Acta Myologica • 2007; XXVI; p. 112-114

Cardiac autonomic nervous system in patients with myotonic dystrophy type 1

V. Rakočević-Stojanović[1], B. Milovanović[2], N. Ivić[2], T. Ille[3], I. Marjanović[1], Z. Stević[1], S. Pavlović[4], D. Lavrnić[1]

[1] Institute of Neurology, Clinical Center of Serbia, Belgrade, Serbia; [2] Departments of Cardiology, CHC B. Kosa, Belgrade, Serbia; [3] Department of Statistics, Medical Faculty, Belgrade, Serbia; [4] Departments of Neurology, CHC B. Kosa, Belgrade, Serbia

The purpose of the present study was to evaluate cardiac autonomic nervous system (ANS) in patients with myotonic dystrophy type 1 (DM1). The function of ANS was studied in 20 patients with DM1 and 15 healthy controls. All subjects were investigated by a battery of six cardiovascular autonomic tests and power spectral analysis of heart rate variability (HRV). Only one patient had normal autonomic function. Two (10%) patients had mild, 10 (50%) moderate and 7 (35%) severe autonomic dysfunction. Thirteen (65%) patients had vagal and 4 (20%) sympathetic hyperactivity. Seven (35%) patients had vagal and 15 (75%) sympathetic dysfunction. Eighteen (90%) patients had orthostatic hypotension. The 24-hour time domain parameters of SDNN (SD of the NN interval) and total power were significantly lower in DM1 patients than in healthy controls ($p < 0.05$). However, other parameters of HRV, such as SDANN (SD of the mean NN, 5-minute interval), low frequency (LF), high frequency (HF) power and the LF/HF ratio were somewhat lower in patients with DM1 than in controls, but this was not statistically significant. There was no significant relationship between autonomic dysfunction and the severity of the disease or CTG repeat length. There was also no correlation between HRV and age. Our findings suggest that sympathetic dysfunction and vagal predominance may both occur in patients with DM1.

Key words: Myotonic dystrophy, autonomic nervous system, heart rate variability

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder due to an instable expansion of sequence CTG on chromosome 19q13.3 in the gene coding for myotonin protein kinase (MDPK) (1, 2). The heart is commonly involved in DM1. Progressive conduction defects and arrhythmias are often found, even in asymptomatic subjects, and considered as predictive of sudden death. Whether cardiac autonomic nervous system (ANS) abnormalities influence or accompany the myocardial degenerative changes in patients with DM1 is not clear.

The purpose of the present study was to evaluate cardiac autonomic nervous system in patients with myotonic dystrophy type 1. Heart rate variability (HRV) is a reproducible non-invasive measure of autonomic activity and provides information on vagal modulation and sympathovagal interactions.

Materials and methods

Twenty DM1 patients, aged 21-55 years (mean ± SD: 42 ± 10 years) and 15 healthy controls (39 ± 13 years) were investigated. The ethical committee of our Institution approved the study, and all subjects gave their informed consent. For DM1 patients, diagnostic criteria included clinical features, electrophysiological findings and CTG repeat size detection using genomic DNA extracted from leukocytes. Each patient and healthy controls underwent a standard 12-lead ECG and 24-hour ambulatory ECG. We analysed the presence of ventricular late potentials (VLP). VLP are a kind of slight bioelectric potentials that require the recording of frequencies ranging from 25 to 400 Hz in order to be recognized. The function of ANS was studied in all patients with DM1 and healthy controls. All DM1 patients had no cardiac conduction and rhythm disturbances on 12-lead electrocardiogram and were able to walk and perform daily activities. Only 3 (15%) patients had peripheral neuropathy as a multisystemic abnormality in DM1 patients. None of them had heart failure, hypertension, ischaemic heart disease, diabetes mellitus or positive glucose tolerance test. None of the patients or controls was taking any relevant medication. All subjects were investigated by a battery of six cardiovascular autonomic tests (according to Ewing) and power spectral analysis of heart rate variability (HRV). Long-term time-domain analysis was measured from the entire useable ECG recording with HRV indices derived from the normal-to-normal RR (NN) intervals. Three HRV indices were measured including standard deviation (SD) of the NN intervals (SDNN) as an

Address for correspondence: Vidosava Rakocevic-Stojanovic, Dr Subotica 6, 11000 Belgrade, Serbia. Tel. +38 111 759568. Fax: +38 111 2768097. E-mail: vidosava_r@yahoo.co.uk

estimate of overall HRV, the SD of the mean NN intervals measured over each 5 minutes (SDANN) as an estimate of long-term components of HRV, and the square root of the mean of the sum of the squares of the NN interval difference (RMSSD) as an estimate of short term components of HRV. Fast Fourier transform was used to determine power for a low frequency component (LF, 0.04-0.15 Hz), a high frequency component (HF, 0.15-0.4 Hz), and a total frequency (TF, 0-0.4 Hz). High frequency R-R interval power is considered to be associated with cardiac parasympathetic activity where as the low frequency components are associated with both parasympathetic and sympathetic activity. The ratio of LF to HF (LF/HF) was used as an index of sympathovagal balance. The increase in the ratio is believed to imply that the sympathetic activity is dominant compared to parasympathetic.

Statistical comparisons of results were made using Spearman's correlation coefficient by rank. The relationship between variables was studied using linear regression analysis. The Fisher two-tailed test and chi-square test were used to assess possible association between two or more variables. A level of significance of $p < 0.05$ was considered.

Table 1. Cardiac autonomic nervous system findings in patients with DM1.

Findings	Patients (n = 20)
Autonomic dysfunction	19 (95%)
Orthostatic hypotension	18 (90%)
Sympathetic dysfunction	15 (75%)
Vagal hyperactivity	13 (65%)
Vagal dysfunction	7 (35%)
Sympathetic hyperactivity	4 (20%)
Normal autonomic function	1 (5%)

Results

Only one patient had normal autonomic function. Two (10%) patients had mild, 10 (50%) moderate and 7 (35%) severe autonomic dysfunction. Thirteen (65%) patients had vagal and 4 (20%) sympathetic hyperactivity. Seven (35%) patients had vagal and 15 (75%) sympathetic dysfunction. Eighteen (90%) patients had orthostatic hypotension. Nine (64%) out of 14 investigated patients had positive ventricular late potentials (VLP) (Table 1). The presence of VLP correlated with sympathetic dysfunction in our patients. The 24-hour time domain parameters of SDNN (SD of the NN interval) and total power were significantly lower in DM1 patients than in healthy controls ($p < 0.05$). However, other parameters of HRV, such as SDANN (SD of the mean NN, 5-minute interval), low frequency (LF), high frequency (HF) power and the LF/HF ratio were somewhat lower in patients with DM1 than in controls, but this was not statistically significant (Table 2). There was no significant relationship between autonomic dysfunction and the severity of the disease or CTG repeat length. There was also no correlation between HRV and age.

Discussion

The present study demonstrates that mostly of our patients with DM1 had autonomic dysfunction. Previous studies disagree on wheather ANS abnormalities occur in patients with DM1. Several authors could not find signifi-

Table 2. 24-hour ambulatory ECG characteristics of patients with DM1 and control group.

Characteristics	Findings	
	DM1 patients (n = 20, ± SD)	controls (n = 15, ± SD)
Average heart rate, beats per minute	74.5 ± 13.8	75.1 ± 6.9
Time domain analysis (24-hour recordings)		
SDNN (ms)	135.8 ± 43.4*	179.1 ± 42.2*
SDANN (ms)	127.8 ± 47.9	160.6 ± 44.7
RMSSD (ms)	34.6 ± 13.6	38.6 ± 17.8
Frequency domain analysis (5 minute supine, resting)		
Low frequency power (ms^2)	715.4 ± 445.7	1049.4 ± 454.2
High frequency power	255.5 ± 177.0	359.1 ± 268.1
Total power	3043.4 ± 1556.3*	4709.6 ± 2093.9*
Low frequency/high frequency ratio	3.4 ± 1.9	4.5 ± 2.1

SD: standard deviation, SDNN: SD of the NN intervals, SDANN: SD of the mean 5-minute NN intervals, RMSSD: square root of the mean of the sum of the squares of the NN interval
*: $p < 0.05$

cant abnormalities in cardiovascular autonomic reflexes in DM1 patients (3-6). Hardin and colleagues reported in a large group of unselected DM1 patients that HRV declines as the DM1 patient ages and as CTG repeat length increases. They found sympathetic predominance which could play a role in a propensity to lethal arrhythmias in DM1 patients (7). Some authors found a mixed, especially parasympathetic, cardiovascular autonomic dysfunction in DM1 patients (8). We found orthostatic hypotension, vagal predominance and sympathetic dysfunction in our patients with DM1 and we didn't find significant correlation between autonomic dysfunction and the severity of the disease or age. Some authors found that total, LF, and HF power were all depressed in the DM1 patients (9). But in our study only SDNN and total power were significantly lower in DM1 patients than in healthy controls. However, other parameters of HRV, such as SDANN, LF, HF and LF/HF ratio were somewhat lower in patients with DM1 than in controls, but this was not statistically significant. We found the presence of VLP in 64% out of 14 investigated patients with DM1. Positive VLP indicate a pathoanatomic substrate in the myocardium that can cause the incidence of ventricular arrhythmia and sudden death within this population (10). The presence of VLP correlated with sympathetic dysfunction in our patients.

Our findings suggest that sympathetic dysfunction and vagal predominance may both occur in patients with DM1. Whether cardiac ANS abnormalities influence or accompany the myocardial dysfunction in patients with DM1 is not clear. We think that ANS dysfunction is one of many systemic disturbances in DM1 patients caused by the same pathogenetic mechanism.

References

1. Brook JD, McCurrach ME, Harley HG, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. Cell 1992;69:385.
2. Meola G. Clinical and genetic heterogeneity in myotonic dystrophies. Muscle Nerve 2000;23:1789-99.
3. Aminoff MJ, Beckley DJ, McLlroy MB. Autonomic function in myotonic dystrophy. Arch Neurol 1985;42:16-20.
4. Bird TD, Reenan AM, Pfeifer M. Autonomic nervous system function in genetic neuromuscular disorders: Hereditary motor-sensory neuropathy and myotonic dystrophy. Arch Neurol 1984;41:43-6.
5. Den Heijer JC, Van Dijk JG, Bollen WL, et al. Assessment of autonomic function in myotonic dystrophy. J Neurol Neurosurg Psychiatry 1991;54:531-4.
6. Pierangeli G, Lugaresi A, Contin M, et al. Autonomic nervous system function in myotonic dystrophy. Ital J Neurol Sci 1992;13:589-92.
7. Bradley A, Hardin BS, Miriam R, et al. Heart rate variability declines with increasing age and CTG repeat length in patients with myotonic dystrophy type 1. A.N.E. 2003;8:227-32.
8. Di Leo R, Rodolico C, De Gregorio C, et al. Cardiovascular autonomic control in myotonic dystrophy type 1: a correlative study with clinical and genetic data. Neuromuscular Dis 2004;14:136-41.
9. Inoue K, Ogata H, Matsui M, et al. Assessment of autonomic function in myotonic dystrophy by spectral analysis of heart-rate variability. J Auton Nerv Syst 1995;55:131-4.
10. Rakocevic-Stojanovic V, Grujic M, Milasinovic G, et al. Analysis of ventricular late potentials in patients with myotonic dystrophy. Srpski Archiv 1997;7-8:219-22.