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LETTER TO THE EDITORS

The proteoglycan–dystrophin complex in genetic cardiomyopathies—lessons from three siblings with limb-girdle muscular dystrophy-2I (LGMD-2I)

Ali Yilmaz · Hans-Jürgen Gdynia · Matthias Ponfick · Albert C. Ludolph · Sabine Rösch · Udo Sechtem

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Sirs:

The term limb-girdle muscular dystrophy (LGMD) is used to describe neuromuscular disorders that are characterized by muscle weakness and wasting predominantly affecting the extremities (proximal to a greater extent than distal). The LGMD family consists of seven autosomal-dominant and 13 autosomal-recessive forms, and a distinction between the different types on clinical criteria alone is difficult and requires protein analysis in muscle biopsies and genetic studies. LGMD has to be distinguished from the much more frequent X-linked dystrophinopathies (e.g. Duchenne muscular dystrophy, DMD) although the clinical picture may be quite similar. Former studies suggested that the prevalence rate of all forms of LGMD disorders is ~7:100.000 [1]. However, since diagnostic capabilities have tremendously improved in the past years, a higher prevalence rate is likely.

LGMD-2I is one of the autosomal recessive forms of the LGMD family and caused by mutations in the Fukutin-related protein gene (FKRP) on chromosome 19q. The most common genetic finding in northern Europe is the homozygous mutation (C826A) in FKRP and is mostly associated with a milder phenotype of muscular dystrophy compared with those who are compound heterozygous. FKRP encodes a putative Golgi-based glycosyltransferase and is involved in posttranslational glycosylation of α-dystroglycan. Mutations in FKRP lead to a glycosylation defect and subsequently downregulation of α-dystroglycan which constitutes an essential component of the proteoglycan–dystrophin complex. The clinical picture of patients with LGMD-2I resembles DMD. Major causes of morbidity and mortality are cardiac and/or respiratory failure. Respiratory involvement with a forced vital capacity lower than 75% has been described in about 50% of affected individuals in one prior study [2]. Although previous studies suggested cardiac involvement to be a frequent finding (in up to 60%) in patients with LGMD-2I [2, 3], the morphological pattern of cardiomyopathy as well as the underlying pathophysiology has not been sufficiently evaluated so far.

Currently, we are performing a cardiovascular magnetic resonance imaging (CMR) study on patients with neuromuscular disorders with special focus on the presence and presentation pattern of cardiomyopathy. The following three siblings with genetically proven LGMD-2I (homozygous C826A mutation on chromosome 19q3) participated in this ongoing research project and underwent a comprehensive CMR study on a clinical scanner (1.5-T Sonata, Siemens, Germany) after obtaining written informed consent.

The first and youngest patient, a 38-year-old male suffered only from minor skeletal muscle weakness (predominantly in the lower extremities) with rapid exhaustion following exercise, and he was still able to walk and slowly climb stairs. Already 5 years previously, a biventricular dilation with impaired left ventricular (LV) systolic function was diagnosed and he was at that time taking an ACE-inhibitor and a β-blocker. Apart from minor dyspnea on exertion, he had no cardiac complaints. In particular, there were no chest pain symptoms and no clinical signs suggestive of myocarditis.

A. Yilmaz (✉) · S. Rösch · U. Sechtem
Division of Cardiology, Robert-Bosch-Krankenhaus, Auerbachstrasse 110, 70376 Stuttgart, Germany
e-mail: ali.yilmaz@rbk.de

H.-J. Gdynia · M. Ponfick · A. C. Ludolph
Department of Neurology, University of Ulm, Ulm, Germany

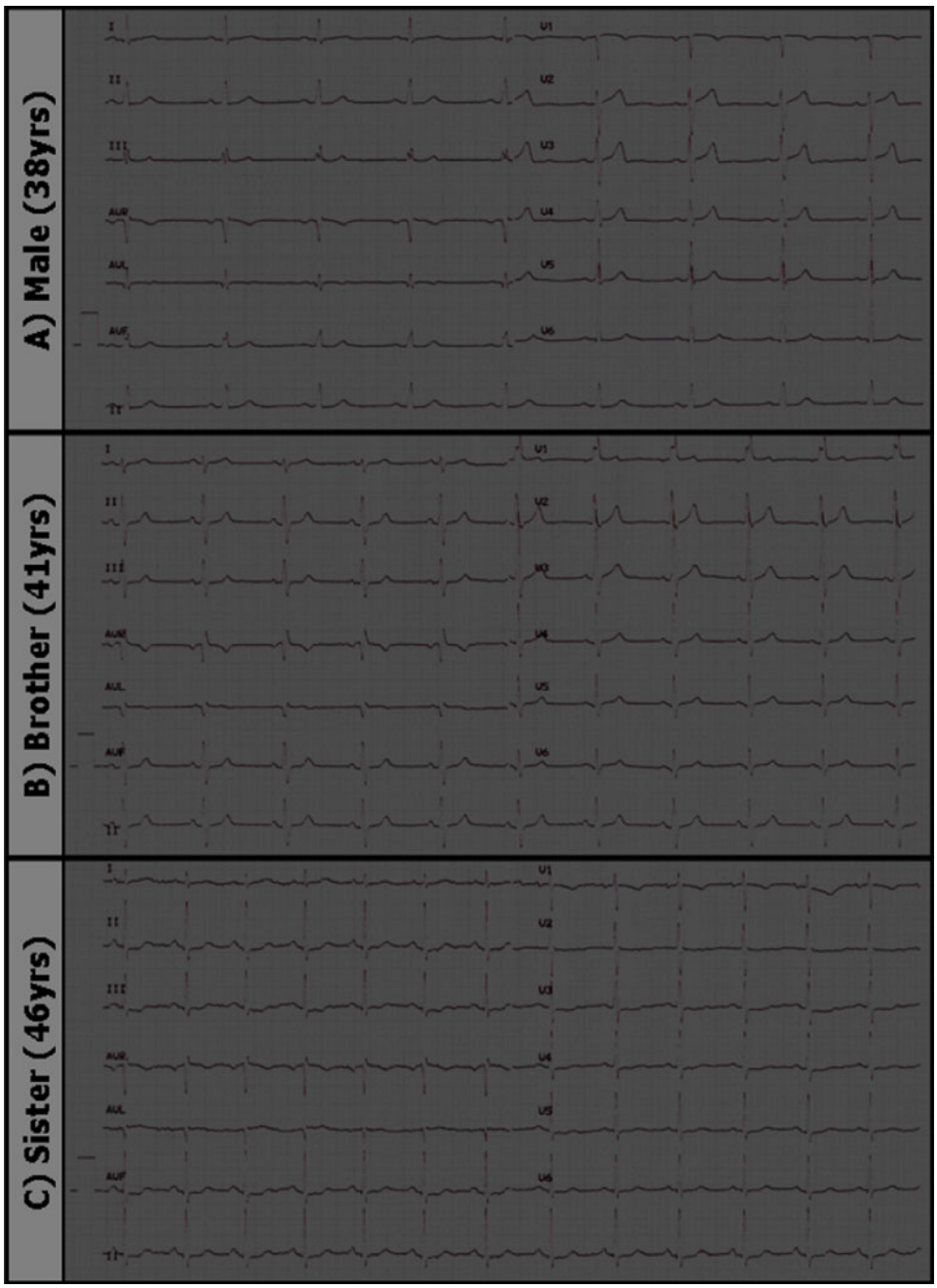

Fig. 1 Resting 12-lead ECGs of all three siblings with LGMD-2I

His resting ECG (Fig. 1a) demonstrated notched QRS-complexes in the inferior leads III and aVF, but no other pathological findings. Blood analysis revealed an elevated total creatine kinase (CK) level of 2,386 U/l (normal < 190 U/l), a slightly elevated creatine kinase-MB (CK-MB) level of 40 U/l (normal < 25 U/l), a normal troponin T (TnT) level of 0.01 ng/ml (normal < 0.03 ng/ml) and a normal NT-proBNP level of 124 pg/ml (normal < 450 pg/ml). The acoustic window during echocardiography was limited and 2D echocardiography demonstrated a reduced left ventricular (LV) systolic function (LV-EF ~50%), but normal values were measured regarding diastolic function (PW-doppler: mitral E/A-ratio 1.2; tissue-doppler: septal E/E′-ratio 6.5) [4].

CMR cine-images demonstrated a reduced LV and right ventricular (RV) systolic function (LV-EF 45% and RV-EF 38%) with regional hypokinesia in the LV inferolateral wall. Contrast-imaging was performed after intravenous application of gadopentetat-meglumin (Magnograf®, Marotrast, Germany) using an inversion-recovery gradient-echo technique. Late-gadolinium-enhancement (LGE)

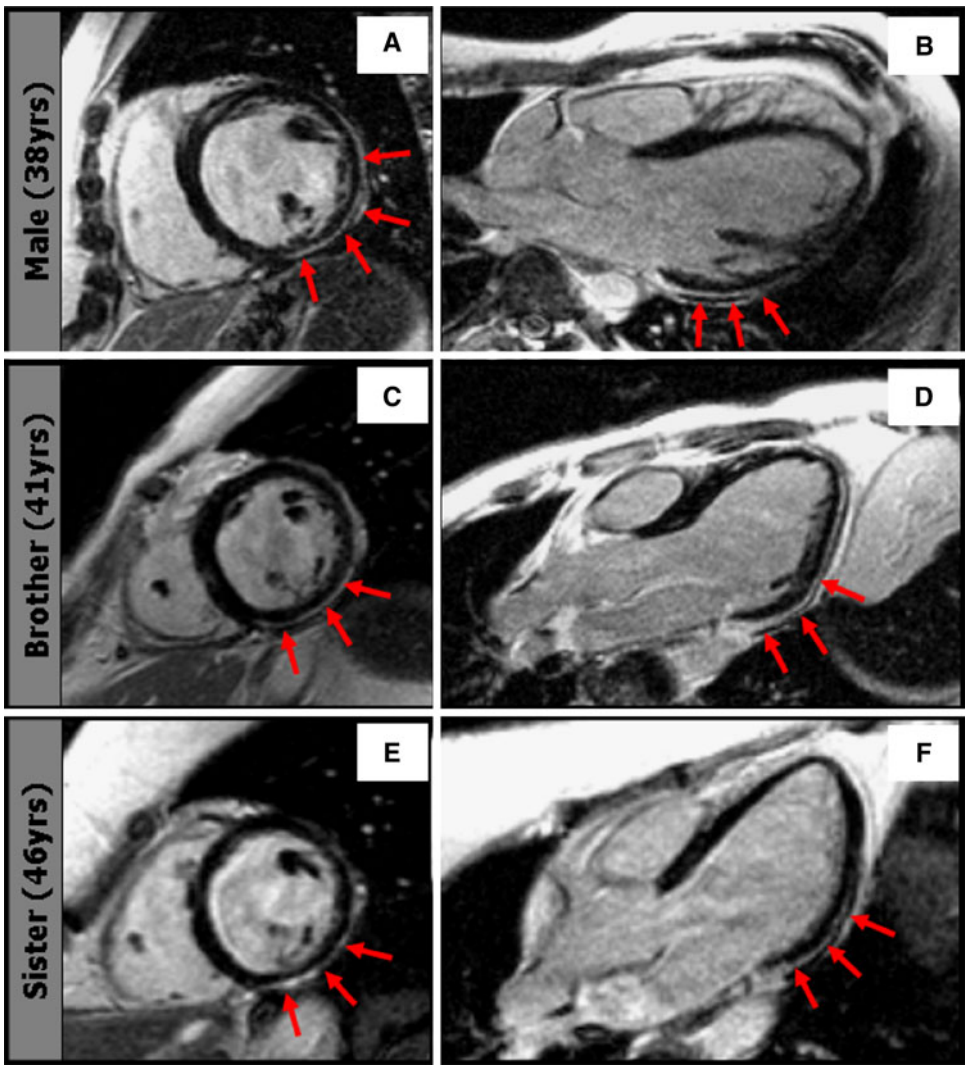

Fig. 2 Short- and long-axis CMR contrast images of three siblings each suffering from LGMD-2I: Each patient—the youngest patient, a 38-year-old male (**a**, **b**), his 41-year-old brother (**c**, **d**) and his 46-year-old sister (**e**, **f**)—demonstrated late-gadolinium-enhancement indicative of myocardial damage in the subepicardium of the inferolateral wall

indicative of myocardial damage was detected in the subepicardium of the LV inferolateral wall (Fig. 2a, b).

The second patient, a 41-year-old male suffered from progressive physical impairment with severe weakness in his arms and legs and was wheelchair-bound since a few years. Just like his younger brother, biventricular dilation with impaired LV systolic function had been diagnosed 5 years earlier during a routine check-up, and he was at that time taking an ACE-inhibitor, a β-blocker, and a diuretic. He complained of shortness of breath and dyspnea on exertion, but he also had no chest pain symptoms and no clinical signs suggestive of myocarditis.

In this patient, resting ECG (Fig. 1b) demonstrated an incomplete right-bundle-branch-block (RBBB), but no ST-segment changes. Blood analysis revealed an elevated total CK level of 1,212 U/l (normal $<$ 190 U/l), a slightly elevated CK-MB level of 45 U/l (normal $<$ 25 U/l), a normal TnT level of 0.01 ng/ml (normal $<$ 0.03 ng/ml) and a normal NT-proBNP level of 88 pg/ml (normal $<$ 450 pg/ml). Again, the acoustic window during echocardiography was limited and 2D-echocardiography demonstrated a reduced LV systolic function (LV-EF $\sim$48%) and there were also signs of impaired diastolic function (PW-doppler: mitral E/A-ratio 0.9; tissue-doppler: septal E/E′-ratio 9.6).

Similar to the findings in his brother, CMR cine-images demonstrated a reduced LV and RV systolic function (LV-EF 48% and RV-EF 47%) with regional hypokinesia in the inferolateral wall. Contrast-imaging demonstrated the presence of LGE in the subepicardium of the LV inferolateral wall (Fig. 2c, d).

The third and oldest sibling was a 46-year-old female. Her impairment of physical ability was in between her two brothers' conditions. She could still walk with support; however, she was unable to climb any stairs. She had undergone cardiac examination together with her brothers 5 years ago and was found to have a normal LV function (EF 60%) without any regional wall motion abnormalities.

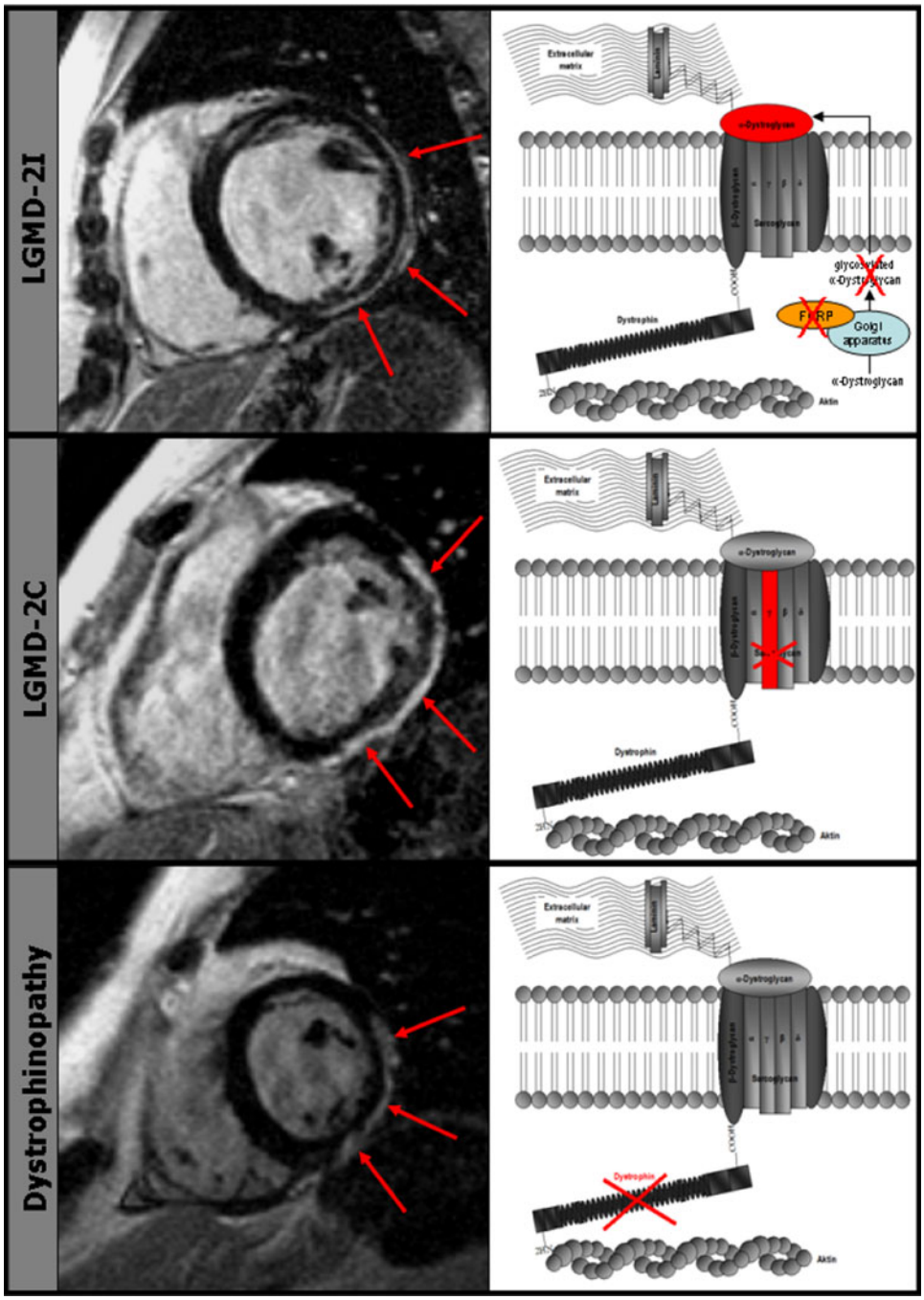

Fig. 3 Short-axis CMR contrast images with corresponding diagrams showing the constitution of the cardiomyocyte cell membrane and demonstrating the connection between the intramembranous proteoglycan complex and the intracellular dystrophin complex in case of a LGMD-2I, LGMD-2C and dystrophinopathy. A subepicardial pattern of myocardial damage in the inferolateral wall is a common finding in these patients with defects in just one component of the proteoglycan–dystrophin complex

At that time, she was suffering from rapid fatigue and dyspnea on exertion. However, there were no chest pain symptoms and she did not take any medication.

In this third patient, resting ECG (Fig. 1b) demonstrated minor ST-segment depression in the leads II, III, aVF, and V2–V4. Blood analysis revealed an elevated total CK level of 475 U/l (normal < 190 U/l), a slightly elevated CK-MB level of 31 U/l (normal < 25 U/l), a normal TnT level of 0.01 ng/ml (normal < 0.03 ng/ml) and a normal NT-proBNP level of 127 pg/ml (normal < 450 pg/ml). 2D echocardiography demonstrated a slightly reduced LV systolic function (LV-EF ~53%), but normal values were measured regarding diastolic function (PW-doppler: mitral E/A-ratio 1.0; tissue-doppler: septal E/E′-ratio 7.9).

CMR cine-images revealed only subtle impairment of LV systolic function (LV-EF 58%) while RV function was normal. However, regional hypokinesia in the inferolateral wall in addition to the presence of LGE in the subepicardium of the LV inferolateral wall (Fig. 2e, f) was again observed. Taken together, all three siblings with LGMD-2I

demonstrated cardiac involvement with various degrees of impairment in LV and RV systolic function, however, with a similar pattern of subepicardial myocardial damage in the LV inferolateral wall.

Cardiac evaluation in these three siblings with LGMD-2I revealed (1) only minor and interindividually differing pathological ECG findings, (2) reduced systolic LV function in all siblings and signs of diastolic dysfunction only in one patient by echocardiography (with the limitation of poor acoustic window in two individuals), and (3) the consistent finding of regional hypokinesia in the inferolateral wall in addition to the presence of LGE in the subepicardium of the LV inferolateral wall by CMR in all siblings.

So far, only one study reported the findings of CMR-based LGE-imaging in patients with LGMD-2I [3]. Nine out of 13 patients (69%) were reported to have some evidence of RV fatty replacement and/or fibrosis (although the detailed methods of diagnosing RV fatty infiltration/fibrosis are not described) while LGE was observed only in 1/13 patient (8%) in the left ventricular (LV) wall. In contrast, all three siblings participating in our study demonstrated a characteristic subepicardial myocardial damage in the inferolateral wall of the LV—suggesting that this cardiac phenotype is related to the genetic abnormality—but no LGE in the RV free wall.

Interestingly, such a characteristic LGE-pattern has recently also been shown in patients with dystrophinopathies [5, 6] as well as in those with other subtypes of LGMD such as γ-sarcoglycanopathy (LGMD-2C) [7] (Fig. 3). So far, the underlying pathomechanism for this distribution of myocardial damage in myopathic patients is unclear. As previously outlined by Lapidos et al. [8], the proteoglycan–dystrophin complex has both mechanical stabilizing and signaling roles in mediating interactions between the cytoskeleton, the cell membrane, and the extracellular matrix. Consequently, destabilization of the proteoglycan–dystrophin complex leads to membrane fragility and loss of membrane integrity, resulting in degeneration not only of skeletal muscle but also cardiomyocytes. Hence, considering the multi-component composition of the proteoglycan–dystrophin complex (as schematically illustrated in Fig. 3) and the similar pattern of myocardial damage in patients with different missing or deficient components of this complex, it seems that such a pattern of myocardial damage may be a characteristic finding indicating the presence of an abnormality in the proteoglycan–dystrophin complex. However, genetically caused abnormalities within the proteoglycan–dystrophin complex should theoretically result in a diffusely reduced cardiomyocyte stability and in turn lead to myocardial damage not only in the LV inferolateral wall. The predominance of myocardial damage in the subepicardium of the LV inferolateral wall suggests that the myocardium of the inferolateral wall either constitutes the weakest element of LV segments and/or has to withstand the highest mechanical stress during LV contraction and relaxation. In any way, unraveling of the underlying pathophysiology of cardiomyopathy in patients with neuromuscular disorders may help to better understand cardiac physiology as well as pathophysiology in other cardiovascular diseases.

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Conflict of interest None.

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