DOI: 10.7860/JCDR/2025/80951.22042

Original Article

Internal Medicine Section

Exploring the Link between Prolactin and Migraine: A Cross-sectional Study

ANANYA KUNDU[1], BARUN KUMAR SEN[2], MOUSUMI MUKHOPADHYAY[3]

BY-NC-ND

ABSTRACT

Introduction: Migraine headaches are a common type of headache that often requires frequent medical attention. In the absence of specific biomarkers, diagnosis of migraine is done by clinical criteria only. Multiple hormones, including prolactin, may have some role in the pathogenesis of migraine. Prolactin, as a laboratory test, can aid in the diagnosis of migraine.

Aim: To compare serum prolactin levels in migraine patients and other primary headaches, and also to explore its association with migraine clinical profile.

Materials and Methods: This cross-sectional study was conducted at the Institute of Post Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital (IPGME&R and SSKM) Hospital, Kolkata, West Bengal, India from February 2015 to June 2016. The present study included 164 adult patients: 82 subjects with migraine and 82 subjects with non migraine, other primary headaches (control). Serum prolactin was measured by Enzyme-Linked Immunosorbent Assay (ELISA), and hyperprolactinemia was defined as >25 ng/mL. An Unpaired two-sample Student's t-test did statistical analysis. The level of significance was considered at p-value <0.05.

Results: In the present study, the mean age among migraine patients was 30.01±7.69 yrs, and among other primary headache patients control was 39.94±7.81 yrs. Among the total 164 patients, 101 (61.59%) patients were females and 63 (38.41%) patients were males; among the total migraine patients, 58/82 (70.73%) were females and 24/82 (29.27%) were males. Mean serum prolactin was significantly higher in migraine patients (25.46±13.28 ng/mL) than in other primary headaches controls (10.39±5.53 ng/mL) (p-value <0.0001). Hyperprolactinemia was observed in 39.02% of migraine patients versus 3.66% of other primary headache patients.

Conclusion: Significantly higher serum prolactin level in migraine patients suggests a potential role in pathophysiology and possible use as a biomarker. Further research is needed on the therapeutic potential of prolactin inhibitory agents.

Keywords: Headache disorder, Hyperprolactinemia, Neuroendocrinology, Neurotransmitter

INTRODUCTION

Headache is one of the most common reasons patients seek medical attention. Migraine, a primary headache, is the second most common cause of headaches and is ranked as the third most prevalent disorder according to the Global Burden of Disease Survey 2010 [1]. Lifetime migraine incidence in women and men is 43% and 18% respectively, according to the American Migraine Prevalence and Prevention (AMPP) study [2].

Migraine headache is characterised by a unilateral, moderate-to-severe throbbing headache, which is exacerbated by physical activity. Along with headaches, patients also suffer from hypersensitivity to vision, auditory, olfactory, and somatosensory stimuli. Usually, patients prefer to stay calm and quiet in a dark, undisturbed room during the headache phase. Nausea, vomiting, and neck pain are common during this phase [3].

Migraine is a complex condition, and its pathophysiology is not completely clear [4]. Many neurotransmitters are implicated in this process [5], and hormones have been shown to play a major role in women [6]. The sensory sensitivity characteristic of migraine is probably due to the dysfunction of the monoaminergic sensory control systems located in the brainstem and thalamus. The hypothalamic-hypophyseal axis plays a role in the pathophysiology of migraine. Many neurotransmitters and hormones, particularly dopamine, Calcitonin Gene–related Peptide (CGRP), and the neurotransmitter 5-Hydroxytryptamine (5-HT; also known as serotonin), are implicated in migraine [7].

Prolactin, an anterior pituitary hormone, in this regard may have some role in the pathogenesis. Sicuteri in 1977 described the role of dopamine as the pathogenesis of migraine and considering the inhibitory effect of dopamine on prolactin secretion from the anterior pituitary gland, the association of prolactin with migraine was found as a direct role and also as a reflector of dopamine's effect on migraine [8].

No specific biomarkers are currently available for migraine diagnosis. Therefore, the diagnosis is dependent on clinical features and is subjective. Several studies have been conducted on the sex hormonal role in migraine [6,9]. A female with different stages of menstrual cycle, pregnancy, showing a different pattern of headache, suggests a sex hormonal role in migraine [9]. The search for laboratory diagnostic features or assays of hormones that may be easily performed and cost-effective, like prolactin, may aid in the diagnosis.

Therefore, the present study was designed to evaluate the clinical profiles of primary headache patients, their serum prolactin levels, and to observe any abnormality of serum prolactin level in migraine patients in comparison to other primary headaches, and to determine whether any association of prolactin level is present with the clinical profile of migraine and its exacerbation.

MATERIALS AND METHODS

This cross-sectional study was conducted in IPGME&R and SSKM Hospital, Kolkata from February 2015 to June 2016. Informed consent was obtained from all patients on enrollment. IPGME&R Institutional Ethics committee approval was obtained for the study [Memo no. Inst/IEC/2015/018].

Inclusion criteria: Adult patients (more than 18 years of age) with migraine and other primary headaches were included in the study.

Migraine was diagnosed according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3) [10] with the following characteristic features (experienced at least 5 attacks that fulfil the following criteria):

- Headache attack duration: Headache attack lasts 4-72 hours (when untreated or unsuccessfully treated)

- Headache characteristics: Headache has ≥2 of the following 4 characteristics: Unilateral location, Pulsating quality, Moderate or severe pain intensity, Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- Non headache symptoms: During headache, the patient has ≥1 of the following: Nausea and/or vomiting, Photophobia and phonophobia

Exclusion criteria: Pregnant and lactating mothers, post menopausal women, menstrual irregularity, users of hormonal preparation, drugs that affect prolactin level, subjects with chronic renal failure, cirrhosis, epilepsy, hypoor hyperthyroidism (hyperprolactinemia, antiepileptic drugs can cause hyperprolactinemia) were excluded.

Sample size calculation: For this study, a pilot study was done with 10 migraine patients, where the prevalence of migraine patients was seen to be 6% with 5% sampling error. The formula used to calculate sample size is:

$$n=Z^2P(1-P)/d^2$$

where n is the required sample size, Z is the Z-score corresponding to the desired level of confidence, P is the expected prevalence, and d is the standard error.

That is how the sample size was calculated to be roughly 82. Thus, 82 migraine patients were taken, and 82 non migraine other primary headache patients were taken. So, a total of 164 patients were selected randomly from the Outpatient Department (OPD) of the study institute.

Study Procedure

Patients were first classified into two groups, irrespective of age and gender, according to the International Classification of Headache Disorders-III (ICHD III) criteria: 1) Migraine and 2) Primary headache other than migraine [10]. For information collection, a prestructured and pretested proforma was used to collect the data and to record relevant clinical examinations.

Prolactin was measured by the ELISA technique (Accubind). In the present study, serum prolactin levels were measured in all patients by the laboratory technicians who were unaware of the study and according to the standard ELISA measurement protocol. The cut-off level for normal serum prolactin was >25 ng/mL. Serum prolactin levels >25 ng/mL were considered as hyperprolactinemia.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences software version 22.0 was used for statistical analysis. In the current study, differences in prolactin levels were analysed among the different headache types using an unpaired two-sample Student's t-test. A p-value <0.05 was considered statistically significant.

RESULTS

In the present study, adult patients (age ≥18 years) with clinical features of primary headache were selected. Out of the 164 patients selected for the study, 82 patients suffered from migraine and 82 patients suffered from other primary headaches, 79 tension-type headaches and 3 cluster headaches (control).

The overall mean age of the total study population was 34.98±9.19 yrs, with a minimum of 18 yrs and a maximum of 63 yrs. Age distribution among migraine patients was 30.01±7.69 yrs, with a minimum of 18 yrs and a maximum of 49 yrs. Age distribution among other primary headache patients was 39.94±7.81 yrs, minimum 23 yrs and maximum 63 yrs. In this study, the mean age of onset of headache in the total study population was 28.64±8.35 yrs. Age of onset among migraine patients was 23.06±6.07 years, and among other primary headache patients was 34.23±6.35 years. Female:male ratio in this study was 2.4:1, which is in accordance with the statistics of the World Health Organisation (WHO) report 2016, in which the ratio is 2:1 [Table/Fig-1].

In the present study, the mean duration of illness of total headache patients was 6.29±4.81 yrs, minimum 1 yr and maximum of 30 yrs; the mean duration of illness of migraine patients was 7.57±5.35 yrs, minimum of 1 yr and maximum of 30 yrs. Mean duration of illness of other primary headaches was 5.01±3.82 yrs. The duration of illness among migraine patients was significantly longer (p-value <0.05) than that of other primary headache patients. In this study, it is seen that, among total headache patients, the mean frequency of headache attack per month was 8.86±6.65 (minimum-1/2 months, maximum-27/months); the mean frequency of headache attack among total migraine patients was 10.37±7.93/months (minimum-1/2 months, maximum-27/months). Mean frequency of headache attack among other primary headaches was 7.36±4.64/months (minimum-1/2 months, maximum-8/months). The difference between the frequency of headache attacks of total migraine patients and other primary headaches was statistically significant (p-value <0.05) [Table/Fig-1].

Variables	Migraine group (Mean±SD)	Control group (Mean±SD)	p-value
Mean age of onset	23.06±6.07	34.23±6.35	<0.0001
Mean age	30.01±7.69	39.94±7.81	0.0001
Mean duration of illness (yr)	7.57±5.35	5.01±3.82	0.001
Episodes per month	10.37±7.93	7.36±4.64	0.004
Gender			
Female	70.73	52.43	0.016
Male	29.27	47.57	

[Table/Fig-1]: Comparison of demographic data among subjects with migraine and the control group ("other primary headaches") is a mix of 79 Tension-Type Headaches (TTH) and 3 cluster headaches. A p-value <0.05 was considered statistically significant.

The overall mean serum prolactin level of total headache patients was 17.93±12.65 ng/mL (minimum-3.33 ng/mL and maximum-74 ng/mL). Mean serum prolactin level among migraine patients was 25.46±13.28 ng/mL (minimum-9.30 ng/mL and maximum-74 ng/mL. Mean serum prolactin level among non migraine other primary headache was 10.39±5.53 ng/mL (minimum-3.33 ng/mL and maximum-28.12 ng/mL) and the difference was statistically significant (p-value <0.0001). Prolactin levels were significantly higher in the migraine group than in the non migraine group (p-value <0.0001) [Table/Fig-2].

Variables	No.	Mean serum prolactin (ng/mL)	Minimum (ng/mL)	Maximum (ng/mL)	Std. Error	p-value
Migraine	82	25.46±13.28	9.30	74	1.5	<0.0001
Control group	82	10.39±5.53	3.33	28.12	0.61	
Total	164	17.93±12.65	3.33	74		

[Table/Fig-2]: Serum prolactin level between migraine and other primary headache patients.
Student's t-test has been done with 95% CI

Hyperprolactinaemia was observed in 21.34% (35/164) of total headache patients. Hyperprolactinemia was observed in 39.02% (32/82) of migraine patients and 3.66% (3/82) of other primary headache patients. Hyperprolactinaemia was observed in both migraine and other primary headache groups, but the level of prolactin was found to be significantly higher in migraine patients than the other group (p=0.001) [Table/Fig-3].

	n (%)	Mean±SD	Std. Error	p-value
Migraine	32 (39.02%)	36.4±15	2.7	0.001
Control group	3 (3.66%)	26.53±1.43	0.83	

[Table/Fig-3]: Hyperprolactinemia in migraine and other primary headaches (control group).
A p-value <0.05 was considered statistically significant

DISCUSSION

Headache is one of the most common symptoms that patients seek medical attention. Migraine is the second most common type of primary headache, preceded by tension-type headache. According to the World Health Organisation (WHO), migraine is ranked as the 19th disabling condition [11], which gives rise to a poor quality of life for its victims. Although the exact aetiology and pathophysiology of this chronic disabling condition are unclear, there have been some associations between migraine and the hypothalamic-pituitary axis, hormones, and different neurotransmitters. Migraine treatment aims to reduce the severity of acute attacks and prevent further recurrence.

Chronic migraine is difficult to control with pharmacological agents alone. Therefore, in the search for new molecules, different studies are ongoing; one study has focused on cabergolin, a long-acting dopamine D2 receptor agonist that acts as an antiprolactin agent that significantly reduces the severity and frequency of headache attacks. Cavestro C et al., found that, among 27 patients of chronic migraine, 7 patients had high prolactin levels [12]. Therefore, considering that prolactin as a potential worsening factor for migraine, they have observed a significant improvement in headache attacks in migraineurs in terms of reducing severity and diminishing frequency of attacks after using cabergoline (0.5 mg) (an antiprolactin agent) twice a week for a few months.

Hyperprolactinemia observed in the current study, particularly in migraine patients (39.02%), can be explained with reference to other studies. Saberi A et al., performed a study in 2011-12 comparing serum prolactin level in 114 female patients with episodic migraine versus chronic migraine [13]. They identified that serum levels of prolactin and hyperprolactinemia were significantly higher in chronic migraine than in those with episodic migraine. In their study, Awaki E et al., tested pituitary function in women with migraine and compared it with healthy controls [14]. They observed higher levels of prolactin in patients with migraine than in healthy controls. The authors suggested serotonergic hyperfunction and dopaminergic hypofunction as the causes of prolactin hypersecretion.

However, Masoud SA and Fakharian E found lower prolactin serum levels during the acute phase of migraine [15]. In another study, Peres MF et al., investigated chronic migraine by measuring melatonin, prolactin, growth hormone and cortisol levels (role of hypothalamus) and found that chronic migraine patients had lower nocturnal prolactin levels [16].

So, the existence of a link between migraine and prolactin is well-established. But why different levels of prolactin in episodic and chronic migraine types occur needs to be elucidated.

Limitation(s)

Even though the results were statistically meaningful, reproduction of the study with a larger number of patients, preferably from different ethnic groups, will confirm the results.

CONCLUSION(S)

Based on observations, it can be concluded that prolactin may play a role in the pathophysiology of migraine. Moreover, as the conventional preventive regimen falls short of 100% success, the therapeutic use of prolactin-inhibitory agents may usher in a new era in the treatment protocol of migraine. In this context, the serum prolactin level may be used as a potential biomarker for this condition and can help in its treatment outcome.

REFERENCES

[1] Global Burden of Disease Study 2010 (GBD 2010) Results by Cause 1990-2010.
[2] Silberstein S, Loder E, Diamond S, Reed ML, Bigal ME, Lipton RB; AMPP Advisory Group. Probable migraine in the United States: Results of the American Migraine Prevalence and Prevention (AMPP) study. Cephalalgia. 2007;27(3):220-29.
[3] Blau JN, MacGregor EA. Migraine and the neck. Headache. 1994;34(2):88-90.
[4] D'Andrea G, Perini F, Terrazzino S, Nordera GP Contributions of biochemistry to the pathogenesis of primary headaches. Neurol Sci. 2004;25(Suppl 3):S89-S92.
[5] Welch KMA. Research developments in the physiopathology of primary headaches. Neurol Sci. 2004;25(Suppl3):S97-S103.
[6] Silberstein SD, Meriam GR. Sex hormones and headache. J Pain Symptom Manage. 1993;8:98-114.
[7] Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 19th Ed. McGraw Hill Professional; 2015:2588.
[8] Sicuteri F. Dopamine the second putative protagonist in headache. Headache. 1977;17:129-31.
[9] Vetvik KG, MacGregor EA Menstrual migraine: A distinct disorder needing greater recognition. Lancet Neurol. 2021;20(4):304-15.
[10] Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders. 3rd edition. Cephalalgia. 2018;38:01-211.
[11] WHO. World Health Organization; Geneva: 2001. The World Health Report. 2001.
[12] Cavestro C, Rosatello A, Micca G, Ravotto M, Marino MP, Asteggiano G, et al. High prolactin levels as a worsening factor for migraine. J Headache Pain. 2006;7:83-89. Doi: 10.1007/s10194-006-0272-278.
[13] Saberi A, Roudbary SA, Elyasi N, Kazemnejad E. Comparison the Serum level of prolactin among patients with chronic and episodic migraine. J Neurol Res. 2013;3:68-72.
[14] Awaki E, Takeshima T, Takahashi K. A neuroendocrinological study in female migraineurs: Prolactin and thyroid stimulating hormone responses. Cephalalgia. 1998;9:187-93.
[15] Masoud SA, Fakharian E. Serum prolactin and migraine. Ann Saudi Med. 2005;25:489-91.
[16] Peres MF, Sanchez del Rio M, Seabra ML, Tufik S, Abucham J, Cipolla-Neto J, et al. Hypothalamic involvement in chronic migraine. J. Neurol. Neurosurg. Psychiatry. 2001;71:747-51.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biochemistry, JISMSR, Howrah, West Bengal, India.
2. Assistant Professor, Department of Neurology, RKMSP VIMS, Kolkata, West Bengal, India.
3. Professor, Department of Biochemistry, IPGMER, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ananya Kundu,
Morya, 4A, 88A, B.L. Saha Road, Kolkata-700053, West Bengal, India.
E-mail: drananyasen@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 04, 2025
- Manual Googling: Sep 12, 2025
- iThenticate Software: Sep 15, 2025 (12%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 28, 2025**
Date of Peer Review: **Jun 20, 2025**
Date of Acceptance: **Sep 18, 2025**
Date of Publishing: **Nov 01, 2025**