Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2024;49(1):121-129
DOI: 10.17826/cumj.1395889

RESEARCH

Prospective analysis of optic nerve diameter and NSE values in patients with refractory headaches

Dirençli baş ağrısı olan hastalarda optik sinir çapı ve NSE değerlerinin prospektif analizi

Naciye Orçan[1], Ayça Açıkalın Akpınar[2], Gülçin Dağlıoğlu[2], Ömer Taşkın[3], Nezihat R. Dişel[2], Özge Bakışkan Tombul[4], Merve Türker[5]

[1] Şehit Kâmil State Hospital, Gaziantep, Turkey
[2] Çukurova University, Adana, Turkey
[3] Yüreğir State Hospital, Adana, Turkey
[4] Başkent University, Adana, Turkey
[5] Niğde Ömer Halisdemir Research and Training Hospital, Niğde, Turkey

Abstract

Purpose: This study aims to investigate the usability of ultrasonographic optic nerve diameter measurement and plasma neuron-specific enolase (NSE) levels in detecting secondary causes of headaches in patients with refractory headaches in emergency department.

Materials and Methods: The study was conducted in a university-based adult emergency department over 3 years. Sixty-six consecutive patients presenting to the emergency department with refractory headaches and 50 healthy volunteers for the control group were included. Information recorded included the duration of complaints, type and location of headache, symptoms, co-morbidities, results of imaging studies, optic nerve diameters, results of lactate, arterial blood gas and NSE levels.

Results: A total of 66 patients were included, comprising 33 females. The mean age was 43.05 ± 17.06 years. Secondary causes of headache were identified in 45 patients (68.2%). Evaluation of ultrasonographic optic nerve diameter revealed that 17 (25.8%) right and 21 (31.8%) left optic nerve diameters were ≥5 mm. Optic nerve diameter values were significantly higher in patients diagnosed with secondary headache compared to those with primary headache, with no statistically significant difference observed in NSE values. Lactate levels in patients with secondary headaches were significantly higher than those in patients with primary headaches.

Conclusion: In patients admitted to the emergency department with refractory headaches and normal imaging, ultrasonographic optic nerve diameter measurement may be preferred as an easily accessible

Öz

Amaç: Bu çalışmanın amacı, acil serviste dirençli baş ağrısı olan hastalarda ultrasonografik optik sinir çapı ölçümü ve plazma nöron spesifik enolaz (NSE) düzeyinin ikincil baş ağrısı nedenlerini saptamada kullanılabilirliğini araştırmaktır.

Gereç ve Yöntem: Çalışma, bir üniversite hastanesi erişkin acil servisinde, 3 yılı aşkın bir süre boyunca yürütülmüştür. Acil servise dirençli baş ağrısı ile başvuran 66 hasta ve kontrol grubu olarak 50 sağlıklı gönüllü çalışmaya dahil edilmiştir. Hastaların şikayetlerinin süresi, baş ağrısının tipi ve yeri, semptomları, eşlik eden hastalıkları, görüntüleme sonuçları, optik sinir çapları, laktat, arteriyel kan gazı ve NSE düzeyleri kaydedilmiştir.

Bulgular: Çalışmaya 33'ü kadın olmak üzere toplam 66 hasta dahil edildi. Yaş ortalaması 43.05±17.06 idi. Hastaların 45'inde (%68.2) ikincil baş ağrısı nedenleri saptandı. Ultrasonografik optik sinir çapı değerlendirildiğinde, 17 (%25.8) sağ ve 21 (%31.8) sol optik sinir çapının ≥5 mm olduğu tespit edildi. Sekonder baş ağrısı tanısı alan hastalarda sağ ve sol optik sinir çapı değerleri anlamlı olarak yüksek bulunurken, NSE değerlerinde istatistiksel olarak anlamlı bir fark bulunmadı. Sekonder baş ağrısı olan hastalarda laktat düzeyleri primer baş ağrısı olan hastalara göre istatistiksel olarak anlamlı derecede yüksekti.

Sonuç: Dirençli baş ağrısı ile acil servise başvuran ve görüntülemesi normal olan hastalarda, ultrasonografik optik sinir çapı ölçümü, ikincil nedenlerin saptanmasına rehberlik etmek için kolay erişilebilir bir yöntem olarak

Address for Correspondence: Ömer Taşkın, Emergency Service, Yüreğir State Hospital, Adana, Turkey
E-mail: omertaskinmd@gmail.com
Received: 30.11.2023 Accepted: 29.02.2024

method to guide the detection of secondary causes. NSE was not an effective in the early selection of patients with secondary headaches.
Keywords: Headache; neuron specific enolase; optic nerve diameter.

tercih edilebilir. NSE, ikincil baş ağrısı olan hastaların erken seçiminde etkili bir yöntem değildir.

Anahtar kelimeler: Baş ağrısı, nöron spesifik enolaz, optik sinir çapı.

INTRODUCTION

Headaches, affecting numerous individuals and posing potential repercussions on work and health, necessitate early detection and treatment of secondary causes for optimal intervention[1,2]Imaging methods like computerized tomography (CT) and magnetic resonance imaging (MRI) are vital for diagnosing increased intracranial pressure. However, CT has limitations in conditions such as acute stroke, pregnancy (due to radiation risks), and potential long-term malignancy risks in young patients. Although MRI offers a radiation-free alternative, its high cost and limited accessibility in emergencies pose challenges. Consequently, ultrasound (US) has become increasingly common in the emergency department (ED). Evaluation of the optic nerve with the linear probe of US is a very practical application and is used in the diagnosis of increased intracranial pressure (ICP). In cases where the optic nerve is more than 5 mm, it is known that the ICP is above 20 cm/H_2O[3]. Ultrasonographic measurement of optic nerve diameter has emerged as a non-invasive and cost-effective method for assessing increased intracranial pressure, particularly valuable in refractory headache cases[4-6].

Neuron Specific Enolase (NSE), an enzyme specific to neurons in the central nervous system (CNS), serves as an early indicator of neuronal damage when measured in blood and cerebrospinal fluid[7,8].

Despite existing literature predominantly focusing on primary and secondary headaches, there is a notable gap in studies concerning optic nerve diameter and NSE levels in refractory headache cases. Our study aims to fill this gap by exploring the potential of ultrasonographic optic nerve diameter measurement and plasma NSE levels in detecting secondary causes of refractory headaches. Especially in Turkey, due to the crowdedness of the EDs, it is often impossible to follow the patient for observation for a long time. Therefore, making a differential diagnosis of patients such as those with refractory headache, which is frequently encountered in EDs and potentially leading to mortal consequences, becomes crucial. Imaging modalities and laboratory tests are often normal in these patients. A marker that can indicate CNS pathology and non-invasive examinations are highly significant. Through this research, we seek to contribute valuable insights to the decision-making process for discharge or hospitalization in the ED management of such patients, addressing a critical aspect of headache management.

MATERIALS AND METHODS

This prospective case-control study conducted in Adult ED of Çukurova University Faculty of Medicine over a period of 3 years, following approval by the Çukurova University non-interventional clinical research ethics committee (dated: November 10, 2017 decision number: 13).

Sample

Patients over 18 years of age with refractory headaches who provided written consent for participation were included. Sixty-six consecutive patients presenting to the adult Emergency Department with refractory headaches and 50 healthy volunteers aged between 18 and 50 years for the control group were included in the study.

Patients with a history of trauma, previously diagnosed CNS disease or any conditions affecting the nervous system, individuals younger than 18 years of age, history of glaucoma, current use of medications potentially affecting cerebrospinal fluid (CSF) pressure, and patients with ocular prostheses were excluded.

Procedure

Refractory headache patients were defined as individuals who had self-treated or received medication from physicians for headache relief without success. Following the emergency treatment approach and stabilization of vital signs, detailed anamnesis, physical, and neurological examinations were conducted in all cases. Information recorded included the duration of complaints, type and location of headache, accompanying symptoms, co-morbidities, results of imaging studies, optic nerve

diameters, lactate levels, and NSE levels. NSE measurement was performed using the Roche Diagnostics Cobas E 411 system.

The researcher, a senior emergency medicine resident, who conducted the study, was qualified in both basic and advanced US techniques, holding a certificate of applicability, and possessed sufficient knowledge and experience in ocular sonography. The entire study was carried out by the same investigator, who also performed bedside USon all enrolled patients. To assess the optic nerve diameter, patients were positioned supine. A linear probe was utilized, and the optic nerve diameter was measured 3 mm posterior to the globe using the Sonosite Fujifilm US device employed in the ED.

Statistical analysis

Sample size was calculated with the G*Power Version 3.1.9.2 software. Based on the effect size in the study "Prospective analysis of single operator sonographic optic nerve sheath diameter measurement for diagnosis of elevated intracranial pressure" by Frumin et al. in 2014 [9], the sample size was calculated as 66 patients in Group 1 (Patients) and 50 patients in Group 2 (Control), for a total of 116 patients. In the study, descriptive statistical analyses such as frequency, percentage, mean, median, minimum, and maximum were used to evaluate the demographic and clinical characteristics of people presented to the ED with headache. For numerical data, student's t test was used to compare means and Mann-Whitney U test was used to compare median values. Independent Groups T-Test was used to compare NSE values between the patients and control groups. The significance level was set as $p<0.05$ for all analyses. IBM SPSS 22.0 program was used to perform the analyses.

RESULTS

A total of 66 patients with refractory headaches were included and 33 (50%) were female. The mean age of the patients was 43.05±17.06 years (range 18-82 years). Three (4.5%) of the patients were pregnant, with gestational weeks determined to be eight weeks for one pregnant woman and 38 weeks for the other two. The control group involved 50 healthy volunteers, of whom 22 (44%) were female. The mean age of the volunteers in the control group was 39.12±13.80.

Forty-seven (71.2%) of the patients reported presenting to the ED for the first time with a severe headache, while 19 (28.8%) had previously visited EDs at external centers. Twenty-eight (42.4%) patients presented to the ED with headache alone, 17 (25.8%) experienced nausea and vomiting, six (9.1%) reported dizziness, and four (6.1%) had syncope in addition to refractory headache. During ED evaluation, eight patients with refractory headache exhibited ongoing symptoms, with five patients (7.6%) displaying altered consciousness, one (1.5%) experiencing loss of limb strength, and two (3%) showing speech impairment upon repeat examinations. See Table 1.

Table 1. Number of ED presentations of patients with refractory headache and symptoms accompanying headache

Variables		**n (%)**
Number of presentations to the ED	1	47 (71.2)
	2	9 (13.6)
	3	5 (7.6)
	4	4 (6.1)
	6	1 (1.5)
Complaints	Pain only	28 (42.4)
	Headache + Vision disorders	1 (1.5)
	Headache + Nausea and vomiting	17 (25.8)
	Headache + Changes in consciousness	5 (7.6)
	Headache + Dizziness	6 (9.1)
	Headache + Fever	2 (3.0)
	Headache + Syncope	4 (6.1)
	Headache + Loss of limb strength during follow-up in the ED	1 (1.5)
	Headache + Speech disorder during follow-up in the ED	2 (3.0)

Abbreviations: ED: emergency department

Thirty-nine (59.1%) of the patients reported throbbing pain, while 27 (40.9%) experienced compressive pain. Additionally, 20 (30.3%) patients reported headache localized to the nape of the neck, 46 (69.7%) to the face, and 44 (66.7%) to the area around the eyes. After physical examination, imaging, and laboratory tests, 45 (68.8%) patients presenting to the ED with refractory headaches were diagnosed with primary headaches, while 21 (31.8%) were diagnosed with secondary headaches. Among the secondary headache diagnoses, 13 (19.7%) patients were diagnosed with tension-type headache, 11 (16.7%) with carbon monoxide (CO) poisoning, 5 (7.6%) with subarachnoid hemorrhage, and 4 (6.1%) with infection. See Table 2.

Computed tomography findings were negative in 51 (77.3%) patients, with other findings outlined in Table 2.

Table 2. Diagnosis and CT findings of the patients

Variables		**n (%)**
Diagnosis	Cluster-type headaches	2 (3.0)
	Tension-type headache	13 (19.7)
	Subarachnoid hemorrhage	5 (7.6)
	Subdural hemorrhage	3 (4.5)
	CO poisoning	11 (16.7)
	Mass	1 (1.5)
	Infection	4 (6.1)
	Sinus vein thrombosis	3 (4.5)
	Stroke, ischemia-induced	3 (4.5)
	Transient ischemic attack	1 (1.5)
	Intraparenchymal hemorrhage	3 (4.5)
	Demyelinating diseases	3 (4.5)
	Migraine	6 (9.1)
	Secondary to dialysis	2 (3.0)
	Hypertensive headache	1 (1.5)
	Pseudotumor cerebri	1 (1.5)
	Intracranial hypotension	1 (1.5)
	Subclavian artery thrombosis	1 (1.5)
	Radiculopathy	1 (1.5)
	Secondary to Wegener's	1 (1.5)
CT Findings	Subdural hematoma	3 (4.5)
	Subarachnoid hemorrhage	5 (7.6)
	Intraparenchymal hemorrhage	3 (4.5)
	Intracranial mass	1 (1.5)
	Abscess, infection	1 (1.5)
	Sinus vein thrombosis	1 (1.5)
	Arterial thrombosis	1 (1.5)
	Normal	51 (77.3)

Abbreviations: CT: computed tomography, CO: carbon monoxide

Thirty-six (54.5%) of the patients were hospitalized, 29 (43.9%) were discharged from the ED, and 1 (1.5%) patient was deceased. It was determined that 17 (25.8%) right and 21 (31.8%) left optic nerve diameters were above 5 mm. The NSE values of the patient group were statistically significantly higher ($p=0.042$) than the control group. There was no statistically significant difference between the NSE values of patients diagnosed with primary and secondary headaches ($p=0.093$); however, the right and left optic nerve diameter values of patients diagnosed with secondary headaches were significantly higher ($p<0.001$). As a result of the investigation of refractory headache, lactate levels in patients with secondary headaches were statistically significantly higher than those in patients with primary headaches ($p<0.001$). See Table 3.

Table 3. The differences between study groups and differences of parameters by headache types

Variable	Study Groups		
	Patients (n=66)	Control (n=50)	*p*
	Mean±SD	Mean±SD	
NSE (ng/L)	29.50±24.73	21.84±10.30	0.042
	Headache Type		
	Primary (n=21)	Secondary (n=45)	*p*
	Mean Med (min-max)	Mean Med (min-max)	
NSE (ng/L)	21.51 20 (6-43)	33.22 22 (6-169)	0.093
Lactate (mEq/L)	1.12 1.0 (0.7-2)	2.4 2 (0.8-7)	0.001
Right optic nerve diameter (mm)	4.09 4 (3.3-5.8)	4.8 4.8 (3.8-6.6)	0.001
Left optic nerve diameter (mm)	4.21 4.2 (2.8-6)	4.97 4.8 (3.8-6.5)	0.001

Abreviations: NSE: Neuron specific enolase, SD: standart deviation

DISCUSSION

When patients present to the ED with headaches, the primary focus is always on diagnosing secondary headaches, as these can lead to mortality and morbidity[10,11]. However, this diagnostic process is not always straightforward. The character and intensity of pain play crucial roles in diagnosing these patients. Studies have indicated that secondary headache causes are prevalent in cases with sudden onset, intense pain, high scores on visual pain scales (VPS), and headaches that do not resolve[12]. Traditionally one out of 25 patients presented to the ED with headache is traditionally diagnosed with a secondary cause[13].

Regarding etiologic factors, primary headaches are at the predominant in EDs[14-16]. Among a total of 66 patients with refractory headache in the present study, 21 (31.8%) were diagnosed with primary headache, while 45 (68.8%) were diagnosed with secondary headache. Given that the study included patients with refractory headaches, a high rate of secondary headaches was expected.

The nature of the patients' pain, experiencing pain of an unprecedented severity, high visual pain scale (VPS) scores, the rate of re-admission to the ED, and the assessment of accompanying symptoms are significant in identifying patients with a secondary etiology. In terms of the nature of pain among the patients included in the study, it was observed that 39 patients (59.1%) experienced throbbing pain, while 27 patients (40.9%) experienced compressive pain. Additionally, regarding the nature of pain in patients with positive imaging findings, it was noted that positive imaging findings were statistically significantly higher in patients experiencing throbbing pain. In a study conducted by Lynch et al.[17], it was reported that among 55 cases resulting in death, accompanying neurological symptoms, often described as red flags, included seizures in 29 patients, sudden and severe pain (thunderclap) in 28 patients, the worst headache experienced in 25 patients, confusion, agitation, or drowsiness in 18 patients, progressive visual or neurological symptoms in 18 patients, and weakness or paralysis in 12 patients. Nausea and vomiting were reported in 17 patients. Other reported signs and symptoms included meningeal irritation, accompanying systemic diseases, ataxia, and pupillary asymmetry.

In the study, nausea, and vomiting (25.8%) and dizziness (9.1%) were the most common symptoms accompanying pain. During the investigative treatment of eight patients with refractory headache in the ED it was concluded that five patients had altered consciousness, one (1.5%) experienced loss of limb strength, and two (3%) had speech impairment upon repeat examinations.

When examining the causes of death in the study by Lynch et al., it was found that 60.4% were due to vascular causes, 16.7% were attributed to primary brain tumors and cysts, and 6.25% were related to meningitis. Among vascular causes, aneurysms accounted for 22.9%, with symptoms such as loss of consciousness, occipital headache, and neck pain potentially accompanied by focal neurological deficits[17].

Other studies have highlighted that headache is a common and significant symptom of ischemic stroke, particularly among young patients. Notably, precursor headache is often a prominent finding in major ischemic events. It has been suggested that headache may hold particular importance as a symptom in infarcts with subcortical versus cortical involvement in the vertebrobasilar system and in large infarcts [18]. In our study, three patients were diagnosed with ischemic stroke, one with transient ischemic attack, one with a hypercoagulopathic condition accompanied by subclavian artery thrombosis, one with Wegener's disease, and three with dural sinus vein thrombosis. In young patients presenting with refractory headaches, investigating secondary vascular causes is crucial. Notably, we observed that three patients with dural sinus vein thrombosis were pregnant, with one at 8 weeks gestation and two at 38 weeks gestation. Therefore, dural sinus vein thrombosis should be considered as a possible diagnosis in pregnant patients presenting to the emergency department with refractory headaches.

Approximately 8% of patients presenting to the ED with thunderclap headache are diagnosed with subarachnoid hemorrahage[19]. In our study, we diagnosed subarachnoid hemorrhage in 5 (7.6%) patients, a rate consistent with findings in the literature.

Given the crowdedness of EDs, it is prudent to consider certain clinical signs and symptoms identified as "red flags" when assessing secondary headaches[10,20]. However, these indicators may sometimes be subjective, and emergency CT imaging may yield normal results even in the presence of significant underlying diseases. In the early stages of conditions such as ischemia, pseudotumor cerebri, dural sinus vein thrombosis, certain rheumatologic diseases with neurological involvement, and in pregnant patients without immediate access to MRI, other clinical conditions may result in negative examinations. Therefore, the availability of laboratory and imaging markers is crucial for facilitating patient selection. Given the inability to exclude secondary headaches with a single effective parameter, extensive laboratory and imaging studies may be necessary in the ED[21].

When reviewing the literature, it becomes evident that optic nerve diameter measurement can serve as an early diagnostic tool for increased ICP and provide initial treatment guidance. In recent years, the utility of cranial US has become increasingly recognized, particularly in pediatric patients. Additionally, optic nerve US has seen more frequent utilization in EDs as a noninvasive and readily accessible method for detecting increased ICP[22,23]. The optic nerve, being a white matter bundle of the CNS maintains a direct connection between the subarachnoid space of the optic nerve and the chiasmatic cistern of the brain[24]. This connection facilitates the free circulation of CSF between both areas. When ICP rises, CSF flows into the perineural subarachnoid space, leading to increased pressure around the optic nerve. Consequently, this results in the enlargement of the dural sheath and an increase in optic nerve sheath diameter[25,26]. In a study by Frumin et al.[9], the cutoff value of optic nerve sheath diameter was found to be >5.2 mm when invasively ICP exceeded 20 mmHg. In this value, sensitivity was 83.3% and specificity was 100%. This cutoff value exhibited a sensitivity of 83.3% and specificity of 100%. Comparison of patients with negative and positive cranial CT imaging revealed significantly higher optic nerve diameter measurements in patients with positive imaging, particularly on the ipsilateral side of the lesion[27].

Unfortunately, the diagnosis of increased intracranial pressure (ICP), particularly in conditions like pseudotumor cerebri, is often delayed. This delay stems from the challenges associated with the invasive method of ICP measurement, which can be difficult for both physicians and patients and is often applied with hesitation. In a retrospective study involving 35 patients diagnosed with pseudotumor cerebri, the CSF opening pressures of patients, initially reported as normal upon admission for severe headaches, were re-evaluated in terms of optic nerve diameter. It was found that 32 out of 35 patients exhibited increased optic nerve diameter. In most cases of pseudotumor cerebri, the enlargement of the optic nerve sheath diameter indicates elevated ICP, even when CT scans yield negative results. Therefore, measuring the diameter of the optic nerve sheath has been recognized as a diagnostic tool in suspected cases of pseudotumor cerebri, aiding in early and accurate diagnosis, preventing misdiagnosis, and ensuring appropriate initial treatment[28]. In our study, comparison of optic nerve diameters between patients with primary headaches and those with secondary headaches revealed significantly higher optic nerve diameters in patients with secondary headaches.

However, the measurement of optic nerve diameter with US requires training. While a significant laboratory test that is easy to perform in the ED could facilitate the recognition of secondary headaches and alleviate the burden on physicians by aiding in the selection of patients for further investigation, unfortunately, there is currently no effective laboratory test for the differential diagnosis of primary and secondary headaches in the ED. In the literature, experimental studies have explored various diseases directly involving the CNS but the available tests have not been routinely adopted. For instance, in a study investigating biomarkers predictive of differentiating stroke patients from stroke-like conditions, biomarkers such as eotaxin, EGFR, S100A12, TIMP-4, and prolactin were found to be significant[29]. Additionally, recent studies have suggested that NSE indicates brain cell damage, particularly in stroke patients. These studies have shown that serum NSE levels are higher in stroke patients compared to the control group and are associated with the infarct area. However, NSE levels were not associated with functional outcome and stroke severity, possibly due to differences in sampling times, as NSE levels typically peak after 24 hours. Therefore, there is a higher correlation between stroke severity and NSE level with later sampling times[29,30]. Furthermore Raabe et al. did not find a statistically significant relationship between NSE levels and contusion volume or extent of damage in patients with head trauma[31]. Other studies have reported that NSE levels were not elevated in benign primary heacaches. For example, in a study of patients with headaches, cerebrospinal fluid (CSF) and serum NSE concentrations in patients with acute benign headaches were not associated with the predicted neuronal damage[32].

In our study, when comparing the NSE values of patients diagnosed with primary and secondary headaches, no statistically significant difference was found (p=0.093), however, the right and the left optic nerve diameter values of patients diagnosed with secondary headaches were significantly higher (p<0.001). Interestingly, when comparing the healthy and patient groups in our study, we observed that the NSE values of the patient group were statistically significantly higher (p=0.042) than those of the control group. This finding suggests that patients with refractory headaches exhibit elevated NSE levels compared to healthy individuals, indicating underlying pathophysiological processes that may not be detected under current emergency conditions.

The exclusion of patients with severe neurological outcomes secondary to headaches at the time of admission was considered to be a potential reason why NSE values were not significantly higher in patients with secondary headaches compared to those with primary headaches. Our study is focused on identifying these patients at an early stage, aiming to prevent consequences such as coma and severe neurological deficits. By identifying and intervening in patients with refractory headaches early on, we hope to mitigate the risk of severe neurological outcomes and improve patient outcomes overall.

As a result of investigating refractory headaches, lactate levels (p<0.001) in patients with secondary headaches were found to be statistically significantly higher than those in patients with primary headaches. This suggests that carbon monoxide poisoning was diagnosed in 8 of the patients with refractory headaches included in our study, and it is believed that this condition led to a significant increase in lactate values due to its impact on tissue perfusion.

The study's focus on a 3rd level university hospital, characterized by a high influx of referrals from sub-institutions and patients with comorbidities, poses challenges in study group. Our center, serving as a hub for migration from rural areas, experiences an elevated incidence of CO poisoning cases, particularly during the winter months covered by the study. The study's location in a level 3 facility, situated at a distance from the city center, introduces constraints, with lower admissions from green and yellow areas compared to the red area, thereby contributing to a relatively small number of patients presenting with refractory headaches. The relatively limited number of participants in the study may present challenges in extrapolating the findings to the broader population and to primary and secondary care hospitals.

In conclusion, among patients with refractory headaches and normal imaging, ultrasonographic optic nerve diameter measurement may be preferred as an easily accessible method to guide the detection of secondary causes. Ultrasonographic optic nerve measurement in pregnant patients presenting to the ED with refractory headache, especially in pregnant patients in whom tomography may not be appropriate, may guide clinicians to differential diagnoses. However, extensive studies on this subject are needed. Although NSE values were significantly higher in patients with refractory headaches compared to the control group, it was determined

that NSE was not an effective marker in the early selection of patients with secondary headaches.

Author Contributions: Concept/Design : NO, AAA; Data acquisition: NO, ÖT, ÖBT, MT; Data analysis and interpretation: NO, AAA, GD, ÖT; Drafting manuscript: NO, AAA, ÖT; Critical revision of manuscript: AAA, ÖT, NRD; Final approval and accountability: NO, AAA, GD, ÖT, NRD, ÖBT, MT; Technical or material support: NO, AAA, GD; Supervision: AAA, GD, NRD; Securing funding (if available): n/a.
Ethical Approval: As this research is a cell culture study, ethics committee approval is not required.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: This study was supported by Çukurova University Scientific Research Projects Coordination Unit (ITU-9879).
Acknowledgements: This study was supported by Çukurova University Scientific Research Projects Coordination Unit (ITU-9879).
Presentations: Some of our findings were presented in the 8th Eurasian Congress on Emergency Medicine Congress as an oral presentation with the title "Prospective Analysis of Optic Nerve Diameter and NSE Values in Patients with Refractory Headaches", in Antalya, Turkey.

REFERENCES

1. Nye BL, Ward TN. Clinic and emergency room evaluation and testing of headache. Headache. 2015;55:1301-8.
2. Robbins MS. Diagnosis and management of headache: a review. JAMA. 2021;325:1874-85.
3. Dubourg J, Javouhey E, Geeraerts T, Messerer M, Kassai B. Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. Intensive Care Med. 2011;37:1059-68.
4. Hassen GW, Bruck I, Donahue J, Mason B, Sweeney B, Saab W, et al. Accuracy of optic nerve sheath diameter measurement by emergency physicians using bedside ultrasound. J Emerg Med. 2015;48:450-7.
5. Kimberly HH, Noble VE. Using MRI of the optic nerve sheath to detect elevated intracranial pressure. Crit Care. 2008;12:181-2.
6. Komut E, Kozacı N, Sönmez BM, Yılmaz F, Komut S, Yıldırım ZN et al. Bedside sonographic measurement of optic nerve sheath diameter as a predictor of intracranial pressure in ED. Am J Emerg Med. 2016;34:963-7.
7. Marangos PJ, Schmechel DE. Neuron specific enolase, a clinically useful marker for neurons and neuroendocrine cells. Annu Rev Neurosci. 1987;10:269-95.
8. Takmaz İ. Ağır kafa travmalarında serumda protein S100B ve Nöron Spesifik Enolaz'ın prognostik değeri (Uzmanlık tezi). Diyarbakır, Dicle Üniversitesi, 2015.
9. Frumin E, Schlang J, Wiechmann W, Hata S, Rosen S, Anderson C et al. Prospective analysis of single operator sonographic optic nerve sheath diameter measurement for diagnosis of elevated intracranial pressure. West J Emerg Med. 2014;15:217-7.
10. Tintinalli J. Tintinalli's Emergency Medicine : A Comprehensive Study Guide (8th Ed.). 2016.
11. Wolf SJ, Byyny R, Carpenter CR, Diercks DB, Gemme SR, Gerardo SJ et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute aeadache. Ann emerg med. 2019/10// 2019;74:e41-e74.
12. Saper JR, Hamel RL, Lake AE. Medication overuse headache (MOH) is a biobehavioural disorder. Cephalalgia. 2005;25:545-46.
13. Walling A. Headache: Headache emergencies. FP Essent. 2018;473:21-5.
14. Benseñor IM, Lotufo PA, Goulart AC, Menezes PR, Scazufca M. The prevalence of headache among elderly in a low-income area of São Paulo, Brazil. Cephalalgia. 2008;28:329-33.
15. Kaniecki RG, Levin AD. Headache in the elderly. Handb Clin Neurol. 2019;167:511-28.
16. Tai ML, Jivanadham JS, Tan CT, Sharma VK. Primary headache in the elderly in South-East Asia. J Headache Pain. 2012;13:291-7.
17. Lynch KM, Brett F. Headaches that kill: a retrospective study of incidence, etiology and clinical features in cases of sudden death. Cephalalgia. 2012;32:972-8.
18. Oliveira FAA, Sampaio Rocha-Filho PA. Headaches attributed to ischemic stroke and transient ischemic attack. Headache. 2019;59:469-76.
19. Edlow JA, Fisher J. Diagnosis of subarachnoid hemorrhage: time to change the guidelines? Stroke. 2012;43:2031-2.
20. Uggetti C, Khouri Chalouhi K, Squarza S, Frediani F, Cariati M. Headache in the emergency department: the role of imaging. Neurol Sci. 2018;39:151-2.
21. Damiani D, Damiani D, Morumbi A, Doutor R, Lima A. Non-invasive intracranial pressure evaluation in an emergency room – point-of-care ultrasonography. Arquivos Brasileiros de Neurocirurgia: Brazilian Neurosurgery. 2019;38:279-83.
22. Blaivas M, Theodoro D, Sierzenski PR. Elevated intracranial pressure detected by bedside emergency ultrasonography of the optic nerve sheath. Acad Emerg Med. 2003;10:376-81.
23. Jang T, Aubin C. The use of serial ocular ultrasonography in the care of patients with head injury. Ann Emerg Med. 2005;45:336-7.
24. Wood JH. Physiology, pharmacology, and dynamics of cerebrospinal fluid. In Neurobiology of Cerebrospinal Fluid 1 (Ed JH Wood):1-16..Springer, Boston, MA. 1980.
25. Liu D, Kahn M. Measurement and relationship of subarachnoid pressure of the optic nerve to intracranial pressures in fresh cadavers. Am J Ophthalmol. 1993;116:548-56.
26. Ueno T, Ballard RE, Macias BR, Yost WT, Hargens AR. Cranial diameter pulsations measured by non-invasive ultrasound decrease with tilt. Aviat Space Environ Med. 2003;74:882-5.

27. Canakci Y, Koksal O, Durak VA. The value of bedside ocular ultrasound assessment of optic nerve sheath diameter in the detection of increased intracranial pressure in patients presenting to the emergency room with headache. Niger J Clin Pract. 2018;21:778-82.
28. Bekerman I, Sigal T, Kimiagar I, Almer ZE, Vaiman M. Diagnostic value of the optic nerve sheath diameter in pseudotumor cerebri. J Clin Neurosci. 2016;30:106-9.
29. Sharma R, Macy S, Richardson K, Lokhnygina Y, Laskowitz DT. A blood-based biomarker panel to detect acute stroke. J Stroke Cerebrovasc Dis. 2014;23:910-8.
30. Abbas A, Aukrust P, Dahl TB, Bjerkeli V, Sagen EB, Michelsen A et al. High levels of S100A12 are associated with recent plaque symptomatology in patients with carotid atherosclerosis. Stroke. 2012;43:1347-53.
31. Raabe A, Grolms C, Keller M, Döhnert J, Sorge O, Seifert V. Correlation of computed tomography findings and serum brain damage markers following severe head injury. Acta Neurochir (Wien). 1998;140:787-91.
32. Casmiro M, Scarpa E, Cortelli P, Vignatelli L. Cerebrospinal fluid and serum neuron-specific enolase in acute benign headache. Cephalalgia. 2008;28:506-9.