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Cardiovascular autonomic reactivity and inflammatory markers in patients with chronic migraine

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ABSTRACT

Background: Common headache disorders, including tension-type migraines and cluster headaches, are related to malfunctions of the autonomic nervous system (ANS). Many autonomic signs of migraines aggravate the discomfort of the episode. Understanding the function and comorbidities of migraine patients depends on tests for assessing the cardiovascular autonomic responsiveness of the ANS. **Aims and Objectives:** The aim and objective of this study is to evaluate the use of cardiovascular reflex testing in adults with chronic migraine and healthy controls. Investigating inflammatory markers in individuals suffering from chronic migraines and controls. **Materials and Methods:** Thirty healthy controls and 30 people suffering from persistent migraines were part of the research. Cardiovascular reflex tests were performed. Inflammatory markers such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-10 were also evaluated. SPSS edition 21 was used for the statistical analysis. For parameters with normal and atypical distributions, the Mann–Whitney test and the unpaired t-test, respectively, were used. **Results:** Among 30 subjects, testing for autonomic reactivity related to chronic migraines revealed significantly lower values than those for control. Patients with chronic migraines had far more inflammatory markers, including TNF-α, IL-1, and IL-10. **Conclusions:** Revealing autonomic dysfunction, the group with chronic migraines had a lower parasympathetic tone and sympathoexcitation than the healthy control group. Future studies should concentrate on ANS dysfunction as a biomarker for early warning signals for drug intake and migraine control.

Key words: Autonomic dysfunction; Migraine; Cardiovascular autonomic reactivity; Sympathetic tone; Parasympathetic tone

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INTRODUCTION

Autonomic nervous system (ANS) dysfunction has been linked to a variety of common headache diseases, including tension headaches, migraines, and cluster headaches. In migraineurs, a range of autonomic symptoms precede, coexist with, and follow headaches.[1-3] These symptoms – which range from nausea to vomiting, hyperhidrosis to palpitations, and pallor to lightheadedness – make an episode more miserable.[4,5] The demonstrated higher risk of myocardial infarction, ischemic stroke, severe cardiovascular disease, and mortality from ischemic cardiovascular disease in migraine patients with and without auras adds yet another therapeutic relevance of ANS dysfunction.[6,7] People who exclusively had auratic migraine had twice as increased risk of ischemic stroke, according to Schürks et al.[8] To underline the point made by Koenig et al., standardized studies of the ANS are indispensable for enhancing our knowledge of the function of the ANS as a whole in migraine patients and the correlation between the ANS and comorbidities linked with cardiology and cerebrovascular disease.

This includes understanding the role of vagally-mediated heart rate (HR) variability. While some research found enhanced sympathetic activity in migraine patients and

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some demonstrated normal sympathetic function, the majority of studies revealed lower sympathetic function in migraine patients. Similarly, whereas some studies found reduced parasympathetic function, others reported adequate parasympathetic cardiovagal function.[9] Miglis continues, describing the range of approaches from which these results were drawn, eventually highlighting the need for ANS testing that is standardized and consistent for use in migraine research.

Aims and objectives

The aim of the study is to evaluate cardiac autonomic functions using cardiovascular reflex tests and inflammatory markers in patients with chronic migraine and healthy controls.

The objective of the study was to assess cardiovascular reactivity in patients with chronic migraine.

MATERIALS AND METHODS

Between January and December of 2023, cross-sectional research was carried out at the physiology department of the Naraina Medical College and Research Centre in Kanpur, India. The Institutional Ethics Committee with ethical clearance number NMCRC/IEC/2023/003 granted the permission to carry out the research on January 3rd, 2023. Thirty patients with chronic migraines were recruited from the medicine outpatient department after providing informed written permission. Two groups of 30 volunteers each, representing both sexes and an age range of 25–40, were involved in the research. There was one group made up of patients with chronic migraines. The healthy controls made up the other group. Pre-existing conditions such as autonomic dysfunction, hepatorenal or endocrine disorders, hypertension, diabetes, heart failure, neurological or psychiatric conditions, substance use disorders, or other significant medical conditions were excluded to maintain a homogeneous study population. Techniques for evaluating the outcomes of cardiovascular autonomic reactivity are included in the study design.[10] By combining many methods to evaluate cardiovascular reflexes, the study adhered to accepted practices. Deep breathing exercises, the Valsalva maneuver, the cold pressor test (CPT), the handgrip test, and the lying-to-stand test (LST) were among these approaches. To reduce the possibility of confusion, participants were instructed not to eat or drink caffeine for 4 h before the experiment began. Throughout the evaluation process, lead II electrocardiogram (ECG) and brachial artery blood pressure (BP) monitoring were done simultaneously.

Test of deep breathing (DBT)

The measurement of deep breathing serves as a proxy for measuring cardiac parasympathetic activity. This is because deep breathing activates the vagus nerve, which is essential for regulating HR. As a result, this evaluation is often referred to as a cardiovagal maneuver. The participants were asked to breathe slowly and deeply, taking around 10 s between each inhalation and exhalation. Six cycles of slow, deep breathing, each lasting 10 s, comprised the deep breathing technique. ECG data wer carefully analyzed throughout this maneuver to calculate HR and the RR interval, or the time gap between heartbeats, for each cycle's inspiratory and expiratory phases. The delta HR, averaged over the course of six breathing cycles, shows the degree of fluctuation in HR between the peak HR during inhalation and the lowest HR during expiration. The average proportional duration between the greatest pulse interval during exhalation and the smallest gap during inhalation during each of the six deep breathing cycles is measured by the expiration-to-inspiration (E: I) ratio.

Valsalva technique

A useful method for evaluating cardiovagal activity, which is another term for parasympathetic nervous system activity, is the Valsalva maneuver. This maneuver assesses the response of the HR to variations in pressure brought on by exerting force on a closed airway. The participants were directed to exert strong expiratory breathing for 15 s into a mouthpiece attached to a sphygmomanometer, with the goal of maintaining a 40 mmHg expiratory pressure. Deep breaths were avoided both before and after the Valsalva maneuver to concentrate on its effects. By dividing the RR interval with the greatest length (phase 4) by the RR interval with the shortest duration (phase 2), one may get the Valsalva ratio.

Handgrip assessment

Using a controlled isometric handgrip exercise, the handgrip test measures variations in diastolic BP (DBP) to assess sympathetic nervous system activity, particularly adrenergic function.

Test of a cold pressor

The CPT uses the DBP responses to cold stimuli to measure sympathetic adrenergic function activity. After taking the subject's baseline BP, the subject is instructed to immerse their right hand in 10°C (cold) water up to the wrist for 1 min. At the same time, the arm opposite the submerged hand has its BP measured. Any rise in DBP over the starting baseline is noted and examined.

Biochemical assays

Following an overnight fast, blood samples were drawn, divided into serum and plasma, and then kept in a freezer at -20°C for biochemical analysis. The enzyme-linked immunosorbent assay was used to evaluate the blood levels of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1 in the patients. The test quantifies the degree to

which matched pairs of antibodies bind to the target. Heating the reagents, diluting the samples, filling the wells with the standard samples and controls, applying the enzyme conjugate, incubating for 60 min, extracting the liquid, cleaning the wells, adding the TMB substrate, incubating for 15 min, and finally giving the stopping solution are all steps in the technique.[11]

The statistical analysis

The statistical software licensed for use in this study for data administration, analysis, and interpretation was IBM SPSS Statistics for Windows, Version 21.0. The researchers employed descriptive statistics, including means and standard deviations, to compile the data for the control group and the chronic migraine group, and then presented their findings. To determine whether there were any statistically significant differences between the two groups, they employed an unpaired t-test. Throughout the investigation, a significance level of $P<0.05$ was upheld, which meant that only results with a probability of occurring by chance of <5% were considered statistically significant.

RESULTS

This research comprised a total of 60 participants, consisting of people with chronic migraine as well as healthy controls. The age range of the participants was between 25 and 40 years old. The average HR of patients with chronic migraine was 83.17±2.73, whereas the average HR of healthy people was 78.39±4.91 beats per minute (bpm), as shown in Table 1.

The delta HR (DBT) of chronic migraine sufferers was 12.51±1.29, but that of healthy persons was 15.26±1.14 (P=0.000*), as shown in Table 2.

The E: I ratio (DBT) of chronic migraine sufferers was 1.12±0.16, whereas healthy persons had a ratio of 1.30±0.22 (P=0.000*). Table 2 demonstrates that the Valsalva ratio was 1.19±0.1 in patients with chronic migraine and 1.47±0.76 in persons without any health issues (P=0.000*). The chronic migraine patients exhibited a substantial drop in the 30:15 ratio and a decline in systolic BP (LST) compared to the healthy control group (P=0.00*). The increase in HR (LST) was substantially greater in patients with chronic migraine (16.19±4.12) compared to the control group (7.65±3.49) (P=0.000*). The handgrip test and CPT findings were statistically insignificant. Table 3 depicts a significant increase in TNF alpha, IL-1 and IL-10 in patients of chronic migraine.

Table 1: Comparison of basal parameters in chronic migraine and healthy controls

Parameters	Chronic migraine Mean±SD	Healthy controls Mean±SD	P-value
Age (years)	35.17±4.92	37.72±6.35	-
BMI	24.10±1.98	24.34±1.57	0.882
Mean heart rate (bpm)	83.17±2.73	78.39±4.91	1.033
Systolic BP (mmHg)	120.89±8.19	119.94±8.83	0.122
Diastolic BP (mmHg)	80.18±4.25	78.82±4.42	0.278

*P<0.05 significant, BMI: Body mass index, BP: Blood pressure, SD: Standard deviation

Table 2: Comparison of cardiovascular reflex test in patients of chronic migraine and healthy controls

Parameters	Chronic migraine mean±SD	Healthy controls Mean±SD	P-value
Delta HR (DBT)	12.51±1.29	15.26±1.14	0.000*
E: 1 ratio (DBT)	1.12±0.16	1.30±0.22	0.000*
Valsalva ratio	1.19±0.13	1.47±0.76	0.000*
30:15 ratio (LST)	1.12±0.26	1.23±0.81	0.000*
Rise in heart rate (LST)	16.19±4.12	7.65±3.49	0.000*
Fall in SBP (LST) (mmHg)	12.79±5.97	3.27±2.85	0.000*
Delta DBP-isometric handgrip test (mmHg)	10.32±6.84	10.76±7.02	0.090
CPT (mmHg)	7.52±5.04	16.32±6.75	0.000*

*P<0.05 significant, LST: Lying to standing test, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CPT: Cold pressor test, SD: Standard deviation, HR; Heart rate

Table 3: Comparison of inflammatory markers in patients of chronic migraine and healthy controls

Parameters	Chronic migraine Mean±SD	Healthy controls Mean±SD	P-value
TNF-α (pg/mL)	150.33±181.06	62.19±31.28	0.00*
IL-1 (pg/mL)	168.23±81.06	74.08±38.22	0.00*
IL-10 (pg/mL)	147.63±135.43	68.23±28.87	0.00*

*P<0.05 Significant, SD: Standard deviation, TNF-α: Tumor necrosis factor-alpha, IL: Interleukin

DISCUSSION

The E: I ratio dropped statistically significantly in our study from the control group (mean=1.30±0.22) to the chronic migraine group (mean=1.12±0.16). The perfect proportion is 1.21. While numbers between 1.11 and 1.20 are seen as borderline, 1.10 is seen as aberrant. The E: I ratio and ΔHR values in the chronic migraine group were lower than in the control group. Studies abound demonstrating that migraine sufferers have far lower levels of ANS functioning than healthy controls. One main effect of migraines is the disruption of baroreceptor and sympathetic signals. Moreover, linked to migraine episodes is the vagal nerve, which implies a lower ANS balance in migraine sufferers.[12,13] The chronic migraine group (mean=1.19±0.13) showed notably lower virtual reality (VR) (P=0.00*) than the

control group (mean=1.47±0.76). Although the readings of both groups fell within the expected range, generally there should be a VR difference of ≥1.21. While readings between 1.11 and 1.20 are seen as borderline, a value of 1.10 is thought to be abnormal. The LST 30:15 ratio was less in the chronic migraine group (mean=1.12±0.26) than in the control group (mean=1.23±0.81). With P=0.000, the variation was statistically significant. The group with chronic migraines showed a decline in all the parasympathetic reactivity tests when compared to the control group, suggesting a parasympathetic tone indicative of autonomic dysfunction. These modifications, though, were not statistically significant. In line with our results, research by Gass and Glaros[14] looked at the cardiovascular reflex test and found that migraineurs had a lower parasympathetic tone and sympathetic overdrive, thereby reducing the variability of the next RR intervals. In our study's chronic migraine sufferers, the parasympathetic reactivity tests – such as the E: I ratio and ΔHR values – showed lower values; these findings point to a reduced parasympathetic tone. Migraine may result from elevated levels of autonomic signaling molecules such as calcitonin gene-related peptide (CGRP), which have effects outside of the blood-brain barrier.[15] Various brainstem sites, including CGRP, point to a potential understanding of migraine etiology. Lack of cerebrospinal fluid testing and sampling difficulties complicate the correlation of CGRP levels with autonomic function.[15] Paroxysmal autonomic symptomatology in peri-ictal migraine would suggest a decrease in autonomic function, most likely from CGRP overgeneration or another neurotransmitter overflow.[16,17] One study suggested that migraine sufferers' major autonomic system and/or neurotransmitter activation were deficient.[18] Still, two investigations revealed increased vasomotor reactivity.[19] By means of the identification of neurotransmitters like CGRP and pituitary adenylate cyclase-activating peptide, researchers can establish a connection between levels of these molecules and ANS failure in migraine. Type 5, a genome-wide association study, identified 38 distinct genomic loci connected with 44 sensitivity markers for migraine types, including the NGF gene linked with hereditary sensory and autonomic neuropathy.[20]

In addition, we observed that the group with chronic migraine had significantly higher levels of inflammatory markers – TNF-α, IL-1, and IL-10 – than the control group. Our results align with earlier research that demonstrated a significant elevation in TNF-α, IL-1, and IL-10 in individuals suffering from chronic migraines.[11] As a consequence, this might be one of the causes of sympathoexcitation in these patients, causing autonomic dysfunction.

It is speculated that this autonomic dysfunction is caused by the stimulation of the trigeminovascular system; this autonomic dysregulation results from migraine. Parasympathetic reactivity helps to restore autonomic functions through behavioral treatment comprising biofeedback, stress management, and relaxation, which has been shown to be successful in treating migraines.[21] Another benefit is that aerobic exercise helps strengthen the parasympathetic nervous system. Aerobic exercise helps to reverse parasympathetic autonomic dysfunction. Parasympathetic reactivity tests will thus be beneficial in these people to raise the parasympathetic tone, which could enable the trigeminovascular system to restore autonomic balance. Therefore, consistent observation of parasympathetic reactivity in patients with chronic migraines can significantly improve the early identification of stroke and cardiovascular diseases. Using it as a screening tool, patients with persistent migraines can identify autonomic (parasympathetic) dysfunction and get either preventative or psychotherapy. To develop better knowledge, further research, including more people, is needed. One can apply tests of the cardiac autonomic reflex for screening. Though they indirectly assess autonomic functions, these tests are considered the gold standard in autonomic testing.

Limitations of the study

The fact that we only used 30 patients as a small sample size was a study limitation. A larger sample size is necessary for results that are more detailed.

CONCLUSIONS

Our research points to a possible connection between ANS dysfunction and chronic migraineurs. In patients with chronic migraines, the study found decreased parasympathetic tone and evidence of sympathoexcitation. This gold standard test incorporates tools to measure autonomic function. The results of these tests may provide useful information about the long-term risk of predicting the morbidity and mortality of cardiovascular complications in chronic migraine patients. Secondly, these tests may serve as a non-invasive screening method to determine the presence and severity of autonomic dysfunction in chronic migraine patients.

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