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Usefulness of Mean Platelet Volume and Neutrophil-to-Lymphocyte Ratio for Evaluation of Children with Familial Mediterranean Fever

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Background: Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of serositis, fever, and rash. Clinical and subclinical inflammatory processes may contribute to atherosclerosis in FMF patients, with mean platelet volume (MPV) as a potential indicator for atherosclerosis risk and neutrophil-to-lymphocyte ratio (NLR) as a marker for subclinical inflammation in these patients. In this study, we investigated whether MPV can be used as an indicator for atherosclerosis risk and if NLR is a marker for subclinical inflammation in FMF patients.

Material/Methods: The study consisted of 75 FMF patients in attack, 157 attack-free patients, and 77 healthy controls. White blood cell count neutrophil-to-lymphocyte ratio, platelet count, MPV, PDW C-reactive protein levels, and erythrocyte sedimentation rate were recorded.

Results: There were no significant differences between attack, attack-free, and control groups in terms of mean MPV and PDW value. NLR value was higher in the attack group. NLR value was similar in attack-free and control groups.

Conclusions: We found that MPV and PDW values are similar in FMF patients and healthy controls. NLR was higher in FMF patients in the attack period. Therefore, our results suggest that MPV and PDW values do not predict atherosclerosis risk in pediatric FMF patients, and NLR may be an indicator for attack period but not attack-free period.

MeSH Keywords: Atherosclerosis • Familial Mediterranean Fever • Inflammation • Mean Platelet Volume

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Background

Familial Mediterranean fever (FMF) is an inherited disease characterized by recurrent attacks of serositis, fever, and erysipelas-like skin rash [1]. The disease is common in Mediterranean countries, and the incidence of the disease has been reported as 1/200 in Ashkenazi Jews and 1/1000 in Turks [2]. Colchicine treatment has been shown to be effective in preventing the development of amyloidosis and in reducing proteinuria [3]. Subclinical inflammation can also be observed in FMF. Because it is associated with atherosclerosis, the diagnosis of subclinical inflammation has become more important [4,5].

It has been suggested that thrombocyte activation has an important role in the pathogenesis of atherosclerosis in various inflammatory diseases. Platelet activation has been thought to play a triggering role in arterial disorders, and mean platelet volume (MPV) is considered a good indicator of platelet activation [6–10]. Platelet distribution width (PDW) is another indicator of platelet activation [8]. Thus, MPV and PDW measurements may help predict the risk of atherosclerosis.

As MPV and PDW measurements are readily available diagnostic parameters, their use in evaluation of diseases that may predispose patients to atherosclerosis has become popular. A few studies have assessed the role of MPV in prediction of atherosclerosis risk in FMF patients [11–17], but they have reported contradictory results. Therefore, it was necessary to investigate the usefulness of MPV in the prediction of such a risk among a relatively large study population. Neutrophil-to-lymphocyte ratio (NLR) may serve as a marker of subclinical inflammation in patients with FMF [18,19].

In this study, we aimed to investigate whether MPV and PDW could be used as parameters for prediction of atherosclerosis risk in FMF patients, and if NLR might be helpful in the diagnosis of subclinical inflammation of FMF.

Material and Methods

Patients diagnosed with FMF according to Tel-Hashomer criteria [19] and who had started colchicine therapy were included in the study. Age- and sex-matched healthy subjects were also included as a control group. Patients with any other systemic disease were excluded. The study population consisted of 75 FMF cases (42 F, 33 M) with an inflammatory attack encountered within the study period, 157 attack-free patients (84 F, 73 M), and 77 (39 F, 38 M) healthy controls. The diagnosis of FMF attack was based on clinical (fever, abdominal pain, skin rash, arthritis, pleuritis) and laboratory (erythrocyte sedimentation rate (ESR) >20 mm/h and C-reactive protein (CRP) >5 mg/l) findings. Consecutive episodes with an interval of at least 10 days were accepted as separate attacks. White blood cell (WBC) count, platelet count, neutrophil count, lymphocyte count, NLR (absolute neutrophil-to-absolute lymphocyte ratio), MPV, PDW, CRP, ESR values, MEFV mutations, and demographic features of the patients were recorded. WBC and platelet counts, MPV and PDW values, and the demographic data of the control group were also noted. Standard EDTA-containing tubes were used for complete blood counts. All blood samples were studied in the same regularly checked analyzer (Abbott CELL-DYN 3700, United States). The study was approved by the local ethics committee.

Statistical analysis

The data were evaluated using SPSS (Statistical Package for Social Sciences) 18.0 program for Windows. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess whether the data were distributed normally. Numerical variables with normal distribution are shown as mean ± standard deviation and these values were compared using either the t test or 1-way ANOVA test. The comparison of the groups with abnormally distributed numerical data was performed with Mann-Whitney U test or Kruskal-Wallis test. Chi-square test was used to compare categorical variables between independent groups. Correlations between parameters with normal and abnormal distribution were computed through Pearson's and Spearman's correlation analysis, respectively.

Results

A total of 75 (42 F, 33 M) FMF patients with attack, 157 (84 F, 73 M) FMF patients without attack, and 77 (39 F, 38M) healthy controls were included in the study. The patient's last-visit data were collected using an electronic patient database. Mean ages were 8.4±3.5 in the attack group, 9.1±3.6 in the attack-free group, and 8.3±3.5 in the healthy control group. Age and sex distribution did not differ statistically between the groups. There was no amyloidosis in any patients. Dose of colchicine used ranged between 0.5 and 2 mg. Leucocyte count was higher than normal 27 (36%) in the attack groups and 6 (3.8%) in attack-free groups. Thrombocyte count was higher than normal value in 61 (81.3%) attack group subjects and 10 (6.4%) attack-free subjects. CRP value was higher than normal in 20 (26.7%) attack group patients and 5 (3.2%) in the attack-free groups. ESR value higher than normal value in 58 (77.3%) and not detected in any of the patients in the attack-free group. When attack and attack-free groups were compared in terms of number of patients who were homozygous, compound heterozygous or heterozygous, there were not any statistically significant differences between groups (p=0.10). There were no significant differences between patients in the attack and attack-free groups in terms of 1-allele or 2-allele mutations (p=0.09).

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Table 1. Comparison of patient characteristics during attack and attack-free period and the controls.

	During FMF attack* (n=75)	Attack free period** (n=157)	Controls*** (n=77)	p
Male/female	33/42	73/84	38/39	*,** NS, *,*** NS, **,*** NS
Age, years	8.4±3.5	9.1±3.6	8.3±3.5	*,** NS, *,*** NS, **,*** NS
ESR, mm/h	29.3±15.4	7.1±3.8	No data	*,** <0.001,
CRP, mg/dl	31.8±37.1	2.0±1.5	No data	*,** <0.001,
WBC, /mm^3	10612±4835	7643±1678	7972±1483	*,** 0.001, *,*** 0.001, **,*** NS
Platelet, ×10^3/mm^3	335±91	302±59	312±59	*,** 0.002, *,*** NS, **,*** NS
MPV, fl	7.79±0.99	7.98±1.10	7.75±1.24	*,** NS, *,*** NS, **,*** NS
PDW, %	17.3±0.9	17.3±1.2	17.2±0.9	*,** NS, *,*** NS, **,*** NS
Neutrophil count, /mm^3	6550±4176	3936±1244	4082±1142	*,** <0.001, *,*** <0.001, **,*** NS
Lymphocyte count, /mm^3	2999±1468	2786±913	2920±776	*,** NS, *,*** NS, **,*** NS
NLR	2.6±2.2	1.6±0.8	1.8±1.3	*,** <0.001, *,*** <0.001, **,*** NS

ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; WBC – white blood cell; MPV – mean platelet volume; PDW – platelet distribution width; NLR – neutrophil-lymphocyte ratio.

Mean ESR, CRP value, and platelet count were higher in the attack group than in the attack-free group (p<0.001, p<0.001, p=0.002, respectively) (Table 1). However, there were no statistically significant differences among the attack, attack-free, and control groups in terms of mean MPV and PDW value (p=0.25, p=0.96) (Table 1).

Mean NLR value was higher in the attack group than in the attack-free group and control group (p<0.001, p<0.001, respectively) (Table 1). No significant difference was found between the attack-free group and control group (p=0.76) (Table 1).

A positive correlation was found between the MPV and PDW in the attack group and the attack-free group (r=0.61, p<0.001 and r=0.66, p<0.001, respectively). A negative correlation was found between platelet counts and MPV in the attack group and the attack-free group (r=–0.36, p=0.001and r=–0.32, p<0.001, respectively). A negative correlation also was found between platelet count and PDW in the attack group and the attack-free group (r=–0.33, p=0.003, r=–0.22, p=0.007, respectively).

Discussion

FMF is a chronic inflammatory disease. Outcomes of clinical and subclinical inflammation are unclear during FMF attack and in the attack-free period. As in other clinical entities accompanied by inflammation, FMF patients are at an increased risk of atherosclerosis development [6,12,13].

Previous studies have investigated associations between MPV and atherosclerosis, myocardial infarction (MI), post-MI prognosis, post-percutaneous coronary intervention outcome, stent thrombosis, in-stent restenosis, stroke, venous thromboembolism, Behçet's diseases with venous thrombosis, gestational diabetes, preeclampsia, rheumatoid arthritis, ankylosing spondylitis, psoriasis, disease activity in ulcerative colitis, subclinical hypothyroidism, celiac disease, and von Willebrand factor in impaired glucose intolerance and in hepatitis B infection [8,21,22].

Hormonal and immune system agents, including thrombopoietin, granulocyte-macrophage colony-stimulating factor, interleukin-1, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), affect maturation of thrombopoietic cells and the release of platelets into circulation [6]. Increased IL-6 and TNF-α were shown in FMF patients during attack and in the attack-free period [4]. MPV is an easily available parameter related with thrombocyte activation, which does not require additional cost. Thrombocyte activation is associated with increased risk of atherothrombosis [6,7].

There is limited data concerning the relationship between MPV and atherosclerosis risk in FMF patients [11–17]. However, results of previous studies are controversial. While higher MPV values have been reported in some of these studies, others have found lower MPV values in attack and attack-free periods of FMF patients compared with the control groups. Furthermore, higher MPV values have been found in the controls and the

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Table 2. Comparison of our results with previous studies.

	Our study	Şahin et al. [11]	Arıca et al. [12]	Makay et al. [13]	Çoban et al. [15]
Number of patients					
Attack	75	60	53	48	–
AFP	157	120	64	63	35
Controls	77	75	57	49	35
Profile of patient	Pediatric	Adult	Pediatric	Pediatric	Adult
MPV	No difference	Lower in attack and AFP	Higher in attacks and AFP	Lower in attacks than AFP and the controls	Higher in AFP than controls
Platelet count	No difference	Higher in attacks than AFP and the controls	Higher in attacks and AFP	Higher in attacks than controls	No difference
PDW	No difference	No data	No data	No data	No data

MPV – mean platelet volume; PDW – platelet distribution width; AFP – attack-free period.

attack-free period compared with the attack period of patients (Table 2) [11–13,15]. Also, MPV was higher in the attack-free group than the control group in a study consisting of pediatric and adult patients. In the same study population, adults had higher MPV values compared to children [17].

Amyloidosis is a serious complication of FMF, leading to end-organ damages. MPV was significantly lower in FMF patients with amyloidosis than in patients without amyloidosis and in control subjects. In addition, FMF patients without amyloidosis had higher MPV values than healthy controls in the same study [16]. However, the results of these studies are controversial in terms of relation of MPV and FMF.

In our study, MPV was comparable between FMF patients with attack, patients in attack-free period, and healthy controls. Our results do not support any of the previous studies reporting MPV as being higher or lower in FMF patients compared to healthy subjects. There was no relationship between MPV and FMF disease in our study population.

On the other hand, PDW is another marker thought to be related with inflammation and atherothrombotic events. PDW indicates thrombocyte activity like MPV. Our study groups had similar PDW and MPV values. We suggest that MPV and PDW values are not affected by inflammation in childhood FMF. All of our study population was under colchicine treatment, which might reduce inflammation and result in lack of significant difference in MPV and PDW values between FMF patients and healthy controls.

FMF patients have higher NLR values, an inflammatory marker, than healthy controls [18,19]. In the present study, we found higher NLR in the FMF attack group than in the attack-free FMF patients and healthy controls, and the latter 2 groups had similar NLR values. Neutrophil count increases during the FMF attack period due to neutrophil shift. It was higher in the attack group compared to the attack free and control groups but lymphocyte count was similar among all 3 groups. Thus, the difference in NLR was due to the difference in neutrophil count between groups. These results suggest that NLR may indicate FMF attack, but NLR cannot be used as a subclinical inflammation marker.

Platelet count, ESR, CRP, and WBC were higher in the attack group than in the attack-free patients and healthy controls, as expected.

MPV was positively correlated with PDW, and it was negatively correlated with platelet count in FMF patients of our study population. Our results are consistent with a study by Sahin et al., performed with FMF patients with attack, and another study by Makay et al. with attack-free FMF patients [11,13]. MPV was reported as negatively correlated with platelet count in patients with coronary artery disease and in healthy persons [23,24]. Our results suggest that inflammatory process in FMF does not affect platelet volume. On the other hand, it has been reported that large platelets are consumed during the serosal inflammation in patients with FMF [6]. This may be another explanation for this inverse correlation.

The cross-sectional design of our study was the main limitation. Also, our study group consisted of a Turkish population and was performed only in 1 center. Thus our results may not be extrapolated to all of the FMF population.

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Conclusions

In conclusion, we found no difference in MPV and PDW values between FMF patients and healthy controls, while NLR was higher in FMF patients in the attack period than in FMF patients in attack-free period and healthy controls. Our results suggest that MPV and PDW values do not predict atherosclerosis risk in FMF children, and NLR may be an indicator for attack period but not attack-free period.

Conflict of interest

There is no conflict of interest.

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