ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2023.88709
Nam Kem Med J 2023;11(1):22-26

Evaluation of Serum TSH and Free T4 Levels in Migraine Patients

Migren Hastalarında Serum TSH ve Serbest T4 Düzeylerinin Değerlendirilmesi

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ABSTRACT

Aim: Migraine is a common neurovascular inflammatory disease that causes disability and is characterized by recurrent headache attacks. The role of thyroid regulation in migraine is poorly understood, and data are conflicting. The aim of this study is to evaluate the association of thyroid hormone levels and migraine types and headache severity.

Materials and Methods: One hundred-fifty migraine patients enrolled in this retrospective study. Demographic and clinical characteristics of the patients, migraine subtypes, frequency and severity, serum thyrothytropine (TSH), and free thyroxin levels were evaluated from records. The Migraine Disability Assessment Questionnaire (MIDAS) and Visual Analog Scale (VAS) were used to assess the severity of migraine. Data analysis was performed.

Results: The mean age was 40.40±10.84 years, and the female to male ratio was 5.1: 1. No significant relationship was found between thyroid hormone levels and headache characteristics of migraine patients and migraine severity (p>0.05). There was no significant relationship between VAS and MIDAS values and TSH levels (p=0.973).

Conclusion: Migraine and thyroid diseases are common diseases in the society. Thyroid diseases and thyroid function tests should be evaluated together when determining the characteristics of migraine and the headache severity. Our data suggest that there is no relationship between thyroid hormone levels and migraine subtypes and severity. Further studies are needed in order to confirm this association.

Keywords: Migraine, serum TSH, serum free T4

ÖZ

Amaç: Migren, tekrarlayan baş ağrısı atakları ile karakterize, dizabilitiye neden olan ve sık görülen nörovasküler enflamatuvar bir hastalıktır. Tiroid regülasyonunun migrendeki rolü tam olarak anlaşılamamıştır ve veriler çelişkilidir. Bu çalışmanın amacı tiroid hormon düzeyleri ile migren tipleri ve baş ağrısı şiddeti arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 150 migren hastası dahil edildi. Hastaların demografik ve klinik özellikleri, migren alt tipleri, sıklığı ve şiddeti, serum tirotropin (TSH), serbest tiroksin düzeyleri kayıt edildi. Migrenin şiddetini değerlendirmek için Migren Dizabilite Değerlendirme Anketi (MIDAS) ve Görsel Analog Skala (VAS) kullanıldı. Verilerin analizi yapıldı.

Bulgular: Hastaların yaş ortalaması 40,40±10,84 yıl, kadın erkek oranı 5.1: 1 idi. Migren hastalarının tiroid hormon düzeyleri ile baş ağrısı özellikleri ile migren şiddeti arasında anlamlı bir ilişki bulunmadı (p>0,05). VAS ve MIDAS değerleri ile TSH düzeyleri arasında anlamlı bir ilişki saptanmadı (p=0,973).

Sonuç: Migren hastalığı ve tiroid hastalıkları toplumda yaygın görülen hastalıklardır. Migrenin özellikleri ve baş ağrısı şiddeti belirlenirken tiroid hastalıkları ve tiroid fonksiyon testleri birlikte değerlendirilmelidir. Verilerimiz, tiroid hormon düzeyleri ile migren alt tipleri ve şiddeti arasında bir ilişki olmadığını düşündürmektedir. Bu ilişkiyi doğrulamak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Migren, serum TSH, serum serbest T4

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Received: 08.01.2023 **Accepted:** 18.01.2023

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INTRODUCTION

Migraine is a chronic, widespread neurovascular inflammatory disease characterized by recurrent moderate and severe headache attacks[1]. Photophobia, phonophobia, nausea, and vomiting are often accompanied by unilateral, throbbing, repetitive headache pain experienced for 4 to 72 hours by the patients[2]. Migraine pain not only affects the work or school performance of patients, but also causes a decrease in their quality of life, family time, and social activities. This condition, which completely or partially affects people's normal activities and lives, has been evaluated as a disability by the World Health Organization. Migraine Disability Assessment Questionnaire (MIDAS) is one of the widely used scales developed to measure disability in migraine patients[3,4]. Migraine can cause disability as well as showing significant co-morbidities with various diseases such as myocardial infarction, stroke, subclinical vascular brain lesions, patent foramen ovale, hypertension, epilepsy, asthma and psychiatric disorders[5,6]. Recently, the relationship between migraine and thyroid functions has been attempted to be established.

Subclinical hypothyroidism (SCH) is a condition characterized by normal free triiodothyronine (fT3) and free thyroxin (fT4) values and slightly increased thyrotropin (TSH) concentrations. Some studies have shown that migraine is associated with an increased risk in the development of both overt and SCH[7,8]. However, the underlying mechanisms of this relationship are still unclear. Although clinical symptoms are very few in SCH, some patients may show neuropsychiatric symptoms such as depression, anxiety, and memory disorders. There are studies that explain hormonal levels related to thyroid function, TSH, T3 and T4 blood concentrations, and migraine pathogenesis[7]. In a previous meta-analysis, serum TSH levels were found to be higher in patients with migraine compared to control groups without migraine, which was statistically significant[9]. However, when we look at the literature, the number of studies investigating the difference between serum TSH and fT4 levels and loss of working days together with pain severity are very scarce. The aim of the present study is to determine whether there is a difference between thyroid function tests (TFT) in patients diagnosed with migraine, defined migraine type and difference between TFT according to loss of working days and pain severity.

MATERIALS AND METHODS

One hundred-fifty patients admitted to Necmettin Erbakan University, Meram Faculty of Medicine, Neurology Outpatient Clinic between January 2021 and July 2022 and diagnosed with migraine (according to International Headache Society) were included in the present study. The study was approved by Necmettin Erbakan University, Meram Medical Faculty Ethics Committee (decision no: 2022/3969, date: 16.09.2022). Patients' files were analyzed retrospectively. Sixteen patients with a history of thyroid disease and using drugs related to thyroid disease, according to their records, were excluded from the present study. Patients' age, gender, biochemical serum TSH and fT4 levels, migraine type, presence of aura, frequency of attacks, duration and severity of attacks were recorded. Serum TSH and fT4 levels were studied by using standard electrochemiluminescence methods. The frequency of attacks refers to the total number of migraine attacks in the last 3 months; yet, whether the patients received treatment or not during the attacks was disregarded. Headache severity was evaluated with VAS. According to VAS 100 mL line 0-4 mL was evaluated as no pain, 5-44 mL as mild pain, 45-74 mL as moderate pain, and 75-100 mL as severe pain depending on the mark on the line[10]. MIDAS Turkish version was obtained by questioning the days on which the patients were unable to work due to the pain and the days when patients' performance decreased by at least 50%[11]. According to MIDAS, little or no disability was defined with a loss of 0-5 days, mild disability with a loss of 6-10 days, moderate disability with a loss of 11-20 days, and severe disability with a loss of 21 days or more[4]. The difference between serum TSH and fT4 values according to migraine type, the presence of aura, and the presence of a relationship with TFT in these patients, whose VAS and MIDAS values were calculated, were all taken into consideration.

Statistical Analysis

In the present study, the data obtained were analyzed using Statistical Package for Social Sciences for Windows 20.0 package program. Categorical variables were expressed as numbers (n) and the chi-square test (and/or Fisher's exact test) was used for the analysis. The Pearson correlation test was also applied to determine the correlations between serum TSH levels and migraine characteristics. Numerical variables were expressed as mean±standard deviation, and the Student's t-test was used to analyze the comparison of the means of two independent groups. A threshold level of <0.05 was considered for statistical significance in all results obtained.

RESULTS

The files of 150 migraine patients were reviewed retrospectively. Sixteen patients with a history of thyroid disease and relevant use of drugs were excluded from the present study. Out of the patients, 112 (83.6%) were female and 22 (16.4%) were male, with an age range between 18 and 65 years. The mean age was 40.40±10.84 years. The type of migraine (chronic, episodic), the presence of aura, headache severity according to VAS, disability score and demographic characteristics according to MIDAS are presented in Table 1. FT4 levels of the patients whose serum TSH level were found to be above 4.2 mU/L were reevaluated.

Eleven (8.2%) subclinical hypothyroid patients with TSH levels above 4.2 mU/L, fT4 levels within the normal range of 0.93-1.7 ng/dL, and no thyroid medication use were determined. Out of the 11 patients diagnosed with SCH, 10 were female and 1 was male.

Out of 134 migraine patients, 36 (26.9%) had migraine with aura and 98 (73.1%) had migraine without aura. The mean TSH value of patients diagnosed with migraine with aura was 2.10±1.46 mU/L, and fT4 was 1.25±0.32 ng/dL. The mean TSH value of patients with migraine but without aura was 2.24±1.58 mU/L, fT4 value was 1.16±0.17 nd/dL. However, no statistically significant differences could be determined in the TSH and fT4 values between the groups. There was no statistically significant difference between them (p=0.761, p=0.097).

Out of the migraine patients, 87 (64.9%) had episodic and 47 (35.1%) chronic migraine episodes. The mean TSH value of patients with chronic migraine was 2.33±1.61 mU/L, fT4 value was 1.19±0.29 ng/dL. The mean TSH value of patients with episodic migraine was 2.14±1.51 mU/L, fT4 value was 1.18±0.19 nd/dL. In terms of TSH and fT4 values, there was no statistically significant difference between the groups (p=0.490, p=0.887).

According to VAS, 2 patients (1.5%) had mild headache, 27 (20.1%) had moderate headache, and 105 patients (78.4%) had severe headache. Considering TSH and fT4 levels of the patients according to the severity of pain, the mean TSH value was 1.10±0.14 mU/L, fT4 value was 1.21±0.16 ng/dL in mild pain; the mean TSH value was 2.41±1.54 mU/L, fT4 value was 1.18±0.22 ng/dL in moderate pain; the meanTSH value was 2.17±1.56 mU/L, fT4 was determined as 1.18±0.23 ng/dL in severe pain, and there was no statistically significant difference among the groups (p=0.248, p=0.836).

Considering the working day loss of the patients, there were 21 patients (15.7%) with little or no disability, 43 (32.1%) with mild disability, 42 (31.3%) with moderate disability, and 28 (20.9%) with severe disability. The mean TSH value of patients with very low disability was 1.98±1.08 and fT4 value was 1.15±0.15. For those with mild disability, the mean TSH value was 2.28±1.81 and fT4 value was 1.16±0.19. For those with moderate disability, the mean TSH level was 2.06±1.27 and fT4 value was 1.21±0.17, and for those with severe disability, the mean TSH value was 2.48±1.79, and fT4 level was 1.21±0.36. There was no statistically significant difference between the groups (p=0.843, p=0.414).

TSH and fT4 levels of the patients are presented in Table 2.

Table 1. Characteristics of patients according to migraine groups

Patients	
Gender (n, %)	
Female	112 (83.6)
Male	22 (16.4)
Aura (n, %)	
Presence of aura	36 (26.9)
Absence of aura	98 (73.1)
Type (n, %)	
Episodic	87 (64.9)
Chronic	47 (35.1)
VAS (n, %)	
Mild	2 (1.5)
Moderate	27 (20.1)
Severe	105 (78.4)
MIDAS (n, %)	
0-5 days	21 (15.7)
6-10 days	43 (32.1)
11-20 days	42 (31.3)
>21 days	28 (20.9)

VAS: Visual Analog Scale, MIDAS: Migraine Disability Assessment Questionnaire

DISCUSSION

In the present study investigating TFT values in migraine patients, TSH level was above 4.2 mU/L in 134 migraine patients and fT4 level was between 0.93 and 1.7 ng/dL. We identified 11 (8.2%) patients diagnosed with SCH, who were in the normal range and did not use thyroid medication. Of the 11 patients diagnosed with SCH, 10 were female and 1 was male. In population-based studies, the prevalence of SCH varies between 4% and 15% and the diagnosis is more common in women[12]. We did not have a control group in our study, but the prevalence of SCH was similar to that in community-based

Table 2. TSH and fT4 levels of the patients

	TSH	p	fT4	p
Presence of aura	2.10±1.46	0.761	1.25±0.32	0.097
Absence of aura	2.24±1.58		1.16±0.17	
Chronic	2.33±1.61	0.490	1.19±0.29	0.887
Episodic	2.14±1.51		1.18±0.19	
VAS				
Mild	1.10±0.14	0.248	1.21±0.16	0.836
Moderate	2.41±1.54		1.18±0.22	
Severe	2.17±1.56		1.18±0.23	
MIDAS				
0-5 days	1.98±1.08	0.843	1.15±0.15	0.414
6-10 days	2.28±1.81		1.16±0.19	
11-20 days	2.06±1.27		1.21±0.17	
>21 days	2.48±1.79		1.21±0.36	

VAS: Visual Analog Scale, MIDAS: Migraine Disability Assessment Questionnaire

studies. Our female patients with SCH were more in numbers compared to male patients.

Hormones synthesized in the thyroid glands are vital for normal development and growth as well as for the development of the central nervous system. Severe deficiency of thyroid hormones results in mental retardation and ataxia during fetal and neonatal periods[13]. Basic evidence has been provided that thyroid hormones are involved in pain processing through the anterior cingulate cortex in mice with experimentally formed hypothyroidism. There are indications that thyroid hormones affect the development of pain/migraine. While hypothyroidism has been found to cause hypersensitivity to noxious thermal, but not mechanical, stimulus in mice, interestingly, pain intensity has been shown to be alleviated by T3 or T4 replacement. The mechanism underlying the effect of hormone therapy was thought to result from an improvement in the balance of glutamatergic and gamma aminobutyric acidergic transmission in the anterior cingulate cortex of hypothyroid mice[14].

In the study conducted by Bhattacharjee et al.[15], investigating the rate of SCH in patients with migraine, they determined the rate of SCH to be significantly higher in patients with migraine compared to the group without. Another study performed by Rubino et al.[16] reported a higher prevalence of migraine in patients with SCH compared to controls (46% vs. 13%, respectively). In their study, they also reported that they did not determine a statistically significant difference in serum TSH levels between SCH patients with and without migraine. The biological mechanisms underlying the relationship between SCH and migraine are unknown. Autoimmune hypothyroidism is a complex disease in which thyroid autoantigens develop on a certain genetic background after exposure to environmental factors. Thyroid autoimmunity is facilitated by single nucleotide polymorphisms in genes that regulate the immune system, such as human leucocyte antigen (HLA) genes, cytokine genes, and thyroid-specific genes. In the pathogenesis of migraine, polymorphisms play a role in some of these genes, such as tumor necrosis factor-alpha and different HLA genes[17-19].

In another study within the relevant literature, the meta-analysis results of Seidkhani-Nahal et al.[20] demonstrated statistically significantly higher TSH concentrations in patients with migraine and in controls without migraine. Based on this meta-analysis, the aim of the present study was to investigate whether there was a difference between serum TSH levels and fT4 levels in patients having migraine with or without the presence of aura, according to the severity of the headache, and type of migraine. The present study could not determine a statistically significant difference between TSH and fT4 levels of 134 migraine patients. The findings presented in the relevant literature were mostly in line with the findings of the present study. In a randomized case-control study, Bigal et al.[21] evaluated the factors associated with the transition from episodic migraine to chronic migraine. Among these factors, hypothyroidism has been found to contribute to the emergence of chronic migraine. In another study, it was shown that the rate of hypothyroidism in patients with migraine was higher than in community-based studies[7]. In addition, in the study of Rubino et al.[16], conducted with clinical subtypes of migraine, it was determined that the prevalence of migraine with and without aura was higher in patients with SCH than in the controls. In a retrospective cohort of consecutive migraine patients, which investigated the presence of migraine co-morbidities, Tietjen et al.[22] defined a subgroup with a high incidence of metabolic co-morbidities (such as hypertension, hyperlipidemia, diabetes mellitus) and hypothyroidism. Spanou et al.[23] could not determine a statistically significant relationship between headache types and thyroid hormone disorders. In terms of headache subtypes and thyroid dysfunctions, no statistically significant relationship could be determined in their study. However, a higher prevalence of thyroid dysfunction in general (20.7%) and a higher prevalence of hypothyroidism specifically (6.3%) in patients with primary headache were reported.

In a study conducted in Russia, only 5% of the migraine patients in the study were reported to have abnormal TSH levels (lower or higher than normal). Nevertheless, lower TSH values were associated with longer-term migraine attacks and had a greater impact on quality of life. Based on these findings, it was suggested that TSH levels should be confirmed in patients with severe migraine[24].

Study Limitations

The lack of a control group and the limited number of patients are the inherent limitations of the present study.

CONCLUSION

In the present study, however, no statistically significant difference could be determined between TSH and fT4 levels and the severity of headache, loss of working days, chronic and episodic migraine. The group with chronic migraine had a higher TSH value than the group with episodic migraine but there was no statistically significant difference between the groups. The pathogenesis of this association requires further research and studies with larger numbers of patients. In the present study, in 8,2% of the migraine patients, SCH was determined. As there was not a control group, comparisons with community-based studies could be made.

Ethics

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University, Meram Medical Faculty Ethics Committee (decision no: 2022/3969, date: 16.09.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A., Design: M.A., Data Collection or Processing: M.A., H.Ç.B., Z.Y., Analysis or Interpretation: M.A., H.Ç.B., Z.Y., Literature Search: H.Ç.B., Z.Y., Writing: H.Ç.B., Z.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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