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ORIGINAL ARTICLE

Evaluation of Hematologic Parameters in Children with Down Syndrome

Down Sendromlu Çocuklarda Hematolojik Parametrelerin Değerlendirilmesi

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ABSTRACT

Objective: Congenital hematological disorders are frequently observed in patients with Down syndrome (DS). In this study, we aimed to investigate peripheral blood-derived inflammation biomarkers such as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and eosinophil-monocyte ratio in patients with Down syndrome.
Material and Methods: Ninety-eight patients with karyotypically ascertained DS and 103 healthy controls were included. All subjects were divided into three age groups: 0-2 years (34 patients, 34 controls), 2-6 years (32 patients, 33 controls), and >6 years (32 patients, 36 controls). Demographic, clinical, and laboratory data of patients with DS who were admitted between June 2010 and December 2021 were reviewed from the file records from the pediatric allergy and immunology department.
Results: Lymphocyte, eosinophil, and eosinophil-monocyte ratio were found to be significantly lower in children with DS compared to controls in group 2 (2-6 years) and group 3 (>6 years). Platelet-lymphocyte ratio was found to be higher in children with DS in group 2 and group 3. There was no statistically significant difference between DS and controls in group 1 (<2 years) in terms of all parameters.
In group 2 (2-6 years) and group 3 (>6 years), there was a statistically significant difference between DS and controls in terms of lymphocyte, eosinophil, platelet-lymphocyte ratio, and eosinophil-monocyte ratio variables (P>0.05).
Conclusion: We found significant differences among lymphocyte, eosinophil, platelet-lymphocyte ratio, and eosinophil-monocyte ratio in patients with DS. As a result, these parameters should be evaluated carefully for clinical outcomes.

Keywords: Down syndrome, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, eosinophil-monocyte ratio, monocyte-lymphocyte ratio

ÖZ

Amaç: Konjenital hematolojik bozukluklar Down sendromunda (DS) sıklıkla gözlenmektedir. Bu çalışmada Down sendromlu hastalarda nötrofil-lenfosit oranı, trombosit-lenfosit oranı ve eozinofil-monosit oranı gibi periferik kan kaynaklı inflamasyon biyobelirteçlerini araştırmayı amaçladık.
Gereç ve yöntem: Çalışmaya karyotipik olarak tanısı konulan DS'li 98 hasta ve 103 sağlıklı kontrol dahil edildi. Hasta ve kontroller üç yaş grubuna ayrıldı: 0-2 yaş (34 hasta, 34 kontrol), 2-6 yaş (32 hasta, 33 kontrol) ve 6-18 yaş (32 hasta, 36 kontrol). Haziran 2010 ile Aralık 2021tarihleri arasındaki demografik, klinik ve laboratuvar verileri, Çocuk Alerji ve İmmünoloji bölümündeki dosya kayıtlarından yazıldı.
Bulgular: Lenfosit, eozinofil ve eozinofil-monosit oranı, DS'li çocuklarda grup 2 (2-6 yaş) ve grup 3'te (>6 yaş) kontrollere göre anlamlı derecede düşük bulundu. Grup 2 ve grup 3'te DS'li çocuklarda trombosit-lenfosit oranı daha yüksek bulundu. Grup 1'de (<2 yaş) DS ve kontroller arasında tüm parametreler açısından istatistiksel olarak anlamlı fark yoktu.
Sonuç: DS'li hastalarda lenfosit, eozinofil, trombosit-lenfosit oranı ve eozinofil-monosit oranı arasında anlamlı farklılıklar bulduk. Sonuç olarak, bu parametreler klinik sonuçlar için dikkatli bir şekilde değerlendirilmelidir.

Anahtar Kelimeler: Down sendromu, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, eozinofil-monosit oranı, monosit-lenfosit oranı

Introduction

Down syndrome (DS) is a syndromic disorder that occurs once in 600-700 live births, characterized by the presence of an extra copy of chromosome 21. DS is characterized by various dysmorphic features, congenital malformations (congenital heart disease and gastrointestinal disease, etc.), and increased respiratory morbidity. DS is also associated with various immunological disorders (1). Hematological malignancies and autoimmune diseases (hypothyroidism, celiac disease, diabetes mellitus, etc.) are more common in children with DS. Recurrent respiratory tract infections are important causes of morbidity and mortality (2). 10% of newborns with DS present with anemia, thrombocytopenia, increased white blood cell count, and a picture that goes with the blast and cannot be distinguished from congenital leukemia because of clonal anomalies (3). Cocchi et al followed 30 DS children from birth to 5 years of age and found that the absolute number of white blood cells (WBC) in DS children gradually decreased from the third to the twelfth month of age and then remained fairly constant over the years. They also showed that absolute lymphocyte counts were lower in children with DS compared to healthy children (1).

Children with DS develop more infections, an increased death rate from sepsis, and an increased incidence of chronic inflammatory conditions (4). The relationship between complete blood count and neutrophil-lymphocyte (NLR), platelet-lymphocyte (PLR), and eosinophil-monocyte (EMR) ratios with inflammation in different diseases have been demonstrated (5-7). Manuel et al. (8) compared the preoperative neutrophil-lymphocyte ratios in children with 30 tetralogies of Fallot (TOF) and 30 ventricular septal defects (VSD) and found a higher neutrophil-lymphocyte ratio in children with TOF compared to children with VSD. The relationship between congenital heart diseases and comorbidities such as hypothyroidism and hypogammaglobulinemia in patients with Down syndrome is unknown.

In this study, we aimed to investigate peripheral blood-derived inflammation biomarkers such as neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and eosinophil/monocyte ratio in patients with DS. In the literature, there are no studies on this subject that reveal the relationship of these parameters with age and clinical findings in children with DS. In this study, the relationship between inflammatory parameters in peripheral blood and clinical findings in different age groups will be evaluated in children with DS.

Material and Methods

Study Population

The study included 98 patients with karyotypically ascertained DS and 103 healthy children. Patients and healthy controls ages ranged from 2 months to 16 years. All subjects were divided into three age groups: 0-2 years (34 patients, 34 controls), 2-6 years (32 patients, 33 controls), and >6 years (32 patients, 36 controls). Demographic, clinical, and laboratory data of the patients who were admitted between June 2010 and December 2021 were evaluated from the file records from the pediatric allergy and immunology department. The patient group who had clinical signs of infection and positive C-reactive protein was excluded from this study. The control group was selected among healthy children who did not suffer from allergic disease, active infection, or immune deficiency. The medical records of all the patients were checked for the presence of a cardiac defect, cardiac operation, adenoidectomy, and hypothyroidism. The study was approved by the University Ethical Board (2021/336).

Table 1: Demographic and clinical features of **patients with** Down syndrome (DS) and controls

	<2 years (group 1)		2–6 years (group 2)		>6 years (group3)	
	DS	Control	DS	Control	DS	Control
	n=34	n=34	n=32	n=33	n=32	n=36
Age, (years)	0 (0-1)	1 (0-1)	4 (2-4.8)	3 (2-4)	8.5 (7-11)	10 (7-13)
***P*-value[1]**	0.09		0.295		0.249	
Gender, n (%)						
Male	20 (51.3)	19 (48.7)	17 (54.8)	14 (45.2)	15 (48.4)	16 (51.6)
Female	14 (48.3)	15 (51.7)	15 (44.1)	19 (55.9)	17 (45.9)	20 (54.1)
***P*-value[2]**	1.000		0.538		1.000	
Congenital heart disease, n (%): Total: 66 (67.4%)						
yes	27 (79.4)	–	21 (65.6)	–	18 (56.3)	–
no	7 (20.6)	–	11 (34.4)	–	14 (43.7)	–
***P*-value[2]**			0.130			
Heart surgery, n (%): Total: 38 (38.8%)						
yes	14 (41.2)	–	13 (40.6)	–	11 (34.4)	–
no	20 (58.2)	–	19 (59.4)	–	21 (65.6)	–
***P*-value[2]**			0.823			
Adenoidectomy, n (%): Total: 17 (17.3%)						
yes	3 (8.8)	–	6 (18.8)	–	8 (2.05)	–
no	31 (91.2)	–	26 (81.3)	–	24 (75.0)	–
***P*-value[2]**			0.215			
Hypothyroidism, n (%): Total: 46 (46.9%)						
yes	16 (47.1)	–	13 (40.6)	–	17 (53.1)	–
no	18 (52.9)	–	19 (59.4)	–	15 (46.9)	–
***P*-value[2]**			0.605			

DS: Down syndrome, Data are median (interquartile range (IQR): 1st quartile-3rd quartile) or numbers (n) and percentages (%), 1: Mann-Whitney *U* test, 2: Chi-square test, $P < 0.05$ was considered a statistically significant

Table 2: Laboratory findings of **patients with** Down syndrome (DS) and controls

Laboratory findings	<2 years (group 1)		*P*-value	2–6 years (group 2)		*P*-value	>6 years (group 3)		*P*-value
	DS n=34	Control n=34		DS n=32	Control n=33		DS n=32	Control n=36	
WBC count (K/uL)	7.62±2.24	8.06±1.99	0.392[1]	6.94±2.37	8.05±1.39	**0.025**[1]	6.22 (5.10-7.75)	6.85 (5.77-7.73)	0.203[2]
Hemoglobin (g/dL)	12.3±1.57	11.6±1.21	0.052[1]	12.8±1.25	12.2±0.83	**0.016**[1]	13.8±1.15	13.3±1.14	0.075[1]
Platelet count (K/uL)	361.9±99.3	332.5±83.5	0.190[1]	331.1±79.4	339.4±86.5	0.690[1]	311.0 (266.0-338.8)	298.5 (246.3-352.0)	0.645[2]
Neutrophil count (K/uL)	2.74±1.22	2.67±1.28	0.818[1]	3.30±1.40	3.48±0.86	0.539[1]	3.39 (2.02-3.78)	3.37 (2.31-3.93)	0.663[2]
Lymphocyte count (K/uL)	3.89±1.51	4.30±1.47	0.261[1]	2.89±1.07	3.67±1.01	**0.003**[1]	2.46±0.82	2.89±0.89	**0.044**[1]
Monocyte count (K/uL)	0.63 (0.52-0.86)	0.73 (0.55-0.93)	0.290[2]	0.53 (0.40-0.75)	0.60 (0.51-0.70)	0.237[2]	0.50 (0.39-0.64)	0.51 (0.44-0.60)	0.417[2]
Eosinophil count (K/uL)	0.16 (0.10-0.28)	0.28 (0.10-0.46)	0.091[2]	0.09 (0.06-0.13)	0.20 (0.14-0.26)	**0.001**[2]	0.08 (0.02-0.12)	0.10 (0.08-0.19)	**0.005**[2]
NLR	0.68 (0.44-1.18)	0.55 (0.38-1.09)	0.411[2]	1.07 (0.84-1.54)	0.95 (0.74-1.18)	0.126[2]	1.49±0.76	1.26±0.56	0.147[1]
PLR	109.8 (69.6-127.3)	82.3 (61.6-98.1)	0.480[2]	119.8 (94.3-149.5)	92.4 (77.0-114.2)	**0.002**[2]	131.9 (107.7-155.9)	103.8 (84.3-138.9)	**0.017**[2]
EMR	0.23 (0.18-0.32)	0.36 (0.16-0.59)	0.164[2]	0.18 (0.12-0.27)	0.34 (0.22-0.47)	**0.001**[2]	0.13 (0.06-0.22)	0.20 (0.15-0.33)	**0.015**[2]
MLR	0.21±0.10	0.21±0.11	0.902[1]	0.19 (0.14-0.25)	0.16 (0.13-0.22)	0.164[2]	0.19 (0.17-0.27)	0.17 (0.14-0.24)	0.188[2]
SIRI	0.51 (0.25-0.88)	0.41 (0.31-0.80)	0.854[2]	0.68±0.38	0.65±0.34	0.749[1]	0.61 (0.45-0.94)	0.51 (0.39-0.96)	0.503[2]
SII	231.8 (167.8-420.9)	197.0 (121.2-302.9)	0.206[2]	383.2±140.2	333.2±121.8	0.129[1]	456.7±224.0	379.5±179.7	0.120[1]

DS: Down syndrome, WBC: white blood cell, NLR: neutrophil-lymphocyte ratio, PLR: platelet- lymphocyte ratio, EMR: eosinophil-monocyte ratio, MLR: monocyte-lymphocyte ratio, SIRI: systemic inflammation response index, SII: systemic immune inflammation index

Values are presented as mean ± standard deviation or median (interquartile range (IQR): 1st quartile-3rd quartile), 1 Independent sample t-test, 2 Mann–Whitney U test

P < 0.05 was considered a statistically significant

Laboratory measurements

Laboratory results including WBC, hemoglobin, platelet, neutrophil, lymphocyte, monocyte, and eosinophil were collected from the electronic medical record network. NLR, PLR, and MLR were calculated using the ratio of neutrophil, platelet, and monocyte counts to lymphocyte counts, respectively. EMR was calculated using the ratio of eosinophil to monocyte. SIRI (systemic inflammation response index) and SII (systemic immune inflammation index) were calculated as follows (SIRI = neutrophil count x monocyte count/lymphocyte count; SII = platelet count x neutrophil count/lymphocyte count).

Statistical Analysis

All analyses were performed using a statistical software package (SPSS for Windows, version 21.0, IBM Corporation, Armonk, NY, USA). Numerical data were expressed as mean ± standard deviation (SD) or median (interquartile range) and categorical variables were described as count (n) and percentages (%). Moreover, we also calculated the numbers (n) and percentages (%) of the patients with DS for some of the important comorbidities (such as hypothyroidism, and cardiac defect). The normality test after Kolmogorov–Smirnov was performed to verify the normal distribution of the continuous variables.

The Chi-square test was used the compare comorbidity distribution and gender between the study groups. Clinical characteristics between groups were evaluated using Student's t-test or the Mann–Whitney U test, as appropriate. Correlations were analyzed with the Pearson test. *P* < 0.05 was considered statistically significant.

Results

Characteristics of the Study Population

The demographical characteristics and clinical features of DS were summarized in Table 1. DS and controls were divided into three groups: group 1 (<2 years) was composed of 34 DS with a median age of 0 ages (IQR: 0-1 years), and 34 controls with a median age of 1 year (IQR: 0-1 years), the group 2 (2-6 years) by 32 DS with a median age of 4 years (IQR: 2-4.8 years), and 33 controls with a median age of 3 years (IQR: 2-4 years) and the group 3 (>6 years) by 32 DS with a median age of 8.5 years (IQR: 7-11 years), and 36 controls with a median age of 10 years (IQR: 7-13 years). No statistically significant difference was found between all three age groups between the DS and control group (group 1: P=0.09, group 2: P=0.295, and group 3: P=0.249).

The gender distribution of the three groups was similar. Group 1 (14 males and 15 females), group 2 (15 males and 19 females), and group 3 (17 males and 20 females). According to their clinical history, 67.4% (66/98) of the DS children had congenital heart disease. The frequency of heart surgery was 38.8% (38/98). Seventeen of the 98 (17.3%) children with DS had a history of adenoidectomy.46.9% (46/98) of the DS children had hypothyroidism. No statistically significant difference between all three age groups of DS for the clinical features (Table 1).

Laboratory findings

We compared simple hemogram parameters and NLR, PLR, EMR, MLR, SIRI, and SII values of three age groups in DS and controls. These results were given in Table 2. There was no statistically significant difference between DS and controls in group 1 (<2 years) in terms of all parameters. In group 2 (2-6 years) and group 3 (>6 years), there was a statistically significant difference between DS and controls in terms of lymphocyte, eosinophil, PLR, and EMR variables (P>0.05). The mean value of lymphocyte count was lower (group 2: P=0.003 and group 3: P=0.044) in both DS groups compared with controls. While the median value of PLR was higher in both of the DS groups (group 2: P=0.002 and group 3: P=0.017), eosinophil count (group 2: P=0.001 and group 3: P=0.005) and EMR (group 2: P=0.001 and group 3: P=0.015) was lower. In group 2 patients with DS had lower WBC level (P=0.025), but hemoglobin concentration was higher (P=0.016).Also, there was a positive correlation between cardiac defect and WBC levels (r = 0.257, P =0.011). NLR and SII variables were positively correlated with a history of cardiac operation (r = 0.221, P = 0.029 and r = 0.250, P = 0.013, respectively). Monocyte and WBC levels were negatively correlated with adenoidectomy history (r = -0.230, P = 0.023 and r = -0.227, P = 0.024, respectively), which was statistically significant.

Discussion

This study identified the changes in the hematological parameters of patients with DS who ranged in age from 2 months to 16 years. To our knowledge, this is the first study in which all NLR, PLR, EMR, MLR, SIRI, and SII were evaluated simultaneously in patients with DS. In the present study, we observed that PLR variables increased and EMR variables decreased in children with DS who were older than two years of age. Also, lymphocyte count was found to be low in patients >2 years old.

Total WBC count and its subtypes count and their ratios (NLR, PLR, EMR, MLR, SIRI, and SII) have recently been used as an indicator of chronic inflammation and can be easily calculated from peripheral blood analysis (9-14). The proportion of circulating leukocytes changes during the inflammatory processes. Neutrophilia is accompanied by relative lymphopenia. In the literature, it has been suggested that NLR and PLR have prognostic importance in cardiovascular diseases and diabetes mellitus, hypertension, hepatic cirrhosis, familial Mediterranean fever, and malignancies (15). It has been reported that high NLR and PLR are associated with the severity of inflammation (16). In our study, although we excluded patients with an active infection, there was a significant increase in PLR values in patients DS >2 years old. These results may be related to low lymphocyte count.

Several groups have proposed that lymphocytes are significantly lower in children with DS at all ages (17-19). In the present report, all the patients >2 years old included in the study had lower lymphocyte counts compared with controls. Reduced ranges of the different lymphocyte subsets were found to be of most significance in childhood, with subsequent improvement over age. Comorbidities and recurrent infections in patients with DS affect peripheral blood distribution in age groups. The patient group under two years of age that had very-severe morbidity and mortality was excluded from the study. Therefore, we think that the lymphocyte count was not found to be low in patients under 2 years of age in our study.

The majority of the studies on children with DS in the literature consisted 0-18 age group and these children were not divided into age groups. In one of these studies that did not divide DS children by age groups, no differences were observed in NLR and lymphocyte count (20). Another study found that WBC count, neutrophil count, total lymphocyte count, monocyte count, and platelet count were lower in patients with DS (19). In this study, we thought that it would be more accurate to divide the patient groups according to age groups. İkincioğullari et al (21) found that immune system cells differ according to age groups in healthy children. In our other study, we also divided patients into three groups and age-related changes were found in memory B cell subsets and CD19 complex (22).

Joshi et al (23) and Mitwalli et al (19) found that the WBC count was lower in children with DS compared to controls. While there was no difference in platelet count in the study of Joshi et al (23), Mitwalli et al (19) reported a significant decrease compared to controls. In our study, WBC count was found to be lower in DS

patients in group 2 compared to the control group, but there was no significant difference in platelet count.

In our study, we found that eosinophil count and EMR were lower than controls in patients with DS >2 years old. The literature concludes that allergen sensitization is not a major contributor to respiratory illnesses in children with DS (24). Verstegen et al. (25) found six of 44 DS patients with elevated IgE, and none of the 28 DS individuals tested had an allergen identified as a trigger for allergy symptoms.

Age-related changes and the relationships between some clinical co-morbidities including cardiac defects and cardiac operation were detected in peripheral blood parameters of children with DS. While cardiac defect was related to WBC count; NLR and SII values were found to be related to a history of cardiac operation. In addition, monocyte counts and WBC were negatively correlated with adenoidectomy. In our control groups, there are no co-morbidities including cardiac manifestation. So, we could not evaluate the association between the cardiac findings and peripheral blood parameters in this study. The relationships in these parameters may be related to the pathogenetic changes in DS. As a result, these parameters should be evaluated carefully for clinical outcomes.

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