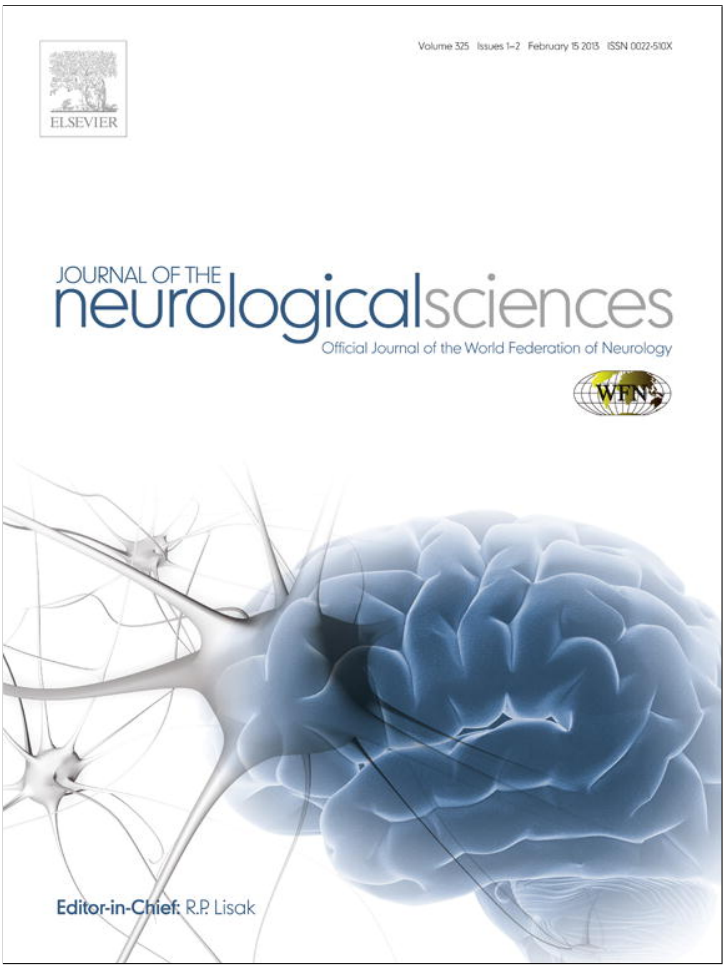

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Autonomic dysfunction in type 2 diabetes mellitus with and without vascular dementia

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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,

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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.

Table 2
Clinical autonomic function tests.

	N	DM	VaD
	n = 23	n = 30	n = 11
Parasympathetic clinical autonomic function tests			
Mean change in HR during deep breathing (HRDB)	9 ± 1.58▪▪▪	7.6 ± 1.32	5.8 ± 1.45▪▪▪
Mean HR response to standing (30/15 ratio)	1.2 ± 0.2▪▪	1.07 ± 0.04*	1.01 ± 0.02▪▪
Mean Valsalva ratio (VR)	1.42 ± 0.08▪▪▪	1.3 ± 0.08*	1.21 ± 0.06▪▪
Sympathetic clinical autonomic function tests			
Mean fall in SBP on standing (ΔSBP) (mmHg)	29.9 ± 2.65▪▪▪	38.16 ± 3.75***	42.72 ± 4.69▪
Mean change in DBP on isometric exercise (ΔDBP) (mmHg)	25.3 ± 5▪▪▪	21.56 ± 3.34	16.4 ± 3.3▪▪

HR — heart rate, SBP — systolic blood pressure, and DBP — diastolic blood pressure.
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.

3.2. Clinical autonomic testing

The prevalence of CAN was 56.6% in DM patients and 81.8% in VaD patients. The averages of results obtained in the parasympathetic tests (HRDB, 30/15, VR) for VaD patients are statistically significant lower than the averages for the control group ($p<0.001$, $p<0.01$, $p<0.001$ respectively) (Table 2). Patients with VaD had impaired HRDB ($p<0.001$), 30/15 ($p<0.01$) and VR ($p<0.01$) in comparison with DM patients in univariate ANOVA. VaD patients had a greater fall in blood pressure on standing than controls ($p<0.001$) and DM patients ($p<0.05$). Patients with VaD had reduced blood pressure responses to isometric exercise in comparison with controls ($p<0.001$). In Pearson correlation the HRDB test correlated negatively with body mass index (BMI) in VaD ($r=-0.78$, $p<0.001$). HRDB, VR correlated negatively with diabetes duration ($r=-0.63$, $p<0.002$) and ($r=-0.35$, $p=0.017$). 30/15 correlated negatively with systolic blood pressure ($r=-0.75$, $p<0.001$) in VaD patients.

3.3. Heart rate variability

Table 3 shows the comparison of measures in time and frequency domain analysis of HRV between the three groups. The SDNN, pNN50% showed statistically significant reduction in the VaD groups when compared to the control group ($p<0.001$). Also we found a reduction in SDNN ($p<0.05$) and pNN50% ($p<0.01$) in VaD patients compared with DM group. The systolic blood pressure correlated significantly negatively with SDNN ($r=-0.40$, $p<0.01$). There was a significant positive correlation between systolic blood pressure and the RMSSD ($r=0.44$, $p<0.01$) and the pNN50 ($r=0.39$, $p<0.05$). Low and high frequency power were reduced in patients with VaD ($p<0.01$, $p<0.0001$, respectively) in comparison with healthy controls. There were no differences between the VaD and DM patients in low frequency power. The LF/HF ratio was lower in the healthy subjects than in the DM ($p<0.001$) and in VaD ($p<0.0001$) subjects (Fig. 1). Increase in the LF/HF component ratio in VaD, DM patients indicated a vagal–sympathetic dysfunction; VaD patients ($p<0.05$) were more affected in comparison with DM patients. Analyzing the frequency domain measures of heart rate variability, diminished heart rate variability correlated significantly negatively with mean systolic blood pressure (LF: $r=-0.39$, $p<0.05$). In the VaD subjects, the LF/HF ratio was correlated significantly with the BMI ($r=0.41$, $p<0.01$) and with HbA1c ($r=0.45$, $p<0.02$).

Table 3
Time and frequency domain analysis of heart rate variability.

Parameters	N	DM	VaD
	n = 23	n = 30	n = 11
R-R (ms)	918 ± 84.02▪▪	836.7 ± 125.7*	757.5 ± 98.2
SDNN (ms)	163.6 ± 16.4▪▪▪	154.1 ± 17.42**	144.7 ± 11.8▪
RMSSD (ms)	34.9 ± 3.2▪	32.28 ± 3.8	27.9 ± 2.12▪
pNN50%	23.7 ± 1.49▪▪▪	22.7 ± 2.7	18.5 ± 2.24▪▪
LF (ms^2)	616.7 ± 54.37▪▪	560.8 ± 49.64*	527.6 ± 61.68
HF (ms^2)	824.8 ± 94.15▪▪▪	661.4 ± 56.1**	575.7 ± 58.4▪▪
LF/HF	0.74 ± 0.06▪▪▪	0.83 ± 0.03***	0.91 ± 0.07▪

SDNN — standard deviation of all NN intervals, RMSSD — square root of the mean of the sum of the squares of differences between adjacent NN intervals, pNN50% — percentage of differences between adjacent NN intervals differing more than 50 ms, LH — low frequency component, and HF — high frequency component.
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.

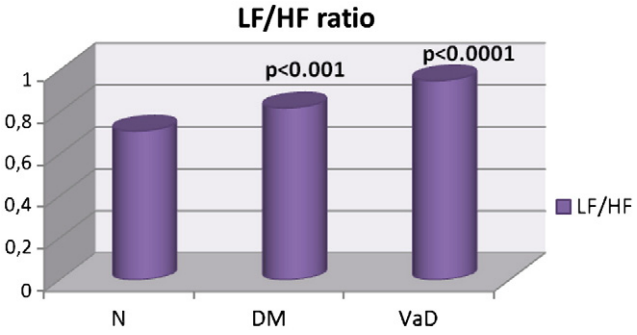

Fig. 1. LF/HF ratio in study groups.

4. Discussion

Diabetes mellitus is associated with a large number of chronic complications which finally result in a premature mortality. Type-2 diabetes is associated with increased inflammation, increased oxidative stress, advanced glycosylated end products, macro and microvascular injury, decreased neurogenesis, reduced neuronal repair, neuronal damage [5].

DM predisposes to impairments in autonomic nervous system (ANS) regulation or endothelial function. Impairments in ANS regulation may contribute to abnormal changes in endothelial cells, resulting in endothelial dysfunction, or impairments in endothelial function may lead to dysfunction in ANS regulation. Endothelial dysfunction is an important early event in the pathogenesis of atherosclerosis, contributing to plaque initiation and progression. Nitric oxide (NO), relaxing factors released by the endothelium, contributes to cerebral arterial and arteriolar dilatation, increases in cerebral blood flow (CBF), and decreases in cerebral vascular resistance. Endothelin-1 is one of the contracting factors released by the endothelium. Insulin resistance decreases NO and increases endothelin-1 activity, favoring vasoconstriction and reducing capillary recruitment [12]. In normal arteries ANS and endothelium share a functional antagonism that maintains vascular tone. There is a tonic balance between the release of vasodilating factors from the endothelium and vasoconstricting factors from sympathetic nerve terminals. Vasoconstriction resulting from the release of norepinephrine from sympathetic nerve terminals may stimulate the increase in NO [13]. NO decreases the sensitivity of smooth muscle cells to the vasoconstrictor effects of the SNS and inhibits central and peripheral SNS activity [14]. In contrast, NO may increase central and peripheral parasympathetic nervous system (PSNS) activity while enhancing sensitivity to PSNS sites of action [14]. The SNS can stimulate the release of endothelin [15]. Endothelin at normal levels may suppress SNS-induced vasoconstriction, whereas excess endothelin release may enhance vasoconstrictive responses to SNS stimulation.

Vascular dementia can be defined as a dementia syndrome likely to be the consequence of lesions of the brain, vascular in origin, irrespective of their ischemic, hemorrhagic or hypoxic nature. Subcortical ischemic vascular dementia refers to lesions that involve the basal ganglia, cerebral white matter and the brainstem and is the most common cause of cognitive decline and VaD in the elderly [16]. Decreased CBF destabilizes synaptic connections and neuronal activity in regions involved in cognitive function (limbic regions, association areas, white matter that links association areas), also in regions involved in autonomic control. White matter lesions can disrupt efferent projections from the nucleus basalis of Meynert resulting in cortical cholinergic denervation [17]. The association between reduced CBF and increased risk of dementia appears to be greater among individuals with diabetes [18], hypertension and heart disease [19].

Baroreflex mechanism has an important role in maintaining perfusion through modulation of the heart rate and contractility via the cardiac ANS [20]. It has been shown that an increase in short-term BP variability is associated with cognitive dysfunction [21]. In patients with CAN, vagal impairment can lead to a predominance of SNS activity which stimulates the renin–angiotensin–aldosterone system and increases heart rate and peripheral vascular resistance.

High midlife cholesterol was associated with poorer late-life cognition, but decreased cholesterol after midlife may reflect poorer cognitive status [22].

Reduced HRV is the earliest indicator of CAN [23]. A recent study reported that presence of CAN, assessed by standard HRV testing, was one of the strongest predictors of ischemic stroke together with age and hypertension [24]. Other studies have demonstrated that an unbalanced sympathetic/parasympathetic tone, with a prevalence of sympathetic activity, is associated with higher cardiovascular mortality in type 2 diabetic patients [25]. In our study the prevalence of CAN in VaD patients was high (81.8 %), cardiovascular reflex tests have shown both sympathetic and parasympathetic failure in VaD disease. A possible limitation of our study is the presence of a small number of subjects. This decreases the statistical power of our study to detect differences between the groups. These results should be confirmed in larger studies specifically addressing the relationship between vascular, metabolic risk factors, autonomic nervous activity and cognitive function. Several subsequent autopsy series have confirmed that patients with dementia have both AD and vascular changes, and pure vascular dementia or pure AD is almost non-existent particularly among the elderly [26,27]. Other studies suggest that brain ischemia promotes the production of beta-amyloid, a key player in AD pathogenesis [28]. This could be another limitation of our study because we agree that most elderly subjects have multiple brain pathologies.

A lot of studies indicate that SDNN, pNN50%, time domain indicators of the HRV, represent the activity of the vagal nerve. In the frequency domain, HF is an index of cardiac vagal nerve tone, while LF represents the SNS activity with vagal modulation. It has been established that LF/HF ratio is a more sensitive measure of increased of sympathetic activity because the vagal modulation affects LF significantly [11]. The analysis of HRV demonstrated that both parasympathetic and sympathetic nerve functions were impaired in DM and VaD patients because the measures of SDNN, pNN50%, HF and LH were significantly lower in DM, VaD groups than in controls. Also significant difference of LF/HF ratio between the three groups suggested that great sympathetic dysfunction was found in VaD patients compared with DM ($p<0.01$) and controls ($p<0.001$). The data reported in the present study indicate that the sympathovagal balance (expressed by the LF/HF ratio) remains consistently altered with a sympathetic overactivity in all VaD subjects.

5. Conclusions

Using standard cardiovascular reflex tests and analysis of HRV we demonstrated an impairment of the autonomic nervous system in VaD patients with marked parasympathetic dysfunction and sympathetic predominance.

Conflict of Interest

The authors have no conflict of interest to declare.

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