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Progression of cardiac involvement in patients with limb-girdle type 2 and Becker muscular dystrophies: A 9-year follow-up study☆

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ABSTRACT

Aim: To assess the degree and progression of cardiac involvement in patients with limb-girdle type 2 (LGMD2) and Becker muscular dystrophies (BMD).
Methods: A follow-up study of 100 LGMD2 (types A–L) and 30 BMD patients assessed by electrocardiogram (ECG) and echocardiography, supplemented by Holter-monitoring at follow-up.
Results: After a median of 8.9 years (range 0.4–13.7), twelve patients had died: LGMD2 ($n = 10$, mean age 61 ± 11 years), BMD ($n = 2$, age 43 and 45 years). Of the remaining 118 patients, 89 completed follow-up: LGMD2 ($n = 64$, age 48 ± 13 years) and BMD ($n = 25$, age 40 ± 13 years).
In BMD, LVEF decreased from 60% (10–62) to 50% (10–64), $p = 0.02$ corresponding to a one percentage drop annually. Among patients with LGMD2, LVEF decreased significantly in patients with LGMD type 2I ($n = 28$) from 59% (15–72) to 55% (20–61), $p = 0.03$, i.e. a 0.4 percentage drop annually, and LVEF ≤ 50% was associated with increased mortality in this subgroup. In LGMD2E, 3/5 patients (60%) at baseline and 4/5 (80%) at follow-up had LVEF ≤ 50%. ECG abnormalities were non-progressive in BMD and in all subgroups of LGMD2. SVT and NSVT were present in both groups: BMD (3/14 (21%) and (2/14 (14%)), LGMD2 (16/51 (31%) and 8/51 (16%)), respectively, all asymptomatic.
Conclusion: LVEF decreased significantly in patients with BMD and LGMD2I, and the majority of patients with LGMD2E had left ventricular systolic dysfunction. This study emphasizes the need for tailored regular cardiac assessments according to molecular diagnosis with special focus on BMD and LGMD types 2I and 2E.

1. Introduction

Becker muscular dystrophy (BMD) and recessively inherited limb-girdle muscular dystrophy type 2 (LGMD2) are rare muscle diseases characterized by progressive muscle weakness of the proximal upper and lower extremities. Cardiac involvement in BMD and LGMD2 varies substantially and may include arrhythmias and hypertrophic or dilated cardiomyopathy [1–6].

BMD is an X-linked inherited disease caused by mutations in the gene encoding dystrophin. Dystrophinopathies also include Duchenne muscular dystrophy (DMD), which has a more severe phenotype with cardiac involvement commonly being present in all patients over 18 years of age [7]. Along with several other proteins, dystrophin is a part of the dystrophin–glycoprotein complex, which has a key role in cell signalling across the sarcolemma and in muscle cell membrane stability [8–12]. The exact mechanism by which lack of dystrophin causes disease is unknown, but it is hypothesized to destabilize the muscle cell mechanically, leading to disruption of the sarcolemma and cell death. The severity of skeletal muscle weakness varies and first symptoms usually appear between the age of 3 and 21 years with a mean age at onset of 11 years [7,13]. Cardiac involvement in BMD is a major concern, even in female carriers, and left ventricular dysfunction can be observed throughout the course of the disease [13–17]. The prevalence of dilated cardiomyopathy in men with BMD ranges from 33 to 49%, and from 0 to 13% in female carriers, and is independent of the severity of skeletal muscle involvement [14,16–19]. Death from heart failure and arrhythmias is estimated to occur in up to 50% of the cases, with a mean age of death at 45 years [16,20].

LGMD2 comprises 17 genetically distinct subtypes LGMD2A–Q [12,21]. The pathogenic mechanism seems to be caused by dysfunctional proteins at several different levels of the muscle cell. This leads to changes in intra- and extracellular enzyme activity and disturbed signal transduction across the plasma membrane, resulting in degeneration and necrosis of skeletal myofibers and cardiomyocytes with gradual

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replacement by fat- and fibrotic tissue [6]. Age of onset ranges from childhood to the fourth decade [7]. Compared to LGMD1, which is autosomal dominantly inherited, the skeletal muscle phenotype of the recessively inherited LGMD2 is more severe and closely resembles that of the dystrophinopathies [22]. Depending on the subtype of LGMD2, age at death ranges from 16 to 67 years, and although cardiomyopathy can be fatal, the impact on prognosis remains unclear in the majority of the subtypes [7,23–25].

Quality of life and survival of patients with muscular dystrophies have improved mainly attributed to recent advances in respiratory management [7]. Furthermore, attention to cardiac involvement in patients with muscular dystrophies is increasing, probably due to an increased molecular genetic knowledge of the different types of muscular dystrophies. As patients live longer, heart failure and arrhythmias contribute more to mortality, stressing the need for more knowledge of the degree and progression of cardiac involvement in these patients.

This longitudinal study assessed cardiac function with electrocardiogram (ECG) and echocardiography for a 9-year period in a cohort of 30 BMD and 100 LGMD2 patients (types A–L) to evaluate cardiac morbidity, mortality and the progression of cardiac involvement.

2. Methods

2.1. Study design

This longitudinal study was conducted at the Departments of Cardiology and Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark and approved by the regional scientific ethics committee (reference number H-d-2008-077).

Baseline methodology has been described in detail [4]. In brief, patients were assessed by medical history, physical examination, 12-lead electrocardiogram (ECG), trans-thoracic echocardiography, and muscle strength testing.

At follow-up, these assessments were repeated and supplemented by 48-hour Holter-monitoring in a subset of patients (65/89 (73%)) and measurements of plasma levels of NT-proBNP.

2.2. Study population

At baseline, 130 patients from 117 families were included (Fig. 1) [4].

All patients eligible for inclusion at time of follow-up were invited, except those who had been re-diagnosed from unclassified LGMD2 to another muscular dystrophy than LGMD2 or BMD (n = 9) (Fig. 1). Those included provided written informed consent. Most recent follow-up data were collected in those patients who died during follow-up.

2.3. Genetic testing

The diagnosis of BMD was based on large deletions of the dystrophin gene, the absence of dystrophin or the presence of a faint, truncated dystrophin band on western blot [4]. All LGMD2 patients types A–I and L were genetically verified at baseline, except for the two patients with LGMD2B, in whom the diagnosis was based on demonstration of absent dysferlin on western blot [4].

2.4. Follow-up investigations

2.4.1. Electrocardiography

A 12-lead ECG was performed using a Burdick Atria 6100 ECG, Richmond, Australia. An abnormal ECG was defined as the presence of: atrial flutter/fibrillation (AFL/AF), atrioventricular block (AVB) grades I–III (AVB grade I: PR-interval ≥ 220 ms), left anterior hemiblock (LAH), right or left bundle branch block (RBBB/LBBB) or incomplete right bundle branch block (IRBBB).

2.4.2. Holter-monitoring

A 48-hour Holter-monitoring was performed using a 3-electrode Lifecard CF (Spacelabs Healthcare, Washington, United States). Holter-monitoring was considered abnormal in the presence of: AVB grades I–III, atrial fibrillation/flutter (AF/AFL), other supraventricular tachyarrhythmia (SVT) (>30 supraventricular premature contractions (SVPC) per hour or runs of ≥20 SVPC), frequent ventricular premature contractions (VPCs) (≥30/h), or non-sustained ventricular tachycardia (NSVT) (minimum of 3 beats at ≥100 bpm).

2.4.3. Echocardiography

Transthoracic echocardiography was performed using a Vivid e9 (General Electric, Horten, Norway). Left ventricular (LV) cavity dimensions, mass and wall thickness and diastolic dysfunction were assessed in accordance with the recommendations of the European Association of Echocardiography and the American Society of Echocardiography [26]. Left ventricular ejection fraction (LVEF) was obtained using the Simpson's biplane method. An abnormal echocardiography was defined as: LVEF ≤ 50%, left ventricular end diastolic diameter (LVEDD) > 53 mm (women) and >59 mm (men), and interventricular septum thickness in diastole (IVSD) > 11 mm. Additionally, echocardiography was used to assess valve disease and to estimate LV mass [27].

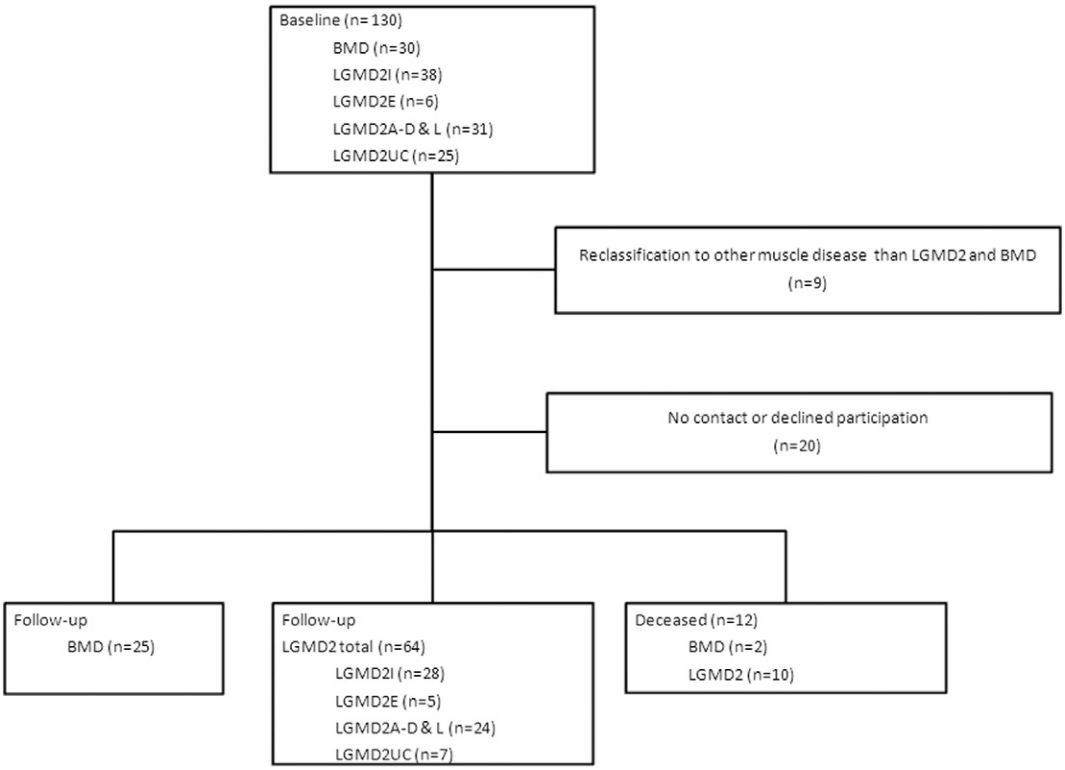

Fig. 1. The flow of patients with Becker muscular dystrophy and limb-girdle muscular dystrophies type 2 from baseline to follow-up.