Akromegali Hastalarında Hematolojik İndeksler ve Tedavi ile İlişkisi

Hematological Indices and Their Relationship with Treatment in Acromegaly Patients

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ÖZ

GİRİŞ ve AMAÇ: *Nötrofil/lenfosit oranı (NLR), monosit/lenfosit oranı (MLR), eritrosit dağılım genişliği (RDW) ve trombosit dağılım genişliği (PDW) popüler inflamasyon markerlarıdır. Bu çalışma akromegali hastalarında NLR, MLR, RDW ve PDW'yi değerlendirmeyi ve akromegali tedavisinin bu parametreler üzerindeki etkisini araştırmayı amaçlamaktadır.*

YÖNTEM ve GEREÇLER: *89 akromegalik hastanın retrospektif NLR, MLR, RDW ve PDW verileri yaş, cinsiyet, hipertansiyon ve diyabet varlığı açısından eşleştirilmiş 60 kontrol grubu ile karşılaştırıldı. Ayrıca hastaların postoperatif sonuçları, medikal tedavi ile hastalık kontrolü sağlanan hastalarda medikal tedavi sonrası sonuçlar ve kontrolsüz hastaların tedavi sonrası verileri preoperatif verileri ile karşılaştırıldı*

BULGULAR: *Ameliyat öncesi aktif akromegali hastalarında NLR ve MLR kontrol grubuna göre anlamlı olarak yüksekti. PDW ve RDW kontrol grubuyla benzerdi. Postoperatif kür sağlanan hastalarda NLR'de anlamlı azalma vardı. MLR'de de azalma sağlandı, ancak fark istatistiksel olarak anlamlı değildi. PDW ve RDW preoperatif değerlerle benzerdi. Remisyon sağlanamayan hastalarda preoperatif değerler medikal tedavi sonrası değerlerle benzerdi.*

TARTIŞMA ve SONUÇ: *NLR, akromegali için yararlı bir inflamasyon belirteci olarak düşünülebilir. Postoperatif kür, akromegali hastalarında inflamasyonda önemli bir azalma sağlayabilir.*

Anahtar Kelimeler: *akromegali, hematolojik indeksler, inflamasyon*

ABSTRACT

INTRODUCTION: *Neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), erythrocyte distribution width (RDW) and platelet distribution width (PDW) have been more popular inflammation markers. The present study aims to evaluate NLR, MLR, RDW and PDW in acromegalic patients and to investigate the effect of acromegaly treatment on these parameters.*

METHODS: *NLR, MLR, RDW and PDW values were compared using retrospective data 89 acromegalic patients and 60 controls matched with respect to age, gender, the presence of hypertension and diabetes mellitus. In addition, patients' postoperative outcomes, outcomes following medical treatment in patients in whom disease control was achieved with medical therapy and post-treatment data of uncontrolled patients were compared using preoperative data.*

RESULTS: *During the preoperative active acromegaly phase, NLR and MLR were significantly higher compared to the control group. PDW and RDW were comparable with the control group. Patients who were cured postoperatively had a significant reduction in NLR. Reduction was also achieved in MLR but the difference was not statistically significant. PDW and RDW were similar with preoperative values. In patients in whom remission could not be achieved, preoperative values and values following medical treatment were comparable.*

DISCUSSION AND CONCLUSION: *NLR can be considered a useful inflammation marker for acromegaly. Postoperative cure can constitute a significant reduction inflammation in acromegaly patients.*

Keywords: *acromegaly, haematological indices, inflammation*

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Başvuru Tarihi: 15.06.2020

Kabul Tarihi:29.04.2021

INTRODUCTION

Acromegaly is a rare endocrine disease caused usually by the pituitary adenoma secreting autonomous growth hormone (GH) (1). GH and insulin like growth factor -1 (IGF-1) mediates many biochemical pathways and promotes cell growth. Acromegaly is therefore associated with severe morbidity and mortality. The most common causes of mortality in acromegaly are cardio-cerebrovascular, respiratory events and malignancies (2-4). Hypertension is observed in 17-51% of acromegalic patients, diabetes mellitus 9-23% and may contribute to increased mortality (5).

The primary treatment choice in acromegaly patients is pituitary surgery. In most patients, medical treatment [somatostatin analogs (SSAs), dopa¬mine agonist and GH receptor antagonists] and/or radiotherapy are used as an adjuvant treatment for disease control postoperatively. With disease control, left ventricle hypertrophy and dysfunction may be improved, dilated cardiomyopathy may be reversed, endothelial function may be improved, and there may be some improvement in diabetes and hypertension (6).

NLR, MLR, PDW and RDW are simple inflammatory markers that can easily be obtained through whole blood count. The interest in these parameters has increased over the recent years. Many studies have shown that these subclinical inflammatory markers are either markers of diabetes mellitus, (7,8) ischemic heart disease, (9,10) malignancies (11,12) and many other diseases (13) are associated with the complications of these conditions or are indicators of their prognoses. Previous studies have established that inflammatory markers including fibrinogen, p-selectin, endothelin, mean platelet volume (MPV) may be elevated in acromegalic patients (14-16). Furthermore, a limited number of studies have demonstrated that the levels of inflammatory markers remained unchanged or were reduced with complete or partial control of the disease (14,17,18).

The relationship of NLR and PLR with glucose status and IGF-1 levels was investigated previously but treatment association has not been studied. Treatment relationship of RDW was evaluated previously. MLR has never been studied in acromegalic patients. The present study aims to compare NLR, MLR, PDW and RDW for inflammatory status between acromegalic patients and matched controls and to determine the changes in these inflammatory markers in patients cured with surgical treatment or in those in whom disease control was achieved following surgical and medical treatment.

METHODS

Patients

The files of 129 acromegaly patients treated in our outpatient clinic between 2009 and 2018 were examined retrospectively. Acromegaly was diagnosed based on the presence of the classic clinical appearance of acromegaly, increased IGF-1 levels according to age and gender, failure to suppress GH below 1ng/ml following 75 g oral glucose tolerance test (OGTT) and presence of adenoma in the pituitary gland with magnetic resonance imaging (6).

Patients with conditions that may affect whole blood count including active infection, inflammatory disease, congenital or acquired hematologic disease, anemia, B12 or folic acid deficiency and those with undertreated pituitary hormone deficiency were excluded from the study. Patients with no whole blood counts during the studied period and those whose some data were missing were also excluded from the study. Thus, 89 patients with diagnosed acromegaly and 60 controls matched with respect to age, gender, hypertension and diabetes mellitus were included in the study. Information on patients' histories, clinical and demographical data, and remission status was retrieved from the patient registry of our outpatient clinic. Patients' GH, IGF-1, neutrophil, lymphocyte, monocyte, RDW and PDW values during the preoperative active disease phase, at postoperative 6 month and following medical treatment in patients in whom cure could not be achieved with surgery were recorded. For patients who had two or more whole blood counts during the same period, the mean of the values was considered. Postoperative cure was defined as baseline or post-OGTT GH<0.4 ng/ml and IGF-1 which fell within the range normal for age and gender. Controlled disease was defined as post-medical treatment IGF-1 value that is within the

normal range for age and gender.

Control group was consist of healthy nondiabetic subjects working in our hospital and diabetic and/or hypertensive patients without any other diseases, in our outpatient clinic. These patients had no other infectious or inflammatory disease that could affect complete blood count. IGF-1 levels were also normal, so that acromegaly was ruled out.

Laboratory analysis

Serum GH was assessed by electrochemiluminescence immunoassay (human GH kit, Architect c8000 Chemistry Analyzer, Abbott Diagnostics). The baseline GH samples were taken at 8 a.m. following an overnight fast. In terms of confirming the diagnosis of acromegaly, blood GH measurements were initially performed following an overnight fasting, and were then repeated every 30 min for a total of 120 min after administration of 75 g glucose. Serum total IGF-1 was assessed by immunometric chemiluminescence assay (IMMULITE 2000, Siemens, Washington, DC,USA).

Neutrophil (2-8 x 103 µl), lymphocyte (1-5 x 103 µl), Monocyte (0.24-0.79x103 µl), RDW (%11.5-14.5) and PDW (16-19) counts were measured using an automated whole blood counter (sysmex XE-2100 , Japan coefficient of variation%3). NLR and MLR were calculated via projection of these data. NLR, MLR, PDW and RDW data of the controls and acromegaly patients during the preoperative active disease period were compared. Preoperative and postoperative 6 month NLR, MLR, RDW and PDW values of the patients in whom postoperative cure was achieved and preoperative and post-medical treatment NLR, MLR, PDW and RDW values of the patients in whom postoperative cure could not be achieved were compared.

The study was performed after obtaining the approval of the ethics board of our hospital (KÜ GOKAEK 2017/162).

Statistical analysis

Statistical analyses were performed using SPSS 17.0 software. (indicate the source and year released) The data were first analyzed for normality using Kolmogorov–Smirnov tests. Nonparametric tests were employed when the distribution of the data was not normal. Variables were also evaluated with Pearson's and exact χ^2 tests. Correlation analysis was done with the Spearmen correlation test. A P value <0.05 was considered statistically significant.

RESULTS

Eighty nine acromegaly patients and sixty control groups were included in this study. There were no statistically significant differences in age, gender, presence of hypertension and diabetes mellitus between the study groups (p>0.05)

Patient's clinical and demographical data are summarized in table I.

Table I. Comparison of demographic data and hematological indices between groups

	Acromegaly (n:89)	Control (n:60)	P value
Gender (women/men)	42/47	32/28	0,46
Age (year)	45±10	48±11	0,1
Diabetes Mellitus	23	17	0,42
Hypertension	28	22	0,6
NLR	1.98(1.63-2.77)	1.30(1.11-1.52)	**<0,001**
MLR	0,23 (0,17-0,32)	0,19 (0,14-0,23)	**0,004**
PDW	17,5 (17-18,1)	17,3 (16,9-17,9)	0,22
RDW	15,4 (14,6-16)	15,2(14,6-16)	0,90

During the preoperative active acromegaly period, NLR (p:0.000) and MLR (p:0.004) were significantly higher compared to the control group.

All patients (n=89) had undergone transsphenoidal pituitary surgery and cure was achieved in 47 (53%) of them following surgery. Disease control was achieved following surgery in 29 patients (33%) with SSAs and/or dopamin agonist cabergoline. Disease control could not be achieved in 13 patients (14%) despite surgery and maximal medical treatment.

In patients in whom postoperative cure was achieved, there was a significant reduction in postoperative sixth month NLR compared to preoperative NLR (p: 0.001). MLR (p:0.058)

decreased, but not statistically significantly. Postoperative sixth month PDW and RDW (p:0,62-0,64 respectively) were similar to the preoperative values. In patients in whom remission was achieved with medical treatment, preoperative values and values after remission was achieved were comparable for all parameters. In patients with uncontrolled disease, preoperative and postoperative values and preoperative and post-medical treatment values were comparable (table II, III, IV, V).

Also, we evaluated the relationship between IGF-1 level and NLR, MLR, PDW and RDW in newly diagnosed acromegaly patients. We could not find any positive correlation between IGF-1 and NLR (r:-0,03 p:0,76), MLR (r:0,02 p:0,82), RDW (r:-0,02 p:0,80), PDW (r: 0,1 p:0.35).

Table II. Evaluation of NLR values of acromegaly patients according to treatment modalities

	Preoperative NLR	Postoperative NLR	aftersurgery + medical treatment NLR	P value
Entire group (n:89)	1.98(1.63-2.77)	1,63(1,30-2,10)	1,67(1,23-1,99)	**0,001- 0,005** respectively
Surgical cure (n:47)	2,18(1,7-2,92)	1,78(1,39-2,16)	-	**0,001**
Controlled disease (surgery+medical) (n:29)	1,71(1,54-2,20)	1,40(1,26-1,85)	1,61(1,19-1,96)	**0,011**-0,112 respectively
Uncontrolled disease (surgery+medical) (n:13)	2,03(1,81-3,005)	1,84(1,19-2,57)	1,86(1,20-2,6)	0,131- 0.15 respectively

Table III. Evaluation of MLR values of acromegaly patients according to treatment modalities

	Preoperative MLR	Postoperative MLR	aftersurgery+ medical treatment MLR	P value
Entire group (n:89)	0,23 (0,17-0,32)	0,20(0,16-0,25)	0,20(,16-,25)	**0,004** - 0,22 respectively
Surgical cure (n:47)	0,24(0,18-0,36)	0,21(0,18-0,28)		0,058
Controlled disease (surgery+medical) (n:29)	0,207(0,148-0,304)	0,182(0,141-0,207)	0,205(0,163-0,241)	**0,004,** 0,218 respectively
Uncontrolled disease (surgery+medical) (n:13)	0,211(0,158-0,282)	0,242(0,133-0,276)	0,243(0,133-0,260)	0,47-0,5 Respectively

Table IV. Evaluation of PDW values of acromegaly patients according to treatment modalities

	Preoperative PDW	Postoperative PDW	aftersurgery+ medical treatment PDW	P value
Entire group (n:89)	17,5 (17-18,1)	17,4(16,9-18,2)	17,6(±1,03)	0,071-0,197
Surgical cure (n:47)	17,4(17-18)	17,4(16,9-18,2)		0,62
Controlled disease (surgery+medical) (n:29)	17,2(16,4-18,4)	17,2(16,4-18,4)	17,7(16,6-18,4)	0,29-0,16
Uncontrolled disease (surgery+medical) (n:13)	17,7(17,3-18,6)	17,6(17-18,7)	17,5(±0,88)	0,77-0,43

DISCUSSION

The most common causes of mortality in acromegaly are cardio-cerebrovascular diseases, respiratory events and malignancies (2-4). Hypertension is seen in 17-51% and diabetes mellitus is seen in 9-23% of the patients, and they contribute to increased mortality (5). İncidence of cardiovascular disease and cardiovascular risk factors increased in acromegaly (20). With IGF-1 normalization, cardiovascular risk decreases but does not return to normal. (21,22). Studies on the levels of circulating inflammatory markers and their relationship to treatment are conflicting in acromegaly patients. (23,24)

The count of white blood cell (WBC) and subtypes and platelet counts are the classic indicators of inflammation (25). Apart from WBC count, NLR and MLR are also potential biomarkers that reflect inflammation and immune response. NLR and MLR, the new markers, are superior to neutrophil, lymphocyte, monocyte, platelet and total leukocyte counts in demonstrating inflammation. Physiologic, pathologic and physical factors affect the number of these blood components, while NLR and MLR ratio remain stable. Several studies have established a positive relationship between NLR and MLR and conventional inflammation markers. More importantly, large studies have shown a predictive effect of NLR and MLR in diabetes mellitus, acute coronary syndrome and several cancers (9,26-28). RDW and PDW reflect diameter differences in erythrocytes and platelets, respectively, and they have been shown in several studies to be inflammation markers (29,30).

Bolero et al. (15) studied inflammatory markers in patients with active acromegaly and in healthy controls. They found that OxLDL, endothelin, ceruloplasmin and thiobarbituric acid reactive substances (TBARS) concentrations were higher in active acromegaly patients compared to the control group, while myeloperoxidase, superoxide dismutase, paraoxonase-1 and platelet activating factor acetylhydrolase levels were comparable to the control group. Another study investigated the effect of prolonged GH and IGF-1 exposure on inflammatory markers and found that tumour necrosis factor (TNF)-alfa and interleukin (IL)-8 levels were higher in acromegaly patients compared to the control group, while hsCRP, homocysteine, IL-1, IL-2 receptor, IL-6 and IL-10 were comparable to the control group (31). In our study, similar this studies NLR and MLR were higher in the active acromegaly group compared to the control group, and RDW and PCT were comparable. As can be seen, the findings regarding the relationship between acromegaly and subclinical inflammation and atherosclerosis markers are inconsistent. These markers reflect all inflammatory states and therefore it may be due to the failure of matching the groups with respect to inflammatory states. Besides, the fact that some inflammatory markers increase while others decrease or remain unchanged in the same study may rather suggest that some inflammatory markers are appropriate markers and others are not. Ucler et al. (32) studied the relationships between NLR and PLR and plasma glucose and IGF-1 levels in newly diagnosed acromegaly patients, and determined a positive correlation between NLR and PLR and IGF-1. They concluded that prolonged IGF-1 exposure elevated atherosclerotic risk markers. The authors compared NLR and PLR values in diabetic and non-diabetic acromegaly patients and in acromegaly patients with impaired fasting glucose (IFG), and determined no difference. The study concluded that NLR and PLR were not practical subclinical inflammatory markers in acromegaly patients with diabetes mellitus or IFG. We examined the relationship between IGF-1 level and NLR, MLR, PDW and RDW in newly diagnosed acromegaly patients, and we could not find any positive correlation between them. We can say that inflammation does not correlate with disease severity.

Ozkan et al. (33) investigated oxidative stress and inflammation markers and their interrelationships in active acromegaly (AA), controlled acromegaly (CA) and control groups. CRP decreased and high mobility group box 1 protein (HMGB1), ox-LDL and total antioxidant capacity (TAC) were similar across AA, CA and control groups. Also they found flow mediated dilatation (FMD) decreased, carotid intima media thickness (CIMT) and epicardial adipose tissue thickness (EAT) increased in acromegaly patients. Early atherosclerosis markers increased, inflammation marker decreased, oxidative stress markers not changed in acromegaly patients in their study. They proposed that inflammation and oxidative stress do not contribute to the

development of atherosclerosis in acromegaly patients. Another study demonstrated that GH, IGF-1, insulin, fibrinogen and intima media thickness were decreased with 6-month lanreotide treatment in acromegaly patients (18). In our study, there was a significant decrease in NLR compared to preoperative values in patients in whom postoperative cure was achieved. There was also a decrease in MLR but the difference was not statistically significant. PDW and RDW were comparable to the preoperative values. In patients in whom remission was achieved with medical treatment, preoperative NLR, MLR, PDW and RDW values and values after remission was achieved with medical treatment were comparable for all parameters. Based on this result, we can say that postoperative cure produced a reduction in the inflammatory state, but disease control with medical treatment can not provide further improvement in the inflammatory state. Ucler et al. (34) investigated the effect of surgical treatment and surgery plus medical treatment on the inflammatory markers of mean platelet volume (MPV) and RDW. Similar to ours, RDW was unchanged in patients who were cured postoperatively. Unlike ours, RDW was increased in those who were controlled by medical treatment. They also were evaluated the other inflammation marker MPV in their study and found similar results with RDW. Another study showed that inflammation marker of MPV levels were higher in acromegaly patients compared to controls. They also found that MPV did not change after treatment of acromegaly patients (35). The relatively small number of patients or the unsuitable marker of MPV to assess inflammation in acromegaly may have led to this result.

Limitations of study

There were some limitations of our study. İt was a retrospective one, classic inflammation and atherosclerosis markers including endothelin and thrombomodulin could not be studied. Therefore, the correlation between the classic markers and NLR, MLR, PDW and RDW, which are considered as new inflammatory markers, could not be evaluated. Again, due to the retrospective nature, patients' body mass indexes and lipid parameters were not available. BMI and hyperlipidemia are parameters with potential impact on NLR, MLR, PDW and PCT.

Conclusion

Acromegaly can be considered an inflammatory disease both due to the direct effect of GH and IGF-1 exposure and due to the inflammatory conditions it causes. In addition, it can be concluded that this inflammation may be reduced especially by achieving cure with surgical treatment and that disease control with medical treatment is not effective in reducing the inflammation. Well-designed prospective studies are needed to support this data. In addition, NLR and MLR are appropriate inflammatory markers to evaluate inflammation in acromegaly, whereas RDW and PDW do not seem to be of much benefit.

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