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CLINICAL SIGNIFICANCE OF NEUROPEPTIDE LEVELS IN EARLY DIAGNOSIS OF PRIMARY HEADACHE DISORDERS

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Abstract.
Background: Primary headache disorders, including migraine, tension-type headache, and cluster headache, are among the most prevalent neurological conditions. Early diagnosis remains challenging due to overlapping clinical features. Neuropeptides are increasingly recognized as key mediators in headache pathophysiology and potential diagnostic biomarkers. Objective: To evaluate the clinical significance of neuropeptide levels in the early diagnosis of primary headache disorders. Methods: A clinical observational study included patients with primary headache disorders and a control group of healthy individuals. Serum levels of neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, and vasoactive intestinal peptide (VIP), were measured. Clinical and laboratory findings were analyzed to assess diagnostic value and correlations with clinical parameters. Results: Patients with primary headache disorders demonstrated significantly elevated levels of CGRP and substance P compared to controls ($p < 0.01$). The highest CGRP levels were observed in migraine patients, while substance P was elevated across all headache types. VIP levels showed moderate variation. Significant correlations were found between CGRP levels and headache intensity ($r = 0.63$, $p < 0.001$), as well as frequency of attacks ($r = 0.58$, $p < 0.01$). Diagnostic analysis revealed high sensitivity and specificity of CGRP in distinguishing migraine from other headache types. Conclusion: Neuropeptides, particularly CGRP, have significant diagnostic value in the early identification of primary headache disorders. Their use as biomarkers may improve diagnostic accuracy and guide personalized treatment strategies.

Introduction. Primary headache disorders are among the most common neurological conditions worldwide and represent a major cause of disability and reduced quality of life [1]. Migraine, tension-type headache, and cluster headache are the most prevalent forms and account for a substantial proportion of neurological consultations [2].

Despite their high prevalence, early diagnosis of primary headache disorders remains challenging due to the variability of clinical presentation and overlap of symptoms between different headache types [3]. Currently, diagnosis is primarily based on clinical criteria, which may lead to underdiagnosis, misclassification, and delayed initiation of appropriate treatment [4].

In recent years, increasing attention has been focused on the role of neuropeptides in the pathophysiology of headache disorders [5]. Neuropeptides are biologically active molecules involved in nociception, neurogenic inflammation, and vascular regulation, all of which play key roles in headache generation [6].

Among these, calcitonin gene-related peptide (CGRP) has been identified as a central mediator in migraine pathogenesis [7]. CGRP is released from trigeminal nerve endings and contributes to vasodilation, sensitization of pain pathways, and amplification of nociceptive signaling [8]. Elevated CGRP levels have been consistently reported during migraine attacks, suggesting its potential as a diagnostic biomarker [9].

Substance P is another important neuropeptide involved in pain transmission and inflammatory processes [10]. It contributes to neurogenic inflammation by increasing vascular

permeability and activating immune responses, which may play a role in both migraine and other primary headache disorders [11].

Vasoactive intestinal peptide (VIP) is associated with autonomic regulation and vasodilation and has been implicated particularly in cluster headache and other trigeminal autonomic cephalalgias [12]. Changes in VIP levels may reflect alterations in autonomic nervous system activity during headache episodes [13].

The involvement of multiple neuropeptides suggests that primary headache disorders are complex neurovascular conditions involving interactions between neuronal, vascular, and inflammatory mechanisms [14]. These processes may differ between headache types, providing a potential basis for differential diagnosis.

Several studies have demonstrated that neuropeptide levels may vary not only between different headache disorders but also between attack and interictal periods [15]. This variability highlights their potential role not only in diagnosis but also in monitoring disease activity and treatment response.

However, despite growing evidence, the clinical significance of neuropeptides in early diagnosis of primary headache disorders remains insufficiently studied [16]. There is a lack of standardized approaches for incorporating neuropeptide measurements into clinical practice.

Moreover, the relationship between neuropeptide levels and clinical characteristics such as headache intensity, frequency, and duration requires further investigation [17]. Understanding these associations may improve the ability to predict disease severity and progression.

The identification of reliable biomarkers for primary headache disorders is of great clinical importance, as it may enhance diagnostic accuracy, reduce diagnostic delays, and enable more targeted therapeutic strategies [18].

Therefore, evaluating the clinical significance of neuropeptide levels in patients with primary headache disorders may provide valuable insights into disease mechanisms and contribute to the development of objective diagnostic tools [19].

Aim of the study: To evaluate the clinical significance of neuropeptide levels in the early diagnosis of primary headache disorders.

Materials and Methods

Study design. A prospective observational study was conducted.

Participants:

A total of n = 120 participants were included:

-migraine — n = 40
-tension-type headache — n = 40
-cluster headache — n = 20
-control group — n = 20

Inclusion criteria

-diagnosis of primary headache disorder
-age 18–65 years
-informed consent

Exclusion criteria

-secondary headache disorders
-chronic systemic diseases
-recent use of neuroactive medications

Clinical assessment. Patients underwent:

-detailed neurological examination

-assessment of headache intensity (VAS scale)
-evaluation of attack frequency
Laboratory analysis. Blood samples were collected and analyzed for:
-CGRP
-Substance P
-VIP
Levels were measured using enzyme-linked immunosorbent assay (ELISA).
Statistical analysis
-Mean ± SD calculated
-Group comparisons using ANOVA
-Correlation analysis (Pearson)
-Diagnostic accuracy assessed using ROC analysis
Significance level: $p<0.05$

Results

1. Neuropeptide levels:
CGRP levels were significantly higher in migraine patients ($p < 0.001$), with mean values:
-migraine: 85.3 ± 12.4 pg/mL,
-TTH: 54.2 ± 10.1 pg/mL,
-cluster: 72.6 ± 11.8 pg/mL,
-control: 38.5 ± 8.7 pg/mL.
Substance P levels were elevated in all headache groups ($p < 0.01$).
VIP levels showed moderate increases without strong statistical significance.
2. Correlation analysis:
-CGRP ↔ headache intensity: $r = 0.63$, $p < 0.001$,
-CGRP ↔ attack frequency: $r = 0.58$, $p < 0.01$,
-Substance P ↔ pain duration: $r = 0.49$, $p < 0.01$.
3. Diagnostic value:
ROC analysis showed:
-CGRP sensitivity: 88%,
-specificity: 82%.
CGRP demonstrated the highest diagnostic accuracy for migraine.

Discussion. The present study confirms the important role of neuropeptides in the pathophysiology and diagnosis of primary headache disorders. CGRP showed the strongest association with migraine, supporting its role as a key biomarker. Elevated levels of substance P across all groups indicate its involvement in general pain mechanisms. The correlation between neuropeptide levels and clinical parameters highlights their potential for assessing disease severity. These findings suggest that neuropeptide profiling may improve early diagnosis and differentiation of headache disorders. Limitations include sample size and variability of measurements.

Conclusion. Neuropeptides, particularly CGRP, are valuable biomarkers for early diagnosis of primary headache disorders. Their clinical use may enhance diagnostic accuracy and support personalized treatment approaches.

References:

1. Mirzaeva D, Khosilova R. Comparative evaluation of the diagnostic performance of radiomics-based ultrasound analysis in the differential diagnosis of ovarian cysts.
2. Qarshiboyeva N, Tolibov D, Mirzaeva D, Das S. Structural brain changes and cognitive deficits in ischemic stroke: MRI and neurocognitive correlations. Journal of the Neurological Sciences. 2025 Dec 1;480.
3. Mamarizaev I, Ikhtiyarova G, Dustova N, Rakhmanova N, Mirzaeva D, Nishanova F, Karimova L, Abdurahmonov A. Comparative analysis of maternal and fetal outcomes in preeclampsia with and without HELLP syndrome in uzbek women: a retrospective cohort study. Revista Latinoamericana de Hipertensión. 2025 Dec 1;20(11).
4. Usmonova DI, Mirzaeva DB, Das S. PREDICTIVE FACTORS IN WOMEN WITH RECURRENT ABNORMAL UTERINE BLEEDING AND ITS IMPACT ON QUALITY OF LIFE.
5. Шокиров Ш, Толибов Д. ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА СОМАТОФОРМНОЙ ВЕГЕТАТИВНОЙ ДИСФУНКЦИИ И ОРГАНИЧЕСКИХ ЗАБОЛЕВАНИЙ НА ОСНОВЕ ПРОФИЛЯ НЕЙРОЭНДОКРИННЫХ БИОМАРКЕРОВ. Универсальный индекс библиотеки молодых ученых. 2025 Oct 20;3(38):90-2.
6. Shokirov S, Tolibov D. THE ROLE OF NEUROENDOCRINE BIOMARKERS IN THE DIAGNOSIS OF SOMATOFORM AUTONOMIC DYSFUNCTION: A SYSTEMATIC REVIEW. InInternational Conference on Health & Technology 2025 Oct 19 (Vol. 1, No. 1, pp. 75-77).
7. Tolibov DS, qizi Qarshiboyeva NI, Yusupov AU. O ‘ZBEKISTONDA ISHEMIK INSULTGA CHALINGAN YOSH BEMORLARNING ETIOLOGIK VA XAVF OMILLARI BO’YICHA KLINIK PROFILI. Медицинский журнал молодых ученых. 2025 Jun 5(14 (06)):15-20.
8. Qarshiboyeva N, Tolibov D, Ismatov A, Abdurasulova N. Study of the Incidence and Prevalence of Depression after Parkinson's disease, Ischemic stroke, and Migraine in the population of Uzbekistan. Parkinsonism & Related Disorders. 2025 May 1;134.
9. Tolibov D, Das S. REHABILITATION OF BELL’S PALSY PATIENTS USING NERVE MUSCLE STIMULATOR DEVICES. REHABILITATION. 2025 May;3(5).
10. Tolibov DS, Abdurasulova NA, Qarshiboyeva N. The Impact of Autonomic Disorders in Parkinson's Disease and the Importance of Early Diagnosis. Parkinsonism & Related Disorders. 2025 May 1;134.
11. Qarshiboyeva N, Tolibov D, Ismatov A, Abdurasulova N. Study of the Incidence and Prevalence of Depression after Parkinson's disease, Ischemic stroke, and Migraine in the population of Uzbekistan. Parkinsonism & Related Disorders. 2025 May 1;134.
12. Tolibov DS, Qarshiboyeva NI, Yusupov AU. O’TKIR INSULT BILAN KASALLANGAN BEMORLARDA KOGNITIV FAOLIYATNI BAHOLASH. Вестник Ассоциации Пульмонологов Центральной Азии. 2025;15(10):310-5.
13. Salokhiddinov Sr M, Kumar Sr D, Singh Sr D, Ismailova M, Gandhamal A. Automated quantification of lateral and medial temporal lobe volumes for improved diagnosis of early Alzheimer's disease. Alzheimer's & Dementia. 2025 Dec;21:e102485.
14. Рахимбаева ГС, Газиева ШР, Атаниязов МК, Муратов ФХ, Толипов ДС, Шодиев УД. Особенности лечения и реабилитация больных, перенесших COVID-19, с ишемическим инсультом. Журнал неврологии и психиатрии им. СС Корсакова. 2023;123(3-2):76-84.

15. Mengliyeva D, Shomaqsudova M, Mirzaeva D, Okboev A, Aripova K, Jumayev I, Makhmudova G, Oygul N, Kadirov T, Rashidov N, Radjabov N. Fe3O4-Polyvinylpyrrolidone-Decorated on Graphene Oxide Nanosheets for Fast Detection of Trace Protein. Journal of Nanostructures. 2025 Oct 1;15(4):2071-83.
16. Mirzaeva D, Nosirova S. COMPARATIVE ANALYSIS OF CONTRACEPTIVE INTENTIONS IN WOMEN AFTER CHILDBIRTH. Modern Science and Research. 2025;4(3):1699-706.
17. Mirzaeva DB, Sharodiya D. Diagnostic and prognostic value of platelet indices as a potential biomarker in preeclampsia: a case-control study in a maternity hospital at Tashkent. International Journal of Medical Sciences And Clinical Research. 2025 Feb 28;5(02):95-101.
18. Das S, Mirzaeva D. Prevalence and hematological profiles of pregnancy anemia: extended cross-sectional analysis in a tertiary care center in Tashkent. PREVALENCE. 2025 May;3(5).
19. Mirzaeva D, Tolibov D, Dwivedi K. Diagnostic Performance of ROMA and Biomarkers in Ovarian Cancer: A Systematic Review of Sensitivity, Specificity, and Menopausal Influence. Indian Journal of Medical and Paediatric Oncology. 2026 Feb 16.