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Evaluation of cardiac and respiratory involvement in sarcoglycanopathies

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Abstract

Sarcoglycanopathies constitute a subgroup of limb-girdle recessive muscular dystrophies due to defects in sarcoglycan complex that comprises five distinct transmembrane proteins called α-, β-, γ-, δ-and ε-sarcoglycans. As it is well known that sarcoglycans are expressed both in heart and in skeletal muscles and a complete deficiency in δ-sarcoglycan is the cause of the Syrian hamster BIO.14 cardiomyopathy, we studied cardiac and respiratory involvement in 20 patients with sarcoglycanopathies by clinical, electrocardiographic, echocardiographic, scintigraphic and spirometric assessments. A normal heart function was found in 31.3% of all patients; a preclinical cardiomyopathy in 43.7%; an arrhythmogenic cardiomyopathy in 6.3% and initial signs of dilated cardiomyopathy in 18.7%. In one patient the data were examined retrospectively. No correlation was found between cardiac and skeletal muscle involvement. With reference to the type of sarcoglycanopathy, signs of hypoxic myocardial damage occurred in β-, γ- and δ-sarcoglycanopathies, while initial signs of a dilated cardiomyopathy in γ- and δ-sarcoglycanopathies were found. A normal respiratory function was observed in 23.5% of all patients, a mild impairment in 35.4%, a moderate impairment in 29.4%, and a severe impairment in 11.7%.

Keywords: Sarcoglycanopathy; Cardiac involvement; Respiratory involvement

1. Introduction

Limb-girdle muscular dystrophies (LGMDs) constitute a genetically heterogeneous group of disorders with dominant or recessive inheritance. Their most common presentation is proximal muscle weakness of the pelvic and shoulder girdle muscles and this shapes a variable clinical pattern ranging from severe to very mild muscular involvement.

So far, eight forms of autosomal recessive limb-girdle muscular dystrophies have been described, four of which are caused by mutations in sarcoglycan complex (SGC) and comprise four distinct transmembrane proteins: α-sarcoglycan (50 kDa DAG, adhalin), β-sarcoglycan (43 kDa DAG, A3b), γ-sarcoglycan (35 kDa DAG), and δ-sarcoglycan (35 kDa DAG), each of them responsible for different types of limb-girdle muscular dystrophies. Recently, a fifth member joined the sarcoglycan gene family, the ε-sarcoglycan – a 48–50 kDa dystrophin-associated glycoprotein, closely related to adhalin [1].

The sarcoglycanopathies – caused by mutations in the α at 17q21.1 [2–5]; β at 4q12 [6–8]; γ at 13q12 [9–13]; δ at 5q33 [14,15] sarcoglycan genes – are respectively called LGMD2D, LGMD2E, LGMD2C and LGMD2F according to the nomenclature suggested by Bushby and Beckmann in 1995 [16]. To date no specific pathology has been linked to defects in the ε-sarcoglycan gene.

Both nonsense and missense mutations in any of the genes encoding α-, β-, γ-, and δ-sarcoglycan proteins, may result in the disruption of the entire SGC complex and are associated with phenotypes ranging from severe Duchenne-like muscular dystrophy to later onset and milder limb girdle muscular dystrophies [12,14,17–21].

The sarcoglycans are variably expressed in both heart and

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Table 1
Clinical and genetic findings in patients with α-, β-and δ-sarcoglycanopathies

N/sex	Gene defect	Clinical course	Age of chair bound (years)	Age at the last check (years)	CK values[a]	Muscle biopsy	Immunohistochemical analysis	Cause of death (age)
N148/F	n.a.[b]	BMD-like	Ambulant	26	10×	Myopathic	absence of 50 DAG	
N149/F	n.a.	BMD-like	Ambulant	32	10×	Myopathic	absence of 50 DAG	
N620/F	C229T	Intermediate	13	46	Normal	Myopathic	not performed	Respiratory failure (48)
N329/F	35–36delA	Mild	22	28	5×	Myopathic	not performed	
N330/M	35–36delA	Mild	Ambulant	26	8×	Myopathic	not performed	
N2858/F	64^65insG/354del GACTA	DMD-like	11, 6	13	15×	Myopathic	absence of all SGs	
N2859/F	64^65insG/354del GACTA	DMD-like	9	17	10×	Myopathic	absence of all SGs	

[a] At the age of diagnosis.
[b] Not available.

skeletal muscles; furthermore a defect in the δ-sarcoglycan gene was demonstrated to be the cause of the Syrian hamster BIO14.6 cardiomyopathy [22]. The aim of this work was to investigate the occurrence of cardiac and respiratory involvement in patients with mutations in sarcoglycan genes and subsequently to relate the clinical phenotype to the gene defect.

2. Patients and methods

Among the 140 familial and/or isolated patients affected by limb-girdle muscular dystrophies, to date 20 cases of sarcoglycanopathies have been ascertained. All of the patients are followed, as outpatients, at the Department of Cardiomyology and Medical Genetics of the Second Naples University.

The diagnosis of autosomal recessive sarcoglycanopathy, first based on the typical pattern of inheritance, increased serum CK levels, and characteristic muscle-wasting distribution, was subsequently confirmed by DNA analysis in 17 patients (85%), and by the immunocytochemical analysis of muscle biopsy specimens in three patients (15%). Clinical data of the most part of patients (age of onset, age of chair-bound, course of the disease) as well as the gene mutations have been previously reported [17,19,20] and are listed in Tables 1 and 2. However, a systematic investigation of cardiac and respiratory involvement had not been performed.

2.1. DNA analysis

DNA was prepared by standard procedures from peripheral frozen blood samples. Mutations in the α-, β-, γ-, and δ-sarcoglycan genes were studied by polymerase chain reaction (PCR) analysis following the procedures previously published [2,6–8,11,12]. Intronic primer sequences for γ-sarcoglycan were kindly provided by Elisabeth McNally. PCR conditions for the δ-sarcoglycan gene have been previously described [15]. Multiple SSCP was performed under different electrophoretic conditions. Differently

Table 2
Clinical and genetic findings in γ-sarcoglycanopathies

N/sex[a]	Gene defect	Age at the last check (years)	Clinical course	Age of chair bound (years)	CK values[b]	Muscle biopsy	Immunohistochemical analysis
N111/F°	del525T	23	Mild	Ambulant	30×	Myopathic	Absence of 35 DAG
N115/F°	del525T	20	DMD-like	11	90×	Myopathic	Absence of 35 DAG
N114M§	del521T	25	BMD-like	26	70×	Myopathic	Not performed
N421/M§	del521T	28	Intermediate	17	100×	Myopathic	Not performed
N2576/F	del521T	10	DMD-like	Ambulant	10×	Myopathic	Not performed
N2799/F	del521T	4		Ambulant	70×	Myopathic	Absence of 50 DAG
N2896/M	341^342insT/del525T	5		Ambulant	62×	Myopathic	Absence of 35 DAG
N2899/F	del521T	34	Mild	Ambulant	20×	Myopathic	Absence of 35 DAG
N234/F#	551T > G	23	Mild	Ambulant	20×	Myopathic	Reduction of all DAGs
N2902/M#	551T > G	22	Mild	Ambulant	40×	Myopathic	Absence of 35 DAG
N950/F	del exon 7	28	severe	16	32×	Myopathic	Not performed
N66/F	del exon 7	28	Mild	Ambulant	50×	Myopathic	Reduction of all DAGs
N3300/M	n.a.	9	Mild	Ambulant	70×	Myopathic	Absence of 35 DAG

[a] °, §, # Indicate pairs of siblings.
[b] At the age of diagnosis.

migrating products were sequenced to reveal the type of mutation [15].

2.2. Immunocytochemical analysis

Muscle samples from biceps or quadriceps biopsies were frozen in liquid nitrogen immediately after removal and stored at − 70°C. Immunochemical staining of frozen sections was performed using the three standard antibodies to dystrophin (Novocastra) as well as to αSG, βSG, and γSG (Ylem). For δSG, a rabbit polyclonal antibody raised against a glutathione *S*-transferase (GST)-δ sarcoglycan fusion protein was used [15].

2.3. Cardiac involvement

Cardiac involvement was investigated by standard and dynamic (Holter) ECG, M-Mode, 2D and Echo-color-Doppler echocardiography. Patients with altered echocardiographic parameters were evaluated by ^{201}Tl SPECT, both at rest and after a dipyridamole stress test, according to the procedure published elsewhere [23].

According to the criteria established by us for dystrophinopathies, and indicated elsewhere (Refs. [24–26] and references therein), the diagnosis of cardiac involvement was based on signs that determine the following different clinical pictures.

- Preclinical cardiomyopathy: shortened PQ segment (PQs); prolonged QT interval; increased QT/PQs ratio (Cardiomyopathic Index) greater than 4.5 [24,25].
- Dilated cardiomyopathy: large Q waves in the left precordial leads; non-perfused segmental ventricular

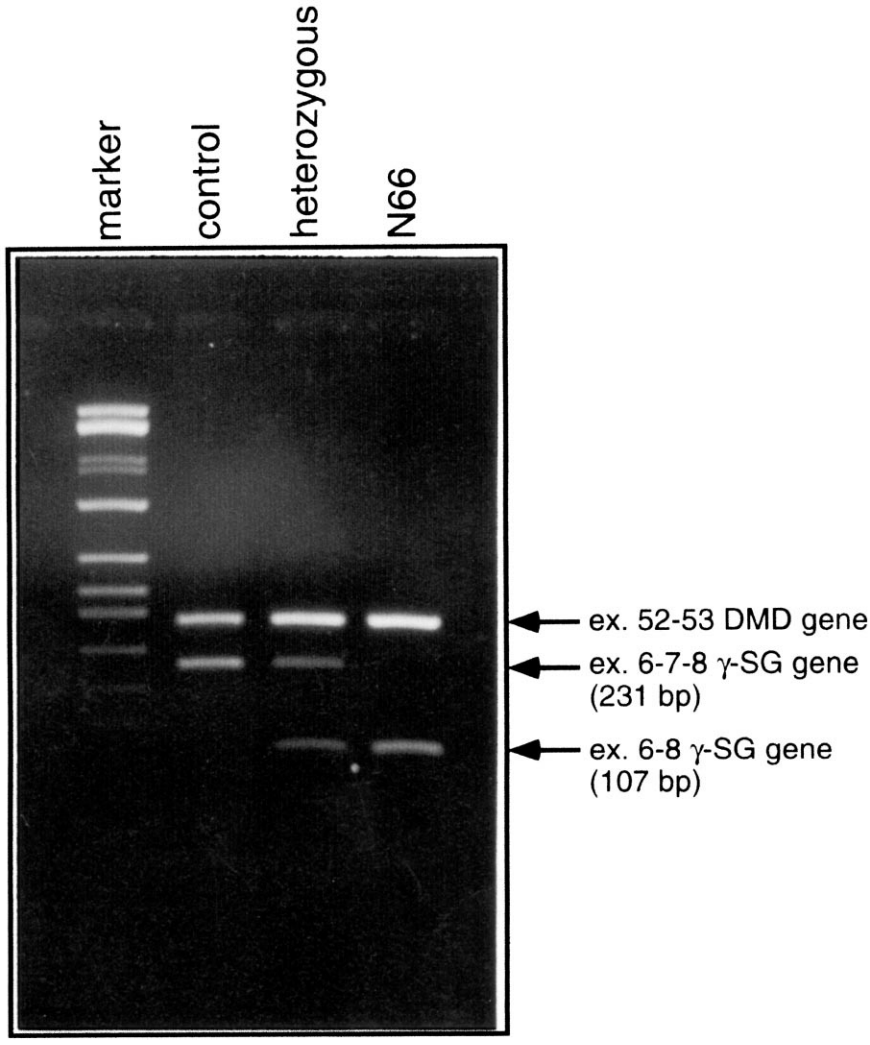

Fig. 1. Duplex PCR amplification on muscle cDNA (ethidium bromide staining). Primers were selected in order to amplify from exon 6 to exon 8 of the γ-sarcoglycan gene (231 bp), together with exons 52–53 of the dystrophin gene as control (325 bp). For the γ-sarcoglycan the following primers were designed: γ-SG/508F CCTGAAGGGGCTCTTTTTGAACATT (exon 6) and γ-SG/738R CTTGGGTAAGCACACAGTTTCAGCA (exon 8). Markers sizes are 5000–2258–1204–1054–794–517–396–338–255–191–143–75 bp. Patient N66, having a homozygous deletion of the entire seventh exon of the γ-sarcoglycan gene, shows a shorter band (107 bp), derived from the direct splicing of exon 6 to exon 8. The resulting product is out of frame (237 instead of 291 aa). In her father, heterozygous for the deletion, a doublet is generated.

walls; evidence of dilated ventricles; reduced ejection fraction (EF); reduced fibre shortening (FS); ratio pre-ejection period/left ventricular ejection time (PEP/LVET) greater than 0.42.

- Arrhythmogenic cardiac involvement: paroxysmal tachycardia; WPW syndrome; supra-ventricular tachycardia; ventricular tachycardia; atrial flutter or fibrillation; bundle branch block; atrio-ventricular block; sino-atrial block; sick sinus syndrome; sino-atrial dysfunction.
- Hypertrophic cardiomyopathy: left ventricular hypertrophy; ventricular pre-excitation; increase in ventricular septum width; ratio ventricular septum diastolic thickness/left ventricular diastolic free wall thickness (echocardiographic cardiac index) higher than 1.5.

Hypertension as far as valvular, metabolic or other secondary cardiac diseases and also respiratory illnesses were previously investigated to exclude a possible interference in the diagnosis.

2.4. Respiratory involvement

Respiratory involvement was investigated by the evaluation of forced vital capacity values (FVC), peak expiration flow (PEF) and flow expiratory volume at the first minute (FEV_1) (Pocket spirometer, Micro Medical Ltd, Rochester, UK).

The respiratory function was considered normal when the percentage of the FVC was more than 85%, compared with the expected values adjusted for age and height.

We arbitrarily indicated a mild respiratory involvement when the percentage of the FVC values was between 85 and 65%, a moderate respiratory involvement when the percentage of the FVC values was between 65 and 40%, and a severe respiratory involvement when the percentage of the FVC values was under 40%.

3. Results

3.1. Analysis of SG gene mutations

We studied 14 families, where 12 (eight females and four males) pairs of sib-ship and eight (six females and two males) isolated patients were affected by primary sarcoglycanopathies.

Mutation in the αSG gene was found in one patient, the βSG gene in two patients, the γSG in 12 patients and the δSG in two patients. In two αSG patients and in one γSG, DNA analysis is still in progress.

The isolated patient with the α-sarcoglycanopathy had a homozygous mutation within exon 3 (229C → T). The two familial cases with β-sarcoglycanopathy showed a homozygous new mutation in exon 2 (35–36 del A, A37G).

Out of 12 patients with molecularly examined γ-sarcoglycanopathy, four (33.3%) carried the single mutation *Δ521T* in exon 6, which changes the reading frame of

Table 3
Cardiological data[a]

N/sex	Age (years)	Gene defect	ECG data		Echocardiographic data						
			ICMc	ECG tracing	LVEDD (mm)	LVESD (mm)	SV (ml)	LVEF (%)	FS (%)	IVS (mm)	LVPW (mm)
N148/F	27	α-Sarco	3.2		52	34	82.1	63	35	8	7
N149/F	33	α-Sarco	4.0		50	31	80.3	68	38	8	10
N620/F	46	α-Sarco	3.1	Pulmonary hypertension	41	29	42.0	57	31	8	9
N329/F	25	β-Sarco	13.4	Inverted T waves in vL-V4-V5-V6-	51	34	76.4	62	33	9	10
N330/M	23	β-Sarco	4.7	Paroxysmal sinus tachycardia	54	36	86.9	62	33	10	10
N111/F	23	γ-Sarco	4.2	Diffused hypoxic damage	51	35	72.9	59	31	8	8
N115/F	20	γ-Sarco	3.3		52	35	78.6	61	33	8	9
N114M	25	γ-Sarco	6.0		40	27	43.4	62	32	9	8
N421/M	28	γ-Sarco	2.4		47	32	61.4	60	32	10	9
N2576/F	10	γ-Sarco	4.9		42	28	49.0	62	33	7	7
N2799/F	4	γ-Sarco	n.a.								
N2896/M	5	γ-Sarco	n.a.								
N2899/F	34	γ-Sarco	n.a.								
N234/F	23	γ-Sarco	4.3		55	37	89.3	61	33	8	9
N2902/M	22	γ-Sarco	n.a.								
N950/F	28	γ-Sarco	4.1		44	36	49.8	57	29	7	8
N66/F	28	γ-Sarco	4.9	Inverted T waves in V4–V6	52	37	71.4	55	29	8	9
N3300/M	9	γ-Sarco	4.6		42	28	52.0	70	36	7	7
N2858/F	13	δ-Sarco	4.3	Pulmonary hypertension	46	30	62.3	64	36	8	8
N2859/F	17	δ-Sarco	4.2		45	29	60.2	59	29	10	9

[a] ICMc, cardiomyopathic index; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; SV, stroke volume; LVEF, left ventricular ejection fraction; FS, fibre shortening; IVS, interventricular septum; LVPW, left ventricular posterior wall; n.a., data not available.

amino acid 174, resulting in 16 missense amino acids and a stop codon. Out of the remaining eight patients, two first-degree cousins showed a mutation at position 184 in exon 6 (551T → G) that changes a valine in glycine; two had a single mutation (*Δ525T);* one a compound mutation (*341^342insT/Δ525T*) and two a deletion involving the entire exon 7 (Fig. 1): a mutation only identified in patients from southern Italy.

The two familial cases with δ-sarcoglycanopathy showed a compound mutation in both alleles in exon 2 (*64^65insG*) of paternal origin, and in exon 4 (*354del GACTA*) of maternal origin, respectively.

All the mutations were tested and not encountered in control populations (in general, > 300 independent chromosomes were examined for each mutation).

3.2. Immunocytochemical analysis

A diagnosis of sarcoglycanopathy was confirmed in the three cases without gene mutations (two α and one γ) by the complete lack of the related protein observed by immunohistochemistry. Furthermore, a complete absence in αSG staining was observed in two patients and a reduction in nine; a complete γSG deficiency was observed in five patients and a reduction in three; a complete deficiency of the entire SG complex was observed in the case of δ-sarcoglycanopathies. In seven patients muscle biopsies were not available.

3.3. Clinical phenotype

The mean age of the patients was 22.15 years and ranged from 4 to 46 years. Five patients showed severe Duchenne-like phenotype and lost the ability to walk at under 14 years of age. Eleven had a milder phenotype, are still ambulant and in their thirties. Of the remaining four (mean age 7 years) the clinical course is not predictable.

3.4. Cardiac involvement

All patients were normotensive. No patient was symptomatic. None of them showed metabolic or valvular diseases. The cardiological data of all patients are listed in Table 3. In one patient the data were analysed retrospectively. The diagnosis of the cardiomyopathy is summarized in Table 5.

Five patients (29.4%) had normal ECG and echocardiographic tracings.

Six patients (35.3%) showed ECG abnormalities, such as: pulmonary hypertension (two cases); ventricular ectopic beats (one patient), confirmed by Holter monitoring; sustained paroxysmal sinus tachycardia (one patient) also confirmed by Holter monitoring; inverted T waves consistent with hypoxic myocardial damage (three patients); tall R waves in leads V1–V2 and deep Q waves in V4–V6 (myocardial fibrosis) (one patient). However, out of seven patients (41.3%) having normal ECGs, two showed a pathological echocardiographic pattern (fractional shortening < 30%, consistent with initial dilated cardiomyopathy). The echocardiographic findings were normal in 14 (82.3%) patients (Table 3). A reduction in left ventricular ejection fraction was observed in one patient affected by γ-sarcoglycanopathy owing to the deletion of the entire exon 7. This last patient was the only one showing simultaneously ECG and echo-cardiographic abnormalities. A reduction in fractional shortening lower than 30% was observed in three (17.6%) patients. Two of them were affected by γ-sarcoglycanopathy and one by δ-sarcoglycanopathy.

A ^{201}Tl SPECT performed at rest and after dipyridamole infusion in the three patients (N329F, N111F, N66F) with inverted T waves or signs of hypoxic damage showed absence of uptake defects in two. Only the patient with γ-sarcoglycanopathy caused by the lack of the entire exon 7 showed a ^{201}Tl uptake reversible defect at the antero-lateral level (see Fig. 2).

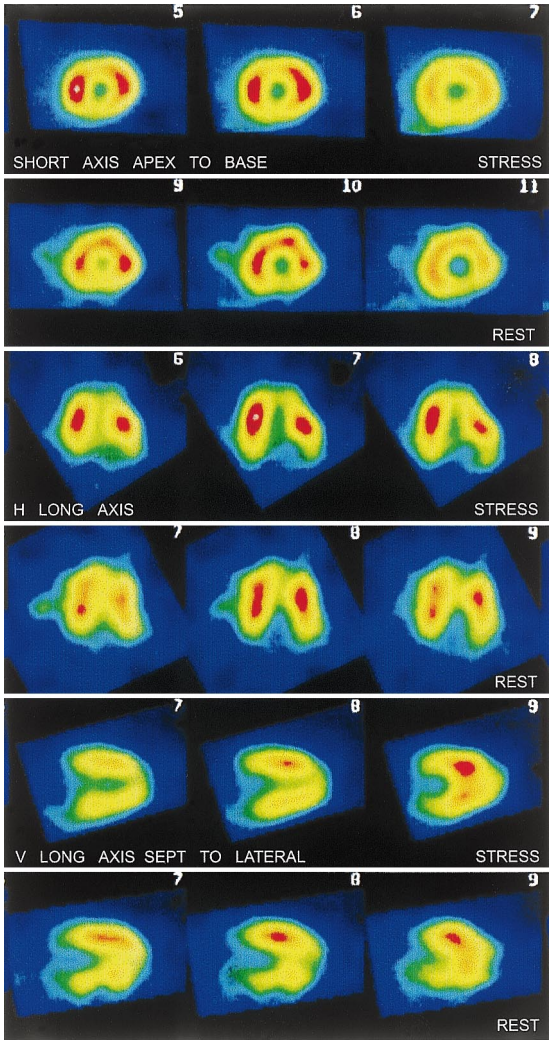

Fig. 2. ^{201}Tl SPECT at rest, and after dipyridamole stress test, in patient N66. Short axis (apex to base) and long axis (septum to lateral) slices are shown displaying 18 myocardial segments. Stress scintigrams show a ^{201}Tl uptake defect in the anterior and lateral wall that partially reversed at rest.

Table 4
Spirometric data

N/sex	Age	Sarcoglycan defect	Spirometric data					
			FVC (ml)	FVC (%)	PEF (ml)	PEF (%)	FEV_1 (ml)	FEV_1 (%)
N148/F	27	α-Sarco	2820	83	3120	76	2750	92
N149/F	33	α-Sarco	3180	90	3360	81	2520	81
N620/F	46	α-Sarco	1130	34	1290	37	930	30
N329/F	25	β-Sarco	2330	56	3550	67	2280	65
N330/M	23	β-Sarco	4500	96	4920	87	3280	83
N111/F	23	γ-Sarco	2160	66	2170	55	1780	62
N115/F	20	γ-Sarco	1590	39	3010	57	1290	37
N114M	25	γ-Sarco	3200	75	4090	76	3090	85
N421/M	28	γ-Sarco	2260	50	3400	47	2040	53
N2576/F	10	γ-Sarco	1920	70	2580	76	1900	83
N2799/F	4	γ-Sarco	n.a.					
N2896/M	5	γ-Sarco	n.a.					
N2899/F	34	γ-Sarco	n.a.					
N234/F	23	γ-Sarco	2540	64	2620	58	2440	69
N2902/M	22	γ-Sarco	4300	90	5120	90	3500	88
N950/F	28	γ-Sarco	1620	45	1870	26	1300	41
N66/F	28	γ-Sarco	2450	88	3330	93	2400	100
N3300/M	9	γ-Sarco	1490	67	1780	63	1420	77
N2858/F	13	δ-Sarco	2630	76	2340	55	2350	81
N2859/F	17	δ-Sarco	2150	54	2200	49	2870	53

3.5. Respiratory involvement

No patient was a smoker nor affected by a respiratory illness. Spirometric data of all patients are listed in Table 4. Table 6 summarizes the type of respiratory involvement.

Four (23.5%) patients had a normal respiratory function. A mild involvement with FVC values ranging from 66 to 83% occurred in six (35.4%) patients. A moderate involvement with FVC values ranging from 45 to 64% was found in five (29.4%). A severe impairment with FVC values under 40% was noted in two (11.7%). One patient (N620F) died from acute lung failure at the age of 48 years.

4. Discussion

Limb-girdle muscular dystrophies (LGMDs) in general, and sarcoglycanopathies in particular, show different clinical phenotypes that range from the severe Duchenne-like muscular dystrophy to later onset Becker-like muscular dystrophy. Cardiac involvement has rarely been investigated in LGMDs compared with the X-linked Duchenne or Becker muscular dystrophies, where it is well known as a significant component of the clinical features.

In patients with DMD-like muscular dystrophy, sinus tachycardia, tall R waves in V1–V2, and deep Q waves have been described, while up to now, there have only been a few reports concerning ECG and/or echocardiographic abnormalities, or occasional descriptions of cardiomyopathy in patients with LGMDs [20,27–33]. Consequently, in these patients a clear genotype–phenotype correlation could not be established, because DNA analysis was not performed. Melacini et al. [34] suggested that a mild cardiac involvement occurred in about 30% of primary sarcoglycanopathies, in their group of patients immunocytochemically diagnosed.

In contrast to previous reports on cardiac involvement in sarcoglycan-deficient LGMD patients, the major part of our patients have been characterized by molecular analysis. A pre-preclinical cardiomyopathy (QT/PQs ratio > 4.5) was observed in about 40% of cases. Signs of an evident cardiac

Table 5
Cardiac involvement in sarcoglycanopathies

	n	Normal heart	Pre-symptomatic cardiomyopathy	Arrhythmogenic cardiomyopathy	Dilated cardiomyopathy
α-Sarcoglycanopathy	3	2 (66.6%)	1 (33.3%)	0	0
β-Sarcoglycanopathy	2	0	1 (50.0%)	1 (50%)	0
γ-Sarcoglycanopathy	13[a]	3 (33.3%)	4 (44.4%)	0	2 (22.2%)
δ-Sarcoglycanopathy	2	0	1 (50.0%)	0	1 (50.0%)
Total	20[a]	5 (31.3%)	7 (43.7%)	1 (6.3%)	3 (18.7%)

[a] Data not available in four patients.

Table 6
Respiratory involvement in sarcoglycanopathies

	n	Normal function	Mild involvement	Moderate involvement	Severe involvement
α-Sarcogylcanopathy	3	1 (33.3%)	1 (33.3%)	0	1 (33.3%)
β-Sarcogylcanopathy	2	1 (50.0%)	0	1 (50.0%)	0
γ-Sarcogylcanopathy	13[a]	2 (20.0%)	4 (40.0%)	3 (30.0%)	1 (10.0%)
δ-Sarcogylcanopathy	2	0	1 (50.0%)	1 (50.0%)	0
Total	20[a]	4 (23.5%)	6 (35.4%)	5 (29.4%)	2 (11.7%)

[a] Data not available in three patients.

involvement (arrhythmogenic or dilated) occurred in about 25% of cases. In α-sarcoglycanopathies cardiac involvement remains a rare occurrence as expected, both for the lower expression of adhalin in heart muscle and a hypothesized substitutive function of the ε-sarcoglycan. Among cases with the γ-sarcoglycanopathies, patients carrying the typical Tunisian mutation Δ*521T* presented a mild cardiac involvement while both cases with the deletion involving the entire exon 7 showed initial signs of a dilated cardiomyopathy (fractional shortening below 30%). In one of them (N66F) the SPECT study showed the presence of a ^{201}Tl uptake reversible defect.

This feature is partially unexpected in subjects where myocardial involvement should be mainly due to replacement of myocytes by fibrous tissue. Gorospe et al. [35] have suggested that an increased number of mast cells – recently shown to accumulate in degenerating muscle tissue and to secrete vasoconstrictor cytokines – could potentiate muscle damage through an ischaemic mechanism besides the altered membrane permeability and the consequent replacement of myocytes by fibrous tissue.

An abnormal coronary smooth muscle function has been also suggested by Gnecchi-Ruscone et al. [36] among the factors involved in the development of cardiomyopathies in β and δ-sarcoglycanopathies; in fact, they demonstrate that the δ-sarcoglycan and, to a lesser extent, the β-sarcoglycan are expressed in the coronary arteries. Although our patient did not undergo a coronary angiography, the presence of coronary artery stenoses can theoretically be excluded for reasons of sex, youth and the absence of glucose or lipid dysmetabolism.

No correlation was found between skeletal muscle and cardiac involvement, as the three patients with the initial signs of a dilated cardiomyopathy where either long-time wheelchair-bound or still ambulant.

Respiratory involvement is a constant feature of Duchenne muscular dystrophy and a cause of death in about 40–50% of all patients. Patients with severe childhood autosomal recessive muscular dystrophy (SCARMD) exhibit a restrictive ventilatory syndrome very similar to that observed in DMD patients, while patients with LGMD phenotype show a respiratory involvement resembling that observed in Becker patients.

In our patients older than 15 years, none of them smokers, a respiratory impairment was present in all types of sarcoglycanopathies, although the most part exhibited a mild to moderate involvement. A severe respiratory insufficiency was observed in α- and γ-sarcoglycanopathies. In one patient with α-sarcoglycan deficiency, the ventilatory failure was the cause of death.

The absence of smoking, or secondary cardiac and respiratory illnesses, possibly influencing the observed data in a population genetically well determined strongly suggest that cardiac and respiratory involvement in sarcoglycanopathies are disease related and can complete the clinical spectrum – as happens in Duchenne and Becker muscular dystrophies. The variable occurrence of cardiac and respiratory involvement in sarcoglycanopathies may be related to the different expression of α-, β-, γ-, and δ-sarcoglycans in heart and muscles.

The limited sample size of the current study obviously hampers definitive conclusions. Longer-term research in a larger patient population will provide more precise information about the occurrence and progression of cardiac and respiratory involvement in sarcoglycanopathies.

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