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Impaired Autonomic and Repolarization Abnormalities are Observed in Patients with Facioscapulohumeral Dystrophy Despite Normal Myocardial Functions

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Abstract

Introduction: Facioscapulohumeral Dystrophy (FSHD) is one of the most common adult muscular dystrophies. We aim to investigate structural, functional and arrhythmic abnormalities in patients with FSHD Type-1.

Methods: Left ventricular mass, left ventricular tissue doppler analysis and myocardial performance index (MPI) were calculated in Type-1 FSHD and healthy controls. A 24-hour ambulatory electrocardiogram (ECG) analysis was performed. T wave peak to end (Tp-e) interval and Tp-e/QT ratio was calculated.

Results: In the study average heart rate was significantly higher (93.6 ± 10.1 min^{-1} *vs.* 74.3 ± 5.6 min^{-1}; $p = 0.000$) and standard deviation of N-N intervals was significantly lower (47.43 ± 15.49 *vs.* 69.85 ± 19.18; $p = 0.001$) in FSHD Group. Tp-e interval was longer (78.6 ± 14.6 msec *vs.* 64.3 ± 16.5 msec; $p = 0.031$) and Tp-e/QT ratio was larger (22.9 ± 3.2 *vs.* 17.8 ± 5.4; $p = 0.018$) in the FHSD Group.

Conclusion: These findings suggest that autonomic and repolarization abnormalities might be observed in patients with FSHD in spite of normal structural and functional myocardial function.

Keywords: Heart rate variability; Myocardial performance index; Musculardystrophy; Tissue doppler; Cardiac repolarization

Introduction

Facioscapulohumeral Dystrophy (FSHD) is one of the most common adult muscular dystrophies. Its prevalence is almost 1:20,000 and it is the third most common muscular dystrophy (MD) after Duchenne's and myotonic dystrophy [1,2]. Facioscapulohumeral Dystrophy is categorized as type 1 or type 2 according to the underlying genetic lesions. Approximately 95% of patients will have disease inherited in an autosomal dominant fashion associated with loss of part of a repeated sequence in the D4Z4 region on chromosome 4q35 and named as Type-1 FSHD [3,4]. Patients with FSHD may have involvement in any skeletal muscle and typically no involvement in extraocular, bulbar and cardiac muscles [1].

Cardiac involvement is not infrequent in various MD's. Cardiomyopathy and heart failure may be seen in X-linked MD's. Also, conduction system abnormalities, heart blocks, cardiac autonomic disturbances and even sudden cardiac death may be observed in various MD's [5]. Cardiac autonomic impairment is mostly linked to myocardial involvement and systolic dysfunction in this patient group [6]. Fibrosis and fibrofatty infiltration of the conduction system might also be responsible for conduction and rhythm abnormalities [5].

Data about cardiac involvement in patients with FSHD are limited. Most of the structural and functional abnormalities are found to be incidental. However, most of the studies were performed with conventional echocardiographic and electrocardiographic criteria. In this study, we aim to perform a thorough cardiac evaluation to patients with FSHD, assess their cardiac structural, functional and cardiac autonomic findings with newer methods not to miss subtle changes.

Methods

Subjects

Our study was conducted in Cukurova University Medical Faculty (CUMF) after being approved by our ethics committee. All steps performed in our study were coherent with Declaration of Helsinki [7].

Study Group Selection

Patients with a genetically confirmed diagnosis of Type-1 FSHD, who were on follow-up by CUMF Neurology Department, were included our study. Exclusion criteria were inability to walk independently, a history of hypertension, arrhythmias, use of sympathicomimetics or beta-blockers. Control group consisted of age and sex matched healthy individuals, without any family history of neuromuscular disorders. Written informed consent was obtained from all subjects before inclusion to the study. Duration of FSHMD was derived by subtracting patientage at the time of the last clinic evaluation and age at the onset of disease.

Genetic Analysis

After the digestion of genomic DNA with restriction enzymes EcoRl, Eco RI/Bln I and Xap I, Southern blotting and hybridization with the DNA-probe p13E11 was performed and D4Z4-locus-specific fragments were detected. Repeats in the normal range (> 10 units) are represented by EcoRl fragments of > 38 kb. DNA-probe p13E11 recognizes also a homologous repeat array on chromosome 10q26. Confirming FSHD1 diagnosis was done by observing short fragments of the D4Z4-locus (FSHD1-repeat) of 19 kb (Eco RI) and 16 kb (EcoRI/Bln I).

Echocardiography

The study was performed using Vivid S5® cardiovascular ultrasound system (3S 1.5-3.6 MHz probe Transthoracic GE Medical System, Buckinghamshire, UK). Cardiac chamber sizes interventricular septum dimension (IVS_d), left ventricular diastolic dimension (LVD_d), left ventricular posterior wall dimension ($LVPW_d$) were measured in long-axis plane and left ventricular mass (LV_{MASS}) was calculated according to the following formula [8].

$LV_{MASS} = 0.8*\{1.04*[(IVS_d)+(LVD_d)+(LVPW_d)]^3 - (LVD_d)^3\} + 0.6$ grams

In the apical four-chamber view, early diastolic filling (E) and atrial contraction (A) waves were measured by pulsed wave (PW) Doppler analysis performed at the level of mitral valve tips. The ratio of E wave to A wave (E/A) were calculated. We also performed tissue Doppler (TD) measurements at the annular base of septal and lateral myocardial walls. We measured systolic (s'), early diastolic filling (e') and atrial contraction (a') waves in both myocardial walls. We calculated the mean wave amplitudes. We also calculated mitral annular to tissue E wave ratio (E/e') AND tissue early filling to tissue atrial contraction wave ratio (e'/a') [9]. For myocardial performance index (MPI) calculation, we measured isovolumetric relaxation time (IVRT), ejection time (ET) and isovolumetric contraction time by TD in septal and lateral left ventricular walls. After taking the means of these measurements, we calculated MPI according to the formula:

$$MPI = (LV_{IVRT} + LV_{IVCT})/LV_{ET}$$

We also performed global cardiac structural evaluation and noted any structural anomaly.

Electrocardiogram (ECG) and Ambulatory ECG Monitoring

The ECG was recorded with a standard digital recorder as 12 simultaneous leads at a paper speed of 50 mm/s. The QTc was obtained using Bazett's formula. The QT interval was measured from the beginning of the QRS to the end of T-wave, defined as the intersection of the tangent to the down slope of the T-wave and the isoelectric line. The Tp-e was measured in each precordial lead and obtained from the difference between QT interval and QT peak interval; measured from the beginning of the QRS until the peak of the T-wave (Figure 1). The ratio of Tp-e interval to QT interval (Tpe/QT) was also calculated. The measurement of each parameter was obtained by averaging three consecutive beats. Mean of all 12 lead measurements is used for statistical analysis.

All patients have undergone DMS (Hunfelden-Dauborn, Germany) ambulatory ECG device for 24 hours. Cardioscan II Premier (DMS) software was used to analyze the recordings. All extra beats and artifact zones were cleared before analysis. Average heart rate (HR) and standard deviation of R-R intervals (SDNN) were measured in time domain analysis of heart rate variability (HRV). In the frequency domain analysis, low frequency (LF; 0.04-0.15 Hz) and high frequency (0.15-0.4 Hz) bands were measured followed by calculation of LF to HF ratio (LF/HF) [10].

Statistical Analysis

Categorical variables were expressed as numbers and percentages, whereas numeric variables were expressed as mean ± SD values. Categorical varibles were compared with chi-square test. Numeric variables were compared with Mann-Whitney-U test. A p - value ≤ 0.05 was considered significant. All of the analysis was performed with SPSS 20 for Mac software.

Results

A total of 14 patients and 14 healthy controls were included in our study. Five patients were female in FSHD group, whereas four healthy individuals were female in the control group (p = 0,383). The most frequent symptom was weakness (7 patients) followed by balance disorder (6 patients) and muscle atrophy (1 patient). Also, eight patients had significant skeletal deformity. None of thepatients had respiratoryfailure. Mean age of FSHD group was similar with control group (27.4 ± 13.8 years *vs.* 29.8 ± 9.3; p = 0.329). Age at onset of FSHMD was 16.1 ± 3.8 yearsandduration of FSHMD was 9.7 ± 4.5 years.

When we evaluate the echocardiographic parameters, LV_{MASS} was similar between two groups (131.9 ± 27.0 gr *vs.* 136.8 ± 16.0; p = 0.482). Also Doppler parameters resembling diastolic and systolic function didn't show significant differences between both groups (Table 1).

The average heart rate was significantly higher in the FSHD group (93.6 ± 10.1 min^{-1} *vs.* 74.3 ± 5.6 min^{-1}; p = 0.000). Also, in time domain analysis, mean SDNN value was significantly lower in FSHD patients (47.43 ± 15.49 *vs.* 69.85 ± 19.18; p = 0.001). However, there wasn't a significant difference in both groups in terms of LF/HF ratio measured in frequency domain analysis (FSHD Group: 5.39 ± 2.90, Controls: 4.52 ± 1.84; p = 0.635). When we look at ECG measurements, QT and QTc parameters didn't show significant difference between both groups; whereas Tp-e interval was longer (78.6 ± 14.6 msec *vs.* 64.3 ± 16.5 msec; p = 0.031) and Tp-e/QT ratio was larger (22.9 ± 3.2 *vs.* 17.8 ± 5.4; p = 0.018) in the FHSD Group (Table 2).

Discussion

Muscular dystrophy (MD) is an inherited heterogeneous disease characterized by progressive weakness in the skeletal muscles. In some forms of MD, cardiac dysfunction affects morbidity and mortality. With the information they obtained during the medical education process when they met previously with this patient group, the neurologists performed heart examinations, or if necessary, treated cardiac dysfunction in diseases such as limb-girdle MD, myotonic dystrophy, Emery-Dreifuss MD, and Duchenne and Becker MD.

In this study, we compared structural, functional and electrical

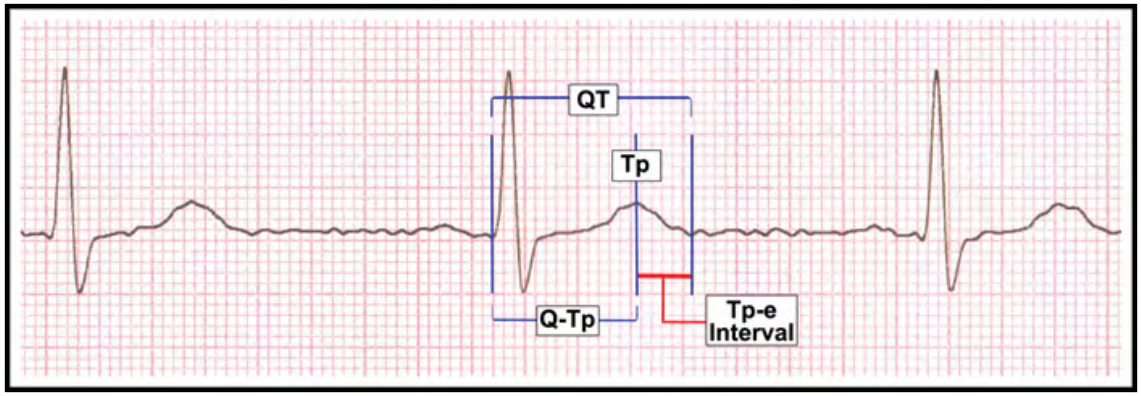


Figure 1: Calculation of Tp-e interval is done by subtraction of Q to T peak interval from QT interval.

Variable	FSHD Group (n = 14)	Controls (n = 14)	*p* - value
Age (years)	27.4 ± 13.8	29.8 ± 9.3	0.329
Female sex n, (%)	5 (35.7)	4 (28.6)	
LV_{MASS} (gr)	131.9 ± 27.0	136.8 ± 16.0	0.482
E_{mitral}(cm/sec)	92.1 ± 21.1	81.4 ± 10.7	0.062
A_{mitral}(cm/sec)	60.9 ± 11.5	63.0 ± 15.9	0.910
E/A	1.58 ± 0.53	1.38 ± 0.40	0.329
e' (cm/sec)	18.0 ± 7.7	14.0 ± 0.4	0.085
a' (cm/sec)	10.8 ± 7.1	10.1 ± 2.3	0.376
s' (cm/sec)	8.6 ± 1.7	8.7 ± 2.5	0.982
Annular E/Tissue e'	5.61 ± 1.41	6.49 ± 2.56	0.874
Tissue e'/Tissue a'	2.07 ± 1.27	1.43 ± 1.51	0.114
LV_{IVRT} (msec)	59.3 ± 8.0	69.4 ± 15.3	0.062
LV_{IVCT} (msec)	62.0 ± 13.0	66.7 ± 8.1	0.077
LV_{ET} (msec)	252.4 ± 25.2	270.0 ± 22.2	0.094
LV_{MPI} (msec)	0.49 ± 0.10	0.50 ± 0.06	0.701

Table 1: Demographic and echocardiographic variables of patients and controls.

Variable	FSHD Group (n = 14)	Controls (n =14)	*p* - value
Average heart rate (min^{-1})	93.6 ± 10.1	74.3 ± 5.6	0.000
SDNN	47.43 ± 15.49	69.85 ± 19.18	0.001
LF (Hz)	908.0 ± 578.2	1020.4 ± 406.2	0.482
HF(Hz)	223.1 ± 173.6	262.2 ± 195.1	0.571
LF/HF	5.39 ± 2.90	4.52 ± 1.84	0.635
QT (msn)	335.4 ± 41.8	364.0 ± 22.7	0.067
QTc (msn)	412.6 ± 40.4	405.7 ± 21.7	0.603
Tpe (msn)	78.6 ± 14.6	64.3 ± 16.5	0.031
Tpe/QT (%)	22.9 ± 3.2	17.8 ± 5.4	0.018

Table 2: Ambulatory rhythm parameter measurements in both groups.

cardiac parameters between genetically confirmed FSHD patients and healthy controls. Echocardiographic evaluation didn't show any significant structural or functional difference between both groups. However, in the analysis of ECG and ambulatory rhythm tests, we have found a significant prolongation in Tp-e interval, Tp-e/QT ratio, and increase in average heart rate and a decrease in SDNN.

The time interval from the peak to the end of the T-wave is a marker of transmural repolarization dispersion and its prolongation has been found to be related with increased sudden cardiac death risk in patients with various heart diseases such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome and structural heart disease [11-14]. As a markerserving as an index of total repolarization dispersion, Tp-e is an independent predictor of sudden cardiac death due to arrhythmic events in patients with structural heart disease. However, Tp-e interval may show changes in different heart rates with different QT intervals. Ratio of Tp-e/QT, however, remains constant in hearts with normal repolarization activity at a range between 15.0-25.0 % [15].Sympathetic stimulation is an important cause of Tp-e prolongation and increase in Tp-e/QT ratio [16].

Heart rate variability evaluation is very valuable in estimating integrity and physiological status of cardiac autonomic activity, as well as predicting vulnerability to serious cardiac arrhythmias [17,10]. Reduced HRV is a sign of disruption of the balance between sympathetic and parasympathetic cardiac autonomic activity in favor of reduced parasympathetic and increased sympathetic activities. Depression of HRV and increased average HR has been found to be associated with increased mortality in various cardiac, non-cardiac conditions; and even asymptomatic individuals [18,19]. In patients with Becker's and Duchenne's Muscular Dystrophy, impairment of cardiac autonomic system was observed; whereas no significant changes were seen in patients with myotonic dystrophy. The former two muscular dystrophies also cause impairment in left ventricular functions and the autonomic disturbances develop in parallel to left ventricular systolic dysfunction. Since left ventricular impairment isn't a common finding in myotonic dystrophies, autonomic significant autonomic changes aren't observed [5].

The literature contains a number of studies related to cardiac involvement in the musculoskeletal dystrophies mentioned above. It is noteworthy that facioscapulohumeralmusculardystrophy (FSHMD) is almost always working less than one hand fingers when several case reports are ignored.

Cardiac involvement was usually reported incidentally in this patient group and doesn't apply to standard diagnostic criteria of FSHD [20]. Study published by van Dijk, et al. demonstrates a significantly higher prevalence of incomplete right bundle branch block in these patients despite lack of structural cardiac anomalies. They concluded that involvement of His-Purkinje system might be an issue in these patients [21]. Trevisan, et al. reported arrhythmic alterations more frequently than expected in FSHD patients. [22]. Galetta, et al. reported that he observed a substrate for arrhythmic risk and heart failure in the study he performed by using signal averaged ECG and echocardiography in FSHD patients [23]. In a previous study performed by Della Marca, et al. slight increase in sympathetic activity and a slight decrease in parasympathetic activity were observed in patients with FSHD. They have made their measurements after a 10-minute ambulatory ECG recording. Since it was a short-term recording, they have observed significant changes in frequency domain analysis. However, their study was not capable of doing time domain analysis [24]. In the present study, we evaluated cardiac autonomic activity by a 24-hour ambulatory ECG recording. We observed significant autonomic impairment in time domain analysis. Also, we evaluated cardiac repolarization by Tp-e analysis and found a significant prolongation in Tp-e and Tp-e/QT intervals. Also, not to miss out subtle cardiac structural and functional abnormalities, we performed tissue Doppler echocardiography in addition to conventional echocardiographic evaluation. Our findings suggest that, autonomic abnormalities don't seem to be related with cardiac structural and functional findings in patients with FSHD.

Even if there are studies showing the presence of cardiac autonomic involvement in muscular dystrophies such as myotonic dystrophy, the underlying mechanism is not clear in patients with muscular dystrophies [25].

Cardiac functional involvement and heart failure progression are the possible responsible mechanisms. Also, involvement of conduction system and autonomic nerves may be other mechanisms for autonomic impairment [5]. Regular exercise training improves cardiac autonomic function and inability to perform regular exercise in muscular dystrophy patients may be an important factor in cardiac autonomic impairment [5,10].

In conclusion, impairment in cardiac autonomic activity may be observed in patients with FSHD despite lack of structural and functional myocardial involvement. However, our sample size is very limited to make precise concerns. Well-planned studies with large sample size are required for more definitive results.

Conflicts of Interest

Authors declared that they have no Conflicts of Interest to disclose.

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