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Value of mean platelets volume in children with familial mediterranean fever: A case–control prospective study from Sulaymaniyah, Kurdistan Region, Iraq

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Abstract:

BACKGROUND: Familial Mediterranean fever (FMF) is characterized by a rise in acute phase reactants (APRs) during the attacks and occasionally in between the attacks. Although mean platelet volume (MPV) is generally not changed, low MPV could be used as an inflammatory marker in FMF and as an indicator of other diseases. This prospective case–control study was carried out in Sulaymaniyah, Iraq, to assess MPV in Kurdish children with different FMF mutations during and in-between the attacks versus healthy controls.

PATIENTS AND METHODS: From 2011 to 2020, 56 gene-positive FMF patients (Group I) and 60 healthy controls (Group II) were enrolled. Besides the routine APRs, MPV was measured in both groups and categorized into low (<7 fl), normal (7–11 fl) and high (>11 fl). Informed consents from all participants and ethical institutional approval were obtained.

RESULTS: Group I age range was 23 months to 16 years with a male to female ratio of 1.8:1 while Group II age ranged from 21 months to 15 years with a male to female ratio of 1.4:1. MPV was normal in (n = 44, 78.6%) of Group I versus (n = 44, 73.3%) of Group II (P = 0.05); low in (n = 8, 14.3%) of Group I versus (n = 4, 6.7%) of Group II (P = 0.05) and high in (n = 4, 7.1%) of Group I versus (n = 4, 6.7%) of Group II (P = 0.05). Low MPV values were relatively more frequent among the homozygotes (n = 4, 50%) and complex heterozygotes (n = 2, 25%) (P = 0.003).

CONCLUSION: The current study showed that MPV was not statistically different between FMF patients and controls, while abnormal MPVs were associated with specific genotypes that may indicate coexistent problems.

Keywords:

Familial Mediterranean fever, genotypes, inflammatory markers, mean platelets volume

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Introduction

Platelets play an important role in inflammatory responses. Different inflammatory factors like coagulants and cytokines are released by platelets. The mean platelets volume (MPV) which is a measure of the average size of the platelets varies according to platelets function and activity. In the last years many articles reported that MPV may be used as an inflammatory marker in different diseases.[1,2] Some reports mentioned an increase in MPV in high altitude and in diseases such as myocardial infarction, cerebrovascular accidents, atherosclerosis, Vitamin D deficiency, thyroid disorders, and cancers. In contrast, chemotherapy and other diseases such as

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rheumatoid arthritis, ankylosing spondylitis, impaired bone marrow function, ulcerative colitis were associated with a decrease in MPV. Genetic disorders may cause either an increase or a decrease in MPV.[3-6]

Familial Mediterranean fever (FMF) is an inflammatory disorder inherited by autosomal recessive gene characterized by recurrent episodes of febrile polyserositis. The disease is especially prevalent in individuals of Mediterranean descent. Due to its non-specific manifestations, FMF may mimic other disorders such as infections, cholecystitis, appendicitis, and arthritis leading to a delay in diagnosis for a long time and predisposing the patients to extensive evaluations and even unnecessary surgery. Patients who do not receive treatment or receive the treatment late in the course of the disease are liable to serious complications such as end stage renal disease and malabsorption secondary to amyloidosis besides failure to thrive in children and infertility in adults. Nevertheless, both acute episodic attacks and late sequelae are quite preventable by treatment with oral colchicine therapy.[7-9]

This prospective case–control study was carried out in Sulaymaniyah Pediatric Teaching Hospital in order to (1) Compare the MPV in children with genetically proved FMV versus healthy controls, (2) Correlate the MPV with different patients' genotypes, and (3) Compare the MPV in patients with FMF during the attacks and in between the attacks.

Patients and Methods

This prospective case–control study was conducted over 9 years (2011–2020) in Sulaymaniyah, Region of Kurdistan, Iraq. The study enrolled 56 Kurdish children with FMF (Group I) and 60 healthy control children (Group II). Patients in Group I were clinically diagnosed according to Tel-Hashomer criteria and all were gene positive. According to Tel-Hashomer, the major diagnostic criteria are recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis), amyloidosis of AA type without a predisposing disease and favorable response to regular colchicine treatment while recurrent febrile episodes, erysipelas-like erythema and FMF in a first degree relative are the minor criteria. Two or more major or one major plus two minor findings are sufficient for FMF diagnosis.[10]

After full history and thorough clinical examination, patients and healthy controls were sent for laboratory investigations including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum iron, total iron binding capacity, serum ferritin, Vitamin D, MPV. Moreover, genetic testing was performed for the patients (Group I) in order to prove the diagnosis, and it was in our plan for all patients from the beginning.

Patients in Group I had laboratory investigations at 2 occasions: during the attack (Group I A; n = 56) and during the attack-free period (Group I B; n = 56). Patients with incomplete information in term of history, clinical examination or investigation were excluded from the study (n = 8; with missing data during attack-free period).

The inclusion criteria for the controls (Group II) included the following: Kurdish nationality, age between 1 and 17-year-old, have relatively same male to female ratio, had no fever at time of test, no history of acute nor chronic problem, had normal white blood cell (WBC), ESR and CRP and were coming just for evaluation.

The MPV was recorded in both patients and controls. The MPV was measured in two private laboratories in femtoliter (fl). In this study MPV values were divided into three categories; low MPV considered when <7 fl, normal MPV between 7 and 11 fl, and large MPV when the measurement >11 fl.[2-6]

Prior to 2016, genetic studies were done abroad as they were not available in Sulaymaniyah but thereafter, 2 private laboratories began to perform these studies. Each patient was genetically rechecked by the same laboratory during the follow-up period and was excluded from the study if a different genetic profile was obtained. Peripheral blood samples in vacutainers containing ethylenediaminetetraacetic acid as anticoagulant were used for genomic DNA extraction by using real prep DNA extraction kit from promega-USA. The MEFV gene variants were genotyped by multiplex real time polymerase chain reaction method detecting 18 common pathogenic variants (Centogene–Turkey). The variants were M694V, M694I, M680I, V726A, E148Q, P369S, A744S, E84K, G304R, E148V, F479L, E167D, T267I, L110P, P283L, K695R, R761H, and E230K/Q.

All were treated with colchicine therapy in a dose 0.5 mg/day for children below 5; 1–2 mg/day for 6–16 years old children and up to 3 mg/day for old children with uncontrolled FMF attacks.

All patients' parents were told that their children will be included in this study and they gave their agreement, and study had been proved by the Ethical Committee in the College of Medicine/University of Sulaimani.

The statistical analysis was performed using the SPSS program(Statistical Package for Social Sciences) version 23 (IBM SPSS) (Armonk, NY, IBM Corp, USA).

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Chi-square tests were used for correlation between variables. $P < 0.05$ was considered statistically significant.

Results

The age range of patients with FMF was between 23 months and 16 years old with a mean of 8.02 ± 3.91 and a male to female ratio of 1.8:1 while in the control group, age ranged from 21 months to 15 years with a mean of 7.77 ± 3.72 and a male to female ratio of 1.4:1. The other demographic characteristics are shown in Table 1.

The triggering factors for attacks in our patients are: Flue and upper respiratory tract infections (46%), Urinary tract infections (31.6%), emotional and physical stresses (12.3%), gastrointestinal infections (8.2%), and others (1.9%).

WBC, ESR, and CRP all had significant statistical association between Group IA and IB while MPV and serum ferritin had no significant statistical correlations as shown in Table 2:

The mean ± standard deviation of MPV in control group (Group II) was 8.05 ± 1.07 fl, for patients in Group IA was 8.01 ± 1.31 fl and for Group IB was 8.25 ± 1.28 fl, respectively. The correlation was statistically not significant ($P = 0.493$) as shown in Table 3.

Normal MPV seems to appear more frequent in heterozygote and compound heterozygote, while low MPV values were relatively more frequent among the complex heterozygote and homozygote, and the correlation was statistically significant ($P = 0.003$), these MPV values were taken during attack period (Group AI) as shown in Table 4.

The gene (M680I) was associated with abnormal MPV in all types of mutations (whether heterozygote, homozygote, compound heterozygote or complex heterozygote) followed by E148Q relatively, these findings during attack period (Group IA) as shown in Table 5.

Discussion

FMF is a chronic auto-inflammatory disease, and like other inflammatory disorders, the patients are prone to some complications. Hence, it is important to identify the accurate markers of inflammation or additional markers that can detect disease activity and the predisposed individual to complications and/or other associated diseases before their appearance.

MPV is reported as an inflammatory marker of disease activity in many connective tissue diseases such as juvenile idiopathic rheumatoid arthritis and ankylosing spondylitis.[11,12] On the other hand, an increase in MPV is considered a predictor of atherothrombotic events.[13] This study took these findings in consideration to identify the significance of MPV in FMF during the attacks and in attack-free period in comparison with healthy controls group and if there was a significance association of MPV values with genotypes of FMF.

All patients in this study were Muslims and from Kurdish nationality, and they were tested gen positive. Their male to female ratio was 1.8:1 with an age range of 23 months to 16 years (mean = 8.02 ± 3.91 year). These age and gender characteristics were similar to those of Fayadh *et al*., Tunca *et al*., and Montazeri *et al*.,[14-16] to the best of my knowledge, there were few previous studies describing FMF in Kurdish nationality.[17]

In the current study, there were high WBC counts during the attacks and mostly of neutrophil type (71.8% of total WBC) and correlation with WBC counts in the attack-free periods was statistically significant ($P = 0.013$). Uslu *et al*., Colak *et al*., Heydari *et al*. and Kucuk *et al*. reported increased WBC counts during the attacks. Moreover, they have considered the neutrophil/lymphocytes ration a useful marker even in the attack-free period.[18-21] On the other hand, Aslan reported leukopenia in 15 patients with FMF.[22] The leukocytosis observed in this study particularly the neutrophilia could be related to FMF disease itself or may be related to bacterial infections triggering FMF attacks.

The ESR and CRP were elevated in our patients especially in attack periods with statistically significant correlation with the attack-free periods ($P = 0.012$ and 0.013 respectively) and can be used as markers of inflammation in FMF. However, serum ferritin had

Table 1: Demographic characteristics of patients with familial mediterranean fever and control group

Demographic characters	Group I, *n* (%)	Group II, *n* (%)
Age (years)		
<2	1 (1.8)	2 (3.3)
2-5	17 (30.4)	19 (31.7)
6-10	22 (39.3)	23 (38.3)
11-14	11 (19.6)	14 (23.3)
>14	5 (8.9)	2 (3.3)
Gender		
Male	36 (64.3)	35 (58.3)
Female	20 (35.7)	25 (41.7)
Residency		
Center	48 (85.7)	47 (78.3)
Peripheral	8 (14.3)	13 (21.7)
Family history of FMF		
Positive	26 (46.4)	24 (40)
Negative	30 (53.6)	36 (60)
Total	56 (100)	60 (100)

FMF=Familial mediterranean fever

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Table 2: Inflammatory markers of Group IA and IB with their genotypes

Laboratory results and genotypes	Group IA, *n* (%)	Mean±SD	Group IB, *n* (%)	Mean±SD	*P*
WBC counts (10^9/L)*					
<4000	2 (3.6)	13196.4±3342.6	3 (5.4)	8416.07±2900.39	0.013
4000-11,000	6 (10.7)	44 (78.6)			
11,100-15,000	30 (53.6)	8 (14.3)			
>15,000	18 (32.1)	1 (1.8)			
Platelets counts (10^9/L)					
50,000-149,999	5 (8.9)	36 (64.3)	7 (12.5)		
150,000-450,000	33 (58.9)	13 (23.2)			
>450,000	18 (32.1)				
MPV (fl)					
<7	8 (14.3)	8.01±1.31	6 (10.7)	8.25±1.28	0.667
7-11	44 (78.6)	47 (83.9)			
>11	4 (7.1)	3 (5.4)			
ESR levels (mm/h)					
<15	1 (1.8)	61.1±16.89	14 (25)	25.55±12.49	0.012
15-45	9 (16.1)	39 (69.6)			
46-75	38 (67.9)	3 (5.4)			
>75	8 (14.3)	0			
CRP levels (mg/L)					
<12	0	66.26±20.17	8 (14.3)	21.17±12.93	0.013
12-48	13 (23.2)	48 (85.7)			
49-85	32 (57.1)	0			
>85	11 (19.6)	0			
Serum ferritin levels (ng/ml)					
<10	9 (16.1)	89.66±42.3	8 (14.3)	83.44±45.00	0.468
10-120	21 (37.5)	29 (51.8)			
>120	26 (46.4)	19 (33.9)			
Genotypes					
Heterozygote			26 (46.4)		
Homozygote			9 (16.1)		
Compound heterozygote			18 (32.1)		
Complex heterozygote			3 (5.4)		
Total			56 (100)		

SD=Standard deviation, MPV=Mean platelet volume, WBC=White blood cell, ESR=Erthyrocyte sedimentation rate, CRP=C-reactive protein

Table 3: Correlation of mean platelet volume between Groups IA, IB and II

MPV (fl)	Group IA, *n* (%)	Group IB, *n* (%)	Group II, *n* (%)	*P*
<7	8 (14.3)	6 (10.7)	4 (6.7)	0.493
7-11	44 (78.6)	47 (83.9)	44 (73.3)	
>11	4 (7.1)	3 (5.4)	4 (6.7)	
Total	56 (100)	56 (100)	60 (100)	

MPV=Mean platelet volume

neither significant elevation nor correlation. Most studies about inflammatory markers in FMF reached similar results in regard to CRP and ESR as acute phase reactants (APRs). Serum ferritin, on the other hand, was not part of APRs in the short lived attacks of FMF according to Yorulmaz *et al*., Basaran *et al*., Korkmaz *et al*., Talaat *et al*. and Stojanovic *et al*.[23-27]

In the current study, the MPV during the attacks was not statistically different from that in the attack-free periods ($P = 0.667$). Likewise, it was not different from that of the healthy controls ($P = 0.493$). Marzouk *et al*., Akdeniz *et al*. and Arica *et al*. reported the use of the MPV as a useful marker in subclinical inflammation together with splenomegaly. Furthermore, they suggested that an increase in the MPV can be an indicator of future atherosclerotic diseases.[28-30] Only one patient in this series had splenomegaly but the MPV was normal. This was not enough for statistical correlation.

According to Üstün *et al*., Karakurt Ö *et al*., Uluca *et al*. and Makay *et al*., regular and early colchicine therapy in children with FMF may mask the significance of MPV as inflammatory marker and as predictor of atherosclerotic disease.[31-34] All patients in this series received colchicine therapy soon after diagnosis. Most of them took colchicine regularly and had an excellent response. On the other hand, Sahin *et al*. observed that MPV deceases in attack and attack-free period in comparison with healthy controls and they attributed the lowered MPV level to secondary thrombocytosis in

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Table 4: Correlation between genotypes and mean platelet volume

MPV (fl)	Genotypes of Group IA				*P*
	Heterozygote	Homozygote	Compound heterozygote	Complex heterozygote	
<7	1 (3.8)	4 (44.4)	1 (5.5)	2 (66.6)	0.003
7-11	24 (92.3)	5 (55.5)	14 (77.7)	1 (33.3)	
>11	1 (3.8)	0 (0.0)	3 (16.6)	0 (0.0)	
Total	26 (100)	9 (100)	18 (100)	3 (100)	56

MPV=Mean platelet volume

Table 5: Genes and mean platelet volume correlation (Group IA)

The gene	MPV (fl)			Total	*P*
	<7	7-11	>11		
M694V	0	7	0	7	0.002
E148Q	0	6	0	6	
V726A	0	7	0	7	
M680I	0	2	1	3	
P396S	1	2	0	3	
M694V-M694V	0	1	0	1	
E148Q-E148Q	1	2	0	3	
M680I-M680I	2	1	0	3	
P396S-P396S	0	1	0	1	
M694I-M694I	1	0	0	1	
E148Q-M694V	0	4	0	4	
V726A-R761H	0	1	0	1	
M694V-V726A	0	2	0	2	
M680I-V726A	0	0	2	2	
E148Q-M680I	1	4	0	5	
E148Q-V726A	0	2	1	3	
M694V-R761H	0	1	0	1	
E148Q-M680I-M694I-M694V	1	0	0	1	
E148Q--M694V-M680I-P369S-V726A	1	0	0	1	
M691V-M694V-V726A	0	1	0	1	
Total	8	44	4	56	

MPV=Mean platelet volume

FMF patients.[35] No patient during the time of this study developed amyloidosis.

It is worthy to mention that FMF may be associated with different diseases that are characterized by low MPV such as vasculitis, juvenile rheumatoid arthritis, inflammatory bowel disease, sacroiliitis, rheumatic fever, systemic lupus erythematous, and Behcet disease.[36] Jae Kim *et al*. suggested the use of increasing in MPV as a marker of improvement in vasculitis, because during active stage the patients have low MPV.[37] Patients with FMF and low MPV in this study deserve further investigations to rule out possible association with the aforementioned diseases.

In this study, patients whose MPV was low ($n = 8$) were double the patients with large MPV ($n = 4$). This may be associated with a low risk of future atherothrombotic events.[13,28-30] Although a good follow-up is needed. The small percentage of patients with low MPV could be due to colchicine therapy which was started immediately after diagnosis.

When low MPV was correlated with genotypes, there was a significant statistical association ($P = 0.003$) with homozygote and complex heterozygote unlike other genotypes (the heterozygote and compound heterozygote). It was quite clear that some genes were associated with abnormal MPV (whether small or large) like M680I gene which was associated with low MPV in homozygote, compound heterozygote and complex heterozygote but not in simple heterozygote, while it was associated with large MPV in simple heterozygote (1 patient) and compound heterozygote. Another gene had the same presentation but with less extent was E148Q gene.

Rabinovich *et al*. reported on 98 patients with rheumatoid arthritis, twelve of them were severe cases and had E148Q mutation while few patients had M694V and V726A mutations.[38] Ben-Chetrit *et al*. concluded that genes of FMF could be associated with other autoimmune disease (s), whose correct early diagnosis is crucial for better outcome.[39] Ekinci *et al*. stated that concomitant diseases particularly juvenile rheumatoid arthritis influence FMF severity, therefore, it may be beneficial to focus on diagnosis and treatment of such diseases, which, if missed, may worsen the course of FMF.[40] A case report by Yurdakul *et al*. and a research paper by Tutar *et al*. showed that some specific FMF mutations had a significant association with rheumatic heart disease particularly M680I mutation.[41,42] In the current study, the most frequent mutation associated with low MPV was M680I mutation, but no patient had clinical evidence of rheumatic heart disease or an autoimmune condition.

Conclusion

The current study showed that MPV was not statistically different between FMF patients and controls and, therefore; MPV could be of little value in FMF if compared with APRs such as the ESR and CRP. On the other hand, abnormal MPV could be associated with specific genotypes that may indicate an associated problem(s) and required further investigations.

Ethical issues

The Ethics Committee of Sulaimani University/School of Medicine approved the study.

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Conflicts of interest

There are no conflicts of interest.

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