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The Levels of Von Willebrand Factor in Adult Patients with Familial Mediterranean Fever and it is Relationship with Platelet Activation

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ABSTRACT

Objective: Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes. Recently few studies have shown that FMF is associated with increased atherosclerosis risk. Therefore, this study was designed to answers the following questions: A) do von Willebrand factor (vWf)- a marker of endothelial damage / dysfunction- levels change in adult FMF patients and B) is there any relationship between vWf and mean platelet volume (MPV)- a determinant of platelet activation- levels?
Materials and Methods: This study was performed in January 2008. We selected 35 patients with FMF and 35 healthy control subjects matched for age, gender, and body mass index. We measured levels of vWf and MPV in all study population.
Results: The level of vWf was significantly higher in the FMF group than in the control group (p=0.001). Also, vWf level was positively correlated with MPV level in FMF group (r=0.694, p=0.001).
Conclusion: Our results suggest that (i) adult patients with FMF tend to have relatively endothelial dysfunction, and (ii) vWf seem to be related to platelet volume in patients with FMF.

Keywords: *Familial Mediterranean fever, Von Willebrand factor, Endothelial dysfunction, Mean platelet volume.*

ÖZET

Yetişkin Ailesel Akdeniz Ateşi Hastalarında Von Willebrand Faktör Düzeyleri ve Bunun Trombosit Aktivasyonu ile İlişkisi

Amaç: Ailesel Akdeniz Ateşi (AAA), serozal ve sinovyal membranların tekrarlayan inflamatuar ateşli atakları ile karakterize otozomal resesif bir hastalıktır. Yakın zamandaki bazı çalışmalar AAA'nın artmış ateroskleroz riskine eşlik ettiğini göstermiştir. Bundan dolayı, bu çalışma şu sorulara cevap vermek üzere tasarlanmıştır: (A) endotel hasarının veya disfonksiyonunun bir belirteci olan von Willebrand faktör (vWf) düzeyleri yetişkin AAA hastalarında değişiklik gösteriyor mu? ve (B) vWf ile trombosit aktivasyonunun bir belirleyicisi olan ortalama trombosit volümü (OTV) arasında bir ilişki var mıdır?
Gereç ve Yöntem: : Bu çalışma Ocak 2008'de gerçekleştirilmiştir. Çalışmaya 35 AAA hastası ile kontrol grubu olarak yaş, cinsiyet ve vücut kitle indeksi açısından benzer 35 sağlıklı kişi alındı. Çalışmaya alınanlarda vWf ve OTV düzeyleri ölçüldü.
Bulgular: vWf düzeyi AAA grubunda kontrol grubuna göre anlamlı olarak yüksekti (p=0.001). Ayrıca, AAA grubunda vWf düzeyi ile OTV düzeyi arasında pozitif korelasyon mevcuttu (r=0.694, p=0.001).
Sonuç: Sonuçlarımız (i) yetişkin AAA hastalarının rölatif olarak endotelyal disfonksiyona sahip olduklarını ve (ii) AAA hastalarında vWf'ün trombosit volümüyle ilişkili göründüğünü düşündürmektedir.

Anahtar Kelimeler: *Ailesel Akdeniz ateşi, Von Willebrand faktör, Endotelyal disfonksiyon, Ortalama platelet volümü*

Familial Mediterranean fever is the prototypic recessively inherited autoinflammatory disease, prevalent among multiple populations from the eastern Mediterranean basin, particularly Jews, Armenians, Turks, and Arabs. FMF is characterized by short recurrent bouts of fever and localized inflammation usually involving the peritoneum, pleura, joints, or skin (1, 2). FMF is caused by mutations in the MEFV gene encoding the pyrin protein thought to be associated with the interleukin-1 related inflammation cascade. Attacks subside spontaneously within one to three days, without residue. Colchicine is the treatment of choice in FMF both for attacks and for prevention of secondary amyloidosis, the most dreaded complication of the disease (3, 4).

Endothelial dysfunction (ED), which is characterized by an imbalance between relaxing and contracting factors, procoagulant and anticoagulant substances, and between pro-inflammatory mediators, may play a particulary significant role in the pathogenesis of atherosclerosis (5). Under physiological conditions, the vascular endothelium produces many substances that are closely involved in hemostasis, fibrinolysis, growth factor synthesis, and the regulation of vessel tone and permeability. One of

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these substances is von Willebrand factor (vWf), which is synthesized by and stored in endothelial cells. vWf is a multimeric glycoprotein, and it is essential for platelet aggregation and adhesion (6). Numerous clinical and experimental reports suggest that a high vWf level reflects endothelial damage or ED. vWf levels have been proposed as an indicator of ED (7). High vWf levels have been shown to have prognostic value in patients with ischaemic heart disease, peripheral vascular disease and inflammatory vascular disease (8).

Recently few studies have shown that FMF is associated with increased atherosclerosis risk (9-11). On the other hand, increased platelet activation plays an important role in the development of atherosclerosis (12). Increased platelet activity is associated with increased platelet volume. Large platelets that contain more dense granules are metabolically and enzimatically more active than small platelets and have higher thrombotic potential (13). Mean platelet volume (MPV), which is routinely determined by complete blood count analyzers, is a parameter reflecting the platelet size, a determinant of platelet activation, is a newly emerging risk factor for atherothrombosis (14). Elevated MPV levels have been identified as an independent risk factor for myocardial infarction in patients with coronary heart disease (15) and for death or recurrent vascular events after myocardial infarction (16). Therefore, this study was designed to answers the following questions: 1) do vWf (a marker of ED damage / dysfunction) levels change in adult FMF patients and 2) is there any relationship between vWf and MPV levels?

MATERIAL AND METHODS

One hundred and sixty two adult patients with FMF, diagnosed in accordance with Tel-Hashomer criteria (17), were registered in the computer files of our departments. Thirty five adult patients with FMF without exclusion criteria were invited to participate. None of the patients refused the study. Thirty five subjects who were the healthy participants who had undergone the check-up program were used as the control group. The controls had similar body mass index (BMI), age, and sex distribution as the FMF group. They underwent a routine physical and laboratory evaluation to ascertain that they had no exclusion criteria. All subjects gave their informed consent to participate in the study.

Clinical and laboratory assessment of FMF patients were performed during an attack-free period. All FMF patients were on colchicine treatment. Colchicine was given orally in one or two daily doses, the total daily dosage ranging from 1.0–2.0 mg. Our FMF patients were in partial remission (defined as significant decrease of attack frequency, duration or intensity).

Exclusion criteria for entry into the study were, sustained hypertension [antihypertensive (present or past) drug use or detection of systolic pressure higher than 140 mmHg and/or diastolic pressure higher than 90 mmHg on three separate occasions], diabetes mellitus [antidiabetic (present or past) drug use or fasting glucose ≥ 126 mg/dl on two separate occasions], obesity (BMI ≥30 kg/m²), smoking, alcohol consumption, hyperlipidemia, cardiac, renal, and other systemic diseases, recent major surgery or illness, and patients on drugs affecting platelet function (e.g. aspirin, warfarin or heparin). Hyperlipidemia was defined in presence of at least one of following conditions; raised plasma triglycerides (>200 mg/dl), total cholesterol (>200 mg/dl), low-density lipoprotein cholesterol (LDL-C >130 mg/dl). Blood pressure was measured by using sphygmomanometer after 5 min of rest in the sitting position. Body weight (kg) and height (m) were measured with the patient in light clothes. The BMI was calculated as the weight (kg)/height squared (m)².

Laboratory Investigations

Blood samples were drawn after a fasting period of 12 hr. Enzymatic colorimetric assay method (Roche Diagnostic GmbH, Mannheim, Germany) was used to measure triglyceride, cholesterol and high density lipoprotein-cholesterol levels. Low density lipoprotein-cholesterol level was calculated according to the Friedewald formula. Fasting plasma glucose level was measured by enzimatic colorimetric assay method (GLU, Roche Diagnostic GmbH, Mannheim, Germany).

Measurement of vWf

Plasma vWf levels were measured quantitatively by STA-LIATEST [(Diagnostica Stago (France)]. All of the samples measured were done at the same run.

Measurement of MPV

We measured MPV in a blood sample collected in citrate (1: 4 v/v) in order to avoid the platelet swelling induced by EDTA, and analysed within 1 hour. A Cell-Dyn 3500 (abbot) was used for whole blood counts.

Statistical analysis

SPSS 10.0 for Windows was used for the statistical analysis. For α=0.05 (between each group) and power=80%, a simple size per group >27 subjects was needed to detect an actual difference. Two-group comparisons (FMF vs. control) were performed with independent *t*-tests. Correlation between levels of vWf and MPV were assessed using Pearson's correlation analysis. Data were expressed as the mean ± SD. A value of $p<0.05$ was considered as statistically significant.

Table 1. *Clinical characteristics and laboratory parameters of the study groups*

Parameter	FMF Group (n=35)	Control Group (n=35)	p values
Male/female	19/16	18/17	NS
Age (yr)	34 ± 9	35 ± 9	NS
Body mass index (kg/m^2)	24.1 ± 3.0	25.3 ± 2.3	NS
SBP (mm Hg)	117.2 ± 9.6	118.2 ± 10.2	NS
DBP (mm Hg)	73.4 ± 5.9	74.4 ± 7.1	NS
Glucose (mg/dl)	84.0 ± 5.9	86.4 ± 6.6	NS
Creatinine (mg/dl)	0.7 ± 0.1	0.8 ± 0.1	NS
ALT (U/l)	23 ± 11	21 ± 8	NS
LDL-cholesterol (mg/dl)	94 ± 20	102 ± 16	NS
Triglyceride (mg/dl)	111 ± 46	113 ± 47	NS
MPV (fl)	8.6 ± 0.9	7.8 ± 0.5	**0.001**
Platelet counts (×10^9/µl)	257000 ± 61000	284000 ± 64000	NS
vWf (%)	113.3±58.4	74.2±50.5	**0.001**

Data were expressed as the mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine amino transferase; MPV, mean platelet volume; vWf, von Willebrand factor; NS, not significant.

RESULTS

The main characteristics and laboratory parameters of study population are reported in Table 1. Age, gender distribution, and body mass index did not differ among the groups. Similarly, metabolic parameters were not different among the study groups as a results of the selection process.

The level of vWf was significantly higher in FMF group than in healthy control group (113.3±58.4 % vs. 74.2±50.5 %, p=0.001). MPV was significantly higher in the FMF group than in the control group (8.6±0.9 vs 7.8±0.5, p=0.001). vWf level was positively correlated with MPV level in FMF group (r=0.694, p=0.001).

DISCUSSION

The vascular endothelium is involved in the production of many essential substances which are involved in cardiovascular pathophysiology. One of these substances which is synthesised by and stored in endothelial cells, is vWf (6). It has been previously shown that increased vWF levels reflect ED and may also have prognostic value in patients with atherosclerotic disease (18). This is the first study, to our knowledge, specifically, to evaluate vWf levels in adult FMF patients. We found that vWf levels were significantly higher in the FMF group than in healthy control group. It has been shown that attack-free period in FMF is characterized by ongoing endothelial damage with elevation of circulating markers of endothelial dysfunction such as thrombomodulin (19), adrenomedullin and nitrite (20). Terekeci et al (21) reported that increased serum asymmetric dimethylarginine (ADMA), an indicator for endothelial dysfunction, in FMF patients compared to healthy controls. Akdogan et al found that endothelium-dependent flow-mediated diatation is reduced in FMF patients compared with healthy controls (22).

On the other hand, we reported that increased MPV levels in adult patients with FMF, in our previous study (23). In contrast, Makay et al reported that MPV is not elevated in pediatric FMF patients on colchicine treatment (24) . We found that vWf showed positive correlation with the platelet volume in patients with FMF. This finding have not been reported previously in FMF patients. When the endothelial layer is injured, collagen, vWF and tissue factor from the subendothelium is exposed to the bloodstream. When the platelets contact collagen or vWF, they are activated (25). Platelet activation is an essential link between inflammatory, thrombotic and atherogenic pathways (26, 27). Activated platelets interact with neutrophils and endothelial cells and through the release of pro-inflammatory agents facilitate participation of immune cells in vascular inflammation and atherogenesis (26, 28).

There are limited study about relationship between vWf and MPV. Ihara et al. reported that positive correlation between vWf and MPV in patients with ischemic heart disease and in patients with aortic aneurysm (29, 30). However, with the current data it is not possible to say whether high vWf levels are the cause of large platelet volume, or not. Future cohort studies will be helpful in providing an answer.

The present study has some limitations. Firstly, the study population was rather small. Thus large-scale studies would be helpful in order to make further comments on the relation between MPV and vWf. The second limitation is that our analyses were based on a single baseline determination that may not reflect the patients' status over long periods.

In conclusion, our results suggest that i) adult patients with FMF, without other cardiovascular risk factors/diseases, tend to have relatively endothelial

dysfunction, and ii) vWf seem to be profoundly related to platelet volume in adult patients with FMF.

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