International Journal of Research in Medical Sciences
Ulu MS et al. Int J Res Med Sci. 2014 Feb;2(1):270-273
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: 10.5455/2320-6012.ijrms20140251

Research Article

Do MEFV mutations influence arterial stiffness in FMF patients?

Memnune Sena Ulu[1]*, Akif Acay[2], Ahmet Ahsen[2], Şeref Yuksel[1], Gürsel Acartürk[3], Mustafa Solak[4]

[1]Department of Nephrology and Hypertension, Afyon Kocatepe University, Afyonkarahisar, Turkey
[2]Department of Internal Medicine, Afyon Kocatepe University, Afyonkarahisar, Turkey
[3]Department of Gastroenterology, Afyon Kocatepe University, Afyonkarahisar, Turkey
[4]Department of Medical Genetics, Afyon Kocatepe University, Afyonkarahisar, Turkey

Received: 21 November 2013
Accepted: 15 December 2013

***Correspondence:**
Dr. Sena Memnune Ulu,
E-mail: drsenaulu@yahoo.com

ABSTRACT

Background: Pulse wave velocity (PWV) is the most used technique to evaluate the arterial elasticity, which is an early indicator of atherosclerosis. We aimed to evaluate if MEFV Mutations influence arterial stiffness in patients with Familial Mediterranean fever (FMF)
Methods: 70 patients diagnosed with FMF and 50 age-and sex-matched controls were included in the study. Genetic analysis of the patients was performed. After the measurement of PWV; the presence of AS was determined.
Results: Mean PWV value and arterial stiffness frequency of FMF patients were significantly higher than the control group ($p < 0.001$, $p < 0.001$) respectively. In addition, FMF patients with M694V mutations had higher PWV values and arterial stiffness frequency than those with other mutations. ($p=0.045$), ($p=0.001$). There were no differences within all genetic mutation types in terms of arterial stiffness frequency.
Conclusions: As a result, due to subclinical inflammation in FMF patients, they have risk for cardiovascular complications. These patients especially those with M694V mutations have to be followed more closely because of increased cardiovascular risk and PWV measurements may be a good tool to detect early development of atherosclerosis.

Keywords: Chronic inflammatory disease, Familial mediterranean fever, MEFV mutations, Pulse wave velocity, Arterial stiffness

INTRODUCTION

Familial Mediterranean Fever (FMF); is a hereditary chronic inflammatory disease. It is characterized by recurrent attacks of fever, peritonitis and pleuritis.[1,2] Screening of causative gene (MEFV) mutations allows for the diagnosis of FMF.[3] Colchicine is an effective medication in the treatment.[4] Subclinical inflammation may continue in some FMF cases, even in the symptom-free periods.[5] The clinical results of subclinical inflammation were not shown in FMF patients without amyloidosis. But they may have risk for cardiovascular complications even without amyloidosis.[6]

Chronic inflammation and atherosclerosis cause arterial vessel wall injury and reduce arterial compliance and elasticity causing endothelial dysfunction.[7] Arterial stiffness is known as an independent indicator for the development of cardiovascular complications.[8] Pulse wave velocity (PWV) may be a good tool to detect the cardiovascular risk in FMF patients like other chronic inflammatory diseases.[9,10] Recently, the effects of the MEFV genotype differences on inflammatory activity have been investigated.[5] But there is not any study in FMF patients evaluating the relationship between arterial stiffness and genetic mutation types by using PWV values. In this study, we aimed to investigate this relationship for the first time.

METHODS

The study was performed between July 2009-June 2013 in departments of Internal Medicine, Medical Genetics in Afyon Kocatepe University, Faculty of Medicine. 70 patients diagnosed with FMF and 50 age-and sex-matched controls were included in the study. The study was approved by the local ethics committee and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Informed written consent form was obtained from all participants. All patients and controls were questioned for a detailed medical history and physical examination. Patients were evaluated according to the Tell Hashomer criteria for the diagnosis of FMF.[11] Genetic analysis of patients were received from the recorded data. Patients with coronary artery disease, peripheral artery disease, hypertension, hyperlipidemia, smoking history, diabetes mellitus, chronic renal failure, used drug affecting arterial stiffness (eg, antihypertensive, antidiabetic, antilipemic such as drugs) were excluded from the study.

Pulse wave velocity measurements

To evaluate the arterial stiffness, pulse wave velocity was measured automatically by 6000 Pulse trace module device (Micromedical, Rochester, United Kingdom). After a minimum of 5 minutes of rest in the supine position, CWD (Continuous Wave Doppler) were recorded from the patients laid-back in a quiet environment with 4 mHz probe placed Carotid and Femoral arteries accompanied by ECG. To obtain the PWV value, the ratio of the distance between the recorded two points and the transition time of the pulse wave between two points was calculated. PWV values were recorded in m/sn. After the calculation of PWV of the patients and the control group; the presence of AS was determined according to the age of the participants in accordance with the recommendations of "The Reference Values for Arterial Stiffness' Collaboration".[12]

Mutation analysis

All molecular examinations of FMF patients were performed in the laboratory of the Medical Genetics Department. Genomic DNA was isolated from peripheral blood sample taken into ethylenediamine tetraacetate (EDTA) tubes. In order to obtain genomic DNA; a puregene DNA isolation kit (Gentra Systems, Minneapolis, MN, USA) was used. Spectrophotometric analysis of DNA molecules (Nanodrop ND-1000) was done to detect the amount and purity of the molecule. The MEFV mutations (M694V, M694I, M680I and V726 located in the tenth exon, and E148Q located in the second exon) in patients were determined with the PCR-ELISA method using PRONTO FMF Kit (Pronto Diagnostics, Rehovot, Israel), while P369S, K695R, A744S, R202Q and R761H mutations were determined with an FV-PTH-MTHFR Strip Assay Kit (Vienna, Austria).

Statistical evaluation

Continuous variables were presented as mean ± SD, and categorical variables were expressed as percentage. Kolmogorov–Smirnov test was used to evaluate the distribution of variables. Student's t test was used for continuous variables with normal distribution, and Mann-Whitney U test was used for continuous variables without normal distribution. Chi-square test was used for categorical variables. Pearson correlation analysis was used to assess the relationships. p value <0.05 was accepted as the significant level. For statistical calculations, SPSS Statistical Software (SPSS for Windows, version 17.0; SPSS Inc. Chicago, IL, USA) was used**.**

RESULTS

The mean age of the patients was 30.67 ± 9.1years and the control group was 32.40 ± 9.1 years. Demographic characteristics of the patients and the control group were shown in Table 1. None of the patients had amyloidosis. Mean duration of the disease was 58.01 ± 69.78 months. All patients had been treated by colchicine in a continuous dose of 1 mg/day to 2 mg/day.

Table 1: Demographic characteristics of patients with FMF and control group.

Variables		FMF (n=70)	Control (n=50)	P
Age(year)		30.67 ± 9.1	32.40 ± 9.1	0.309
Sex †	Male	31 (44.3)	22 (44)	0.364
	Female	39 (55.7)	28 (56)	
BMI (kg/m²)		24.4 ± 4.4	24.3 ± 3.4	0.906

*All parametres were expressed as mean ± S.D unless otherwise stated.

† Expressed as number (perccent).

Mean PWV value of FMF patients was 7.31 ± 1.1 and the control group was 6.47 ± 1.1. AS frequency of FMF patients was 72.9% and the control group was 28%. Mean PWV value and AS frequency of FMF patients were significantly higher than the control group (p <0.001, p <0.001) respectively. Disease duration was not correlated with PWV.

In the genetic analysis of the patients, 54 patients (77.1%) were heterozygous, 12 (17.1%) were homozygous, 1 (1.4%) had co-heterozygous and 3 (4.3%) were had no mutations. Genetic structure of the FMF patients was shown in Table 2. According to these groups, there were no differences in terms of arterial stiffness frequency. Besides, in the analysis of PWV and AS frequency of

patients according to M694V mutation, FMF patients with M694V mutations had higher PWV values (7.53 ± 1.2 and 6.94 ± 1.0 respectively) and arterial stiffness frequency (86.4% and 50% respectively) than the other mutations (p=0.045), (p=0.001) respectively.

Table 2: Genetic structure of the FMF patients.

Mutations	Mutation type	Number (%)
No mutation	-	3 (4,3)
Homozygous	M694V	10 (14.3)
	M680I	2 (2.9)
	R202Q with M694V heterozygous	1 (1.4)
Heterozygous	M694V	7 (10.0)
	E148Q	9 (12.9)
	V726A	7 (10.0)
	A744S	1 (1.4)
Compound heterozygous	M694V-E148Q	5 (7.1)
	M694V-R761H	4 (5.7)
	M694V-R202Q	1 (1.4)
	M694V-M694I	5 (7.1)
	M694V-V726A	5 (7.1)
	M694V-M680I	4 (5.7)
	M680I-V726A	3 (4.3)
	E148Q-P369S	3 (4.3)

All parametres were expressed as number (perccent).

DISCUSSION

This is the first study investigating the relationship between arterial stiffness in FMF patients according to their genetic mutation types by using PWV measurements. The most important finding of our study was that, FMF patients with M694V mutations had higher PWV values.

PWV which is an early sign of atherosclerosis, is affected in chronic inflammatory diseases such as RA, SLE, systemic sclerosis.[9,10] Recently, Yıldız M et al found slightly higher PWV levels in patients with FMF[13] Besides, some studies defending vice versa.[14] In our study, all patients had been treated by Colchisin, but despite this, PWV values and AS frequency of patients were significantly higher than the control group. According to these results, it may be said that, FMF patients have higher risk of atherosclerosis and PWV measurement may be an indicator of arterial stiffness as an early sign of atherosclerosis.

Ongoing low-grade inflammation was shown not only in FMF patients but also in carriers of MEFV mutations.[15] Recently, the effects of the MEFV genotype differences with the severity of clinical picture and inflammatory activity were shown by Colak B and homozygous M694V mutation was found associated with a more severe disease course in FMF.[5] Akdoğan A et al. showed that, brachial artery flow-mediated dilatation impairs in FMF patients with homozygous M694V mutation more than the others.[16] In our study, FMF patients with M694V mutations had higher PWV values and arterial stiffness frequency.

As a conclusion, due to subclinical inflammation in FMF patients outside the attacks, they have risk for cardiovascular complications. These patients especially those with M694V mutations have to be followed more closely because of increased cardiovascular risk and PWV measurements may be a good tool to detect early development of atherosclerosis.

Limitations of the study

In our study, it could be useful to investigate the relationship between arterial stiffness and the development of amyloidosis in patients with FMF, but we could not do this comparison because any of our patients had not amyloidosis. We believe that studies investigating on this relationship in a larger number of FMF patients with amyloidosis will contribute to the literature. Besides, in order to determine the effect of mutations on arterial stiffness, studies with larger participants are needed.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the local ethics committee

REFERENCES

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967;43(2):227-53.
2. Berkun Y, Eisenstein E, Ben-Chetrit E. FMF - clinical features, new treatments and the role of genetic modifiers: a critical digest of the 2010-2012 literature. Clin Exp Rheumatol 2012;30(3 Suppl 72):90-5.
3. Ben-Chetrit E, Touitou I. The impact of MEFV gene identification on FMF: an appraisal after 15 years. Clin Exp Rheumatol 2012;30(3 Suppl 72):S3-6.
4. Unverdi S, Inal S, Ceri M, Unverdi H, Batgi H, Tuna R, Ozturk MA, Guz G, Duranay M. Is colchicine therapy effective in all patients with secondary amyloidosis? Ren Fail 2013;35(8):1071-4.
5. Colak B, Gurlek B, Yegin ZA, Deger SM, Elbek S, Pasaoglu H, Dogan I, Ozturk MA, Unal S, Guz G. The relationship between the MEFV genotype, clinical features, and cytokine-inflammatory activities in patients with familial mediterranean fever. Ren Fail. 2008;30(2):187-91.
6. Onat A, Direskeneli H. Excess cardiovascular risk in inflammatory rheumatic diseases: pathophysiology and targeted therapy. Curr Pharm Des 2012;18(11):1465-77.

7. Park S, Lakatta EG. Role of inflammation in the pathogenesis of arterial stiffness. Yonsei Med J 2012;53(2):258-61.
8. Deloach SS, Townsend RR. 'Vascular stiffness: Its Measurement and Significance for Epidemiologic and Outcome Studies.' Clinical Journal of American Society of Nephrology 2008;3:184-92.
9. Yildiz M, Soy M, Kurum T, Ozbay G. Increased pulse wave velocity and shortened pulse wave propagation time in young patients with rheumatoid arthritis. Can J Cardiol 2004;20(11):1097-100.
10. Zeng Y, Li M, Xu D, Hou Y, Wang Q, Fang Q, Sun Q, Zhang S, Zeng X. Macrovascular involvement in systemic sclerosis: evidence of correlation with disease activity. Clin Exp Rheumatol 2012;30(2 Suppl 71):S76-80.
11. Livneh A, Langevitz P, Zemer D et al. Criteria for the diagnosis of Familial Mediterranean Fever. Arthritis Rheum 1997:40.1879-85.
12. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 2010;31(19):2338-50.
13. Yildiz M, Masatlioglu S, Seymen P, Aytac E, Sahin B, Seymen HO. The carotid-femoral (aortic) pulse wave velocity as a marker of arterial stiffness in familial Mediterranean fever. Can J Cardiol 2006;22(13):1127-31.
14. Sari I, Karaoglu O, Can G, Akar S, Gulcu A, Birlik M, Akkoc N, Tunca M, Goktay Y, Onen F. Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. Clin Rheumatol 2007;26(9):1467-73.
15. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet 2001;9:473-83.
16. Akdogan A, Calguneri M, Yavuz B, Arslan EB, Kalyoncu U, Sahiner L, et al. Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. J Am Coll Cardiol 2006;48(11):2351-3.

DOI: 10.5455/2320-6012.ijrms20140251
Cite this article as: Ulu MS, Acay A, Ahsen A, Yuksel S, Acartürk G, Solak M. Do MEFV mutations influence arterial stiffness in FMF patients? Int J Res Med Sci 2014;2:270-3.