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Original Research Article

Left ventricular function in Duchenne muscular dystrophy with relation to some clinical parameters

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Abstract

Duchenne muscular dystrophy (DMD) is a severe X-linked disease due to loss of dystrophin in skeletal and cardiac muscle. The aim of the study was to evaluate cardiac involvement in DMD patients and to correlate it with age, ventilatory function and muscle strength. Forty five male, genetically verified DMD patients at mean age of 11,5±4,3 years, underwent clinical examination, ECG and transthoracic echocardiography. Forced vital capacity and forced expiratory volume in 1 s were assessed. North star assessment score and Medical Research Council grading method were used for muscle strength and functional disability evaluation. Left ventricular systolic (LV) dysfunction was found in 24,4% of the patients and some impairment in diastolic function in 53.3%. The earliest finding was decreased early diastolic myocardial velocities at lateral mitral annulus, registered in patients 10 years of age. A positive correlation was found between muscle weakness parameters and ventilatory function with some of the indices of LV function. LV dysfunction was a common finding in DMD and its prevalence and severity increased with age. The parallel decrease in peripheral, respiratory and cardiac muscle function confirmed the common pathological molecular mechanism of muscle impairment.

Key words: Cardiac involvement, Duchenne muscular dystrophy, Functional disability, LV function, Muscle strength, Ventilatory function

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked myopathy caused by mutations in the DMD gene, leading to a complete absence of functional dystrophin. Dystrophin is a cytoskeletal protein, localized on the inner surface of the sarcolemma. It is a part of the dystrophin associated glycoprotein complex, which is the link between the cellular cytoskeleton of the muscle fiber and the extracellular matrix and stabilizes the sarcolemma during muscle contractions (Lapidos et al., 2004). In DMD the complete loss of dystrophin destabilizes the sarcolemma, making the muscle fibers susceptible to contraction injury. DMD is the most common and severe muscle dystrophy with the most severe heart involvement (D'Orsogna et al., 1988; Finsterer et al., 2003). The clinical manifestations are characterized by progressive muscle weakness leading to severe disability, respiratory failure, dilated cardiomyopathy and heart failure (Emery et al., 1995). The impairment of the ventilatory and cardiac function has the greatest negative impact on prognosis. The progress in the respiratory care with the implementation of ambulatory mechanical ventilation has led to an increased survival (Eagle et al., 2002). Cardiac involvement emerges as the leading cause of morbidity and mortality, which requires a special attention to early diagnosis and timely treatment (Spurney, 2011).

The purpose of the study was to evaluate cardiac involvement in a group of patients with DMD and to assess its correlation with clinical parameters such as age, ventilatory function and muscle strength.

MATERIALS AND METHODS

We evaluated 45 male patients with genetically verified

DMD, aged 6 to 23 years (mean±SD, 11,5±4,3 years). The patients underwent a thorough clinical examination, electrocardiography and echocardiography. Respiratory function, including vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), was tested in 33 subjects. A restrictive type respiratory failure was defined when FVC<75% and FEV1<75%. A comprehensive clinical neurological assessment was performed in 35 patients. Functional disability and muscle strength were evaluated using the North star assessment score (NSA) and the MRC scale for m. deltoideus and m. quadriceps femoris (Mazzone et al., 2009; van Swieten et al., 1988).

Cardiac evaluation

Twelve lead electrocardiograms (ECG) were performed. An ECG was considered abnormal when it revealed one or more of the following signs: different from sinus rhythm,A-V block, all types of intraventricular block, low or high voltage of the QRS complex, deviations in the ST segment and T wave, pathological Q wave or a prolongation of QT interval.

All patients underwent complete echocardiographic examinations, including 2D, M-mode, spectral and color Doppler techniques, tissue Doppler imaging (TDI) with an ultrasound machine Aloka Prosound alfa 10.The echocardiographic studies were performed and recorded, and all the measurements were done in accordance with internationally approved standards (Evangelista et al., 2008; Lang et al., 2006). The assessment of LV systolic function included end diastolic and end systolic dimension (EDD, ESD) and volumes (EDV, ESV), fractional shortening (FS) and ejection fraction (EF). The EF was measured using the Simpson method and for abnormal, values below 55% were accepted. We used the Z score in patients under the age of 16 for the evaluation and comparison of the LV dimensions. Pathological Z score > 2 was accepted and body surface area (BSA) was taken in consideration (Lopez et al., 2010).

The indices used for LV diastolic function assessment were transmitral maximal early diastolic velocity (E wave), maximal late diastolic velocity (A wave), E/A ratio, deceleration time (DT) and left atrium dimensions (diameter and area). Tissue Doppler Imaging (TDI) was used to measure early and late mitral annular diastolic velocities (e' and a') at septal and lateral mitral valve annulus, following which the E/e' ratio was calculated, where e' is the average value of septal and lateral e'.The severity of the diastolic dysfunction was defined as per the recommendations of the American Society of Echocardiography (Nagueh et al., 2009).

The parameters used for right ventricular (RV) assessment were RV and right atrium dimensions, RV free wall thickness, RV systolic pressure, tricuspid annular plane systolic excursion (TAPSE) and peak systolic myocardial velocity (s wave) (Jurcut et al., 2010).

Statistical methods

The data were processed with IBM SPSS Statistics 19.0. The following methods were applied:

1. Descriptive analysis
2. Variation analysis
3. Graphical analysis
4. Fisher's exact test
5. Non-parametric test of Shapiro-Wilk
6. Student's t test
7. Non-parametric test of Man- Whitney

P is considered significant if < 0,05

RESULTS

From the 45 evaluated DMD patients 51% were aged 6 to 10 years, followed by 29% in the age group between 11 and 15 years and 20% above 16 years. Twenty three DMD patients (51,1%) were wheel-chair bound, the youngest patient was 9 years old.

The demographic and clinical results are presented in Table 1.

Cardiac assessment was performed at a mean age of 11,5±4,3 years. Symptoms of overt heart failure (dyspnea) were reported in 2 patients at the age of 16 and 20 years respectively (4,4%). Sinus tachycardia (HR>100 beats/min) was found in 16 (35,6%) patients, with average heart rate of 114±11,5 beats/min. For the whole group of patients the average heart rate was 97±15,6 beats/min. The highest heart rate was found in the youngest patients (6 - 7 y) and after the age of 17. Blood pressure was within normal limit ranges in all of the affected with mean systolic BP - 113,8±10,5 mmHg and mean diastolic blood pressure - 75±5,4 mmHg.

Specific ECG changes – tall R wave in V1,V2 with pathologic R/S ratio and deep Q waves in I, II, III, aVL, aVF, V5,V6 were registered in 41 (91,1%) of the evaluated patients. No rhythm and conduction abnormalities were registered on ECG.

Echocardiography revealed normal dimensions, volumes, EF and FS (Table 1) in the group as a whole. After dividing the patients in different age groups we found increased ESD (z-score> 2) in 6(13,3%)patients in the age groups of 16, 21 and 23 years and increased EDD in one 16 years old patient. In 10 (22,2%) patients we observed FS < 30% and EF < 55%. i.e. LV systolic dysfunction – mild (EF 45%-55%) in 7 patients, moderate (EF 35% -45%) in 2 and severe (EF<35%) in one patient. LV systolic dysfunction was present in all the patients after the age of 15 (Table 2). Regional wall motion abnormalities – inferolateral hypokinesia were observed in 5 (11,1%) patients (one patient at the age of 15 and

Table 1. Demographic, clinical and echocardiographic data of the evaluated DMD patients.

Parameters	Results	min/max
Age, years	11,5±4,3	6-23
Male/female	45/0	
Height (cm)	141,8 ±19,6	112-178
Weight (kg)	42,6 ±17,3	20-75
HR (beats/min)	97,02±15,61	68-138
SBP/mmHg	113,8± 10,5	100-130
DBP/mmHg	75± 5,4	70-80
EDD, mm	39,8±6,69	28-62
z-score	-0,36±1,59	-5,1 - 3,8
ESD, mm	27,27±7,06	17-53
z-score	0,38±1,97	- 3,8 -4,1
EF Sim, %	59,33±9,33	27-74
FS Teih, %	32,16±6,67	15-43

Table 2. LV systolic function parameters in relation to the age.

Age/years	N	HR beats/min	EDD mm	EDD z-score	ESD mm	ESD z-score	FS Teih %	EDV ml	ESV ml	EF Sim %
6	3	115	35,8	0,2	22,0	-0,1	38,3	44,7	17,6	61,3
7	4	108	38,3	0,4	25,0	0,5	35,3	55,5	22,8	58,8
8	5	90	34,4	-1,1	22,4	-0,6	31,4	48,8	18,8	61,8
9	5	90	36,0	-0,7	23,8	-0,2	33,8	53,6	17,8	66,8
10	6	97	38,5	-0,4	24,7	-0,3	36,3	83,0	36,0	57,0
11	6	87	37,8	-0,9	25,5	-0,2	33,2	64,3	24,5	61,2
12	1	88	41,0	-0,4	26,0	-0,4	38,0	76,0	23,0	65,0
13	2	108	42,0	-0,9	26,5	-1,8	36,5	63,0	25,0	61,0
14	2	89	41,5	-0,6	28,5	0,3	32,5	62,5	23,5	64,0
15	2	99	39,5	-1,9	28,5	-0,03	28,5	68,5	30,5	53,5
16	4	101	53,5	2,2	43,0	4,5	20,3	137,5	83,3	41,0
17	1	88	46,00	0,19	34,00	1,77	27,00	96,00	48,00	54,0
20	2	107	38,0	-2,4	26,5	-0,93	33,5	69,5	30,50	62,0
21	1	118	45,0	-0,12	37,0	2,75	18,0	75,0	42,0	44,0
23	1	87	53,0	1,56	40,0	3,2	23,0	110,0	56,0	48,0

4 at the age of 16 years), all with LV systolic dysfunction.

Abnormalities in some of the parameters of LV diastolic function were present. The patients were divided in 4 age groups – 1st (6-9 years), 2nd (10-13 years), 3rd (14-18 years), 4th (19-23 years). Diastolic function abnormalities were found in 24 (53,3%) patients, including all the patients with systolic dysfunction (Table 3). Reduced E/A ratio was present in all 13(28,9%) patients from the 3rdand 4th age groups. Reduced early diastolic velocities (e') at the lateral mitral annulus were registered in 24 (53,3%) patients from the 2nd, 3rd and 4th groups and at the septal annulus in 4(8,9%) patients from the 4th group. Impaired relaxation was the predominant type of LV diastolic dysfunction. A restrictive filling pattern with increased E/e' ratio>15 was found in two patients - one with severe LV systolic dysfunction, the other with LV hypertrophy. Left atrial enlargement was not present.

Dimensions of the right ventricle and right atrium were within normal ranges. In 7 (16%) patients reduction of tricuspid annular systolic velocity (s'<10 cm/s) was observed, which may be a sign of subclinical RV systolic dysfunction, most probably due to myocardial involvement. We could not find a correlation with LV systolic function impairment.

Restrictive respiratory failure with decrease of both FVC and FEV1 was found in 14 (42%) of the evaluated patients. The mean age of patients with respiratory insufficiency was 11,5 years, as it was present in all the patients after the age of 11 and in two patients at the age of 10 years. Five of the patients (15%) were on ambulatory noninvasive ventilation and the youngest patient was at the age of 12. According to the NSA score 18 (51%) patients were with 0 and 1 score (severely disabled). A positive correlation was found between muscle weakness parameters (NSA score and MRC scale values) and e'septal velocity (p<0,41; p<0,33 respectively) and also with e'lateral velocity (p<0,005; p<0,004 respectively) (Table 4). More cases with

Table 3. LV diastolic function parameters in relation to the age.

Age/ Years	6-9	Normal values	10-13	Normal values	14-18	Normal values	20-23	Normal values
N	17		15		9		4	
E, cm/s	100,2±4,7	94,4±14,8	87,1±5,3	94,5±16	83,8±7,5	90,3±17,8	62,7±16,9	60-80
A,cm/s	57,3±7,8	49,4±12,5	58,7±5,6	49,5±13,8	57,6±7,3	45,5±13,2	56,7±12,2	19-35
E/A	1,9±0,4	2,0±0,5	1,5±0,2	2,0±0,6	1,6±0,1	2,1±0,7	1,2±0,5	1.5 ±0.4
DT, ms	147,4±9,0		185,3±28		166,3±23,8		194,7±33,6	166 ± 14
e' sept., cm/s	14,1±1,1	13,4±1,3	11,7±2,1	14,5±2,6	12,0±3,2	14,9±2,4	9,0±2,7	15.5± 2.7
e' lat., cm/s	18,5±2,5	17,2±1,3	13,5±4,3	19,6±3,4	14,7±2,3	20,6±3,8	12,3±1,5	19.8± 2.9
E/e'	6,6±0,9	6,5±1,8	7,2±1,4	5,8±1,4	7,0±2,1	5,6±1,4	8,2±3,7	

Table 4. Correlations between clinical and echo parameters

	e' lat – p value	e' sept – p value	EF – p value
Age	<0,001	0,034	0,030
NSA score	0,058	0,529	0,703
MRC m. deltoideus	0,005	0,041	0,053
MRC m. quadriceps femoris	0,004	0,033	0,100
Ventilatory function	0,226	0,13	0,010

decreased ventilatory function were found in the group of patients with reduced e'septal and e' lateral, without reaching significance. A positive correlation was found between the decreased ventilatory function and the reduced fractional shortening and ejection fraction ($p<0,018$; $p<0,010$ respectively). In patients with systolic dysfunction, we also observed decreased NSA score and MRC scale values, but without reaching significance. All the parameters worsened with age.

DISCUSSION

DMD becomes clinically apparent before the age of 5 years and is characterized by progressive muscle weakness and wasting. Usually the patients become wheelchair dependent before the age of 13. The most common cause of death in about 73% of the patients is respiratory failure due to progressive loss of the respiratory muscles strength and the development of scoliosis (Phillips et al., 2001; Simonds et al., 1998). The heart becomes involved before the age of 14 in about 30% of the patients, in 50% - before the age of 18 and in all the older patients (Muntoni, 2003). The heart muscle involvement leads to dilated cardiomyopathy and congestive heart failure. Heart involvement is initially asymptomatic and most DMD patients remain asymptomatic for years inspite of the progression of cardiac dysfunction because of their limited daily activities. Presence of sinus tachycardia may suggest early cardiac involvement (Gulati et al., 2005). Persistent tachycardia in the absence of myocardial dysfunction may be due to autonomic dysregulation (Lanza et al., 2001). Overt symptoms due to heart failure appear in about 30% of cases (Nolan, 2003). This leads to relatively late diagnosis of heart involvement. Hence, detection of early presymptomatic cardiac involvement in DMD patients is crucial. Moreover, early detection of latent myocardial involvement and timely use of drugs such as angiotensin converting enzyme inhibitors or beta-blockers could be beneficial for delaying progression of heart failure in DMD patients (Towbin, 2003).

The conducted study revealed cardiac involvement as early as 10 years of age, with increasing severity with age. Heart failure symptoms were uncommon. ECG changes were registered early in the course of the disease, which is in line with previous reports (Bhattacharyya et al., 1997; Perloff et al., 1967). The most common signs were the tall R waves in V1-V3 leads with pathologic R/S ratio. It is supposed that this is due to loss of electrical forces as a result of fibrosis in the posterior basal wall. As the fibrosis expands to the lateral wall, deep Q waves appear in I, AVL, V6 and more rarely in II, III,AVF and anterior (V1-V4) leads (Spurney, 2011). The gold standard for the LV systolic function assessment in DMD patients remains the ejection fraction and fractional shortening, measured by conventional echocardiography (Kirchmann et al., Provide year). Our study revealed normal values of these parameters in the evaluated group as a whole, due to the fact that half of the patients were under the age of 10 and another one third under the age of 15 years. We found increased end systolic dimensions and volumes and smaller increase in the end diastolic parameters in the patients with reduced

left ventricular EF and FS. Changes in the diastolic function preceded the systolic dysfunction. The first signs of LV impairment were the reduced early diastolic velocities at the lateral mitral valve annulus after the age of 10, i.e. preceding the systolic dysfunction (Markham et al., 2006). This finding correlates with histological data showing myocyte degeneration and replacement fibrosis and fatty tissue at the inferior-lateral wall of the LV (Moriuchi et al., 1993). These data are confirmed by CMR in DMD patients (Moreo et al., 2009). According to previous reports, reduced myocardial velocities in DMD patients are found as early as 8.8 years of age (Giatrakos et al., 2006). Other authors describe reduced diastolic myocardial velocities at inferolateral and anterolateral LV wall earlier, in patients at mean age of 7,9 years (Markham et al., 2006; Mertens et al., 2008). These studies show the presence of subclinical LV impairment, before the reduction of EF and FS. The reduced early diastolic myocardial velocities may be used as an early marker of cardiac involvement and can draw our attention to close follow-up of LV systolic function. This is important because timely initiation of treatment with ACE inhibitors and beta-blockers improves the prognosis in DMD patients with cardiomyopathy (Bogdanovich et al., 2004; Duboc et al., 2005; Duboc et al., 2007; Ramaciotti et al., 2006).

The prognosis in DMD patients is unfavorable. Most of the patients die before the age of 25 from cardiac and respiratory complications. Screening guidelines are released for early diagnosis of cardiac involvement (Dubowitz, Provide year). The patients with DMD must undergo a cardiac exam with ECG and echocardiography as early as the age of 6 or at diagnosis and every 2 years till the age of 10, and annually after that and also before any surgical intervention.

CONCLUSION

LV dysfunction was a common finding in DMD patients and its prevalence and severity increased with the age. The earliest signs of LV impairment were found to be the reduced early diastolic myocardial velocities. This finding could draw the attention to close monitoring of LV function and early therapeutic intervention in patients at risk. The parallel decrease in skeletal, respiratory and cardiac muscle function confirms the common pathological molecular mechanism of muscle impairment.

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