



## Original Article

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# Clinical Characteristics of Migraine and Serum Beta-Endorphin Levels in Undergraduate Students in Osun State, Nigeria

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## Abstract

**Purpose:** Migraine is a common neurological disorder diagnosed using the International Classification of Headache Disorders (ICHD). Beta-endorphin has pain-reducing properties and may serve as a future prognostic marker for migraine. This study aimed to assess the clinical characteristics of migraine and compare serum beta-endorphin levels in migraine patients and healthy controls among young undergraduate students.

**Methods:** This comparative cross-sectional study was conducted among undergraduate students at Obafemi Awolowo University, Nigeria. Fifty participants with migraine headaches were recruited using purposive sampling according to the ICHD-3 criteria. Healthy controls were recruited using convenience sampling and matched for age and sex. A study questionnaire was administered to all participants. Serum beta-endorphin concentrations in both migraineurs and healthy controls were measured using enzyme-linked immunosorbent assays. The beta-endorphin levels between migraine patients and healthy controls were compared using the Mann-Whitney U-test. The data were analyzed using SPSS version 26.0. A p-value of <0.05 was considered statistically significant.

**Results:** A total of 12 males and 38 females were recruited in both groups. The most commonly used medication for acute migraine treatment was paracetamol, while amitriptyline was the most frequently used prophylactic. Median serum beta-endorphin levels were significantly lower in the migraine group, at 385.4 pg/mL (328.5–423.4 pg/mL), compared to the control group, at 442.9 pg/mL (357.5–477.6 pg/mL) (p=0.01).

**Conclusion:** Serum beta-endorphin levels were significantly lower in young adults with migraine, suggesting a potential role for reduced endogenous analgesia in migraine pathophysiology. This supports the potential utility of beta-endorphin as a prognostic biomarker for migraine.

**Keywords:** Amitriptyline, Beta-endorphin, Migraine disorders

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## INTRODUCTION

Migraine is a primary headache disorder characterized by lateralized, intense, throbbing, or pulsatile head pain.<sup>1</sup> Common triggers for migraine attacks include emotional stress, alcohol, specific foods, insufficient or excessive sleep, strong odors, missing meals, and menstruation. The estimated 1-year prevalence is approximately 15% in the general population, and migraine is three times more common in women than in men.<sup>2,3</sup> In Africa, an estimated 56 million people suffer from migraine.<sup>4</sup> In Nigeria, Aderinto et al.<sup>5</sup> reported a prevalence of 16%, while Mustapha et al.<sup>6</sup> found a prevalence of 26.8% in Osun State. Studies among tertiary school students revealed lower prevalence rates: 2.4% in Ilorin,<sup>7</sup> 5.9% in Calabar,<sup>8</sup> and 8.9% in Enugu.<sup>9</sup> Migraine is believed to result from a combination of vascular and neurological events in the cranial meninges. The hypothalamus, trigeminovascular system, and brainstem are key structures implicated in migraine pathogenesis. Beta-endorphin is produced, along with other peptides, during the processing of proopiomelanocortin into adrenocorticotrophic hormone, and exerts an analgesic effect.<sup>10</sup> Misra et al.<sup>11</sup> reported reduced serum beta-endorphin levels in patients with chronic migraine, with increased levels associated with symptom relief. Numerous studies have explored the prevalence, frequency, clinical profile, and triggers of migraine, and some have examined disability in undergraduate students with migraine in Nigeria.<sup>7,12,13</sup> However, none of those studies have compared neurotransmitter levels between migraineurs and non-migraineurs. Such comparison may provide a prognostic index and inform future management strategies for migraine patients. Therefore, this study aimed to determine the clinical characteristics of migraine headaches among the study population and to compare serum beta-endorphin levels in migraine patients and controls.

## MATERIALS AND METHODS

### 1. Ethics approval and study design

This was a comparative cross-sectional study conducted among undergraduates of Obafemi Awolowo University, Ile-Ife, Osun State, following approval from the Health Research Ethics Committee of the Institute of Public Health

and the Vice-Chancellor of the University. Ile-Ife is located at the intersection of roads from Ibadan, Ilesha, and Ondo. Obafemi Awolowo University, founded in 1961,<sup>14</sup> has a health center offering both preventive and curative services to the University community. The study was conducted between November 2022 and October 2023. A sample size of 50 was used for both the migraine and control groups. This was calculated using the formula for comparing the means of two independent groups,<sup>15</sup> using the values obtained from the study of Misra et al.<sup>11</sup> Participants with migraine headaches were recruited using purposive sampling. Information about the study was disseminated through various channels (Class and Hall WhatsApp platforms, and departmental notice boards) to invite students with recurrent headaches to the clinic. Inclusion criteria were students aged 18 years or older. Exclusion criteria included a history of chronic mental illness such as schizophrenia, physical illnesses such as epilepsy, pain disorders, stroke, other headache disorders, and current use of opioid-containing medications. These exclusions were based on participant history. Participants who met the International Classification of Headache Disorders, third edition criteria for migraine were recruited from those presenting with headaches at the clinic. Study questionnaires were administered to eligible participants, followed by venous blood sample collection.

Age- and sex-matched controls were recruited using convenience sampling from the halls of residence, based on the same inclusion and exclusion criteria.

The first section of the questionnaire collected socio-demographic information, while the second section assessed the clinical characteristics of migraine headaches. Questionnaires were administered by the study authors. Participants were further subclassified into chronic migraine ( $\geq 15$  day/mo), high-frequency migraine (9–14 day/mo), medium-frequency migraine (5–8 day/mo), and low-frequency migraine (1–4 day/mo).<sup>1</sup>

Participants underwent 20 minutes of physical rest in the supine position.<sup>16</sup> Venipuncture was then performed to obtain 5 mL of venous blood under strict aseptic conditions, collected into plain bottles for beta-endorphin assay. Samples were centrifuged at 4,000 rpm for 20 minutes, and serum was separated. The serum was transferred to cryovials, labeled, and stored at  $-80^{\circ}\text{C}$  until analysis. Assays were conducted in the chemical pathology laboratory under the

supervision of a consultant chemical pathologist. Human beta-endorphin enzyme-linked immunosorbent assay (ELISA) kits from Wuhan Fine Biotech Co., Ltd. (Expiration date: 16-12-2023, Catalog number: EH0696), with a detection range of 15.62–1,000 pg/mL and using a competitive ELISA method, were employed for the assay. The micro-titer plate was pre-coated with the target antigen. During the assay, the target in each sample competed with a fixed amount of target antigen on the solid-phase support for binding to biotinylated detection antibodies specific to beta-endorphin. Excess conjugate and unbound samples or standards were washed off the plate, after which horseradish peroxidase-streptavidin was added to each well and incubated. TMB substrate solution was then added. The enzyme-substrate reaction was terminated by adding sulfuric acid, and the resulting color change was measured spectrophotometrically at 450 nm. The concentration of beta-endorphin in each sample was determined by comparing the optical density values to a standard curve.

2. Statistical analysis

Numeric variables, such as age and serum beta-endorphin concentration, were tested for normality using the Shapiro-Wilk test. Normally distributed data were summarized using mean and standard deviation, while non-normally distributed data were summarized using the median and interquartile range. Categorical data, such as sex and migraine-associated symptoms, were summarized as frequencies and proportions. Serum beta-endorphin concentrations between migraineurs and healthy controls were compared using the Mann-Whitney U-test. Receiver operating characteristic curve analysis was performed, including calculation of the area under the curve, sensitivity,

and specificity, to determine the beta-endorphin concentration threshold that best differentiated migraineurs from non-migraineurs in this study sample. Data were analyzed using the SPSS software, version 26.0 (IBM Corp.). A p-value of <0.05 was considered statistically significant.

RESULTS

1. Socio-demographic and anthropometric characteristics of the study subjects

The socio-demographic characteristics of the study participants are summarized in Table 1. There were 12 males (24.0%) and 38 females (76.0%) in both the migraine headache group and the control group. The median age and interquartile range for the migraine headache group was 22.0 years (20.8–25.0 years), and for the healthy control group, 22.0 years (21.0–24.0 years). The body mass index of respondents in the migraine group was 22.2 kg/m<sup>2</sup> (19.4–26.0 kg/m<sup>2</sup>), compared to 21.3 kg/m<sup>2</sup> (19.3–24.5 kg/m<sup>2</sup>) in the control group. This difference was not statistically significant (p=0.38).

2. Pattern of migraine headaches and medication use among the study participants

The characteristics of migraine headaches and medication use among study participants are shown in Table 2. The median duration of headache per episode was 21.0 hours (6.3–48.0 hours), with a median duration of 30.0 months (12.0–48.0 months) since diagnosis. The monthly cost of treatment was 500.0 naira (200.0–2,000.0 naira). Nausea was present in 20 participants (40.0%), vomiting in 11 (22.0%), and photophobia/phonophobia in 48 (96.0%).

Table 1. Socio-demographic and anthropometric characteristics of the study subjects

Variable	Category	Study group		Statistics
		Migraine headache group (n=50)	Healthy group (n=50)	
Age (yr)		22.0 (20.8–25.0)	22.0 (21.0–24.0)	U=1,220.0, p=0.83
Sex	Male	12 (24.0)	12 (24.0)	$\chi^2=0.05$ , p=0.82
	Female	38 (76.0)	38 (76.0)	
Marital status	Single	45 (90.0)	47 (94.0)	Fisher's=0.54, p=0.72
	Married	5 (10.0)	3 (6.0)	
Body mass index (kg/m <sup>2</sup> )		22.2 (19.4–26.0)	21.3 (19.3–24.5)	U=1,124.0, p=0.38

Values are presented as median (interquartile range) or number (%).  
U, Mann-Whitney U-test.

**Table 2. Pattern of migraine headaches and medication use among the study participants (n=50)**

Variable	Frequency
Average duration of headache per episode (hr)	21.0 (6.3–48.0)
Duration since diagnosis of migraine headache (mo)	30.0 (12.0–48.0)
Average cost of treatment of migraine headache (naira)	500.0 (200.0–2,000.0)
Nausea	
No	30 (60.0)
Yes	20 (40.0)
Vomiting	
No	39 (78.0)
Yes	11 (22.0)
Photophobia/phonophobia	
No	2 (4.0)
Yes	48 (96.0)
Premonition signs	
No	23 (46.0)
Yes	27 (54.0)
Types of premonition signs (n=27)	
Sensory	11 (40.7)
Visual	8 (29.6)
Both	5 (18.5)
Others	3 (11.1)
Migraine prophylaxis	
No	42 (84.0)
Yes	8 (16.0)
Medication for prophylaxis (n=9)	
Propranolol	1 (11.1)
Amitriptyline	7 (77.8)
Amitriptyline+propranolol	1 (11.1)
Medications for acute migraine	
Paracetamol	21 (42.0)
Ergot preparation	8 (16.0)
Aspirin	5 (10.0)
Sumatriptan	5 (10.0)
None	1 (2.0)
Others	10 (20.0)
Frequency of migraine headache	
Chronic migraine	17 (34.0)
High frequency migraine	4 (8.0)
Medium frequency migraine	10 (20.0)
Low frequency migraine	19 (38.0)

Values are presented as median (interquartile range) or number (%).

The most common medication used for acute migraine treatment was paracetamol, followed by other medications and ergot preparations. Eight migraine participants (16.0%) were on prophylactic therapy, with amitriptyline being the most frequently used prophylactic. Regarding headache frequency, 34% of respondents reported chronic migraine, while 38% experienced low-frequency headaches.

### 3. Triggers of migraine headaches

The triggers of migraine headaches are depicted in [Figure 1](#). Stress and poor sleep accounted for 35.7% and 25.4% of reported triggers, respectively. Other triggers included hunger (14.3%), menstruation (9.5%), ovulation (4.8%), odors (4.8%), excessive sleep (2.4%), missed meals (2.4%), and specific foods such as smoked meat and fish (0.8%).

### 4. Serum beta-endorphin levels in migraineurs and controls

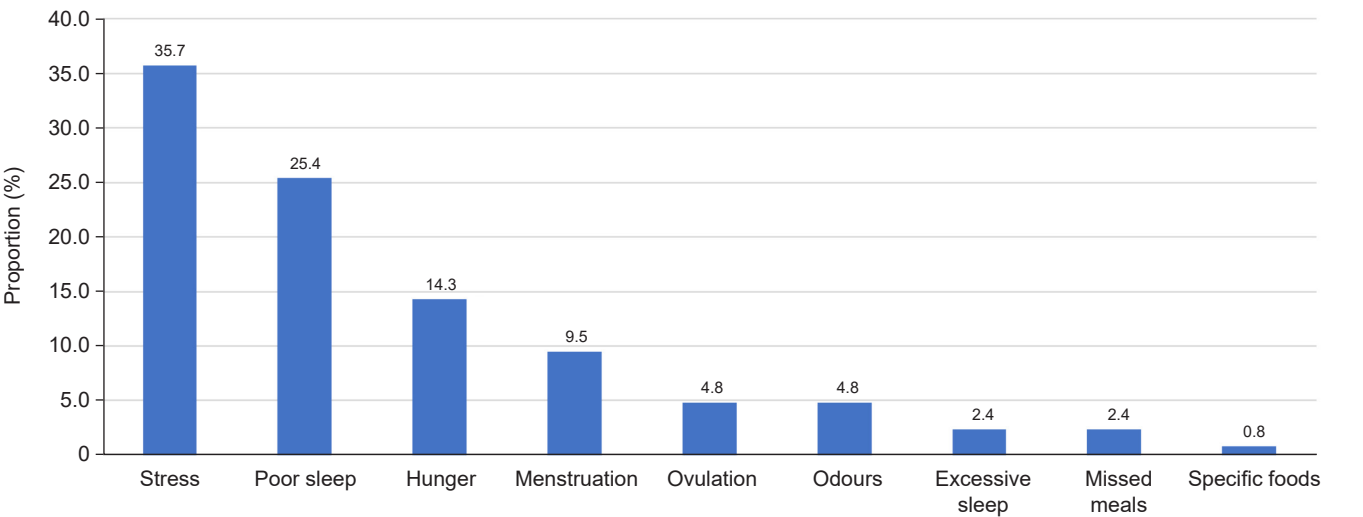
As shown in [Table 3](#), and [Figure 2](#), the median serum beta-endorphin level in migraineurs was 385.4 pg/mL (328.5–423.4 pg/mL), compared to 442.9 pg/mL (357.5–477.6 pg/mL) in the control group. This difference was statistically significant ( $p=0.01$ ).

### 5. Receiver operating characteristic curve for beta-endorphin and migraine headaches

[Table 4](#) and [Figure 3](#) demonstrate that a beta-endorphin level 403.4 pg/mL predicts the absence of migraine headaches, with a sensitivity and specificity of 64.0% and 71.4%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were 66.7% and 69.6%, respectively.

### 6. Relationship between the frequency of migraine headaches and serum beta-endorphin

[Table 5](#) summarizes the relationship between the frequency of migraine headaches, and serum beta-endorphin. No statistically significant relationship was found between headache frequency and any of these factors.

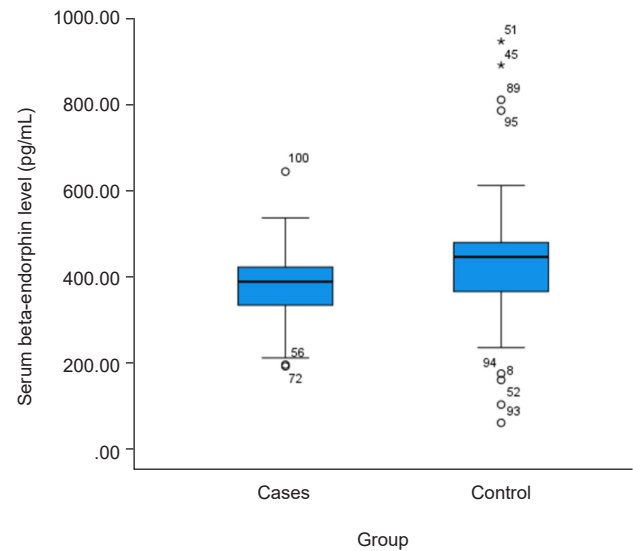


**Figure 1.** Triggers of migraine headache.

**Table 3.** Comparison of mean serum beta-endorphin among migraine patients and healthy control

Variable	Intervention group		Statistics
	Migraine headache group (n=50)	Healthy group (n=50)	
Serum beta-endorphin (pg/mL)	385.4 (328.5–423.4)	442.9 (357.5–477.6)	U=843,000, p=0.01

Values are presented as median (interquartile range).



**Figure 2.** Box plot showing beta-endorphin levels in migraine patients and controls.

**DISCUSSION**

This study is the first to assay serum beta-endorphin levels among migraineurs in Africa. Median serum beta-endor-

phin was significantly lower in young adults with migraine compared to controls, consistent with findings from previous studies,<sup>17,18</sup> suggesting a potential role for reduced endogenous analgesia in migraine pathophysiology. This finding supports the consideration of beta-endorphin as a possible prognostic biomarker for migraine.

A statistically significant relationship was observed between serum beta-endorphin levels and the presence of migraine. A cut-off value of less than 403.4 pg/mL yielded a sensitivity of 64.0%, specificity of 71.4%, PPV of 66.7%, and NPV of 69.6% for diagnosing migraine. However, this level of sensitivity and specificity is relatively low to qualify serum beta-endorphin as a standalone biomarker for migraine, especially when compared to serum serotonin, which has been reported to be lower in migraine patients, with both sensitivity and specificity of 80%.<sup>19</sup> No correlation was found between headache frequency and serum beta-endorphin levels in this study, a finding that aligns with the results of Misra et al.,<sup>20</sup> who also observed no initial correlation but subsequently reported a positive association—a 50% reduction in headache frequency with increased serum beta-endorphin—after one month

**Table 4.** Receiver operator characteristics of beta-endorphin and migraine headache

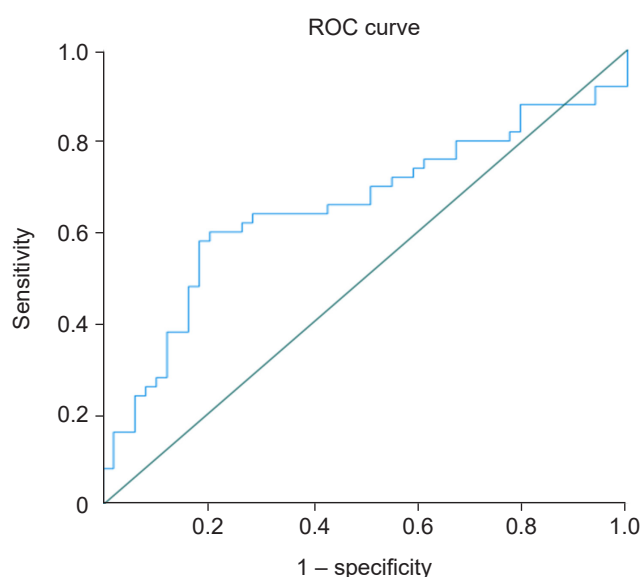
	AUC	p-value	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut off value (pg/mL)
Beta-endorphin	0.70	0.01	0.54–0.77	64.0	71.4	66.7	69.6	403.4

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

**Table 5.** Relationship between the frequency of migraine headaches and serum beta-endorphin

Variable	Frequency of headache				Statistics
	Chronic migraine	High-frequency migraine	Medium frequency migraine	Low frequency migraine	
Serum beta-endorphin	371.4 (299.5–415.8)	380.2 (322.5–465.3)	385.5 (315.2–435.3)	387.4 (305.9–416.7)	H=0.255, p=0.968

Values are presented as median (interquartile range).

**Figure 3.** Receiver operating characteristic (ROC) curve of serum beta-endorphin levels in migraine headache patients versus controls.

of repetitive transcranial magnetic stimulation. Repetitive transcranial magnetic stimulation, a non-pharmacologic approach to migraine management, has been shown to increase serum beta-endorphin and reduce headache frequency. Regular aerobic exercise also increases circulating beta-endorphin and is recommended for migraine patients due to its beneficial effect on headache frequency.<sup>21</sup> In contrast, a study on knee osteoarthritis—another inflammatory pain condition—found that non-invasive brain stimulation improved inflammatory markers but decreased beta-endorphin levels.<sup>22</sup> This paradoxical

reduction in beta-endorphin, despite pain relief from non-invasive brain stimulation, may be due to persistently decreased beta-endorphin secretion in chronic pain conditions.<sup>23</sup>

This study also provides insight into the clinical features and treatment patterns of young migraineurs in Africa. The higher prevalence of migraine in females has been attributed to estrogen sensitivity, genetic factors, and differences in stress and pain perception.<sup>24</sup> Paracetamol was the most commonly used analgesic for acute migraine treatment, consistent with previous reports.<sup>25,26</sup> This is likely due to its widespread availability, affordability, and popularity among university students.<sup>27</sup> However, paracetamol is not very effective for acute migraine attacks. The low rate of sumatriptan use may be attributed to its high cost and limited accessibility, a trend seen in other African settings.<sup>28</sup>

Most respondents identified two or more migraine triggers, with stress being the most frequently reported, as in other studies.<sup>26</sup> Stress, defined as emotional strain in response to challenging life events,<sup>29</sup> is prevalent among university students in Nigeria, who often experience both physical stress (such as walking long distances to class) and mental stress (focusing during lectures, studying for exams). Academic-related stress is reportedly higher in developing countries.<sup>30</sup> Poor sleep was a trigger for migraine in 25.4% of participants, consistent with findings from other research.<sup>31,32</sup> Migraineurs are known to have poorer sleep quality, shorter sleep duration, and more daytime sleepiness than non-migraineurs.<sup>32,33</sup> Variations exist in the clinical characteristics of migraine across different popula-



tions. While photophobia and phonophobia were frequent in this study, the prevalence of nausea was lower than in an Egyptian study by Oraby et al.<sup>34</sup> The proportion of respondents with chronic migraine was higher (34.7%) than in the population-based CaMEO study in the United States (8.8%).<sup>35</sup> A hospital-based study in North West Nigeria by Ali et al.<sup>13</sup> reported a chronic migraine rate of 69.2%, much higher than the 24.7% found in a similar study in Taiwan.<sup>36</sup> These differences may reflect disparities in healthcare delivery between continents. Chronic migraine may result from delays in diagnosis and effective treatment, potentially due to poor health-seeking behavior and limited knowledge of headache disorders among primary care physicians, who are often the first point of contact.<sup>13,37</sup>

The median serum beta-endorphin level was significantly lower in young adults with migraine than in controls, suggesting that reduced endogenous analgesia may play a role in migraine pathophysiology and supporting the possibility that beta-endorphin might serve as a prognostic biomarker for migraine. This study is the first to assay serum beta-endorphin among migraineurs in Africa. However, it was limited to undergraduate students, a predominantly healthy age group, limiting the generalizability of these findings to other age groups. Factors such as recent meals, sexual activity, ictal versus interictal status, headache severity, response to abortive medication, preventive therapy, or menstrual cycle phase—which could all influence beta-endorphin levels—were not controlled for. Migraine data were self-reported via questionnaire, introducing the possibility of recall bias and under- or over-reporting of symptoms.

## AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

## AUTHOR CONTRIBUTIONS

Conceptualization: AO, AI, AA; Data Curation: AS, UE; Supervision: MF, MK; Writing—original draft: AO, AI, AS, UE, AA; Writing—review & editing: AA, MF, MK. All authors read and approved the final manuscript.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Not applicable.

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