Journal of Neurology (2019) 266:1367–1375
https://doi.org/10.1007/s00415-019-09267-3

ORIGINAL COMMUNICATION

Congenital myopathies are mainly associated with a mild cardiac phenotype

Helle Petri[1] · Karim Wahbi[2] · Nanna Witting[3] · Lars Køber[1] · Henning Bundgaard[1] · Emna Kamoun[4] · Geoffroy Vellieux[4] · Tanya Stojkovic[4] · Anthony Béhin[4] · Pascal Laforet[5,6] · John Vissing[3]

Received: 9 November 2018 / Revised: 27 February 2019 / Accepted: 4 March 2019 / Published online: 14 March 2019

Abstract

Background To evaluate the prevalence of cardiac involvement in patients with congenital myopathies and the association to specific genotypes.

Methods We evaluated patients with physical examination, electrocardiogram, echocardiography, and 48-h Holter monitoring. Follow-up was performed for major events.

Results We included 130 patients, 55 men (42%), with a mean age of 34 ± 17 years. A genetic diagnosis was established in 97 patients (75%). Right bundle branch block was observed in three patients: 2/34 patients with a ryanodine receptor 1 (*RYR1*) and 1/6 with a tropomyosin two gene (*TPM2*) gene mutation. Echocardiography showed left-ventricular hypertrophy in five patients: 2/17 and 3/34 patients with a Dynamin 2 (*DNM2*) and a *RYR1* mutation, respectively. One patient with a myosin heavy-chain (*MYH7)* mutation had dilated cardiomyopathy and heart failure. On Holter monitoring, frequent ventricular premature contractions were observed in one patient with a *DNM2* mutation. Two patients with a *TPM2* and a *RYR1* mutation, respectively, had a single short run of non-sustained ventricular tachycardia. Atrioventricular nodal re-entry tachycardia was observed in a 20-year-old man with an *actin 1 gene* mutation. During follow-up (median 8.4 years), four patients died, all of non-cardiac causes.

Conclusion Congenital myopathies are generally associated with a mild cardiac phenotype. Our findings substantiate the literature and indicate that, except for patients with specific genotypes, such as *MYH7* and *TTN* mutations, repeated cardiac assessments can be minimized, given a normal initial cardiac screening at time of diagnosis.

Keywords Congenital myopathies · Arrhythmia · Echocardiography · Heart failure

Introduction

Congenital myopathies (CM) are a group of inherited neuromuscular diseases with early onset and substantial phenotypic, genetic, and histological variation [15]. The prevalence is estimated to be one in 26,000–28,000, with mutations in *RYR1* (encoding ryanodine receptor 1) being the most prevalent (≈ 1 in 90,000) [3]. Historically, the diagnosis of CM was based on demonstration of characteristic histopathological features in muscle, but molecular genetic advances have shown that one histological feature can be associated with multiple genotypes and vice versa [17, 22, 48].

Clinically, CMs are characterized by hypotonia and weakness, usually from birth, with a static or slow progressive clinical course [17, 32]. Patients typically present with facial weakness, generalized hypotonic posture, proximal muscle

✉ Helle Petri
Hellepetri1@gmail.com

1 Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

2 APHP, Cochin Hospital, Cardiology Department, Centre de Référence de Pathologie, Neuromusculaire Nord/Est/Ile de France, Paris-Descartes, Sorbonne Paris Cité University, 75006 Paris, France

3 Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

4 Myology Institute, Nord/Est/Ile de France Neuromuscular Center, Pitié-Salpêtière hospital, APHP, Paris, France

5 Neurology Department, Nord/Est/Ile de France Neuromuscular Center, Raymond Poincaré Teaching Hospital, APHP, 92380 Garches, France

6 END-ICAP, INSERM U1179, Université Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France

weakness, and dysfunction of the respiratory and bulbar muscles [17, 32, 38]. Severity of symptoms varies widely, from neonates with generalized and life-threatening weakness to older patients with subtle proximal muscle weakness.

Cardiac involvement in CM has only been sparsely reported [17, 32]. However, hypertrophic [8, 27, 30, 41], dilated [1, 14, 29, 31, 42] and left-ventricular non-compaction cardiomyopathy [11, 40] as well as sudden death [24] have been described, mainly in infants. The existing literature relies on smaller studies often restricted to specific CM genotypes and a systematic cardiac assessment has not been performed in the existing larger cohort studies [3, 9, 10, 22, 44]. Therefore, knowledge about the association between cardiac involvement and genetic subgroups of CMs is sparse.

We describe the prevalence and types of cardiac involvement in 130 patients with CM and the association with specific genetic mutations. In addition, follow-up was performed for major evens (sudden cardiac death, cardiac, and all-cause mortality).

Methods

Study design

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

Patients were evaluated with history, physical examination, 12-lead ECG, trans-thoracic echocardiography, and 48-h ECG monitoring (Holter monitoring). Blood samples were analyzed for plasma levels of NT-proBNP, creatine kinase (CK) and myoglobin, and screened for liver, renal, and thyroid diseases.

We collected follow-up data on all included patients, exclusively regarding mortality (time and cause of death) and hospitalization for cardiac causes. Repeated cardiac assessments were only performed in patients with clinical significant cardiac involvement.

Study population

All genetically classified patients with CM registered at the Neuromuscular Clinic at Rigshospitalet and at Petié Salpêtriére Hospital were invited to participate. Unclassified French patients suspected of having CM were not included as such patients were not systematically registered at the Paris site.

All participating patients provided written informed consent. Patients with adult onset, as evidenced by history and clinical findings, fast progression, creatine kinase levels ≥ 600 U/l, dystrophic features as the main histological finding, or other explanation of disease, were excluded from the study.

Genetic testing

DNA was isolated from a 6 ml EDTA blood sample using a standard desalting procedure and the PCR amplified exons of the genes investigated were sequenced from genomic DNA. The following proteins and related genes were analyzed: skeletal muscle alpha actin 1 (*ACTA1*), amphiphysin (*BIN1*), dynamin 2 (*DNM2*), beta myosin heavy chain (*MYH7*), myotubularin (*MTM1*), nebulin (*NEB*), skeletal muscle ryanodine receptor (*RYR1*), α-subunit of the skeletal muscle voltage-gated sodium channel (*SCN4A*), selenoprotein N (*SEPN1*), and tropomyosin2 and 3 (*TPM2* and *TPM3*). The choice of specific genetic tests was mainly informed by the presence of suggestive clinical and histopathological features and, where available, muscle imaging features. Genes were analyzed by either single-gene Sanger sequencing or by next-generation-sequencing technique, using either a gene panel or exome approach [48].

In this manuscript, we use the term "mutation" about the genetic variations that categorize the specific subgroups, as these mutations are either previously described, well-established disease-causing genetic variants or assumed disease-causing genetic variants (predicted by various in silico prediction tools).

Electrocardiography

Standard ECG was obtained and the ECG was considered abnormal in the presence of; atrial flutter/fibrillation (AFL/AF), other supraventricular tachyarrhythmia (SVT) including atrial and re-entry tachycardia, atrioventricular block (AVB) grades I–III (AVB I: PR interval > 200 ms), right and left bundle branch block (RBBB/LBBB), and prolonged QTc interval (> 450 ms in men and > 470 ms in women) using Bazett´s formula ($QTc = QT/\sqrt{RR}$).

Echocardiography

Echocardiography was performed and the examinations were obtained and analyzed by a single operator/observer at each hospital (HP and KW). The examinations were discussed with other members of the study group in case of uncertainty or suboptimal image quality. Three consecutive heart cycles were recorded and images were obtained at a frame rate of ≥ 60 frames/s.

Two-dimensional parasternal images were used to determine left-ventricular (LV) cavity dimensions and wall thickness. LV volumes were determined using the biplane Simpson model. Left atrial (LA) volume was calculated from the

biplane area-length method with maximum volume before mitral valve (MV) opening (LA_{max}) and minimum volume just before MV closure (LA_{min}). Volumetric and dimensional measurements of the left ventricle and left atrium were indexed to body surface area. All volumetric analyses were performed in accordance with the recommendations from the European association of echocardiography and the American society of echocardiography [20]. Left-ventricular systolic dysfunction (LVSD) was defined as a biplane left-ventricular ejection fraction (LVEF) ≤ 50%.

Holter monitoring

A 48-h Holter monitoring was performed and was considered abnormal in the presence of: AVB grades I–III, AF/AFL, other supraventricular tachyarrhythmia (> 30 SVES/h or runs of ≥ 20 SVES), frequent ventricular premature contractions (VPCs) (≥ 30/h), and non-sustained ventricular tachycardia (NSVT) (minimum of three beats at ≥ 100 bpm). Recordings were evaluated by a single observer at each site (HP + KW) and discussed in the study group in case of difficulties in interpretation.

Statistics

Data were analyzed with IBM SPSS Statistics version 22. Normally distributed values are expressed as means ± SD. Data with skewed distribution are given as median (range).

Categorical variables were summarized by frequency counts (%). Results of continuous variables are presented as median (range). Comparison among groups was assessed using Mann–Whitney U-test. A p value ≤ 0.05 was considered statistically significant.

Results

Study population

We included a total of 130 patients with a mean age of 34 ± 17 years, 75 women, mean age 36 ± 18 years and 55 men, mean age 31 ± 15 years, 57 vs. 73 patients representing the French and Danish cohort, respectively. Patients were grouped according to genetic mutation (Table 1). 19 patients were < 18 years old, range 8–17 years. A genetic diagnosis was established in 97 patients (75%), while the remaining 33 patients, all originating from the Danish cohort, relied on a clinical and histopathological diagnosis of CM. Ten patients refused to participate due to long distances to the hospital. There was no significant demographic, genetic, or disease severity differences between these patients and the remaining study participants.

In patients with *RYR 1* mutations, patients with cardiac involvement were significantly older than the remaining patients in this subgroup. There was no significant difference in age between patients with and without cardiac involvement in the remaining subgroups (Table 2).

Cardiac involvement

Symptoms

The most predominant symptoms were muscular weakness and fatigability, which, in varying degree, were present in all patients. In total, three patients (2%) had experienced syncope, and dyspnoea was reported in 16 (16%), palpitations in 17 (13%), peripheral oedema in 2 (2%), and angina in 5 patients. None of the patients had hypertension.

Biochemistry

Median CK was 96 U/l (range 18–600; normal range: 50–270 U/l), but mildly elevated in 13% of the patients. Myoglobin was mildly elevated in 25% of the patients. NT-proBNP was available in 69 (53%) of the patients, all within normal range [median 9 pmol/l (9–22)] (Table 1).

ECG and Holter monitoring

Cardiac findings are summarized in Table 1.

All patients with abnormal cardiac findings on ECG and Holter monitoring were asymptomatic, except for one patient: a 20-year-old man with an *ACTA1* mutation, who complained of dyspnoea for the last 6 months. Spirometry showed a forced vital capacity of 55% of expected, ECG and echocardiography was normal, but Holter monitoring revealed atrioventricular nodal re-entry tachycardia (AVNRT) with a maximal frequency of 190 bpm. The AVNRT was treated successfully with radiofrequency ablation.

RBBB was present in three patients: a 36-year-old woman with a *RYR1* mutation, normal echocardiography, and Holter monitoring; a 55-year-old woman, also with a *RYR1* mutation and minimal LV hypertrophy on echocardiography (interventricular septum and left-ventricular posterior wall dimensions both measuring 12 mm, no available Holter monitoring), and a 73-year-old man with a *TPM2* mutation and otherwise normal cardiac parameters.

Abnormal findings on Holter monitoring were present in the following patients: a 52-year-old woman with a *DNM2* mutation had frequent VPC (8.129 VPCs/48 h), normal ECG and echocardiography. Two patients (men, aged 62 and 80 years) both with a *RYR1* mutation, had frequent SVES (1661 and 8770 SVES/48 h, respectively) and the

Table 1 Demographic and cardiac findings in patients with genetically classified and unclassified congenital myopathies

	All	ACTA1	BIN1	DNM2	MTM1	MYH7	NEB	RYR1	SCN4A	SEPN1	TPM2	TPM3	TTN	UC
Patients (*n*)	130	5	1	17	4	15	8	34	1	3	6	2	1	33
Age (years), mean (SD)	34 (17)	20 (13)	46	41 (15)	29 (13)	48 (20)	29 (14)	35 (16)	30	28 (5)	40 (20)	22 and 27	13	26 (14)
Gender (*n*), men/women	55/75	3/2	0/1	7/10	2/2	4/11	3/5	15/19	0/1	0/3	3/3	2/0	1/0	15/18
SBP (mmHg), mean (SD)	127 (18)	130	130	126 (23)	ND	148 (11)	140 (13)	124 (17)	ND	134	133 (27)	ND	ND	114
DBP (mmHg), mean (SD)	75 (11)	67	80	74 (14)	ND	93 (4)	76 (6)	73 (10)	ND	74	71 (11)	ND	ND	82
CK (U/l), median (range)	96 (18–600)	38 (23–66)	136	123 (18–517)	116 (26–211)	262 (51–505)	24 (21–104)	74 (22–600)	118	151 (149–152)	104 (28–480)	124 (45)	ND	97 (23–460)
Myoglobin (ug/l), median (range)	35 (20–350)	24 (20–28)	ND	54 (26–281)	32 (28–35)	NA	23 (20–61)	39 (20–131)	57	47 (32–62)	22 (20–266)	52 (6)	ND	35 (20–350)
ECG (*n*)	126	5	1	17	4	14	8	31	1	3	6	2	1	33
IRBBB (*n*)	24	0	0	2	1	0	2	4	0	1	0	1	0	13
RBBB (*n*)	3	0	0	0	0	0	0	2	0	0	1	0	0	0
PR interval (ms), median (range)	150 (99–200)	148 (112–150)	150	136 (102–175)	154 (152–155)	160 (138–200)	152 (138–188)	151 (99–200)	110	142 (122–166)	145 (122–188)	152 (134–170)	168	140 (108–186)
QRS interval (ms), median (range)	86 (60–168)	84 (76–88)	74	82 (68–116)	91 (84–136)	83 (60–100)	97 (70–104)	90 (72–130)	74	78 (70–82)	88 (82–168)	97 (92–102)	74	84 (68–114)
QTc interval (ms), median (range)	403 (354–477)	399 (396–463)	379	397 (369–477)	436 (395–437)	405 (385–460)	396 (380–450)	403 (354–440)	381	396 (394–308)	401 (367–420)	387 (386–388)	411	403 (369–437)
Echocardiography (*n*)	124	5	1	16	3	14	8	31	1	3	6	2	1	33
LVEF (%), median (range)	65 (29–80)	55 (55–65)	65	64 (55–80)	55 (55–75)	63 (29–79)	55 (55–60)	63 (55–77)	55	55	58 (55–65)	55	55	55 (55–60)
IVS (mm), median (range)	8 (3–13)	8 (5–10)	8	8 (7–13)	6 (4–9)	9 (7–12)	8 (5–9)	8 (3–12)	7	7 (6–7)	7 (6–11)	6 (4–8)	4	8 (4–11)
LVEDD (mm), median (range)	45 (30–74)	43 (30–40)	48	46 (37–54)	38 (24–42)	45 (37–74)	49 (38–54)	46 (33–54)	43	35 (31–40)	47 (44–54)	42 (38–45)	40	43 (33–51)
LVPW (mm), median (range)	9 (4–15)	9 (7–10)	7	7 (6–11)	7 (6–8)	8 (6–10)	8 (4–10)	8 (4–15)	7	7	7 (5–8)	6 (4–8)	6	8 (1–9)
Holter monitoring (*n*)	72	4	1	5	2	2	6	11	1	2	5	2	1	30
AF/AFL (*n*)	0	0	0	0	0	0	0	0	0	0	0	0	0	1[#]
Freqent VPC > 30/h, (*n*)	1	0	0	1	0	0	0	0	0	0	0	0	0	0
SVT, (*n*)	5	1	0	0	0	0	0	2	0	0	0	0	0	2
NSVT	0	0	0	0	0	0	0	1*	0	0	1*	0	0	0

DBP diastolic blood pressure, *IVS* interventricular septum, *LVEDD* left-ventricular end-diastolic diameter, *LVEF* left-ventricular ejection fraction, *LVPW* left-ventricular posterior wall, *NSVT* non-sustained ventricular tachycardia, *ND* not determined, *PAF* paroxysmal atrial fibrillation, *RBBB* right bundle branch block, *SBP* systolic blood pressure, *SVT* supraventricular tachycardia, *VPC* ventricular premature contractions, *UC* unclassified congenital myopathy

*single run of NSVT

#Paroxysmal atrial fibrillation

Table 2 Comparison of age according to patients with and without cardiac involvement

	Cardiac involvement		No cardiac involvement		*p* value
	n	Age (years), mean (SD)	*n*	Age (years), mean (SD)	
ACTA1	1	20	4	22 (12)	1.00
BIN1	0		1	46	
DNM2	3	53 (1)	14	39 (15)	0.12
MTM1	1	25	3	30 (13)	0.66
MYH7	1	44	14	50 (19)	0.32
NEB	2	31 (4)	6	31 (13)	1.00
RYR1	7	45 (17)	27	33 (14)	0.05
SCN4A	0		1	30	
SEPN1	1	23	2	31 (3)	0.22
TPM2	2	56 (17)	4	32 (12)	0.36
TPM3	1	27 (0)	1	22 (0)	0.32
TTN	0		1	13	
UC	13	24 (12)	20	28 (15)	0.5

62-year-old man also had a single short run of NSVT. A 40-year-old asymptomatic woman with a *TPM2* mutation, normal ECG and echocardiography, had a single short run of NSVT without indication for further investigation or treatment.

Furthermore, 3/33 patients with unclassified CM had an abnormal Holter: two patients with SVT (a 41-year-old woman and a 35-year-old man) and a 32-year-old man with paroxysmal atrial fibrillation.

None of the patients had AVB grades I–III, prolonged QTc interval, or indication for pacemaker implantation.

Echocardiographic findings

One patient had reduced LVEF: a 44-year-old man, diagnosed with CM and a *MYH7*-mutation (c.5401G > A) at the age of 36 years. At age 44 years, he was diagnosed with dilated cardiomyopathy (DCM), LVIDD 74 mm, severe heart failure (LVEF 29%) and had an ICD implantation for primary prevention. The patient was later hospitalized for pulmonary oedema and is currently (age 48 years) awaiting a heart transplantation. There has been no anti-tachycardia pacing or shock therapy from the ICD.

The remaining patients had normal right-ventricular function median (range) TAPSE 22 (16–31 mm), normal left-ventricular ejection fraction (LVEF ≥ 50%), and structurally and functionally normal valves.

In total, five patients had LV hypertrophy on echocardiography: as previously mentioned, a 55-year-old woman with a *RYR1* mutation, two patients with *DNM2* mutations with IVS at 12 and 13 mm (two men, 52 and 54-year-old, respectively); a 38-year-old woman with a *RYR1* mutation (IVS 12 and LVPW 15 mm), and a 32-year-old woman with a *RYR1* mutation (IVS at 13 mm). The patients had normal cardiac findings otherwise.

Additional findings

One patient, a 78-year-old man with a *MYH7* mutation (c.5186_5188del) and normal cardiac assessment, had four family members (two sons, one daughter, and one nephew) who were diagnosed with the same *MYH7* mutation and had ICDs implanted (two sons after cardiac arrest and the two remaining patients for primary prevention). Unfortunately, we have no available cardiac data for these patients.

Follow-up for cardiac and all-cause mortality

During follow-up [median (range) 8 years (0.6–26)], four patients died; three men (age 13, 25, 70 years) with *TTN*, and *RYR1* mutations and unclassified CM, respectively, and one woman (age 72 years) with a *DNM2* mutation. All three men died of respiratory insufficiency. The two men, age 13 and 25 years, had an echocardiography performed at admission few days prior to death to assess if there was an underlying cardiac cause to their respiratory insufficiency and both patients had normal echocardiographic parameters. There were no available data concerning cause of death in the 72-year-old woman.

Discussion

In the present study, we systematically investigated a large cohort of patients with CM, aged 6–80 years (mean 34 ± 17 years) for cardiac involvement and the association to specific genetic mutations. One patient with a *MYH7* mutation had DCM, severe heart failure, and an ICD for primary prevention. The remaining patients had normal left- and right-ventricular ejection fraction, no clinical significant valve disease, or indication for ICD- or pacemaker implantation. During follow-up (median 8.4 years) regarding mortality, four patients died, all of non-cardiac causes.

RBBB has been shown to associate with a ~ 30% increased mortality risk mainly due to cardiovascular disease [5]. The prevalence of RBBB in our cohort was low, and for men, comparable with a large cohort study of healthy individuals (men 1.8% vs. 1.4%) [5]. However, compared with the same study, we found a notably higher prevalence in women (2.6% vs. 0.5%) [5]. During follow-up, none of the patients with RBBB developed cardiac symptoms or was diagnosed with further cardiac involvement. RBBB has not previously been associated with CM. Therefore, the prognostic value of RBBB in our patients remains uncertain and

underlines the importance of follow-up of patients with CM with an abnormal cardiac assessment at time of diagnosis.

Except for one patient with a *MYH7* mutation, none of the patients fulfilled the criteria for DCM or hypertrophic cardiomyopathy (HCM) or had symptoms and/or signs of heart failure. In accordance, there are no larger studies reporting an association between adult CMs and cardiomyopathy or heart failure. However, HCM and DCM in patients with CM have been reported in small series or case reports, mainly in neonates secondary to respiratory insufficiency, and mainly in patients with nemaline myopathy, often lacking a genetically verified diagnosis [2, 8, 14, 18, 27–31, 39, 41, 42]. If cardiomyopathy occurs in patients with CM, independently of primary respiratory insufficiency, considerations should include recessive mutations in *TTN* and *MYH7*, which, in a few cases, have been associated with minicore-like disease with early development of DCM and HCM, ventricular arrhythmias, and sudden cardiac death [6, 7, 16, 17, 36, 43, 45, 47, 49]. We included one patient with a *TTN* mutation; a 12-year-old male with normal cardiac examination at inclusion, who died of respiratory failure less than 1 year after the cardiac examination.

As mentioned previously, 1/15 patients with *MYH7* mutations had DCM and severe heart failure. Mutation in *MYH7* is one of the most common causes of isolated hypertrophic cardiomyopathy [23]. Mutations accounting for the cardiac or skeletal muscle disorders cluster in different parts of the protein, where most cardiomyopathy related mutations are located in the globular head domain, potentially affecting the binding sites for actin, whereas those related to skeletal myopathy are usually located in the distal regions of the rod domain [13, 46]. However, there is a great overlap of phenotypes as cases with both heart and muscular manifestations have been described [13].

For several of the disease-causing mutations of CM, other isoforms of the involved proteins are expressed in adult human cardiomyocytes, which may explain the mild cardiac phenotype in patients with CM. *RYR1* is, for example, not known to be associated with cardiac disease, as it is not expressed in adult human cardiomyocytes, whereas *RYR2* is highly associated with catecholaminergic polymorph ventricular tachycardia and SCD [4, 19, 37].

We included only one patient with mutation in *SCN4A*, who had no cardiac involvement. Current knowledge about cardiac involvement in these patients is very limited, but our findings are in accordance with the first report of this disease in 12 patients with *SCN4A* mutations, who all had normal cardiac parameters [50].

Except for patients with *RYR1* mutations, patients with cardiac involvement were not significantly older than patients without cardiac involvement. The *RYR1* subgroup is the largest in this study, and the lack of significance in age difference between patients with and without cardiac involvement in the remaining subgroups may be due to the small sample size.

Larger studies are needed to explore the association between functional and clinical expression of the underlying specific mutations in patients with CM.

Our findings are in contrast with the observations in patients with other neuromuscular diseases, such as Myotonic dystrophy type 1 (DM1), Becker (BMD), and Duchenne and certain subtypes of limb-girdle muscular dystrophies, which are known to be associated with much more severe cardiac phenotypes and in whom regular cardiac follow-up is mandatory [21, 25, 26, 33–35]. In DM1, conduction abnormalities and arrhythmias are highly prevalent and the previous studies report a prevalence of reduced pump function of ~ 20%, which is approximately seven times higher than in the background population [34, 35].

According to The American Heart Association, cardiac disease in CMs is rare, and given the diversity of clinical manifestations in the various CMs, there are no evidence-based data to drive guidelines [12]. The present study supports this statement, and in line with the recommendations from AHA, it seems reasonable to perform cardiac evaluation with clinical examination, ECG, Holter monitoring, and echocardiography at time of CM diagnosis, with follow-up assessments determined by the presence of abnormal findings on the initial screening or development of cardiac symptoms [12]. However, in accordance with a recent review by Jungbluth et al. and our current findings, more regular follow-up is needed in patients with *MYH7* and *TTN* mutations [17].

In our study, patients with unclassified CM had no significant cardiac involvement, indicating that there is no need for increased cardiac surveillance, although it should be noted that the review by Jungbluth et al. [17] recommends regular cardiac monitoring in these patients.

Taken together, we found a very low prevalence of and mainly only mild cardiac involvement in patients with genetically classified and unclassified CMs. Our findings together with the existing literature indicate that, with the exception for patients with specific genotypes, such as *MYH7* and *TTN* mutations, repeated cardiac assessments can be minimized in patients with CM, given a normal initial cardiac screening at time of diagnosis. However, we acknowledge that our findings need to be confirmed in larger studies.

Strengths and limitations

We systematically assessed a large cohort of patients with CMs for cardiac involvement and reached a genetic diagnosis in 75% of the patients. Although we achieved a high diagnostic rate, we need to explore the genetic basis for the remaining unresolved CMs [22]. Nevertheless, it strengthens our findings that the cardiac findings are similar in both

patients with and without a genetic diagnosis, demonstrating that CMs are generally associated with a mild cardiac phenotype. Patients were systematically assessed with conventional non-invasive cardiac modalities (ECG, echocardiography, and Holter monitoring), which is commonly sufficient to detect significant cardiac involvement. However, other diagnostic tools are more adequate for detecting subtle myocardial changes such as fibrosis and fat infiltration. Strain rate and tissue velocity by echocardiography and especially cardiac magnetic resonance (CMR) are potential additive and sensitive tools for accurate detection of such changes, which are possible predictive markers of cardiac outcome.

Our study showed that CMs are generally associated with a mild cardiac phenotype. However, we acknowledge that, due to the small sample size of several genotypes, definite conclusions about cardiac involvement cannot be drawn and stresses the need for larger studies, assessing the association between cardiac involvement and specific CM genotypes. Furthermore, we need to explore the degree of cardiac involvement in neonates and early childhood as we only included patients above 8 years of age in this study.

Conclusion

In this study, we found a very low prevalence of and mainly only mild cardiac involvement in patients with genetically classified and unclassified congenital myopathies.

Our findings substantiate the literature and indicate that, except for patients with specific genotypes, such as *MYH7* and *TTN* mutations, repeated cardiac assessments can be minimized, given a normal initial cardiac screening at time of diagnosis.

Funding This work was supported by The Research Foundation of Rigshospitalet, The Danish Heart Foundation, The Lundbeck Foundation, and The Stibo Foundation.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Agrawal PB, Pierson CR, Joshi M, Liu X, Ravenscroft G, Moghadaszadeh B, Talabere T, Viola M, Swanson LC, Haliloglu G, Talim B, Yau KS, Allcock RJ, Laing NG, Perrella MA, Beggs AH (2014) SPEG interacts with myotubularin, and its deficiency causes centronuclear myopathy with dilated cardiomyopathy. Am J Hum Genet 95:218–226
2. Al-Ruwaishid A, Vajsar J, Tein I, Benson L, Jay V (2003) Centronuclear myopathy and cardiomyopathy requiring heart transplant. Brain Dev 25:62–66
3. Amburgey K, McNamara N, Bennett LR, McCormick ME, Acsadi G, Dowling JJ (2011) Prevalence of congenital myopathies in a representative pediatric united states population. Ann Neurol 70:662–665
4. Broendberg AK, Nielsen JC, Bjerre J, Pedersen LN, Kristensen J, Henriksen FL, Bundgaard H, Jensen HK (2017) Nationwide experience of catecholaminergic polymorphic ventricular tachycardia caused by RyR2 mutations. Heart 103:901–909
5. Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E (2013) Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. Eur Heart J 34:138–146
6. Carmignac V, Salih MA, Quijano-Roy S, Marchand S, Al Rayess MM, Mukhtar MM, Urtizberea JA, Labeit S, Guicheney P, Leturcq F, Gautel M, Fardeau M, Campbell KP, Richard I, Estournet B, Ferreiro A (2007) C-terminal titin deletions cause a novel early-onset myopathy with fatal cardiomyopathy. Ann Neurol 61:340–351
7. Cullup T, Lamont PJ, Cirak S, Damian MS, Wallefeld W, Gooding R, Tan SV, Sheehan J, Muntoni F, Abbs S, Sewry CA, Dubowitz V, Laing NG, Jungbluth H (2012) Mutations in MYH7 cause multi-minicore disease (MmD) with variable cardiac involvement. Neuromuscul Disord 22:1096–1104
8. D'Amico A, Graziano C, Pacileo G, Petrini S, Nowak KJ, Boldrini R, Jacques A, Feng JJ, Porfirio B, Sewry CA, Santorelli FM, Limongelli G, Bertini E, Laing N, Marston SB (2006) Fatal hypertrophic cardiomyopathy and nemaline myopathy associated with ACTA1 K336E mutation. Neuromuscul Disord 16:548–552
9. Darin N, Tulinius M (2000) Neuromuscular disorders in childhood: a descriptive epidemiological study from western Sweden. Neuromuscul Disord 10:1–9
10. de VM, de Voogt, la Riviere WG GV (1992) The heart in Becker muscular dystrophy, facioscapulohumeral dystrophy, and Bethlem myopathy. Muscle Nerve 15:591–596
11. Esposito T, Sampaolo S, Limongelli G, Varone A, Formicola D, Diodato D, Farina O, Napolitano F, Pacileo G, Gianfrancesco F, Di IG (2013) Digenic mutational inheritance of the integrin alpha 7 and the myosin heavy chain 7B genes causes congenital myopathy with left ventricular non-compact cardiomyopathy. Orphanet J Rare Dis 8:91
12. Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, Judge DP, Lal AK, Markham LW, Parks WJ, Tsuda T, Wang PJ, Yoo SJ (2017) Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. Circulation 136:e200–e231
13. Fiorillo C, Astrea G, Savarese M, Cassandrini D, Brisca G, Trucco F, Pedemonte M, Trovato R, Ruggiero L, Vercelli L, D'Amico A, Tasca G, Pane M, Fanin M, Bello L, Broda P, Musumeci O, Rodolico C, Messina S, Vita GL, Sframeli M, Gibertini S, Morandi L, Mora M, Maggi L, Petrucci A, Massa R, Grandis M, Toscano A, Pegoraro E, Mercuri E, Bertini E, Mongini T, Santoro L, Nigro V, Minetti C, Santorelli FM, Bruno C (2016) MYH7-related myopathies: clinical, histopathological and imaging findings in a cohort of Italian patients. Orphanet J Rare Dis 11:91
14. Gatayama R, Ueno K, Nakamura H, Yanagi S, Ueda H, Yamagishi H, Yasui S (2013) Nemaline myopathy with dilated cardiomyopathy in childhood. Pediatrics 131:e1986–e1990
15. Hermans MC, Pinto YM, Merkies IS, de Die-Smulders CE, Crijns HJ, Faber CG (2010) Hereditary muscular dystrophies and the heart. Neuromuscul Disord 20:479–492
16. Homayoun H, Khavandgar S, Hoover JM, Mohsen AW, Vockley J, Lacomis D, Clemens PR (2011) Novel mutation in MYH7 gene associated with distal myopathy and cardiomyopathy. Neuromuscul Disord 21:219–222

17. Jungbluth H, Treves S, Zorzato F, Sarkozy A, Ochala J, Sewry C, Phadke R, Gautel M, Muntoni F (2018) Congenital myopathies: disorders of excitation-contraction coupling and muscle contraction. Nat Rev Neurol 14:151–167
18. Kim SY, Park YE, Kim HS, Lee CH, Yang DH, Kim DS (2011) Nemaline myopathy and non-fatal hypertrophic cardiomyopathy caused by a novel ACTA1 E239K mutation. J Neurol Sci 307:171–173
19. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, Donarum EA, Marino M, Tiso N, Viitasalo M, Toivonen L, Stephan DA, Kontula K (2001) Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation 103:485–490
20. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John SM, Stewart W (2006) Recommendations for chamber quantification. Eur J Echocardiogr 7:79–108
21. Lund M, Diaz LJ, Ranthe MF, Petri H, Duno M, Juncker I, Eiberg H, Vissing J, Bundgaard H, Wohlfahrt J, Melbye M (2014) Cardiac involvement in myotonic dystrophy: a nationwide cohort study. Eur Heart J 35:2158–2164
22. Maggi L, Scoto M, Cirak S, Robb SA, Klein A, Lillis S, Cullup T, Feng L, Manzur AY, Sewry CA, Abbs S, Jungbluth H, Muntoni F (2013) Congenital myopathies–clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. Neuromuscul Disord 23:195–205
23. Marian AJ, Braunwald E (2017) Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res 121:749–770
24. Marseglia L, D'Angelo G, Manti S, Salpietro V, Arrigo T, Cavallari V, Gitto E (2015) Sudden cardiac arrest in a child with nemaline myopathy. Ital J Pediatr 41:20
25. Mavrogeni S, Markousis-Mavrogenis G, Papavasiliou A, Kolovou G (2015) Cardiac involvement in Duchenne and Becker muscular dystrophy. World J Cardiol 7:410–414
26. Mavrogeni SI, Markousis-Mavrogenis G, Papavasiliou A, Papadopoulos G, Kolovou G (2018) Cardiac involvement in duchenne muscular dystrophy and related dystrophinopathies. Methods Mol Biol 1687:31–42
27. Mir A, Lemler M, Ramaciotti C, Blalock S, Ikemba C (2012) Hypertrophic cardiomyopathy in a neonate associated with nemaline myopathy. Congenit Heart Dis 7:E37–E41
28. Muller-Hocker J, Schafer S, Mendel B, Lochmuller H, Pongratz D (2000) Nemaline cardiomyopathy in a young adult: an ultraimmunohistochemical study and review of the literature. Ultrastruct Pathol 24:407–416
29. Nagata R, Kamimura D, Suzuki Y, Saito T, Toyama H, Dejima T, Inada H, Miwa Y, Uchino K, Umemura S, Shimizu M (2011) A case of nemaline myopathy with associated dilated cardiomyopathy and respiratory failure. Int Heart J 52:401–405
30. Nakajima M, Shima Y, Kumasaka S, Kuwabara K, Migita M, Fukunaga Y (2008) An infant with congenital nemaline myopathy and hypertrophic cardiomyopathy. J Nippon Med Sch 75:350–353
31. Nomura S, Funabashi N, Sekiguchi Y, Masuda S, Kuwabara S, Misawa S, Daimon M, Uehara M, Miyaiuchi H, Komuro I, Kobayashi Y (2011) Dilated cardiomyopathy with centronuclear myopathy in a young male. Int J Cardiol 150:213–216
32. North KN, Wang CH, Clarke N, Jungbluth H, Vainzof M, Dowling JJ, Amburgey K, Quijano-Roy S, Beggs AH, Sewry C, Laing NG, Bonnemann CG (2014) Approach to the diagnosis of congenital myopathies. Neuromuscul Disord 24:97–116
33. Petri H, Ahtarovski KA, Vejlstrup N, Vissing J, Witting N, Kober L, Bundgaard H (2014) Myocardial fibrosis in patients with myotonic dystrophy type 1: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 16:59
34. Petri H, Vissing J, Witting N, Bundgaard H, Kober L (2012) Cardiac manifestations of myotonic dystrophy type 1. Int J Cardiol 160:82–88
35. Petri H, Witting N, Ersboll MK, Sajadieh A, Duno M, Helweg-Larsen S, Vissing J, Kober L, Bundgaard H (2014) High prevalence of cardiac involvement in patients with myotonic dystrophy type 1: a cross-sectional study. Int J Cardiol 174:31–36
36. Petropoulou E, Soltani M, Firoozabadi AD, Namayandeh SM, Crockford J, Maroofian R, Jamshidi Y (2017) Digenic inheritance of mutations in the cardiac troponin (TNNT2) and cardiac beta myosin heavy chain (MYH7) as the cause of severe dilated cardiomyopathy. Eur J Med Genet 60:485–488
37. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, Sorrentino V, Danieli GA (2001) Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 103:196–200
38. Romero NB, Clarke NF (2013) Congenital myopathies. Handb Clin Neurol 113:1321–1336
39. Ryan MM, Schnell C, Strickland CD, Shield LK, Morgan G, Iannaccone ST, Laing NG, Beggs AH, North KN (2001) Nemaline myopathy: a clinical study of 143 cases. Ann Neurol 50:312–320
40. Simsek Z, Acar G, Akcakoyun M, Esen O, Emiroglu Y, Esen AM (2012) Left ventricular noncompaction in a patient with multiminicore disease. J Cardiovasc Med (Hagerstown) 13:660–662
41. Skyllouriotis ML, Marx M, Skyllouriotis P, Bittner R, Wimmer M (1999) Nemaline myopathy and cardiomyopathy. Pediatr Neurol 20:319–321
42. Taglia A, D'Ambrosio P, Palladino A, Politano L (2012) On a case of respiratory failure due to diaphragmatic paralysis and dilated cardiomyopathy in a patient with nemaline myopathy. Acta Myol 31:201–203
43. Uro-Coste E, Arne-Bes MC, Pellissier JF, Richard P, Levade T, Heitz F, Figarella-Branger D, Delisle MB (2009) Striking phenotypic variability in two familial cases of myosin storage myopathy with a MYH7 Leu1793pro mutation. Neuromuscul Disord 19:163–166
44. van der Kooi AJ, de Voogt WG, Bertini E, Merlini L, Talim FB, Ben YR, Urtziberea A de VM (2006) Cardiac and pulmonary investigations in Bethlem myopathy. Arch Neurol 63:1617–1621
45. van der Linde IHM, Hiemstra YL, Bokenkamp R, van Mil AM, Breuning MH, Ruivenkamp C, Ten Broeke SW, Veldkamp RF, van Waning JI, van Slegtenhorst MA, van Spaendonck-Zwarts KY, Lekanne Deprez RH, Herkert JC, Boven L, van der Zwaag PA, Jongbloed JDH, Bootsma M, Barge-Schaapveld DQCM (2017) A Dutch MYH7 founder mutation, p.(Asn1918Lys), is associated with early onset cardiomyopathy and congenital heart defects. Neth Heart J 25:675–681
46. Walsh R, Rutland C, Thomas R, Loughna S (2010) Cardiomyopathy: a systematic review of disease-causing mutations in myosin heavy chain 7 and their phenotypic manifestations. Cardiology 115:49–60
47. Wang J, Wan K, Sun J, Li W, Liu H, Han Y, Chen Y (2018) Phenotypic diversity identified by cardiac magnetic resonance in a large hypertrophic cardiomyopathy family with a single MYH7 mutation. Sci Rep 8:973
48. Witting N, Werlauff U, Duno M, Vissing J (2017) Phenotypes, genotypes, and prevalence of congenital myopathies older than 5 years in Denmark. Neurol Genet 3:e140
49. Yuceyar N, Ayhan O, Karasoy H, Tolun A (2015) Homozygous MYH7 R1820W mutation results in recessive myosin storage myopathy: scapuloperoneal and respiratory weakness with dilated cardiomyopathy. Neuromuscul Disord 25:340–344

50. Zaharieva IT, Thor MG, Oates EC, van KC, Hendson, Blom G, Witting E, Rasmussen N, Gabbett M, Ravenscroft MT, Sframeli G, Suetterlin M, Sarkozy K, D'Argenzio A, Hartley L, Matthews L, Pitt E, Vissing M, Ballegaard J, Krarup M, Slordahl C, Halvorsen A, Ye H, Zhang XC, Lokken LH, Werlauff N, Abdelsayed U, Davis M, Feng MR, Phadke L, Sewry R, Morgan CA, Laing JE, Vallance NG, Ruben H, Hanna P, Lewis MG, Kamsteeg S, Mannikko EJ, Muntoni R F (2016) Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or 'classical' congenital myopathy. Brain 139:674–691