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Progression of cardiomyopathy in patients with muscular dystrophy - a CMR-based extensive follow-up study

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Background: Becker (BMD) and Duchenne (DMD) muscular dystrophies (MD) are X-linked progressive neuromuscular disorders. Cardiac involvement with a non-ischemic, myocarditis-like pattern of left ventricular (LV) myocardial fibrosis leading to dilated cardiomyopathy is a major cause of morbidity and mortality. Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) is increasingly used for (initial) diagnosis as well as for subsequent surveillance of cardiac disease in MD patients. However, CMR-based follow-up data are still limited in MD patients.
Methods: Between 2007 and 2016, n=112 DMD/BMD males underwent comprehensive CMR studies including (amongst others) cine- and LGE-imaging. In n=83 of these patients (31±14 years; 22% DMD and 78% BMD) at least one follow-up (FU) CMR study was performed.
Results: CMR parameters at baseline were as follow: LV-EDVi = 81±25 ml/m^2, LV-EF = 55±11%, LV-mass = 58±16 g/m^2, and n=54 (65%) MD patients were LGE-positive. After a median FU period of 6 years (range 1 to 10 years), there was an increase in LV-EDV to 87±25 ml/m^2 (p=0.004 vs. baseline), a decrease in LV-EF to 52±11% (p<0.001 vs. baseline) and in LV-mass to 55±14 g/m^2 (p=0.024 vs. baseline). The proportion of MD patients with an impaired LV function (LV-EF <55%) increased from 45 to 49% (p=NS) and those with a LV-EF ≤35% from 6 to 8% (p=NS). At FU, the prevalence of LGE-positive MD patients significantly increased to 78% (p=0.08 vs. baseline). In the n=54 LGE-positive MD patients at baseline, median LGE extent (%LV-mass) increased from 9% (1 to 44%) to 11% (1 to 40%) (p<0.001) and the number of LGE-positive segments increased from 4 (1 to 13) to 7 (1 to 16) (p<0.001). The prevalence of a transmural pattern of LGE increased from 28% to 46% in these patients (p=0.023). Those n=11 initially LGE-negative MD that developed LGE at follow-up showed a median LGE extent of 2% (0.5 to 15) and 3 (1 to 9) segments, whereas none of them presented a transmural LGE pattern.
Conclusion: MD patients suffer from progressive cardiomyopathy that can be non-invasively assessed by CMR and that is characterized by a progressive increase in LGE prevalence and extent as well as a concurrent decline in LV-EF and LV-mass. This is the first follow-up study using CMR that examined the cardiac disease course in MD patients for up to 10 years.

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Clinical characteristics and natural history of dilated cardiomyopathy due to BAG3 mutations

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Background: The BAG3 (BLC2-associated athanogene 3) gene codifies for an anti-apoptotic protein that localizes on the sarcomere Z-disc. BAG3 mutations have been related with dilated cardiomyopathy (DCM), but only a small number of cases have been reported.
Objectives: This study sought to describe the phenotype and natural history characteristics in a large multicentric cohort of DCM caused by BAG3 mutations.
Methods: Clinical, electrocardiographic and echocardiographic data from 133 BAG3 mutation carriers (60.2% males, 36.2±15.8 years) followed at 21 European centers were included. Localization of BAG3 in cardiac tissue was analyzed in patients with truncating BAG3 mutations using immunohistochemistry.
Results: DCM penetrance among BAG3 mutation carriers at first evaluation was 54.8%. After a median follow-up of 33 months (IQR: 6–91.5), 73.7% of patients exhibited DCM with 46.8% of subjects who initially did not show DCM. Age at disease onset was earlier in men than in women (34.7±14.7 vs 43.0±14.02; p=0.01). The incidence of the composite endpoint of death, left ventricular assist device (LVAD), heart transplantation (HTx), aborted sudden cardiac death (SCD) and appropriate ICD shock was 4.2% per year in the entire cohort and 7.7% per year among individuals with overt DCM at first evaluation. Age at DCM onset, left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and non-sustained ventricular tachycardia (NSVT) were related with the composite endpoint in BAG3 mutation carriers (Figure 1). Only 1 patient (0.8%) exhibited muscular involment. Myocardial tissue from BAG3 mutation carriers with overt DCM showed myofibrillar disarray and relocation of protein BAG3 outside sarcomeric Z discs.

	No serious clinical events during follow-up (n=92)	Serious clinical events during follow-up (n=24)	p
Male sex (%)	73.2	26.8	0.13
Female sex (%)	85.1	14.9	
Missense mutation (%)	17.4	23.1	0.57
No missense mutation*(%)	82.6	76.9	
Age at first evaluation	40.1 ± 15.0	34.6 ± 15.7	0.13
QRS width (ms) on 1st ECG	93.9 ± 17.6	96.6 ± 18.5	0.59
Negative T waves on 1st ECG (%)	14.3	33.3	0.054
LVEDD (mm) on 1st echo	56.8 ± 9.1	65.5 ± 10.9	<0.001
LVEF (%) on 1st echo	48.3 ± 14.0	27.9 ± 14.5	<0.001
TAPSE (mm) on 1st echo	20.8 ± 4.3	17.5 ± 2.7	0.14
NSVT on Holter monitor (%)	23.3	62.5	0.03
CK (UI/L)	102.1 ± 59.0	117.5 ± 119.7	0.48

CK: Creatin kinase, LVEDD: Left ventricular end diastolic diameter, LVEF: Left ventricular ejection fraction.
*: Non-sense, insertion-deletion and splice mutations
BAG3 mutation carriers: Event predictors

Conclusions: DCM caused by mutations in BAG3 is characterized by an earlier onset in males, a high but incomplete penetrance at 40 years of age and a poor prognosis. Its phenotype is cardiac specific, with a predominance of heart failure complications over arrhythmias. A younger age of DCM onset, increased LVEDD, reduced LVEF and the presence of NSVT are related with an adverse prognosis during follow-up in patients with this DCM subtype.

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Innovative approach for risk stratification of LMNA-related cardiomyopathy: results from an integrated cardiological and neurological 10-year follow-up multicentre study

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Background: Mutations in the LMNA gene have been associated with neuromuscular (N) and cardiac (C) manifestations, with possible overlapping phenotypes. However, nowadays risk stratification of sudden death and heart failure (HF) in LMNA-related cardiomyopathy is based on cardiological predictors only.
Purpose: We present results from a multicentre registry of LMNA mutation carriers undergone a complete integrated C and N evaluation, with the longest follow-up published so far.
Methods: 164 LMNA mutation carriers (median age 38 y; 51.2% females) were enrolled from 13 referral centers. All of them underwent a combined C and N assessment at the time of enrollment and 2/y for 10 y median FU, including ECG, Holter monitoring, and imaging data. Further detailed clinical information were collected retrospectively. The purpose of the study was to describe natural history of the disease and to stratify cardiac risk based on an innovative multispecialistic approach.
Results: Disease onset was more commonly N (53% of cases, median age 25y), preceding C phenotype by 11y. However, by the end of FU, 90% of the population had signs of electrical and -later- structural heart disease. Overall, 10 patients (6.1%) died, 14 (8.5%) underwent heart transplantation (HTx), and 32 (19.5%) experienced malignant ventricular arrhythmias (MVA). Furthermore, 15 and 6 patients, respectively, showed gait loss and respiratory failure from neuromuscular disease. Multivariable analysis showed three independent predictors for the composite endpoint of cardiac death, HTx and MVA: nonsustained ventricular tachycardias (HR 3.98, 95% CI 1.72–9.21, p=0.001), baseline left ventricular ejection fraction <50% (HR 3.83, 95% CI 1.75–8.38, p=0.001) and tendon retractions (TR) in skeletal muscles (HR 4.22, 95% CI 1.70–10.47, p=0.002). TRs predicted outcome independently of number, site, timing of occurrence and specific myopathy (LGMD, EDMD, LCMD, mild phenotypes). Non-missense mutations were associated only to end-stage HF, but not to MVA. Further remarkable findings emerged from analysis of subgroups: 1) in spite of a better global outcome, asymptomatic relatives were not free from significant disease (with MVA or end-stage HF observed in 4 cases); 2) patients with combined N+C involvement were younger

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