ORIGINAL ARTICLE

THE ROLE OF CALCITONIN GENE-RELATED PEPTIDE AND PENTRAXIN-3 IN MIGRAINE PATHOPHYSIOLOGY AND DIAGNOSIS

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ABSTRACT

Background: Migraine is a prevalent neurological disorder with increasing evidence supporting an underlying neuroinflammatory mechanism. Inflammatory biomarkers such as calcitonin gene-related peptide (CGRP) and pentraxin-3 (PTX3) are thought to play a key role in migraine pathophysiology.

Objective: To compare clinical features, triggering factors, inflammatory cell profiles, and serum levels of CGRP and PTX3 in migraine patients and healthy controls.

Methods: It is a case–control observational study. A total of 80 participants aged 18–45 years were enrolled, including 40 clinically diagnosed migraine patients and 40 age- and sex-matched healthy controls. Clinical symptoms, migraine triggers, and prophylactic drug use were recorded using a structured questionnaire. Hematological parameters, including neutrophil and lymphocyte counts, were assessed through complete blood analysis. Serum CGRP and PTX3 concentrations were measured using enzyme-linked immunosorbent assay (ELISA). Appropriate statistical tests were applied, with $p < 0.05$ considered statistically significant.

Results: Photophobia and phonophobia were reported in 85% and 80% of migraine patients, respectively ($p < 0.001$). Nausea and vomiting occurred in 77.5% and 40% of cases, while none of the controls reported these symptoms ($p < 0.001$). Stress (90%), intense light, skipping meals, and sleep disturbances were the most common migraine triggers. Migraine patients demonstrated significantly higher neutrophil counts (60.7 ± 8.3 vs. 56.0 ± 6.7; $p = 0.006$) and lower lymphocyte levels (33.4 ± 7.5 vs. 37.5 ± 5.7; $p = 0.007$). Median serum CGRP and PTX3 levels were significantly elevated in migraine patients compared to controls ($p < 0.001$).

Conclusion: Migraine is associated with prominent clinical symptoms, identifiable triggers, and systemic inflammatory changes. Elevated CGRP and PTX3 levels highlight their potential role as biomarkers of migraine-related neuroinflammation.

Keywords: Migraine, CGRP, PTX3, Neuroinflammation, Case–control study, Biomarkers; Neurogenic inflammation; Vascular dysfunction

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INTRODUCTION

Migraine is a poorly understood pulsating headache that is severe in nature and is deeply intertwined with human history. It is one of the most common neurological ailments, with the Global Burden of Disease (GBD) estimating over 1.1 billion cases in 2019. The same study ranked migraine headache 22nd in 1990 and 14th in 2019 in the disability-adjusted life years (DALYs) incurred in the Global Burden of Disease (GBD) list of 369 disorders.[1,3] Furthermore, migraine has consistently

represented the second highest non-fatal burden in both 1990 and 2019, as measured by age-standardized years lived with disability (YLDs).[4,5] Migraine is a chronic, complex neurological disorder marked by episodic headache attacks of a certain degree of severity lasting anywhere between 4 and 72 hours. The discomfort is usually one-sided, punctate in nature, and worsens with common physical exertion.[3,6] It is often accompanied by nausea, sensitivity to bright light (photophobia) and sound (phonophobia). Migraine disproportionately affects women, especially of reproductive age, which makes it a major contributor to personal, social, and economic burden. This condition is frequently divided into four stages: (i) Prodromal or Preheadache Period, (ii) Aura Phase, (iii) Headache Phase, and (iv) Postdrome Phase.[7,9]

The trigeminovascular pathway is thought to cause migraine headaches, through its activation and involvement. There is a large body of observational evidence supporting that activation of trigeminal sensory afferent nerves, which innervate certain cranial structures, the meninges and large blood vessels, is necessary to trigger a migraine headache.[10,12] There are several biomarkers under study that may help in early diagnosis and treatment of migraine. Calcitonin gene related peptide (CGRP) is produced from the trigeminal nerve fibers and trigeminal nerve stimulation causes antidromic CGRP release, producing vasodilation. CGRP is a critical inflammatory peptide and its levels are predominantly increased in migraine episodes.[13,15] Another promising biomarker is Pentraxin-3 (PTX3), a long-chain inflammatory protein secreted primarily by vascular endothelial cells. PTX3 is released during inflammatory and pain processes, where it may further stimulate the trigeminovascular system and contribute to migraine pathogenesis. Beyond migraine, PTX3 is also implicated in a variety of inflammatory and vascular diseases.[16]

Taken together, these findings highlight the role of inflammatory mediators such as CGRP and PTX3 in migraine generation. However, data exploring their combined diagnostic value in migraine patients remains limited. A comparative assessment of these two biomarkers may help in establishing an objective laboratory-based tool to complement clinical diagnosis, particularly in resource-limited settings. Identifying reliable, objective biomarkers like CGRP and PTX3 may improve differentiation between migraineurs and healthy individuals, facilitate earlier diagnosis, and potentially guide targeted treatment strategies.

In Pakistan, migraine is common yet often underdiagnosed and undertreated due to limited awareness, scarce diagnostic resources, and a reliance on over-the-counter symptomatic management. Nationally representative data reveal a 1-year prevalence of migraine at approximately 22.9 %, notably higher than the global average of around 15 %.[17] Among medical students in Lahore, prevalence figures range from 20.4 % to 28 %, with female students again showing higher incidence.[18] Such high prevalence, especially among young adults, puts a considerable strain on academic performance and quality of life. The socioeconomic burden is pronounced: untreated migraine contributes to workplace and academic absenteeism, social impairment, and reduced productivity. Yet local research on objective, cost-effective biomarkers remains scarce.

Investigating CGRP and PTX3 levels in Pakistani migraine patients and comparing them to healthy controls could fill this critical gap. Such a study would provide locally relevant evidence, enabling development of affordable diagnostic strategies tailored to Pakistan's healthcare context. This, in turn, could enhance early detection, improve management outcomes, and ultimately reduce the personal and societal burden of migraine.

METHODS

This case–control observational study was conducted in Institute of Molecular Biology and Biotechnology (IMBB), University of Lahore, Lahore Pakistan. Ethical approval was obtained from Institutional Review Board of the University of Lahore dated: 26/03/2020 and no IMBB/UOL/22/2013. This study was conducted on adults aged 18–45 years from July 2020 to March 2021. Patients diagnosed with migraine constituted the case group, while age- and sex-matched healthy individuals without a history of migraine or other inflammatory or neurological disorders served as controls. Migraine diagnosis was made based on international criteria of headaches beta version. Participants with acute infections, chronic inflammatory diseases, or those on immunomodulatory therapy were excluded.

Written informed consent was taken from all the participants. The sample size was calculated using the formula for comparison of two independent means, incorporating the expected difference between group means and standard deviations obtained from a previously published parent study.[19] We calculate the sample size by using the formula:

$$n = \frac{2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

$$n = \frac{\left\{ z_{1-\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)} \right\}^2}{(P_1 - P_2)^2}$$

Where

$\sigma 2$ = variance $Z1-\alpha$=confidence level

$Z1-\beta$=power of test μ_o= population mean # 1

μa= population mean #2

We inducted 80 individuals in study, 40 migraine patients and 40 healthy controls, for the better power of the study. Demographic data, body mass index (BMI), clinical symptoms, triggering factors, and use of prophylactic medications were recorded using a structured questionnaire. Venous blood samples were

collected from all participants under standardized conditions. Complete blood counts were performed to assess neutrophil and lymphocyte levels. Serum levels of pentraxin-3 (PTX3) and calcitonin gene-related peptide (CGRP) were measured using enzyme-linked immunosorbent assay (ELISA) and by following the protocol provided by the manufacturers.

For statistical analysis SPSS 21 was used. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were expressed as frequencies and percentages. Independent sample tests and Mann–Whitney U test were used to compare cases and controls as appropriate. A p-value <0.05 was considered statistically significant

RESULTS

Different age groups participants were inducted in the study ranging from 18 to 45 years. Mean age of the patients were 25.57 ±5.93 and of controls were 26.15 ±7.19. Between cases most patients were females. BMI of the of the most of the patients were between range 18-25. 85% of the cases complaint about photophobia and 80 % had phonophobia, and the difference between cases and controls was highly significant i.e. p value is <0.001. The control group did not report nausea, whereas in migraine cases there was nausea during attack in 31(77.5%) of the cases. The difference here was highly significant with p value <0.001. Vomiting was present in 16 (40.0%) of the cases when there was a migraine attack and it was never a problem in the control group. Therefore, this occurrence of vomiting problem was significant with p value <0.001. Only 8(20.0%) of the cases had some type of food as precipitating factor for migraine in their history. The factor was also significant with p-value 0.003. The prophylactic drugs' use was also significantly present in 12 (30.0%) of the migraine patients with p-value <0.001. These findings justify that clinical symptoms such as photophobia, phonophobia, nausea, and vomiting are hallmark features of migraine and strongly differentiate patients from healthy controls, consistent with migraine diagnostic criteria. The presence of prophylactic drug use and precipitating factors further supports that these patients had established disease with recurrent attacks.

Several factors were reported to trigger migraine. 90% of the patients complain that the stress is the basic triggering factor for them. Skipping meals and disrupted sleep also triggered migraine in most patients. Other triggering factors include traveling, noisy environment, certain smells, hormonal fluctuations specially in women, climate changes and strenuous exercise. Frequencies of triggering factors are given in table 1.

The high prevalence of stress, light, noise, and sleep disturbances as triggers supports their central role in migraine pathogenesis and aligns with recent studies showing psychosocial and environmental triggers as key contributors to attack initiation.

It was found that the cases with migraine consisted of neutrophil counts 60.7±8.3 whereas for the healthy control group consisted of 56.0±6.7. Two groups were found significant for the difference of the neutrophil counts with p-value 0.006. The lymphocyte levels were greater for control group with mean value of 37.5±5.7 and that for the migraine group was 33.4±7.5. The difference was also significant with p value 0.007.

Table-1: Percentage of triggering factors that causes migraine

Trigger factors	Reported as a trigger % (n)
Stress	90% (36)
Skipping meals	77.5% (31)
Sleep disturbances	67.% (27)
Hormonal fluctuation	20.0% (8)
Traveling	62.5% (25)
Exposure to loud noise	62.5% (25)
Intense light	77.5% (31)
Strong odours	42.5% (17)
Physical exertion	25% (10)
Weather variation	35% (14)
Particular food items	32% (13)

Table-2: Neutrophils and Lymphocytes comparison between cases and controls

Inflammatory Cells	Cases (± SD)	Controls (± SD)	*p*-value
Neutrophils	60.7 ± 8,3	56.0 ± 6.7	0.006
Lymphocytes	33.4 ± 7.5	37.5 ± 5.7	0.007

Table-3: Levels of PTX3 and CGRP in cases and controls

Biomarker	Cases (Median IQR)	Controls (Median IQR)	p-value
CGRP (ng/L)	99.6 (64.4-163.4)	14.8 (10.9-24.3)	<0.001
PTX3 (pg/L)	100.5 65.5-165.2)	31.15 (15.5-27.4)	<0.001

The raised neutrophils and reduced lymphocytes in cases suggest an ongoing systemic inflammatory response, supporting the hypothesis that migraine is not only a neurological but also an inflammatory disorder.

Serum PTX3 and CGRP levels were obtained from both cases and controls and were compared by using Mann-Whitney U test. PTX3 and CGRP levels were significantly higher in cases as compared to controls. Median IQR value for PTX3 in cases was calculated to be 100.5 (65.5-165.2) pg/L and for controls was calculated as 31.15 (15.5-27.4) pg/L. Median IQR value for CGRP in cases was calculated to be 99.6 (64.4-163.4) ng/L and for controls was calculated as 31.15 (15.5-27.4) ng/L. *p*-value was obtained as <0.001 for both and was significant.

This significant elevation of CGRP and PTX3 strongly indicates their role as biomarkers of migraine pathophysiology, particularly in reflecting trigeminovascular activation and neuroinflammation.

DISCUSSION

This is unique research of its type to examine the function of CGRP and PTX3 simultaneously in migraine patients in determining their values and comparing it with healthy individuals. Perhaps a couple of neurological diseases have been investigated so comprehensively, and the principles for their mechanism have developed as much as migraine. Against all this colossal amount of information, the "migraine riddle" still hasn't been solved.[20,21] We found in our study that blood levels of CGRP and PTX3 in migraine patients were greater than in healthy controls. CGRP has been implicated in trigeminal nerve fibres and dura mater vasodilation neuropathic inflammatory response involved in migraine pathogenesis. In previous studies, levels of CGRP in adult patients were measured and the levels were found to be significantly higher than in the controls.[22,24] Our findings supported these conclusions. PTX3 causes neuroinflammation by activating TGVS. PTX3 released from endothelial cells of inflamed vessels is considered as a pathogenic factor for diagnosis of migraine. Our findings align with a study conducted by Fahmy EM et al., states that level of PTX3 is significantly elevated in migraine patients.[25] Thus recent research confirms that interictal CGRP levels remain elevated in both episodic and chronic migraine, reflecting persistent trigeminovascular activation and central sensitization. Similarly, PTX3 elevation has been demonstrated in chronic migraine and is linked to endothelial dysfunction and neuroinflammation, supporting our results.

We assume that increased CGRP and PTX3 in interictal migraine patients is associated with cerebrovascular dysregulation of central nervous system control, an important factor in migraine genesis. Most studies have observed enhancement in vascular hyperexcitability to photophobia, phonophobia, nausea and vomiting, and stress specifically. Other people were sensitive to skipping meals, sleeping, noise, strong odor, and physical activity. In this research, we found that CGRP and PTX3 is associated with central sensitization during recurrent painful episodes of migraine. When released from the peripheral synapses of afferent axons, the CGRP is involved in pain transmission and elicits inflammation. Many previous studies support that CGRP increases in migraine episodes. Endothelial inflammation and damage causes PTX3 increase and causes nociceptors stimulation and initiate pain in migraine.[24,26] These observations highlight that migraine is not merely a transient headache disorder but a chronic inflammatory and vascular condition with biochemical markers detectable even outside acute attacks.

Regarding CGRP, some reports challenge its utility as an interictal biomarker. One clinical discussion notes that serum CGRP levels may not be elevated between attacks, implying that CGRP increase may be limited to acute phases. This contrasts with our findings showing elevated CGRP even outside of attacks. Regarding CGRP, some reports challenge its utility as an interictal biomarker. One clinical discussion notes that serum CGRP levels may not be elevated between attacks, implying that CGRP increase may be limited to acute phases.[24] This contrasts with our findings showing elevated CGRP even outside of attacks. As for PTX3, while elevated interictal PTX3 is supported by studies, the broader literature acknowledges that findings regarding endothelial and inflammatory markers in migraine, including PTX3, can be variable across studies depending on design, migraine subtype, and timing of sampling.

Some previous studies elaborate that there was no rise of CGRP and PTX3 in chronic migraine but elevated in acute migraine.[27,28] This can be due to the body's defence mechanism against inflammatory process. Migraine is considered an inflammatory condition, and both the CGRP and PTX3 are raised in various inflammatory diseases like stroke, myocardial infarction and multiple sclerosis etc. These hematological findings are in agreement with recent studies showing altered neutrophil-to-lymphocyte ratios in migraine, reinforcing the role of systemic inflammation.[29]

In our study neutrophils are significantly raised and lymphocytes are slightly decreased in migraine patients which suggest acute inflammatory process and a previous study also suggest that in acute migraine attack the inflammatory markers are significantly raised.[26] While our findings demonstrate elevated interictal CGRP and PTX3 levels, among others, not all studies have observed similar results. For instance, research evaluating neutrophil-to-lymphocyte ratio (NLR) found no significant difference between episodic or chronic migraine patients in the interictal phase compared to healthy controls, suggesting that systemic inflammatory markers like NLR may not consistently reflect migraine-related inflammation outside of attacks.[30] A recent case–control study found that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) did not significantly differ between migraine patients and controls in the interictal period, suggesting these markers may not always reflect migraine-associated inflammation outside of attacks. A study assessing systemic immune-inflammation index (SII) reported no consistent increase in neutrophil or lymphocyte counts in interictal migraine patients, in contrast with elevations observed during attacks.[31] Another interictal study failed to detect elevated lymphocyte or neutrophil counts, indicating that hematologic inflammation may be more dynamic and less detectable between migraine.[32,33] In our study BMI was not raised and the patients were not obese, that is contrary to another study by Togha M at el., where BMI was raised in migraine patients.[34] Stress was a significant triggering factor in our study and female are greater sufferers, hormonal fluctuations may cause migraine

attack. This factor is also supported by a previous study.[35] The predominance of stress and hormonal fluctuations as triggers in females highlights psychosocial and endocrine contributions to migraine, which are consistently reported in recent literature.[36]

Some limitations of this study need to be overcome. The first problem is that our results are derived from a single measure of CGRP and PTX3 blood levels, which might not reflect the research participants' condition thoroughly. Our findings support the potential clinical application of CGRP and PTX3 in the early diagnosis of migraine and in guiding targeted prophylactic strategies. However, given the variability in biomarker expression reported across different studies, larger multicenter trials with standardized sampling protocols are warranted to confirm their diagnostic utility and establish their role in individualized migraine management. Future longitudinal studies with serial measurements are needed to determine dynamic changes in these biomarkers during different migraine phases and in response to therapy.

CONCLUSION

Migraine patients demonstrated significantly higher frequencies of characteristic clinical symptoms and identifiable triggering factors compared to healthy controls. The presence of altered neutrophil and lymphocyte counts, along with elevated serum CGRP & PTX3 levels, indicates an underlying inflammatory component in migraine pathophysiology. These findings support the concept of migraine as a neuroinflammatory disorder and suggest that CGRP and PTX3 may serve as useful biomarkers for disease activity and potential therapeutic targeting.

LIMITATIONS OF THE STUDY

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ETHICAL APPROVAL

Ethical approval was granted by the Institutional Review Board of the University of Lahore dated: 26/03/2020 and no IMBB/UOL/22/2013

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTIONS

MT: Experimental setup, performed laboratory work, data collection and analysis, drafting the results section.
SR: Conceived idea, literature review, manuscript writing**.**
MK: Experimental design, statistical analysis, data interpretation, writing the discussion and conclusion.
AQ: Supervision, methodology, critically review
NK: Interpretation of results, revised manuscript.
AF: Sample preparation, data acquisition, critical review
ZC: Literature review, manuscript writing
TM: expert view of results, editing the manuscript.
All Authors: Approval of the final version of the manuscript to be published

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