Int. Adv. Otol. 2013; 9:(2) 186-192

ORIGINAL ARTICLE

The Relationship Between Arterial Stiffness and Cochlear Functions in Adult Familial Mediterranean Fever Patients

Sahin Ulu, Abdulkadir Bucak, M. Sena Ulu, Filiz Yilmaz, Fatih Yucedag, Abdullah Aycicek, Mustafa Solak

Department of Otorhinolaryngology, Afyon Kocatepe University, Faculty of Medicine, Afyonkarahisar, Turkey (SU, AB, FY, AA)
Department of Internal Medicine, Division of Nephrology Afyon Kocatepe University, Faculty of Medicine, Afyonkarahisar, Turkey (MSU)
Department of Internal Medicine, Afyon Kocatepe University, Faculty of Medicine, Afyonkarahisar, Turkey (FY)
Department of Medical Genetics, Afyon Kocatepe University, Faculty of Medicine, Afyonkarahisar, Turkey (MS)

Objective: Familial Mediterranean Fever (FMF) is an hereditary disease accompanied by chronic inflammation which may cause endothelial dysfunction. Pulse wave velocity (PWV) is an early marker to determine the endothelial dysfunction. The relationship between the cochlear damage and chronic inflammation were shown before. We aimed to evaluate the hearing levels of FMF patients due to chronic inflammation by using PWV measurement, DPOAE and high frequency audiometry for the first time.

Methods: 43 FMF patients and 44 age-sex-matched controls were included in the study. Auditory Evaluation, Otoacoustic emission measurement and PWV measurements were performed.

Results: Hearing levels of FMF patients were worse than control group in many frequencies (p=0.002, p= 0.027, p=0.036) respectively. In the patient group, positive correlation was found between PWV values and hearing loss. In addition, PWV values were inversely correlated with DPOAE in DP values at the 2.8, 4, 6, 8 kHz frequencies and at the 4 kHz frequency in SNR (r= -0.344, p=0.024) ; (r= -0.301, p=0.05); (r= -0.309, p=0.043); (r= -0.328, p=0.032) , (r= -0.331, p=0.03) respectively.

Conclusion: Frequency of hearing loss in FMF patients was higher than healthy subjects as well as hearing levels of FMF patients were decreased with the increase of PWV values. FMF disease can cause hearing loss by involvement of the inner ear due to endothelial dysfunction without amyloidosis. The regularly follow up of auditory function in FMF patients may be helpful to prevent early possible hearing loss.

Submitted : 12 June 2013 *Accepted : 02 July 2013*

Introduction and Objective

Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease which was common in the past in Jews, Turks, Armenians, and Arabs and recently observed in other countries due to transportation amenities. FMF is characterized by recurrent attacks of fever, peritonitis, pleuritis and arthritis [1]. Chronic inflammation in FMF patients can be seen both during the attack and attack free periods [2]. Acute or chronic inflammation reduce arterial compliance and may cause endothelial dysfunction [3]. Pulse wave velocity (PWV) is an early marker to determine the endothelial dysfunction, arterial stiffness and can be used in many inflammatory diseases and FMF [4,5].

The relationship between the cochlear damage and inflammatory factors is well known [6-9]. In the previous studies, cochlear involvement was shown by high-frequency audiometry and distortion product otoacoustic emissions (DPOAE) in chronic inflammatory diseases such as celiac disease and Behçet [10-12]. Cochlear involvement may be seen in

Corresponding address:
Sahin Ulu
Department of Otolaryngology, Afyon Kocatepe University, Faculty of Medicine,
03200, Afyonkarahisar, Turkey.
Telephone: 0272 2463303 Fax: 0 272 2463300
e-mail: drsahinulu@yahoo.com

FMF disease like the other chronic inflammatory pathologies too. Recently, in a study by Demirel et al, cochlear functional impairment was identified during FMF attacks in children due to affected cochlear blood flow [13]. But to our knowledge, there has not been any study in adults with FMF investigating the cochlear function and the etiology of hearing loss. Based on this background, we aimed to evaluate the possible hearing disorders in FMF patients due to vascular pathologies via chronic inflammation by using PWV measurement, DPOAE and high frequency audiometry.

Materials and Methods

The present study was conducted in Otorhinolaryngology-Head-Neck Surgery, Internal medicine and Cardiology Clinics of Afyon Kocatepe University Faculty of Medicine Hospital between June 2012- April 2013. 43 patients diagnosed with FMF and 44 age-and sex-matched controls were included in the study. Patients with FMF were diagnosed according to Tell Hashomer criteria[14] and genetic mutations were received from the recorded data. All patients were using colchicine since the diagnose time. The study protocol was approved by the ethics committee of Afyon Kocatepe University Faculty of Medicine and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Written informed consent form was obtained from all participants before the study.

Patients and control group, who agreed to be included in the study were questioned for age, smoking, family history, any chronic disease, any risk factors, dietary compliance and used drugs. A detailed physical examination was performed. Patients which had any acute inflammation, chronic inflammatory disease (such as Celiac disease, Behçet, inflammatory bowel disease and etc.), any infection, diabetes mellitus, systemic hypertension, hyperlipidemia, acute or chronic renal failure, chronic liver disease, chronic obstructive pulmonary disease, any atherosclerotic disease (such as coronary artery disease, peripheral arterial disease), connective tissue disease, amyloidosis, allergic rhinitis, smoking history and any otologic disease (such as chronic otitis media, otosclerosis, acoustic trauma history and Meniere's disease), used drug affecting arterial stiffness (such as antihypertensive, ant diabetic, antilipemic drugs) and patients under 18 years old and over 61 years old were excluded from the study.

Auditory Evaluation: Primarily ("Maico MI 34 diagnostic GmbH impedance meter" Maico Diagnostic GmbH, GERMANY) tympanogram of the patients were obtained to prove that middle ear function was normal. Tonal and high frequency audiometry were performed in patients with type "A" tympanogram. Bone and air conduction thresholds were determined with tonal audiometry. "Understanding the threshold of speech" and "Speech discrimination score" was determined with speech audiometry. For these tests "Interacoustics Clinical Audiometer AC 40 device" and earphones "TDH-39P" (Interacoustics A/S, DENMARK) were used. During the high-frequency audiometry earphones changed with "Koss R80" digital headphones and the test was continued with stimulant. During audiometry, air conduction thresholds were measured and recorded with 250, 500, 1.000, 2.000, 4.000, 8.000, 10.000, 12.000, 14.000, 16.000 Hz frequencies, and bone conduction thresholds were measured and recorded with 500, 1.000, 2.000, 4.000 Hz frequencies..

Otoacoustic emission measurement: Measurement of otoacoustic emissions (OAE) were performed using routine diagnostic audiometry along with DPOAE (Otodynamics Ltd. EZ Screen 2,USA) . DPOAEs were measured at seven different frequencies ranged from 1000 to 8000 Hz (1000, 1400, 2000, 2800, 4000,6000 and 8000 Hz). By calculating the difference between distortion products (DP) and noise 2 standard deviation, signal to noise ratios (SNR) for each frequency were achieved.

PWV measurements: PWV measurements were performed in the department of Cardiology. To evaluate the arterial stiffness, PWV was measured by 6000 Pulse trace module device (Micro medical, Rochester, United Kingdom). 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 Electrocardiogram. PWV is automatically calculated

by the device using the ratio of the distance between two recorded points and the transition time of the pulse wave. PWV values were recorded in m /sec.

(PWV = the distance between the carotid artery and femoral artery / the pulse wave reach time from carotid artery to femoral artery: m / s)

Statistical Evaluation

Continuous variables were presented as mean ± SD and categorical variables were expressed as percentage. Kolmogorov-Smirnov test was used to evaluate of the distribution of variables. Student's t-test (independent sample t-test) was used for continuous variables those with normal distribution and Mann-Whitney U test was used for continuous variables those without normal distribution. Chi-square test was used for categorical variables. Pearson correlation analysis were used to assess the relationship of audiometric parameters and the other data. $p < 0.05$ value was accepted as significant level. For statistical calculations, SPSS statistical software (SPSS for Windows, version 17.0. Inc. Chicago, IL, USA) was used.

Results

The mean age of the patients group was 33.2±12.12 years and the control group was 31.8±8.8 years respectively. 27 of the patients (62.8%) were male and 16 of them (37.2%) were female. In the control group there were, 15 (34.1%) males and 29 (65.9%) were females. Demographic characteristics of the patients and the control group were shown in Table 1

There were statistically significant differences between FMF patients and the control group in terms of hearing levels at all frequencies except 250 and 16000 Hz (Table 1). Pure Tone Averages of the groups were shown in Figure 1.

Statistically significant differences were also found between FMF patients and the control group in DPOAE measurements at the frequencies DP 1.4 and 6 kHz, and in SNR measurements at the frequencies 4 kHz *(p=0.002, p= 0.027, p=0.036) respectively* (Table 2). In the patient group, positive correlation was found between PWV values and hearing loss at 2000, 4000,

Table 1. Demographic and audiometric data of the groups (Audiometric testing revealed a significant difference in hearing levels between groups.)

Variables	Patient group	Control group	P value
Age (year)	33.2±12.12	31.8±8.8	NS
BMI	23.74±5.26	24.68±4.08	NS
Hz250	18,49±7,11	13,64±4,22	NS
Hz500	15,58±8,10	11,02±2,54	<0.001
Hz1000	14,76±8,58	10,00±2,41	<0.001
Hz2000	13,60±7,34	11,25±2,87	<0.001
Hz4000	18,37±11,93	11,93±4,60	<0.001
Hz8000	24,65±20,01	16,13±6,89	<0.001
Hz10000	31,39±18,90	17,72±4,37	<0.001
Hz12000	36,51±19,47	21,59±8,05	<0.001
Hz14000	40,34±16,70	29,61±10,02	0.003
Hz16000	68,83±47,53	38,86±13,41	NS
PTA	14,62±7,39	10,77±1,58	<0.001
SRT	17,55±7,97	14,09±2,47	<0.001
SD*	94,51±3,49	95,88±,61	<0.001

All parameters were expressed as mean ± standard deviation unless otherwise stated
** Data were expressed as percentage (%)*
p <0.05 value was accepted as significant level and the significant differences between the groups were shown in bold
NS: not significant
PTA: Pure Tone Average
SRT: Speech Recognition Threshold
SD: Speech discrimination

8000,10000,12000,14000 Hz frequencies of the odyogram *(r=0.355, p=0.019); (r=0.426, p=0.002); (r=0.379, p=0.014); (r=0.310, p=0.048); (r=0.330, p=0.035); (r=0.438, p=0.005) respectively.*

In addition, in the patient group, PWV values were inversely correlated with DPOAE in DP values at the 2.8, 4, 6, 8 kHz frequencies and at the 4 kHz frequency in SNR *(r= -0.344, p=0.024) ; (r= -0.301, p=0.05); (r= -0.309, p=0.043); (r= -0.328, p=0.032), (r= -0.331, p=0.03) respectively* (Figure 2).

Genetic profiles of the patients were given in Table 3. When the relationship between auditory functions and the gene mutation were evaluated, any relationship was not found. Besides there was no relationship between hearing loss levels and M694V mutation, which is the most common type in patients.

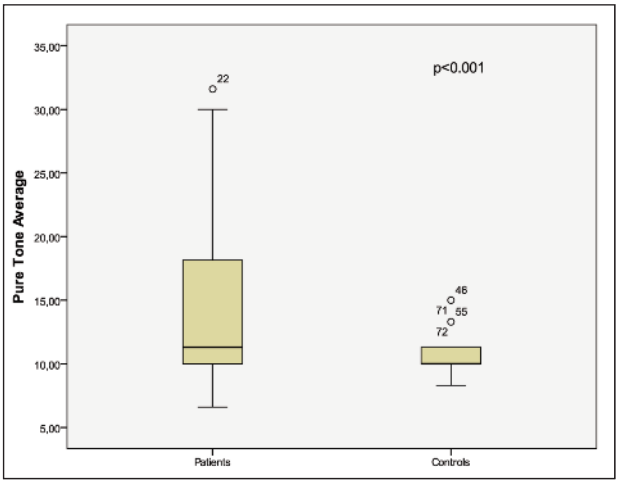

Figure 1. Pure Tone Averages of the groups

Table 3. Genetic mutations of the patients according

Mutation type	n
M694V heterozygous	4
M694V homozygous	5
E148Q heterozygous	6
E148Q homozygous	1
V726 heterozygous	5
M694V-E148Q heterozygous	5
M694V-R761H heterozygous	3
M694V-V726A heterozygous	2
M694V-M680I heterozygous	4
E148Q-P369S heterozygous	2
M694V heterozygous-R202Q homozygous	1
K695R heterozygous	1
Absent	4
Total	43

Table 2. Comparison of average DPOAE results of the patients with FMF and the controls. Signal to Noise Ratio (SNR), Distortion Product(DP)

Variables		Patient group	Control group	P value
1 kHz	DP	2,65±9,05	5,78±8,97	NS
	SNR	6,10±11,34	6,68±12,21	NS
1.4 kHz	DP	4,55±10,13	10,88±5,68	0.002
	SNR	10,76±8,57	13,52±6,66	NS
2 kHz	DP	10,73±7,474	9,10±7,07	NS
	SNR	10,7±7,47	14,43±6,80	NS
2.8 kHz	DP	06±10,13	6,12±6,85	NS
	SNR	9.13±8.15	13,40±6,03	NS
4 kHz	DP	2,35±14,29	8,99±12,79	NS
	SNR	11,72±14,44	14,81±6,74	0.036
6 kHz	DP	-2,42±13,56	3,63±9,61	0.027
	SNR	5,29±9,93	9,53±9,22	NS
8 kHz	DP	-11,55±11,53	-9,70±11,97	NS
	SNR	-0,70±8,77	,33±11,11	NS

All parameters were expressed as mean ± standard deviation unless otherwise stated
p <0.05 value was accepted as significant level and the significant differences between the groups were shown in bold
NS: not significant
DP: Distortion product
SNR: signal to noise ratio

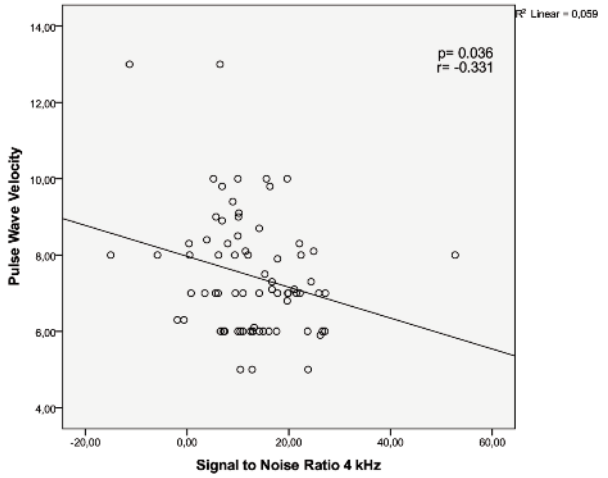

Figure 2. The relationship between Pulse Wave Velocity measurement and 4 kHz frekansta Signal to Noise Ratios

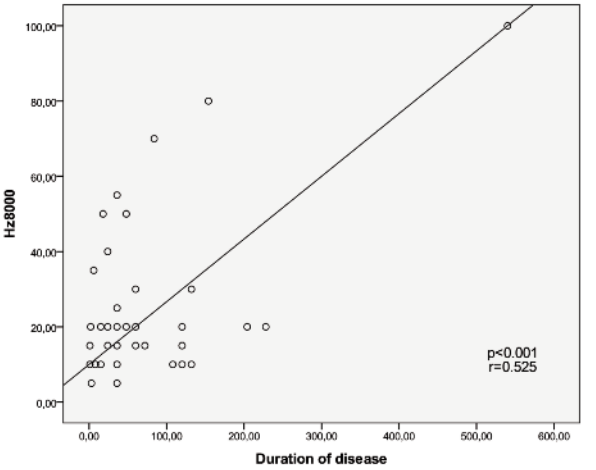

Figure 3. The relationship between the duration of disease and the hearing loss at 8000 Hz

Diagnosis duration was positively correlated with hearing loss levels at the 8000 Hz of audiogram, and inversely correlated with SD (Speech discrimination) values *(r=0.525, p<0.001; r=-0.301, p=0.05) respectively* (Figure 3).

Discussion

Cochlea may be affected in chronic inflammatory diseases. In the previous studies S. Leo et al. and later Solmaz et al. showed cochlear involvement by DPOAE and high frequency audiometry in Behçet and Celiac disease which present with chronic inflammation [11,12]. In FMF disease, which have subclinical inflammation even outside attacks, cochlea may also be affected due to endothelial dysfunction caused by chronic inflammation [13-15]. In parallel with this, in our study, hearing levels in patients with FMF were detected lower than the healthy control group indicating cochlear involvement.

Akdogan et al. have identified the impaired endothelium-dependent vasodilatation in FMF at the attack free periods by using brachial artery flow-mediated dilatation. And they reported endothelial dysfunction and increased risk of atherosclerosis in FMF patients [16].

Increased PWV, namely arterial stiffness prevents blood supply and nutrition of cochlear outer hair cells and may cause a decrease in the electromotility response of outer hair cells [17]. In our study, PWV values were correlated with DP and SNR levels which determined by otoacoustic emissions in FMF patients and also hearing levels at many frequencies in audiometric measurements were found impaired. This results show that, hearing loss due to chronic inflammation -induced endothelial dysfunction and arterial stiffness may be seen in FMF patients in the early stage even in those without amyloidosis. MEFV mutations were found to be associated with the severity of inflammatory diseases. It is known that; homozygous M694V mutation is associated with a more severe disease course and increased amyloidosis in FMF [15]. On the other hand, FMF gene mutations were reported to be aggravating factors for hearing loss, in rheumatoid arthritis (RA) [18, 19]. However, Koybasi et al. did not identify any relationship between the genetic mutations and hearing levels. In our study, there was no relationship between genetic mutation types and hearing loss too but this result may be due to the small number of the study patients [20].

Conclusion

As a conclusion, FMF disease can cause hearing loss by involvement of the inner ear via endothelial dysfunction occur before the development of amyloidosis we suggest that, the regularly follow up of

auditory function in FMF patients may be helpful as their routine renal function monitoring, to prevent possible hearing loss.

Limitations of our study:

Number of the patients in terms of genetic mutation distribution were lower thus the relationship between hearing loss and genetic mutations were not evaluated in sound manner. Also the relationship between hearing loss and the treatment was not evaluated because all of the patients were using colchicine. In addition FMF disease may be considered together with the other genetic diseases causing renal and hearing function impairment such as Alport syndrome but this situation could not evaluated because all the patients were at early stages and their renal functions were normal. We believe that, studies with broad participation would shed light on this issue in the future.

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