Early Disease Onset and Arthritis Are Predictors of Chronic Kidney Disease Development in FMF Patients

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Research Article

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Abstract

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

Method: One hundred seventy eight FMF patients who were followed up between 2000 and 2020 were included in the study. FMF diagnosis was made according to the Tel-Hashomer criteria. Genetic tests were studied in cases which there was suspicion of diagnosis. Clinical and demographic characteristics of patients and all laboratory data including urea, creatinine, estimated glomerular filtration rate (eGFR), 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 number of patients with late disease onset and the percentage of kidney biopsy performed were higher in the genetic test group. There was no difference in the inflammatory parameters. The risk factors associated with the development of CKD were early disease onset and arthritis attacks.

Conclusion: 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.

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, 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, M6980I in Exon 10 and the E148Q mutation in Exon 2 (2, 3). FMF 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, 6, 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.

Materials And 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 (DM), hypertension (HT), and chronic inflammatory diseases), and non-regular follow up were excluded from the study. The endpoints of the study were renal replacement therapy requirement and death in the course of follow-up. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic blood pressure (DBP) ≥ 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. FMF diagnosis was made according to Tel-Hashomer criteria. Genetic test was obtained in cases 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. CKD was diagnosed using the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The patients were divided into three 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 two subgroups according to their fibrinogen levels: those with subclinical inflammation had ≥ 400mg/dL and without subclinical inflammation had < 400mg/dL. The patients were divided into three 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.

Laboratory analyses: The urea, creatinine, estimated glomerular filtration rate (eGFR), and 24-hour urine proteinuria levels of the patients were recorded at the time of the first and last admission. eGFR was calculated according to the formula CKD-EPI. The arithmetic mean of the 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 four 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 fist checked for normality of distribution using the Kolmogrov-Smirnov and Shapirov-Wilk test. Normally distributed data are presented as the mean ±

standard deviation. Non-normally distributed data are represented as the median (inter-quartile range). Independent samples T test was used to compare parametric continuous variables between groups. Mann Whitney U was employed for the comparison of non-parametric variables. Pearson's X2 or Fisher's exact were 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%).

It was found that fever and arthritis attacks were lower, patients with late disease onset, the percentage of appendectomy and biopsy were higher in the genetic test group (Table 1). The results of the laboratory data are shown in Table 2. It was observed that urea, creatinine, and proteinuria levels were higher; albumin and eGFR levels were lower at the time of final admission in the genetic test group. 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 WBC, 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 common 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).

FMF 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. The percentage of kidney biopsy was found to be higher in the genetic test group. Thirteen of the 16 biopsy patients belonged to this group, and when

the files were examined, 12 of them had amyloidosis. The clinic of two amyloidosis patients (15.3%) was found to be phenotype II. This rate was found to be 13.3% in the study by Yazilitas et al and 17.1% in the study by Huzmeli et al (10, 11).

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). Nikolay A et al. also reported that the development of AA amyloidosis was 2.28 times more prevalent when recurrent arthritis attacks (23). 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 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, two had FSGS, and one 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 3.28 fold, and kidney failure 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, were observed to be an independent risk factor for the development of CKD.

List Of Abbrevations

FMF: Familial Mediterranean fever

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

DM: Diabetes mellitus

HT: Hypertension

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

KDIGO: Kidney Disease: Improving Global Outcomes

ESR: Erythrocyte sedimentation rate

CRP:C-reactive protein

SAA: Serum amyloid A

MPGN: Membranoproliferative glomerulonephritis

ISSF: International Severity of Scoring System

MASIF: Medication adherence scale for FMF

Declarations

Ethical approval and consent to participate: The protocol for the research project has been approved by a suitably constituted Ankara Training and Research Hospital Ethics Committee of the institution within

which the work was undertaken (Approval number: 26.06.2020/291) and that it conforms to the provisions of the Declaration of Helsinki. Patient's written informed consent was taken.

Consent for publication: Not applicable

Availability of data and materials: All data analyzed during this study are included in article and also available from the corresponding author on reasonable request.

Competing interest: All authors declare no conflict of interest

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Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by R.B, M.D. The first draft of the manuscript was written by R.B, MD and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

Comparison of demographic between groups

Parameters	All patients (n:178)	Genetic test group (n:97)	Non-genetic test group (n:81)	P
Gender(female) (%)	%60.1	%56.7	%64.2	0.309
Age of disease onset(%)				
Early onset	%51.1	%39,.2	%65.4	
Adult onset	%42.7	%51.5	%32.1	0.001
Late onset	%6.2	%9.3	%2.5	
Drug compliance(%)	%91	%87.6	%95.1	0.084
Drug dose (≤ 2/day) (%)	%64.6	%66	%63	0.675
Number of attacks (≤ 2/year) (%)	%87.1	%88.7	%85.2	0.491
Abdominal pain(%)	%89.3	%88.7	%90.1	0.753
Fever(%)	%74.2	%67	%82.7	0.017
Chest pain	%9	%10.3	%7.4	0.5
Arthritis(%)	%71.9	%62.9	%82.7	0.003
ELE(%)	%0.6	%0	%1.2	0.455
Appendectomy(%)	%8.4	%13.4	%2.5	0,009
Family history(%)	%32.6	%38.1	%25.9	0.083
Renal biopsy(%)	%9	%13.4	%3.7	0.024
CKD at first admission(%)	%13.5	%16.5	%9.9	0.198
CKD at last admission(%)	%19.1	%27	%7	0.001
Subclinical inflammation(%)	%23.6	%26.8	%19.8	0.270

ELE: erysipelas like erythema, CKD: Chronic kidney disease

Table 2

Comparison of laboratory data between groups

Parameters	All patients (n:178)	Genetic test group (n:97)	Non-genetic test group (n:81)	P
Age(years)	34.53±10.72	35 (16)	29 (11,5)	0.001
Age at diagnosis(years)	21.7±11.5	22(13.5)	15(14)	0.000
Follow up time(years)	6.12±3.94	7(8)	6(6)	0.357
MBP(mmHg)	81.46±7.09	80 (12)	80 (3)	0.699
Glucose(mg/dL)	87.94±7.90	87.9±7.42	87.9±8.48	0.953
CRP(mg/L)	2.11±3.57	0.8 (1.7)	0.8(2.3)	0.845
ESR(mm/h)	12.01±11.09	8(10)	9(10.5)	0.493
Fibrinogen (mg/dL)	354.6±90.3	336(101.5)	331 (78)	0.242
Urea at first admission(mg/dL)	25.29±13.22	24 (8.5)	22 (10)	0.056
Creatinine at first admission(mg/dL)	0.86±0.22	0.87 (0.22)	0,81 (0.2)	0.233
eGF at first admission (ml/min/1,73m^2)	101.3±22.3	95.8 (36.6)	104 (31.1)	0.107
Proteinuria at first admission (mg/day)	346.79±1486.46	200 (100)	200 (50)	0.107
Urea at last admission(mg/dL)	27±12.72	26 (11.5)	22 (11)	0.01
Creatinine at last admission(mg/dL)	0.86±0.66	0.79 (0.22)	0.74 (0.18)	0.03
eGF at last admission (ml/min/1,73m^2)	107.53±22.1	108 (31.8)	116 (21)	0.006
Proteinuria at last admission (mg/day)	156.9±824.7	226±966	73±608	0.014
Albumin(g/dl)	4.46±0.56	4.4 (0.4)	4.6 (0.45)	0.019
Uric acide (mg/dL)	4.54±1.13	4.49±1.2	4.59±1.06	0.566
WBC(10^6/L)	7605±1832	7768±2073	7409±1483	0.194
Neutrophils(10^6/L)	4718±1667	4897±1813	4503±1456	0.117
Lymphocytes(10^6/L)	2167±604	2117±588	2226±622	0.232
	282123±81833	260000(98500)	276000(97500)	0.157

Platelet(10^6/L)				
NLR	2.42±1.37	2.11 (1.34)	1.96 (1.28)	0.116
PLR	139.33±53.16	128.4 (55)	129.3 (47.8)	0.786
Hemoglobin(g/dL)	13.58±1.65	13.8±1.51	13.3±1.78	0.036
RDW-CV (%)	14.88±5.88	13.6 (1.8)	14.4 (3.1)	0.021

MBP: Mean Blood Pressure, CRP:C-reaktive 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 distrubition width

Table 3

Cox regression analysis of risk factors affecting chronic kidney disease 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-reaktive protein ESR: erythrocyte sedimentation rate

Table 4

Cox regression analysis of risk factors affecting amyloidosis in FMF patients

UNIVARIATE					**MULTIVARIATE**			
Parametre	β	HR	95%CI	P	β	HR	95%CI	P
Gender	-0.653	0.521	0.175-1.550	0.241	-	-	-	-
Genetic mutation	-0.949	0.387	0.152-0.983	**0.046**	-	-	-	-
Number of attacks	0.229	1.257	0.279-5.674	0.766	-	-	-	-
Dose drug	0.738	2.092	0.703-6.226	0.185	-	-	-	-
Age of disease onset	1.344	3.836	1.641-8.963	**0.002**	1.623	0.197	0.047-0.820	**0.026**
Abdominal pain	0.941	0.390	0.107-1.420	0.153	-	-	-	-
Fever	0.629	0.533	0.174-1.637	0.272	-	-	-	-
Arthritis	1.386	3.999	0.519-30.782	0.183	-	-	-	-
CRP	0.124	0.883	0.669-1.166	0.382	-	-	-	-
ESR	0.051	1.052	1.021-1.085	**0.001**	-	-	-	-
Fibrinogen	0.008	1.008	1.004-1.012	**0.000**	-	-	-	-
WBC	0.000	1	1-1.001	**0.008**	-	-	-	-
Neutrophils	0.000	1	1-1.001	**0.027**	-	-	-	-

CRP:C-reaktive protein ESR: erythrocyte sedimentation rate, WBC: White blood cell