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EVALUATION OF THE CORRELATION BETWEEN NEUTROPHIL-LYMPHOCYTE RATIOS AND BODY MASS INDEX AND CEREBROSPINAL FLUID PRESSURE IN IDIOPATHIC INTRACRANIAL HYPERTENSION (1)

İDİOPATİK İNTRAKRANİAL HİPERTANSİYONDA NÖTROFİL LENFOSİT ORANLARI VE VÜCUT KİTLE İNDEKSİ İLE BEYİN OMURLİK SIVISI BASINCI ARASINDAKİ İLİŞKİNİN DEĞERLENDİRİLMESİ

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Öz: Amaç: İdiyopatik intrakranial hipertansiyon (IIH) beyinde yapısal bir lezyon ve beyin omurilik sıvısında (BOS) anormal bir bulgu olmaksızın kafa içi basınç artışı sendromunun belirti ve bulgularının olduğu bir hastalıkdır. IIH obesite ve inflamasyonla ilişkilendirilmektedir. Biz çalışmamızda IIH da nötrofil lenfosit oranları(NLO) ve vücut kitle indeksi(VKİ) ile BOS basıncı arasındaki ilişkiyi değerlendirmeyi amaçladık. **Yöntem:** Baş ağrısı ve papil ödemi olup BOS açılış basıncı 25 cmH_2O ve üzeri ve BOS biyokimyası normal olan modifiye Dandy kriterlerine göre yeni IIH tanısı almış 41 (%87.2) kadın, 6 (%12.8) erkek 47 hasta ve 39(%83) kadın, 8 (%17) erkekten oluşan ve yaş ve cinsiyet uyumlu 47 sağlıklı gönüllü alınarak VKİ, Beyaz küre sayıları, NLO , BOS basınçları ve kranial manyetik rezonans görüntüleme(MRG) bulguları değerlendirildi. **Bulgular:** NLO oranı hasta grubunda 2,3952±1,09 kontrol grubunda 1,9711±0,74 idi ve hasta grubununda anlamlı derecede yüksekti(p=0,02). Beyaz küre sayıları hasta grubunda 7,93±1,91 kontrol grubunda 7,11±1,42 anlamlı derecede yüksek bulundu(p=0,02). VKİ hasta grubunda 30,23±2,84, kontrol grubunda 26,31±3,97 olup anlamlı derecede yüksekti(p=0.00). NLO ile BOS basıncı arasında bir ilişki bulunamakla birlikte(p=0,58) NLO için kestirme değeri 1,95 olarak hesaplanmış ve 1,95 ve üzeri NLO değerleri ile BOS basıncı arasında anlamlı bir ilişki saptanmıştır(p=0,04). VKİ ile BOS basıncı ve NLO arasında pozitif yönlü bir ilişki saptandı(p=0.001, r= 0,79; p=0,03, r= 0,21).**Sonuç:** IIH etyopatogenezi tam olarak anlaşılamamış olup mevcut bulgular obesite ve ona bağlı enflamasyonla ilişkilendirilmektedir. Bizim sonuçlarımız serum NLO düzeyinin IIH da inflamasyonu göstermede bir marker olarak kullanılabileceğini ve artmış inflamasyonun VKİ ve BOS basıncı ile ilişkili olabileceğini göstermektedir.

Anahtar Kelimeler: İdiopatik İntrakranial Hipertansiyon, Nötrofil Lenfosit Oranları, İnflamasyon, Vücut Kitle İndeksi

Abstract:Aim: Idiopathic intracranial hypertension (IIH) is a disease with signs and symptoms of increased intracranial pressure syndrome without a structural lesion in the brain and an abnormal finding in the cerebrospinal fluid (CSF). IIH is associated with obesity and inflammation. In our study, we aimed to evaluate the correlation between neutrophil-lymphocyte ratios (NLR) and body mass index (BMI) and CSF pressure in IIH. Method: Forty-seven patients consisting of 41 (87.2%) women and 6 (12.8%) men who had headache and papilledema, a CSF opening pressure of 25 cmH_2O and above, and normal CSF biochemistry and were newly diagnosed with IIH according to the modified Dandy criteria, and 47 age-and gender-matched healthy volunteers consisting of 39 (83%) women and 8 (17%) men were included in the study, and their BMI, white blood cell counts, NLR, CSF pressures and cranial magnetic resonance imaging(MRI) findings were evaluated. **Results:** The NLR ratio was 2.3952±1.09 in the patient group and 1.9711±0.74 in the control group and was significantly higher in the patient group (p=0.02). The white blood cell counts were found to be significantly higher with 7.93±1.91 in the patient group and 7.11±1.42 in the control group (p=0.02). BMI was significantly higher with 30.23±2.84 in the patient group and 26.31±3.97 in the control group (p=0.00). Although there was no correlation between NLR and CSF pressure (p=0.58), the cut-off value for NLR was calculated to be 1.95, and a significant correlation was found between the NLR values of 1.95 and above and the CSF pressure (p=0.04). A positive correlation was found between BMI and CSF pressure and NLR (p=0.001, r= 0.79; p=0.03, r= 0.21). **Conclusion:** The etiopathogenesis of IIH has not been fully understood, and the existing findings are associated with obesity and related inflammation. Our results indicate that serum NLR level can be used as a marker to show inflammation in IIH and that increased inflammation may be associated with BMI and CSF pressure.

Keywords: Idiopathic Intracranial Hypertension, Neutrophil Lymphocyte Ratio, Inflammation, Body Mass Index

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INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disease with signs and symptoms of increased intracranial pressure syndrome without a structural lesion in the brain and an abnormal finding in the cerebrospinal fluid (CSF) (Friedman, 2010:380-385). IIH is most frequently observed in obese women of childbearing age (Kesler and Gadoth,2001:12-14), and its incidence is 1 to 2 per 100.000 (Durcan et al., 1988:875-877). Headache and temporary loss of vision are the most common symptoms in IIH. Headache has a throbbing or pressure character in the frontal, retro-orbital region. The pain is daily, constant and has a character that increases with coughing and standing. While visual acuity and color vision are relatively preserved, visual fields are mainly affected. Loss of vision may be insidious until irreversible damage occurs. In IIH, papilledema is typically bilateral and symmetrical. However, it can also be asymmetrical or unilateral. If it is not treated, progressive loss of vision and blindness due to optic atrophy may occur. Furthermore, patients may have complaints of diplopia, pulsatile tinnitus, fullness in the ear, inability to hear low-frequency sounds, and vertigo (Wall, 2010:593-617). Many factors, such as increased CSF production, decreased CSF absorption, occlusion of the dural venous sinuses, and increased cerebral blood flow, have been proposed in the etiology of IIH. However, the pathophysiology of existing abnormal CSF dynamics is still uncertain (Skau et al., 2006:384-99). IIH has been associated with drug exposure such as vitamin A, oral contraceptives, growth hormone, steroids, minocycline, tetracycline, sulphasalazine, and many etiologies such as Behçet's disease, arteriovenous malformations, sleep disturbances including obstructive sleep apnea syndrome (OSAS), extracranial venous hypertension secondary to cardiac septal defect, systemic lupus erythematosus, uremia, iron deficiency anemia, some endocrine changes such as menstrual irregularities, hyperthyroidism, hypothyroidism (Baykan, 2015:63-72). Although the cause of IIH is not known exactly, it has been reported to be strongly associated with obesity, especially in women of childbearing age (Kesler and Gadoth, 2001:12-14). The contribution of inflammatory mechanisms and changes in cytokine levels have recently been demonstrated in the etiopathogenesis of IIH (Altıokka-Uzun et al., 2017:525-531). There are studies showing that the correlation between obesity and IIH depends on a proinflammatory condition (Andrews et al., 2014:217–225). The differential number of white blood cells is a biomarker that is commonly used to show systemic inflammation (Guzel et al., 2016: 54–57). Neutrophils and lymphocytes play significant roles in the inflammatory processes. Neutrophil and lym-

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phocyte counts undergo temporary changes under inflammatory conditions. The neutrophil/lymphocyte ratio (NLR) is calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes. As a systemic inflammation index, NLR has been determined to be a useful index for the differential diagnosis or prognostic prediction of diseases. NLR is also an inexpensive marker that can provide important information about the patient's inflammatory activity and is easily available (Qin et al., 2016:372-376). Recent studies have revealed that the NLR is a better marker in showing systemic inflammation compared to neutrophil or lymphocyte count alone (Guzel et al., 2016: 54–57). In our study, we aimed to determine the level of NLR, which is an easily accessible marker of systemic inflammation, in IIH patients, and to show its correlation with BMI and CSF pressure, if any.

METHOD

In our study, the files of the patients, whose IIH, headache and pseudotumor cerebri diagnoses were entered into the automation system between 2016-2018, were examined, and 47 newly diagnosed patients who had headache and papilledema, a CSF opening pressure of 25 cmH_2O and above, and normal CSF biochemistry according to the modified Dandy criteria, and 47 age-and gender-matched healthy volunteers were included in the study by obtaining their consents. From among the patients and healthy volunteers, those who use oral contraceptives, systemic inflammatory disease, active infection, head trauma, malignancy, diabetes, thyroid disease, hypertension, anemia, renal failure, psychiatric disease, and liver failure were not included in the study . The demographic data, CSF pressure values, and cranial magnetic resonance imaging (MRI) findings of the patients were obtained from the files of patients. Body mass index (BMI) was calculated by dividing the body mass in kilograms by the square of the body length in meters. The ethics committee approval of our study was obtained from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University, and the ethics committee approval number is 2018-10/13.

EVALUATION of BIOCHEMICAL and HEMATOLOGICAL PARAMETERS

Dry tubes were used for biochemical analysis, and EDTA tubes were used for hematological tests. The complete blood count was analyzed from blood samples taken from the participants on the Mindray BC-6800 device using Diagon kits, and the kits of the same company were used by the fully automatic nephelometric method on a Beckman Coulter AU5800 (Beckman Coulter Inc, Hialeah, Florida) device for biochemical analysis. The NLR was obtained by dividing the neutrophil

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count in the measured whole blood count by the number of lymphocytes.

STATISTICAL METHOD

The data obtained from our study were uploaded to the SPSS 22.0 program and used in the evaluation of the data. The Kolmogorov-Smirnov test was used when the parametric test assumptions were fulfilled, the independent sample t-test was used while comparing the measurements obtained from two independent groups, the one-way ANOVA test was used while comparing more than two independent groups, the Mann-Whitney U test was used when the parametric test assumptions could not be fulfilled, Pearson's collation analysis was used to determine the correlations between the variables, the chi-square test was used to evaluate the data obtained by counting, and the error level was considered to be 0.05. For NLR, the area under the curve was found to be 0.632, this area size was statistically significant, and confidence intervals of 95% were found to be 0.519-0.746. Accordingly, the predictive value for NLR was found to be 1.95, and the sensitivity value for it was 63.8%, and the specificity value was 53.2%.

RESULTS

While 47 patients included in the study consisted of 41 (87.2%) women and 6 (12.8%) men, the control group consisted of 39 (83%) women and 8 (17%) men. While the ratio of women was statistically higher in both patient and control groups, the ratio of men was statistically lower, and there was no significant difference in gender distribution between the two groups (p=0.562). The mean ages of the patient and control groups were 33.80±5.29 and 32.34±5.16 years, respectively, and the difference between the groups was insignificant (p=0.11). It was evaluated that the patients cranial MRI findings were normal 25 (53.19%), empty sella was 11 (23.40%), transverse sinus hypoplasia was 6 (12.76%), the increased CSF in the optic nerve sheath was 5 (10.63%). The NLR ratio was 2.3952±1.09 in the patient group and 1.9711±0.74 in the control group and was significantly higher in the patient group (p=0.02) (p=0.02). The white blood cell counts were found to be significantly high with 7.93±1.91 in the patient group and 7.11±1.42 in the control group (p=0.02). BMI was significantly high with 30.23±2.84 in the patient group and 26.31±3.97 in the control group (p=0.00). The patients CSF pressure was 35.78± 9.21 (Table 1).

Although there was no correlation between NLR and CSF pressure (p=0.58), the cut-off value for NLR was calculated to be 1.95, and a significant correlation was found between NLR values above this value and CSF pressure (p=0.04) (Table 2). A positive correla-

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tion was found between BMI and CSF pressure and NLR (p=0.001, r= 0.79; p=0.03, r= 0.21). No correlation was found between the patients' white blood cell count and CSF pressure and BMI (p=0.48, p=0.57). Furthermore, no correlation was found between the white blood cell count and BMI of the control group (p=0.51).

When NLR, CSF pressure, and BMI were compared with the cranial MRI findings in the patient group, no significant correlation was found (p=0.71, p=0.18, p=0.98) (Table 3).

Table 1. Demographic Characteristics of The Patient and Control Groups

	Patient group (n=47)	Control group (n=47)	p
Female, n (%)	41(%87,2)	39(%80)	0.56
Age (year)	33.8±5.29	32.34±5.16	0.11
White blood cell count (10^9/ml)	7,93±1,91	7,11±1,42	0,02
NLR	2,39±1,09	1,97± 0,74	0,02
BMI(kg/m²)	30,23±2,84	26,31±3,97	0,00
CSF pressure (cm H_2O)	35.78± 9.21		
Cranial MRI findings			
	Normal 25(%53,19)		
	Empty sella 11(%23,40)		
	Transverse sinus hypoplasia 6(%12,76)		
	Increased CSF in the optic nerve sheath 5(%10,63)		

Table 2. Correlation of Patients With an NLR 1,95 and Over 1.95 and Below 1.95 with CSF Pressure

	Patient (n=47)	CSF pressure (cm H_2O)	p
NLR 1,95 and over 1.95	30	37,85±8,70	0,04
NLR below 1.95	17	32,14±9,22	

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Table 3. Correlation of NLR, CSF Pressure, and BMI with Cranial MRI Findings

Cranial MRI findings	Patient (n=47)	NLR	p
Normal	25	2,48±1,23	
Empty Sella	11	2,11±0,79	0,717 Increased CSF in
the optic nerve sheath	5	2,23±0,62	
Transverse sinus hypoplasia	6	2,67±1,31	
		CSF pressure (cm H_2O)	
Normal	25	33,30±6,88	
Empty Sella	11	36,90±9,65	
Increased CSF in the optic nerve sheath	5	41,80±16,20	0,18
Transverse sinus hypoplasia	6	39,08±8,65	
		BMI(kg/m²)	
Normal	25	30,24±2,84	
Empty Sella	11	30,00 ±2,86	0,98
Increased CSF in the optic nerve sheath	5	30,40±3,84	
Transverse sinus hypoplasia	6	30,50±2,66	

DISCUSSION

IIH is a disease with signs and symptoms of increased intracranial pressure syndrome without a structural lesion in the brain and an abnormal finding in the cerebrospinal fluid (Friedman, 2010:380-385). Although the cause of IIH is not known exactly, it has been shown to be strongly associated with obesity, especially in women of childbearing age (Kesler and Gadoth, 2001:12-14). Daniels et al. showed that there was a correlation between BMI and IIH, and they reported that increased weight was associated with disease recurrence (2007: 635–41). Likewise, our results also showed that there was a statistically significant correlation between BMI and CSF pressure. In another study, it was emphasized that the loss of vision was more severe in obese IIH patients compared to non-obese patients (Szewka et al., 2013:4–8). Since our study was a retrospective study, we could not reach the data related to the severity of vision loss from the patient files. Therefore, we did not evaluate the correlation between BMI and loss of vision. The contribution of inflammatory mechanisms and changes in cytokine levels have recently been demonstrated in the etiopathogenesis of IIH (Altıokka-Uzun et al., 2017:525-531). The differential number of white blood cells is a biomarker that is commonly used to show systemic inflammation. Recent studies have revealed that the

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NLR is a better marker in showing systemic inflammation compared to neutrophil or lymphocyte count alone (Guzel et al., 2016: 54–57). In our study, although we found that white blood cell counts were significantly higher in the patient group compared to the control group, we could not show the correlation between these high values and BMI and CSF pressure. Obesity was shown to be associated with higher IL-17 levels both in rats and humans (Pini and Fantuzzi, 2010: 51-8; Sumarac-Dumanovic et al., 2009: 151-156). There are studies showing that the unexplained correlation between obesity and IIH depends on a proinflammatory condition (Alexandra et al., 2008:212–220). Adipose tissue acts as an endocrine organ that secretes cytokines and hormones and contributes to a systemic proinflammatory condition (12. Stofkova, 2009: 157-168). Weight loss significantly reduces circulating proinflammatory cytokine levels and is an important component of IIH treatment (de Mello et al., 2008: 192-199). Sinclair et al. argued that cytokines and adipokines released from adipose tissues in obesity increased cortisol level, which may lead to increased intracranial pressure by increasing CSF release from the choroid plexus and decreasing CSF absorption from arachnoid granulation (2008:212-220). It was argued that microthrombi in the arachnoid villi could be one of the key factors in impaired CSF drainage in IIH patients, in whom obesity is a prothrombotic condition (Sinclair et al., 2008:212-220). It was evaluated that the prevalence of circulating prothrombotic factors was higher in obese IIH patients compared to non-obese IIH patients, and it is argued that proinflammatory cytokines such as IL-17 and IL-2 can facilitate the formation of microthrombi by mediating thrombosis and thus reduce CSF drainage and that the thrombus itself can also stimulate cytokine release (Edwards et al., 2013:234-244.). Sundholm et al. showed that major inflammatory activation might be a risk factor in the development of IIH (2020:1-11). While it was shown in a study that chemokine (CC motif)-ligand 2 (CCL2) was increased in the CSF of IIH patients compared to controls (Dhungana et al., 2009: 282-285.), it was shown in another study that there was a significant increase in CSF IL-6 levels in IIH patients compared to controls (Kermani et al., 2008: 205-208). Furthermore, in another study, it was shown that there was a correlation between increased CSF leptin and IL-6 level in CSF and waist circumference (Ball et al., 2009: 863-869). Oligoclonal bands, a marker of intrathecal inflammation, were found to be positive in the CSF of approximately one-third of IIH patients (Altıokka-Uzun et al., 2015;1153-1161). IL-1β, IL-8, and TNF-α levels of proinflammatory cytokines in serum and CSF of IIH patients were found to be increased, especially during relapse (Samancı et al.,

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2017:525- 531). In another study in which 14 different cytokines were studied, IL-17 and IL-2 levels were found to be higher in CSF compared to the control group, which was reported to support intrathecal inflammation (Edwards et al.,2013:234-244). El-tamawy et al. found that serum IL-4, IL-10, and TNF alpha levels were higher in IIH patients compared to the control group and that TNF alpha levels were higher in IIH patients with positive oligoclonal bands. They did not find a correlation between IL-4, IL-10, and TNF alpha levels and BMI (2019:1-5). Unlike that study, in our study, we found a positive correlation between BMI and NLR and CSF pressure. Furthermore, we found a significant correlation between patients with NLR of 1.95 and above and CSF pressure. However, we could not find any correlation of these findings with cranial MRI findings.

In our study, we used serum white blood cell count and NLR to show inflammation in IIH patients and found it significantly higher in IIH patients. Furthermore, our data showed that there was a significant correlation between the values of NLR 1.95 and above and CSF pressure. With these results, it can be considered that NLR can be used as a biomarker to show inflammation in IIH patients. Furthermore, due to its correlation with CSF pressure, these values may provide an idea about CSF pressure in the follow-up of IIH patients. The BMI of our IIH patients was higher compared to the control group, and we found a positive correlation between BMI and CSF pressure and NLR, which supports the effect of obesity both on inflammation and CSF pressure, similarly to other studies.

In conclusion, the etiopathogenesis of IIH has not been fully understood, and the existing findings are associated with obesity and related inflammation. With the results obtained, it can be said that increased inflammation can be demonstrated in IIH patients with serum NLR level, which is an easily accessible and inexpensive method, and that increased NLR may be associated with BMI and increased CSF pressure.

Our study had some limitations. Firstly, the number of patients was relatively low. Since our study was retrospective, some data such as vision loss severity and visual field assessment could not be accessed from the patient files. White blood cell count and NLR were evaluated only in patient sera in order to show inflammation. Furthermore, patients were not re-evaluated after medical and/or surgical treatment and weight loss. In future studies, the evaluation of CSF pressure and BMI with more inflammatory markers in both CSF and serum before and after treatment with a higher number of patients may help to shed light on the etiology of IIH.

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