Ann Med Res 2020;27(12):3260-6

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.01.049

Original Article

Hematological parameters in pediatric patients with primary headache

Erhan Aksoy

Dr. Sami Ulus Pediatric and Training Hospital, Clinic of Pediatric Neurology, Ankara, Turkey

Abstract

Aim: The present study aimed to evaluate the pain parameters in children with primary headache according to the International Classification of Headache Disorders, 3rd edition, diagnostic criteria and to investigate the role of hematological parameters in diagnosis in case the distinguish is difficult especially in children with migraine and tension headache.

Materials and Methods: Medical data belonging age, gender, headache characteristics, hematological parameters of the outpatients with headache consulted in Beştepe Child Neurology Outpatient Clinic of Dr. Sami Ulus Children's Hospital between July 2017 and August 2019 were examined retrospectively. SPSS statistical software was used to perform statistical data analysis.

Results: A total of 243 patients (151 female, 92 male) were included in the study. The mean age was 13.68 ± 2.25 years. One hundred and one (58 female, 43 male) patients were diagnosed with migraine and 142 (93 female, 49 male) with tension type headache. Migraine presented the characteristics of unilateral (61.2%), pulsatile (88.5%) headache of moderate to severe intensity that worsens with physical activity, occurs usually in mornings (%46,5) and is accompanied by nausea or by photophobia and phonophobia (%34,3). Tension-type headache presented the characteristics of circumferential (53,2%), pressing (87.7%) headache of mild severe intensity that is triggered by school stress and accompanied phonophobia (65.2%), and occurs usually in evenings (55.3%). White blood cells, neutrophil, monocyte, monocyte-lymphocyte ratio and neutrophil-lymphocyte ratio were significantly higher in patients with migraine and lymphocyte and platelet counts were significantly higher in patients with tension type headache.

Conclusion: In terms of shining a light on the future, consideration of the contribution of hematological parameters to differential diagnosis as a diagnostic support, due to the difficulties associated in particular with the presence of overlapping symptoms in the differential diagnosis of migraine and tension headache in childhood could make a significant difference.

Keywords: Childhood primary headaches; migraine; tension-type headache; hematological parameters; monocyte lymphocyte ratio; neutrophil lymphocyte ratio

INTRODUCTION

Headaches are one of the most common medical complaints and reasons for attending a doctor. The prevalence before and after the adolescence period degree is 2.5% and 5% respectively (1-3). In a study with Finnish school-aged children, the headache prevalence reported 37% at age 7 and increased to 69% by age 14 (4). In a study conducted with elementary school children in Turkey, this rate was reported as 49.2% (5). Primary headaches are recurrent and chronic nonprogressive, idiopathic, neurological diseases. They are considered as normal, except the attacks. According to the International Classification of Headache Disorders 3rd edition (ICHD-3), the primary headaches have been classified as migraine, tension-type headache (TTH), cluster headache and other primary headache disorders (3).

Migraine is characterized concurrent symptoms, such as photophobia, phonophobia, nausea, vomiting, and sensitivity to sensory stimuli (2,6). A number of prodromal symptoms may occur before, during and after headache. The majority of the patients may suffer from mood swings as fatigue, loss of appetite, desire for different foods, thirst, and restlessness (6). In ICHD-3, migraine has been described as with or without aura (3). In migraine without aura, pain develops gradually, lasts average of 4-72 hours, and usually shows unilateral location on frontal

Received: 14.01.2020 **Accepted:** 30.04.2020 **Available online:** 29.12.2020
Corresponding Author: Erhan Aksoy, Dr. Sami Ulus Pediatric and Training Hospital, Clinic of Pediatric Neurology, Ankara, Turkey
Email: aksoyerhan24@gmail.com

or temporal lobe. They are a severe type of pulsating headache. It is accompanied by desire for sleep, sleeping may help reduce the headache severity (2,3,6). To fulfill the diagnostic criteria of migraine, the patient must have had at least 5 headache attacks and the secondary causes for headache should be excluded. A visual phenomenon that typically lasts 5-60 minutes occurs in migraine with aura. Patients may experience blurry or grayed spots, or floaters. At least two attacks are required for fulfilling criteria (3,6). Childhood headaches, especially migraine, are different from adults in various ways. Nausea and vomiting during migraine attacks are more prominent in children than adults. The duration of the migraine attack tends to be shorter than in adults (5).

TTH (tension-type headache) is other a primary headache disorder lasting from 30 minutes to 7 days with mild or moderate intensity on bilateral location (mostly all around the head) where no nausea or vomiting and no more than one of photophobia or phonophobia occurs. Exclusion of secondary causes and at least 10 episodes of headache are essential for fulfilling criteria. In ICHD-3, episodic (infrequent, frequent) and chronic subtypes of TTH have been identified (3). A distinguishing feature between migraines and tension headaches is that migraines lead a drastic deterioration on everyday activities (2,3,6). The diagnosis of headache in children is subject to general interpretation of clinical symptoms (6). Focusing on a child's behavior (fadedness, the desire to sleep in a quiet and dark room, squinting in bright light, hyperosmia, withdrawal from everyday activities, aggravation of pain during menstruation) and discovering clues from those can contribute significantly to the diagnosis (2,3,6,).

In the light of this information, the primary objective of this study is to assess the pain parameters of children with primary headache, excluding the secondary causes, according to the ICHD-3 diagnostic criteria. However, the contribution of hematological parameters to diagnostic support, as it is difficult to distinguish TTH from migraine, is planned as another objective of the study.

MATERIALS and METHODS

The outpatients who referred with headache to Beştepe Child Neurology Outpatient Clinic of Dr. Sami Ulus Children's Hospital between July 2017 and August 2019 were included in this study. Medical data belonging age, gender, headache characteristics, hematological parameters of the patients were examined retrospectively. At first, secondary causes were excluded in outpatients presenting with headache. Electroencephalography (EEG) and brain magnetic resonance imaging (MRI) have also been performed in case of clinical necessity. The patients, excluding the secondary causes, were classified as primary headache syndrome according to ICHD-3 diagnostic criteria considering the history and examination findings (3).

Sub-definitions such as aura, episodic (infrequent, frequent), chronic has been coded under the title of migraine or TTH for ensuring homogenization and size of samples in the groups as much as possible. While this coding, as headache parameters, was performed, it is sought to answer the questions on severity of pain, duration of pain, pain quality (pulsatile, pressing or tightening), pain location (unilateral, bi-frontal, circumferential, suboccipital), onset of pain (morning, afternoon, evening), concurrent symptoms (photophobia, phonophobia, nausea, vomiting), whether there is an increase/decrease in daily physical activities (walking or climbing stairs), pain relief (sleep, medication). However, a number of children experienced difficulty to express some questions such as aura or severity of pain. For example, the severity of pain is a subjective concept; numericalization of it provides convenience in clinical evaluation. Therefore, VAS (visual analog scale) has been used. The scores vary from 0 to 10, where a score of 0 indicates "no pain" and 10 indicates "the worst pain imaginable". The score, which the child headache severity corresponds to in this scoring, is estimated. Emojis containing facial expression are used for the children who are incapable of expressing themselves. Therefore, observations of the parents during the questions answered by children were noted. The hematological parameters from the complete blood count (CBC), which among the headache routines of these patients, an inexpensive test that can be easily performed in almost every patient and examined in every laboratory were also taken into consideration in this study. Hemoglobin (HB), white blood cell (WBC), platelet (PLT), neutrophil (N), monocyte (Mo), lymphocyte (L), ratio obtained by dividing monocyte to lymphocyte (MLR), ratio obtained by dividing neutrophil to lymphocyte (NLR) are considered as CBC parameters.

Patients with headache relating to anemia, polycythemia, history of iron therapy in the past 12 months, overuse of analgesics which may lead to several changes in CBC, central nervous system (CNS) infections, cerebral sinovenous thrombosis (CSVT), pseudotumor cerebri, space occupying lesions as tumors or abscesses, hydrocephalus, subarachnoid hemorrhage, trauma, sinusitis, otitis, hypoglycemia, hypertension, chronic disease or other (mouth, teeth, eyes) secondary causes were excluded from the study. The ethics committee of Dr. Sami Ulus Pediatric and Training Hospital approved the study protocol (Project Number: 2019/10).

Statistical Analysis

IBM SPSS (version 21.0, SPSS Inc., Chicago, IL, USA) statistics was used to perform data analysis. The hematological parameters and headache were compared with each other. According to the data entered to SPSS, while CBC was present in all patients, partial deficiencies in headache parameters were observed. Due to the retrospective nature of the study design, the assessment was made on the available pain parameters. Kolmogorov-Smirnov test is conducted to determine if a random sample of a given distribution is appropriate. Data were summarized by number (percentage) and mean ± standard

deviation [For nonparametric distributed data; median [interquartile range (IQR)]. Nonparametric (Mann–Whitney U, chi-square test) and parametric (Student's t-test) tests were used for the comparisons between migraine and TTH groups. These two groups were compared also by the Cramer's V coefficient in terms of variables such as onset time of pain, location, type, concurrent symptoms, triggering factors and pain relief. The value of P <0.05 was considered statistically significant.

RESULTS

A total of 243 patients [151 females (62.10%), 92 males (37.90%)] were included in the study. The mean age of the patients is 13.68±2.25 years (range: 4.6-19 years), 14.18±3.48 for females and 12.85±2.95 for males (p: 0.003). Demographic characteristics are presented in Table 1. Migraine group consisted of 101 patients (41%) of 58 females and 43 males; and TTH consisted of 142 patients (59%) of 93 females and 49 males. The headache characteristics of both groups are summarized in Table 2. The severity of headache was higher in patient with migraine than with TTH (P = 0.000).

There were also significant differences between two groups in terms of type of pain, onset time, location, concurrent symptoms, triggering factors, and pain relief, that reflect the diagnostic characteristics of headache. However, no significant difference observed in terms of age, gender, duration of headache before admission and duration of the pain (Table 2). As shown in Table 2, migraine occurs mostly in the mornings (46.5%) and is typically unilateral (61.2%), moderate-to-severe (VAS> 5), pulsating (88.5%), accompanied by nausea and/or photophobia and phonophobia (%34.3) and aggravated by physical activity. TTH occurs mostly in the evenings (55.3%), and is circumferential (53.2%) mild severe (VAS≤ 5), pressing or tightening (87.7%) and accompanied by phonophobia (65.2%) and aggravated by school stress. Although not statistically significant, females were numerically dominant in both groups. WBC, N, Mo, MLR and NLR values in patients with migraine, and L and PLT values in TTH patients were significantly high (Table 3).

Table 1. The demographic characteristic of primary headache

Age at admission[a], y	13.68±2.25
Gender F/M (F %)	151/92 (61.2)
Primary headache characteristics	
Duration of headache before admission[b], m	24.00 (12.00-40.00)
Duration of pain[b], h	6 (4-10)
Severity of pain[b], VAS (1-10)	5 (4-7)
Hematological parameter characteristics	
Hemoglobin[a], g/dL	13.08±0.89
WBC count[a], 10^3/µl	7.50±2.02
Thrombocyte count[a], 10^3/µl	306.13±76.36
Neutrophil count[b], 10^3/µl	3.80 (2.80-5.40)
Lymphocyte count[b], 10^3/µl	2.30 (1.90-2.80)
Monocyte count[b], 10^3/µl	0.50(0.40-0.60)
MLR[b]	0.20 (0.15-0.26)
NLR[b]	1.59 (1.12-2.30)

y:year; F:female; M:male; m:mount; h:hour; VAS: visual analog scale (the scores vary from 0 to 10);
WBC:White blood cell; MLR: monocyte- lymphocyte ratio; NLR: Neutrophil- lymphocyte ratio;
[a]parametric distribution values are presented as mean± SD;
[b]nonparametric distribution values are presented as median (interquartile range)

Table 2. The headache characteristics of migraine and tension-type headache (TTH) children				
Characteristics	Migraine	TTH	P	Cramer's V
Age, y	13.25±3.62	13.97±3.11	NS	
Gender F/M (% F)	58/43 (57.4)	93/49 (65.5)	NS	
Duration of headache before admission. m	28.06±16.43	25.94±17.51	NS	
Duration of the pain , h	9.83±10.25	9.04±9.75	NS	
Severity of the pain, VAS	6.46±1.52	4.67±1.44	0.000	
Quality of the pain n (%)			0.000	0.757(phi)
Pulsatile	77(88.5)	15(12.3)		
Pressing or tightening	10(11.5)	107(87.7)		
Onset of the pain n(%)			0.000	0.509
Morning	46(46.5)	12(8.5)		
Afternoon	40(40.4)	51(36.2)		
Evening	13(13.1)	78(55.3)		
Location of the pain n(%)			0.000	0.645
Unilateral	60(61.2)	10(7.1)		
Bi-frontal	26(26.5)	33(23.4)		
circumferential	8(8.2)	75(53.2)		
Suboccipital	4(4.1)	23(16.3)		
Concurrent symptoms n(%)			0.000	0.796
a-Photophobia	10(10.1)	48(34.8)		
b-Phonophobia	15(15.2)	90(65.2)		
c-Nausea	1(1.0)	0		
d-Vomiting	2(2.0)	0		
a+b+c	34.3(34.3)	0		
a+b	24(24.2)	0		
Other combinations	13(13.2)	0		
Precipitants n(%)			0.000	0.343
No	26(32.1)	42(38.5)		
School stress	20(24.7)	52(47.7)		
Exercise	35(43.2)	15(13.8)		
Pain relieving factors n(%)			NS	
Sleeping	46(45.5)	6+1(43.0)		
Use of analgesics	55(54.5)	81(57.0)		

y:year; F:female; m:mount; h:hour; VAS: visual analog scale; NS: not significant

Table 3. The hematological parameters of migraine and tension-type headache (TTH) children			
Hemoglobin, g/dL	13.04±0.87	13.12±0.91	NS
WBC count. 103/µl	673.8 (411.2-820.8)	684.5 (475.8-779.2)	595.5 (129.5-788.5)
7.86±2.09	7.24±1.93	0.014	27.3 (15.9-177.3)
Thrombocyte count, 103/µl	292.10±70.42	313.42±73.95	0.025
Neutrophil count, 103/µl	4.57±1.89	4.02±1.77	0.014
Lymphocyte count, 103/µl	2.29±0.73	2.49±0.82	0.034
Monocyte countb, 103/µl	0.61±0.48	0.45±0.13	0.000
MLR	0.29±0.36	0.19±0.06	0.000
NLR	2.28±2.14	1.90±2.17	0.024

WBC:white blood cell; MLR: monocyte- lymphocyte ratio;NLR: Neutrophil- lymphocyte ratioNS: not significant

DISCUSSION

We investigated the characteristics of headache and hematological parameters in pediatric patients with migraine or TTH in this study. The symptoms have been found to start in childhood in the history of migraine patients diagnosed in adulthood (8). As the headache parameters were evaluated, it has been drawn attention that the presence of the unilateral (61.2%), pulsatile (88.5%) headache that mostly occurs in mornings (46.5%) in migraineurs and circumferential (53.2%), pressing or tightening (87.7%) headache mostly occurring in evenings (55.3%) in TTH patients was the most significant contrasting feature (p:0,000). In a study by Maytal et al., it was found that presence of unilateral pain in migraineurs is considered as gold standard diagnostic tool, the sensitivity and specificity is 34%, 86% respectively (9). In another study by Mortimer et al., it has been shown that 86% of children with migraine who aged 8-11 years has headache which described as pulsating (10). The same study showed that bi-frontal headache was seen in 28% of children with migraine. In our study, this rate was reported to be 26.5% in children with migraine. In an elementary school study supporting our study, it was found that in migraineurs, of the pain 98.6% is unilateral and 62.5% is pulsatile, and 62.0% occurs in the mornings and pain in TTH patients 53,4 % occurs usually in evenings (5). A study from has reported a primary recurrent headache prevalence of 21%, migraine prevalence of 7.2%, and TTH prevalence of 7.8% in children aged 7–17 years (11,12). Chronic migraine affects approximately 2% of the world population (13). It has been reported that the prevalence of TTH varied between 7.8% - 57.5% in school-age children and adolescents (14-17). Migraine is equally common in the two sexes prior to puberty. It then becomes 2–3 times more common in girls than in boys (15) . In a study, it was reported that of the migraineurs, 77.02% were female and 22.98% were male (11). Even though this result is not statistically significant for our study, 41% patients had migraine, and 57.4% of migraineurs were female. TTH was noted in 59% patients, and 65.5% of them were females. Similarly, no difference between patients with TTH and migraine in terms of mean age was reported. In a study has shown that TTH was diagnosed at a younger age than migraine (5). Although not statistically significant in our study, 56,3% of children aged less than 15 suffer from TTH, 43,7% from migraine.

In primary headache, especially migraine, excessive excitability of cerebral cortex enhances through the ion channels. The locus coeruleus and dorsal raphe nucleus on the brainstem act as generator provide adrenergic and serotonergic signals to cortex and dural vascular structures. This generator induces the activation of the trigeminovascular system, leads to inflammation of the meningeal vascular structures that initiate pain, and central and peripheral stimulation of trigeminal afferents. Biochemical changes occur during this process. Many conditions such as neuroinflammation, cytokines, neuropeptides and vasomotor changes have been held responsible for this pathogenesis. Although the pathophysiology of TTH is not fully understood, thought to be similar to migraine and be two ends of the end of same spectrum (18). Pain is associated with stress, and caused by the contraction of pericranial myofascial muscles and stimulation of tension-sensitive nociceptive receptors (6,7) .

There are a limited number of studies showing the correlation between headache and hematological parameters. These studies have focused mainly on adults with migraine (11,19,20). Hence, data on the diagnostic support of hematological parameters in childhood headache are very limited. Serum biomarkers of NLR, MLR showing peripheral inflammation and oxidative stress are widely used in chronic neurological diseases (21-23). In addition, the NLR has been shown to have a predictive value for cardiovascular disease, stroke and cancer prognosis (24-26). Similarly, it emphasizes that significantly higher NLR values of subarachnoid hemorrhage patients than migraine and other headaches group values can be considered as a clinical prognostic factor (27). Another study shown that L level decreased and N, NLR and MLR levels increased in migraine (11). In another study, NLR was shown to increase during migraine (28).

In this study, WBC, N, Mo, MLR and NLR values in migraine, and L and PLT values in TTH were significantly higher. The association between migraine and PLT value is controversial. A few studies have reported that PLT activation or volume is increased in migraine (29,30). Another study stated that PLT values are higher in TTH compared to migraine (31). In this respect, thrombocytopenia has been reported in patients with migraine especially during attacks, these patients have been exposed to splenectomy or steroid treatment (32). Similarly, in another study have reported that platelet activation, leukocyte-platelet aggregation, platelet-fibrinogen affinity increased during pathogenesis in patients with migraine, the thrombocytopenia, due to consumption, has been observed (33). Results similar to adults have been yielded from a couple of childhood studies regarding to this subject (34,35). As reported in another study that serotonin receptors enhancing platelet aggregation has been found to be decreased in patients with TTH, since platelets don't function properly, levels have increased (36). In our study, similar to these studies, PLT values were found to be significantly higher in TTH than in migraine.

This study has a variety of limitations. It was observed that there is insufficient data on main pain parameters available when the files were examined. The limitations of this study specifically draw attention in various data such as prodromal phase before the pain, prevalence of recurring pain, motion sickness, skipping meals, craving for specific foods (chocolate, ice cream, chips, soda, etc.), relationship with menstruation, family history. In this respect, our study is limited in terms of differentiation of migraine and TTH. This situation may be associated with the utilization and intensity of outpatient clinic due

to being reference hospital. The studies including these parameters, which have a significant effect on diagnostic support, will undoubtedly produce new information that furthers our study.

CONCLUSION

As a conclusion, secondary causes should be excluded according to history, neurological examination and related test in patients presenting with headache. According to the results of our study regarding primary headache, the severe pain that had a unilateral, pulsatile quality that started mostly in the mornings in migraineurs, and the mild pain that had a circumferential, pressing or tightening quality that started mostly in the evenings in TTH patients has been identified as our primary objective. In terms of diagnostic support, high values of WBC, N, Mo, MLR, NLR were evaluated in favor of migraine and high levels of L and PLT in favor of TTH and realized as our second objective. As the common point of our objectives in terms of shedding light on the future, due to the difficulties in the differential diagnosis of childhood migraine and TTH with regards to the presence of overlapping symptoms, the contribution of hematological parameters to differential diagnosis will make a significant difference. Further research is needed to strengthen and improve our study.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The ethics committee of Dr. Sami Ulus Pediatric and Training Hospital approved the study protocol (Project Number: 2019/10).

REFERENCES

1. Dueland AN. Headache and Alcohol. Headache 2015;55:1045-49.
2. Burch R. Migraine and Tension-Type Headache: Diagnosis and Treatment. Med Clin North Am 2019;103:215-33.
3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.
4. Arruda MA, Guidetti V, Galli F, et al. Primary headaches in childhood--a population-based study. Cephalalgia 2010;30:1056-64.
5. Ozge A, Bugdayci R, Sasmaz T, et al. The sensitivity and specificity of the case definition criteria in diagnosis of headache: a school-based epidemiological study of 5562 children in Mersin. Cephalalgia 2002;22:791-8.
6. Kahriman A, Zhu S. Migraine and Tension-Type Headache. Semin Neurol 2018;38:608-18.
7. Jensen R. Pathophysiological mechanisms of tension-type headache: a review of epidemiological and experimental studies. Cephalalgia 1999;19:602-21.
8. Cheng H, Treglown L, Green A, et al. Childhood onset of migraine, gender, parental social class, and trait neuroticism as predictors of the prevalence of migraine in adulthood. J Psychosom Res 2016;88:54-8.
9. Maytal J, Young M, Schecter A, Lipton RB. Pediatric migraine and the International Headache Society (IHS) criteria. Neurology 1997;48:602–7.
10. Mortimer MJ, Kay J, Jaron A. Childhood migraine in general practice: clinical features and characteristics. Cephalalgia 1992;12:238–43.
11. Yazar HO,Yazar T, Aygün A, et al. Evaluation of simple inflammatory blood parameters in patients with migraine. Ir J Med Sci 2020;189:677-83.
12. Zwart JA, Dyb G, Holmen TL, et al. The prevalence of migraine and tension-type headaches among adolescents in Norway. The Nord-Trøndelag Health Study (Head-HUNT-Youth), a large population-based epidemiological study. Cephalalgia 2004;24:373-79.
13. Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep 2011;15:70-8.
14. Anttila P, Metsähonkala L, Aromaa M, et al. Determinants of tension-type headache in children. Cephalalgia 2002;22:401-8.
15. Poyrazoğlu HG, Kumandas S, Canpolat M, et al. The prevalence of migraine and tension-type headache among schoolchildren in Kayseri, Turkey: an evaluation of sensitivity and specificity using multivariate analysis. J Child Neurol 2015;30:889-95.
16. Yılmaz Ü, Çeleğen M, Yılmaz TS, et al. Childhood headaches and brain magnetic resonance imaging findings. Eur J Paediatr Neurol 2014;18(2):163–70.
17. Ozge A, Sasmaz T, Cakmak SE, et al. Epidemiological-based childhood headache natural history study: after an interval of six years. Cephalalgia 2010;30:703-12.
18. Cady RK. The convergence hypothesis. Headache 2007;47:44-51.
19. Welch KM, Nagesh V, Aurora SK, et al. Periaqueductal gray matter dysfunction in migraine: Cause or burden of illness? Headache 2001;41:629-37.
20. Stanzani MM. Migraine attacks, aura, and polycythemia: a vasculo neural pathogenesis? J Neural Transm (Vienna) 2011;118:545-7.
21. Yazar HO, Yazar T. Serum inflammation biomarkers are associated with stages of Parkinson's disease. Ann Med Res 2019;26:1488-92.
22. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease. Biomed Rep 2016;4:519-22.
23. Ozdemir HH. Analysis of the albumin level, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in Guillain-Barré syndrome. Arq Neuropsiquiatr 2016;74:718-22.
24. Park MG, Kim MK, Chae SH, et al. Lymphocyte-to-monocyte ratio on day 7 is associated with outcomes in acute ischemic stroke. Neurol Sci 2018;39:243-9.
25. Auezova R, Ryskeldiev N, Doskaliyev A, et al. Association of preoperative levels of selected blood inflammatory markers with prognosis in gliomas. Onco Targets Ther 2016; 11:6111-7.
26. Köklü E, Yüksel İÖ, Arslan Ş, et al. Is elevated neutrophil-to-lymphocyte ratio a predictor of stroke in patients with intermediate carotid artery stenosis? J Stroke Cerebrovasc Dis 2016;25:578-84.

27. Eryigit U, Altunayoglu CV, Sahin A, et al. The diagnostic value of the neutrophil-lymphocyte ratio in distinguishing between subarachnoid hemorrhage and migraine. Am J Emerg Med 2017;35:1276-80.
28. Karabulut KU, Egercioglu TU, Uyar M, et al.The change of neutrophils/lymphocytes ratio in migraine attacks: a case-controlled study. Ann Med Surg (Lond) 2016;10:52-6.
29. Zeller JA, LindnerV, FrahmK, et al. Platelet activation and platelet-leucocyte interaction in patients with migraine. Subtype differences and influence of triptans. Cephalalgia 2005;25:536-41.
30. Varol S, Akıl E, Çevik MU, et al. Investigation of mean platelet volume and platelet count in the blood of patients with migraine. Turk J Neurol 2013;19:90-2.
31. Benedick A, Zeharia, A, Markus TE. Comparison of thrombocyte count between pediatric patients with migraine or tension-type headache: a retrospective cohort study. J Child Neurol 2019;34:824-9.
32. Peatfield RC, Gawel MJ, Guthrie DL, et al. Platelet size: no correlation with migraine or monoamine oxidase activity. J Neurol Neurosurg Psychiatry 1982;45:826-9.
33. Kozubski W, Walkowiak B, Cierniewski CS, et al. Platelet fibrinogen receptors in migraine patients. Headache 1987;27: 431-4.
34. Bassi B, Parodi E, Messina M, et al. Screening for genetic and acquired thrombophilia in a cohort of young migrainous patients. J Headache Pain 2003;4:138-45.
35. Herak DC, Antolic MR, Krleza JL, et al. Inherited prothrombotic risk factors in children with stroke, transient ischemic attack, or migraine. Pediatrics 2009;123:653-60.
36. De Clerck FF, Janssen PA. Amplification mechanisms in platelet activation and arterial thrombosis. J Hypertens Suppl 1990;8:87-93.