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Original Article

Evaluation of Cardiovascular Autonomic Functions in Migraine Individuals

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Abstract

Introduction: A migraine is a multifactorial brain disorder characterized by recurrent disabling attacks of a headache and associated autonomic features affecting 20% of females and 6% of males. Neural explanation of migraine pathogenesis has revealed that the autonomic nervous system plays a pivotal role in the cascade of events leading to migraine.

Materials and Methods: This study evaluates the cardiovascular autonomic function tests in migraine individuals. The study was among 20-50 years of 30 healthy volunteers as a control group and 30 patients with migraine as study group. The standard autonomic cardiovascular function tests such as orthostatic standing test (OST), deep breathing (DB), isometric handgrip test (IHG), and cold pressor test (CP) were performed.

Results: There was a significant reduction in the modification of RR interval as evidenced by decrease in HR during the IHG and CP and also a significant decrease in the diastolic blood pressure when compared to the controls. The 30/15 ratio during OST test showed a statistically significant difference when compared to the controls. The E/I ratio was, however, was not statistically significant. All these suggest a sympathetic hypofunction.

Conclusion: These observations indicate a definite sympathetic hypofunction which might have activated the trigeminovascular system in causing a throbbing headache. An improved understanding of the role of sympathetic function in migraineurs may help to prevent and more effectively treat migraine and other headaches.

Key words: Autonomic function, Headache, Migraine, Sympathetic activity

INTRODUCTION

A migraine is a multifactorial brain disorder characterized by recurrent disabling attacks of a headache with autonomic features and with neurological aura symptoms. It is a ubiquitous familial disorder that begins in childhood, adolescence or in early adult life and runs with diminishing frequency during advancing years of age. WHO ranks migraine as one of the top 20 leading neurological causes of disability. It is estimated that 12% of world's population suffer from migraine and in India, of 1200 million populations there are 150-200 million migraineurs under treatment. The gender prevalence of migraine is about 20% in females and 6% in males. In regards to work, migraine leads reduced productivity and absenteeism Campinha-Bacote.[1] Migraine is a heterogeneous disorder, where attacks vary in duration, frequency, severity, character and associated with physical and emotional disability. The anxiety and panic disorder have sympathetic overactivity with stress being the most important triggering factor. Migraine is also associated with ischemic stroke.[2] Neural explanation of migraine pathogenesis revealed that the autonomic nervous system (ANS) plays a pivotal role in the cascade of events leading to migraine attack. This study proceeds with testing migraine subjects by performing battery of tests on cardiac autonomic functions and finding the sympathetic or parasympathetic dysfunction in the heart and relate this with the pathogenesis of migraine.

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MATERIALS AND METHODS

A case-control study was done in tertiary care hospital, ethical clearance and Patient's informed consent was obtained. Patient's ages from 20 to 50 years were included in the study in both groups. The study group consists of newly diagnosed cases of migraine fulfilling International Headache Society (IHS) criteria for migraine were included in the study group. They were not on any medication for a headache and were screened for normal respiratory, cardiac, renal and hepatic functions. Patients with other causes of a headache such as cluster headache, tension headache, sinus headache and patients with hypertension, diabetes, ischemic heart disease, and neuromuscular disorder were excluded from the study. Niviqure ambulatory digital electrocardiogram (ECG) recorder (INCO), pulse rate and NIBP recorder – PLANET-50, sphygmomanometer, handgrip dynamometer, and cold water filled basin were used for autonomic testing. The study subjects were asked to fill a pro forma to assess the severity of migraine and also ANS questionnaire to assess the autonomic dysfunction. 30 subjects in each group were subjected to a battery of autonomic function tests along with resting heart rate (HR) variability as described by Ewing *et al.*[7] These tests examine the variability of HR at rest and its response to normal physiologic stimuli by various manoeuvres. The subjects tested during headache-free intervals between 10 and 12 AM, Any medication including caffeine, nicotine and alcohol and vigorous exercise should be avoided on the day of testing. The test should be performed in a quiet room with controlled temperature ranging from 25°C to 28°C and lighting subdued and mobile phones switched off. The subjects were instructed about various manoeuvres that would be employed and allowed to practice these manoeuvres. The subject was made to rest quietly, in the awake and supine position for a minimum period of ten minutes. After cleaning the site with sprit the exploring electrode one in the right shoulder and another in left shoulder and the reference electrode in right subcostal region was placed. Rest period was increased to 30 min and during this time ECG was acquired by continuous recording for 5 min (320 s) which is needed for short term ECG analysis. After screening for the artefact an editing it, the results were fed to HRV analysis software. The analogue to the digital conversion of the resting ECG signal was done using AD converter with a sampling frequency of 1024/s. Power spectral analysis of the converted ECG signal was done using fast Fourier transformation (FFT). Mean respiratory rate (RR), mean HR, total power, low frequency (LF), high frequency (HF), and LF/HF were estimated. A battery of tests proposed by Wang and Mishra (2006)[16] was performed. Orthostatic standing test (OST) which tests both the sympathetic and parasympathetic reactivity of ANS and deep breathing (DB) which tests the intactness of parasympathetic function were performed after giving enough rest in between the tests to the subjects. It was further proceed by doing isometric handgrip (IHG) test and cold pressor (CP) test for evaluating the sympathetic reactivity. The differences in autonomic functions in study and control group were assessed accordingly and evaluated using SPSS software version 11.0.1.

RESULTS

About 30 patients were recruited in each group, mean age of control group 33.27 ± 5.58 and mean age of case group 31.97 ± 8.20. Female dominant in group, 24 in controls and 26 in cases group, which shown females are more prone to migraine. The mean body mass index of control and case group are 26.01 ± 1.26 and 25.84 ± 1.37 which is statistically insignificant ($P = 0.626$). Table 1 compares the resting HR, diastolic blood pressure (DBP) and systolic blood pressure (SBP), between the cases and controls. Mean value for HR and mean value of DBP between cases and control was not significant. However, the mean value of SBP showed a $P = 0.001$ which was highly significant. The mean value of HR, RR interval and total power were also not statistically significant ($P > 0.05$). Table 2 compares the resting HRV between cases and controls among parasympathetic dominant subjects. There was a statistically significant drop in LF and LF/HF ratio and an increase in HF in migraine patients when compared to controls. Table 3 compares the increase in HR above the resting value during the handgrip test in cases and controls. The *P* value was highly significant ($P = 0.001$). There was also an increase in DPB above the resting value during IHG test which was highly significant ($P = 0.010$). Table 4 compares the increase in HR and DPB above the resting value during CP Test in cases and controls. The *P* value was very highly significant ($P = 0.000$) for the increase in HR. The increase in DPB above the resting value during CP test was also highly significant ($P = 0.004$). Table 5 shows the comparison of parameters obtained in OST namely 30/15 ratio, SPB, DBP difference from the resting value in cases and control. The 30/15 ratio was highly significant ($P < 0.01$). The SBP and DBP changes during OSTs were also highly significant. Comparison of E/I ratio during DB between cases and control. The *P* value was not statistically significant ($P = 0.422$).

DISCUSSION

The ANS is strongly influenced by sympathetic and parasympathetic divisions. The extent of the control by these two limbs varies from individual to individual. In our study, the resting HR measurement signifies the autonomic tone at rest while, the cardiovascular response by stressors

Table 1: Comparison of all parameters of case and control subjects (*n*=30)

Parameters	Controls	Cases	*P* value**
HR/min	78.07±5.92	77.63±7.72	0.808
SBP mmHg	120.93±4.66	111.80±12.78	0.001
DBP mmHg	76.67±4.91	74.00±8.47	0.142
LF	44.13±10.03	40.76±15.23	0.316
HF	55.70±10.05	59.23±15.23	0.293
LF/HF	0.867±0.464	0.834±0.624	0.803
HR mean	78.17±7.07	76.79±10.80	0.562
RR mean	0.857±0.111	0.807±0.150	0.148
Total power	2538.80±1686.80	3019.97±9292.28	0.781

**Student's t-test. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LF: Low frequency, HF: High frequency, RR: Respiratory rate

Table 2: Comparison of HR variability between cases and controls among parasympathetic dominant subjects (*n*=22)

	Controls	Cases	*P* value
LF	38.94±4.13	33.67±9.74	0.027
HF	60.83±4.49	66.33±9.74	0.023
LF/HF	0.648±0.116	0.538±0.218	0.044

HR: Heart rate, LF: Low frequency, HF: High frequency

Table 3: Comparison of HR and DBP changes during isometric hand grip test between cases and controls

Vitals	Controls	Cases	*P* value
HR/min	12.20±1.69	8.33±5.43	0.001
DBP mmHg (1 min)	7.77±2.39	6.00±2.74	0.010

HR: Heart rate, DBP: Diastolic blood pressure, SD: Standard deviation

Table 4: Comparison of DBP changes during cold pressor test between cases and controls

Vitals	Controls	Cases	*P* value
HR/min	11.50±1.81	8.23±2.99	<0.0001
DBP mmHg (1 min)	9.07±2.00	7.17±2.87	0.004

HR: Heart rate, DBP: Diastolic blood pressure

Table 5: Orthostatic standing test: Comparison of 30/15 ratio, changes in SBP and DBP between cases and controls

Characteristics	Controls	Cases	*P* value
30/15 ratio	1.11±0.049	1.23±0.295	0.039
SBP mmHg	−2.83±5.58	7.47±4.63	0.001
DBP mmHg	3.80±3.37	−2.13±4.66	<0.0001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

which is essentially reflexive in nature, signifies the autonomic reactivity (Deepak *et al.*[3]). Spectral analysis applied to inter-beat interval (HR variability) has been considered as a useful parameter for determining ANS functions providing information on both sympathetic and parasympathetic functions. They give frequency specific contribution to HR power spectrum which can be evaluated by FFT. The frequency domain analysis gives an idea of the LF and HF variables. LF is an index for sympathetic activity, which in this study was not statistically significant, but was less than the control group showing mild sympathetic hypofunction. On further analysis of the individual migraine subjects, 22 of the 30 subjects showed a parasympathetic dominance as reflected by the high HF and 8 of the subjects showed sympathetic dominance (with high LF). When these 22 subjects were compared with the controls, there was statistically significant difference between the spectra of migraine group and control group. The LF/HF ratio which is used to indicate the balance between the sympathetic and parasympathetic tone was significantly reduced in our study, quantifying the overall parasympathetic dominance. Mikamo *et al.*[4] substantiated the sympathetic hypofunction by measuring the low concentration of norepinephrine levels among the migraineurs. However, in the time domain analysis, there was no significant change in mean HR and mean RR, when compared to the control groups. The autonomic reactivity was assessed in the study group by viewing the reflex response of the cardiovascular system to lab stressors like standing from supine position, undergoing hand grip exercise and by giving a painful stimulus by immersing the hand in cold water. The parasympathetic reactivity and sympathetic reactivity were separately tested by these stressors. In DB test which assesses the parasympathetic reactivity of ANS, there was no statistically significant difference in study and control groups. This reveals the intactness of parasympathetic function of ANS. In orthostatic hypotension test the parasympathetic component is functionally unaffected while the sympathetic division fails to bring back the blood pressure to normal. These findings suggest possible role of autonomic nervous involvement in pathogenesis of migraine. The result of this study was consistent with the study done by Havanka-Kanniainen *et al.*[5] and Stephen, 2004. The study group also suffered from orthostatic intolerance as reflected from symptoms such as dizziness, lightheadedness, and unsteadiness. Cerebral hypoperfusion which was assessed by visual disturbances defined as flashes of light and fortification spectra was seen in five of the migraineurs revealing autonomic instability. The IHG test is a simple, non-invasive test. It measures the activity of peripheral sympathetic system acting through the efferent fibers supplying the heart and thus producing an increase in HR and blood pressure.[6] This exercise reflex which withdraws parasympathetic and increases sympathetic activity failed to respond in our study group as evidenced by decrease in DPB and HR when compared to the controls. This was consistent with study done by Havanka-Kanniainen *et al.,*[5] Mosek *et al.*,[7] and Pogacnik *et al.,*[8] which showed a smaller sympathetic activation in response to stressor. In CP test, another physiological stress test which assesses the efferent sympathetic outflow,

there was a statistically significant decrease in DPB and the failure to increase the HR. However, Rubin *et al.*[9] found no significant difference between migraineurs and controls in response to CP test. Thus, the results of HR variability at rest showed a sympathetic hypofunction, and when the heart was given a challenge by the lab stressors, there was disturbance in the balance between the sympathetic and parasympathetic systems. This could lead to increased susceptibility to migraine headaches and also changes the system to reacts with the triggers at low threshold.[10] The cause of sympathetic dysfunctional in migraineurs is due to decreased norepinephrine (NE) concentration leading to subsequent increase in the cotransmitters like dopamine (immediate precursor of NE) prostaglandins, neuropeptide Y and adenosine from the sympathetic neurons (Sherbourne *et al.*, 1992).[11,12] The clinical symptoms of migraine can be linked to these cotransmitters. The symptoms like nausea and vomiting in migraineurs (7%) can be due to increase in excessive dopamine, throbbing headache (40%) can be due to the action of prostaglandins and the sedation in migraineurs (10%) can be associated with elevated levels of adenosine. Stress, an important provocation factor for migraine also contributes to the pathogenesis of migraine by depleting the NE. All these activate trigeminal system leading to throbbing headache of migraine. This well explains the therapeutic role of triptans and ergot alkaloids in treating headache by bringing about vasoconstriction thereby blocking the effects of the cotransmitters. This study would have been more valid if the NE levels were measured and the ANS activity was assessed by the cephalic vasomotor response. An understanding of the role of sympathetic functions and dysfunction in migraine may help to prevent or more effectively treat migraine and other headaches.

CONCLUSION

Evaluation of cardiovascular functions in migraine individuals reveals sympathetic hypofunction with an intact parasympathetic activity as indicated by a significant reduction of sympathetic modulation of RR intervals in the study group. An increase in HF power (an indicator of parasympathetic activity) reveals a parasympathetic dominance. Pathogenesis of migraine may be attributed to a depletion of norepinephrine with a concomitant increase in cotransmitters leading to activation of the trigeminovascular system resulting in throbbing headaches. An improved understanding of the role of sympathetic function and its dysfunction may help to prevent or effectively treat migraine and other headaches.

REFERENCES

1. Campinha - Bacote, D.L.,Kendle, J. B., Jones, C.,Callicoat, D.,Webert, A,Stoukides, C,Kaul, A.F.(2005).Impact of migraine management program on improving health outcomes. Disease Management, 8(6), 382-391
2. Scher, PhD, G. M. Terwindt, MD, PhD, H. S.J. Picavet, PhD, W. M.M. Verschuren, MD, PhD, M. D. Ferrari, MD, PhD and L. J. Launer, PhD Cardiovascular risk factors and Migraine, Neurology 2005;64:614-620.
3. Deepak K.K, Rajesh K.Sharma, R.L.Bijlani and Rao P.S; Short term physical training alters cardiovascular autonomic response amplitude and latencies. Indian j. physio pharmacol 2004;48(42):165-193.
4. Mikamo, K., Takeshima, T., & Takahashi, K. (1989). Cardiovascular sympathetic hypofunction in muscle contraction headache and migraine. Headache 29; 86-89.
5. Havanka-Kanniainen H, Tolonen U, Myllylä VV. Autonomic dysfunction in adult migraineurs.Headache.1986; 26:425-430.
6. Bannister R, Mathias C. Testing autonomic reflexes. In: Bannister R, editor. Autonomic Failure, New York; Oxford University Press, 1988:289-307.
7. Amnon Mosek, MD; Vera Novak, MD, PhD; Tonette L. Opfer-Gehrking, Jerry W.Swanson, MD; Philip A.Low, MD, Autonomic Dysfunction in Migraine;Headache 1999;39:108-117
8. Pogacnik, T., Sega, S., Pecnik, B., & Kiauta, T. (1993). Autonomic function testing in patients with migraine. Headache, 33, 545-550.
9. Rubin, L.S., Graham, D., Pasker, R., & Calhoun, W. (1985). Autonomic nervous system dysfunction in common migraine. Headache, 25, 40-48.
10. Aaron Shechter, Stewart WF, Silberstin SD, Lipton RB, Migraine and autonomic nervous system: a population–based, case control study. Neurology.2002;58:422-427.
11. Todorov LD, Mihaaylova-Todorova ST, Bjur RA, Diffrential cotransmission in sympathetic nerves:role of frequency of stimulation and prejunctional autoreceptors.J pharmacol Exp Ther. 1991; 290; 241-246.
12. Truru H, Tanimitsu N Role of perivascular sympathetic nerves and regional differences in the features of sympathetic innervation of the vascular system.

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