Journal of the Neurological Sciences 325 (2013) 6–9

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Autonomic dysfunction in type 2 diabetes mellitus with and without vascular dementia

Daniela Matei [a,*], C.D. Popescu [b], B. Ignat [b], R. Matei [c]

[a] University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Faculty of Biomedical Engineering, Biomedical Sciences, Romania
[b] University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Faculty of General Medicine, Department of Neurology, Romania
[c] Technical University "Gh. Asachi" of Iasi, Faculty of Electronics, Telecommunications and Information Technology, Romania

ARTICLE INFO

Article history:
Received 30 January 2012
Received in revised form 10 September 2012
Accepted 1 November 2012
Available online 4 December 2012

Keywords:
Diabetes mellitus
Vascular dementia
Ewing's tests
Low- and high-frequency bands

ABSTRACT

Introduction: Autonomic dysfunction has been implicated in sudden cardiac death and cognitive impairment in diabetes.
Objectives: Objectives of the study were to examine the associations between vascular, metabolic risk factors, autonomic and cognitive function in patients with diabetes mellitus.
Method: We investigate autonomic function in 45 participants with type 2 diabetes and in 23 age related normal subjects, using Ewing's tests and power spectral analysis of heart rate variability. Mini Mental State Examination and Hachinski's ischemic scale were used to identify vascular dementia. Only 11 patients were diagnosed with vascular dementia.
Results: The glycosylated haemoglobin, triglycerides, and systolic blood pressure had much larger values in vascular dementia patients compared to the controls. The averages of results obtained in heart rate deep-breathing, Valsalva ratio and lying-to-standing tests for vascular dementia patients are statistically lower than the averages for controls. Vascular dementia patients had a greater fall in blood pressure on standing ($p<0.001$) and reduced blood pressure responses to isometric exercise ($p<0.001$) in comparison with controls. Also they had an increase in the mean heart rate at rest ($p<0.05$), a decrease in time domain parameters of heart rate variability ($p<0.001$), and an increase in the low/high frequency component ratio ($p<0.001$) indicating a vagal-sympathetic dysfunction.
Conclusions: Using standard cardiovascular reflex tests and analysis of heart rate variability we demonstrated an impairment of the autonomic nervous system in vascular dementia patients with marked parasympathetic dysfunction and sympathetic predominance.

1. Introduction

Vascular dementia (VaD) is the second most common form of dementia, after Alzheimer's disease (AD) [1]. It is also thought that the prevalence of mixed vascular dementia has been largely underestimated [2]. Several studies suggest that the risk of developing dementia is increased when a patient is exposed to vascular risk factors such as hypertension, diabetes mellitus (DM), peripheral arterial disease, and smoking, which usually are associated with cerebrovascular disease and vascular dementia [3,4]. DM is a group of metabolic disorders with the common manifestation of hyperglycemia caused by defective insulin secretion, defective insulin action, or both [5]. Diabetes patients are at increased risk for developing micro and macro-vascular complications. Cardiovascular autonomic neuropathy (CAN) is one of the most common complications of DM, but detection of CAN is not a practical screening method for a large number of diabetic patients [6]. Research has shown that increased activity of the sympathetic nervous system (SNS) is associated with an increased risk of cardiovascular events, such as myocardial infarction, stroke or sudden cardiac death [5,6]. Cardiovascular reflex tests based on heart rate variability (HRV) and blood pressure (BP) changes with stress are the most commonly used methods to detect CAN [7]. The objectives of the study were to examine the associations between vascular, metabolic risk factors, autonomic and cognitive function in patients with type 2 DM.

2. Methods

2.1. Participant recruitment and inclusion criteria

45 participants with type 2 DM and 23 age related normal subjects were investigated in our study. Diagnosis and classification of diabetes were based on guidelines of the Expert Committee Report of the American Diabetes Association [5]. The subjects under study were in the age group of 65–85 years and the duration of diabetes was 10–25 years. Patients with myocardial infarction, acute brain injury,

* Corresponding author at: Department of Biomedical Sciences, Faculty of Medical Bioengineering, "Gr.T.Popa" University of Medicine and Pharmacy, 9–13 Kogalniceanu Street, 700454, Iasi, Romania. Tel./fax: +40 232 213573, +40 728 024243 (mobile).
E-mail address: dvm2202@yahoo.com (D. Matei).

0022-510X/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2012.11.001

arrhythmias, atrioventricular block or bundle branch block and frequent extrasystoles were excluded from the study. Inclusion criteria for the controls were the absence of any history of diabetes, normal levels of fasting serum glucose, normal cognitive status and with two normal consecutive electrocardiograms in the course of one month. Any individuals who were taking drugs known to affect autonomic nervous system activity (ANS) were also excluded from the study. The study was carried out in accordance with the Helsinki Declaration. All subjects participated voluntarily after being given a detailed explanation of the purpose of the study.

2.2. Clinical and paraclinical assessment

Height, weight and body circumferences, systolic and diastolic blood pressure were measured in all subjects; body mass index (BMI, kg/m^2) was calculated as weight divided by height squared; waist-to-hip ratio (WHR) was defined as waist circumference divided by hip circumference. History and evidence of cardiovascular disease, hypertension, past history of heart attacks, peripheral vascular disease, and strokes were recorded. In all patients there were measured: fasting blood glucose, total cholesterol, high density lipoprotein cholesterol (HDL), and triglycerides.

Mini-Mental Status Examination (MMSE) was used in screening cognitive status of DM patients. MMSE assesses a broader range of functions, such as the examination of attention and concentration, the evaluation of the orientation capacity to time and place, instantaneous recall, short term memory, writing and constructional capacities, the use of language and executive functions. A score of less than 23 out of 30 were considered evidence of significant cognitive impairment. In 15 patients with DM we found cognitive impairment.

For diagnosed VaD all suspected dementia cases were analyzed according to the criteria of the: NINDS-AIREN (National Institute for Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences [8], Ischemic Score of Hachinski [9] and modified ischemic score (including computer tomography — CT or magnetic resonance imaging — MRI). Diagnosis of VaD according to NINDS-AIREN criteria implies a diagnosis of dementia plus a diagnosis of cerebrovascular disease with history of cerebro-vascular disease (over the last 3 months), neurological examination and neuroimaging. The Hachinski ischaemic score is based on the multi-infarct concept of VaD and may not perform as well in detecting other subtypes of VaD. It has been modified to include CT or MRI findings. VaD clinically manifests through: history of vascular disease, abrupt onset, stepwise course, preservation of judgment, focal neurological signs, mixed cortical-subcortical features, emotional incontinence. The absence of cerebral vascular lesions on CT or MRI excludes the diagnosis of VaD. Features on CT or MRI that are suggestive of VaD include cortical or subcortical infarctions, multiple lacunar strokes and white matter hyperintensities. After these examinations were performed, 11 DM patients were diagnosed with VaD. 4 DM patients were diagnosed with other forms of dementia and they were excluded from the study.

2.3. Clinical autonomic function tests and measurement of heart rate variability

Using BIOPAC Acquisition System, we monitored the HRV in basal condition and during Ewing's tests [7]. HRV was analyzed following the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [10]. Clinical autonomic function tests were carried out according to Ewing's battery, three tests for heart rate variations which depend mainly on parasympathetic activity — heart rate deepbreathing (HRDB), Valsalva ratio (VR) and lying-to-standing tests (30/15), and two tests for blood pressure (BP) response which depend mainly on sympathetic activity — diastolic blood pressure rise with sustained hand grip (ΔDBP) and postural hypotension on standing (ΔSBP). A score of 2 or larger denoted CAN. Evaluation of the tests, which depend on changes in heart rate, was performed using published tables based on age [10]. Short time ECG data were digitized and stored on computer for subsequent off-line analysis. From these measurements using simultaneously fast Fourier and Wavelet transform, HRV parameters were calculated. The ectopic bits or artifacts were manually edited. Time-domain parameters used were Mean–R–R, standard deviation of all NN intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), and percentage of differences between adjacent NN intervals differing more than 50 msec (pNN50 %) [11]. Frequency Domain HRV measured were low frequency component — LF<0.15 Hz, high frequency component — HF>0.15 Hz (as an indicator of parasympathetic function), very low frequency component (VLF) associated with the slow regulation mechanism such as thermoregulations and Total Power (TP) [11]. We analyzed LF and HF power, LF/HF ratio (considered an index of cardiac sympathetic/parasympathetic tone balance).

2.4. Statistical analysis

Statistical analyses were performed using SPSS, version 4.0.1 (SPSS, USA) and EPI INFO V 6.01 program. The results were expressed as mean ± standard deviation. Test t — Student or variance analysis (ANOVA) was used to determine the differences between the groups. The standard linear regression analysis and the Pearson correlation coefficient r were used for determining relationship between parameters. The values $p<0.05$ were considered statistically significant.

3. Results

3.1. Clinical and biochemical features in the groups study

The patients were divided as follows: group **N** (n = 23) included normal controls, group **DM** (n = 30) included DM patients without VaD and group **VaD** (n = 11) included DM patients with VaD. The demographic and clinical data of subjects are shown in Table 1. The diabetes duration was much longer in VaD than in DM patients ($p<0.05$). The BMI ($p<0.05$), fasting blood sugar, HbA1c, triglyceride ($p<0.001$), total cholesterol ($p<0.01$), systolic blood pressure ($p<0.05$) and resting heart rate ($p<0.01$) for the DM patients were much elevated compared with control group but more reduced in VaD patients ($p<0.05$). VaD subjects had HDL-cholesterol more reduced ($p<0.001$) compared with control group (Table 1).

Table 1
Clinical and biochemical features of the groups.

Parameters	N	DM	VaD
	n = 23	n = 30	n = 11
Age (years)	74.2 ± 2.9	72.5 ± 3.08	74.1 ± 2.47
Diabetes duration (years)	–	15.4 ± 3.28	18.4 ± 2.1•
BMI (Kg/m^2)	25.38 ± 2.11	28.5 ± 3.97*	26.85 ± 2.27
Waist/hip ratio	0.83 ± 0.04	0.88 ± 0.03*	0.85 ± 0.04
Fasting blood sugar (mg/dl)	86.8 ± 14.1••	138.9 ± 32.6***	123.5 ± 9.52•
HbA1c (%)	3.92 ± 0.44••	7.84 ± 0.44***	6.91 ± 0.72•
Total cholesterol (mg/dl)	173.2 ± 9.5•	211.2 ± 21.1**	189.1 ± 17.82•
HDL-cholesterol (mg/dl)	50.5 ± 2.29•••	46.6 ± 2.91**	43.5 ± 3.35
Triglyceride (mg/dl)	124.3 ± 21.3••	184.2 ± 31.2***	161.3 ± 14.36•
SBP (mmHg)	121.2 ± 10.18•	136.7 ± 17.83*	129.6 ± 8.31
DBP (mmHg)	65.7 ± 12.1	72.18 ± 15.98	68.1 ± 12.4
Resting HR (beat/min)	62.1 ± 7.85•	69.3 ± 10.8**	67.8 ± 11.7

BMI — body mass index, glycosylated haemoglobin — HbA1c, SBP — systolic blood pressure, DBP — diastolic blood pressure, and HR — heart rate.
Data: expressed as mean ± standard deviation;
* — $p<0.05$; ** — $p<0.01$; *** — $p<0.001$ for difference between controls and DM without VaD.
• — $p<0.05$; •• — $p<0.01$; ••• — $p<0.001$ for difference between DM without and with VaD.
▪ — $p<0.05$; ▪▪ — $p<0.01$; ▪▪▪ — $p<0.001$ for difference between controls and DM with VaD.