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ORIGINAL ARTICLE

# Demographic and Characteristics of Primary Headache in Egyptian Epileptic Patients

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## ABSTRACT

**Background**: Migraine pathophysiology has been linked to neuroinflammation. During a migraine attack, trigeminal activation results in the release of calcitonin gene-related peptide (CGRP), which stimulates the release of inflammatory cytokines and plays an important role in migraine, primary headache disorders, and possibly epilepsy. This study aimed to investigate the different types of primary headache disorders among epileptic patients to find out the clinical correlation between serum CGRP level and severity and type of headache among these patients, which can reflect management strategy for better management options of this common comorbidity.

**Methods:** This study was conducted at the Neurology Department and Outpatients Epilepsy and Headache Clinics, Faculty of Medicine, Zagazig University, on 69 patients with epilepsy who were divided into two groups: group (1): 46 epileptic patients suffering from primary headache disorder, and group (2): 23 epileptic patients without headache. The level of calcitonin gene-related peptide was measured.

**Results:** CGRP was significantly higher in epileptic patients with headaches than those without headaches. CGRP expression ≥61: shows sensitivity of 75%, specificity of 83.3%, and accuracy of 78.3% to discriminate epileptic patients with migraine headaches from epileptic patients with tension headaches.

**Conclusions:** The serum CGRP levels were significantly more in migraine patients and were correlated with characteristics like throbbing type of pain, stress and inadequate sleep.

**Keywords:** Primary headache; Calcitonin gene-related peptide; Epilepsy

## INTRODUCTION

The most prevalent recurrent neurological disorders are primary headache and epilepsy. They share many characteristics, including an episodic nature, shared underlying pathogenic mechanisms, imbalances between facilitatory and inhibitory neurotransmitters, and modifications to membrane channel function [1].

Both of them, particularly migraine, are frequently co-occurring in the same people. It's interesting to note that the prevalence of epilepsy in migraine patients ranges from 1 to 17%, which is significantly higher than the prevalence in the general population, which is between 0.5 and 1%. Additionally, the prevalence of migraine increased in epileptic patients relative to non-epilepsy patients [2]. Additionally, due to their comorbidity, one of

these illnesses may mimic or cause the other [3].

Calcitonin gene-related peptide, or CGRP, is a neuropeptide made up of 37 amino acids that is produced by splicing the calcitonin gene. Two forms of CGRP, CGRPα and CGRPβ, have been identified [4].

Widespread expression of the calcitonin gene-related peptide causes cerebral vasodilation, which is linked to the pain pathways during migraine attacks. It is also expressed in sensory trigeminal neurons and the peripheral and central nervous systems [5]. Trigeminal activation during a migraine attack causes the production of CGRP, which causes neurogenic inflammation and vasodilation in the leptomeningeal arteries, resulting in pain that is characteristic of a migraine episode [6].

According to a number of studies, the blood level of CGRP is higher in migraine patients than in healthy individuals. Since the level of CGRP is higher in chronic migraine than in episodic migraine, it may also be helpful in the diagnosis of chronic migraine [7].

The use of CGRP antagonists for migraine prophylaxis was approved in 2018 as a consequence of the recent years' fast collection of information about their role in migraine patients [8].

Given the high prevalence of headaches, particularly migraines, in patients with epilepsy, it is imperative that clinicians pay closer attention to this prevalent comorbidity as it may have an impact on treatment options and the selection of antiepileptic drugs [9].

## METHODS

69 epileptic patients were diagnosed in the Neurology Department and Outpatient Epilepsy and Headache Clinics at Zagazig University, Faculty of Medicine,during the period from May 2023 to May 2024. Patients were given written informed consent outlining the procedure and any potential risks, and IRB permission was obtained (Number: 10921). Two groups of sixty-nine participants, twenty-one male and forty-eight female, ranging in age from 22 to 53 years, were created: group (1) consisted of twenty-six epileptic patients with main headache disorder, and group (2) consisted of twenty-three epileptic patients without headache.

Individuals whose epilepsy has been verified by the diagnostic standards established by the International League Against Epilepsy (ILAE) [10].Participants in the study were to be at least 18 years old and have a verified diagnosis of primary headache condition as defined by the International Headache Society (IHS) [11]'s third edition of the International Classification of Headache condition (ICHD-3).

The study excluded patients with behavioral abnormalities, learning disabilities, psychogenic seizures, or secondary epilepsy, patients with secondary headache disorders or medication overuse headache, patients who were medically unstable or in urgent need of medical attention, patients who had received any preventive migraine treatment within the previous week, patients who were under the age of 18, pregnant women, patients with inflammatory or autoimmune diseases, hypertension, diabetes mellitus, obesity and metabolic syndrome were not included in the study.

The epilepsy sheet and the headache impact test 6 (HIT6) questionnaire were used to gather information about the patients' past. A general and neurological examination was also performed to confirm the type of

headache and to determine its cause. Routine laboratory tests included the complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver function tests (LFT), kidney function tests (KFT), and random blood sugar (RBS). ELISA, an enzyme-linked immunosorbent assay, was used to assess the calcitonin gene-related peptide.

Within a day of the migraine headache starting, two 10-milliliter blood samples were taken in the laboratory department of Zagazig University. These samples were placed in glass tubes with 1500 kallikreininactivator units of trasylol and 35 micrograms of dipotassium EDTA. After being placed in an ice bath, the tubes were centrifuged for 15 minutes at 4°C at 2000×g. After the plasma was extracted from the cells, it was kept at -80°C and examined using an ELISA kit that was sold commercially.

The six-item HIT-6 questionnaire, which assesses the frequency of severe headaches, was completed by the subjects. The six items are scored on a frequency basis, with a total score ranging from 36 to 78. We made use of the HIT-6's verified Arabian translation. Based on the acquired HIT-6 score, the disability was assessed using the following four impact grades [12]: little-to-no impact (grade 1: HIT-6 score: 36-49), moderate impact (grade 2: HIT-6 score: 50-55), substantial impact (grade 3: HIT-6 score: 56-59) and severe impact (grade 4: HIT-6 score: 60-78).

EEG data was obtained using 21 surface electrodes positioned in accordance with the global 10-20 system. The EEG apparatus (XEROX, model number 900w, power 100-240 volts, serial number F1AC7B0046089, manufactured by Taipei Country 234 Taiwan company) was used for recording, along with photic stimulation, hyperventilation for three minutes (if there are no contraindications), and an EEG electrode placement wire system guide. The patient, who was seated comfortably, was given an explanation of the test. During the test, the majority of patients were told to remain in a resting-awake condition with their eyes closed. The EEGs of those who were unable to remain awake were recorded while they were asleep. To lower the impedance between the subject's scalp and the electrodes, a piece of cotton was used to apply gel to the scalp. The international 10-20 system, which is based on the general strategy of measuring the distance between two fixed anatomical points, such as the nasion (the point where the nose bridge meets the forehead) and the inion (prominent point on the occiput), was used to apply the electrodes. Electrodes were then placed along that line at 10% or 20% intervals.

## STATISTICAL ANALYSIS

(IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp.2015) was used to gather, tabulate, and statistically analyze all of the data. The Receiver Operating Characteristic (ROC) curve, Fisher Exact Test, Anova Test, Mann Whitney U Test, Spearman Correlation Coefficient, and Fisher Exact Test were employed.

## RESULTS

There was no significant difference between epileptic patients with headache and those without regarding demographic data and characters of epilepsy. CGRP was significantly higher in epileptic patients with headache than those without headache (Table 1).

The area under curve (AUC) equals 1 and 95% confidence interval (1-1). It is very good to discriminate epileptic patients with headache from epileptic patients without headache (Figure 1).

There was a significant difference between the epileptic patients with migraine regarding postictal timing of headache that was higher in episodic migraine than chronic migraine, while there was no significant difference regarding other characters and treatment of epilepsy. There wasa statistically significant difference between epileptic patients with migraine regarding triggers, $p<0.05$.Stress was the main triggerin episodic migraine, while work overload was the main trigger in chronic migraine (Table 2).

The area under curve (AUC) equals 0.864 and 95% confidence interval(0.753-976). So CGRP is good for discriminating epileptic patients with migraine headache from epileptic patients with tension headache (Figure 2).

CGRP expression ≥61: shows sensitivity of 75%,specificity of 83.3% and accuracy of 78.3% to discriminate epileptic patients with migraine headache from epileptic patients with tension headache (Table3).

There was a significant positive correlation between CGRP and headache frequency, headache impact test-6 score, while there was a significant negative correlation with duration of headache. Otherwise, there was no correlation with other parameters(Table4).

CGRP was significantly higher in timing {preictal, ictal, postictal} compared to ictal timing (Table).CGRP was significantly lower in grade I compared to {grades III, IV}.CGRP was significantly lower in grade II compared to {grade IV}(Table5).

**Table 1:** Baseline data of the studied groups

| | | Epileptic patients with headache (n=46) | Epileptic patients without headache (n=23) | Pvalue |
|---|---|---|---|---|
| **Age (years)** | Mean ± SD | 41.27± 8.41 | 39.56 ± 9.20 | 0.476 |
| | Range | 27-53 | 22-53 | |
| **Sex** | Male | 11 (23.9%) | 10 (43.5%) | 0.096 |
| | Female | 35 (76.1%) | 13 (56.5%) | |
| **Occupation** | Yes | 17 (37.0%) | 9 (39.1%) | 0.861 |
| | No | 29(63.0%) | 14 (60.9%) | |
| **Family history of epilepsy** | Yes | 18 (39.1%) | 7 (30.4%) | 0.479 |
| | No | 28 (60.9%) | 16 (69.6%) | |
| **Family history of headache** | Yes | 7 (15.2%) | 2 (8.7 %) | 0.728 |
| | No | 39 (84.8%) | 21 (91.3%) | |

| | | Epileptic patients with headache (n=46) | Epileptic patients without headache (n=23) | Pvalue |
|---|---|---|---|---|
| **Age of onset**<br>**Mean ± SD**<br>**range** | | 22.34 ± 5.85<br>11-32 | 21.69 ± 5.88<br>11-31 | 0.565 |
| **Type of epilepsy** | | | | |
| Focal | | 32 (69.6%) | 12 (52.2%) | 0.299 |
| Generalized | | 10(21.7%) | 9 (39.1%) | |
| Focal with secondary generalization | | 4 (8.7%) | 2 (8.7%) | |
| **Frequency of epileptic attacks** | | | | |
| several attack /week(most frequent) | | 6 (13.0%) | 1 (4.3%) | 0.771 |
| one attack / month | | 8 (17.4%) | 5 (21.7%) | |
| one attack / year | | 16 (34.8%) | 8 (34.8%) | |
| less than one attack per year (least frequent) | | 16 (34.8%) | 9 (39.1%) | |
| Duration of attack (min)<br>Median (range) | | 2.26 ± 1.17<br>2(1-4) | 2.82 ± 1.07<br>3(1-4) | 0.053 u |
| **Number of used antiepileptic drugs** | | | | |
| Monotherapy | | 22 (47.8%) | 7 (30.4%) | 0.374 |
| Polytherapy | | 22 (47.8%) | 15 (65.2%) | |
| No treatment | | 2 (4.4%) | 1 (4.4%) | |
| **CGRP** | Mean ± SD | 67.08±18.78 | 25.17±2.99 | <0.001 |
| | Range | 41-99 | 21-30 | |

Data expresses as mean, (standard deviation),(range), t, Student't test, compared between groups, p>0.05 no significant, χ 2:Chi square test, f:fisher exact test

**Table 2:** Characters and treatment of epileptic patients with migraine

| | Epileptic patients with migraine (n=28) | | P value |
|---|---|---|---|
| | Episodic migraine (n=16) | Chronic migraine (n=12) | |
| **Age of onset**<br>Mean±SD<br>Range | 24±5.3<br>13-30 | 22.66±6.08<br>15-32 | 0.542 |
| **Type of epilepsy** | | | |
| Focal | 10 (62.5%) | 10(83.3%) | 0.174 |

| | Epileptic patients with migraine (n=28) | | P value |
|---|---|---|---|
| | Episodic migraine (n=16) | Chronic migraine (n=12) | |
| Generalized | 4 (25.0%) | 0 | |
| Focal with secondary generalization | 2 (12.5%) | 2 (16.7%) | |
| **Frequency of attacks** | | | |
| >1 week | 2 (12.5%) | 2 (16.7 %) | 0.321 |
| >1 month < 1 week | 2 (12.5%) | 2 (16.7%) | |
| >1 year < 1 month | 4 (25.0%) | 6 (50%) | |
| < 1 year | 8 (50%) | 2 (16.7%) | |
| **Duration of attack (min)**<br>Mean±SD<br>Range | 2.8±1.2<br>1-4 | 1.8 ±1.1<br>1-4 | 0.066 |
| **Timing of headache**<br>Preictal<br>Ictal<br>Postictal<br>Interictal | 2 (12.5%)<br>0 (0%)<br>14 (87.5%)<br>0 (0.0%) | 0 (0.0%)<br>0 (0%)<br>6 (50.0%)<br>6 (50.0%) | **0.004*** |
| **Monotherapy** | 8 (50%) | 4(33.3%) | 0.211 |
| **Polytherapy** | 8 (50%) | 6 (50.0%) | |
| **No treatment** | 0 (0%) | 2 (16.7%) | |
| **Characters of headache** | | | |
| **Throbbing** | 16 (100.0%) | 12 (100.0%) | |
| **Aura** | | | |
| Yes | 6 (37.5%) | 2 (16.7%) | 0.401 |
| no | 10 (62.5%) | 10 (83.3%) | |
| **Triggers** | | | **0.026*** |
| Stress | 6 (37.5 %) | 0 (0.0%) | |
| Abnormal sleep | 6 ( 37.5%) | 4 (33.3%) | |
| Workload | 4 (25.0%) | 8(66.7%) | |
| **Location** | | | 0.241 |
| Unilateral | 12 (75.0%) | 6 (50.0%) | |
| Bilateral | 4 (25.0%) | 6 (50.0%) | |
| **Duration headache (hr)** | 15.5±10.8<br>4-36 | 9.33±3.9<br>6-16 | 0.22 |
| **Headache impact test-6 score** | 70.1±6.8<br>62-78 | 66.83±10.3<br>54-80 | 0.316 |

Data expresses as mean, (standard deviation), (range), t, Student't test, or u: mann whitnney u test compared between groups, $\chi 2$:Chi square test, f:fisher exact test, $p>0.05$ no significant, *$p<0.05$ significant

**Table 3:** Performance of gene-related peptide (CGRP) in detecting epileptic patients with migraine headache from tension headache

| Cut off level | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| CGRP ≥61 | 75% | 83.3% | 87.5% | 68.2% | 78.3% |

**Table 4:** Correlation between CGRP and different parameters

| | CGRP | |
|---|---|---|
| | **r** | **p** |
| **Age** | -0.026 | 0.832 |
| **Age of onset** | 0.057 | 0.643 |
| **Frequency of headache** | **0.559**** | **0.0001** |
| **Duration headache per hours** | **-0.461**** | **0.001** |
| **Headache impact test-6 score** | **0.530**** | **0.0001** |

**Table 5:** CGRP of epileptic patients with headache according to timing and HIT-6 grade

| | | Timing of headache | | | | P value |
|---|---|---|---|---|---|---|
| | | preictal (n=6) | ictal (n=2) | interictal (n=8) | postictal (n=30) | |
| **CGRP** | Mean ± SD | 68.83±23.87 | 42±0 | 74.3±16.73 | 66.5±17.97 | **0.041*** |
| | Median | 57.5 | 42 | 79 | 61 | |
| | Range | 45-99 | 42-42 | 46-88 | 41-98 | |
| | | **HIT-6 grade** | | | | P value |
| | | Grade I (n=10) | Grade II (n=8) | Grade III (n=2) | Grade IV (n=26) | |
| **CGRP** | Mean ± SD | 52.8±5.73 | 57±17.57 | 87.5±0.71 | 74.1±18.37 | **0.001** |
| | Median | 54 | 50 | 87.5 | 76.5 | |
| | Range | 41-60 | 42-88 | 87-88 | 41-99 | |
| | | | | ***,** | ***,^** | |

*Grade I significant {gradeIII,IV}.^GradeII significant {grade IV}.
Data expresses as mean, (standard deviation),median (range), Kruskall Wallius test, p>0.05 no significant, *p<0.05 significant

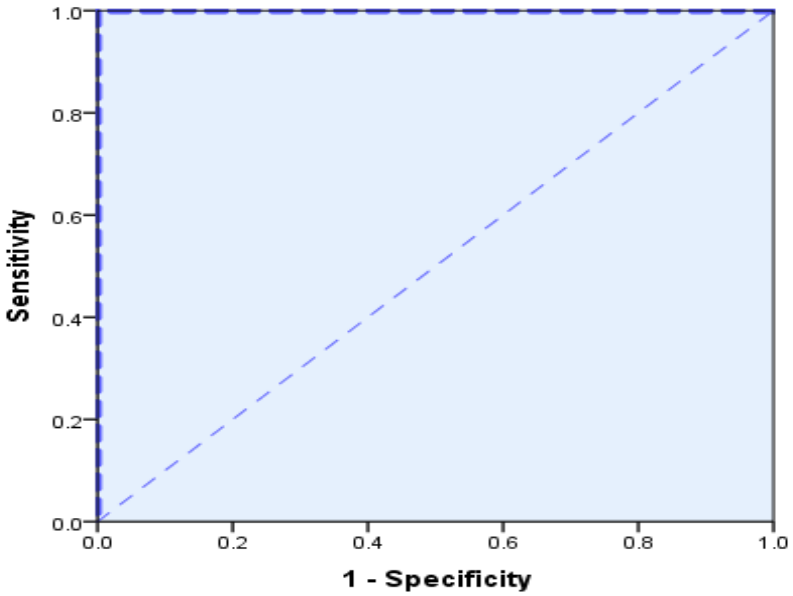


**Figure (1):** ROC curve for calcitonin gene-related peptide (CGRP) in detecting epileptic patients with headache.

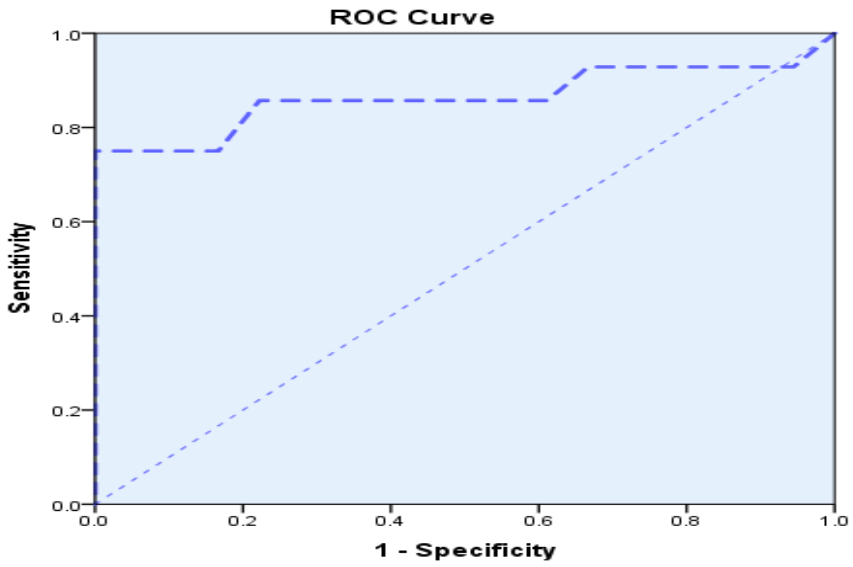


**Figure (2):** ROC curve for calcitonin gene-related peptide (CGRP) in detecting epileptic patients with migraine headache from epileptic patients with tension headache.

## DISCUSSION

Epilepsy is one of the most prevalent neurological conditions in the world, affecting about 50 million individuals. Compared to people without epilepsy, those who have the condition are far more likely to report having a poor health-related quality of life (HRQOL). But determining the burden of epilepsy is a more complicated process that takes into account not just physiological dysfunction but also psychological and social dysfunction in addition to epileptic episodes [13].

The quality of life is negatively impacted by a number of comorbidities, which can range from uncommon physical conditions like asthma or digestive issues to mental or

cognitive impairment. Headache, particularly migraine, is among the most prevalent co-occurring conditions in epilepsy. About 24% of people with epilepsy also suffer from migraines. In addition, individuals with epilepsy had a 2.4-fold higher likelihood of developing migraine compared to the general population. Conversely, the prevalence of epilepsy in migraineurs ranges from 1 to 17%, which is significantly higher than the prevalence of epilepsy in the general population [14].

Primary headache and epilepsy have a reciprocal relationship in which one can occur before or later, or even simultaneously. Headache episodes are temporally associated with the incidence of epileptic seizures, occurring as preictal, ictal, postictal, or interictal occurrences. Epilepsy and headaches frequently coexist [15].

The 37 amino acid neuropeptides that make up calcitonin gene-related peptide (CGRP). There are two variations: αCGRP and β-CGRP. Both the central and peripheral nerve systems contain αCGRP. Because of its location in the digestive tract, β-CGRP plays an endocrine function. CGRP has multiple roles, one of which is its major function of vasodilating the central and peripheral blood arteries. There are several theories as to the mechanics underlying the trigeminal ganglia's release of CGRP during migraine attacks. The most widely accepted explanation is that there is neuroinflammation[11].

In order to better understand the clinical correlation between serum CGRP levels and the severity and type of headaches experienced by epileptic patients, this study looked into the various primary headache disorders that these patients may have. This information can be used to inform management strategies for better ways to address this common comorbidity.

According to our current investigation, there was no statistically significant difference in age or sex between patients with epilepsy who also had headaches and those who did not.

In agreement with our findings, Han[2]claimed that there was no discernible difference in age or gender between the migraine and control groups. El Sheikh et al. [16]demonstrated that there was no discernible difference in age or sex between migraine patients and controls. Mameniškienė et al. [9]revealed that the frequency of headaches among individuals with epilepsy did not differ statistically significantly based on a person's sex.

Unlikely, Duko et al. [15]revealed that, in comparison to men, women had a significantly greater pooled prevalence of headaches among epilepsy patients. Steiner et al. [17]established that headaches are typically more common in women than in men in the general population. This could be clarified by the fact that sex hormones are linked to primary headaches like migraines. In females, sex hormones impact the cells surrounding the trigeminal nerve and the associated cerebral vasculature. Particularly crucial for sensitizing these cells to migraine triggers are the oestrogens, which are hormones that control female reproductive and sexual development at their peak levels in females of childbearing age.

In the current investigation, we discovered that the differences between epileptic patients with and without headaches in terms of age at onset, type of epilepsy, duration of epilepsy, frequency of attacks, length of attack, and quantity of antiepileptic medications taken were statistically insignificant.

In the same context, Osama et al.

[18]observed that the type of headache and medication type had a statistically negligible connection. The monotherapy group experienced significant headache impact more frequently than the polytherapy group, although there was no statistically significant difference.Mainieri et al. [1]found that individuals getting polytherapy experienced headaches more frequently, and they hypothesized that patients who are refractory to multiple treatments may experience headaches frequently as well.

On the other hand, Sayed et al. [19]revealed that the age at which epilepsy began, the length of the epilepsy, the kind of epilepsy, the frequency of seizures, and the EEG results were all statistically significantly different between the two groups. However, there were no statistically significant variations between the two groups' family histories of headaches.

According to our most recent research, people with epilepsy who also had headaches had much greater CGRP levels than those who did not.

Our results were in concordance with those reported byKhatoon et al. [11]who confirmed that the test group's average CGRP levels were greater than those of the controls, which were 61.30±24.37, at 149.00±93.86. There was a statistically significant difference. The usefulness of CGRP as a migraine biomarker or diagnostic aid is questionable. Its function as a diagnostic tool is indicated by a statistically significant value. Nonetheless, we suggest that its function is contingent upon the stage of headache at which it is evaluated. At baseline, adult patients had greater CGRP levels than healthy controls. Adults with migraine attacks have higher plasma CGRP levels, and these increases are correlated with the severity of the headache.

This was in accordance with Han[2],who stated that the migraine group's CGRP level was noticeably higher than that of the normal group. By stimulating cytokine release, CGRP may be the cause of migraines. Inflammation and pain are two physiological processes in which cytokines are crucial. Pro-inflammatory cytokines (TNFα, IL 1β, IL 6) and anti-inflammatory cytokines (IL 10) have been shown to be important in modulating pain threshold and may also be involved in the sensitization of trigeminal nerve fibers. In migraines, cytokines may be associated with inflammation and hyperalgesia. According to Osama et al. [18], there is a statistically significant increase in headache prevalence in the epileptic group compared to the non-epileptic group.

In agreement with our results, Ho et al. [20] found that migraine headaches cause elevated CGRP plasma concentrations in the external jugular venous blood. Only women with migraines experience headaches from intravenous CGRP, and CGRP antagonists are useful in the treatment of acute migraines. Ashina[21]discovered that, in comparison to the healthy group, migraineurs' CGRP level stays elevated outside of the headache phase.Fusayasu et al. [22]discovered that migraineurs' blood and saliva have higher levels of CGRP during the interictal stage.

We discovered in this study that there was a statistically significant difference in postictal headache timing between the analyzed groups, with episodic migrainers experiencing a higher postictal timing of headache than chronic migrainers.

Similar findings were obtained by Osama et al. [18],who demonstrated that patients with focal to bilateral tonic-clonic seizures, compared to those with focal and primary generalized seizures; had significantly more

interictal headaches (p=0.04) based on the type of seizure; there was no correlation between the types of seizure and pre- or postictal headaches.Sayed et al. [19]stated that in terms of the period of headache, postictal headache is the most prevalent form, followed by interictal and, less frequently, preictal headache. This may be explained by the increased ease with which cortical spreading depression can be attained in the post-seizure phase and the triggering influence of epileptic seizures on headache occurrence. Mainieri et al. [1]claimed that patients with migraineurs had a substantial correlation with postictal headache (post-IH). Additionally, there was a strong correlation found between post-IH and tonic-clonic seizures, high seizure frequency, and antiepileptic polytherapy.

According to our current research, there was a statistically significant difference ($p<0.05$) in the migraine triggers between epileptic individuals.The primary cause of episodic migraines was stress, but the primary cause of chronic migraines was work overload.

In the same context,Khatoon et al. [11]demonstrated a statistical correlation between features such as throbbing pain, stress, and insufficient sleep and blood CGRP levels. This indicates that migraine risk factors include stress, insufficient sleep, and throbbing pain. After their initial visit to the hospital, patients were prescribed either dual therapy or monotherapy based on an examination of their symptoms.

In the current investigation, patients with chronic migraine had a considerably greater CGRP than patients with episodic migraine or those without headaches. Additionally, compared to epileptic patients without headaches, CGRP was considerably higher in patients with episodic migraine.

These results were compatible with Cernuda-Morollón et al. [23],who showed that, in comparison to control healthy women, women with episodic migraine, and patients with episodic cluster headaches, CGRP levels were considerably higher in patients with chronic migraine. El Sheikh et al. [16]stated that results indicated that the CGRP plasma level was significantly higher in patients with chronic migraine as compared with the control group.Cernuda-Morollón et al. [23]have discovered that a significant number of women with chronic migraines and a lesser extent of women with episodic migraines have an interictal increase in CGRP plasma levels, which is correlated with the intensity of the headache.

## CONCLUSIONS

Serum CGRP levels considerably increased in migraineurs and were associated with symptoms such as throbbing pain, tension, and insufficient sleep. Therefore, the measurement of serum CGRP levels can be used as a diagnostic tool for migraine when the clinical characteristics coincide or when the migraine is still in its early stages and not all diagnostic criteria have been met. It is necessary to conduct more multicenter and large sample size research. It is advised that more research be done to compare CGRP during and after an attack.

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