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Factors Affecting Serum S100b and Neuron Specific Enolase Levels in Cases of Chronic Migraine

Kronik Migrenli Olgularda Serum S100B ve Nöron Spesifik Enolaz Düzeylerine Etki Edan Faktörler

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Abstract

Objective: This study aimed to investigate whether there were increases in NSE and S100B levels, which indicate cellular damage in the brain in patients with chronic migraine, and if there were increases, whether there was a change in NSE and S100B levels compared to baseline along with clinical improvement after treatment.

Material and Methods: Thirty individuals diagnosed with chronic migraine who presented to the Neurology Clinic of Fırat university Hospital were included in the patient group, and 20 healthy volunteers were included in the control group. Patients with chronic migraine received a 3-month treatment with amitriptyline at a dose of 75 mg/day. Serum NSE and S100B levels were measured in the patient and control groups at the beginning of the study. Serum NSE and S100B levels were measured again in the patient group after 3 months of amitriptyline treatment.

Results: In this study, no statistically significant difference was found in S100B and NSE levels between the control group and the chronic migraine patient group. No statistically significant difference was observed in serum S100B and NSE levels before and after treatment in the chronic migraine patient group. However, correlation analysis revealed a weak, positive, and non-significant correlation between S100B and NSE levels before treatment. After treatment, this relationship became moderately positive and statistically significant.

Conclusion: Based on the results of this study, monitoring S100B and NSE, believed to be markers of neuronal damage, may be useful in monitoring the effectiveness of treatment in chronic migraine patients, unlike in healthy individuals.

Keywords: Chronic Migraine, Neuron Specific Enolase, S100B, treatment response

Öz

Amaç: Bu çalışmada kronik migreni olan hastalarda beyinde hücresel hasarı gösteren NSE ve S100B düzeylerinde artış olup olmadığı, artış var ise tedavi sonrası klinik iyileşme ile birlikte NSE ve S100B düzeylerinde başlangıca göre değişiklik olup olmadığını araştırmak amaçlanmıştır.

Gereç ve Yöntem: Fırat Üniversitesi Hastanesi Nöroloji Kliniği'ne başvuran kronik migren tanılı 30 kişi hasta grubuna ve 20 sağlıklı gönüllü kontrol grubuna dahil edildi. Kronik migreni olan hastalar amitriptilin 75 mg/gün dozunda 3 aylık tedavi aldı. Hasta ve kontrol gruplarında çalışma başlangıcında serum NSE ve S100 B düzeyleri ölçüldü. Hasta grubunda 3 aylık amitriptilin tedavisi sonrası tekrar serum NSE ve S100 B düzeyleri ölçüldü.

Bulgular: Bu çalışmada kontrol grubu ile kronik migren hasta grubu arasında S100B ve NSE düzeylerinde istatistiksel olarak anlamlı bir fark bulunmamıştır. Kronik migren hasta grubunda tedavi öncesi ve sonrası serum S100B ve NSE düzeylerinde istatistiksel olarak anlamlı bir fark gözlenmemiştir (tümü $p > 0,05$). Ancak korelasyon analizi, tedavi öncesinde S100B ve NSE düzeylerinin zayıf, pozitif, anlamsız bir korelasyon gösterdiğini ortaya koymuştur (Spearman'ın $\rho = 0,302$, $p = 0,104$). Tedaviden sonra bu ilişki orta derecede pozitif ve istatistiksel olarak anlamlı hale gelmiştir (Spearman'ın $\rho = 0,511$, $p = 0,004$).

Sonuç: Bu çalışmanın sonuçlarına göre nöronal hasar belirteçleri olduğuna inanılan S100B ve NSE'nin izlenmesinin, sağlıklı bireylerden farklı olarak kronik migren hastalarında tedavinin etkinliğini izlemede faydalı olabileceği düşünülmüştür.

Anahtar kelimeler: Kronik Migren, Nöron Spesifik Enolaz, S100B, tedavi yanıtı.

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Introduction

Migraine is a multifactorial neurovascular syndrome characterized by headaches which are at the front and other symptoms accompanied that develops in persons with a hereditary predisposition and is influenced by several triggering factors (1).

As to the diagnostic criteria established by the International Headache Society (IHS), chronic migraine is a specific form of headache characterized by the occurrence of headaches on 15 or more days per month for a duration of over 3 months. Additionally, these headaches must match the diagnostic criteria for migraine, manifesting on at least 8 days per month (2). Chronic migraine has significant impacts on the quality of life, including severe restrictions in daily activities, frequent absences from school and work, and substantial expenses for treatment (3).

S100 calcium-binding protein B (S100B) is a protein that forms a coiled-coil structure and has a domain that binds to calcium. This protein is linked to increased production of NF-kB, which leads to the cell survival, proliferation, and gene up-regulation. This process is related with several neurological disorders through the activation of the MAPK pathway. The S100B protein is plays a crucial role in Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia, and epilepsy. This is because the increased production of this protein directly initiates neuroinflammation that specifically affects astrocytes. S100B induces toxicity when subjected to stress via its receptor binding to advanced glycation end products (AGE). S100B also contributes to neuroprotective processes by minimizing microgliosis and suppressing the production of tumor necrosis factor (TNF-alpha). Elevated S100B levels are valuable for assessing the release of inflammatory markers, nitric oxide, and neuronal death caused by excitotoxicity (4).

Neuron specific enolase (NSE) is the predominant enolase isoenzyme and is a 78 kD gamma-homodimer. It is expressed primarily by neurons and neuroendocrine cells. The NSE measurement is commonly employed to evaluate the degree of neurological tissue injury. Neurons produce significant amounts of NSE into the bloodstream during neurological disorders or traumas, making NSE levels a useful signal for evaluating neurological damage. For instance, high levels of NSE are commonly seen in neurological disorders such traumatic brain damage, hypoxic-ischemic brain injury, brain tumor, cerebral infarction, cerebral hemorrhage, epilepsy, and ischemia/reperfusion brain injury after cardiac arrest (5).

This study aims to assess cellular damage in the brain of chronic migraine patients by analyzing serum NSE levels, which indicate neuronal damage, and serum S100B levels, which indicate glial damage. The study also investigates whether the extent of cellular damage is influenced by factors such as age, gender, family history of the disease, duration of the disease, its relationship with treatment, and the patient's clinical recovery after treatment.

Materials and Methods

The study comprised a patient group consisting of 30 individuals, both male and female, over the age of 18, who were diagnosed with chronic migraine, without any co-morbid disease and who applied to the Neurology Clinic and headache outpatient clinic at a medical school hospital between October 2015 and May 2016. Approval for the research was received from Non-Interventional Research Ethics Committee. Informed consent forms were obtained from all volunteers participating in the study. The control group consisted of 20 healthy volunteers, both male and female, who were over 18 years old and had no pre-existing medical conditions. Consent forms were acquired from individuals who were part of both the patient and control groups.

The study's inclusion criteria for the chronic migraine group were as follows:

- Individuals who are at least 18 years old and are male or female
- Having been diagnosed with chronic migraine based on the criteria established by the IHS

- Not having undergone any preventive treatment in the past three months
- No history of symptomatic drug abuse headache
- No presence of any other systemic or metabolic disease apart from chronic migraine

The control group will consist of persons who meet the following criteria:

- Both males and females who are older than 18 years
- No history of primary or secondary headache as per the IHS criteria
- No current or past diagnosis of a systemic or neurological disease.

Individuals with systemic diseases (diabetes, liver, kidney diseases), neurological disorders (epilepsy, stroke, etc.), psychiatric disorders (major depression, bipolar disorder), history of head trauma, active infections, malignancy, or any other conditions that might influence S100B and NSE levels were excluded from the study. Additionally, individuals with regular medication use were not included.

A comprehensive medical history was obtained for all patients. Both the curriculum vitae and family history information were documented. The patients had neurological exams. A comprehensive medical history was obtained from the chronic migraine patients and/or their relatives who participated in the study. This included information about their family history, habits, type of migraine headache, duration, frequency, location, presence of aura, and current and past medications used.

In order to treat chronic migraine in patients, amitriptyline, a tricyclic antidepressant, was initiated at a daily dose of 25 mg for patients with chronic migraine. The dosage was then escalated by 25 mg per week until it reached a daily level of 75 mg. Patients had a 3-month treatment period with a daily dosage of 75 mg.

All the analgesics they were using were terminated. Patients were permitted to use nonsteroidal anti-inflammatory medications or triptans, no more frequently than once per week, if required.

At the start of the study, venous blood samples were collected from individuals in both the patient and control groups to assess the levels of serum NSE and S100B. Serum samples were collected from all patients during the **interictal (attack-free)** period, when they were not experiencing headaches. After 3 months of chronic migraine medication, venous blood was collected from the patient group to assess the levels of serum NSE and S100B.

An investigation was conducted into the correlation between serum aS100B and NSE levels and age, family history of the disease, disease duration, and treatment for the patients.

In the investigation, a 5 ml sample of blood was collected from the cubital vein. Following centrifugation of the venous blood samples at 2000 rpm, the serum samples were kept at a temperature of -80ºC until the day of the research. The levels of serum human NSE (YH Biosearch Laboratory, Catalogue no: YHB2142Hu, Shanghai, China) and serum human S100B (YH Biosearch Laboratory, Catalogue no: YHB3336Hu, Shanghai, China) were measured using the ELISA (Enzyme-linked immunosorbent assay) method in accordance with the instructions provided in the commercial kits. The measured values were reported in ng/mL for NSE and ng/L for S100B. For both parameters, intra-Assay: CV was <10, inter-assay: CV<12.

According to the manufacturer's specifications, the measurement ranges for the ELISA kits used were as follows: S100B: 0.05 ng/mL - 10 ng/mL, NSE: 0.2 ng/mL - 25 ng/mL.

All analyses were performed strictly according to the manufacturer's recommended protocol ((YH Biosearch Laboratory, Catalogue no: YHB2142Hu, Shanghai, China, YH Biosearch Laboratory, Catalogue no: YHB3336Hu, Shanghai, China).

Statistical Analysis

The data was analyzed using the SPSS 21.0 package, which is a statistical analysis programme. Following the completion of normality and homogeneity tests, it was determined that our parameters were into the non-parametric category. Consequently, the Mann

Whitney-U test was employed to compare across groups, the Wilcoxon test was utilized for before-after comparisons within groups, and Spearman's correlation test was utilized to examine correlations.

The Mann-Whitney U test is a non-parametric statistical test used to assess whether there is a significant difference between the medians of two independent groups. It is especially preferred when the data do not follow a normal distribution or when the sample size is small. The test works based on ranking the data; all observations from both groups are ranked together, and each observation is assigned a rank. The U statistic is then calculated based on these ranks. The Mann-Whitney U test is often considered a non-parametric alternative to the independent samples t-test and is suitable for ordinal data or continuous data that are not normally distributed. The resulting p-value is used to determine whether there is a statistically significant difference between the groups. The Wilcoxon test is a non-parametric statistical test used to evaluate differences between **two related (paired) groups.** It serves as an alternative to the **paired samples t-test** when the assumption of normality is not met. The test works by analyzing the signs (positive or negative) and magnitudes of the differences between paired observations. First, the differences between each pair are calculated, the absolute values of these differences are ranked, and then the ranks are given positive or negative signs based on the direction of the difference. The sums of the positive and negative ranks are then compared. The Wilcoxon signed-rank test is commonly used in situations such as **pre-test and post-test designs** or when measurements are taken on the **same individuals under two different conditions or at two different times.** The test result indicates whether there is a statistically significant difference between the two related groups. Spearman's correlation test is a non-parametric measure used to assess the strength and direction of the **monotonic relationship** between two variables. Unlike Pearson's correlation, it does not assume that the data are normally distributed or that the relationship is linear. Instead, it evaluates how well the relationship between the two variables can be described by a consistent increase or decrease. Spearman's correlation works by ranking the data for each variable and then calculating the correlation between these ranks. The resulting correlation coefficient, called **Spearman's rho (ρ)**, ranges from -1 to +1. A value close to +1 indicates a strong positive association, a value close to -1 indicates a strong negative association, and a value around 0 suggests no meaningful relationship between the variables. This test is especially useful when dealing with ordinal data or when the assumptions of parametric correlation methods are violated. The data are shown as the median value, (min-max). $p<0.05$ was considered significant.

Results

Out of the total number of patients, 28 were female and 2 were male. The control group included of 12 females and 8 males. The average age of the patients was 34.2 ± 6.5 years, whereas the average age of the control group was 32.4 ± 6.6 years. There was no statistically significant difference in gender and age averages between the patient and control groups ($p>0.05$). The individuals did not have any history of chronic disease other from migraine. Demographic and clinical findings of the groups are given in Table 1.

Table 1. Demographic and Clinical Data of the Study Population

Group	**Number (n)**	**Age (Mean ± SD)**	**Sex (Female/Male)**	**Presence of Aura**	**Family History of Migraine**
Chronic Migraine Patients	30	34.2 ± 6.5	28 / 2	4 with aura / 26 without aura	Evaluated
Control Group	20	32.4 ± 6.6	12 / 8	None	None

All 30 patients with chronic migraines included in the study had undergone one or more preventative treatments at certain times during their illness. Patients who met the inclusion criteria for this study were those who did not excessively utilize medicine and did not receive prophylaxis in the past 3 months. Brain magnetic resonance (MR) imaging revealed ischemic gliotic foci in 18 out of 30 individuals diagnosed with chronic migraine. The brain MRI of the remaining 12 chronic migraine patients showed no abnormalities. Out of a total of 30 patients, 4 exhibited the symptoms necessary to be diagnosed as migraine with aura, while the other patients did not have aura. The control group, comprised of healthy volunteers, had no prior record of medication usage or other medical conditions.

Evaluation of serum S100B and NSE levels of patient and control groups before treatment

A comparison was made between the serum S100B and NSE concentrations of the patient and control groups before treatment. There was no statistically significant difference between the two groups (Table 2; $p>0.05$).

Table 2. Serum S100B and NSE levels of patients and control groups before treatment

Groups	**Before Treatment; S100B (pg/L) Med (min-max)**	**Before Treatment; NSE (ng/ml) Median(min-max)**
Control	3417,02 (347,00-6318,30)	9, 5420 (1,60-25,00)
Patient	760,45 (403,71-2746,06)	5, 4545 (1,88-12,70)
p value	0>0,05	0>0,05

Data are expressed as Median (min-max) (Mann Whitney -U test).

Evaluation of serum S100B and NSE levels of the patient group before and after treatment

There was no significant difference between the patients' serum NSE and S100B levels when compared before and after treatment. (Table 3; p>0.05).

Table 3. Serum S100B and NSE levels of patients before and after treatment

Groups	**S1000B (ng/L)** **Med (min-max)**	**NSE (ng/ml)** **Med (min-max)**
Before Treatment	760,4590 (403,71-2746,06	5,4545(1,60-25,00)
After Treatment	710,6085 (178,32-6318,30)	5,8095 (1,61-34,67)
p value	p>0.05	p>0.05

Data are expressed as Med(min-max) (Wilcoxon test)

Evaluation of serum S100B and NSE levels of patients before and after treatment according to family history of migraine

Comparing the serum S100B and NSE levels of patients before and after treatment based on familial migraine history revealed no statistically significant difference between the two groups (Table 4, p>0.05).

Table 4. Serum S100B and NSE levels of patients before and after treatment according to family history of migraine

Family History of the Migraine,	**Before Treatment**		**After Treatment**	
	S100B(ng/L) Med (Min-Max)	**NSE (ng/ml) Med (Min-Max)**	**S100B(ng/L) Med (Min-Max)**	**NSE (ng/ml) Med (Min-Max)**
Not available	660,8305 (403.71-2171. 86)	5,4545 (1.88-12.709	711,7790 (471.61-6318.30)	5,8095 (2.90-34.67)
Available	904.7955 (535.56-2746.06)	5.7630 (3.76-11.15)	677.0180 (178.32-2047.06)	5. 4675 (1.61-12,81)
p value	**p>0.05**	**p>0.05**	**p>0.05**	**p>0.05**

Data are expressed as Med(min-max) (Mann Whitney U-test) FHM: Family history of migraine.

Evaluation of serum S100B and NSE levels of the patient group before treatment in terms of correlation

When the serum S100B and NSE levels of the patient group before treatment were evaluated in terms of correlation, there was no statistically significant difference between S100B and NSE levels (Table 5).

Table 5. Correlation of serum S100B and NSE levels of the patient group before treatment

			Correlation	
			Before	**Before**
	Patient		**S100B**	**NSE**
Spearman's rho	**S100B**	**r**	1.000	302**
		p		.104
		n	30	30
	NSE	**r**	,302**	1,000*
		P	.104	
		N	30	30

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

Evaluation of serum S100B and NSE levels of the patient group after treatment in terms of correlation

The correlation analysis revealed that, prior to treatment, S100B and NSE levels showed a weak positive, non-significant correlation (Spearman's ρ = 0.302, $p = 0.104$). After treatment, this relationship became moderately positive and statistically significant (Spearman's ρ = 0.511, $p = 0.004$), indicating a strengthened association between the two biomarkers following treatment. (Table 6).

Table 6. Correlation of serum S100B and NSE levels of the patient group after treatment

			Correlation	
	Patient Group		**After Treatment**	**After Treatment**
			S100B	**NSE**
Spearman's rho	**S100B**	r	1,000	,511**
		p		,004
		N	30	30
	NSE	r	,511**	1.000
		p	,004	
		N	30	30

** Correlation is significant at the 0.01 level (2-tailed)

Evaluation of serum S100B and NSE levels of the control group in terms of correlation

When serum S100B and NSE levels of the control group were evaluated in terms of correlation, there was no significant correlation between S100B and NSE levels (Table 7).

Table 7. Correlation of serum S100B and NSE levels of the control group

			Correlation	
	Control		**S100B**	**NSE**
Spearman's rho	S100B	R	1.000	.051
		P		.831
		N	20	20
	NSE	R	.051	1.000
		P	.831	
		N	20	20

Evaluation of serum S100B and NSE levels of patients according to age before treatment

When the serum S100B and NSE levels of patients aged <30 years were compared with the patient group aged ≥30 years before treatment, there was no significant difference between the two groups (Table 8, p>0.05).

Table 8. Serum S100B and NSE levels of patients according to age before treatment

Patient Group (n=30)	**Before Treatment**	**Before Treatment**
	S100B (ng/L)	**NSE (ng/ml)**
<30 years	1008.345±546.090	4.444±5.270
>30 years	881.532±529.092	2.857±4.629
p value	p>0,05	p>0,05

Evaluation of serum S100B and NSE levels of patients according to age after treatment

When serum S100B and NSE levels of patients aged <30 years were compared with the patient group aged ≥30 years after treatment, there was no significant difference between the two groups (Table 9, p>0.05).

Table 9. Serum S100B and NSE levels of patients according to age after treatment

	Patient Group (n=30)	
	After Treatment S100B (ng/L)	**After Treatment NSE (ng/ml)**
<30 years	797.3828±445.084	5f2253±l, 84181
>30 years	1348.2969±1708.345	7, 6748± 6, 83406
p value	p>0,05	p>0,05

Evaluation of serum S100B and NSE levels of the control group according to age

When the serum S100B and NSE levels of healthy volunteers aged <30 years in the control group were compared with the healthy volunteers aged ≥30 years, there was no significant difference between the two groups (Table 10, p>0.05).

Table 10. Serum S100B and NSE levels of the control group according to age

	Control Group (n=20)	
	S100B (ng /L)	**NSE (ng/ml)**
<30 years	1008.3453±546, 09027	4, 444 ±5, 2705
>30 years	881,5325*529,09216	2, 857 ±4, 6291
p value	p>0,05	p>0,05

Discussion

The purpose of this study was to determine whether serum NSE and S100B levels, which indicate cellular damage in the brain, increase in patients with chronic migraine, and if so, whether there is a correlation between clinical improvement after treatment and changes in NSE and S100B levels relative to their baseline levels.

According to the results of this study, no statistically significant changes were observed in serum S100B and NSE concentrations between pre- and post-treatment periods in chronic migraine patients (all $p > 0.05$). Although absolute levels did not change significantly, the correlation between S100B and NSE increased from a weak and non-significant level before treatment (Spearman's $\rho = 0.302$, $p = 0.104$) to a moderate and statistically significant level after treatment (Spearman's $\rho = 0.511$, $p = 0.004$). Additionally there was no correlation identified between the levels of S100B and NSE in the control group.

Recent studies have examined the levels of serum NSE, a sensitive marker for neuronal damage, and serum S100B, an indicator of glial cell damage, to determine if cellular damage occurs in the brain during the headache and interictal periods in migraine patients. In these investigations, conflicting findings were observed (6-9).

Recently, there has been a growing interest in using brain biomarkers in therapeutic applications (10,11). NSE, an enzyme dimer involved in brain glucose metabolism, and S100B, a dimeric intracellular

calcium-binding protein, are widely studied as indicators of central nervous system (CNS) involvement. These markers continue to be popular in current studies (12-15). Thus far, many studies examining the levels of serum S100B and NSE in patients with migraines have shown conflicting results (6-9).

This study conducted a pre- and post-treatment evaluation of patients with chronic migraine, in contrast to previous studies, and compared them with a control group. The study found no significant difference in serum S100B and NSE levels between the control group and chronic migraine cases, both before and after treatment.

A comparative analysis was conducted by Teepker et al. to assess the S100B and NSE levels in 21 individuals with migraines and 21 healthy volunteers. An increase in S100B levels was detected during migraine attacks, and the highest values were found during the 2–4-day pain-free period following the attack. Serum NSE levels decreased slightly both during and after the attack. Researchers interpreted the study's findings as demonstrating that there is long-term disruption of the blood-brain barrier during and after migraine attacks, and that the drop in serum NSE concentrations excludes neuronal cell death. Teepker et al. emphasized the need for more investigations to assess the relevance of S100B and NSE and their appropriateness as potential diagnostic markers in migraine (8).

In a 2020 study by Yilmaz et al., it was proposed that elevated ictal serum S100B and NSE levels, as well as high interictal S100B levels compared with controls, may be related with glial and/or neuronal brain damage of migraine and long-term disruption of the blood-brain barrier. They indicated that higher interictal serum S100B levels in migraine patients might imply an insidious and gradual damaging process (16).

The study conducted by Gönen et al. in 2021 examined individuals with episodic migraine, chronic migraine, and healthy controls. The researchers discovered that levels of serum NSE and S100B were notably higher in both the episodic and chronic migraine groups compared to the control group. Furthermore, within the migraine groups, the increase in levels was greater in the chronic migraine group than in the episodic migraine group. According to their research, the impacts on neurons and glial cells persisted both during the duration of pain attacks and in periods without attacks (17).

Chu et al. conducted a meta-analysis in 2022, including 9 case-control studies. They reported that S100B levels were elevated in patients with migraines compared to controls. The researchers highlighted the importance of investigating S100B as a potential target for migraine treatment (18).

Nevertheless, several researchers have discovered that the specificity of S100B levels, which indicate central nervous system (CNS) damage, is restricted due to the fact that extracranial injuries can also result in increased levels even in the absence of brain damage. In order to prevent this issue, it was suggested that assessing serial S100B levels in conjunction with other biomarkers and accurately documenting peripheral damage would be beneficial (19).

The study done by Derwall et al. in Germany in 2009 investigated the impact of moderate therapeutic hypothermia on S100B levels in individuals who experienced cardiac arrest outside the hospital and were successfully resuscitated. The study determined that while the early predictive value of S100B was satisfactory, it was inadequate in the later phase (20).

In the 2020 study conducted by Riesco et al., a total of 43 participants with chronic migraine, 19 with episodic migraine, 22 with cluster headache, and 29 healthy volunteers were included. The study found that there was no apparent increase in serum S100B levels during the interictal stage in patients with chronic migraine. The researchers said in this study that S100B levels are not a valuable peripheral biomarker in chronic migraine (21). The study conducted by Çelikbilek et al. Research was done with 49 individuals who suffer from migraines, and it was shown that the levels of serum S100B in these individuals were significantly lower compared to the control group. Researchers emphasized the need for

more study to identify the significance of S100B in the clinical assessment of migraine (9).

Furthermore, while NSE is widely accepted as an important molecule for directly assessing neuronal damage, it has been shown to also be involved in the process of neuron repair. Research has demonstrated that NSE plays a crucial role in regulating the survival, differentiation, and regeneration of neurons by activating the PI3K/Akt and MAPK/ERK signaling pathways (22-24). Given the dual involvement of NSE in injury and repair mechanisms, it is possible to account for the incongruous findings observed in studies pertaining to migraine patients thus far.

It should be noted that both S100B and NSE may originate from peripheral sources such as muscle, endothelium, and erythrocytes. In primary headache disorders like migraine, whether these biomarkers fully reflect neuronal damage remains controversial. Nevertheless, increases in S100B and NSE levels are widely considered in the literature as indirect indicators of neuronal-glial response rather than definitive evidence of neuronal injury. Given that measurements were performed during the interictal period, these values cannot be expected to represent brain damage with absolute certainty (25-27).

We conducted research to assess the relationship between a family history of migraine and the levels of S100B and NSE in patients with chronic migraine. However, we didn't observe any significant difference. In addition, the levels of S100B and NSE were assessed based on age (<30 years vs. ≥30 years) in migraine patients before and after treatment. There was no significant difference between the two groups.

Our study found no statistically significant difference in S100B and NSE levels between the control group and the chronic migraine patient group and no statistically significant difference in S100B and NSE levels in control group between before and after treatment. Interestingly, although absolute levels did not change significantly, the correlation between S100B and NSE increased from a weak and non-significant level before treatment to a moderate and statistically significant level after treatment in the chronic migraine patient group. This suggests that treatment may have influenced the interplay between astrocytic activity (reflected by S100B) and neuronal integrity (reflected by NSE), potentially leading to more synchronized biomarker fluctuations. A strengthened association between these markers could indicate that neuro-glial responses become more aligned after clinical stabilization, even in the absence of marked changes in their absolute serum levels. No correlation was seen between S100B and NSE levels in the group of healthy volunteers. Therefore, while there is no significant difference in S100B and NSE levels between the group of patients with chronic migraines and the group of healthy individuals, it has been discovered that tracking S100B and NSE, which are believed to be markers for neuronal damage, could be beneficial in monitoring the effectiveness of treatment in chronic migraine patients, unlike in healthy individuals. Additionally, this may suggest that, unlike healthy individuals, patients with chronic migraine experience a complex neuroglial effect.

Nevertheless, the inconsistent findings in various studies indicate that further research is necessary to establish the use of serum S100B and NSE levels as reliable indicators of neuronal damage for diagnosing chronic migraine and assessing the effectiveness of treatment.

This study is limited by its small sample size and the lack of evaluation of ictal or interictal periods. Additionally, subgroup analyses based on family history and the presence or absence of aura are among the limitations of the study. One notable characteristic of this study is that it employed S100B and NSE levels to assess treatment response (both before and after treatment) for the first time.

Conclusion; based on this study, it was concluded that while serum NSE and S100B levels are not a definitive diagnostic biomarker for chronic migraine, they can be valuable in assessing the effectiveness of treatment in chronic migraine patients, as opposed to healthy individuals. The findings of this study can be used as a preliminary investigation for future studies with bigger sample sizes that will examine the effectiveness of serum NSE and S100B levels as

biomarkers in monitoring the response to therapy in individuals with chronic migraines.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical Approval: Ethical approval for this study was obtained from the Fırat University Non-Interventional Research Ethics Committee, based on decision number 02 of its meeting number 03, dated February 10, 2015.

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