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Hematological Parameters and Leukocyte Formulas in Predicting Celiac Disease in Children with Iron Deficiency Anemia

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ABSTRACT

Objective: Celiac disease (CD) is a systemic inflammatory disease associated with a number of hematological findings. The most common symptom other than the intestinal system is iron deficiency anemia (IDA). It is difficult to distinguish IDA that occurs in CD from nutritional IDA. In this study, the use of hematological parameters and leukocyte formulas, which are reported to be of diagnostic importance in inflammatory diseases, as a screening test in predicting CD in children with IDA was investigated.

Methods: Forty-six children with CD and IDA, 46 children with nutritional IDA and 46 healthy children as a control group were included in the study. The patient files were examined retrospectively. The blood count parameters [Hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte, leukocyte, neutrophil, lymphocyte, platelet count] of the patients before starting iron therapy were recorded. Leukocyte formulas [neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), RDW/lymphocyte ratio (RLR)] were calculated.

Results: There was no difference between the patient and control groups in terms of age and gender distribution ($p>0.05$). Hb, MCV, MCH, MCHC values of CD+IDA and IDA groups were lower than the values of the control group ($p<0.001$, for all), RDW, RLR, PLR values, and platelet count were higher than the values of the control group ($p<0.001$ and $p<0.001$; $p<0.05$ and $p<0.01$; $p<0.05$ and $p<0.05$; $p<0.001$ and $p<0.05$, respectively). Leukocyte, neutrophil, lymphocyte, erythrocyte counts, MPV, PDW, NLR were found to be similar in the patient and control groups ($p>0.05$ for all). There was no difference between the patient groups in terms of NLR, PLR, and RLR ($p>0.05$ for all).

Conclusion: Our study showed that hematological parameters and leukocyte formulas are not useful in predicting CD in children with IDA.

Keywords: Child, celiac disease, iron deficiency anemia, hematological parameters, leukocyte formulas

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INTRODUCTION

Celiac disease (CD) is an autoimmune disease of the small intestines triggered by a protein called gluten, found in dietary wheat, barley and rye in genetically susceptible individuals. It is an irreversible but treatable multifactorial disease (1). It is a common disease worldwide and its prevalence varies between 0.3-3% (1). In pathogenesis; the conversion of glutamine-forming gliadin proteins to deamide peptides by the tissue transglutaminase enzyme in the intestinal submucosa plays a role in presenting these peptides, which are resistant to proteolysis, to CD4+ T-cells, which trigger an inflammatory reaction by binding to HLA-DQ2 and/or DQ8 molecules on the surface of antigen presenting cells in the lamina propria (2). Activation of these cells causes epithelial cell destruction and villous atrophy, probably mediated by non-gluten-specific intraepithelial cytotoxic T-lymphocytes (3). Villous atrophy reduces the functional capacity of the intestine, resulting in malabsorption (4).

Iron deficiency anemia (IDA) is a well-known clinical form of CD. Evaluating patients with IDA without gastrointestinal symptoms as nutritional iron deficiency and trying to treat them with different iron preparations many times causes the diagnosis of celiac to be missed or delayed. Delay in diagnosis leads to increased treatment costs and causes patients to apply to the hospital unnecessarily many times. Red cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), RDW/lymphocyte ratio (RLR) were used as laboratory tests to help evaluate the diagnosis of CD, adherence to a gluten-free diet, and the severity of histopathological findings (5-8). Screening suspected celiac patients with the use of these frequently used laboratory indices and biomarkers before proceeding to the diagnostic steps in children with IDA may be an advantage.

In this study, the usability of hematological parameters, NLR, PLR and RLR formulas as a screening test in predicting CD in children with IDA was investigated.

METHODS

In this single-centered, cross-sectional, retrospective study, 57 children (IDA+CD group) who were followed up in the pediatric hematology and oncology outpatient clinic with IDA unresponsive to iron treatment and diagnosed with celiac by the pediatric gastroenterology department, 46 children diagnosed with nutritional IDA (IDA group) and 46 healthy children (control group) were included in this study. The diagnosis of CD was made by clinical, serological, histopathological and genetic correlations.

The file records of all children included in the study were reviewed retrospectively. Hemoglobin (Hb) at diagnosis, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte, leukocyte, neutrophil, lymphocyte, platelet count, ferritin level, transferrin saturation were recorded. Leukocyte formulas (NLR, PLR, RLR) were calculated. Laboratory parameters of the three groups were compared.

Anemia is defined as a Hb level below 11 g/dL at the age of 6 months-5 years, 11.5 g/dL at the age of 5-11 years, and below 12 g/dL at the age of 12-18 years (9); iron deficiency was defined as a transferrin saturation of <16% and a ferritin level of <12 µg/L for children under the age of five, and <15 µg/L for children over the age of five (10). The study was conducted in accordance with the principles of the Declaration of Helsinki and approval was obtained from the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee on 06.11.2018 (decision no: 26).

Exclusion Criteria

In the CD and IDA group, a total of 11 patients, including 6 patients who had received iron therapy in the last three months before admission, and 5 patients with acute inflammation at the time of admission, were excluded from the study.

Laboratory Analyzes

All blood samples were collected after 8 hours of fasting. Complete blood count was performed freshly on an automated blood count analyzer (Beckman Coulter LH750, Kraemer Blud. Brea, CA, US). Blood samples taken into flat tubes for biochemical analysis were centrifuged at 1,500 g for 10 minutes, then their serum was separated and studied within the same day. Serum iron level was analyzed by photometric method (Cobas c502, Roche Diagnostics, Germany), ferritin level was analyzed by electrochemiluminescent method (Cobas E-602, Roche Diagnostics, Germany). Transferrin saturation was calculated with the formula serum ironx100/total iron binding capacity.

Statistical Analysis

SPSS 21 (IBM SPSS Corp.; Armonk, NY, USA) package program was used for statistical analysis of the data. Categorical data were expressed as frequency (n) and percentage (%). Shapiro-Wilk test was used to evaluate the normality distributions of the data. In the comparisons between groups, descriptive statistics were given as mean ± standard deviation for data showing conformity with normal distribution, and median (25-75%) for non-conforming data. One-Way ANOVA test was used for data conforming to normal distribution, and Kruskal-Wallis H test was used for variables not conforming to normal distribution. $P<0.05$ was considered statistically significant.

RESULTS

A total of 138 children were included in the study. The patient group consisted of 92 (CD+IDA group: 46, IDA group: 46) and the control group consisted of 46 children. Number of girls/boys in CD+DA group, IDA group, and control group were 25/21, 30/16, 24/22; median ages were 7 (3.7-10), 5.5 (2.8-13.2), 6 (4.8-10.2) years, respectively. There was no difference in age and gender distribution between the three groups ($p>0.05$ for all). There was no difference between the three groups in terms

J Acad Res Med 2021;11(2):187-91

of erythrocyte, leukocyte, neutrophil, lymphocyte count, MPV, PDW, NLR values (p>0.05, for all). Hb, MCV, MCH, MCHC values of CD+IDA group are lower than control group (p<0.001, for all); RDW, PLR, RLR values and platelet count were higher than control group (p<0.001, p<0.05, p<0.05, p<0.001, respectively). Hb, MCV, MCH values of the CD+IDA group were higher than the IDA group (p<0.05, p<0.001, p<0.001, respectively) and lower than the control group (p<0.001, for all). There was no difference between CD+IDA and IDA group in terms of NLR, PLR, and RLR (p>0.05, for all). Transferrin saturation of CD+IDA group was higher than that of IDA group (p<0.001) and ferritin level was similar (p>0.05). The characteristics and laboratory parameters of the study groups are shown in Table 1.

DISCUSSION

IDA is the most common sign of CD other than the intestinal system at the time of diagnosis (11,12). It has been found that the frequency of IDA is between 6-82% (13-17) and anemia is associated with greater disease severity and slower histological recovery in response to a gluten-free diet (18-20). For this reason, it is important to diagnose CD and start treatment in a short time in patients with CD accompanied by IDA.

It is known that RDW is an early indicator of iron deficiency and altered erythropoiesis in celiac patients (5). In two studies conducted in large patient series, it was reported that elevated RDW is a sensitive marker for the diagnosis of celiac in patients with strong clinical suspicion (21,22). Our study showed that the RDW values of the CD+IDA group and the IDA group were similar, therefore, RDW could not be an indicator for the diagnosis of celiac in the presence of IDA.

The MPV is a marker of platelet function and activation and is affected by inflammation. The relationship between changes in MPV and celiac was first reported by O'Grady et al. (23). O'Grady et al. (23) and Purnak et al. (24) found that MPV in celiac patients was higher than the values in the control group, Demirezer Bolat et al. (25) reported that the MPV value was similar in the patient and control groups. In two studies, it has been reported that MPV is a useful biomarker to monitor adherence to the diet in the three-month period after starting a gluten-free diet (24,26). Demirezer Bolat et al. (25), on the other hand, reported that MPV is not useful either in the diagnosis of celiac or in monitoring adherence to diet (in a 1-year follow-up). In our study, we found that the MPV value in the CD+IDA group was similar to that of the IDA and control groups. Our results supported that MPV could not be used in the diagnosis of CD.

Apart from anemia in celiac patients, leukopenia, thrombocytopenia (27) and lymphopenia (5,28) are other hematological abnormalities reported. It has been reported that low lymphocyte counts are

Table 1. Characteristics and laboratory parameters of the patient and control groups

	CD+IDA group (n=46)	IDA group (n=46)	Control group (n=46)	p
Age (years)	7 (3.7-10)	5.5 (2.8-13.2)	6 (4.8-10.2)	>0.05
Gender (female/male)	25/21	30/16	24/22	>0.05
Hb (g/dL)	10 (8.5-10.4)	9.5 (8.3-10.6)	12.7 (12.0-13.1)	$<0.05^{a}$ $<0.001^{b.c}$
RBC ($x10^6/mm^3$)	4.8 (4.5-5.1)	4.7 (4.4-5.0)	4.8 (4.6-4.9)	>0.05
MCV (fL)	66.8±5.1	63.2±5.6	79.0±3.1	<0.001
MCH (pg)	21.5±2.2	19.9±2.5	26.3±3.4	<0.001
MCHC (%)	32 (31-33.2)	31.6 (30.2-32.5)	33.3 (32.9-33.7)	$<0.001^{b.c}$
RDW (%)	17.9 (15.8-19.7)	19.5 (12.8-14.7)	13.3 (12.8-14.7)	$<0.001^{b.c}$
Leukocyte count ($x10^9/L$)	7.8 (6.2-9.1)	7.9 (6.1-9.5)	7.7 (6.1-9.2)	>0.05
Neutrophil count ($x10^9/L$)	3.3 (2.4-4.4)	3.5 (2.3-5.2)	3.2 (2.6-4.4)	>0.05
Lymphocyte count ($x10^9/L$)	3 (2.4-5)	2.9 (2.2-4.7)	2.9 (2.3-4.2)	>0.05
Platelet count ($x10^9/L$)	356 (283.5-405)	339 (267.2-397)	270 (245.7-319)	$<0.001^{b}$ $<0.05^{c}$
MPV (fL)	8.4 (7.8-9.1)	8 (7.6-8.9)	8 (7.6-8.6)	>0.05
PDW (%)	16.6 (16.3-17.4)	16.6 (16.4-17.1)	16.4 (16.2-16.7)	>0.05
NLR	1.1 (0.7-1.5)	1.1 (0.7-2.2)	1.1 (0.7-1.6)	>0.05
PLR	111.3 (82.1-154.4)	117 (71.6-158.8)	85.9 (70.7-112.9)	$<0.05^{b.c}$
RLR	5.7 (4.2-7.4)	6.6 (3.8-8.7)	4.5 (3.4-5.5)	$<0.05^{b}$ $<0.01^{c}$
Saturation (%)	8 (4-8.9)	5.1 (3.9-7.1)	-	<0.001
Ferritin (ng/mL)	6 (4-8.9)	6.9 (4.2-8.7)	-	>0.05

Hb: hemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, MPV: mean platelet volume, PDW: platelet distribution width, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, RLR: RDW/lymphocyte ratio [a]comparison of CD+IDA group and IDA group, [b]Comparison of CD+IDA group and control group, [c]comparison of IDA group and control group, IDA: iron deficiency anemia, CD: celiac disease, RBC: red blood cell

J Acad Res Med 2021;11(2):187-91

associated with celiac (5,28,29). Studies have shown that the diagnostic power of NLR and PLR indices for celiac is high (6,7), and the diagnostic power of RLR is better than NLR and PLR (5). Uslu ve ark. (8) have shown that the number of neutrophils in celiac patients compared to the control group at the time of diagnosis is high, the number of lymphocytes is low, NLR is high, the number of neutrophils and NLR values in patients who do not follow the diet after a year of gluten-free diet remain high, and the neutrophil number and NLR values in those who follow the diet are at the same level as the control group and they have also shown that NLR is useful for predicting patients who are not compliant with the gluten-free diet. It is thought that changes in the leukocyte formula in active CD may be related to lymphocytic infiltration in the gastrointestinal tract and inflammation and cytokines that play a role in the pathogenesis of the disease (7). In our study, we showed that there was no difference between the patient groups and the control group in terms of leukocyte, neutrophil and lymphocyte count NLR values, RLR and PLR values were higher than the control group, and there was no difference between the CD+IDA group and IDA group in terms of the same parameters. The reason for the difference in RLR and PLR values was probably that the RDW and platelet values of the patient groups were significantly higher than the control group. High RDW and platelet values were also a finding that could be explained by iron deficiency. Therefore, we thought that this difference was not specific to CD.

CD, similar to many other autoimmune diseases, includes innate and acquired immune responses (30). Both experimental and clinical studies emphasize the importance of iron's effects on innate immunity (decreased bactericidal activity, respiratory burst in neutrophils) and cellular immunity (decreased lymphocyte proliferation and delayed hypersensitivity responses) (31,32). Iron has important effects on the immune system due to its growth and differentiation stimulating properties, especially in lymphocytes (33). Iron is also important for monocyte/macrophage differentiation (34). Iron is also critical for enzymes involved in deoxyribonucleic acid synthesis and is an essential element for the proliferative phase of lymphocyte activation, and this phase can be weakened when iron is deficient (35). This may result in altered expression of cell surface markers and decreased T-cell proliferation (36). The fact that we did not find any change in hematological indices such as NLR and PLR in many inflammatory diseases in the CD+IDA group can be explained by the fact that iron deficiency affects the immune response and the response of the developing immune system to inflammatory events is different in children.

Study Limitations

The small number of patients and the retrospective nature of the study.

CONCLUSION

It was determined that the inflammatory response was different in children with CD accompanied by IDA, and that the NLR, RLR and PLR formulas did not have diagnostic power for the diagnosis of CD. There is a need for studies showing how humoral and cellular immunity are affected when these two conditions are combined, which cause changes in the immune system.

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and approval was obtained from the Eskişehir Osmangazi University Non-Invasive Clinical Research Ethics Committee on 06.11.2018 (decision no: 26).

Informed Consent: Retrospective study.

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J Acad Res Med 2021;11(2):187-91

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