ORIGINAL RESEARCH PAPER | Medical Science | Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

An Assessment of HRV in Female Migraine Patients During Headache Free Period.

KEYWORDS: Migraineurs with aura, HRV, sympathetic hyperactivity

DurgavatiTak | Jyotsna shukla | Amitabh Dube

Bajrang Tak | Kapil dev Mathur

ABSTRACT ***Background:*** *Migraine is the 3rd most prevalent and 7th leading cause of disability worldwide. It is a chronic neurological disorder that has diverse autonomic manifestations. Yet, there are less conclusive studies available regarding dysfunctions of the autonomic nervous system in migraineurs during headache free periods.*
Objective: *To assess and compare the HRV in female migraine patients during headache free period and age matched healthy female controls.*
Material and Methods*: Forty diagnosed female migraine patients age ranging between 30-40years, fulfilling the criterias of ICHD 2004 formed the study group. Age matched 40 healthy female subjects froms SMS Medical College were taken as control. The assessment of Heart Rate Variability was done by recording the 5 minutes E.C.G.by RMS ECG machine The analogue ECG signals were converted to digital signal and stored in the computer for offline Frequency Domain analysis. Statistical analysis was performed using SPSS software version 20 and unpaired student t-test to derive the level of significance.*
Results: *The mean of HF n.u. in % in migraine patients was 37.95±8.54 and of controls subjects was 63.48±3.37. (p-value 0.000) The mean of LF n.u.in % in migraine patients was 62.05±8.54 and of control subjects was 36.52±3.37. (p-value 0.000) The mean of LF/HF ratio of migraine patients was 1.77±0.59 and of control subjects was 0.58±0.08. (p-value 0.000)*
Conclusion: *Migraineurs during headache-free periods are found to have sympathetic hyperactivity. Therefore, an early understanding of the autonomic nervous system dysfunctions in migraine patients can help in diagnosis, prevention and treatment.*

Introduction

Migraine is a complex neurobiological disorder that has been recognized since antiquity. (1) It is a disabling headache disorder characterized by intermittent attacks with a number of physiological and emotional stressors associated with or provoking each attack. (2) The Global Burden of Disease Study 2013 found migraine to be the third commonest disease in the world and it is the sixth highest cause of disability worldwide. (3) Analysis of heart rate variability (HRV) has nowadays become one of the most popular methods of autonomic nervous system evaluation. It is based on the observation that even at rest the duration of RR intervals is not constant but continually fluctuates around the mean value. Extremely complex neural mechanisms are responsible for these fluctuations. They are based mainly on interactions between the sympathetic and parasympathetic nervous system. Activity of the sympathetic and parasympathetic nervous system continually fluctuates, which results from mutual interactions.

Migraine is a chronic neurological disorder that has diverse autonomic manifestations. Yet, there are less conclusive studies available regarding dysfunctions of the autonomic nervous system in migraineurs during headache free periods. Hence present study was undertaken with the aim of evaluating the autonomic nervous system activity in female migraineurs during interictal period using HRV

Material and Method

Material and Method

The study was conducted in the Upgraded Department of Physiology in association with the Department of Neurology, S.M.S. Medical college and Hospital, Jaipur, Rajasthan from 1st June 2014 to 31st May 2015.

Forty diagnosed female migraine patients with aura age ranging between 30-40 years, fulfilling the criteria of IHSC-2 (International Headache Society Criteria-2*)* formed the study group. Age matched 40 healthy female subjects from SMS Medical College were taken as control subjects.

Ethical Statement:- This study was approved by the Institutional Research Review Board of SMS Medical College and Hospital.

All patients and subjects gave written informed consent to participate in this study categorized into two groups: Group A: female migraine patients with aura; and Group B: healthy female control subjects.

Inclusion criteria: Adult female migraine with aura 30-40 years age**,** follicular phase of regular menstrual cycle (28 days)**,** BMI 18-25 kg/m^2 were included in study.

Exclusion criteria: Body Mass Index ≥ 25 kg/m^2 or ≤18 kg/m^2 **,** Chronic illnesses Diabetes mellitus, Hypertension, Thyroid dysfunction affecting the autonomic function**,** Medications like antihypertensive, antidepressants, anti-anxiety drugs affecting the autonomic functions were excluded from study.

All subjects were tested between 10 am to 12.30 pm under similar laboratory conditions and were allowed to adapt themselves to experimental and environmental conditions for 30 minutes so that they were comfortable, as anxiety and stress can affect autonomic functions. After explaining exact procedure of each test following instructions were given to the subjects

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

To avoid coffee, nicotine or alcohol 24 hours prior and food 2 hours prior of autonomic function testing.

The room ambient temperature was maintained at 24-25°C.

Heart Rate Variability (HRV)
The assessment of Heart Rate Variability was done by recording the 5 minutes E.C.G.by RMS ECG machine (DECG 1/ 63041/ADBXB). The analogue signal was converted to digital signal by National Instrument software NI-DAQ Version 8.0.

For short term analysis of HRV ECG was recorded in the supine posture for 5 minute after 15 minute of supine rest in a quiet environment.

After acquiring the ECG as digital signals, all the recording were manually corrected if required.

The analogue ECG signals were converted to digital signal and stored in the computer for offline Frequency Domain analysis. For processing, the detection of R wave was done by HRV Soft version 1.1 developed by AIIMS, New Delhi. In the Frequency Domain analysis the power spectrum for HRV was calculated with the fast fourier transformation (FFT) based method (4).

The normalized units were calculated as (5)

H.F. (n.u.) for assessing Parasympathetic Nervous System activity

HF (Absolute Unit) / LF (Absolute Unit) + HF (Absolute Unit) ×100

L.F. (n.u.) for assessing Sympathetic Nervous System activity

LF (Absolute Unit) / LF (Absolute Unit) + HF (Absolute Unit) ×100

Statistical Analysis
The numerical data are in the form of mean±SD

Unpaired student t-test was applied to calculate the level of significance using SPPS version 20.

Level of significance was assigned at p-value <0.05

Observations
Table 1 Anthropometric parameters

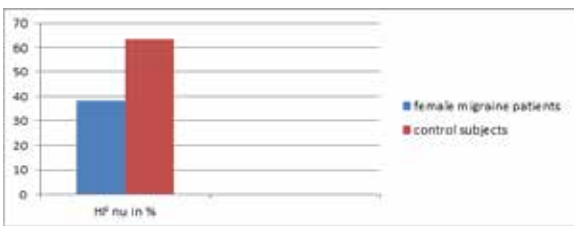
Parameters	Female migraine patients with aura (n=40)	Control subjects (n=40)	t-value	p- value	Significance
Age(years);	35.15± 3.26	34.20±2.86	1.385	0.170	NS
Weight (Kg.)	51.27±3.44	52.52±2.75	-1.795	0.07	NS
Height (meter)	1.52±0.046	1.53±0.037	-1.178	0.242	NS
B.M.I.(Kg/ m^2)	22.22±1.34	22.42±1.12	-0.724	0.471	NS

(NS) Non significant, (S) Significant, (HS) Highly significant

Table 2 Frequency domain parameter of HRV

Test parameter	Female migraine patients with aura (n=40)	Control subjects (n=40)	t-value	p-value	Significance
H. F. nu (normalized unit) %	37.95±8.54	63.48±3.37	-17.587	0.000	HS
L. F. nu (normalized unit) in %	62.05±8.54	36.52±3.37	17.587	0.000	HS

(NS) Non significant, (S) Significant, (HS) Highly significant



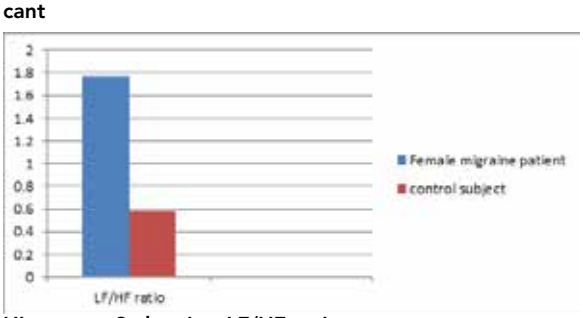
Histogram 1 showing High frequency normalized unit (HF nu) in percentage

Histogram 2 showing Low frequency normalized unit (LF nu) in percentage

Table 3 LF/HF ratio

Test parameter	Female migraine patients with aura (n=40)	Control subjects (n=40)	t-value	p-value	Significance
LF/HF Ratio	1.77±0.59	0.58±0.08	12.641	0.000	HS

(NS) Non significant, (S) Significant, (HS) Highly significant



Histogram 3 showing LF/HF ratio

Results
The mean of normalized unit of high frequency in % (HF n.u.) in migraine patients was 37.95±8.54 and of controls subjects was 63.48±3.37. (Table 5) (p-value 0.000) (Histogram 7)

The mean of normalized unit of Low Frequency in % (LF

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

n.u.) in migraine patients was 62.05±8.54 and of control subjects was 36.52±3.37. (Table 10) (p-value 0.000) (Histogram 11)

The mean of LF/HF ratio of migraine patients was 1.77±0.59 and of control subjects was 0.58±0.08. (Table 11) (p-value 0.000) (Histogram 12)

Discussion

The clinical symptoms of migraine are broadly established to be related to the involvement of the autonomic nervous system and disturbance of the autonomic nervous system, a primary characteristic of migraine. (Melek M. et al) [6]

Based on cardiovascular tests, vasomotor reactions to temperature changes and responses to pharmacological tests, as well as changes in biochemical parameters, hypo- as well as hyper functioning of both the sympathetic and parasympathetic nervous system have been suggested. (Appenzeller O. et al.) [7]

A number of case-control studies (Ebinger M.W. et al [8], Appel S. et al [9], Gotoh F. et al [10]) of cardiovascular function reported sympathetic hyperfunction even when using single-lead ECG monitoring in migraine patients in interictal period

The heart continually oscillates between acceleration and deceleration in a tug-of-war within the autonomic nervous system, controlled by "pacemakers" in the heart that create the heart's rhythms. The high frequency power spectrum reflects parasympathetic (vagal) tone. The mean normalized unit of high frequency component (HF n.u.) in % for the migraine patients was 37.95±8.54% and of the control groups was 63.48±3.37 %. (Table 2) (p-value 0.000) (Histogram 1).In our study HF n.u. was lower in migraine patients showing impaired parasympathetic activity.

In heart rate variability the low frequency power spectrum was evaluated in the range from 0.04 to 0.15 Hz. This band reflects sympathetic activity. The mean normalized units of low frequency component LF (n.u.) in % for migraine patients it was 62.05±8.54% as compared to the control subjects where mean was 36.52±3.37 %.(Table 2) (p-value 0.000) (Histogram 2).The study shows that in migraine female patients low frequency in normalized unit was significantly more indicating sympathetic hyperactivity.

Our study results are comparable with study conducted by Rauschel V. et al.[11] found the mean of high frequency power in migraine patients 3323±5754 ms^2 compared to control subjects 4166± 6971 ms^2 low frequency (LF) power in migraine patients was 4369±5454 ms^2 and in control subjects 4215± 3937 ms^2.

Appel S. et al. [9] used 24-hour EKG Holter recordings to evaluate autonomic functions in migraine patients. By using a spectrum analysis of heart rate fluctuations, he found an increased in power in the lower frequency band (below 0.15 Hz), suggesting sympathetic hyperfunction and a concomitant reduction in the higher frequency band (0.3 Hz) (parasympathetic hypofunction). This may correspond to an imbalance between the sympathetic and parasympathetic function and is consistent with our results.

In spite of the heterogeneity of the published results, the most often discussed interpretation concerning the alteration of autonomic functions in migraine patients in the literature are sympathetic hyper-activation and/or parasympathetic hypo-activation. The major finding of the present study was also the presence of sympathetic hyperactivity and impaired parasympathetic activity in migraine patients as compared to control subjects. Exact cause of sympathetic hyperactivity is not proven in migraine patients. Possible cause of sympathetic hyperactivity may be due to stress of phobic headache and subsequent headache attack. This is supported by a cross-sectional study, in which migraine patients were found to have elevated plasma levels of cortisol, an indicator for stress, during headache free period.(Ziegler D.K.et al.[12]). It is also supported by stress-provocation study, involving mental and physical stressors have suggested sympathetic and parasympathetic changes in migraine patients between attacks compared to healthy subjects.(Avnon Y. et al.[13]) .

Thus regular assessment of autonomic functions can be used as a biomarker for early detection and subsequent management of cardiovascular morbidity and mortality in female migraine patients with aura.

Conclusion

The involvement of the autonomic nervous system in migraine pathophysiology is complex and heterogeneous. Most published results suggest either a sympathetic hyperactivity and or parasympathetic hypo-activity. Our study results point in the same direction with a net increased sympathetic tone. Thus, it is concluded that female migraineurs during headache free periods are found to have sympathetic hyperactivity.

Strength, Limitations and Recommendations

Certainly, the strength of our study is the careful selection and monitoring of the migraine patients, ensuring that all patients were recorded in headache free period and were free of preventive drugs or recent intake of analgesics

As we only obtained a single interictal recording, it can also not be ruled out that autonomic function test parameters change during the migraine cycle.

The study was conducted in a limited time period on a small sample size. Better results may be obtained with a larger sample size and larger time period

References

1. Blau J.N. (1992). *Migraine: theories of pathogenesis.* Lancet; 339:1202-1207.
2. Stewart W.F., Shechter A. and Rasmussen B.K.(1994). *Migraine prevalence. A review of population-based studies.* NEUROLOGY;44(6): S17–S23.
3. Global Burden of Disease study 2013 collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 3 01 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet; (2015) vol.386 (no.9995):743- 800.
4. Task force of European society of cardiology and the North American society of pacing and Electrophysiology. (1996). *Heart Rate variability standards of measurement, physiological interpretation and clinical use.* Circulation;93:1043- 1065.
5. Pichon A., Bisschop C.D., Denjean A. (2005). *Parasympathetic airway response and heart rate variability before and at the end of methacholine challenge.* Chest;127:23-29.
6. Melek, E. Seyfeli, M. Duru, T. Duman, F. Akgul, and F. Yalcin. Autonomic dysfunction and cardiac repolarization abnormalities in patients with migraine attacks. Medical Science Monitor, 2007;13(3): 47-49.
7. Appenzeller O. Reflex vasomotor functions: clinical and experimental studies in migraine. Res Clin Stud Headache 1978; 6: 160-166
8. Ebinger M.W.,Krishnan S., and Schuger C.D., "Mechanisms of ventricu-

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

lar arrhythmias in heart failure," Current Heart Failure Reports. 2005; 2 (3):111–117.

9. Appel S., Kuritzky A, Zahavi I., Zigelman M, and Akselrod S., "Evidence for instability of the autonomic nervous system in patients with migraine headache," Headache, 1992; 32(1): 10–17.
10. Gotoh F., Kanda T, and Sakai F., "Serum dopamine β hydroxylase activity in migraine," Archives of Neurology, 1976; 33(9): 656–657.
11. Rauschel V., Straube A., Süß F., Ruscheweyh R., Rauschel. (2015). *Responsiveness of the autonomic nervous system during paced breathing and mental stress in migraine patients.* The Journal of Headache and Pain;16:82
12. Ziegler D.K. et al.(1979).*Circadian rhythms of plasma cortisol in migraine*. J Neurol Neurosurg Psychiatry; 42:741-748.
13. Avnon Y. et al. (2004). *Autonomic asymmetry in migraine: augmented parasympathetic activation in left unilateral migraineurs.* Brain; 127:2099-2108.