EVALUATION OF HEART INVOLVEMENT IN CALPAINOPATHY (LGMD2A) USING CARDIOVASCULAR MAGNETIC RESONANCE

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ABSTRACT: *Introduction*: Cardiac dysfunction occurs in several forms of limb girdle muscular dystrophy (LGMD). The aim of this study was to investigate cardiac involvement in calpainopathy (LGMD2A). *Methods*: Cardiovascular evaluation was performed in 10 patients with genetically verified LGMD2A by echocardiography, 3 Tesla - cardiovascular magnetic resonance, 24-h electrocardiography recordings with heart rate variability (HRV) analysis, and 24-h blood pressure recordings. *Results*: No patient with calpainopathy showed impairment of left or right ventricular function. One patient had a small amount (2% of left ventricle mass) of late gadolinium enhancement. HRV analysis revealed no significant difference compared with external reference data. *Conclusions*: The main finding of this study is the lack of cardiac involvement in patients with calpainopathy. Cardiac involvement was not found, even in individuals with advanced age and greater disease severity. Furthermore, we did not observe an overall reduction of cardiac autonomic regulation in calpainopathy.

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Abbreviations: BP, blood pressure; CMR, cardiovascular magnetic resonance; DMD, Duchenne muscular dystrophy; ECG, electrocardiography; HRV, heart rate variability; LGE, late gadolinium enhancement; LGMD2A, calpainopathy; LGMD, limb girdle muscular dystrophy; LV, left ventricle; LVEDV, left ventricular end diastolic volume; MD, muscular dystrophy; rMSSD, mean square of successive differences between normal sinus RR intervals; RV, right ventricle; RVSP, right ventricular systolic pressure; RVEDV, right ventricular end diastolic volume; SDANN, standard deviation of all averaged normal sinus intervals; SDNN, standard deviation of all normal sinus RR intervals; SDNNi, the mean of the standard deviations of all normal sinus RR intervals; TTE, transthoracic echocardiography

Key words: calpainopathy; cardiac magnetic resonance imaging; echocardiography; heart rate variability; LGMD2A; muscular dystrophy

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Limb girdle muscular dystrophies (LGMD) are progressive muscle diseases that lead to muscle weakness and wasting, predominantly of shoulder and pelvic girdle muscles of both men and women. Significant cardiac involvement has been documented in LGMD2C-F, 2I, and LGMD1B, and rarely in the LGMD1C and 2B subtypes.[1–4]

Table 1. Baseline clinical characteristics and disease severity in patients with limb-girdle muscular dystrophy type 2A.

Patient	Presenting age	Gender	Ambulatory	Scapular winging	Joint contracture	Family history	CK (μkat/L)
1	55	W	Yes	No	No	No	14
2	32	W	Yes	Bilateral	Achilles	No	9
3	29	M	Yes	No	No	No	29
4	28	M	No	Bilateral	Achilles	Yes	17
5	25	W	No	Bilateral	Achilles	No	22
6	51	W	No	Bilateral	Achilles	No	5
7	31	M	Yes	No	No	Yes	54
8	23	W	Yes	Bilateral	Achilles	Yes	24
9	27	M	Yes	No	No	No	8
10	39	W	Yes	No	Achilles	No	12

Cardiac involvement has been studied in a large consecutive series of LGMD2A patients in the United Kingdom, and the studies have shown that it is not a feature of calpainopathy (LGMD2A).[5] However, standard cardiac screening methods such as electrocardiography (ECG) and transthoracic echocardiography (TTE)[6,7] are often unremarkable[8,9] and cannot detect and quantify myocardial damage at early stages of disease. In contrast, cardiovascular magnetic resonance (CMR) can reveal early cardiac involvement, even if standard cardiac evaluation is normal.[8,9] The aim of this study was to investigate a series of LGMD2A patients by standard cardiac methods (24-h ECG, 24-h blood pressure [BP] recording, and TTE) and CMR imaging.

METHODS AND MATERIALS

We evaluated 10 patients with genetically confirmed LGMD2A who were referred to our hospital for evaluation of cardiac involvement in calpainopathy. From January to September 2013, all patients who were treated in the neuromuscular outpatient clinic of the University Hospital Dresden with LGMD2A were offered a cardiovascular evaluation, including 24 h ECG and BP recordings, TTE, and CMR. Of a total of 20 patients, 3 refused to participate due to reduced mobility. Four patients were unable to perform the CMR breathing maneuvers and were not included in the analysis.

Calpain 3-deficiency was established according to the standard reported by Fanin et al.[10] DNA analysis was performed in all patients. In 3 patients, only 1 pathogenic mutation was found. Although they presented with the typical calpain 3-deficient phenotype, they were not included in the study. The remaining 10 patients had mutations in the *CAPN3* gene (7 compound heterozygous, 3 homozygous, Supplementary Table 1, available online). All participants provided written informed consent, and the study was approved by the Ethics Committee, Technical University of Dresden, Germany. All study procedures were in accordance with the ethical standards outlined in the 1975 Declaration of Helsinki, as revised in 1983.

Statistical Analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences version 18 (SPSS Inc., Chicago, Illinois). Qualitative variables were expressed as counts and percentages, and normally distributed quantitative variables were expressed as mean ± 1 SD. Comparison of numerical variables was performed using the unpaired Student *t*-test.

RESULTS

Baseline characteristics of the patient population are shown in Table 1. Ten patients from unrelated families (4 men, 6 women) were confirmed to have a calpainopathy. Mean serum creatine kinase level was 19.4 μkat/L (normal range, men 0.4–3.25 μkat/L, women 0.4–2.83 μkat/L). TTE, CMR, 24-h ECG, and 24-h BP-data are shown in Supplementary Table S2.

No patient showed impairment of left or right ventricular function. Furthermore, left and right ventricle sizes were within normal ranges, except in 1 patient. In 1 patient a small amount (2% of LV-mass) of late gadolinium enhancement (LGE) was found at the insertion areas of the right ventricle (RV) at the anterior ventricular septum.

In the 24-h ECG-recordings, 1 patient was newly diagnosed with atrial fibrillation (patient 6, Table 1). All other patients had normal sinus rhythm. Four of the 10 patients showed supraventricular and ventricular ectopic beats, although their frequency was less than 100 beats per day in each patient.

In 24-h BP-recordings, there was no evidence of arterial hypertension. In 3 of the 10 patients we demonstrated a "nondipping BP profile," which is defined as night-time average systolic BP reduction less than 10% with respect to day values.

Heart rate variability parameters (HRV) are summarized in Supplementary Table S3. Overall, calpain-deficient patients had significantly lower standard deviation values of all normal sinus RR intervals (SDNN), mean square of successive

differences between normal sinus RR intervals (rMSSD), and standard deviation of all averaged normal sinus intervals (SDANN) compared with the reference group.[11] Further analysis per decade revealed that only the SDNN (125 ± 31 ms vs. 177 ± 37; $P = 0.004$) and the mean of the standard deviations of all normal sinus RR intervals (SDNNi) (55 ± 14 ms vs. 78 ± 18 ms; $P = 0.008$) values in the younger group (20–29 years) and the rMSSD (53 ± 34 ms vs. 24 ± 11 ms; $P = 0.001$) values in the older group (50–59 years) differed significantly from the reference group.

DISCUSSION

The main finding of this study is the absence of cardiac involvement, even in patients with severe calpain deficiency.

Only 1 of 10 patients was found to have a small area of LGE. The location at the insertion areas of the RV is a common pattern of LGE. In the RV insertion area, LGE has been characterized histologically and represents an expanded extracellular space, which is formed by the rearrangement of intersecting myocardial fibers, rather than by replacement fibrosis.[12]

These results are in agreement with preliminary reports which failed to find clinical cardiac involvement in these patients.[5] In our opinion, the echocardiography-based studies are, however, not suitable to detect subclinical changes in muscular dystrophy. As shown by several studies in patients with Duchenne muscular dystrophy (DMD), cardiac fibrosis may be present, even if left ventricular function is not significantly impaired. However, no cardiac dysfunction, scarring, or fibrosis could be detected in these LGMD2A patients, even with the more sensitive method of CMR.

There are several reports of autonomic dysfunction in DMD patients,[13,14] which was characterized by a significant decrease in parasympathetic and a significant increase in sympathetic activity.[15] We also found a significant overall difference in the HRV parameters of the calpainopathy patients compared with a reference group. After adjustment for age, however, only the SDNN and SDNNi values in the 20–29 year group and the rMSSD values in the 50–59 year group were significantly different from the reference group. This suggests that there is no overall reduction of cardiac autonomic regulation in calpainopathy.

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