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High prevalence of cardiac involvement in patients with myotonic dystrophy type 1: A cross-sectional study

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ABSTRACT

Background: Patients with myotonic dystrophy type 1 (DM1) have a three-fold higher risk of sudden cardiac death (SCD) than age-matched healthy controls. Despite numerous attempts to define the cardiac phenotype and natural history, existing literature suffers from low power, selection-bias and lack of controls. Thus, the optimal strategy for assessing cardiac involvement in DM1 is unclear.
Method: In this large single-centre study, we evaluated 129 unselected DM1 patients (49.6% men), mean (SD) age 44 (14.7) years with family history, physical examination, electrocardiogram (ECG), echocardiography, Holter-monitoring and muscle strength testing.
Results: Cardiac involvement was found in 71 patients (55%) and included: 1) Conduction abnormalities: atrioventricular block grade I (AVB grade I) (23.6%), AVB grade II (5.6%), right/left bundle branch block (5.5/3.2%) and prolonged QTc (7.2%); 2) arrhythmias: atrial fibrillation/flutter (4.1%), other supraventricular tachyarrhythmia (7.3%) and non-sustained ventricular tachycardia (4.1%); and 3) structural abnormalities: left ventricular systolic dysfunction (20.6%) and reduced global longitudinal strain (21.7%). A normal ECG was not significantly associated with normal findings on Holter-monitoring or echocardiography. Patients with abnormal cardiac findings had weaker muscle strength than those with normal cardiac findings: ankle dorsal flexion (median (range) 4.5 (0–5) vs. 5.0 (2.5–5), $p = 0.004$) and handgrip (median 4.0 (0–5) vs. 4.50 (2–5), $p = 0.02$).
Conclusion: The cardiac phenotype of DM1 includes a high prevalence of conduction disorders, arrhythmias and risk factors of SCD. Systematic cardiac screening with ECG, Holter-monitoring and echocardiography is needed in order to make a proper characterization of cardiac involvement in DM1.

1. Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominantly inherited neuromuscular disorder caused by an unstable expansion of a tri-nucleotide (CTG) repeat on chromosome 19 in the 3′ untranslated region of the myotonic dystrophy protein kinase gene [1].

Cardiac involvement in patients with DM1 is a major concern and includes an increased risk of conduction disturbances, arrhythmias, compromised systolic and diastolic function and sudden cardiac death (SCD) [2,3]. Nevertheless, cardiac involvement is mainly described in smaller studies with low power or limited to studies of electrocardiographic or studies of echocardiographic abnormalities [2–8]. This restricted focus also applies for the existing longitudinal studies [3,9–16] e.g. the study by Groh and co-authors investigating specific ECG-predictors of SCD [2]. The cardiac phenotype of DM1 is complex with unpredictable progression and is not necessarily correlated with the severity of neuromuscular involvement [2,3]. The cardiac conduction disorders are probably caused by myocardial fibrosis, fat infiltration and hypertrophy frequently identified in autopsies from patients with DM1 [17–19]. These changes may also be a substrate for supraventricular and ventricular arrhythmias and also play a key role in the development of the observed systolic dysfunction [4,17,20].

Patients with DM1 rarely report cardiac symptoms despite cardiac involvement. This may mainly be due to the reduced cardiac demand caused by the impaired skeletal muscle function. Consequently,

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arrhythmias may remain unnoticed e.g. atrial tachyarrhythmia, which is an independent predictor of SCD [2,15,21]. Early detection of cardiac involvement is pivotal in order to optimize early intervention which may consequently reduce cardiac symptoms and manifestations.

In this single-centre study, we performed a systematic cardiac assessment including cardiac symptoms, ECG, Holter-monitoring and echocardiography. With this systematic approach, we aimed at investigating the complete cardiac phenotype of DM1 and the association between abnormal findings on each of the used modalities. Secondly, short term follow-up was performed exclusively for selected major events (cardiac and all-cause mortality) to assess if a possible minimum time between cardiac follow-up could be recommended.

2. Methods

2.1. Study design

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

Patients were evaluated by family-history, physical examination, 12-lead ECG, transthoracic echocardiography, 48-hour ECG-monitoring (Holter-monitoring) and muscle strength testing. Blood samples were analyzed for plasma levels of NT-proBNP, creatinine kinase (CK) and myoglobin and screened for liver, renal and thyroid diseases. All blood-samples were analyzed in the same laboratory and results were adjusted for age and gender, when appropriate.

SCDs in relatives below or above the age of 50 years were registered. Lastly, we collected short-term follow-up data exclusively regarding selected major events (cardiac and all-cause mortality) and registered number and cause of deaths.

2.2. Study population

All adult patients, age ≥18 years, with genetically confirmed DM1 were invited to participate and enrolled from December 2010 to December 2012. None of the patients were selected according to age, gender or cardiac symptoms and those included provided written informed consent. A thorough telephone interview was performed in those patients who did not want to participate. Patients were asked about cardiac symptoms and informed about the necessity of seeking medical advice in case of heart specific symptoms. Holter-parameters were compared to a healthy control group from The Copenhagen Holter study [22]. These controls were enrolled from April 1998 to June 2000 and enrolment was not designed to specifically match the DM1 cohort.

2.3. Genetic testing

Genetic testing had been performed earlier as part of the diagnostic work-up and the heterozygous presence of an abnormally expanded CTG repeat allele was confirmed either by Southern-blot analysis and/or by triplet repeat primed polymerase chain reaction [1,23].

2.4. Electrocardiography

A 12 lead ECG was performed using a Burdick Atria 6100 ECG. An ECG was considered abnormal in the presence of: atrial flutter/fibrillation (AFL/AF), other supraventricular arrhythmia including atrial and re-entry tachycardia, atrio-ventricular block (AVB) grades I–III (AVB I: PR-interval >220 ms), right and left bundle branch block (RBBB/LBBB), incomplete right bundle branch block (IRBBB) and prolonged QTc (>450 ms in men and >470 ms in women) using Bazett's formula ($QTc = QT/\sqrt{RR}$). Additionally, we assessed the presence of cardiac abnormalities separately in patients with PR-interval > 240 ms. All ECGs were analyzed by one investigator (HP) and in case of uncertainty discussed with other members of the study group.

2.5. Echocardiography

Echocardiography was performed using a Vivid e9 (General Electric, Horten, Norway) and the examinations were obtained and analyzed by a single operator/observer (HP). 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 and analyzed with EchoPac BT 11.1.0; General Electric, Horten, Norway.

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 volume was calculated from the biplane area-length method with maximum volume before mitral valve (MV) opening (LAmax) and minimum volume just before MV closure (LAmin). Volumetric and dimensional measurements of the left ventricle and left atrium were indexed to body surface area when appropriate. All volumetric analyses were performed in accordance with the recommendations from the European Association of Echocardiography and the American Society of Echocardiography (ASE) [24]. Left ventricular systolic dysfunction (LVSD) was defined as a biplane left ventricular ejection fraction (LVEF) ≤50%.

Doppler recordings of mitral inflow were performed by placing a 2.5 mm sample volume at the tip of the MV leaflets during diastole and recording the pulsed-waved Doppler signal. Peak velocities of early (E) and atrial (A) diastolic filling and MV deceleration time were measured and the E/A ratio was calculated. Continuous-wave Doppler recordings of the LV outflow tract were obtained and aortic valve opening and closure times were measured. Pulsed-wave Doppler tissue imaging recordings were performed at the lateral and medial mitral annulus with measurements of myocardial peak early (E′). The E/E′ ratio was calculated from the lateral values of E/E′. Diastolic dysfunction was assessed and graded in accordance with ASE's recommendations based on the following parameters: e′ lateral, LA volume, MV deceleration time, E/A ratio and E/e′ [25].

2.6. Left ventricular longitudinal strain analysis

LV longitudinal function was assessed by global longitudinal strain (GLS) using a semiautomatic algorithm (Automated Functional Imaging (AFI); GE). Briefly, manual positioning of three points was performed in each of the three apical projections, enabling the software to semi-automatically track the myocardium throughout the heart cycles. Careful inspection of tracking and manual correction, if needed, was performed and in case of unsatisfactory tracking the segment was excluded from speckle tracking analysis. The algorithm then calculated the overall GLS as the average value of all three projections. Normal values of GLS between −22.1% and −15.9% (mean, −19.7%; 95% CI (−20.4% to −18.9%)) have been reported previously [26]. Abnormal GLS was defined as GLS above −15.9%.

2.7. Holter-monitoring

A 48-hour Holter-monitoring was performed with a 3-electrode Lifecard CF (Spacelabs Healthcare). Holter-monitoring 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 VPCs (≥30/h) and non-sustained VT (NSVT) (minimum of 3 beats at ≥100 bpm). Recordings were evaluated by a single observer (HP) and discussed in the study group in case of uncertainty.

Holter-parameters were compared to a healthy control group comprising 285 healthy individuals (74.4% men, mean (SD) age 57.6 (2.5) years). This control-group and the method used for the evaluation of Holter-results have been previously described in detail [27].

2.8. Cardiac involvement and neuromuscular affection

Muscle strength was graded from 0 to 5 using the Medical Research Council scale (MRC) (0 = no ability to contract muscle, 5 = normal strength). In patients with DM1, early affection occurs primarily in the distal muscles. Therefore, we investigated the association between handgrip (dominant hand) and ankle dorsal flexion and abnormal cardiac findings. Neurological assessments were performed by experienced neurologists (JV, NW, SHL).

2.9. Statistics

Data were analyzed with IBM SPSS Statistics version 19. A p-value ≤ 0.05 were considered statistically significant. Normally distributed values are expressed as means ± SD. Data with skewed distribution is given as median (range).

Categorical variables were summarized by frequency counts (percentage) and differences among groups were evaluated using chi-square test. Results of continuous variables are presented as median (range) and comparisons between categories were made with Mann-Whitney U test. Correlation analyses were performed using Spearman Correlation.

The prevalence of any given parameter was first assessed in the total study cohort. Secondly, we corrected all parameters for familiar relations using chi-square test, comparing the prevalence of any given parameter from all included patients vs. the prevalence of the equivalent parameter from the oldest representative in each family.

3. Results

3.1. Study population

We invited 171 patients with DM1 to participate in this study. Forty-two patients did not participate: two due to severe neuromuscular involvement and "lacking energy", 25 due to lack of interest in scientific research projects and long distances to our hospital, 13 did not respond to repeated invitations and two died of non-cardiac causes prior to inclusion. A thorough telephone interview regarding cardiac symptoms was performed in the 27 patients who refused to participate and none of the patients had any cardiac complaints. Thus, we included 129 patients with genetically confirmed DM1 from 73 families (64 men (49.6%), mean (SD) age 44.0 (14.7) years. Gender specific