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Original Article

Routine echocardiography in patients with myotonic dystrophy type 1

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Abstract

Background: Myotonic dystrophy type 1 (DM1) is an autosomal-dominant disease. One third of DM1 patients die suddenly, most of them due to the heart conduction abnormalities and arrhythmias. The aim of this study was to analyze echocardiographic findings in a large cohort of DM1 patients.
Methods: This retrospective study comprised 111 patients and 71 healthy controls (HCs) matched for gender and age.
Results: Mitral valve (MV) prolapse was observed in 23% of our DM1 patients vs. 8.5% of HCs ($p < 0.05$). Left ventricle (LV) systolic dysfunction was observed in 6% of patients and none of the HCs ($p < 0.05$). Frequency of diastolic dysfunction showed no significant difference between DM1 patients and HCs (8.1% vs. 15.5%, $p > 0.05$). Systolic dysfunction was more common in patients with severe electrocardiographic (ECG) abnormality (18.8% vs. 2.7%, $p < 0.01$).
Conclusion: One fourth of DM1 patients have MV prolapse. Approximately 15% of DM1 patients have systolic or diastolic LV dysfunction. These patients should have benefit from medical therapy. Furthermore, it seems that treatment of conduction defects might prevent development of the heart failure (HF).

Keywords: Echocardiography; Left ventricle dysfunction; Mitral valve prolapse; Myotonic dystrophy type 1

1. Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal-dominant disease caused by CTG repeat expansion within the DMPK gene.[1] DM1 is a multisystemic disorder affecting muscles, eyes, endocrine system, central and peripheral nervous system and the heart. It is well known that one third of DM1 patients die suddenly, most of them due to the heart conduction abnormalities and arrhythmias.[2,3] Thus, early identification and treatment of the cardiac impairments is the main key for prevention of sudden death in DM1 patients.

DM1 patients are usually clinically asymptomatic regarding heart involvement, probably due to the limited level of activity and consequently reduced cardiac demand. However, significant impairments may be observed even on regular cardiologic examination. Standard and 24-h Holter electrocardiography (ECG) reveal atrioventricular and intraventricular conduction disturbances, prolonged QTc interval, non specific ST and T changes, and to a lesser degree supraventricular and ventricular arrhythmias.[3,4] Relatively frequent findings on echocardiography are mitral valve (MV) prolapse and hypertrophy and dilation of the left ventricle (LV) with rare overt systolic and diastolic dysfunction.[4] Severe

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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conduction abnormalities and arrhythmias, as well as LV systolic dysfunction/heart failure (HF), are defined as significant predictors of mortality in DM1.[3,5]

The aim of this study was to analyze routine echocardiographic findings in a large cohort of DM1 patients during their hospitalization in a single tertiary center.

2. Methods

This retrospective study comprised 111 consecutive adult DM1 patients hospitalized for the first time at the Neurology Clinic, Clinical Center of Serbia in Belgrade from January 1, 2006 until December 31, 2013. Neither of them received any cardiologic drugs. Patients with congenital form of DM1 were excluded. The following forms were included according to the age at onset: childhood (before age of 10), juvenile (10–20 years), adult (20–40 years), and late adult (after year of 40). Genetic confirmation of the diagnosis was obtained by registering CTG repeat expansion in the DMPK gene for all patients in addition to typical clinical and electromyographic data. Seventy-one healthy controls (HCs) were selected from the group of 133 healthy subjects examined by the same cardiologist as a part of regular check-up during the same period of time in order to be matched for gender and age with DM1 patients. HCs were not examined for CTG repeat length, but none of them had any symptoms of myotonic dystrophy, nor did they have relatives diagnosed with this disorder. The study was approved by the Ethical Board of the Neurology Clinic (#29/X-5 from October 22, 2012).

The clinical charts were reviewed in order to obtain sociodemographic data and to assess severity of disease according to the Muscular Impairment Rating Scale (MIRS).[6]

Cardiologic examination and detailed analysis of 12-lead rest ECG were performed by an experienced cardiologist (E.C.) and reevaluated by another independent cardiologist (S.R.). According to Groh et al.,[2] severe ECG abnormality included at least one of the following: rhythm other than sinus; PR interval of 240 ms or more; QRS duration of 120 ms or more; second-degree or third-degree AV block.

Echocardiographic study was performed in the left lateral decubitus position using ultrasound system equipped with a 2.5-MHz transducer (ProSound Alpha 10, Aloka, Japan). Echocardiography was feasible in all subjects, and measurements were performed by the same cardiologist (E.C.) and reanalyzed by independent observer (S.R.). If there was a disagreement, consensus on the finding was made. Routine echocardiographic studies consisted of M-mode, two-dimensional and Doppler blood flow measurements (continuous-wave, pulsed-wave and color flow mapping), from parasternal (long- and short-axis), apical (two- and four-chamber) and subcostal views. All measurements were averaged over three cardiac cycles. Analyses were performed in accordance with the recommendations of the European Association of the Echocardiography and the American Society of Echocardiography. According to our laboratory, systolic dysfunction of the LV was considered if ejection fraction (EF) was <55% and significant systolic dysfunction if EF was <45%. Diastolic dysfunction was defined as follows: normal systolic function and E/A reversal (abnormal relaxation pattern, i.e. atrial filling velocity (A) of the LV is higher than early (E) filling velocity), with or without left atrial enlargement.

For comparison between two groups, chi square test, Fisher test and Student *t* test were used as appropriate. Spearman coefficient was used for correlations. Statistical significance was two-sided with α sets at 0.05 for statistical significance and 0.01 for high statistical significance.

3. Results

The main sociodemographic and clinical features of this study's DM1 patients and HCs are presented in Table 1. These two groups were well matched for gender and age ($p > 0.05$).

Cardiologic and ECG findings are reported in Table 2. Patients with DM1 had lower blood pressure and more common severe ECG abnormalities compared to HCs ($p < 0.01$).

Heart valve echocardiographic findings are given in Table 3. MV prolapse was found in 23.0% of DM1 patients versus 8.5% of HCs ($p < 0.05$), while maximal mitral velocity was lower in DM1 patients ($p < 0.01$), but this was not of clinical significance. On the other hand, mild aortic regurgitation and tricuspid valve fibrosis were even more common in HCs ($p < 0.05$ and $p < 0.01$, respectively).

EF between 45% and 55% was observed in 1.9% of patients, and EF < 45% in 5.6% of patients, while all HCs had EF > 55% ($p < 0.05$) (Table 4). Decreased global contractility of LV was present in 6.3% of DM1 patients compared to 0% of HCs ($p < 0.05$), while segmental wall motion abnormalities was present in 9.7% of patients and 0% HCs ($p < 0.01$). Increased end-systolic diameter of LV was observed in 6.5% of DM1 patients, and this parameter was normal in all HCs ($p < 0.05$).

Table 1
Main sociodemographic and clinical features of DM1 patients and HCs.

Features	DM1	HCs	Test, p
N	111	71	–
Males (%)	45.1	51.4	Chi square, 0.41
Age (mean ± SD)	42.2 ± 10.9	42.3 ± 11.6	*t* test, 0.96
Age at onset of disease (mean ± SD)	23.6 ± 10.9	–	–
Form (%)			
Childhood onset	12.6	–	–
Juvenile onset	23.4	–	–
Adult onset	55.9	–	–
Late adult onset	8.1	–	–
Duration of disease (mean ± SD)	18.4 ± 10.0	–	–
CTG repeats (mean ± SD)	815.6 ± 805.8	–	–
(Median, minimum, maximum)	748, 177, 1534	–	–
MIRS (%)			
Mild (I, II, III)	63.3	–	–
Severe (IV, V)	36.7	–	–
MIRS (mean ± SD)	3.3 ± 1.0	–	–
FVC below 70% (%)	26.2	–	–

DM1 = myotonic dystrophy type 1; HC = healthy control; SD = standard deviation; MIRS = Muscular Impairment Rating Scale; FVC = forced vital capacity.

Table 2
Clinical and electrocardiographic findings in DM1 patients and HCs.

Features	DM1	HCs	Test, p
N	111	71	–
Arterial tension (mmHg)			
Systolic**	111.4 ± 13.6	123.4 ± 14.8	*t* test, 0.0001
Diastolic**	73.0 ± 9.5	82.2 ± 10.5	*t* test, 0.0001
Conduction and rhythm			
Frequency**	66.1 ± 11.9	71.3 ± 12.7	*t* test, 0.007
Bradycardia (%)*	27.6	11.9	Chi square, 0.02
Severe ECG abnormality (%)**	28.8	7.1	Chi square, 0.001
Early repolarization (%)	10.8	5.6	Chi square, 0.23
Atrial fibrillation (%)	1.8	0.0	Fisher, 0.26
VES (%)	5.4	2.8	Fisher, 0.72
Signs of coronary heart disease			
ST elevation (%)	5.4	0.0	Fisher, 0.56
Inverse T wave (%)	11.7	1.4	Fisher, 0.18
Pathological Q (%)	2.7	0.0	Fisher, 0.14

DM1 = myotonic dystrophy type 1; HC = healthy control; ECG = electrocardiography; VES = ventricular extrasystoles; SD = standard deviation; *p < 0.05, **p < 0.01.

Table 3
Heart valve echocardiographic findings in DM1 patients and HCs.

Features	DM1	HCs	Test, p
N	111	71	–
Aortic valve			
Enlarged ostium (%)	2.7	0.0	Fisher, 0.34
Fibrosis (%)	18.0	16.9	Chi square, 0.89
Aortic diameter (cm, mean ± SD)	2.92 ± 0.33	2.94 ± 0.28	*t* test, 0.69
Regurgitation (%)*	1.8	9.9	Fisher, 0.01
Maximal velocity (m/s, mean ± SD)	1.30 ± 0.30	1.32 ± 0.18	*t* test, 0.65
Mitral valve			
Enlarged (%)	56.6	49.3	Chi square, 0.78
Fibrosis (%)	7.5	8.5	Chi square, 0.83
Prolapse (%)	23.0	8.5	Chi square, 0.03
Regurgitation (%)	26.1	28.2	Chi square, 0.31
Maximal velocity (m/s, mean ± SD)**	0.83 ± 0.09	0.88 ± 0.08	*t* test, 0.0001
Pulmonary valve			
Regurgitation (%)	6.3	2.8	Fisher, 0.29
Maximal velocity (m/s, mean ± SD)	1.01 ± 0.15	1.02 ± 0.18	*t* test, 0.70
Tricuspid valve			
Fibrosis (%)	0.0	12.7	Fisher, 0.0001
Regurgitation (%)	45.0	38.0	Chi square, 0.59
Maximal velocity (m/s, mean ± SD)	0.70 ± 0.08	0.68 ± 0.09	*t* test, 0.45

DM1 = myotonic dystrophy type 1; HC = healthy control; SD = standard deviation; *p < 0.05, **p < 0.01.

Frequency of diastolic dysfunction showed no significant difference between DM1 patients and HCs (8.1% vs. 15.5%, p > 0.05). In each group, only one patient had diastolic dysfunction with increased diameter of the left atrium.

At least mild clinical symptoms and signs of HF were observed in all patients with significant systolic dysfunction (EF < 45%), and in one of two with EF between 45% and 55%. On the other hand, only one (11.1%) of nine patients with diastolic dysfunction was symptomatic.

Systolic dysfunction was more common in patients with severe ECG abnormality (18.8% vs. 2.7%, p < 0.01). We did not find association between diastolic dysfunction and ECG abnormality (p > 0.05).

Echocardiographic impairments were correlated with all sociodemographic and clinical parameters listed in Table 1. The following associations were observed: patients with impaired global and regional contractility of the LV were older (51.6 ± 8.7 vs. 41.5 ± 10.8 years, and 49.1 ± 5.7 vs. 41.8 ± 11.1 years, p < 0.05, respectively). CTG repeat length did not correlate with cardiologic findings. Since childhood-onset and late-onset groups were small, comparisons were made only between juvenile and adult groups, and we did not observe significant differences in cardiac findings.

4. Discussion

In our study, MV prolapse was found in 23% of DM1 patients vs. 8% of HCs. In accordance with this, frequency of MV prolapse was reported to be from 13% to 40% in different cohorts of DM1 patients.[7] According to the American Heart Association, antibiotics prophylaxis is not advised in routine use, even before having a dental procedure. On the other side, a majority of clinicians point out that antibiotic prophylaxis should be considered in patients with mitral valve prolapse until concrete clinical evidence is provided to dispute against the use of this strategy.[8] This may be particularly applicable in DM1 patients, who commonly have cardiac conduction defects and arrhythmias.

We found more common mild aortic regurgitation in HCs compared to DM1 patients, which might be explained by the fact that hypertension is more common in general population than in DM1 patients. This is probably due to the impairment of the smooth muscles of blood vessels in DM1.[9] Furthermore, hypotension and lower prevalence of the metabolic syndrome among DM1 patients may explain the relatively low percentage of tricuspid fibrosis in DM1 patients.[10]

LV systolic dysfunction was observed in 6% of our patients. In line with this, 6% of subjects had global and 10% had regional hypocontractility of the LV wall, while 6% had increased end-systolic diameter of the LV. Although systolic dysfunction was reported in significantly higher percentage in some series of DM1 patients, meta-analysis showed an overall prevalence of 7.2%, which is similar to our results and significantly higher than in patients with arterial hypertension or in general population, where prevalences are 2.8% and 2.3%, respectively.[11] All of our DM1 patients with EF of LV below 45% had at least mild symptoms of heart failure. Clinical signs of HF were not obvious, which might be explained by the limited level of activity in DM1 patients. Previous study reported that DM1 patients with HF were at four-times higher risk of all-cause death, and at six-times higher risk of cardiac death.[5] Although there is no a single clinical trial that showed benefit from the treatment of HF in DM1, it seems logical that DM1 patients should benefit from the medical therapy. Since beta blockers are reported to be poorly tolerated in DM1 due to fatigue and cardiac

Table 4
Echocardiographic findings of cardiac chambers and walls in DM1 patients and HCs.

Features	DM1	HCs	Test, p
N	111	71	–
Left ventricle			
End-diastolic diameter increased (>5.6 cm, %)	7.5	7.2	Chi-square, 0.83
End-systolic diameter increased (>4.1 cm, %)*	6.5	0.0	Fisher, 0.03
Septum thickness increased (>1.1 cm, %)	0.0	1.5	Fisher, 0.75
Posterior wall thickness increased (>1.1 cm, %)	0.9	1.1	Fisher, 0.83
Aberrant chordae tendineae (%)	17.1	28.2	Chi-square, 0.08
Septal fibrosis (%)	17.3	21.1	Chi-square, 0.66
Global contractility decreased (%)*	6.3	0.0	Fisher, 0.03
Segmental wall motion impairment (%)**	9.7	0.0	Fisher, 0.007
Relaxation pattern abnormal (E < A)	8.1	15.5	Chi-square, 0.12
Abnormal with left atrial enlargement	0.9	1.4	Fisher, 0.66
Ejection fraction (%)	61.3 ± 7.5	62.2 ± 3.4	*t* test, 0.35
Decreased (<55%, %)*	7.5	0.0	Fisher, 0.03
Decreased (<45%, %)*	5.6	0.0	Fisher, 0.04
Left atrium diameter increased (>4.0 cm, %)	6.5	4.4	Fisher, 0.36
Right ventricle diameter increased (>2.7 cm, %)	0.0	1.5	Fisher, 0.61
Pericardial effusion (%)	10.0	9.9	Chi-square, 0.78
Pericardial fibrosis (%)	61.8	70.4	Chi-square, 0.53

DM1 = myotonic dystrophy type 1; HC = healthy control; SD = standard deviation; E/A = atrial filling velocity/early filling velocity; *p < 0.05, **p < 0.01.

conduction abnormalities, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists seem to be good choices.[4] ACE inhibitors are shown to diminish heart fibrosis and hypertrophy in mice with hypertrophic cardiomyopathy.[12]

Severe ECG abnormality associated with systolic dysfunction of our DM1 patients. Some degree of electromechanical correlation has been demonstrated in several previous studies on DM1 subjects.[13,14] DM1 patients with prolonged PR or QRS intervals are at four-times higher risk to develop LV systolic dysfunction or HF.[5] It is possible that conduction defects cause mechanical impairments, thus treatment of conduction defects with pacemakers and implantable cardioverter defibrillator (ICD) might prevent development of heart failure. On the other hand, it is possible that both electrical and mechanical impairments have the same substrate, fibrosis of the myocardium and conduction system, that was described in several histopathological studies in DM1 patients and DM1 animal models.[9]

Our patients with decreased regional and global contractility of the LV were older. Similarly, systolic dysfunction correlated with age of patients in several studies, and one large study reported that HF was virtually absent in DM1 patients before the age of 40.[7] On the other hand, systolic dysfunction did not correlate with CTG repeat size, neither in our nor in previous studies.[7] In some studies the CTG expansion size correlated with the rate of progression of cardiac disease,[15,16] however, the correlation with clinical cardiac disease has not been observed in all studies.[17,18] Cardiac conduction disturbances showed more consistent correlation with male gender, age and duration of disease than with CTG repeats.[19] One possible explanation is that analysis of CTG repeats from peripheral blood leucocytes can underestimate CTG repeat lengths compared to skeletal and cardiac muscle tissue, where expansion lengths are much longer.[4]

Pure diastolic dysfunction (impaired relaxation) of the LV was present in 9% of DM1 patients, which was even less frequent than in HCs. This partially might be in association with significantly lower percentage of hypertension in DM1 patients.[10] Also, aortic regurgitation that was more common in HCs might cause eccentric LV hypertrophy and structural changes of the myocardium, which can explain diastolic dysfunction. Only one of our DM1 patients with diastolic dysfunction had left atrium enlargement and symptoms of HF. Mild diastolic dysfunction previously was found in 5%–50% of DM1 patients depending on the selection of patients, applied techniques and sample size.[4] Diastolic dysfunction in DM1 might be explained by fibrotic degenerative changes of the myocardium that prevent expansion of the LV, by heart myotonia, and by impaired calcium metabolism in cardiomyocytes. Significance of the diastolic dysfunction in DM1 is not known, and there are no recommendations for treatment of this condition. However, studies on subjects from general population showed that the prognosis in diastolic dysfunction is as poor as in systolic dysfunction.[20] In contrast with systolic dysfunction, diastolic dysfunction in our DM1 patients was not associated with neither ECG abnormalities or with patients age.

The main limitation of our study is that we did not use any non-conventional method for heart investigation. For instance, heart rate variability, heart rate turbulence and electrophysiological studies may identify subtle subclinical cardiac impairments in DM1.[4] Tissue Doppler echocardiography and magnetic resonance imaging (MRI) may reveal systolic and diastolic dysfunction of LV, even in DM1 patients with normal ECG and routine echocardiography.[13] Integrated backscatter ultrasound imaging and contrast MRI may discover heart fibrosis.[13] However, the significance of all of these findings and their relevance for DM1 prognosis is not known since follow-up studies are missing. Furthermore, these methods are

not widely available in clinical practice, while our aim was to analyze structural heart abnormalities obtained with routine, widely available methods in clinical settings even in developing countries.

In conclusion, LV systolic dysfunction was found in 6% of patients, and an additional 8% had diastolic dysfunction. These patients should benefit from medical therapy. Since association between severe ECG abnormality and systolic dysfunction was observed, it seems that treatment of conduction defects might prevent the development of heart failure.

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