

Research Article

Co-evaluation of Red Cell Distribution Width Changes in Different Group of Familial Mediterranean Fever Patients

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Abstract

Objectives: Our aim in this study is to evaluate the Red cell distribution width (RDW) levels in individuals with FMF who refer to our clinic and to investigate their usefulness as a prognostic factor.

Methods: Participants of this work, who referred to our policlinics between January 2016 and January 2017, were recruited through the patient database of our hospital. The study included 86 patients. In the FMF group, there were total of 56 patients (35 females, 21 males), and in the control group, there were 30 patients (19 females and 11 males). There were no clinical interventions. Blood RDW measurements were determined in both fmf and control groups.

Results: We didn't reach any statistical importance between healthy individuals and patients with heterozygous and homozygous FMF.

Conclusion: In our work, we didn't consider rdw as a useful marker between groups which have different mutations.

Keywords: Autoimmunity, heterozygote, red cell distribution width

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Familial Mediterranean Fever (FMF) is caused by the mutations in the MEFV gene, which is the Mediterranean gene mapped at chromosome 16p 13.3. It is an autosomal recessive disease. It is also an autoimmune disease. Patients usually suffer from recurrent fever, serositis and arthritis attacks. Skin lesions in the form of erysipelas can be seen. It is commonly seen in people who live in Mediterranean region. Like Jewish, Armenian, Turkish, and Arabic communities.^[1, 2]

The pyrin marenostin, a Mediterranean gene (MEFV), is an important component of the inflammation. There is a continuously inflammation during disease progression. The MEFV gene contains about 10 exons and 3505 nucleotides.^[3, 4] In neutrophils, inflammatory cytokines such as interferon gamma enhance MEFV gene expression.

Pyrin protein consists of 781 amino acids. It is thought to have a through or an indirect effect in inflammation.^[5] It has been stated that Pyrin is efficient in the inhibition of inflammation.^[1]

Previous serological studies suggested a mild inflammation of MEFV in many heterozygous patients with increased C-reactive protein. FMF is known as an autosomal recessive inherited situation, but it is not fully recessive, and in some cases, the heterozygous mutations associated with clinical symptoms have been found.^[6]

RDW shows the variation in size of erythrocytes.^[7] Rdw is frequently studied parameter in daily clinical examination. In recent years according to some studies RDW may be a useful prognostic factor in cardiovascular diseases, rheumatoid

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arthritis, and progressive inflammatory conditions.^[8-10]

High RDW refers to the presence of anisocytosis, and it reflects chronic inflammation and increased levels of oxidative stress.^[11]

The levels of acute phase proteins increases during the attacks in FMF. The protein pyrin, which is a MEFV product, inhibits pro-inflammatory cytokines and increases the anti-inflammatory mediators.

Also, this inflammatory situation goes on in 30% of patients in the non-attack period and causes amyloidosis complication.^[12] In the current study, we evaluated the RDW levels in FMF patients.

Methods

The patients who referred to our clinics between January 2016 and January 2017 were evaluated through the patient database of our hospital. The records were screened retrospectively. There were a total of 86 patients in two groups. There were 56 patients (35 female, 21 male) in the FMF group, and 30 patients (19 female, 11 male) in the control group. This study was Ethically approved by Amasya University Hospital in the scientific meeting occurred on 10th of October, 2017.

Patients with known anemia, heart failure, renal insufficiency, hypothyroidism, and hyperthyroidism didn't included to the study. Patient's liver enzymes and blood creatinine were normal. Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were in the normal range. Patients in non-attack period were included to the study. Blood RDW measurements (normal values: 11.5-14.5%) were measured on the MindRay 6800 hemogram instrument. Blood samples were first isolated using the Magne-

sialb instrument. Then, PCR was performed using the real time PCR method with Montania 4896 instrument.

Results

GraphPad Prism version 6.00 (GraphPad Software, La Jolla California USA) was used for statistical analysis. Normality of the distribution in groups was demonstrated by the Shapiro-Wilk normality test. One-way ANOVA was used to compare quantitative data. The Chi-Square test was used to examine gender differences. The results were evaluated in a 95% confidence interval and a significance level of $p < 0.01$. The age average of these patients was 27.2 in females and 32.6 in males in the control group. In FMF subgroups, the age average in the heterozygote group was 32.8 in females and 27.3 in males. In the homozygote group, it was 32 in females and 20 in males. In compound heterozygote group, it was 47 in females and 27.3 in males, and lastly, it was 47 in females in the complex heterozygote group, which didn't include any male patient. This information is presented in table 1.

The gender differences in RDW is demonstrated in Table 2. No statistically significant difference was observed between two genders.

RDW-CV percentages were 13.71 ± 1.151 in the control group, 14.07 ± 3.479 in the heterozygous group, 13.70 ± 0.355 in the homozygous group, 14.03 ± 0.937 in the compound heterozygote group and 14.15 ± 1.202 in the complex heterozygote group. In Compound Heterozygote and Control group the distribution was considered normal according to the Shapiro-Wilk normality test (Table 3). In Homozygote group and Complex Heterozygote group, number n was low, so the normality test could not be performed. As is shown in the figure 1, there was no statistically significant difference between the groups ($p < 0.05$).

Table 1. Age average of groups

	Control Group			Heterozygote			Homozygote			Compound Heterozygote			Complex Heterozygote		
	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female	Overall
Arithmetic mean	32.69	27.23	29.96	30.88	27.34	29.11	20	32	26	29.66	47	38.33	-	24.5	24.5

Table 2. Gender differences according to patient groups

Gender	Heterozygote (n=44)		Homozygote (n=4)		Compound heterozygote (n=7)		Complex heterozygote (n=2)		χ^2	p
	n	%	n	%	n	%	n	%		
Female	26	65.3	3	75	4	57.1	2	100	0.4167	0.936
Male	17	34.7	1	25	3	42.9	0	0		

Table 3. RDW (%) averages and normality tests in control and patient groups

	Patient groups				Control group
	Heterozygote	Homozygote	Compound Heterozygote	Complex Heterozygote	
RDW %	14.07±3.47	13.70±0.35	14.03±0.93	14.15±1.20	13.71±1.51
Shapiro-Wilk normality test p value	<0.0001	n number low+	0.112*	n number low+	0.153*

*: The distribution was considered normal in the Shapiro-Wilk normality test; (+) As the number n was low, the normality test could not be performed.

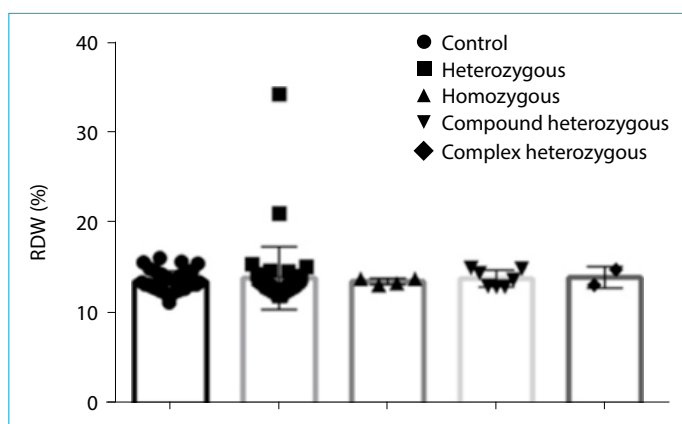


Figure 1. The levels of RDW between patient and control groups. There was no statistically significant difference between the groups ($p < 0.05$).

Discussion

FMF is characterized by recurrent fever, serositis, and fever episodes. Recent developments in molecular genetics have shown the complexity of FMF heredity and pathogenesis. Despite the identification of the gene-derived FMF, the pathogenesis didn't understood clearly.^[13, 14]

Pyrin is associated with inflammatory markers.^[15] Some experimental studies showed that pyrin is very important in inflammation and apoptosis. Mutant Pyrin has been shown to cause excessive IL-1 release and inflammation. In a study Gavrilin M and friends showed that mononuclear cells which are infected with Burkholderia cenocepacia and Francisella novicida increase caspase-1 activation and IL-1 level.^[16]

FMF is autosomal recessive. There are over 310 mutations in the MEFV gene.^[17] In a study by Erden G and friends reported that M694V, M680I, V726A, and E148Q are the prevalent mutations.^[18] M694V mutation colchicine resistance is responsible for a serious disease like amyloidosis, and in patients who carry this mutation, have high risk of early onset of the disease, and E148QV is along with low disease prevalence. Pathogenic significance is unknown. Homozygous E148Q is rare in those patients with clinical FMF.^[15] Also, in a study with 110 patients by Tüzün A et al.^[19] they found M694V mutation (75%) as the most common one proceeded by M680I mutation (34%), V726A mutation

(17%), and E148Q mutation (6%).

RDW is studies routinely in complete blood count. It shows anisocytosis and the variation in the red sphere cell dimensions in the situation of inflammation and malnutrition.^[20, 21]

RDW is useful for typing anemias. However, its relation with inflammation has been considered recently. And it may be a predictive marker in inflammatory diseases.^[22]

Inflammation protects cell damage by microorganisms and toxins. Blood vessels, leukocytes, mediators arising from plasma proteins play a role. Increased cytokines with inflammatory stimuli can cause systemic findings. These findings include fever, CRP, increased fibrinogen, and leukocytosis. Recently, studies on RDW increase in inflammatory diseases have been made.^[23]

We searched if RDW can be use as a marker in patients who have FMF.

In a study conducted by Uslu A et al.^[24] they found RDW levels high in patients with FMF. It was high in homozygous M694V mutation, especially when compared to other mutations. They noted that RDW reflects inflammation patients with FMF and can be use as a marker.

In a study by Özer et al.^[25] investigated the platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), and RDW in children with FMF and found them to be high. Among them, they found NLR more reliable.

Gozde Y et al.^[26] investigated in 89 FMF patients with persisting inflammation, in non-attack period. They found RDW to be high and low MPV in non-attack period.

In our study, we did not find statistically significant differences in RDW ratios between patient and control groups. There is no difference between the heterozygous, homozygote, complex heterozygote, and compound heterozygote groups too. Our study was retrospective so we had some limitations. We did not know about the patients' colchicine or other agents they used. The number of patients we recruited was low. We classified the groups as homozygotes, heterozygotes, complex heterozygotes, and compound heterozygotes. We have limited number of patients so we

can not classify them according to the mutations, and we think that this has an effect on the results. We think that the studies to be done by classifying according to the mutations with more patients will be more beneficial.

Conclusion

According to the results that we obtained, there is no statistically significant differences in RDW ratios between patient and control groups. So it seems RDW may not be use as a prognostic marker in FMF. But our study had some limitations. We did not know about the medications that patients used such as colchicine or other agents. The number of patients was low. Further researches to be done in the light of these information will provide more significant result.

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Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

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