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Autonomic impairment in patients with migraine

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Abstract. – OBJECTIVE: Heart rate variability analysis of electrocardiogram is becoming an increasingly common method to non-invasively evaluate autonomic nervous function. The aim of the study was to investigate cardiac autonomic function in subjects with and without migraine by using 24-hour ambulatory electrocardiographic recordings.

PATIENTS AND METHODS: We investigated 27 subjects with migraine (10 with migraine with aura and 17 without aura) during headache free periods and 10 age-matched healthy control subjects. The migraine was diagnosed using the International Classification of Headache Disorders 2nd Edition criteria. Beck Depression and Beck Anxiety Inventory forms were completed by all subjects. Time and frequency-domain of HRV was analyzed for two periods: diurnal and nocturnal.

RESULTS: We found an increased frequency of anxiety and depressive symptoms in migraine patients, especially in migraine with aura group. The heart rate variability parameters SDNN, RMSSD, high frequency were decreased and low frequency was increased in migraine patients during night period compared with normal subjects, most affected were migraine with aura patients. During day period we found modification for SDNN, RMSSD and high frequency parameters only in migraine with aura group.

CONCLUSIONS: Reduced parasympathetic activity with sympathetic predominance was found in migraine patients during the night period, most affected being migraine with aura patients.

Key Words:
Migraine, heart rate variability, sympathetic nervous system, parasympathetic nervous system, low frequency, electrocardiography.

Introduction

Migraine is a chronic neurovascular disorder characterized by intermittent attacks of severe headache with or without aura. Typically the headache is unilateral and lasts from 2 to 72 hours[1]. The autonomic nervous system (ANS) involvement is suggested by many symptoms and signs including nausea, diarrhea, cold extremities, light and sound sensitivity or dizziness during attacks. Some people with migraine headaches perceive an aura: a transient visual, sensory, language, or motor disturbance which signals that the headache will occur[2]. Migraine, and specifically migraine with aura, has been associated with increased risk of ischemic stroke, particularly among young women[3]. Abnormalities in the sympathetic nervous system (SNS)[4] or parasympathetic nervous system (PNS)[5] have been found in migraine patients during the headache-free phase.

The aim of the study was to investigate cardiac autonomic function in teenagers with and without migraine by using 24-hour ambulatory ECG monitoring with heart rate variability (HRV) evaluation while also assessing the severity of this dysfunction and its relation to the type of migraine.

Patients and Methods

Participant Recruitment and Inclusion Criteria

Twenty-seven subjects (mean age of 26.7 ± 2.12 years) with migraine were evaluated during the pain-free period; 10 with migraine with aura (MA) and 17 with migraine without aura (M). We confined the study to women aged 20 to 35 years who had suffered from migraine for more than 1 year and had at least one migraine attack per month.

The diagnosis of migraine was made using criteria of the International Classification of Headache Disorders 2nd Edition (ICHD-II) [6]. The control

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group (C) consisted of 10 age and sex-matched healthy control subjects. Patients who were on any prophylactic headache treatment or had a systemic disease that might interfere with heart rate such as: cardiovascular or neurological diseases, endocrine dysfunction or pregnancy were excluded.

Participation was voluntary, all subjects gave their informed consent before entering the study. The study was carried out in accordance with the Helsinki Declaration.

Clinical Assessment

All the subjects underwent detailed history taking and neurological examination. Migraine cases underwent all examinations in a headache free period (> 3 days after a migraine attack). Subjects were assessed by interview upon smoking, alcohol intake, oral contraceptives use. The average alcohol intake in the past year was based on question inquiry upon drinking frequency and quantity of drinks per occasion and categorized into none, moderate (1-3 drinks/day) and high (>3 drinks/day).

Weight and height were used to calculate body mass index (BMI – weight [kg]/height² [m]). In all subjects there were measured: fasting plasma glucose, total cholesterol, high density lipoprotein cholesterol and triglycerides. Blood pressure (BP) was measured using an electronic device.

Psychological Evaluation

The psychological evaluation included two self-reporting questionnaires aimed at assessing anxiety and depression. The questionnaire to assess anxiety consisted of Beck Anxiety Inventory (BAI), which is a 21-item scale with a scoring range from 0 to 63 points, high scores indicating a more severe anxiety[7]. In order to measure the severity of depression we used Beck depression inventory (BDI-II) which is composed of a 21-item rated on a 4-points scale and a total score results after ratings summation for the individual items. The total score ranges from 0 to 63 points. Higher scores indicate greater depressive symptoms[8].

Heart rate Variability Measurement

Autonomic nervous system function was evaluated by heart rate variability (HRV) analysis during 24-hour ambulatory electrocardiographic (ECG) recording. 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 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 %)[9].

In Frequency Domain HRV based on fast Fourier transform there were measured low frequency component (LF < 0.15 Hz) taken as an indicator of both vagal and sympathetic function, high frequency component (HF ≥ 0.15 Hz) as an indicator of parasympathetic function, very low frequency component (VLF) and total power (TP)[9].

We have analyzed normalized LF power = LF/(TP-VLF) and normalized HF powern = HF/(TP-VLF). The ratio of LF/HF was considered as an index of cardiac sympathetic/parasympathetic tone balance.

Statistical Analysis

Statistical analyses was performed using STATISTICA 6.0. The comparison of demographic data between the groups of migraine patients and control was performed using Chi-square test (for dichotomous and categorical data, e.g. alcohol consumption, cigarette smoking) and Student's *t*-test or variance analysis (ANOVA) for continuous data. The results were expressed as mean ± standard deviation. The Pearson correlation coefficient r was used for determining the relationship between parameters. The $p < 0.05$ value was considered statistically significant.

Results

Demographic, Clinical and Biochemical Data in the Study Groups

The patients were divided as follows: group C (n=10) included controls, group M (n=17) included migraine without aura patients and group MA (n=10) included migraine with aura patients. The demographic, clinical and biochemical data of subjects is shown in Table I.

There was no significant differences regarding age between the three groups (F=0.3, p=0.681). The average age was 26.1±2.5 years in the control group, 26.7±2.12 years in patients with M, and 25.8±2.3 years in MA.

Body mass index was 24.8±2.11 kg/m² in C, 24.2±2.7 kg/m² in M patients, and 23.5±2.5 kg/m² in MA patients with no significant differences between groups, p=0.772.

Positive family history of migraine was reported in both groups of migraine patients (M 35.2%, MA

Table I. Clinical and biochemical features of the group.

Parameter	C N = 10	M N = 17	MA N = 10
Age (years)	26.1 ± 2.5	26.7 ± 2.12	25.8 ± 2.3
BMI (kg/m²)	24.8 ± 2.11	24.2 ± 2.7	23.5 ± 2.5
Medical family history (%)			
- migraine	10†	35.2	40*
- diabetes mellitus	20	23.5	20
- hypertension	20†	47.05	60*
High alcohol use (>3 drinks/day) (%)	10	5.88	10
Smoking (%)	20	29.4	20
Duration of migraine attack (h)	-	9.4 ± 6.1‡	16.3 ± 11.2
Fasting blood sugar (mg/dl)	83.8 ± 16.1	88.1 ± 18.3	76.2 ± 14.1
Total cholesterol (mg/dl)	169.2 ± 9.5	167.2 ± 11.5	171.2 ± 8.3
HDL-cholesterol (mg/dl)	52.5 ± 2.2	52.1 ± 2.7	49.7 ± 2.2
Triglyceride (mg/dl)	109.1 ± 12.7	113.1 ± 17.3	142.5 ± 23.8*
SBP (mmHg)	126.2 ± 21.2	131.2 ± 29.1	128.1 ± 21.5
DBP (mmHg)	77.2 ± 11.1	78.1 ± 10.7‡	89.7 ± 11.8*
HR (beat/min)	69.1 ± 7.2	68.5 ± 9.1	70.4 ± 7.5
BAI	9.88 ± 5.01	14.93 ± 9.23‡	25.88 ± 14.92*
BDI	9.11 ± 4.67	10.06 ± 7.23‡	19.3 ± 11.85*

Data are expressed as number (%) or as means ± standard deviation; BMI – Body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, BAI – Beck anxiety inventory, BDI – Beck depression inventory.
†$p < 0.05$ for difference between migraine without aura groups and controls.
*$p < 0.05$ for difference between controls and migraine with aura groups.
‡$p < 0.05$ for difference between migraine with and without aura groups.

40%) with $p<0.05$ compare with control group. Medical family history proved that patients with migraine with aura had more hypertension cases ($p<0.01$) in their family compared with control group. Alcohol consumption and smoking were reduced with no significant difference between groups (alcohol $p = 0.726$, smoking $p=0.562$).

The length of migraine attack (h) was more prolonged in migraine with aura compared to migraine without aura (16.3±11.2 h vs. 9.4 ± 6.1 h, $p<0.05$). Migraine with aura sufferers had increased triglycerides value ($p<0.05$) compared to control group. There was no significant difference in fasting blood sugar, total cholesterol and HDL-cholesterol values between the study groups.

Systolic blood pressure levels and heart rate did not differ within the groups. Diastolic blood pressure was increased in subjects with migraine with aura compared to normal controls (89.7±11.8 mmHg vs. 77.2±11.1 mmHg, $p<0.05$).

Psychological Evaluation

BAI was 9.88±5.01 in C vs. 14.93±9.23 in M patients, $p<0.152$ and 25.88±14.92 in MA patients with $p<0.007$ when compared to C group and $p<0.050$ when compared to M group. Minimal or mild anxiety (score 0-15) was found in 9 patients (90%) in control group, 12 patients in M group (70.5%) and in 5 patients with MA (50%). Moderate anxiety (score 16-25) was found in 1 patient of C group (10%), in 5 patients of M group (29.5%) and in 3 MA patients (30%). Severe anxiety (scores 26-63) was found in 2 MA patients (20%).

BDI was 9.11±4.67 in controls vs. 10.06±7.23 in M patients with $p=0.727$ and 19.3±11.85 in MA, with $p<0.028$ when compared to controls and $p<0.022$ when compared to M patients. Minimal or mild depression (score 0-19) was found in all patients in control group, in 16 migraine patients without aura (94.1%) and in 7 (70%) migraine with aura patients. Moderate depression was found in 1 patient of M group and in 3 patients of MA. We found an increased frequency of anxiety and depressive symptoms in migraine patients, especially in migraine with aura group.

Heart Rate Variability

Time-domain and frequency parameters of HRV can be observed in Table II.

Mean heart rate (HR) beat/minute and RR during daytime did not differ between groups, but the values of night recordings showed increased HR among migraine with aura patients when compare with control group (MA: 70.1±9.1

Table II. Time and frequency domain HRV parameters.

Parameter	C N = 10	M N = 17	MA N = 10
Mean HR (beat/min)			
- day	76.4 ± 11.6	78.1 ± 7.91	77.1 ± 11.8
- night	64.2 ± 9.4	65.5 ± 10.7	70.1 ± 9.1*
Mean RR (ms)			
- day	797.3 ± 124.4	829.2 ± 95.5	820.6 ± 74.06
- night	923.6 ± 84.5	897.5 ± 76.2	859.1 ± 108.3*
SDNN (ms)			
- day	92.6 ± 34.7	89.3 ± 24.9	87.11 ± 35.2*
- night	83.4 ± 23.6†	76.7 ± 38.1‡	69.5 ± 37.6*
RMSSD (ms)			
- day	49.6 ± 11.7	47.7 ± 10.9	43.6 ± 8.3*
- night	63.2 ± 16.2†	56.5 ± 11.7‡	51.6 ± 7.3*
pNN50%			
- day	11.7 ± 8.6	9.9 ± 8.2	9.2 ± 6.4
- night	22.7 ± 14.1	21.3 ± 6.1	19.7 ± 11.7
LF (nu)			
- day	68.1 ± 10.4	65.6 ± 8.21	67.3 ± 8.8
- night	47.3 ± 11.2†	51.3 ± 5.5‡	59.11 ± 12.1*
HF (nu)			
- day	36.4 ± 11.7	37.6 ± 13.1	32.6 ± 11.4*
- night	54.6 ± 10.2†	49.7 ± 11.2‡	41.5 ± 10.1*
LF/HF			
- day	2.1 ± 0.7	2.1 ± 0.5	2.2 ± 0.5
- night	1.2 ± 0.5	1.3 ± 0.5	1.7 ± 0.5*

Data: expressed as means ± standard deviation;
†p < 0.05 for difference between migraine without aura groups and controls
*$p < 0.05$ for difference between controls and patients with migraine with aura;
‡$p < 0.05$ for difference between migraine with aura and migraine without aura

beat/min vs. C: 64.2±9.4 beat/min, $p<0.05$) and RR reduction among the same patients (MA: 859.1±108.37 ms vs. C: 923.6±84.5 ms, $p<0.02$).

SDNN during day time was found to be lower in migraine with aura than controls (MA: 87.11±35.2 ms vs. C: 92.6±34.7 ms, $p<0.05$). During night period SDNN was decreased in both migraine groups (MA: 69.5±37.6 ms vs. C: 83.4±23.6 ms, $p<0.01$; M: 76.7±38.1 ms vs. MA: 69.5±37.6 ms, $p<0.05$).

Migraine with aura had lower RMSSD than controls both day and night periods (day-MA: 43.6±8.3 ms vs. C: 49.6±11.7 ms, $p<0.03$; night-MA: 51.6±7.3 ms vs. C: 63.2±16.2 ms, $p<0.001$), and also was lower than in migraine group without aura during night ($p<0.05$).

LF in migraine groups was increased during night period compared with normal subjects (MA: 59.11±12.1 nu vs. C: 47.3±11.2 nu, $p<0.01$) and in migraine without aura (51.3±5.5 nu, $p<0.05$). HF during day period was reduced in MA group when compared with control group (MA: 32.6±11.4 nu vs. C: 36.4±11.7 nu, $p<0.05$). HF during night was 41.5±10.1 nu in migraine with aura vs. 54.6±10.2 nu in control with $p<0.01$ and 49.7±11.2 nu in migraine without aura with $p<0.05$. LF/HF was increased during night in MA patients 1.7±0.5 vs. 1.2±0.5 in controls, $p<0.04$.

Using Pearson correlation analysis the SBP was correlated with BMI (r= 0.85, $p<0.003$) and with LF (r= 0.42, $p<0.02$). HF spectral value of HRV was negatively correlated to triglycerides (r= -0.45, $p<0.05$), with BDI score (r= -0.79, $p<0.006$), and BAD score (r= -0.81, $p<0.001$). BDI score was also correlated with LF/HF (r= 0.73, $p<0.003$).

Discussion

The migraine pathogenesis is not completely understood, several theories, such as the vascular theory, neuronal excitation, neurotransmitter levels variations, trigeminal sensory–parasympa-

thetic reflex or autonomic dysfunction have been proposed as possible disease pathways.

The autonomic nervous system imbalance, characterized by sympathetic hyperfunction and parasympathetic hypofunction was reported in patients with migraine[10]. Aura symptoms, such as photosensitivity may be due to this imbalance[11].

Low HRV has been proposed as a disease characteristic[12]. High HRV is associated with highly functional prefrontal cortex inhibitory activity over subcortical structures which make the body to be well adapted to the environment[12]. Low HRV is associated with reduced prefrontal inhibitory control over subcortical structures such as the amygdala and is linked with anxiety and depression[12]. In our study we found an increased frequency of anxiety and depressive symptoms in migraine patients, especially in migraine with aura group.

In this study, we tried to analyze the ANS involvement in migraine using HRV on long-term 24-hour ECG. Time and frequency-domain analysis of HRV was achieved for two periods: diurnal (7-12 a.m.) and nocturnal (0-6 a.m.). The time domain analysis parameters, i.e., SDNN, RMSSD, are thought to reflect the activities of the parasympathetic nervous system. LF power (0.02-0.15 Hz) has been reported to be modulated by both sympathetic and parasympathetic activities, whereas the HF power is mediated by parasympathetic nervous system[9]. Therefore, the LF/HF ratio represents the balance of autonomic nervous system.

The significant decrease of SDNN, RMSSD and HF indicates parasympathetic dysfunction in migraine groups during night headache free periods, most affected were migraine with aura patients. Also LF in both migraine groups was increased during the night period compared with normal subjects ($p<0.01$ for MA and $p<0.05$ for M group). LF/HF was increased during night in MA patients 1.7±0.5 vs. 1.2±0.5 controls, $p<0.01$.

In both groups of migraine patients we discovered an autonomic nervous system dysfunction, the most marked SNS and PNS impairment being present in the group of migraine with aura sufferers. In these group we showed the highest BDA and BDI scores. In MA patients we pointed out the the sympathetic component predominance associated with parasympathetic hypo-activation especially at night with loss of circadian rhythms.

High cardiac vagal tone can be used as an index of adaptive emotional regulation and social engagement[13]. Depressed mood has been shown to be associated with SNS dominance[14] and decreased parasympathetic cardiac control in reaction to stress, with reduced baroreflex cardiac control[15].

Stress, depression and poor sleep quality can contribute to the occurrence of migraine[16]. The activation of the hypothalamus-pituitary-adrenal axis in stressful situations has been associated with a higher migraine activity[17]. Most migraine attacks start or end at night[18]. It is not clear why but serotoninergic and dopaminergic dysfunction, hormonal fluctuations, central sensitization or drugs over-use are some of the discussed pathophysiological mechanisms[19,20].

When asked about sleep quality and dreaming, migraine patients complained about bad sleep quality. The vast majority also experience negative sensations such as anxiety, fear or terror and contents such as perception of fall, unsuccessful efforts to do various things, fights, death of relatives, etc. These observations suggest that there is some malfunction in the prefrontal cortex, limbic system, amygdala, and hypothalamus, elements involved in dream and migraine pathophysiology[21].

Dysfunction of corticolimbic structures have been implicated in visceral hypersensitivity which is present in migraine[22]. Activation of the limbic system, amygdala, and anterior cingulate cortex observed in rapid eye movement sleep are involved in cardiovascular regulation and could reflect responses to intense emotions suck as fear and anxiety found in migraine patients during night[23].

Individuals with high level of stress, anxiety and depression display an imbalance between PNS and SNS activity what was revealed in our study.

A possible limitation of our study is the presence of a small number of subjects. This decreases the statistical power to detect differences between the groups, not allowing us to generalize our results. These results should be confirmed in larger studies specifically addressing the relationship between autonomic functions and migraine. The use of self-report instruments in order to diagnose depression and anxiety was another shortcoming. Further pathophysiological migraine mechanisms might be explained using simultaneous brain imaging and electrophysiological evidence which in the present study was not possible.

Conclusions

Reduced parasympathetic activity with sympathetic predominance was found in migraine patients more pronounced during the night period,

most affected were those with migraine with aura. The current findings suggest that anxiety and depression are more likely to be associated with reduced cardiac vagal modulation.

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Conflict of Interest Statement:

The Authors declare that they have no conflict of interests.

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