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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Complete Blood Count Parameters as Prognostic Markers for Remission of Graves' Disease with Medical Therapy in Children

Tam Kan Sayımı Parametrelerinin Çocuklarda Graves Hastalığı'nın Medikal Tedavi ile Remisyonu için Prognostik Belirteç Olarak Değerlendirilmesi

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ABSTRACT

Objective: Graves' Disease (GD) is an autoimmune disease that causes hyperthyroidism. This study intended to find out whether leukocyte, neutrophil, lymphocyte, platelet counts, and neutrophil-to-lymphocyte ratio (NLR) and systemic immun-inflammation index (SII) have an association with the remission of GD.

Material and Methods: Thirty-seven children who have GD have been included in the study. Anthropometric measurements, physical examination and medical history of patients were recorded. Leukocyte, neutrophil, lymphocyte, platelet counts, NLR and SII at the time of diagnosis and at the end of medical therapy were compared between patients in remission (group 1) and patients not in remission (group 2).

Results: The rate of patients in remission was 54%. The presence of palpitation was higher in group 2 than group 1 (p=0.026). At the time of diagnosis, the leukocyte and neutrophil counts were higher in group 1 (p=0.001 and p=0.014, respectively). While the absence of palpitation increased the rate of remission 6.0 (95% CI: 1.1-33.1) times, the rate of remission increased 2.4 (95% CI: 1.1-5.2) times as the neutrophil count increased (p=0.041 and p=0.031, respectively). In group 2, there was an increase in leukocyte and neutrophil counts, NLR and SII after medical therapy compared to the levels at the time of diagnosis (p=0.049, p=0.008, p=0.002 and p=0.001, respectively).

Conclusion: Presence of palpitation and lower neutrophil count at the time of diagnosis and increase in leukocyte count, neutrophil count, NLR and SII levels after medical therapy could be prognostic markers for not achieving remission with medical therapy of GD in children.

Keywords: Graves' Disease, Children, Remission, Prognostic Markers, Neutrophil-To-Lymphocyte Ratio, Systemic Immun-Inflammation Index

ÖZ

Amaç: Graves hastalığı (GH), hipertiroidizme neden olan otoimmün bir hastalıktır. Lökosit, nötrofil, lenfosit, trombosit sayıları ve nötrofil-lenfosit oranı (NLO) ve sistemik immün-enflamasyon indeksinin (SII) GH remisyonu ile bir ilişkisi olup olmadığını bulmayı amaçladık.

Gereç ve Yöntem: Çalışmaya GH olan otuz yedi çocuk dahil edildi. Hastaların antropometrik ölçümleri, fizik muayeneleri ve tıbbi öyküleri kaydedildi. Remisyonda olan (grup 1) ve remisyonda olmayan (grup 2) hastaların tanı anında ve medikal tedavi sonunda lökosit, nötrofil, lenfosit, trombosit sayıları, NLO ve SII değerleri karşılaştırıldı.

Bulgular: Remisyondaki hasta oranı %54 idi. Çarpıntı varlığı grup 2'de grup 1'e göre daha yüksekti (p=0,026). Tanı anında lökosit ve nötrofil sayıları grup 1'de daha yüksekti (sırasıyla p=0,001 ve p=0,014). Çarpıntı olmaması remisyon oranını 6,0 (%95 CI: 1,1-33,1) kat artırırken, nötrofil sayısı arttıkça remisyon oranı 2,4 (%95 CI: 1,1-5,2) kat artmış olarak bulundu (p=0,041 ve p= sırasıyla 0.031). Grup 2'de medikal tedavi sonrası lökosit ve nötrofil sayılarında, NLO ve SII'de tanı anına göre artış saptandı (sırasıyla, p=0,049, p=0,008, p=0,002 ve p=0,001).

Sonuç: Çocuklarda tanı anında çarpıntı olması ve nötrofil sayısının düşük olması, medikal tedavi sonrasında ise lökosit sayısı, nötrofil sayısı, NLO ve SII düzeylerinde artış olması GH'da medikal tedavi ile remisyona girmemeye ilişkin prognostik belirteçler olabilir.

Anahtar Kelimeler: Graves Hastaliği, Çocuklar, Remisyon, Prognostik Belirteçler, Nötrofil-Lenfosit Orani, Sistemik Immün-Enflamasyon Indeksi

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INTRODUCTION

Hyperthyroidism occurs due to an inappropriately high synthesis and secretion of thyroid hormone by the thyroid gland and the most frequent causes are Graves' disease (GD) and toxic nodular goiter (1). GD is an autoimmune disease that causes hyperthyroidism through the stimulation of a thyroid stimulating hormone receptor antibody (TRAb), but the exact pathogenic mechanisms are not fully clear. The incidence of GD is about 1-3/100,000 patients per year in children and adolescents (2). The diagnosis is made by a biochemically confirmed thyrotoxicosis, positive TRAb, a hypervascular and hypoechoic thyroid gland (ultrasound) and associated orbitopathy (1).

There is no consensus on the optimal treatment of GD in children and adolescents because every treatment has some complications. The treatment options are anti-thyroid drugs, surgical interventions or radioactive iodine therapy and most patients are initially treated with anti-thyroid drugs (3,4).

Remission rates have been reported at about 30% in children (5). There are many studies evaluating the predictive factors for remission. Absence of goiter, lower TRAb levels at diagnosis, older age at diagnosis, lower free thyroxine (fT4) levels at diagnosis, higher initial medical therapy dosage, and longer duration of medical therapy are shown to have a relation with the remission rate (2,6,7). In some autoimmune and cancer diseases new blood count-derived inflammatory indexes such as neutrophil-to-lymphocyte ratio (NLR), systemic immune inflammation index (SII), and a platelet/lymphocyte ratio have been searched for the prediction of progress of the disease (8-10). Natural killer cells were evaluated as an immunological

Table 1: Demographic and clinical characteristics of two groups at the diagnosis

	Group 1 (n=20)	Group 2 (n=17)	p
Age (years)	14.5 ± 3.0	14.0 ± 3.0	0.57
Sex (M/F)	1/19	6/11	**0.033**
Height (SDS)	-0.06 ± 1.27	0.10 ± 1.0	0.68
Weight (SDS)	-0.10 ± 1.38	-0.03 ± 1.15	0.87
BMI (SDS)	-0.07 ± 1.30	0.05 ± 1.29	0.86
Puberty stage			0.66
1	1 (5%)	1 (5.9%)	
2	1 (5%)	2 (11.8%)	
3	3 (15%)	1 (5.9%)	
4	0 (0%)	1 (5.9%)	
5	15 (75%)	12 (70.5%)	
Admission complaint			
Weight loss	7 (35%)	4 (24%)	0.45
Palpitation	8 (40%)	13 (76%)	**0.026**
Sweating	2 (10%)	2 (12%)	0.86
Tremor	2 (10%)	1 (6%)	0.65
Increased appetite	1 (5%)	0 (0%)	0.91
Swelling in the neck	3 (15%)	3 (18%)	0.83
Family history of dysthyroidism			0.13
None	6 (30%)	5 (29%)	
1st degree	2 (10%)	5 (29%)	
2nd degree	11 (55%)	9 (53%)	
3rd degree	2 (10%)	1 (6%)	
Goiter			0.72
None	5 (25%)	6 (35%)	
Grade 1b	4 (20%)	3 (18%)	
Grade 2	10 (50%)	6 (35%)	
Grade 3	1 (5%)	2 (12%)	

Group 1: patients in remission, Group 2: patients not in remission, M: male, F: female, SDS: standart deviation score, BMI: body mass index

Table 2: The medical therapy status and the laboratory parameters at the diagnosis of group 1 and group 2

	Group 1 (n=20)	Group 2 (n=17)	p
Medical therapy time (months)	17 (10-32)	36 (36-36)	**<0.001**
Initial dose (mg/kg/day)	0.38 (0.34-0.48)	0.37 (0.35-0.42)	0.95
TSH (mU/L)	<0.01	<0.01	0.99
fT4 (ng/L)	30.2 (21.7-41.2)	36.3 (25.7-41.4)	0.46
fT3 (ng/L)	13.4 (8.4-20.0)	15.7 (14.4-19.4)	0.14
TPOAb (kU/L)	565 (186-716)	418 (246-782)	0.84
TgAb (kU/L)	343 (217-609)	441 (211-757)	0.49
TRAb	4.5 (1.7-12.6)	7.2 (4.1-10.4)	0.29
Leukocyte count (10^9/L)	7.7 (6.7-9.3)	6.5 (5.8-6.9)	**0.001**
Neutrophil count (10^9/L)	3.8 (3.2-5.1)	3.1 (2.5-3.7)	**0.014**
Lymphocyte count (10^9/L)	2.6 (2.2-3.2)	2.4 (2.1-2.9)	0.46
Platelet count (10^9/L)	312 (279-336)	235 (216-332)	0.11
NLR	1.6 (0.9-2.1)	1.2 (0.8-1.6)	0.41
SII	502 (260-732)	409 (204-486)	0.08

Group 1: patients in remission, Group 2: patients not in remission, TSH: thyroid stimulating hormone, fT4: free thyroxine, fT3: free triiodothyronine, TPOAb: thyroid peroxidase antibody, TgAb: thyroglobulin antibody, TRAb: thyroid stimulating hormone receptor antibody, NLR: neutrophil/lymphocyte ratio, SII: systemic immune inflammation index.

driver in GD and it was concluded that immunotherapy may be the future in autoimmune diseases, including GD (11). Evaluating the mechanisms and events in autoimmune diseases is required to identify new immunological cellular biomarkers (11).

This study intended to evaluate the clinical and laboratory findings of children with GD, according to the response to medical therapy, and find out whether leukocyte, neutrophil, lymphocyte, platelet count from the whole blood count parameters and NLR and SII from the blood-count derived systemic immune-inflammation indexes have an association with remission of the disease.

MATERIALS AND METHODS

The patient group of 37 children, aged 0-18 years old, who were diagnosed and in follow-up between April 2015- December 2022 from the Pediatric Endocrinology outpatient clinic of our hospital with the diagnosis of GD were included in the study. The patients and the families of the participants were informed about the study, and signed consent forms before being included in the study. The study was conducted in accordance with the 1964 Helsinki Declaration after approval was given by the Ethics Committee of the hospital (date:06 March 2023/ approval no:75). Diagnostic criteria for GD was made within the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism (1). Patients were diagnosed with GD in the presence of biochemically confirmed thyrotoxicosis, positive TRAb, a hypervascular and hypoechoic thyroid gland (ultrasound) and associated orbitopathy. The patients who had any kind of drug use before they were diagnosed with GD and who did not have a regular follow-up were excluded.

Participants' data of birth dates, sex, height and weight measurements, puberty stage, goiter examination, admission complaint, family history of dysthyroidism, initial medical therapy dose (mg/kg/day) and medical therapy time were recorded. Height, weight measurements, and the body mass index (BMI) (ratio of the weight in kilograms to height in meters squared- kg/m^2) values and their standard deviation scores (SDS) were calculated through the reference values of Turkish children (12). All patients were treated with methimazole. The levels of thyroid stimulating hormone (TSH), fT4, free triiodothyronine (fT3), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), TRAb, and complete blood count parameters such as leukocyte, neutrophil, lymphocyte, and platelet count at the diagnosis were recorded from the files of the patients. NLR and SII (neutrophil x platelet / lymphocyte counts) were calculated (8).

The patients were divided into two groups: group 1, which was comprised of patients in remission, and group 2, which was comprised of patients not in remission. Remission was defined as maintenance of euthyroidism for more than 12 months after medical therapy cut-off before 36 months and the absence of any relapses during the follow-up period. Patients who did not achieve euthyroidism despite 36 months of medical therapy were considered not in remission (1).

The complete blood count parameters of leukocyte, neutrophil, lymphocyte, and platelet count were recorded, and NLR and SII were calculated at the time of the medical therapy cut-off in group 1 and at the 36th month of the medical therapy in group 2. Group 1 and group 2 were compared on all parameters. The complete blood count parameters were compared in group 1 and group 2 at the diagnosis and at the time of the medical therapy cut-off in group 1 and at the 36th month of the medical therapy in group 2.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether the parameters were distributed normally or non-normally. Categorical variables were expressed as a percent and their comparisons were analyzed with the Chi-square test. Normally distributed parameters of numerical variables (age, height, weight and BMI) were given as a mean ± standard deviation and a Student-t test was used for comparisons. Parameters that did not show normal distribution were given as a median (25-75th percentile) and the Mann-Whitney U test was used

Table 3: The complete blood count parameters of group 1; at the diagnosis and at the time of medical therapy cut-off and group 2; at the diagnosis and at the 36th month of medical therapy

	Group 1 (n=20)			Group 2 (n=17)		
	At diagnosis	At the time of medical therapy cut-off	p	At diagnosis	At 36th month of medical therapy	P
Leukocyte count (10^9/L)	7.7 (6.7-9.3)	7.4 (6.2-9.6)	0.28	6.5 (5.8-6.9)	6.7 (6.0-8.4)	**0.049**
Neutrophil count (10^9/L)	3.8 (3.2-5.2)	4.1 (2.9-5.6)	0.48	3.1 (2.5-3.7)	3.7 (2.9-5.3)	**0.008**
Lymphocyte count (10^9/L)	2.6 (2.2-3.2)	2.3 (1.8-3.1)	0.06	2.4 (2.1-2.9)	2.2 (1.7-2.5)	0.06
Platelet count (10^9/L)	312 (279-336)	298 (250-329)	0.67	235 (216-332)	264 (242-317)	0.41
NLR	1.6 (0.9-2.1)	1.8 (1.3-2.9)	0.31	1.2 (0.8-1.6)	2.0 (1.4-2.5)	**0.002**
SII	502 (260-732)	516 (363-951)	0.50	409 (204-486)	547 (300-752)	**0.001**

Group 1: patients in remission, Group 2: patients not in remission, NLR: neutrophil/lymphocyte ratio, SII: systemic immune inflammation index

for comparisons between the two groups. The Wilcoxon test was used to compare the laboratory parameters of GD patients at diagnosis and at the time of the medical therapy cut-off in group 1 and at 36th month of the medical therapy in group 2. The parameter effects that were found to be different between group 1 and group 2 at the time of diagnosis on remission rate after medical therapy were analyzed by a logistic regression analysis, and odds ratios and 95% confidence intervals (CI) were given as outcome variables. All statistical analyses were performed using SPSS 17 (SPSS Inc., Chicago, Illinois, USA) and a value of p <0.05 was considered significant.

RESULTS

The number of patients in remission was 20 (54%). Demographic and clinical characteristics of the two groups at diagnosis are given in Table 1.

Group 1 and group 2 were homogeneous for age, height SDS, weight SDS, BMI SDS, puberty stage, family history of thyroid dysthyroidism and goiter grade (p>0.05 for each). The male sex ratio and the presence of palpitations in the admission complaints were higher in group 2 than in group 1 (p=0.033 and p=0.026, respectively) (Table 1).

The medical therapy status and the laboratory parameters at the diagnosis of group 1 and group 2 are given in Table 2.

The initial medical therapy dose was similar in group 1 and group 2 (p=0.95). There was no difference in TSH, fT4, fT3, TPOAb, TgAb, TRAb, lymphocyte count, platelet count levels, NLO and SII at diagnosis between group 1 and group 2 (p>0.05 for each). The leukocyte and neutrophil count levels were higher in group 1 than in group 2 (p=0.001and p=0.014, respectively) (Table 2).When the effects of sex, palpitation and neutrophil count at the GD diagnosis on remission rate after medical therapy were examined; while sex did not have a significant effect, the absence of palpitation increased the rate of remission 6.0 (95% CI: 1.1-33.1) times and the rate of remission increased 2.4 (95% CI: 1.1-5.2) times as the neutrophil count increased (p=0.29, p=0.041 and p=0.031, respectively).

The complete blood count parameters of group 1; at diagnosis and at the time of medical therapy cut-off and group 2; at diagnosis and at the 36th month of medical therapy are given comparatively in Table 3.

It was observed that the leukocyte, neutrophil, lymphocyte and platelet counts, and NLR and SII of the group 1 did not differ at the time of the medical therapy cut-off compared to the diagnosis time (p>0.05 for each). In group 2, there was an increase in leukocyte and neutrophil counts, NLR and SII after 36 months of medical therapy compared to the diagnosis time (p=0.049, p=0.008, p=0.002 and p=0.001, respectively) (Table 3).

DISCUSSION

In this study, the presence of palpitation was found lower while the leukocyte and neutrophil counts at the time of the GD diagnosis were found to be higher in the remission group but not in the remission group after medical therapy. In addition, an increase was observed in the leukocyte count, neutrophil count, NLR and SII after medical therapy compared to the levels at the time of diagnosis in the group that did not achieve remission.

The remission rate of GD was reported to be 30-33% after 2 years of medical therapy (2,6), but Tunç et al. reported a remission rate of 53.4% after 42.14±14.35 months follow-up (13). In this study the remission rate was 54% which was similar to the rate Tunç et al. (13) reported. In this study the remission of the disease was described as the maintenance

of euthyroidism for more than 12 months after the medical therapy cut-off before 36 months, so the patients were treated for 36 months and then evaluated after this period. Longer follow-up with medical therapy is thought to be the reason for the higher rates of remission in the study.

There is a strong predominance of cases in females, as in all thyroid pathologies (5). Researchers checked to see if there was a gender-related difference in remission. Some studies concluded that males were less likely to achieve remission than females (14-16), whereas other studies reported no difference between sexes for remission (6,7,13). In this study, there were more males in the group not in remission, but when the effect of gender on GD remission rate was examined; it was showed that sex did not have a significant effect on remission.

GD patients were admitted with complaints of palpitation, weakness, digestive disorders, thermophobia, polydipsia, sleep disorders, weight loss and more (17). In this study, palpitation was the most common admission complaint in accordance with the other studies (13,16,18) and in the absence of palpitation, the rate of remission increased 6.0 (95% CI: 1.1-33.1) times. A literature search was performed and there were no studies done investigating the association of admission complaints and remission rates. From this point of view, this is the first study evaluating the relation of admission complaints and remission rates of GD. We suggest that the presence of palpitation at diagnosis could be a prognostic factor in the progress of the disease.

It is known that blood cells of neutrophils, lymphocytes, monocytes and platelets have important roles in autoimmune diseases (19). In recent years, new inflammatory markers, including NLR, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte (MLR) ratio and SII were researched to investigate the severity of inflammation in some autoimmune diseases (10,19,20). Hyperthyroidism was reported to have a relationship to leukocyte differentials including altered PLR and NLR (21,22). In a few studies including adults and focusing on the differences between GD and controls, NLR and PLR of GD patients were found to be similar with the control group at the diagnosis time (23,24). In our study, NLR and SII were similar in both groups at diagnosis, whereas leukocyte and neutrophil counts were higher in group 1, and as the neutrophil count increased, the rate of remission increased 2.4 (95% CI: 1.1-5.2) times. Since the neutrophil count constitutes approximately half of the leukocyte count, it was considered that the significance was due to the neutrophil count. This finding indicated that the neutrophil count at the GD diagnosis could be a prognostic marker for the prognosis of GD to medical therapy.

This study found a significant increase in the leukocyte count, neutrophil count, NLR and SII in group 2 after three years of medical therapy when compared with the initial diagnosis. This is the second important finding of this study. It is known that neutrophilia and lymphocytopenia may be observed in inflammation (25) and higher NLR and SII may be the mark of poor progression in inflammatory diseases (22). In light of this information, it is thought that these findings in the group that did not go into remission may be due to ongoing inflammation, unlike the group that went into remission. Since these significant increases in leukocyte count, neutrophil count, NLR and SII were at the end of the medical therapy, this finding suggests that an increase in these parameters during follow-up compared to the results at the time of diagnosis may be prognostic markers for the prognosis of GD to medical therapy. Studies with a larger number of participants are needed in the future to support these findings.

This study had several limitations. Firstly, the sample size was small due to the low incidence of GD in children. Secondly, we could not obtain all the laboratory results of the patients during follow-up, only the data at the end of the medical therapy were used. It may also be useful to include laboratory data during the follow-up period in future studies.

CONCLUSION

Results of this study suggest that the presence of palpitation and lower neutrophil count at the time of diagnosis and an increase in the leukocyte count, neutrophil count, NLR and SII levels after medical therapy could be prognostic markers for not achieving remission with medical therapy of GD in children.

Ethics Committee Approval: This study was approved by the ethics committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (06.03.2023 / 75)

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.B., E.V.; Data Acquisition- D.B.; Data Analysis/Interpretation- E.V.; Drafting Manuscript- D.B.; Critical Revision of Manuscript- D.B., E.V.; Final Approval and Accountability- D.B., E.V.

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