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Original Article

The effect of growth hormone deficiency on inflammatory markers in Sheehan's syndrome

Murat Alay[1], Saliha Yildiz[1], Aysegul Sakin[2], Gulcin Miyase Sonmez[3]

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey
[2]Department of Internal Medicine, Van Research and Training Hospital, Van, Turkey
[3]Department of Internal Medicine, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey

Abstract

Aim: Mean platelet volume (MPV), lymphocyte count (LC), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are currently gaining interest as new markers of inflammation and independent risk factors for cardiovascular diseases. The aim of this study was to evaluate the effect of growth hormone (GH) deficiency on MPV, NLR, and PLR values in patients with Sheehan's syndrome.

Materials and Methods: 23 women with Sheehan's syndrome (SS), and 30 healthy women as control group were included in the study. The study was performed retrospectively. Demographic and clinical characteristics, hormone and haematological parameters of subjects were evaluated. MPV, NLR, PLR and LC values were compared between two groups.

Result: The mean age of SS and control groups were 53.1 ± 11.1 and 55.1 ± 10.5 years, respectively. MPV, PLR, NLR were lower and LC was higher in SS group than the control group. (p = 0.010, 0.033, 0.017, 0.010 respectively). A significant positive correlation was found between insulin-like growth factor1 (IGF1) and MPV, PLR in the SS group (p = 0.003 r: 0.62, p: 0.033 r: 0.46).

Conclusion: MPV, NLR, PLR were lower and LC was higher in SS group compared to control group. There was a significant positive correlation between IGF1 and MPV, PLR in the SS group. These results showed that growth hormone deficiency led to a decrease in some inflammatory markers such as MPV, NLR, PLR. Increased LC in these patients may indicate inflammation.

Keywords: Mean platelet volume; neutrophil to lymphocyte; sheehan syndrome

INTRODUCTION

Sheehan syndrome is defined as postpartum pituitary dysfunction due to pituitary necrosis. It usually occurs because of serious hypotension or shock caused by large volume hemorrhage during delivery (1,2). It has been reported that pituitary insufficiency caused by sheehan syndrome is very infrequent in the developed regions and countries due to well-advanced obstetric care (3,4). It is probably the most common cause of pituitary insufficiency in developing countries. Varying degrees of hypopituitarism occurs in 32% of women who have massive postpartum bleeding history (5,6). The presence of a typical obstetric history in women with clinical evidence of hypopituitarism is an important clue for SS. The diagnosis of SS is made by assessment of pituitary function with pituitary hormone levels or provocative tests and pituitary gland imaging.

In the literature, we have not found any study that investigated the relationship between inflammatory markers and pituitary hormone deficiencies in Sheehan syndrome. Various studies of estrogen and growth hormone (GH) deficiency, demonstrate that deficiencies of these hormones cause blood pressure changes, hyperlipidemia and visceral fat accumulation, and ultimately accelerate atherosclerosis due to the release of proinflammatory cytokines and increase the risk for cardiovascular disease mortality (7,8).

Atherosclerosis is the main underlying cause of coronary heart diseases. Platelets and their interaction with the vessel walls play a major role in atherogenesis and coronary thrombus formation (9). MPV is a measurement of platelet volume calculated with complete blood count devices. It has been known that elevated MPV values correlate with metabolically active, larger platelets and also increased risk of thrombosis (9,10). In the literature, the relationship between high MPV levels and increased cardiovascular disease incidence has been demonstrated. (11-13).

NLR, PLR and other hematological inflammation markers have been stated as independent risk factors and predictors of various diseases (14,17,18).

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Corresponding Author: Murat Alay, Department of Endocrinology and Metabolism, Faculty of Medicine, Yuzuncu Yil University, Van, Turkey **E-mail:** dr.muratalay@hotmail.com

In our study, we aimed to evaluate the effect of growth hormone (GH) deficiency on MPV, NLR and PLR values, in patients with Sheehan's syndrome who do not receive GH replacement.

MATERIALS and METHODS

Subjects

This study was conducted retrospectively reviewing the electronic medical record of the subjects. 23 patients who were previously diagnosed with SS and followed up by Yuzuncu Yil University Medical School, Department of Endocrinology and age matched 30 healthy women as control group were enrolled in the study. Between June 2018 and May 2019, medical history, physical examination, routine laboratory tests, pituitary hormone analysis, pituitary MR imaging of the all participants were reviewed. 23 female patients with SS were treated with corticosteroids and levothyroxine substitution, without GH replacement. Eight premenopausal women with SS were receiving hormone replacement therapy. The ages of the SS patients were between 33-81 years. Sheehan Syndrome was diagnosed based on history of postpartum hemorrhage, deficiency of pituitary hormones after dynamic tests, and the presence of empty sella on pituitary gland MRI. The control group consisted of 30 healthy women in a similar age range (34-79 years) with the SS group. There were 7 premenopausal women in the control group. Detailed anamnesis, age, weight height, body mass index (BMI; kg/m^2), arterial blood pressure and laboratory values of all subjects were recorded.

Patients with a history of taking anti-platelet agents, renal failure, coronary artery disease, hematological disorders, cerebrovascular event, hepatic or biliary disease, cancer, acute or chronic infection, auto-immune disease, hyperlipidemia, diabetic nephropathy, diabetic retinopathy and iron deficiency or nutritional anemia were excluded from the study. Participants did not take iron or vitamin supplements.

The study was approved by the Regional Ethics Committee for Medical Research at Van Yuzuncu Yil University and was performed according to the declaration of Helsinki.

Fasting venous blood samples were taken in the morning after an overnight fast of at least 8 hours. Complete blood count (CBC) tests were analyzed using an automated hematology analyzer (Coulter Hmx; Beckman Coulter [UK] Ltd, High Wycombe). Based on data from the CBC analysis, NLR was obtained by dividing neutrophil count by lymphocyte count and PLR was measured by dividing platelet count by lymphocyte count. The reference range of MPV, a parameter that is routinely measured in CBC analysis, was considered to be 7.0 to 11.0 fl.

Serum GH was measured using an electro-chemiluminescence-immunoassay (ECLIA) (hGH kit, Architect c8000 Chemistry Analyzer, Abbott Diagnostics, IL, USA). The immunochemiluminescent assay was used to evaluate IGF-1 (IMMULITE 2000, SIEMENS, USA). IGF-I levels were assessed using reference intervals adjusted for age.

Statistical Analysis

Data distribution normality was assessed using the Shapiro–Wilk test. Continuous variables were presented as means±SD if normally distributed and as medians (minimum–maximum) if not+ normally distributed. Group differences were assessed using Student's t-test or the Mann–Whitney U-test. Correlations between laboratory levels, clinical and metabolic parameters were evaluated using Pearson's correlation (for normally distributed data) or Spearman's rank test (for not normally distributed data). Chi-square test and likelihood ratio test were used to determine the relationships between categorical variables. P <0.05 was considered statistically significant.

RESULTS

Tweenty-three female patients with SS (mean age 53.1 ± 11.1 years) and 30 healthy female subjects (mean age 55.1±10.2 years) were enrolled in the study. SS and control groups did not differ significantly in age, systolic blood pressure, diastolic blood pressure, weight, height and BMI (Table 1).

Table 1. Comparison of demographic data of case and control group

Caracteristics	Sheehan syndrome (n=23)	Control (n=30)	p*
Weight(kg)	66.5±10.8	67.9±7.64	0.610
Height(cm)	153.7±4.77	151.9±4.06	0.180
BMI(kg/m^2)	28.7±3.58	28.7±4.23	0.973
Age	53.1±11.9	55.1±10.2	0.534
Systolic Blood Pressure	119.9±5.96	79.4±6.28	0.774
Diastolic Blood Pressure	72.7±7.03	73.2±7.43	0.839

BMI: Body Mass Index
* Paired t-test was used for comparison of the groups

The last delivery age was 32.4±7.06 with the mean disease duration 22.7 ± 10.7 years in SS group. The mean delay in the diagnosis of SS (the period between delivery and diagnosis of SS) was 14.6±8.1 years (Table 2).

Table 2. Delay in time of diagnosis

	N	Mean
Age of mother at diagnosis	23	47.0±9.6
Age of mother at last birth	23	32.4±7.0
Delay in diagnosis	23	14.6±8.1
Estimated disease duration	23	22.7±10.7

GH, IGF1, MPV, PLR and NLR were lower and LC was higher in the SS group (p = 0.013, 0.001 0.010, 0.033, 0.017, 0.01 respectively) (Table 3).

In receiver-operating characteristic (ROC) curve analysis, the MPV for Sheehan's syndrome was found to be ≤ 8.35 fL with 69.6% sensitivity and 75% specificity (Figure 1).

Table 3.Statistical comparison of laboratory values

Caracteristics		Sheehan syndrome Median(min- max)	Control Median(min-max)	p
GH	(ng/ml)	0.15(0.05-1.23)	0.98(0.05-7.65)	0.013 *
IGF-1	(ng/ml)	50.9(15-138)	90.9(15-263)	0.001*
Estradiol	(pg/ml)	10(239-10)	21(208-10)	0,000 *
MPV	(fl)	8.40(7.40-9.90)	8.90(0.55-8.00)	0.010 *
NLR		1.20(0.57-8.01)	1.83(0.85-3.53)	0.017*
PLR		90.71(43.38-201.16)	111.23(51.16-288.70)	0,033 *
LC	(/mm^3)	3457 ± 1126	2389 ± 858	0,01**
PC	(/mm^3)	302533±67920	270421± 73897	0.12**
NC	(/mm^3)	4577 ± 2392	4093 ± 1412	0.40**

MPV: Mean platelet volume, GH: Growth Hormone, N/LR: Neutrophil-to-lymphocyte ratio, IGF-1: Insulin-like growth factor 1, LC: Lymphocite count, PC: Platelet count, NC: Neutrophil count.
* Mann-Whitney U Test, ** Student T test

Table 4. Correlation between labarutovar parameters of case group

Caracteristics		MPV	PLR	NLR
IGF1	Pearson Correlation	.623**	.467*	0.19
	Sig. (2-tailed)	0.00	0.03	0.42
fT3	Pearson Correlation	.430*	-0.16	-0.28
	Sig. (2-tailed)	0.04	0.46	0.19
fT4	Pearson Correlation	.430*	-0.16	-0.28
	Sig. (2-tailed)	0.04	0.46	0.19
GH	Pearson Correlation	0.29	0.12	-0.10
	Sig. (2-tailed)	0.17	0.58	0.65
TSH	Pearson Correlation	-0.17	0.24	-0.10
	Sig. (2-tailed)	0.44	0.26	0.64
ACTH	Pearson Correlation	0.37	0.10	-0.24
	Sig. (2-tailed)	0.12	0.69	0.32
Estradiol	Pearson Correlation	0.28	0.20	-0.03
	Sig. (2-tailed)	0.18	0.35	0.89
FSH	Pearson Correlation	0.22	0.05	-0.20
	Sig. (2-tailed)	0.31	0.81	0.35
LH	Pearson Correlation	0.34	0.17	-0.14
	Sig. (2-tailed)	0.11	0.43	0.50

ACTH: Adrenacorticoid hormone, FSH: Follicule Stimulating Hormone, LH: Luteinizing Hormone, TSH: Thyrotrophin-Stimulating Hormone, fT4: Free thyroxine, fT3: Free Triiodothyronine

There was no correlation between GH, ACTH, TSH, LH, FSH, estrogen, and MPV, NLR, PLR, but there was a significant positive correlation between IGF1 and MPV, PLR in SS group (p = 0.003 r: 0.62, p: 0.033 r: 0, 46) (Table 4).

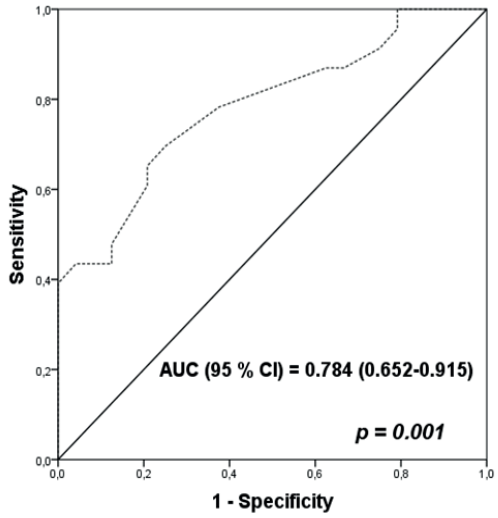

Figure 1. RoC curve according to MPV value of patients with Sheehan's Syndrome

DISCUSSION

Adults with hypopituitarism have a 2-fold higher risk of death from cardiovascular disease than healthy individuals (19). The development of atherosclerotic lesions is considered to be caused by chronic inflammatory processes. (20). It is demonstrated that the deficiencies of estrogen and growth hormone (GH) cause hyperlipidemia, blood pressure changes and visceral fat accumulation, and increase the risk of cardiovascular mortality by stimulating inflammation (17,18). Elevated MPV is found to be related with the inflammation and increased risk of cardiovascular disease (21-23). In this study, we compared MPV, NLR, PLR values, which were shown as an inflammatory marker, between healthy control group and patients with Sheehan syndrome. We found decreased MPV, NLR, PLR levels and increased lymphocyte count in patients with SS.

Postmenopausal estrogen deficiency significantly increases the risk of cardiovascular disease (17). Butkiewicz et al. compared MPV values of post-menopausal and pre-menopausal women and reported no statistical difference between the groups. (27). In another study, Ranganath et al. investigated the effect of hormone replacement therapy (HRT) on MPV before and at the end of the 6-week HRT period in post-menopausal women. They showed a significant increase in MPV after 6 weeks of HRT (28). Similar to this study, we found a significant decrease in MPV in SS group. We believe that the decrease in MPV may be associated with gonadotropin deficiency in SS.

Arikan et al. determined increased serum TNF-α and IL-8 levels in newly diagnosed acromegalic subjects compared to control group (24). Ersoy et al. reported no significant difference in MPV levels between acromegaly and control groups, but a significant decrease in MPV was observed 6 months after therapy (25). Furthermore, Unübol et al. demonstrated an increase in MPV in patients with acromegaly (26). Similar to the studies in the literature, we found low MPV levels in SS patients with low IGF 1. According to these results, we think that high MPV levels in patients with acromegaly were low in SS patients because of Growth Hormone deficiency. There may be two reasons for this; either MPV levels are associated with GH levels rather than inflammation, or high growth hormone levels in acromegaly activates inflammatory processes.

Ücler et al. reported that there was a significant positive relationship between NLR, PLR and IGF-1 levels in newly diagnosed acromegalic patients, and suggested that this may be evidence of inflammation in acromegalic patients (29).

In our study, IGF 1 levels were positively correlated with MPV and PLR levels in patient with SS. We found a statistically significant decrease in MPV, NLR, PLR values and a significant increase in LC in SS group. ($p = 0.010$, 0.017, 0.033, 0.01, respectively).

The direct effect of hormone deficiencies on hematopoiesis can affect hematological parameters (30,31). In the literature, individual case reports and case series of Sheehan's syndrome presenting with pancytopenia or bone marrow abnormalities were reported. In these cases, it was determineted that multiple anterior pituitary hormone deficiencies were responsible for pancytopenia and replacement of hormones resulted in improvement in blood count values (30). Sohmiya et al. suggested that administration of rhGH in adults with GH deficiency led to increased serum G-CSF levels and neutrophil counts (31).

In our study, we could not obtain the expected inflammatory marker changes in gonadotropin or growth hormone deficiency, except for an increase in LC and a decrease in MPV. These results suggest that changes in complete blood count parameters in SS patients can be explained not only by inflammatory processes but also hormone deficiencies It is clear that there is a complex relationship between pituitary hormone deficiency and inflammatory cells.

We have not found any study in the literature investigating the effect of hormone deficiency on MPV, NLR, PLR, LC in Sheehan syndrome. This is the first study on this subject. The limitations of this study were that it contained low number of cases and no other inflammatory markers (such as C-Reactive Protein (hsCRP), interleukin (IL)18, IL18 binding 169 protein (IL18BP) and IL6 level).

In conclusion, we demonstrate that MPV, NLR and PLR levels were significantly lower and LC was higher in patients with SS. In our study, MPV and PLR were significantly correlated with the presence of SS.

CONCLUSION

We believe that hematological changes in SS involve complex processes that cannot be explained for a single reason. Our observations may help improve the understanding of the interactions between pituitary hormone deficiency and human hematopoiesis. Larger prospective studies are needed to evaluate the relationship between inflammatory parameters and hormone deficiencies in sheehan's syndrome.

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

Financial Disclosure: There are no financial supports.

Ethical approval: The study was approved by the Regional Ethics Committee for Medical Research at Van Yuzuncu Yil University.

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