuperscript{37} Lamins A and C are nuclear intermediate-filament proteins that closely interact with emerin and other nuclear membrane proteins, thereby forming a proteinaceous meshwork (the nuclear lamina) that...
underlies the inner nuclear membrane (Figure 1). This meshwork has an important role in maintaining the architecture and mechanical strength of the nucleus; it also serves as a scaffold for various other nuclear factors involved in DNA replication, chromatin organization, and transcription.\textsuperscript{38–41} Deficiency in either emerin or lamin A/C typically results in the triad of contractures, muscle weakening, and cardiac conduction defects by mechanisms that remain elusive.

Cardiac involvement in EDMD patients is common and usually becomes evident in the third decade as muscle weakness progresses,\textsuperscript{4} although cardiac manifestations have also been reported in young adults without muscle weakness. Because cardiac dysfunction portends a high risk of sudden death,\textsuperscript{42} careful follow-up of these patients is mandatory. In EDMD, the normal myocardium is gradually replaced by fibrous and adipose tissue, a process that usually starts in the atria (leading to atrial arrhythmias), often involves the atrioventricular node (leading to conduction abnormalities sometimes requiring pacemaker implantation), and eventually affects the ventricles (causing progressive dilatation and systolic failure).\textsuperscript{43,44} Because sudden death may be the presenting symptom in this disease, cardiac screening of relatives (including female carriers with X-linked EDMD) has been recommended.\textsuperscript{7,44}

**CMR Imaging Phenotype**

In EDMD, CMR data are limited owing to the rarity of the disease but also because of the frequent need for pacemaker implantation in this population (particularly in the more advanced stages of the disease). A study by Smith et al\textsuperscript{45} in 8 patients with the AD subtype of EDMD (EDMD2; LMNA gene mutation at 1q21) showed that early-stage disease does not display apparent fibrosis, despite the presence of more subtle myocardial abnormalities, including a decrease in systolic circumferential strain in the infero-septal segment. This suggests a different pathogenesis of cardiac involvement in EDMD compared with DMD/BMD, wherein fibrosis typically precedes systolic dysfunction.

**Limb-Girdle MDs**

**Clinical and Genetic Features**

LGMD refers to a group of disorders with great clinical and genetic heterogeneity, all characterized by weakness affecting the proximal musculature. AD and autosomal recessive inheritance patterns have been identified. The more common autosomal recessive subtypes usually have an earlier age of onset and show more rapid disease progression compared with AD variants. The subtypes mostly associated with cardiac involvement (manifested as conduction disorders and/or myocardial disease) are those associated with a defect in the genes coding for the α- (LGMD2D), β- (LGMD2E), γ- (LGMD2C), or δ- (LGMD2F) subunits of the dystrophin-associated sarcoglycan complex in heart and skeletal muscle (Figure 1).\textsuperscript{46} Cardiomyopathy is also very common in LGMD2I, caused by a mutation in fukutin-related protein (FKRP). FKRP is an enzyme involved in the glycosylation of α-dystroglycan, a peripheral membrane component of the dystrophin-associated glycoprotein complex. Posttranslational glycosylation by FRKP allows α-dystroglycan to bind with the extracellular matrix, making it an important component in the link among cytoskeleton, sarcosomal dystrophin-associated glycoprotein complex, and extracellular matrix.

The AD subtype LGMD1B is also caused by a defect in the LMNA gene coding for lamin A/C, resulting in a phenotype similar to AD EDMD but with a different distribution of muscle involvement. The pelvic girdle weakness in LGMD1B is slowly progressive, sparing the lower muscles. In addition, contractures and cardiac disease manifestations (atrioventricular block, sudden death, atrial paralysis, atrial fibrillation/flutter, and dilated cardiomyopathy) tend to occur later compared with AD EDMD.\textsuperscript{47,48}

Different mutations involving the LMNA gene have been described, resulting in a clinically heterogeneous group of disorders (laminopathies) spanning MD, progeria, familial partial lipodystrophy, and Charcot-Marie-Tooth disease. The MDs associated with LMNA gene mutations that cause cardiac disease include the autosomal variants of EDMD, LGMD1B, and a third disorder commonly referred to as dilated cardiomyopathy with conduction-system disease. The last, though initially linked to chromosome 1p1-1q1,\textsuperscript{49} was later associated with mutations in the lamin A/C gene (1p1-q21 locus).\textsuperscript{50} Patients with this defect develop sinus node dysfunction, atrioventricular node dysfunction, ventricular arrhythmias, and adult-onset cardiomyopathy, with little clinical evidence of skeletal myopathy. The inheritance pattern is AD with high penetrance, and patients have a high risk of sudden death.\textsuperscript{50}

**Cardiac Imaging Phenotype**

In lamin A/C cardiomyopathy, we have demonstrated midmyocardial scarring of the basal interventricular septum by LGE that occurs well before the onset of ventricular dilatation and systolic dysfunction (Figure 4) and that may herald conduction-system disease.\textsuperscript{51} This midwall fibrosis is similar in distribution to that observed at autopsy and, in our experience, is often associated with diastolic dysfunction. Further studies are needed to define the prognostic significance of midwall fibrosis in this population, as it may represent a substrate for the potentially fatal ventricular arrhythmias seen in these patients as reported in other cardiomyopathies.\textsuperscript{52–54} Whereas skeletal muscle disease may not be readily apparent clinically, we have detected clear alterations involving the medial head of the gastrocnemius muscles by magnetic resonance imaging (Figure 5), similar to that described in patients with EDMD2.\textsuperscript{55} This suggests the presence of a continuum between phenotypes with predomi- nant cardiac involvement and phenotypes with cardiac and skeletal muscle compromise.\textsuperscript{56}

Gaul et al\textsuperscript{57} recently described the CMR findings in 9 patients with LGMD2I (due to a mutation in the FKRP gene). They found CMR to be more sensitive than conventional diagnostic investigations (ECG and echocardiography) for detecting cardiac involvement, which was manifest as a decrease in ejection fraction and/or an increase in LV volumes and mass. Unfortunately, no results from late gadolinium-enhancement imaging were reported in that study. Our own experience with CMR in patients with LGMD2I suggests that an early stage, when LV size and function are still normal, midmyocardial scarring may be
observed. As cardiomyopathy advances, extensive myocardial fibrosis is apparent (Figure 6).

A similar pattern of fibrosis was recently reported by Yilmaz et al58 in a patient with LGMD2C. Taken together, these findings suggest that different abnormalities within the dystrophin-sarcoglycan-dystroglycan complex may all lead to cardiomyocyte instability and damage, eventually resulting in a characteristic (but nonspecific) pattern of fibrosis.

**Myotonic Dystrophy**

**Clinical and Genetic Features**

Myotonic dystrophy (DM) is an AD MD that produces progressive skeletal muscle wasting and cardiac conduction abnormalities; multisystem manifestations include cataracts, testicular failure, hypogammaglobulinemia, and insulin resistance. As shown in the Table, 2 types of DM have been identified. DM1 is the most common form and is associated with abnormal expansion of a CTG-trinucleotide repeat sequence in the \( \text{DMPK} \) gene that codes for MD protein kinase, a protein mainly expressed in smooth, cardiac, and skeletal muscle cells. Disease severity and age of onset in DM1 are correlated with CTG expansion length, and the number of repeats can increase from 1 generation to the next (anticipation). DM2, on the other hand, is associated with an expanded CCTG-tetranucleotide repeat in a totally unrelated gene, coding for zinc finger protein. In both cases, the gene...
including the abnormal repeat sequences is transcribed into RNA but not translated. The mutant RNA accumulates in the nucleus and disturbs the function of RNA-binding proteins that normally participate in splicing of premessenger RNA into mature mRNA. This eventually results in abnormal function of different genes, including those coding for the muscle-specific chloride channel CIC-1 and insulin receptor, at least partially explaining the features of myotonia and insulin resistance in patients with DM.

Atrioventricular and intraventricular conduction defects are common in both DM1 and DM2. Infranodal block is likely an important cause of sudden death in these patients. As in many other types of MD, cardiac arrhythmias may occur early in the disease course, that is, in the absence of severe neuromuscular impairment. Structural heart disease is also frequently observed in DM, with LV dilatation or hypertrophy observed in at least partially explaining the features of myotonia and insulin resistance in patients with DM.

Beyond LGE

Cardiac Imaging Phenotype

Patients with DM may present with cardiomyopathy, which usually is more benign in DM2 than in DM1. CMR may help define the LV abnormalities of the disease: dilatation, systolic dysfunction, hypertrophy, and occasionally, noncompaction. Typical LGE patterns have not been reported in DM. In our experience, mild midwall fibrosis involving the septum is occasionally present; the clinical significance of this finding in DM remains uncertain.

Myocardial Strain Analysis

The assumption that cardiac dysfunction can be prevented (or at least attenuated) in patients with MD has led to the belief that therapy should be initiated at an early stage of the disease, rather than delayed until ventricular dilatation or systolic dysfunction becomes apparent. CMR has been proposed as a sensitive screening tool for that purpose by its ability to show myocardial fibrosis, even when the left ventricle is otherwise structurally normal. Another means of revealing occult cardiac dysfunction in patients with MD may be provided by strain analysis. Ashford et al. used CMR tagging to show that boys with DMD exhibit abnormal global and segmental circumferential strain compared with age- and sex-matched controls, despite similar LV volumes and ejection fractions. Similar findings were recently reported by Hor et al., who showed that abnormalities in myocardial strain preceded both the age-dependent decline in ejection fraction and the appearance of myocardial fibrosis in DMD patients. This group recently showed that strain analysis better captures the serial decline in LV function compared with ejection fraction. The sensitivity of strain imaging analysis by CMR could potentially be used not only to reveal occult cardiac dysfunction but also to assess the efficacy of existing or novel therapeutic agents.

Some questions remain, however, regarding these tools, particularly in terms of their accuracy for measuring strain on a segmental (rather than global) level, but also with respect to the reproducibility of strain measurements among centers. Prospective and multicenter studies that randomize patients to therapeutic decision making with or without strain imaging analysis are therefore critically needed before these new techniques can become adopted into the clinical management of patients with MD.

Fat Versus Water Imaging

Histologic studies of autopsy hearts from DMD patients suggest a component of fat infiltration, described as “predominantly epicardial” in a small case series. CMR may distinguish fat by cine or LGE imaging techniques that take advantage of the consistent difference in the resonance frequency of water versus fat protons. Studying 3 DMD dogs with these techniques, Kellman et al. demonstrated extensive epicardial hyperenhancement on LGE imaging that was, at least in part, attributable to fat. Our experience in 1 patient with early myocardial disease by the same technique suggests that LGE in patients with dystrophin-associated cardiomyopathy may also demonstrate a component of fatty infiltration (Figure 7; movie file 3 in the online-only Data Supplement). T2-weighted CMR, which depicts myocardial water distribution, may provide additional insights into the myocardial disease of DMD.

Suggested CMR Protocol and Clinical Implications of Findings

Suggested CMR Protocol

When designing a CMR examination for the patient with MD, the key clinical questions should be addressed: What is the degree of LV dysfunction? What evidence is there for myocardial disease? What pattern of disease is present? What is the likelihood of functional recovery? Acquisitions should
include cine imaging in all standard long-axis and contiguous short-axis planes; real-time cine techniques may be necessary in patients who have difficulty breathholding. Fat-suppressed or fat-only cine imaging, when available, may help delineate the extent of myocardial fat infiltration. Finally, LGE acquisition forms the cornerstone of any CMR protocol in patients with cardiomyopathy, and the same is true in evaluating the MD patient. Although the optimal contrast dose and acquisition timing have not been specifically interrogated in MD cardiomyopathy LGE imaging, our experience suggests that values similar to those used for other nonischemic cardiomyopathies (save amyloidosis) perform well. If fat and water can be distinctly imaged with specialized LGE sequences, these may shed further insight into the extent of fibrosis versus fatty infiltration of the myocardium. Although the absence of hyperenhancement has established value in predicting response to, for instance, medical and resynchronization therapies in other cardiomyopathy populations, the predictive value in MD-associated myocardial disease remains to be established. Given the evidence that subclinical abnormalities in regional strain may precede overt contractile dysfunction, strain analysis may be included at centers where robust postprocessing affords reproducible results.

Clinical Implications of Findings
In the adult guidelines as “impaired left ventricular (LV) function, hypertrophy, or geometric chamber distortion.”73 Pediatric guidelines also advocate angiotensin converting enzyme inhibitor therapy for subclinical LV dysfunction74; notably, neither document addresses the management of myocardial fibrosis that may be present in the absence of regional strain. Our approach is to initiate angiotensin converting enzyme inhibitor and occasionally aldosterone antagonist therapy, given the proven antifibrotic effect of both in other cardiomyopathy populations,75 if CMR demonstrates myocardial fibrosis in the MD patient and particularly in the lamin A/C mutation-positive patient. Whereas 1 prospective, randomized trial in children with DMD supports a possible long-term benefit with angiotensin converting enzyme inhibitors even when the initial LV ejection fraction by echocardiography is normal,76 it is unknown whether any of these patients had subclinical fibrosis in the absence of CMR data. A strategy of fibrosis-guided initiation of cardioprotective drug therapy requires prospective, randomized trial data before it can be widely advocated.

Electrophysiologic testing should be considered in MD-associated cardiomyopathies known to affect the conduction system, such as DM and lamin A/C. Timing of such may be informed by symptoms suspicious for conduction-system disease or conduction abnormalities by ECG.77 We have observed longer PR intervals in lamin A/C patients with septal fibrosis by CMR relative to those of mutation-positive patients without evident fibrosis51; longitudinal studies are suggested to test the predictive value of hyperenhancement for pacemaker requirement in appropriate DM and lamin A/C patients.

Cardiac Disease in MD: Genotype Versus Phenotype
One of the major problems for clinicians dealing with the cardiovascular complications of MD is that clear correlations between genotype and phenotype have been difficult to achieve. It remains unclear why distinct mutations may result in a clinically indistinguishable phenotype, whereas strikingly different phenotypes may result in carriers of identical gene mutations or even among affected siblings. In this respect, MD-associated cardiomyopathies are no different from other heritable cardiomyopathies (hypertrophic cardiomyopathy, for instance). Although there is little doubt that genotype plays a central role in initiating the cardiomyopathic process, the ultimate cardiovascular phenotype is likely also determined by other multiple interacting factors, including genetic background effects, biomechanical stress pathways (with loss of functional myocardium creating additional stress on the remaining viable heart muscle), and modifying effects of calcium cycling and signaling.78,79

A better understanding of clinical variability in MD-associated myocardial disease will therefore require identification of modifying genes and improved knowledge of gene-protein function and protein interactions. Importantly, it will also benefit from continued advances in cardiac phenotyping; lack of sensitivity in the armamentarium of diagnostic tests has previously impaired detection of early cardiac involvement in many of these patients. The greater sensitivity and reproducibility of CMR to demonstrate early abnormalities or subtle changes in serial assessment offer the promise of better defining the natural history and offer significant value in developing novel therapeutic approaches for these disorders. It is hoped that this review’s demonstration of the limitations of the state of the art in imaging phenotype prompts synergistic efforts among geneticists, molecular biologists, and CMR specialists to eventually generate new insights into the pathogenesis and expression of cardiac disease in MD, which is critically needed to help reduce the burden of heart disease in this patient population.

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