Cardiac Involvement in Patients With Limb-Girdle Muscular Dystrophy Type 2 and Becker Muscular Dystrophy

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Objective: To investigate the extent of cardiac involvement in patients with 1 of the 12 groups of recessively inherited limb-girdle muscular dystrophy type 2 (LGMD2A-L) and Becker muscular dystrophy (BMD).

Design: Prospective screening.

Setting: Neuromuscular Clinic and Department of Cardiology at Rigshospitalet.

Patients: One hundred one patients with LGMD2A-I and BMD and 29 patients with LGMD2 and no molecular diagnosis.

Main Outcome Measures: Clinical investigation, echocardiography, and electrocardiographic findings.

Results: Cardiac involvement was present in 24 of 100 patients (24%) with LGMD2A-I and in 14 of 30 patients (47%) with BMD. Only a few patients with LGMD2A and unclassified LGMD2 had mild cardiac involvement, whereas 29% and 67% of patients with LGMD2I and LGMD2E, respectively, had cardiac involvement. Cardiac involvement was not correlated with age, muscle strength, or the level of dystrophic changes on muscle biopsy.

Conclusions: This study demonstrates a high prevalence of cardiac involvement in patients with LGMD2I, LGMD2E, and BMD. Patients with LGMD2A, LGMD2D, and unclassified LGMD2 have a much lower and milder prevalence of cardiac involvement.

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Recessively inherited limb-girdle muscular dystrophy type 2 (LGMD2) and X-linked inherited Becker muscular dystrophy (BMD) affect the proximal musculature of the upper and lower extremities. Symptoms can appear from early infancy to late adulthood. Patients with LGMD2 can be divided into 12 subgroups (LGMD2A-L). Affected proteins are often located in the dystrophin-associated glycoprotein complex, the sarcomere, or proteins involved in the homeostasis of these protein complexes. Becker muscular dystrophy is caused by dysfunction of dystrophin. Specific diagnosis of LGMD2 and BMD relies on genetic analyses or demonstration of protein deficiencies on Western blot.1

Dilated cardiomyopathy (DCM) and premature cardiac death in patients with muscular dystrophies is known.2 Similar to the skeletal muscle of patients with muscular dystrophies, the pathoanatomical evidence of cardiac involvement is the replacement of myocardium by connective tissue. However, the relative risk of involvement of skeletal vs cardiac muscle differs among muscular dystrophies, which calls for differentiated management of patients. A specific molecular diagnosis has only recently become available for most patients with LGMD2, and, for that reason, cardiac involvement is not well described in the different LGMD2 subtypes.

The aim of this study is to assess cardiac involvement in a large group of patients with LGMD2 compared with patients with BMD who also have an LGMD2 muscle phenotype and in whom cardiac involvement is better described.

Methods

Patients

Patients with molecularly well-defined LGMD2A-I and BMD and patients with LGMD2 without a molecular diagnosis were recruited from the Neuromuscular Clinic at Rigshospitalet. In total, 130 patients from 117 families were included. Fourteen patients were diagnosed as having LGMD2A, 2 as having LGMD2B, 17 as having sarcoglycanopathy (LGMD2C-E), 38 as having LGMD2I, and 30 as having BMD (Table 1). Twenty-nine patients fulfilling the diagnostic criteria for LGMD2 had no molecular diagnosis. The 29 patients with unclassified LGMD2 had no pro-
tein deficiencies on multiplex Western blotting, and the following 3 genes were sequenced in all: TRIM32, FKRP, and CAPN3. In the group with unclassified LGMD2, no patient had elbow contractures or rigid spine (as seen in LGMD1B), none had vacuoles in muscle fibers (as seen in LGMD1A), and all had positive staining for caveolin 3. Thus, sporadic LGMDs with dominant inheritance were not likely present in the cohort of unclassified LGMD2.

**CLINICAL AND LABORATORY INVESTIGATIONS**

Muscle strength was measured using a handheld dynamometer. One examiner (M.-L.S.) performed strength testing in all the patients. Muscle strength was calculated as the percentage of the mean strength found in 29 healthy sex-matched controls. The following muscle groups were tested for strength: elbow flexion, wrist extension, handgrip, hip flexion, adduction, and abduction, knee flexion, and ankle dorsiflexion and plantar flexion. Maximal walking distance was assessed by means of interview. Muscle biopsies were performed in 98 patients, and dystrophic changes were graded on a scale from 0 to 3 according to the amount of fibrosis, the number of necrotic cells, cell size variability, the number of central nuclei, and the fat infiltration present in each biopsy sample. Except for the 2 patients with LGMD2B, in whom the diagnoses were based exclusively on demonstration of absent dystrophin on Western blot, all the other patients with LGMD2A-1, including those with no biopsy sample, had genetic confirmation of their diagnosis. Large deletions of the dystrophin gene were found in 19 of the 30 patients with BMD, and in the remaining 11, the diagnosis was based on the absence of dystrophin or the presence of a faint, truncated dystrophin band on Western blot. Muscle biopsy samples were processed according to standard histologic and immunohistochemical techniques, and multiplex Western blots included antibodies for dystrophin (2 antibodies); merosin; myosin heavy chain; α-sarcoglycan; β-dystroglycan; dysferlin; the 30-, 60-, and 94-kDa fragments of calpain 3; and telethonin.

Respiratory function was assessed by means of forced vital capacity and forced expiratory volume in the first second of expiration, with normal values defined as greater than 75% of the sex-, age-, and height-adjusted norm.

Echocardiography (ECHO) was performed within a few weeks of the clinical examination according to the American Society of Echocardiography guidelines. Cardiac dimensions (intraventricular septum [IVS] thickness and left ventricular end diastolic) diameter were measured from 2-dimensional images, and left ventricular ejection fraction (LVEF) was assessed in 5% intervals. Dilated cardiomyopathy was defined as a left ventricular end diastolic diameter greater than 5.3 cm for women and 5.9 cm for men if a compliant decrease in LVEF was found. An IVS thickness greater than 1.2 cm was defined as a sign of hypertrophy, and marginally increased IVS thickness was set at 1.1 to 1.2 cm. An LVEF of 55% or greater was considered normal; 50%, moderately decreased; 45% or less, severely decreased. Patients with an LVEF of 45% or less were referred to their local cardiology department for continued follow-up and treatment. The LVEF values were obtained in all 130 patients, whereas left ventricular end diastolic diameter and IVS measurements were missing for 2 patients owing to poor image quality. All patients with cardiac involvement were interviewed regarding signs and symptoms of cardiac decompensation (dyspnea at rest and peripheral edema).

Electrocardiograms (ECGs) were analyzed by 1 of us (L.K.) in 104 of 130 patients using standard 12-channel surface ECG. The phenotype of the 26 patients without an available ECG did not distinguish itself from other members of the same group. The following variables were investigated: pathologic Q waves, PQ interval, left and right bundle branch block, incomplete right bundle branch block, left ventricular hypertrophy (defined as Sokolow-Lyon criteria [SV1 + RV5 or RV6 > 35 mV, where SV1 is S wave in V1; RV5, R wave in V5; and RV6, R wave in V6]), atrial fibrillation/flutter, atrioventricular conduction block, and left anterior hemiblock. The presence of ventricular extrasystoles was also recorded. Cardiac involvement was defined as the presence of 1 or more of the following abnormalities on ECHO or ECG: LVEF of 50% or less, IVS thickness greater than 1.2 cm, left bundle branch block, atrial fibrillation/flutter, and atrioventricular conduction block.

**STATISTICAL ANALYSIS AND ETHICS**

Values are given as mean (SE). P < .05 (2-tailed testing) was considered significant. Differences among groups were assessed using an unpaired t test. All the investigations were performed with participant informed consent, and the study was approved by the ethics committee of Copenhagen.
RESULTS

Of 130 patients included in this study, 38 (29%) had signs of cardiac involvement, 31 based on ECHO abnormalities alone, 5 based on combined ECHO and ECG abnormalities, and 2 based solely on ECG abnormalities (Figure 1). A total of 24% (24 of 100) of the patients with LGMD2 and 47% (14 of 30) of the patients with BMD had cardiac involvement.

Figure 1. Left ventricular ejection fraction (LVEF) in patients with limb-girdle muscular dystrophy (LGMD2) and Becker muscular dystrophy (BMD). Each symbol represents a patient. All values are shown at nominal value except for LVEF 60%, which is clustered at and above the 60% line. IVS indicates intraventricular septum; LVEDD, left ventricular end diastolic diameter. The LVEF under 50% is delineated below both horizontal dashed lines; LVEF of 50%, between both dashed horizontal lines; and LVEF over 50%, above both horizontal dashed lines. The solid symbols mark the LVEF of the individual patient; the open symbols not only mark the LVEF of the patient but also inform us that the patient was found to have a dilated LVEDD (open circle), marginally increased IVS (open triangle), or hypertrophy (open circle).

Table 2. Cardiopulmonary Findings in Patients With LGMD2 and BMD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CI in Males/Females, No.</th>
<th>Abnormal ECHO in Males/Females, No.</th>
<th>Abnormal ECG in Males/Females, No.</th>
<th>Septal Hypertrophy, No.</th>
<th>FEV1/FVC Ratio, % of Normal</th>
<th>Respiratory Aide, No.</th>
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<tbody>
<tr>
<td>LGMD2A</td>
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<td>0/1</td>
<td>0/1</td>
<td>0</td>
<td>18 (6)</td>
<td>0</td>
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<tr>
<td>LGMD2B</td>
<td>1/0</td>
<td>1/0</td>
<td>0</td>
<td>0</td>
<td>75 (6)</td>
<td>0</td>
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<tr>
<td>LGMD2C</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0</td>
<td>31 (8)</td>
<td>3</td>
</tr>
<tr>
<td>LGMD2D</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0</td>
<td>24 (14)</td>
<td>5</td>
</tr>
<tr>
<td>LGMD2E</td>
<td>2/2 (1)</td>
<td>2/2</td>
<td>0/0</td>
<td>0</td>
<td>70 (6)</td>
<td>4</td>
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<tr>
<td>826C&gt;A</td>
<td>5/3 (1)</td>
<td>5/4</td>
<td>2/0</td>
<td>2/1</td>
<td>68 (5)</td>
<td>3</td>
</tr>
<tr>
<td>LGMD2I</td>
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<td>2/1</td>
<td>0/1</td>
<td>1/2</td>
<td>28 (4)</td>
<td>5</td>
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<td>BMD</td>
<td>14 (6)</td>
<td>14</td>
<td>1</td>
<td>5</td>
<td>71 (5)</td>
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<td>1/0</td>
<td>1/3</td>
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</tbody>
</table>

Abbreviations: BMD, Becker muscular dystrophy; CI, cardiac involvement; DCM, dilated cardiomyopathy; ECG, electrocardiogram; ECHO, echocardiogram; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IVS, intraventricular septum; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction.  
Cardiac involvement was defined as the presence of 1 or more of the following abnormalities on ECHO or ECG: LVEF of 50% or less, IVS thickness greater than 1.2 cm, left bundle branch block, atrial fibrillation/flutter, and left ventricular conduction block. Numbers in parentheses represent the number of patients with symptoms of CI, which included dyspnea at rest and peripheral edema.  
Abnormal ECHO findings were defined as an LVEF of 50% or less, IVS thickness greater than 1.2 cm, left ventricular end diastolic diameter greater than 5.3 cm for women and 5.9 cm for men.  
Severe ECG abnormalities were those described for CI. Moderate ECG abnormalities were defined as inferior right bundle branch block, left anterior hemiblock, and ventricular extrasystoles.  
Respiratory function was set at 0 for patients who were dependent on a tracheal respirator. Respiratory aides included bilevel positive airway pressure assistance and a tracheal respirator.

Of the 130 patients, 20 (15%) had an LVEF of 45% or less and 13 (10%) had a marginally decreased LVEF of 50% (Figure 1). Nine patients with cardiac involvement had symptoms of congestive heart failure not correlated with age; DCM was detected in 10 of the 38 patients with cardiac involvement (Table 2). Seven patients had cardiac involvement based on ECG abnormalities. Thus, conduction abnormalities were rare and they were evenly distributed among subgroups (Table 2).

Thirteen patients, all with either BMD or LGMD2I, had an increased left ventricular end diastolic diameter. Ten of these 13 patients also had decreased LVEF, indicating DCM. The IVS thickness was increased in 7 patients, 4 of whom also had decreased LVEF. Three patients with unclassified LGMD2 had increased IVS thickness but without relation to LVEF.

Of the 38 patients with cardiac involvement, 16 (42%) had lost ambulation, which did not differ significantly from the percentage of patients who had lost ambulation in the group without cardiac involvement (32 of 92 [35%]). Of the 38 patients with cardiac involvement, 12 (32%) required ventilatory support, which was higher than in the group without cardiac involvement (13 of 92 [14%]) (Table 1). Muscle strength, walking distance, severity of dystrophic changes on muscle biopsy, age, and age at symptom onset did not correlate with cardiac involvement (Figure 2).

Respiratory function was decreased in half of the patients (66 of 130 patients). Respiratory function was severely affected in patients with LGMD2C-E (decreased by 69% [8%]) and in patients who were compound heterozygous for the LGMD2I 826C>A mutation (decreased by 72% [7%]). In these groups, ambulation was lost in all but 1 patient. Respiratory function was only moderately decreased in patients with unclassified LGMD2 and in patients with BMD and LGMD2I who were homozygous for the 826C>A mutation.
Figure 2. Left ventricular ejection fraction (LVEF) in patients with limb-girdle muscular dystrophy type 2 (LGMD2) I (A and B), LGMD2A (C and D), LGMD2B-E (E and F), Becker muscular dystrophy (BMD) (G and H), and unclassified LGMD2 (I and J) compared with their age and muscle strength. Muscle strength was calculated as the percentage of the mean strength found in healthy sex-matched controls. There was no significant correlation between LVEF and age or percentage decreased muscle strength. The LVEF values of 60% are shown as 59% to 64%.
and was not affected in patients with LGMD2A or LGMD2B. Overall, there was a significant decrease in muscle strength in patients with impaired respiratory function compared with those with normal function (Figure 3). Of 130 patients, 25 required some form of ventilatory support (bi-level positive airway pressure or tracheal respiration), and all had lost ambulation.

Figure 3. Percentage of decreased muscle strength vs decreased respiratory function (A) and cardiac involvement (B) in patients with limb-girdle muscular dystrophy type 2 and Becker muscular dystrophy. *There was a significant decrease in muscle strength in patients with decreased respiratory function (P<.001).

MAIN FINDINGS

The main findings of this study are as follows. (1) The overall prevalence of cardiac involvement in all the patients with LGMD2 (24%) is not as high as that in patients with BMD (47%) but is substantially higher than the 1% expected cardiac involvement for this age group in Denmark. (2) There is a distinct variability among LGMD2 subtypes regarding cardiac involvement, with LGMD2I and LGMD2E having a high prevalence of cardiac involvement (comparable with that in BMD), whereas patients with LGMD2A, LGMD2D, and unclassified LGMD2 are generally spared. (3) Echocardiographic abnormalities showing decreased pump function were more common than rhythm disturbances on ECG. (4) There is no correlation between severity of cardiac involvement and age, and there is also no correlation between cardiac involvement and muscle strength in patients with LGMD2 and BMD. (5) Decreased respiratory function was significantly correlated with decreased muscle strength but not with cardiac involvement.

The rate of cardiac involvement in BMD has previously been reported to be 44% to 65%. The evidence of cardiac involvement in patients with LGMD2 is much less solid than in those with BMD. The new information provided by the present study reinforces the importance of applying the same criteria for cardiac screening, treatment, and monitoring of patients with LGMD2 as those currently used for patients with BMD.

VARIABILITY IN CARDIAC INVOLVEMENT IN LGMD2 AND BMD

LGMD2A

Patients with LGMD2A had practically no cardiac involvement. The apparent lack of cardiac involvement in LGMD2A is in line with the lack of calpain 3 expression in adult human cardiomyocytes, although CAPN3 transcripts are present. The lack of cardiac involvement in patients with LGMD2A did not relate to age or to a milder skeletal muscle phenotype because patients were, in fact, on average older than patients in the other LGMD subgroups, and muscle strength corresponded to that found in patients with homozygous LGMD2I and BMD, in whom cardiac involvement was much more prevalent (Figure 2).

LGMD2I

The present study found a cardiac involvement rate of 29% in patients with LGMD2I. Cardiac involvement in this group has previously been reported to be 10% and 55% using different cardiac involvement definitions and investigations. In the present study, a higher prevalence of cardiac involvement was seen in males (38%) vs females (18%) with LGMD2I. Poppe et al. reported a similar finding, in which 83% of males and 42% of females with LGMD2I had certain or possible cardiac involvement. Of the 38 patients with LGMD2I, 15 had cardiac involvement based on ECHO findings of left ventricular regional wall motion abnormality and 6 had possible cardiac involvement based on abnormal P wave notching on ECG. The present study does not support previous findings showing a tendency toward an association between the severity of cardiac and skeletal muscle involvement in LGMD2I.

LGMD2C-E

The absence of cardiac involvement in patients with LGMD2D corresponds to molecular findings of differential expression of sarcoglycan complex proteins in mouse skeletal and cardiac muscle. There is evidence that ε-sarcoglycan, an α-sarcoglycan homologue, can substitute for α-sarcoglycan in cardiac musculature and, thus, mitigate the loss of this protein. In accordance with this, α-sarcoglycan-deficient mice have a severe skeletal muscle phenotype but no signs of cardiac involvement. Also, cardiac investigations, totaling 12 patients, have previously shown evidence of significant cardiac involvement in only 1 patient with LGMD2D.

The high prevalence of cardiomyopathy (67%) seen in patients with β-sarcoglycan deficiency (LGMD2E) in the present study agrees with findings reported by Fa-nin et al., who found cardiac involvement in 3 of 6 patients. Similarly, γ-sarcoglycan deficiency is thought to
be associated with DCM, which the limited findings in the 2 patients with LGMD2C also suggest.

**LGMD2B**

The marginal cardiac involvement found in 1 of 2 patients in the present study does not contribute conclusive evidence about cardiac involvement in this condition. Cardiac involvement has not been studied systematically in LGMD2B, but cardiac investigation findings in patients with LGMD2B have been normal so far.

**BMD**

The prevalence of DCM in patients with BMD corresponded well with previous findings. Cardiac involvement differed markedly among 5 affected brothers, obviously carrying the same mutation, and in the remaining group, irrespective of skeletal muscle involvement. The dissociation of cardiac and skeletal muscle involvement, also found in patients with LGMD2I in the present study, has previously been described in BMD.

**LGMD2**

Of all patients with LGMD2, 20% to 30% (and 22% in the present study) lack molecular characterization after thorough investigation. This patient group needs clinical follow-up similar to patients with classified LGMD2, but close cardiac monitoring may be less important because few patients in this group have abnormal cardiac findings (and any findings are mild).

Despite the high prevalence of cardiac involvement in patients with LGMD2 and BMD, symptoms of decompensation occur late; therefore, detection requires active cardiac investigation. This is important because early treatment may have a cardioprotective effect. Cardiac involvement in LGMD2 and BMD is amenable to various treatments, and studies have shown that left ventricular function can be stabilized and improved with treatment. Based on findings in this study, we recommend that all patients with LGMD2 be screened with initial ECHO and ECG on diagnosis. Patients with unclassified LGMD2, LGMD2A, and LGMD2D need not receive further regular screening if findings are normal, but abnormal ECHO findings should be monitored yearly. Patients with normal ECHO findings but having LGMD2C, LGMD2E, LGMD2I, or BMD, where there is an increased incidence of cardiac involvement, should be monitored every 2 years by means of ECHO, as suggested earlier.

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Author Contributions: Dr Sveen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sveen and Vissing. Acquisition of data: Sveen, Thune, Kober, and Vissing. Analysis and interpretation of data: Sveen, Thune, and Vissing. Drafting of the manuscript: Sveen, Thune, Kober, and Vissing. Critical revision of the manuscript for important intellectual content: Sveen and Vissing. Statistical analysis: Sveen and Vissing. Obtained funding: Sveen and Vissing. Administrative, technical, and material support: Sveen, Thune, Kober, and Vissing. Study supervision: Sveen, Kober, and Vissing.

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