RESEARCH ARTICLE

A STUDY OF AUTONOMIC FUNCTIONS IN THE PATIENTS OF EPISODIC MIGRAINE

Background: Autonomic disturbances are common in the patients of migraine, predominantly sympathetic hypofunction was observed while parasympathetic system also showed abnormal behavioral response. There is no comprehensive study regarding these aspects in migraineurs in India.
Aims & Objective: To study the state of autonomic nervous system in the patients of episodic migraine during interictal period.
Materials and Methods: This case control study done employing a sample of 54 migraine cases selected from the outpatient department, GB Pant hospital Delhi. Selection of patients was based on the clinical diagnosis by neurologists and each case fulfilling the International headache society criteria 2004 irrespective of aura status. The control pool was formed by 30 normal healthy participants from Maulana Azad Medical College. All participants were aged between 20 to 40 years. Informed consent was taken from all the participants and the ethical clearance was obtained from the college. Sympathetic function tests: handgrip test, cold pressor Test, sympathetic skin response and parasympathetic function tests: resting heart rate, standing to lying Ratio, 30: 15 ratio, Valsalva Ratio and tachycardia Ratio. Assessment of the autonomic system was carried out during headache free interval.
Results: Of the sympathetic tests, the sympathetic skin response showed a significant statistical difference between cases and controls while remaining parameters showed no statistical significance. Of the parasympathetic tests, none of them revealed any statistical significance between cases and controls.
Conclusion: In contrast to many western studies which showed sympathetic hypofunction, we observed sympathetic hyperfunction during the interictal period, while parasympathetic system was normal.
Key Words: Migraine; Autonomic Nervous System; Autonomic Functions

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INTRODUCTION

Migraine is a common, primary, chronic-intermittent neurovascular headache disorder characterized by episodic severe headache accompanied by autonomic nervous system dysfunction and in some patients, transient neurologic symptoms known as migraine aura.[1,2] The word migraine is derived from the term hemicrania, and is defined as a paroxysmal headache, commonly but not invariably unilateral, recurrent at irregular intervals and often associated with visual disturbances and other disorders of cerebral function and vomiting.[3] Autonomic functions have been found to be distinctly disturbed in migraine. There are numerous studies done in the past to suggest that there is an autonomic dysfunction in patients of migraine, sympathetic hyperfunction, sympathetic hypofunction and parasympathetic dysfunction have all been noticed. In the American migraine study, Migraine prevalence was 17.6% for women and 6% for men paralleling the Rasmussen et al. estimates.[4]

During headache-free periods, migraineurs may have a reduction in sympathetic function compared to non-migraineurs. Migraine shares significant diagnostic and clinical features with both pure autonomic failure and multiple system atrophy, yet represents a distinct subtype of chronic sympathetic dysfunction. Migraine is most similar to pure autonomic failure in terms of reduced supine plasma norepinephrine levels, peripheral adrenergic receptor supersensitivity, and clinical symptomatology directly related to sympathetic nervous system dysfunction. However, the sympathetic nervous system dysfunction in migraine differs from pure autonomic failure and multiple system atrophy in that it occurs in an anatomically intact system. It is proposed that the sympathetic dysfunction in migraine relates to an imbalance of sympathetic co-transmitters. An enhanced understanding of the sympathetic dysfunction in migraine may help to more effectively diagnose, prevent, and/or treat migraine and other types of headache.[5]

MATERIALS AND METHODS

This case control study was conducted in the Department of Physiology, Maulana Azad Medical College in association with the Department of Neurology GB Pant hospital, New Delhi. The study was conducted on 84 subjects of which 54 (Group B) were diagnosed migraine patients. The remaining 30 (Group A) age matched normal

subjects included in the control group were obtained from Maulana Azad Medical College, New Delhi. After taking informed consent from all the participants and the ethical clearance was obtained from the college the subjects were categorized into two groups: Group A: Controls; and Group B: Cases

Inclusion Criteria: All adult patients of either sex, in the age group of 20 to 40 years, presenting with a history of headache satisfying the International Headache Society criteria-2 for primary episodic migraine were enrolled for the study.

Exclusion Criteria: Migraine patients with diabetes mellitus, hypercholesterolemia disorders, patients taking blood pressure medications and oral contraceptives. Migraine patients with history of any illness known to affect ANS system. All secondary causes of headache were excluded by appropriate clinical and radiological examinations.

All Subjects were tested under similar laboratory conditions and were allowed to acclimatize themselves to experimental and environmental conditions for one hour so that they were relaxed and rested, as anxiety and stress can affect autonomic functions. The procedure of each and every test was explained to the subjects before conducting the tests.

Autonomic Function Tests: The autonomic function tests were conducted with the help of a Polyrite-D machine manufactured by RMS. The following autonomic function tests were performed in all the participants:

Parasympathetic Function Tests: Resting Heart Rate, Standing to Lying Ratio, 30: 15 Ratio, Valsalva Ratio and Tachycardia Ratio.

Sympathetic Function Tests: Handgrip Test (HGT), Cold Pressor Test (CPT) and Sympathetic Skin Response (SSR).

Statistics: Results of the study were analysed statistically using ANOVA.

RESULTS

In table 1, the mean SBP of the cases was 122.70 ± 9.23 and the median was 125, while the mean and median SBP of the controls is 122.87 ± 6.80 and 123 respectively. The mean SBP of the cases is less than that of the controls and the difference between cases and controls is statistically insignificant as suggested by the p value of 0.933 derived applying ANOVA. The same table 1 shows the DBP of cases and controls which are 77.44 ± 7.062 and 74.97 ± 3.97, median is 78 for cases and 74 for controls. Although the mean DBP of cases is more when compared to the mean DBP of controls there is no statistical significance between the two groups using the parametric test.

During hand grip test the mean value for change in systolic blood pressure (SBP) in cases was 21.48 ± 3.89, median is 20 and that of controls was 22.13 ± 3.67 while median is 22 respectively as shown in table 1. The same table shows that the mean change in diastolic blood pressure (DBP) in cases to be 17.22 ± 3.35 and median to be 16 as compared to mean change in diastolic blood pressure of 17.47 ± 2.10 in controls, who had a median of 18. But none of the values were significant statistically using ANOVA.

During cold pressor test the mean value for change in systolic blood pressure (SBP) in cases was 16.47 ± 2.74 and median was 16, that of controls was 16.46 ± 1.72 while their median was 16 as shown in table no.(1), p value is 0.863 applying ANOVA . The same table shows that the mean change in diastolic blood pressure (DBP) in cases to be 12.11 ± 5.20 and median was 12 as compared to mean change in diastolic blood pressure of 12.20 ± 4.23 in controls, while the median was 12, p value is 0.859. None of the values were significant statistically.

As shown in table 1 controls had a mean value for latency of SSR as 1.55 ± 0.08, median was 1.55 when compared to a mean of 1.44 ± 0.16 and median of 1.50 in cases. The difference in the values was found to be statistically significant. The p value was 0.0004. The mean value and median for resting heart rate in cases were 78.63 ± 8.71 and 76 beats per minute respectively as compared to 79.33 ± 4.44 and 80 beats per minute respectively in control group as shown in table 2. The mean value for resting heart rate was less in cases in comparison to that of controls. But this difference was statistically insignificant as the p value is 0.681 applying ANOVA.

The mean value for the S/L ratio in controls was 1.06 ± 0.02 where as in cases it was 1.08± 0.04, median was 1.07 in both cases and controls as shown in table 2. We could not find any statistical significance for these values of controls and cases using ANOVA. As shown in table 2, the mean value for the lying to standing ratio (30:15) in controls was 1.06 ± 0.02 as compared to 1.08 ± 0.04 in cases. The median value for the parameter was 1.06 in controls compared to 1.07 cases, though, this increase when compared statistically with controls is found to be

insignificant using ANOVA.

Table-1: Sympathetic Function Tests

Parameter		Cases (n=54)	Controls (n=30)	p value
Resting SBP (mm Hg)	Mean ± S.D.	122.70 ± 9.23	122.87 ± 6.80	0.933
	Median	125	123	
	Range	96 – 136	110 – 132	
Resting DBP (mm Hg)	Mean ± S.D.	77.44 ± 7.062	74.97 ± 3.97	0.081
	Median	78.00	74.50	
	Range	60 – 92	68 – 84	
HGT SBP – Resting SBP (mm Hg)	Mean ± S.D.	21.48 ± 3.89	22.13 ± 3.67	0.455
	Median	20	22	
	Range	14 – 32	16 – 30	
HGT DBP – Resting DBP (mm Hg)	Mean ± S.D.	17.22 ± 3.35	17.47 ± 2.10	0.718
	Median	16.00	18.00	
	Range	12 – 28	14 – 22	
CPT SBP – Resting SBP (mm Hg)	Mean ± S.D.	16.47 ± 2.74	16.46 ± 1.72	0.863
	Median	16.00	16.00	
	Range	10 – 24	14 – 20	
CPT DBP – Resting DBP (mm Hg)	Mean ± S.D.	12.11 ± 5.20	12.20 ± 4.23	0.859
	Median	12.00	12.00	
	Range	08 – 18	10 – 24	
Sympathetic Skin Response	Mean ± S.D.	1.44 ± 0.16	1.55 ± 0.08	0.0004 (<0.05)
	Median	1.50	1.55	
	Range	1.00 – 1.70	1.26 – 1.69	

Table-2: Parasympathetic Function Tests

Parameter		Cases (n=54)	Controls (n=30)	p value
Heart Rate	Mean ± S.D.	78.63 ± 8.71	79.33 ± 4.44	0.681
	Median	76.00	80.00	
	Range	67 – 102	70 – 88	
S/L Ratio	Mean ± S.D.	1.07 ± 0.09	1.07 ± 0.03	0.806
	Median	1.07	1.07	
	Range	0.80 – 1.40	1.02 – 1.13	
30 : 15 Ratio	Mean ± S.D.	1.08 ± 0.04	1.06 ± 0.02	0.091
	Median	1.07	1.06	
	Range	1.00 – 1.23	1.03 – 1.72	
Valsalva Ratio	Mean ± S.D.	1.48 ± 0.71	1.49 ± 0.35	0.515
	Median	1.48	1.49	
	Range	1.35 – 1.72	1.44 – 1.56	
Tachycardia Ratio	Mean ± S.D.	0.74 ± 0.06	0.75 ± 0.04	0.827
	Median	0.75	0.75	
	Range	0.58 – 0.86	0.69 – 0.83	

The mean value of valsalva ratio in controls was 1.49 ± 0.35 and while in cases it was 1.48 ± 0.71, as shown in table 2, median was 1.48 and 1.49 for controls respectively. Though the mean value for Valsalva ratio was lower in patients of migraine cases as compared to Controls, however the statistical significance could not be established. p value was 0.515 using ANOVA. The mean value for tachycardia ratio for both controls and cases were found to be very close. The mean value of Tachycardia ratio in controls was 0.75 ± 0.04 and while in cases it was 0.74 ± 0.06, both groups had a median of 0.75 as shown in table 2. The difference in the values was found to be negligible and statistically insignificant as the p value was 0.827 applying ANOVA. Out of the five parameters of the parasympathetic function tests none of them had any significant difference when the values of cases and controls were compared. Hence the parasympathetic nervous system of our study group is functioning normally in patients of episodic migraine during interictal period.

DISCUSSION

Numerous studies have said that a disturbance of the autonomic nervous system is a primary characteristic of migraine.[6-11] Although evaluations of autonomic function in migraine have been reported, the results are conflicting**.** The most common findings are sympathetic hypofunction[12,13] but higher sympathetic tone[14,15] or parasympathetic dysfunction[12,16] had also been reported. There is a major finding from our study involving migraineurs. The autonomic nervous system has been found to be functioning abnormally.

The resting heart rate, Valsalva ratio, standing to lying ratio, 30:15 ratio and tachycardia ratio are all representatives for analyzing the functioning of the parasympathetic system. In our study none of them showed any statistical difference when the values of those ratios for migraineurs were compared with that of healthy individual controls. Hence we concluded that the parasympathetic nervous system in the group of migraineurs that were enrolled in our study to be functioning normally. Previous studies by Pierangeli G et al. had also shown an intact and normal parasymapathetic system[17] which is in acceptance with our study.

The systolic blood pressure between cases and controls showed no statistical significance while the diastolic blood pressure has been found to be higher in migraineurs although statistical difference could not be found when compared to that of controls and this increased diastolic blood pressure could be secondary to sympathetic hyperfunction or due to reflex response to sympathetic hypofunction. Similar results were also shown in previous studies done by Aaron Shechter BA et al. to assess the autonomic nervous system.[18]

In the handgrip test, the rise in diastolic blood pressure just before the release of hand grip was considered for evaluation. Studies done by Pogacnik T et al. had revealed that HGT showed a statistically significant decrease in response in migraineurs.[13] In our study we found out that the migraineurs showed a slightly decreased rise in the diastolic blood pressure just before the release of the handgrip when compared to that of healthy controls. In accordance with this finding we may contemplate that there is a sympathetic hypofunction in migraineurs but the small difference between the two groups was not

proved to be statistically significant.

Cold Pressor test is also done to assess the status of the sympathetic system of an individual. Here cold acted as a painful stimuli. In the studies done in the past no differences were found between the case and control groups when comparing blood pressure response to a psychological stressor.[18] In our study we found no significant difference when the values of normal controls were compared to that of migraineurs.

The sympathetic skin response is a very good indicator of the integrity of peripheral sympathetic cholinergic function.[19] In the study conducted by Yildiz SK et al. the mean latencies were longer and the maximum amplitudes were smaller on the symptomatic side compared with the asymptomatic side in attack and in interictal periods.[18]

In the study that we conducted, we observed that the latencies in the patients of migraine were found to be shorter than normal healthy individuals and the results showed a significant statistical difference between the case and the control groups. Seeking justification for this contradictory appearance of latencies in our study we decided that such a difference might have occurred due to the highly unpredictable and capricious behaviour of the autonomic nervous system in migraineurs. Hence, after assessing the sympathetic skin response, we found out that the sympathetic nervous system showed hyper-function in the group of migraine patients in our study.

CONCLUSION

1. Assessment of the sympathetic system showed no statistical significance for hand grip test and cold pressor test but sympathetic skin response showed statistical significance, the latencies of cases were shorter than that of controls and hence we conclude that migraineurs in our study had sympathetic hyperfunction during headache free state.
2. Assessment of the parasympathetic system showed statistical significance for none of the 5 parameters viz. resting heart rate, standing to lying ratio, 30:15 ratio, Valsalva ratio and tachycardia ratio and therefore we conclude a normal parasympathetic function in the migraineurs of our study group during headache free state.
3. An enhanced understanding of the sympathetic dysfunction in migraine may help to more effectively diagnose, prevent, and or treat migraine and other types of headache.

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