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Original Article

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Early Disease Onset and Arthritis are Predictors of Chronic Kidney Disease Development in Familial Mediterranean Fever Patients

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ABSTRACT

Objective: Familial Mediterranean fever is an autosomal recessive genetic disease characterized by fever and serositis attacks. The most important complication is amyloidosis. In Familial Mediterranean fever patients, chronic kidney disease can develop without amyloid development. The aim of the study is to evaluate the development of chronic kidney disease in familial Mediterranean fever patients and to determine the factors that are involved in this development.

Methods: One hundred seventy-eight familial Mediterranean fever patients who were followed up between 2000 and 2020 were included in the study. Familial Mediterranean fever diagnosis was made according to the Tel-Hashomer criteria. Genetic tests were obtained in cases in which there was suspicion of diagnosis. Clinical and demographic characteristics of patients and all laboratory data including urea, creatinine, estimated glomerular filtration rate, and proteinuria in 24-hour urine at the time of first and last admission were evaluated.

Results: The mean age of the patients was 34.53 ± 10.72, the follow-up period was 6.12 ± 3.94, and the diagnosis age was 21.7 ± 11.5 years. The percentage of chronic kidney disease development at first and last admission was 13.5% and 19.1%, respectively. The risk factors associated with the development of chronic kidney disease were early disease onset and arthritis attacks.

Conclusion: The role of genotype characteristics in the development of chronic kidney disease has not been determined. Patients diagnosed with familial Mediterranean fever disease at an early age and especially with arthritis attacks should be closely monitored in terms of the risk of developing chronic kidney disease.

Keywords: Amyloidosis, arthritis, chronic kidney disease progression, familial mediterranean fever, non-amyloidosis glomerulopathy

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INTRODUCTION

Familial Mediterranean fever (FMF) disease is an autosomal recessive genetic disease characterized by fever and serositis attacks. Although it is distributed worldwide, it generally affects Mediterranean populations, especially Turks, Arabs, Jews, and Armenian.[1] The MEFV gene is localized on the short arm of chromosome 16 and encodes a 781 amino acid pyrin protein. The most common mutations are M694V, V726A, M694I, and M6980I in Exon 10 and the E148Q mutation in Exon 2.[2,3] Familial Mediterranean fever diagnosis is made according to Tel-Hashomer criteria. In studies conducted by the international FMF consortium, genetic tests are accepted to support the diagnosis. It has been recommended that patients be treated even if the mutation analysis is normal and clinical symptoms support the diagnosis of FMF.[4]

The most important complication of FMF disease is amyloidosis. Risk factors for the development of amyloidosis have been reported as a M694V mutation, male gender, age of disease onset, and frequency of attacks.[5-7]

However, there was not enough information about the presence of non-amyloid kidney diseases and factors that may cause predisposition to chronic kidney disease (CKD) in these studies. The aim of the study was to evaluate the development of CKD in FMF patients and to determine the factors that play a role in this development.

METHODS

Patients and Study Design

Two hundred forty-nine FMF patients who were followed up between 2000 and 2020 were retrospectively analyzed. Patients with malignancy, active infection, data deficiencies, diseases associated with the development of CKD (e.g., diabetes mellitus, hypertension, and chronic inflammatory diseases), and non-regular follow-up were excluded from the study. The endpoints of the study were kidney replacement therapy requirement and death in the course of follow-up. Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg on repeated measurements, or both, or by the use of antihypertensive drugs. Diabetes was defined as a fasting glucose level ≥7.0 mmol/L, a glycated hemoglobin ≥6.5%, or use of antidiabetic drugs. The study continued with 178 patients. Familial Mediterranean fever diagnosis was made according to Tel-Hashomer criteria. Genetic test was obtained in cases in which there was suspicion of diagnosis. Demographic characteristics (age, gender, FMF family history, and kidney biopsy status) and clinical characteristics (abdominal pain, chest pain, fever, arthritis, erysipelas-like erythema, appendectomy history, drugs, drug doses, drug compliance, number of attacks, age at diagnosis, duration of follow-up, and whether there was CKD at the time of first and last admission) were recorded. Blood pressure of patients was measured at the first admission. Mean blood pressure (MBP) is calculated with a standard formula (SF) as follows: MBP = diastolic blood pressure (DBP) + 1/3 [systolic blood pressure (SBP) - DBP]. Chronic kidney disease was diagnosed using the 2012 Kidney Disease: Improving Global Outcomes criteria. The patients were divided into 3 groups according to their age of diagnosis: early onset under 20 years old; adult-onset aged 21-40 years old; and late-onset aged 41 and over. The patients were also divided into 2 subgroups according to their fibrinogen levels: those with subclinical inflammation had ≥400 mg/dL and without subclinical inflammation had <400mg/dL. The patients were divided into 3 groups according to their genetic features: Group I, patients with M694 V homozygous mutation; Group II, M694V heterozygous or M694V combined heterozygous; and Group III, non-M694 V homozygous, heterozygous, or combined heterozygous. All procedures performed in studies involving human participants were in accordance with ethical standards of our Hospital Ethics Committee with the Helsinki declaration (approval number: 26.06.2020/291). Patients' written informed consent was taken.

MAIN POINTS

- Although the most important complication of familial Mediterranean fever (FMF) disease is amyloidosis, chronic kidney disease (CKD) can develop without amyloid development in FMF patients.
- The risk factors associated with the development of CKD were early disease onset and arthritis attacks. The role of genotype characteristics in the development of CKD has not been determined.
- Patients diagnosed with FMF disease at an early age and especially with arthritis attacks should be closely monitored in terms of the risk of developing CKD.

Laboratory Analyses

The urea, creatinine, estimated glomerular filtration rate (eGFR), and 24-h urine proteinuria levels of the patients were recorded at the time of the first and last admission. Estimated glomerular filtration rate was calculated according to the formula CKD-EPI. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimate of kidney function was calculated as recommended: for women with a plasma creatinine ≤0.7, (plasma creatinine/0.7)$^{-0.329}$ × (0.993)^{age} (× 166 if Black; × 144 if White or Other); for women with a plasma creatinine >0.7, (plasma creatinine/0.7)$^{-1.209}$ × (0.993)^{age} (× 166 if Black; × 144 if White or Other); for men with a plasma creatinine ≤0.9, (plasma creatinine/0.9)$^{-0.411}$ × (0.993)^{age} (× 163 if Black; × 141 if White or Other); for men with a plasma creatinine >0.9, (plasma creatinine/0.9)$^{-1.209}$ × (0.993)^{age} (× 166 if Black; × 144 if White or Other). The arithmetic mean of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen levels in all controls of the patients were recorded. In addition, complete blood count, uric acid, total protein, albumin, glucose, and mean blood pressure were evaluated. Blood samples were measured in the morning after an overnight fast. Molecular diagnosis of FMF was carried out in our hospital laboratories. Peripheral blood samples of the patients were obtained for DNA extraction. A reverse hybridization test method by FMF strip assay (ViennaLab labordiagnostika Gmbh, Vienna, Austria) was performed. Twelve mutations (E148Q, P369S, F479L, M680I G/C, M6980 I G/A, 1692 del, M694V, M694I, V726A, K695R, A744S, R791H) were investigated. The assay includes 4 successive steps for which reagents are provided: (a) DNA isolation from blood samples, (b) in vitro multiple amplification reaction, (c) hybridization of amplification products, and (d) detection of bound biotinylated sequences. Amplifications were conducted on an Applied Biosynthesis Thermocycler 9700 using the protocol supplied by the manufacturer.

Statistical Analyses

Analyses were conducted using BM Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA). All data were first checked for normality of distribution using the Kolmogrov–Smirnov and Shapirov test. Normally distributed data are presented as the mean ± standard deviation. Non-normally distributed data are represented as the median

(inter-quartile range). Pearson's χ^2 or Fisher's exact was used for categorical variables. Univariate and multi-variate cox regression analyses were applied to determine the factors affecting the development of CKD and amyloidosis.

RESULT

The mean age of the patients was 34.53 ± 10.72, the mean follow-up period was 6.12 ± 3.94, and the mean diagnosis age was 21.7 ± 11.5 years. The most common symptoms in the patients were abdominal pain 89.3%, fever 74.2%, and arthritis 71.9%. Subclinical inflammation was observed in 23.6% of the patients. At the first admission, 24 (13.4%) patients had CKD (stage-1 n = 11, stage-2 n = 11, stage-3 n = 1, stage-4 n = 1). In the last admission, this number increased to 40 (22.4%) patients (stage-1 n = 10, stage-2 n = 20, stage-3 n = 2, stage-4 n = 1, stage-5 n = 2). Five patients started on dialysis. Genetic testing was performed in 97 patients. The most common genetic mutations were M694V (40.2%), M694V/M680I (11.3%), M694V/V726A (8.2%), M680I (7.2%), V726A (5.2%), and M694V/E148Q (5.2%). Clinical features and laboratory data of all patients are shown in Table 1.

According to their age of diagnosis, the patients were divided into 3 groups like early onset, adult onset, and late onset. The percentage of kidney biopsy and CKD development at first and last admission were lower in late-onset group (Table 2). Regression analysis showed that arthritis and early disease onset are independent risk factors for the development of CKD in FMF patients. The role of genetic mutations has not been found (Table 3). Although the factors associated with amyloidosis in univariate cox regression analysis were white blood cell, neutrophil, fibrinogen, ESR, genetic tests (presence of M694V), and early disease onset , only early disease onset was found to be associated with amyloidosis in multivariate regression analysis (Table 4).

DISCUSSION

MEFV gene belonging to FMF disease is localized in the short arm of chromosome 16 and contains more than 50 mutations. Ethnic and environmental factors can change the phenotypic characteristics of the mutation. Although the symptoms have been observed before the age of 20 in 90% of the patients, it may also appear clinically in advanced ages.[8] The clinic emerged after the age of 40 in 6.2% of our patients. The most clinical symptom was abdominal pain with 89.3%. According to the data of the Turkish FMF study group, the most common complaint reported was abdominal pain in the Turkish population with a rate of 93.7%.[9]

Familial Mediterranean fever diagnosis was made according to Tel-Hashomer criteria and genetic tests were performed to support the diagnosis. In our study, 97 patients were given genetic testing. The tests were performed more frequently in patients whose findings started at a late age. Kidney biopsy was performed in 16 patients. Amyloidosis was detected in 12 patients. The clinic of 2 amyloidosis patients (15.3%) was found to be

Table 1. Clinical Features and Laboratory Data of All Patients

Parameters	All patients (n: 178)
Gender (female) (%)	60.1
Age of disease onset (%)	
Early onset	51.1
Adult onset	42.7
Late onset	6.2
Drug compliance (%)	91
Drug dose (≤2/day) (%)	64.6
Number of attacks (≤2/year) (%)	87.1
Abdominal pain (%)	89.3
Fever (%)	74.2
Chest pain (%)	9
Arthritis (%)	71.9
ELE (%)	0.6
Appendectomy (%)	8.4
Family history (%)	32.6
Kidney biopsy (%)	9
CKD at first admission (%)	13.5
CKD at last admission (%)	19.1
Subclinical inflammation (%)	23.6
Age (years)	34.53 ± 10.72
Age at diagnosis (years)	21.7 ± 11.5
Follow-up time (years)	6.12 ± 3.94
MBP (mmHg)	81.46 ± 7.09
Glucose (mg/dL)	87.94 ± 7.90
CRP (mg/L)	2.11 ± 3.57
ESR (mm/h)	12.01 ± 11.09
Fibrinogen (mg/dL)	354.6 ± 90.3
Urea at first admission (mg/dL)	25.29 ± 13.22
Creatinine at first admission (mg/dL)	0.86 ± 0.22
eGF at first admission (mL/min/1.73 m^2)	101.3 ± 22.3
Proteinuria at first admission (mg/day)	346.79 ± 1486.46
Urea at last admission (mg/dL)	27 ± 12.72
Creatinine at last admission (mg/dL)	0.86 ± 0.66
eGF at last admission (mL/min/1.73 m^2)	107.53 ± 22.1
Proteinuria at last admission (mg/day)	156.9 ± 824.7
Albumin (g/dL)	4.46 ± 0.56
Uric acid (mg/dL)	4.54 ± 1.13
WBC (10^6/L)	7605 ± 1832
Neutrophils (10^6/L)	4718 ± 1667
Lymphocytes (10^6/L)	2167 ± 604
Platelet (10^6/L)	282 123 ± 81 833
NLR	2.42 ± 1.37
PLR	139.33 ±5 3.16
Hemoglobin (g/dL)	13.58 ± 1.65
RDW-CV (%)	14.88 ± 5.88

ELE, erysipelas like erythema; CKD, chronic kidney disease; MBP, mean blood pressure, CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate; WBC, white blood cell, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, RDW: red cell distribution width.

Table 2. Comparison of the 3 Groups in Terms of Clinical Features

Parameters	Early Onset (n = 91)	Adult Onset (n = 76)	Late Onset (n = 11)	*P*
Gender (female) (%)	50.5	43.9	5.6	.878
Drug compliance (%)	50.6	43.8	5.6	.413
Drug dose (≤2/day) (%)	49.6	43.5	7	.772
Number of attacks (≤2/year) (%)	49.7	43.2	7.1	.333
Abdominal pain (%)	50.3	43.4	6.3	.823
Fever (%)	55.3	38.6	6.1	.155
Chest pain (%)	56.3	43.8	0	.544
Arthritis (%)	53.1	39.8	7	.415
Appendectomy (%)	20	60	20	.009
Family history (%)	51.7	41.4	6.9	.945
Kidney biopsy (%)	31.3	43.8	25	.003
CKD at first admission (%)	29.7	54.2	16.7	.015
CKD at last admission (%)	26.5	47.1	26.5	.001
Subclinical inflammation (%)	50.7	42.6	66	.907

CKD: chronic kidney disease.

phenotype II. This rate was found to be 13.3% in the study by Yazılıtaş et al[11] and 17.1% in the study by Huzmeli et al.[10]

The most important complication of FMF disease is amyloidosis. Although the rate of amyloidosis in studies conducted by rheumatology clinics ranged between 2.7% and 5.5%,[12,13] this rate ranged between 12% and 29.8% in studies conducted by nephrology clinics.[14] In the present study, 6.74% of the patients were found to have amyloidosis, and early diagnosis of the disease was found as the triggering factor for amyloidosis. The causes affecting the development of amyloidosis have been studied for a long time. The most common causes are M694V mutation,[4] E148Q mutation,[15] male gender, age of disease onset, and frequency of attacks.[6,7] Mukhin et al[23] also reported that the development of AA amyloidosis was 2.28 times more prevalent when recurrent arthritis attacks. A relationship similar to the increase in serum amyloid A (SAA) mRNA production in synovial cells in patients with rheumatoid arthritis[24] may also be valid in FMF patients.

In fact, the most important factor in amyloid development is an increase in SAA production by the liver. The most important factor that increases SAA production is inflammation, especially IL-6.[16] In some patients with FMF, acute phase reactants are at high levels even during the attack-free period.[17,18] The presence of subclinical inflammation triggers many complications such as growth failure, puberty delay, and osteoporosis.[19]

Inflammation also plays an important role in the pathogenesis of CKD. Circulating pro-inflammatory cytokines have been shown to stimulate endothelial and leukocyte cells in the kidney. As a consequence, production of reactive oxygen species and new pro-inflammatory mediators have been shown to disrupt the endothelial structure in the kidney and activate the coagulation system. The microvascular response created by the kidney against changes in circulation is disrupted and damage has been shown to occur in the nephrons.[20] The uninhibited inflammation in FMF with abnormal response to antigens and complement consumption during attacks might facilitate

Table 3. Cox Regression Analysis of Risk Factors Affecting CKD in FMF Patients

Univariate					Multivariate			
Parameters	β	**HR**	**95% CI**	***P***	β	**HR**	**95%CI**	***P***
Gender	0.443	0.642	0.254-1.619	0.348	-	-	-	-
Abdominal pain	0.285	0.752	0.172-3.292	0.705	-	-	-	-
Fever	0.925	2.522	0.577-11.03	0.219	-	-	-	-
Arthritis	0.847	0.429	0.165-1.113	0.008	1.270	0.281	0.098-0.805	0.018
Chest pain	3.194	0.041	0.00-26.6	0.334	-	-	-	-
Drug dose	0.226	0.798	0.304-2.097	0.647	-	-	-	-
Number of attacks	0.868	2.381	0.315-17.976	0.4	-	-	-	-
Age of disease onset	2.018	0.130	0.043-0.413	0.000	2.476	0.084	0.024-0.290	0.000
Genetic mutations	1.474	4.367	1.264-15.091	0.02	-	-	-	
CRP	0.197	0.821	0.593-1.13	0.237	-	-	-	-
ESR	0.024	0.977	0.919-1.038	0.448	-	-	-	-
Fibrinogen	0.002	0.998	0.992-1.005	0.637	-	-	-	-

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 4. Cox Regression Analysis of Risk Factors Affecting Amyloidosis in FMF Patients

Univariate					Multivariate			
Parameter	β	**HR**	**95% CI**	***P***	β	**HR**	**95% CI**	***P***
Gender	-0.653	0.521	0.175-1.550	.241	-	-	-	-
Genetic mutation	-0.949	0.387	0.152-0.983	**.046**	-	-	-	-
Number of attacks	0.229	1.257	0.279-5.674	.766	-	-	-	-
Dose drug	0.738	2.092	0.703-6.226	.185	-	-	-	-
Age of disease onset	1.344	3.836	1.641-8.963	**.002**	1.623	0.197	0.047-0.820	**.026**
Abdominal pain	0.941	0.390	0.107-1.420	.153	-	-	-	-
Fever	0.629	0.533	0.174-1.637	.272	-	-	-	-
Arthritis	1.386	3.999	0.519-30.782	.183	-	-	-	-
CRP	0.124	0.883	0.669-1.166	.382	-	-	-	-
ESR	0.051	1.052	1.021-1.085	**.001**	-	-	-	-
Fibrinogen	0.008	1.008	1.004-1.012	**.000**	-	-	-	-
WBC	0.000	1	1-1.001	**.008**	-	-	-	-
Neutrophils	0.000	1	1-1.001	**.027**	-	-	-	-

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, familial Mediterranean fever; HR, hazard ratio; WBC, White blood cell.

the development of glomerular disease.[21] In our study, CKD was observed in 24 of the patients when they first applied to our clinic. After 7 years of follow-up, this number increased to 40. Twelve of these patients had amyloidosis in biopsy, 2 had FSGS, and 1 had IGA nephropathy and another had MPGN. Similar results were obtained with a small number of studies investigating non-amyloid kidney diseases.[10,11,22]

Early diagnosis and presence of arthritis were determined as factors associated with the development of CKD. The role of genetic mutations was not found. In a recent study by Babaoglu et al conducted with 917 FMF patients, the age of onset of the patients whose inflammation continued even during the attack-free period was shown to present earlier; they were exposed to more frequent attacks of arthritis. It was found that this condition increased the development of amyloidosis by 3.59-fold, proteinuria development by 3.28-fold, and kidney failure by 4.18 fold.[19] In addition, in early disease onset FMF patients, the International Severity of Scoring System (ISSF) was observed to be higher in FMF.[25]

Our study is limited by retrospective design of the study and SAA and IL-6 have not been studied. The drug compliance with a standard method as MASIF (medication adherence scale for FMF) and disease severity by ISSF were not assessed.

CONCLUSION

The most important complication of FMF is amyloidosis. However, due to the difficulty of suppressing inflammation in FMF, there is a tendency to develop non-amyloid glomerulonephritis and CKD. Genotypic influence in the development of CKD could not be determined in our study. However, early disease onset, especially arthritis attacks, was observed to be an independent risk factor for the development of CKD.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ankara Training and Research Hospital (Date: June 26, 2020, Decision No: 291).

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

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