Changes in Cerebral Blood Flow in Patients with Familial Mediterranean Fever

Gözde ÇETİN¹, Uygur UTKU², Nurhan ATİLLA³, Kadir GİŞİ¹, Mehmet SAYARLIOĞLU¹

¹Department of Internal Diseases, Division of Rheumatology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

²Department of Neurology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

³Department of Chest Diseases, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

ABSTRACT

Introduction: It is known that there is a relationship between systemic inflammation and atherosclerosis. Atherosclerosis is one of the best-known causes of cerebrovascular diseases. The aim of this study was to assess cerebral blood flow velocity using transcranial Doppler (TCD) ultrasonography in patients with familial Mediterranean fever (FMF).

Methods: A total of 30 patients aged from 20 to 50 years with FMF were enrolled in the FMF group consecutively. The control group (non-FMF group) consisted of 30 age- and sex-matched randomly selected patients without FMF who had other diagnoses such as fibromyalgia and did not have risk factors for atherosclerosis. Bilateral peak-systolic, end-diastolic, and mean blood flow velocities in the middle cerebral artery (MCA), values of Gosling's pulsatility index, and values of Pourcelot's resistance index were recorded using TCD

ultrasonography by a neurosonologist blinded to the FMF and control groups.

Results: There were 30 participants in the FMF group in remission (male/female: 4/26, mean age: 34.7±5.9 years) and 30 participants in the control group (male/female: 4/26, mean age: 32.3±4.7 years). C-reactive protein levels and bilateral blood flow velocities in the MCA were significantly higher in the FMF group than in the control group.

Conclusions: This study suggests that persistent clinical and subclinical inflammation in patients with FMF causes an increase in cerebral blood flow velocities. Our findings provide an insight into this association between FMF and cerebrovascular diseases.

Keywords: FMF, inflammation, atherosclerosis, TCD, stroke

INTRODUCTION

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by repeated attacks of fever, abdominal pain, pleuritic chest pain, and arthritis. The occurrence of nervous system manifestations in FMF is rare and their association with FMF is still uncertain (1,2). Additional neurologic disorders have been reported in FMF, such as posterior reversible encephalopathy syndrome (PRES), demyelinating lesions, and ischemic stroke (3,4,5). Attacks of FMF with clinical inflammation are only the tip of the iceberg (6). Increases in clinical and subclinical inflammation in FMF might lead to susceptibility to vascular comorbidities such as atherosclerosis, heart disease, and life-threatening secondary systemic amyloidosis due to endothelial dysfunction in FMF patients (7,8). The aim of this study was to assess cerebral blood flow velocities using transcranial Doppler (TCD) ultrasonography in patients with FMF.

METHODS

A total of 30 consecutively admitted patients aged from 20 to 50 years with a diagnosis of FMF who fulfilled the Livneh criteria for FMF were enrolled in the FMF group. The non-FMF group consisted of 30 age- and sex-matched randomly selected patients who did not have any risk factors for atherosclerosis, such as diabetes, hypertension, and coronary artery disease. All patients with FMF were using colchicine and were not in an attack period. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured. Consent was obtained from the local ethics committee, and all participants gave formal consent.

TCD ultrasonography examination was performed with a Multidop X DWL TCD device after the patient had rested for 10 minutes in the supine position. The right and left middle cerebral arteries (MCAs) were insonated from the temporal windows at a depth of 50-65 mm with 2 MHz pulsed Doppler probes. Bilateral peak-systolic, end-diastolic, and mean blood flow velocities in the MCA, pulsatility index values, and resistance index values were recorded. The results for the FMF group were compared with the results for the non-FMF group.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences 15.0 program (SPSS Inc.; Chicago, IL, USA). A paired t-test and cross-tabs tests were used for statistical analysis, and a value of p<0.05 was considered to be significant.

Correspondence Address: Uygur Utku, Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, Kahramanmaraş, Türkiye E-mail: utkuzar@gmail.com

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Table 1. Symptomatic features of FMF patients

	FMF group (n=30)
Age of FMF diagnosis (years)	21.3±9.3
Time between onset and diagnosis (months)	74.7
Disease duration (months)	173
Subjects with a family history of FMF	17
Abdominal attack	28 (93.3%)
Joint attack	22 (73.73%)
Chest attack	18 (60%)
Erysipelas-like erythema	2 (6.7%)
Effort-associated leg pain	20 (66.6%)
Presence of transient hematuria and proteinuria during attacks	6 (20%)
#of patients with amyloidosis	0 (0%)
#of family members with amyloidosis	1 (3.4%)
FMF: Familial Mediterranean Fever	

Table 2. Transcranial Doppler data for FMF group compared with data for control group

	FMF group (n=30)	Control group (n=30)	p
L peak-systolic BFV	143.3±19.5	104.5±13	<0.001
L end-diastolic BFV	56.4±13.5	38.4±6.2	<0.001
L mean BFV	90.9±13.8	61.8±8.2	<0.001
L PI	0.87±0.07	0.9±0.09	0.78
L RI	0.59±0.03	0.6±0.05	0.57
R peak-systolic BFV	145.2±22.3	103.5±17.05	<0.001
R end-diastolic BFV	59.5±13	36.7±12.36	<0.001
R mean BFV	90.7±15.47	63.2±10.5	<0.001
R PI	0.8±0.08	0.85±0.09	0.89
R RI	0.62±0.04	0.63±0.06	0.63
L: left; R: right; PI: Pulsatility index; RI: Resistance index; BFV: blood flow velocity; FMF: Familial Mediterranean Fever			

RESULTS

The mean ages were 34.7±5.9 years in the FMF group (male/female: 4/26) and 32.3±4.7 years in the non-FMF group (male/female: 4/26). Clinical features of the FMF patients are given in Table 1. The median colchicine dose used by the FMF patients was 1.50 mg/day. None of the patients with FMF had amyloidosis. The mean values of CRP levels and ESR were 5.8±3.5 mg/L (normal range: 0-5 mg/L) and 17.4±8.5 mm/h, respectively, in the FMF group. CRP levels were significantly higher in the FMF group than in the non-FMF group (5.8±3.5 mg/L versus 3.2±0.15 mg/L). Bilateral peak-systolic, end-diastolic, and mean blood flow velocities in the MCA were significantly higher in the FMF group than in the non-FMF group (Table 2). The values of the pulsatility index and resistance index were not significantly different between the two groups.

DISCUSSION

The occurrence of nervous system manifestations is rare in FMF. Neurologic disorders such as PRES, demyelinating disorders, and ischemic stroke have been reported in FMF patients. The association between FMF and ischemic cerebrovascular diseases has not been studied thoroughly (5). Recently, there has been considerable attention concerning the possible

causal role of systemic inflammation in the development of atherosclerosis in patients with FMF (9). We attempted to determine cerebral blood flow velocities using TCD ultrasonography in patients with FMF, because increased cerebral blood flow velocities are significantly associated with ischemic cerebrovascular diseases (10).

We found that the peak-systolic, end-diastolic, and mean blood flow velocities were significantly higher in the FMF group than in the non-FMF group. However, the values of the pulsatility index and resistance index were not significantly different between the two groups. Correct interpretation of the pulsatility index is complex, because it depends not only on cerebrovascular resistance but also on several systemic and cerebral variables (11,12). The Rotterdam Study reported that increased mild-to-moderate cerebral blood flow velocity was due to diffuse atherosclerosis or vasoconstriction. Therefore, the mechanisms that underlie this condition (increased velocities but normal pulsatility index values) are most likely to be due to mild diffuse subclinical atherosclerosis (10,12).

It has been reported that inflammation (assessed by a high-sensitivity CRP assay) was frequently present in FMF, even in patients receiving colchicine therapy and in remission, which was the case for the present FMF patients (13). Studies investigating markers of early arterial wall alterations in FMF are also scarce and controversial. The intima media thickness (IMT) of the carotid arteries and endothelial dysfunction are used to define preclinical atherosclerosis. Significant increases in both IMT in the carotid and femoral arteries and blood flow velocities have been reported in patients with FMF in comparison with healthy controls (14,15).

This study suggests that persistent clinical and subclinical inflammation associated with atherosclerosis in patients with FMF causes increases in cerebral blood flow velocities. Our findings provide an insight into this association between FMF and cerebrovascular diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kahramanmaraş Sütçü İmam University School of Medicine.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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